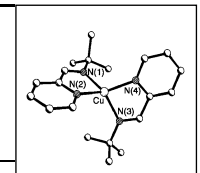
Atom transfer radical cyclisation reactions mediated by copper complexes



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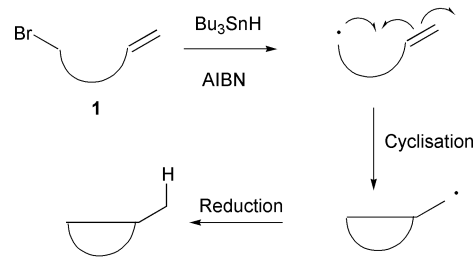
This article describes recent advances in the use of copper complexes in mediating atom transfer radical cyclisation reactions (ATRC). Recent developments have included the design of activated complexes which mediate the cyclisation of tri-, di-, and mono-halo derived substrates at ambient temperatures. Using this methodology, cyclisation to give a variety of ring sizes (4–18 membered rings) has been demonstrated. In addition tandem and radical–polar cross-over reactions have also been developed. The design of solid supported and perfluorous complexes that mediate cyclisations may make this approach to the synthesis of rings more attractive towards industrial applications.

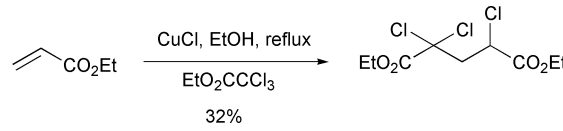
1 Introduction

The efficient preparation of cyclic systems continues to be an important area of modern organic chemistry. The formation of such cyclic systems by carbon–carbon bond formation has increasingly been achieved by the use of free radical cyclisation protocols.[1] The majority of such reactions are mediated by organostannane or organosilane reagents (*e.g.* Bu_3SnH or $HSi(SiMe_3)_3$) (Scheme 1).[1]

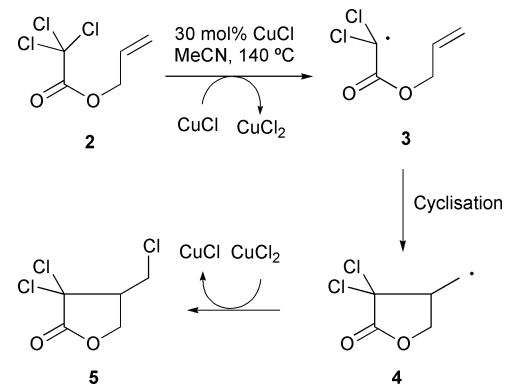
The disadvantage of these methods is that they are reductive in nature, *i.e.* the cyclised radicals are 'quenched' by the addition of a hydrogen atom from the mediating reagent. This approach can be limited as it leads to the loss of two functional groups. For example, cyclisation of **1** with Bu_3SnH leads to the loss of both the radical precursor (halogen) and the radical acceptor (alkene). In addition, the use of organostannane reagents is complicated by their high toxicity, high expense and purification problems. Transition metal catalysed intermolecular addition of polyhalocarbon derived molecules to alkenes has been known for some time (Scheme 2).[2] The intramolecular version of this reaction, atom transfer radical cyclisation (ATRC), can provide a convenient method for the construction of various ring systems. In particular ATRC reactions of 2,2,2-trichlorinated carbonyl compounds have been reported with a range of metal catalysts, *e.g.* Ni metal,[3] $RuCl_2(PPh_3)_3$, and $FeCl_2(P(OEt)_3)_3$.[4] However, by far the most successful catalysts have been those derived from copper(I)-based halogen compounds.[4] These oxidative atom transfer cyclisations involve redox reactions between copper(I) and copper(II) complexes. Thus, reaction of an activated trichloroacetate such as **2** with CuCl in MeCN at 140 °C in a pressure bottle for 1 hour generates the initial radical **3** and $CuCl_2$ (Scheme 3).[5] After cyclisation the newly formed (more reactive) primary radical **4** reacts with $CuCl_2$ to regenerate the CuCl catalyst and furnish



Scheme 1 Reductive cyclisations using Bu_3SnH.



Scheme 2



Scheme 3 Oxidative copper(I) mediated atom transfer radical cyclisation.

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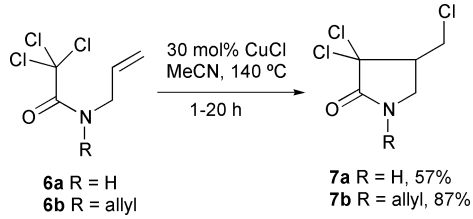
the cyclised product **5**. The use of copper complexes in mediating radical cyclisations thus has a number of advantages over alternative reductive methods including: (a) the low cost of copper halides, (b) the ease of work-up of the reactions, and (c) the catalytic nature of the processes.

2 Reactions mediated by CuCl and CuCl–bipyridine complex

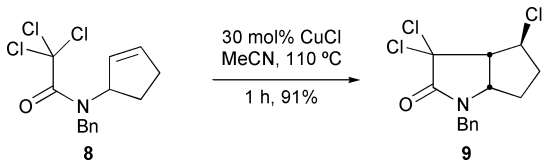
2.1 Reactions using CuCl

Atom transfer radical cyclisation mediated by catalytic amounts of CuCl has been utilised to prepare not only γ-lactones but also γ-lactams.[6,7] Heating both the trichloroacetamide derivatives **6a,b** with CuCl in MeCN at 140 °C furnished the desired 5-*exo* atom transfer products **7a,b** in 57% and 87% yield respectively (Scheme 4).[6] No products arising from 6-*endo* cyclisation were



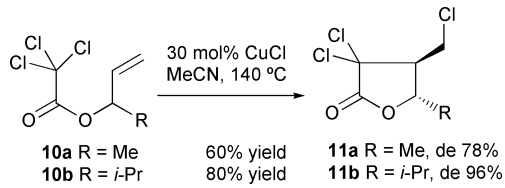
Scheme 4

detected. Using this protocol it was possible to cyclise both secondary **6a** and tertiary **6b** amides, although the cyclisation of the tertiary amide **6b** was the more efficient of the two. Bicyclic lactams were also readily prepared using this approach providing access to pyrrolidine alkaloid skeletons (*e.g.* **9**). Cyclisation of **8** at 110 °C furnished one diastereoisomer **9** containing the *cis* fused ring junction in 91% yield (Scheme 5).[7]



Scheme 5

The cyclisation of trichloroacetates derived from secondary alcohols **10a,b** proceeds with excellent diastereoselectivity to furnish predominantly the *trans* diastereomers **11a,b** (Scheme 6).[8] Interestingly the stereochemical outcome of the cyclisation

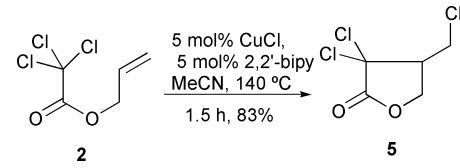


Scheme 6

reactions of **10** was similar to those obtained using other free radical processes.

2.2 Effect of copper salt, solvent and other additives

Screening of other copper salts indicated that a range were effective in mediating the cyclisation of trichloroacetate **2** at elevated temperatures including Cu_2O, $Cu(NO_3)_2{\cdot}H_2O$, and Cu(CCPh).[8] The concentration of the reactions was also found to be crucial, with relatively high concentrations leading to telomerisation of the substrate. While a range of solvents was investigated, only acetonitrile and alcohols were found to be effective in mediating the cyclisation of trichloroacetate **2**.[8] However, the addition of an equimolar amount of 2,2′-bipyridine (bipy) to CuCl was found to accelarate the rate of the reaction fourfold (Scheme 7).[8] In general, the addition of either



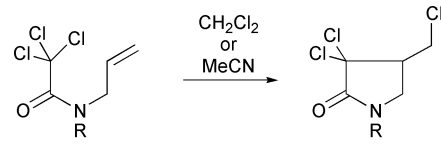
Scheme 7

amine or pyridine ligands to atom transfer reactions has been found to cause rapid rate accelerations for a variety of cyclisation and intermolecular addition reactions (see Sections 4.1–4.4).

2.3 Use of copper halide–2,2′-bipyridine complexes

Ligands may act to accelerate atom transfer processes by solubilising the CuCl, or by altering the redox potential of the catalyst system, or by both. Screening the substrates **12a–c** with various ligand systems indicated that the use of 30 mol% of a 1 : 1 mixture of CuCl–bipy in CH_2Cl_2 catalysed the cyclisation more rapidly than CuCl in MeCN.[9] Other solvents such as 1,2-dichloroethane and THF were also compatible with the use of CuCl–bipy as a mediator. Thus, with this more activated catalyst system it was possible to cyclise a variety of substrates at room temperature or below. The nature of the *N*-protecting group was also found to affect the rate of the cyclisation (Table 1).

Table 1 Effect of *N*-protecting group and bipyridine on rate and yield of reaction

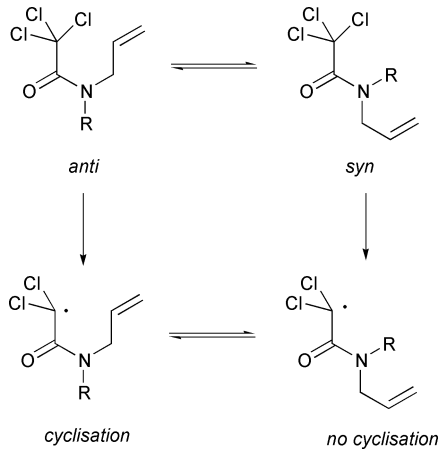


Substrate	Catalyst (mol%)[a]	Temp./°C	Time/h	Yield (%)
12a	CuCl (30)	80	18	68
12a	CuCl–bipy (30)	rt	1	98
12b	CuCl (30)	rt	24	97
12b	CuCl–bipy (5)	rt	0.2	91
12c	CuCl (30)	80	4	80
12c	CuCl–bipy (30)	rt	2	78

[a] Reactions with CuCl were run in MeCN, reactions with CuCl–bipy were run in CH_2Cl_2.

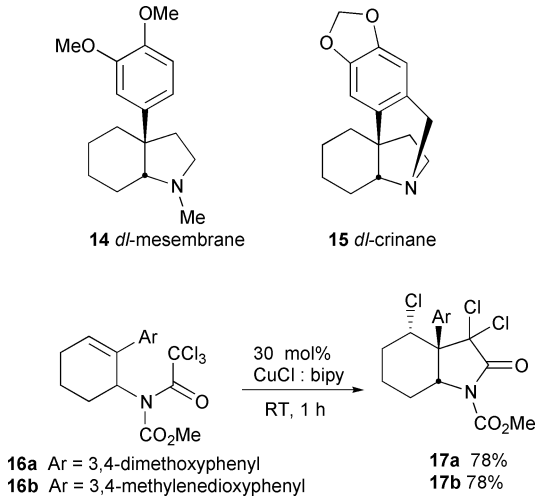
In general the cyclisation of α-*N*-allylcarbamoyl radicals (derived from **12**) is a difficult process requiring high temperatures, primarily due to the high barrier to rotation which characterises the amide bond. Only one conformer can cyclise (*anti*) and the nature of the *N*-protecting group alters the conformer population, thus bulky or electron withdrawing substituents (**12b,c**) favour cyclisation by shifting the equilibrium towards the *anti* conformer (Scheme 8).[10]

This phenomenon has been used to good effect in the formal total synthesis of both mesembrane **14** and crinane **15**.[10]



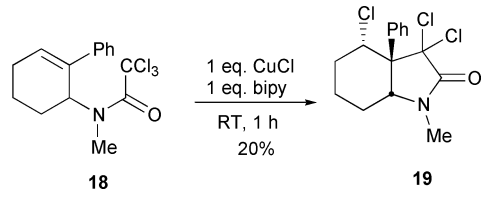
Scheme 8

Cyclisation of **16a,b** with 30 mol% CuCl–bipy furnished the products **17a,b** in 78% and 78% yield respectively (Scheme 9).



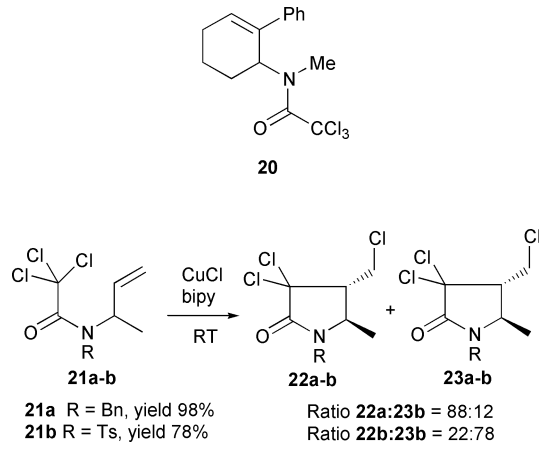
Scheme 9

Manipulation of these intermediates to the *dl*-natural products, mesembrane **14** and crinane **15**, was then accomplished using standard chemistry.[10] Attempts to mediate the cyclisation of **18** which contained the desired *N*-Me group only produced low yields (20%) of the desired product **19** (Scheme 10) due to population of rotamers unfavourable to cyclisation (*e.g.* **20**).[10]

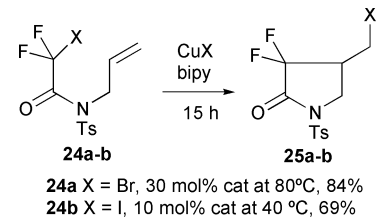


Scheme 10

The stereochemical outcome of the 5-*exo* cyclisation of simple precursors was also found to be *N*-protecting group dependent with *N*-benzyl compound **21a** leading to the *trans* isomer **22a**, while the *N*-tosyl substrate **21b** led to the *cis* product **23b** predominantly (Scheme 11).[9] The electron withdrawing *N*-tosyl group has also been used to facilitate the cyclisation of various *N*-allylhalodifluoroacetamides **24** to give α,α-difluorinated-γ-lactams **25** (Scheme 12). The reactivity of halodifluoroacetamides was found to decrease in the order I > Br >> Cl (using CuI, CuBr and CuCl–bipy mixtures respectively).[11]

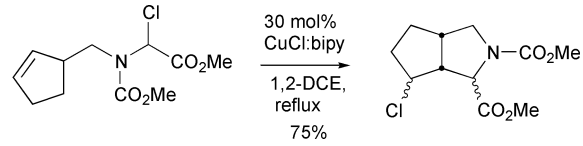


Scheme 11



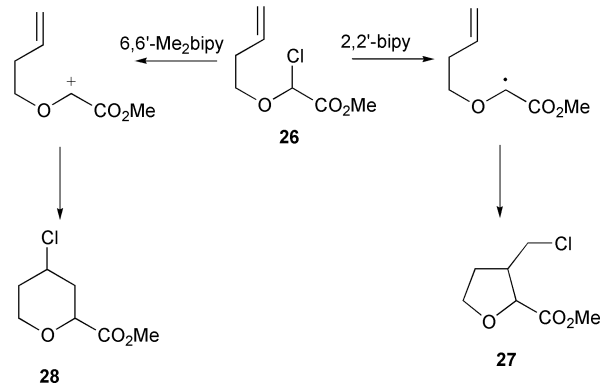
Scheme 12

The highly activated nature of the CuCl–bipy catalyst system allows the cyclisation of mono-halo substrates at elevated temperatures (80 °C). Hence, application of this protocol to the synthesis of cyclic amino acids has also been reported.[12] Best results were obtained when the reactions were performed at 80 °C for 18 hours (Scheme 13). A variety of solvents were found



Scheme 13

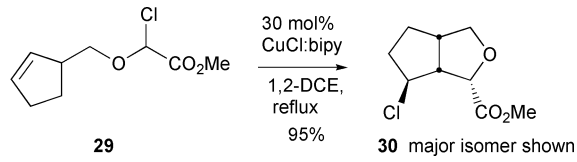
to be compatible with the cyclisation of the glycine derived radicals, however the use of good hydrogen atom donors like THF, dimethoxyethane and acetone led to substantial amounts of reduced cyclisation products. The regioselectivity and stereoselectivity of the cyclisations were found to parallel those obtained from Bu_3SnH mediated cyclisations. In analogous chemistry the cyclisation of radicals derived from 2-(alk-3-en-1-oxy)-2-chloroacetates was possible (Scheme 14).[13] Inter-



Scheme 14

estingly the regioselectivity of the reactions was dependent upon the copper complex used. Hence, cyclisation of **26** with

CuCl–2,2′-bipyridine proceeded as expected to give the 5-*exo* product **27**, while the use of 6,6′-bipyridines led exclusively to the 6-*endo* product **28**.[13] This was rationalised as being due to the different ligands promoting either a radical or cationic cyclisation pathway respectively. The use of CuCl–bipy in the cyclisation of a range of 2-(alk-3-en-1-oxy)-2-chloroacetates furnished 3-(1-chloroalkyl)-substituted tetrahydrofurans in good yields. Hence, cyclisation of **29** furnished **30** in 95% yield as an 82 : 18 mixtures of isomers respectively (Scheme 15). The

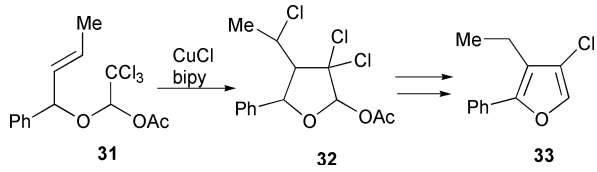


29 **30** major isomer shown

Scheme 15

chlorine substituent incorporated in the products could be used to good effect in further chemistry (*e.g.* lactonisation reactions). The utilisation of this atom transfer–lactonisation protocol allowed for the efficient total synthesis of the natural products avenaciolide and isoavenaciolide.[13]

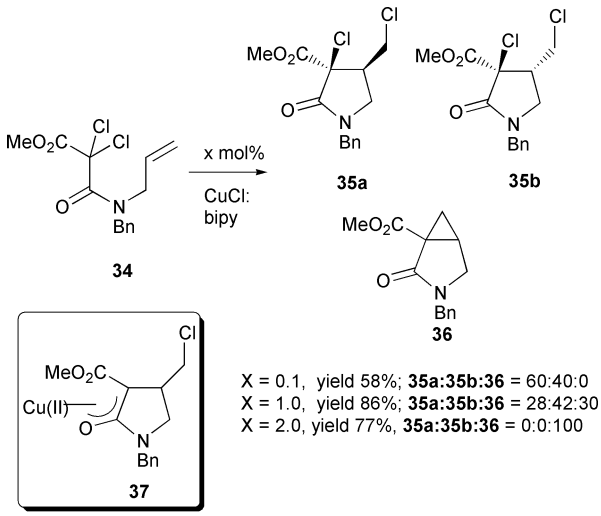
A 1 : 1 mixture of CuCl–bipy has also been used in the synthesis of 2,3-disubstituted 4-chlorofurans.[14] Hence, reaction of 1-acetoxy-2,2,2-trichloroethyl allyl esters **31** with 30 mol% CuCl–bipy in refluxing 1,2-dichloroethane (DCE) furnished the polychlorinated tetrahydrofurans **32**. Dechloroacetoxylation with Zn dust followed by tandem dehydrohalogenation–aromatisation with *t*-BuOK and 18-crown-6 led to the desired furan derivatives **33** (Scheme 16).[14] The reaction of di-



31 **32** **33**

Scheme 16

chloromalonic derivatives, where the halogens are adjacent to two carbonyl groups, leads to a variety of products depending upon the relative amount of CuCl–bipy used (Scheme 17.[15] For

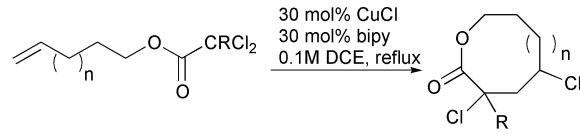


Scheme 17

example with 10 mol% only the two diastereomers **35a,b** arising from 5-*exo* cyclisation were detected (in a 6 : 4 ratio), however when a stoichiometric amount of copper complex was utilised the bicyclic cyclopropane product **36** was also detected and the ratio of **35a,b** had reversed.[15] The use of two equivalents of CuCl–bipy led to exclusive formation of the 3-azabicyclo[3.1.0]hexan-2-one **36**. This was postulated to arise *via* a sequential radical cyclisation followed by an intramolecular nucleophilic substitution reaction by the Cu(II) enolate **37**.[15]

3 Medium ring heterocycles

The synthesis of medium ring lactones and lactams (8–12 membered rings) continues to be an active area of research due to the large number of natural products that contain these frameworks. Although there is a range of methods to prepare such systems, the use of radical chemistry to facilitate macrocyclisations is less developed. Medium-sized lactones can be efficiently prepared by the reaction of di- and trichloroacetates using CuCl–bipy (Scheme 18).[16] Reaction of

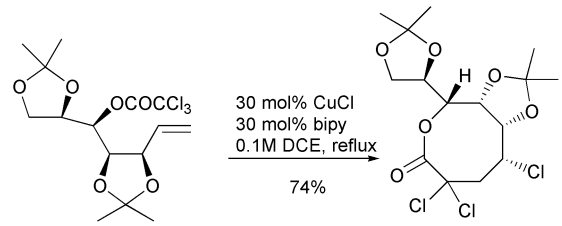


38a R = Cl, n = 1
38b R = Cl, n = 2
38c R = H, n = 1
38d R = H, n = 2

39a 60% yield
39b 59% yield
39c 75% yield (70:30)
39d 57% yield (70:30)

Scheme 18

compounds **38a–d** in the presence of 30 mol% CuCl–bipy in a 0.1 M solution of refluxing 1,2-dichloroethane for 18 hours furnished the desired products **39a–d** in various yields (57–75%). The *endo* mode of cyclisation was exclusively observed and corresponds to that predicted by calculations and other reported radical processes.[16] This is primarily observed in systems which contain a relatively long chain due to the fact that the most stable conformation for the ester function (s-*trans*) does not impede the cyclisation process. The reactions were found to proceed in various solvents including refluxing benzene. A wide range of 8-membered ring systems have been prepared *via* this approach, including the highly functionalised lactone **40** in 74% yield as a single diastereomer (Scheme 19).[17]

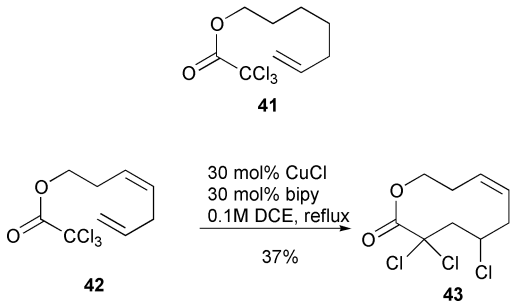


40

Scheme 19

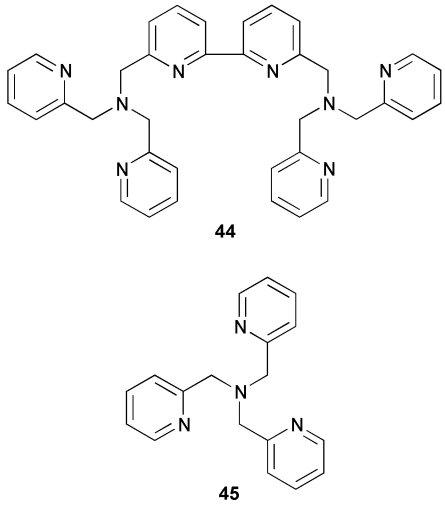
While it was possible to prepare 8- and 9-membered rings in good yield *via* this protocol it was not possible to prepare larger ring sizes, unless a rigid element of functionality was built into the cyclisation precursor. Thus, while cyclisation of **41** failed with only telomers being detected, the related system **42** successfully gave the 10-membered lactone **43** in 37% yield after three days at reflux (Scheme 20).[18] Presumably the rigid element incorporated in the carbon chain promotes intramolecular addition *via* entropy effects.

It was found that 0.3 equivalents of CuCl–bipy was essential for all the macrocyclisations reported above. If less catalyst was used lower yields resulted due to catalyst decomposition before

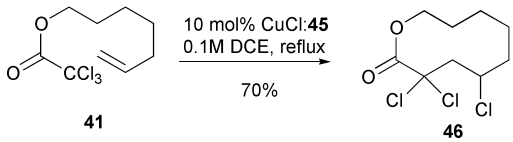


Scheme 20

completion of the reaction. It was also found crucial to facilitate these reactions using concentrations between 0.07–0.02 M in solution to avoid telomerisation processes.[18] The high efficiency of these medium ring cyclisations coupled with the fact that it was impossible to cyclise **38c** using reductive Bu_3SnH technology has prompted some researchers to speculate that the reactions may be proceeding *via* metal co-ordinated radicals or that cyclisation is taking place within the co-ordination sphere of the copper complex leading to a templating process.[18] Despite the versatility of this procedure for the preparation of 8- and 9-membered rings, the inability to cyclise larger systems without rigid control elements, and the need for relatively large amounts of catalyst (0.3 equivalents) to facilitate the reactions is a distinct disadvantage. This has prompted a number of researchers to investigate a range of alternative copper complexes to mediate ATRC reactions. Recently, Verlhac *et al.* reported that the multidentate pyridine ligands **44** and **45** were superior to bipyridine in a range of macrocyclisation reactions.[19]

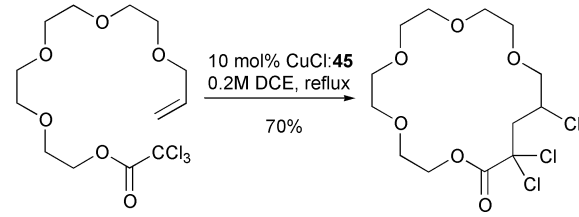


Thus, cyclisation of **38a** could be achieved in 99% yield with 0.1 equivalent of catalyst derived from ligand **44** (only 47% yield was obtained under identical conditions with bipyridine as ligand). Even more impressive was that it was possible to produce **39a** in 90% yield with only 0.03 equivalents of the catalyst derived from the more active tripyridylamine ligand **45**. In fact, the use of this ligand system enabled macrocyclisations of substrates which were impossible using bipyridine as ligand (Scheme 21)[19] (*e.g.* heating **41** with 0.1 equivalent of CuCl–**45**

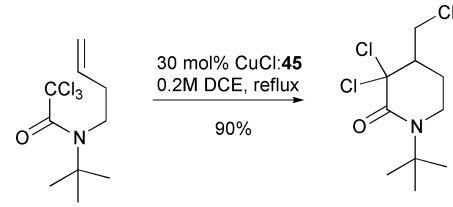


Scheme 21

furnished **46** in 70% yield whereas only telomers were isolated when CuCl–bipy was utilised). A range of crown ethers, Scheme 22)[20] and δ-lactams, (Scheme 23) have also been prepared using this approach.[21]



Scheme 22



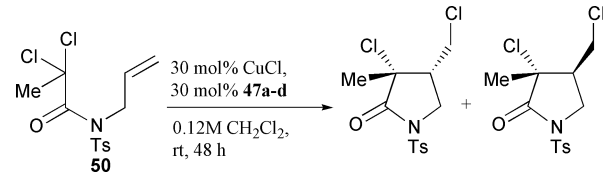
Scheme 23

4 Reactions mediated by other CuCl and CuBr complexes

4.1 Second generation of copper catalysts and structure–activity relationships

The discovery that different ligands can modify the reactivity, yield and selectivity of atom transfer reactions has prompted various groups to investigate the use of alternative ligand systems in cyclisation reactions. The ability to fine-tune both the solubility and redox potential of the catalysts by varying the ligand has enabled a range of highly activated catalyst systems to be prepared. In addition the choice of ligand used can often modify the product distribution significantly (see Table 2). By

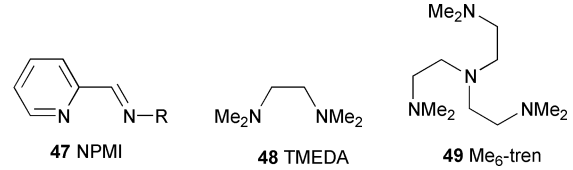
Table 2 Effect of *N*-alkyl group on cyclisation of **50**



Ligand	R group	Relative rate[a]	dr
47a	*n*-Bu	45	18 : 82
47b	*i*-Bu	28	28 : 72
47c	*s*-Bu	3	32 : 68
47d	*t*-Bu	1	51 : 49

[a] Relative rate with respect to the reaction of ligand **47d**.

far the most useful of the new more active generation of atom transfer catalysts are those based upon a) *N*-alkyl-2-pyridylmethanimines (NPMI) **47**,[21–26] b) *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) **48**,[27–30] and c) *N*,*N*,*N*′,*N*′,*N*″,*N*″-hexamethyltriethylenetetramine (Me_6-tren) **49**.[21,25,26,31]



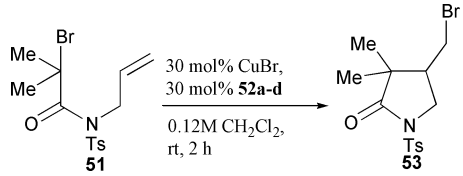
4.2 *N*-Alkyl-2-pyridylmethanimines (NPMI's)

In systems where copper halides are used in conjunction with bipy, the bipy is thought to primarily serve to solubilise the

copper halide as [Cu(I)(bipy)$_2$]X. In addition, the low lying LUMO π^* orbital, present in the conjugated π-system of bipy, is able to accept electron density from the metal and hence serve to stabilise the Cu(I) oxidation state. The structurally similar NPMI ligands have also been reported to solubilise Cu(I) halides and also have low lying π^* orbitals.[22] However, the relative ease of preparation of these ligands (easily prepared by reaction of commercially available amines with pyridine carbaldehydes in the presence of $MgSO_4$) has allowed a whole range of catalysts with different solubilities, steric and electronic structures to be prepared.[23] Structure–activity relationships have indicated that the nature of the imine substituent is crucial in controlling the rate and selectivity of the cyclisation reaction. Hence, cyclisation of **50** with the range of ligands shown indicates that bulky substituents retarded the rate of cyclisation significantly (Table 2).[23] In addition the diastereoselectivity of the process was also affected by the nature of the *N*-alkyl group. The optimum ratio of ligand to copper halide was found to be 2 : 1.[22,23]

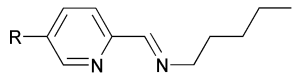
The solubility of the complexes could be altered by tailoring the length of the *N*-alkyl substituent (*e.g.*, **47e** R = *n*-Pr the catalyst was soluble in water at room temperature, insoluble in toluene at room temperature but soluble in toluene at 110 °C). The active nature of the catalyst **47f** (R = *n*-pentyl) allowed for the cyclisation of mono-halosubstrates such as **51** at room temperature.[23] Screening of a range of electronically modified ligands **52a–d** in the cyclisation of **51** (Table 3) indicated that

Table 3 Effect of pyridyl group on cyclisation of **51**



Ligand	R group	Ratio **51** : **53**
52a	H	41 : 69
52b	Me	34 : 66
52c	OMe	73 : 27
52d	NO_2	>98 : 2

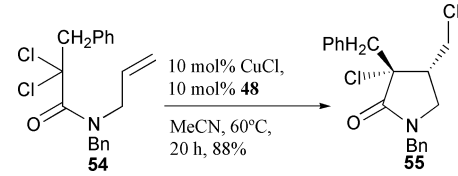
the order of reactivity was **52b** > **52a** > **52c** > **52d** (paralleling σ_m in relation to the pyridine nitrogen). This suggests that inductive effects onto the pyridine nitrogen and not resonance effects onto the imine nitrogen are the dominant features for this class of ligand in cyclisation reactions.[24] The ligand **52b** which contained a mildly inductive electron donating group (which causes an increase in the energy of the ligand LUMO and thus a decrease in the relative stability of the Cu(I) oxidation state) showed a rate enhancement, whereas those with electron withdrawing inductive groups caused a decrease in the rate of reaction. Thus the rates of ATRC reactions may well parallel the basicity of the pyridine nitrogen.[24]



52a-d NMPI

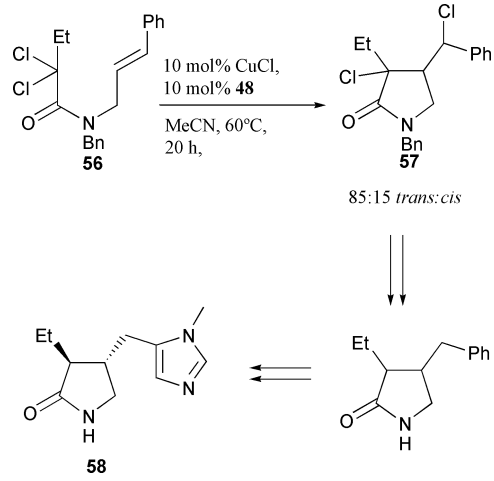
4.3 *N*,*N*,*N*′,*N*′-Tetramethylethylenediamine (TMEDA)

One of the major disadvatages of the CuCl–bipy reagent system is that substantial amounts of catalyst (normally 30 mol%) of this relatively expensive reagent are required for efficient catalysis. The use of the more reactive CuCl–TMEDA reagent combination furnishes a catalyst system which gives better yields at lower catalyst loading in simple ATRC reactions. In addition, cyclisations can often be carried at out at lower temperatures than with CuCl–bipy. An added advantage is the relative inexpense of the TMEDA additive. As in the case of the bidentate NMPI ligands, the optimum ratio of the bidentate TMEDA ligand to CuCl was found to be 2 : 1.[27] Thus CuCl–(TMEDA)$_2$ complex can mediate efficient 5-*exo* cyclisations of a range of trichloro and dichloroacetamide derivatives. Cyclisation of **54** with 10 mol% CuCl–(TMEDA)$_2$ in acetonitrile for 20 hours at 60 °C furnished the product **55** as one diastereomer in 88% yield (Scheme 24).[27] Interestingly, attempts to cyclise this



Scheme 24

substrate with CuCl–bipy failed, indicating the importance of utilising the correct choice of ligand for a given cyclisation. The influence of the *N*-benzylic protection in the CuCl–(TMEDA)$_2$ catalysed 5-*exo* cyclisation of a range of chiral substrates has been examined.[28,29] The steric nature of the *N*-substituent was not found to influence the stereoselectivity of the cyclisations to any significant extent.[28] The synthetic utility of CuCl–(TMEDA)$_2$ promoted cyclisation has been explored by application to the formal total synthesis of pilolactam **58** (Scheme 25)[28] and in the synthesis of 3-benzyliminopyrrolidin-2-ones.[30]



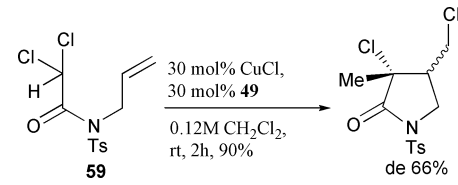
Scheme 25

4.4 *N*,*N*,*N*′,*N*′,*N*″,*N*″-Hexamethyltriethylenetetramine (Me$_6$-tren)

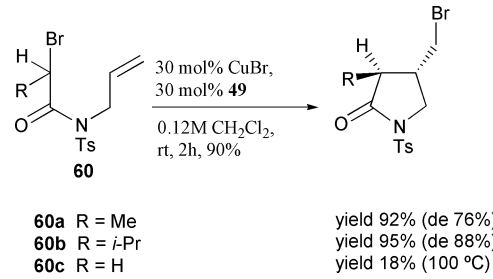
The origin of the reported improvement in the activity of CuCl(TMEDA)$_2$ relative to CuCl(bipy) has been speculated to arise due to the fact that simple copper(amine) complexes have lower redox potentials than copper(pyridine) complexes. Ghelfi and co-workers reported that the optimium ratio for copper halide–TMEDA was 1 : 2 indicating that two equivalents of bidentate ligand are required to make the active catalyst.[27] As a consequence of this observation a range of other multidentate amine ligands have also been screened in ATRC reactions. The most active polydentate amine ligand found to date is the tetradentate Me$_6$-tren ligand **49**.[21,31] The use of a 1 : 1 ratio of copper halide:**49** in various solvents was found to produce a catalyst far more active than either bipyridine, NMPI or TMEDA. Thus cyclisation of **59** proceeded only slowly at room temperature with NMPI **52** (72 h, 15% conversion) but rapidly

(less than 2 h, yield 90%) with Me_6-tren **49** (Scheme 26). The more activated nature of the catalyst allowed cyclisation to take place with lower catalyst loadings, thus cyclisation of **50** was accomplished with only 5 mol% catalyst at room temperature in 24 hours.[21,31] While it was possible to use even lower catalyst loadings at room temperature (*e.g.* 0.5 mol%) the reaction only proceeded to give a 33% conversion in the same 24 hour period. Cyclisation of a range of monohalosubstrates **60a,b** was possible at room temperature (Scheme 27). Cyclisation of the primary bromide **60c** was possible, albeit at elevated temperature. The product was obtained in low yield due to competing amide cleavage.[21]

Using this protocol it was not necessary to use vigorously dried glassware or solvents. In addition work-up of the reactions was facile, as the crude reaction mixture was passed through a small silica plug and the solvent removed to furnish the atom transfer products directly. Attempts to mediate 8-*endo* macrocyclisations of *N*-tosylamide **61** using this ligand system failed, with the main products being the rearranged compound **62** as well as unreacted starting material **61**.[21] The rearranged product **62** was postulated to arise *via* a competing 5-*exo ipso* aromatic radical substitution to give **63** followed by re-aromatisation followed by C–S bond cleavage to give **64**, loss of SO_2 and reduction of the resulting amide radical (Scheme 28).



Scheme 26

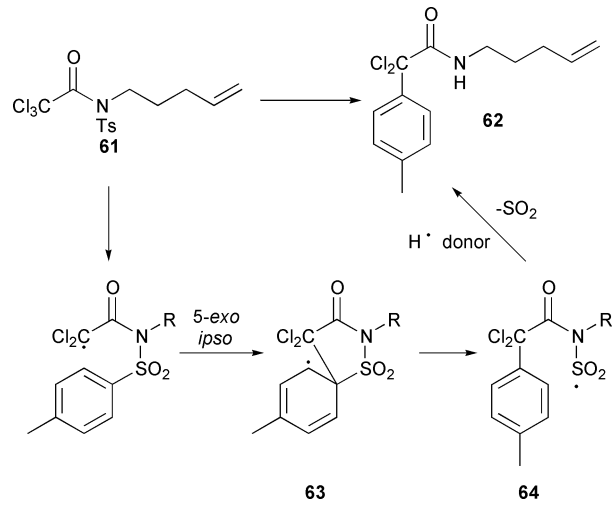


Scheme 27

5 Sequential reactions

The ability of copper(I) complexes to catalyse both cyclisation (ATRC) and intermolecular addition (ATRA) reactions has been exploited in a variety of tandem sequences. Intermolecular addition reactions are generally slower than intramolecular processes and this phenomenon has been used in sequential reactions. Thus, heating trichloroacetamide **12b** with methylenecyclohexane **65** with 10 mol% CuCl–bipy at 83 °C for 1 hour furnished the functionalised product **66** in 85% yield as almost a single diastereomer (Scheme 29).[32] In this case after cyclisation, the activated nature of the α,α-dichlorocarbonyl functionality in **13b** allows for the generation of a new cyclic radical **67**. This then undergoes an intermolecular addition reaction and is trapped by atom transfer from the $CuCl_2$–bipy generated in the second initiation step.[32]

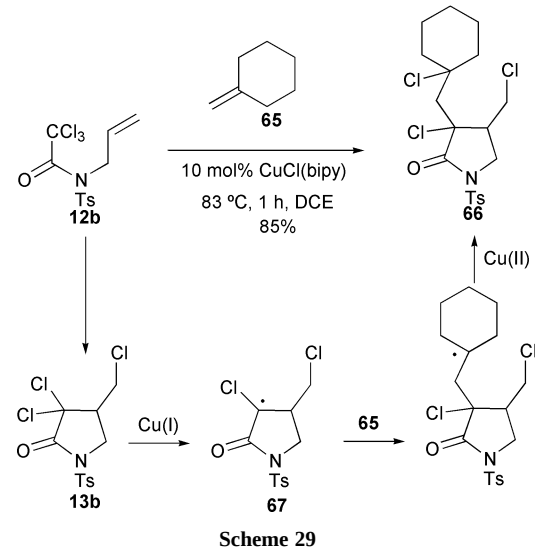
This approach has also been used to facilitate tandem cyclisations. Thus reacting **68** at room temperature with 30 mol% CuCl–bipy at 40 °C furnished the two diastereomers **70** in 83% yield. Purification using silica chromatography furnished the corresponding exocyclic alkenes **71** after elimination of HCl (Scheme 30).[32]



Scheme 28

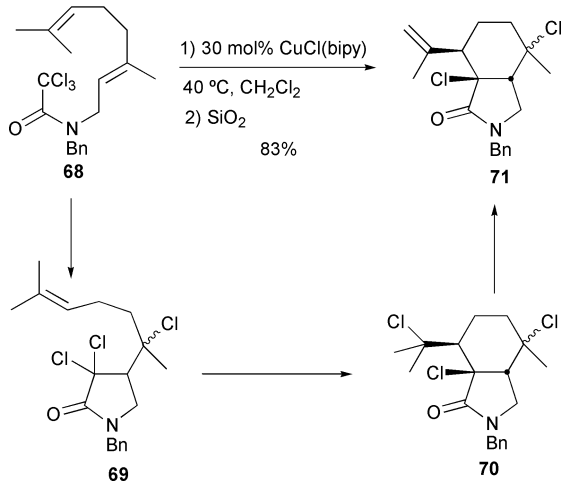
6 Solid supported ATRC catalysts

In order to facilitate work-up of atom transfer reactions as well as develop re-usable catalysts the immobilisation of pyridine–imine ligands onto solid supports has been investigated. Reaction of pyridine-2-carbaldehyde with aminopropylated silica followed by stirring of the polymer with a solution of either CuCl or CuBr furnished dark brown catalysts **72** (Scheme 31) which were active in ATRC of trichloro-, dichloro- and monobromo-substrates.[33] Both efficient 5-*exo* and 5-*endo* cyclisations could be mediated using this reagent system. However, the supported catalyst was less active than its equivalent homogeneous counterpart **52a**. Hence, reaction of the solid-supported catalyst with *N*-tosyl-*N*-allyl-2,2,2-trichloroacetamide **12b** in dichloromethane at room temperature furnished the expected atom transfer product **13b** in 92% after 3 hours. The catalyst was reclaimed by filtration and was then re-used with a new batch of **12b** to give **13b** in 90% yield after 18–24 hours. The decrease in activity of the catalyst system upon re-use was not found to be due to leaching of the copper

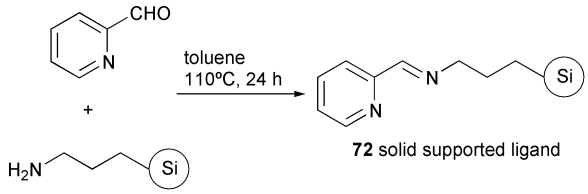


Scheme 29

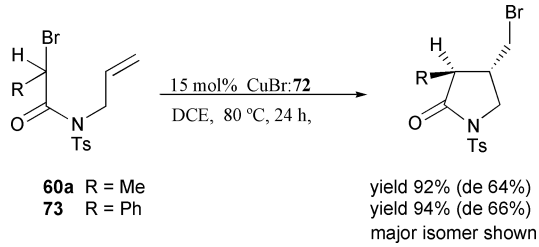
from the polymer bound catalysts but due to the formation of an inactive $CuCl_2$ complex. A wide range of substrates could be cyclised including secondary monohalo-substrates and unsubstituted amides (Scheme 32). The diastereoselectivity of the processes was similar to that observed in homogenous catalysis.[33]



Scheme 30



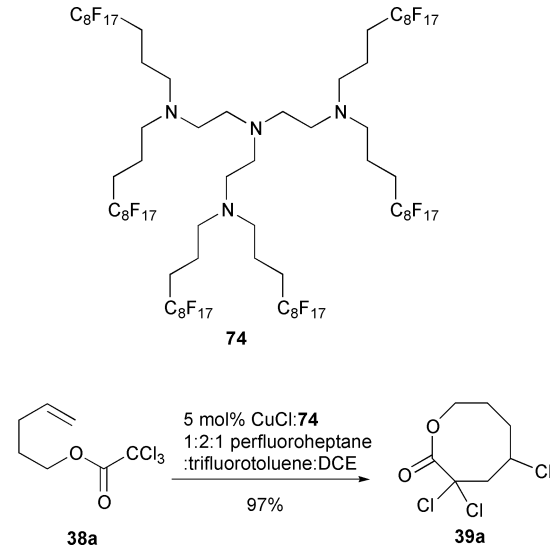
Scheme 31



Scheme 32

7 Perfluorous substituted ATRC catalysts

The use of perfluorous catalysis in a variety of organic reactions has been developed. Generally two phases (a perfluorous solvent and an organic solvent) are used in the reactions. In this approach the perfluorinated catalyst is confined to the perfluorous phase while the organic reactants and products are confined to the organic phase. At elevated temperatures the two phases are miscible allowing the desired reaction to be catalysed while at low (normally ambient) temperatures the phases are immiscible thus allowing easy separation of products from catalysts. In addition the inertness of most perfluorous solvents makes them relatively environmentally friendly. The perfluorinated analogue **74** of Me_6-tren **49** was shown to be soluble in perfluorocyclohexane.[34] The ligand itself was used as a 1 : 1 mixture with CuCl and screened in the macrocyclisation reaction of trichloroester **38a**. Cyclisation was much slower using **74** in the perfluorous solvent than when the corresponding non-perfluorinated ligand in 1,2-dichloroethane was used under convenional ATRC conditions. However, reaction of **38a** with 5 mol% of the catalysts derived from CuCl and **74** furnished **39a** in 97% yield after 10 hours (Scheme 33).[34] Recycling of the catalysts was accomplished by simple decantation of the perfluorous layer under argon. Even after the fourth recycling protocol the catalyst was still active and led to no drop in ultimate conversion (run 1, 96%; run 2, 95%; run 3, 93%; run 4, 91%), although the reaction rate was retarded slightly. Analysis by atomic absorption spectroscopy indicated that only 1–2% of the copper was leached into the organic phase during each run.

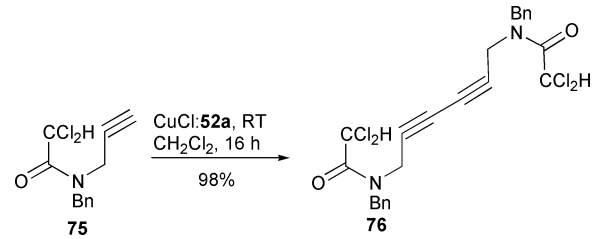


Scheme 33

The addition of iron powder to the reactions was shown to improve the yield of the reactions.[34]

8 Cyclisation onto alkynes

Cyclisation onto alkynes under ATRC conditions can often be complicated by facile oxidative dimerisation. Thus reaction of **75** with 1 equivalent of CuCl–**52a** furnished the coupled dimer **76** in 98% yield (Scheme 34).[25] The use of alternative *N*-protecting groups which facilitate cyclisation such as *N*-Ts or *N*-Boc allow facile cyclisation with a variety of ligands. Hence, reaction of either **77a,b** with 30 mol% CuCl–**52a** furnished the atom transfer products **78a,b** arising from two chlorine atom transfers. Cyclisation and subsequent removal of a second halogen atom to give the allyl radicals **79a,b** followed by a second atom transfer furnish the observed products (Scheme 35).[25]

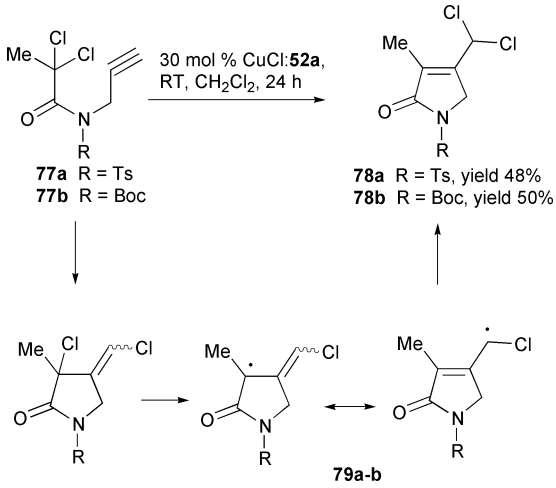


Scheme 34

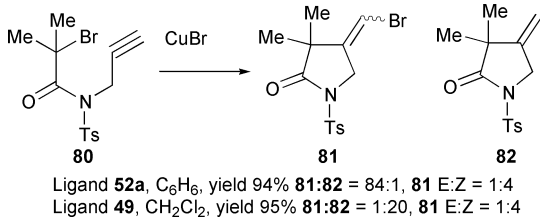
Cyclisation of the mono-bromo precursor **80** gave both the expected atom transfer product **81** plus the reduced product **82** arising from abstraction of a hydrogen atom by the intermediate vinyl radical (Scheme 36). The ratio of these compounds was dependent upon both the solvent and/or ligand employed for the reaction. Hence, cyclisation with CuCl–**52a** in benzene gave a 84 : 1 ratio of **81** : **82** in 94% combined yield while reaction with CuBr–**49** in THF furnished the reduced compound **82** as the major product **81** : **82** = 1 : 20.[21,25]

9 5-*endo* Cyclisations. Radical–polar crossover reactions

While 5-*exo* cyclisations have been extensively studied, the mediation of the less common 5-*endo* cyclisations has attracted less interest. Recently Zard has employed his Ni metal

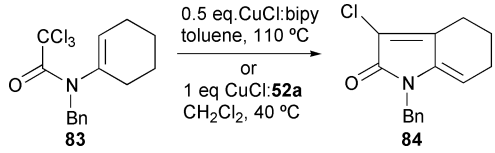


Scheme 35



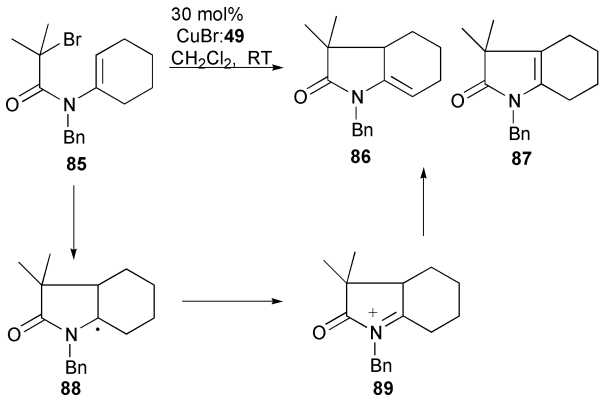
Scheme 36

procedure to mediate cyclisation of trichloroacetamides in a 5-*endo* mode with the products being similar to those obtained using copper catalysis.[35] Treatment of trichloro-substrate **83** with either CuCl–bipy[36,37] or CuCl–**52a**[26] has been reported to give the diene **84** (in 94 and 70% yields, respectively) (Scheme



Scheme 37

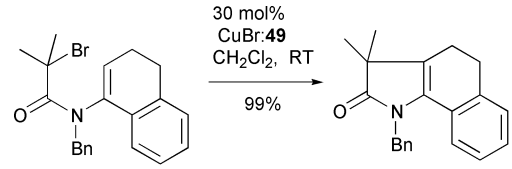
37). Monohalo-substrate **85** furnished two alkene products **86** and **87** in 82% yield (1 : 1 ratio) (Scheme 38).[26] Mechanist-



Scheme 38

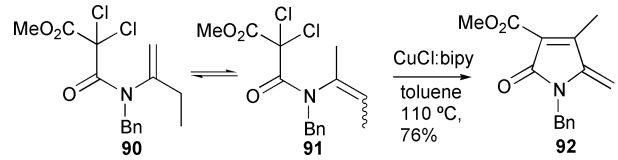
ically the reaction has been postulated to take place *via* an initial 5-*endo* radical cyclisation to give **88** followed by Cu(II) mediated oxidation of the tertiary radical to the corresponding *N*-acyliminium ion **89** followed by elimination of a proton to furnish the two regioisomers **86** and **87**.[26]

The reaction was found to be general with a variety of ring sizes and ring substitutions (Scheme 39).[26,36,37] Reaction of the



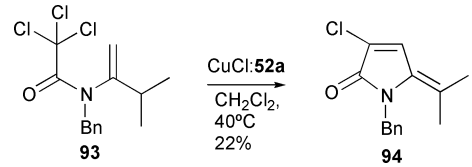
Scheme 39

enamide **90** at 110 °C furnished the diene **92** arising through cyclisation of the thermodynamically more stable alternative enamide **91** (Scheme 40).[36] Presumably the isomerisation to the



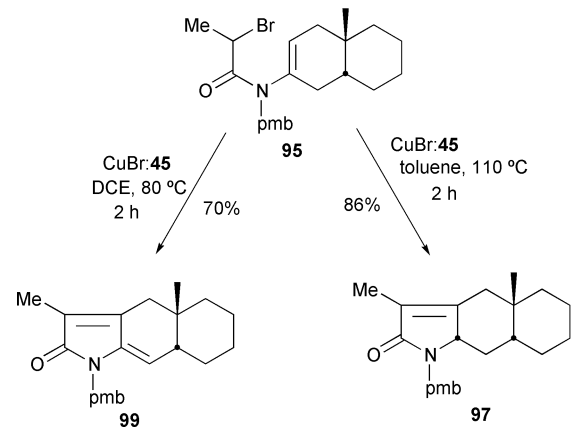
Scheme 40

thermodynamic enamide **91** is more rapid than cyclisation at this temperature. In contrast, cyclisation of trichloro-substrate **93** at lower temperature underwent exclusive cyclisation *via* the kinetic enamide (Scheme 41).[26]



Scheme 41

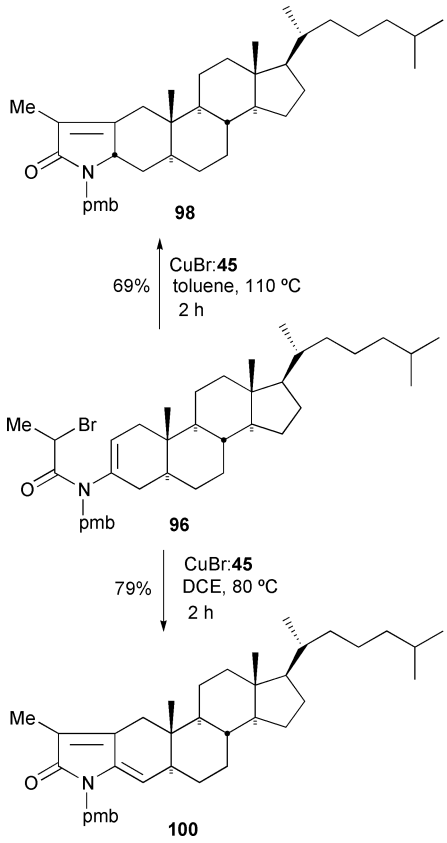
While it was not possible to mediate 5-*endo* cyclisation of secondary monohalo-substrates (*e.g.* **95**) using ligands **49** and **52a**,[26] it was possible using the tripyridyl ligand **45**.[38] Reaction of enamides **95** and **96** with 1 equivalent of CuBr–**45** in refluxing toluene gave the α,β-unsaturated lactams **97** and **98** in 86 and 69%, respectively (Schemes 42 and 43). Interestingly, if



Scheme 42

1,2-dichloroethane was used instead, the corresponding dienes **99** and **100** were producted exclusively.[38]

These dienes are likely to be produced by further oxidation of the monoenes **97** and **98** under these reaction conditions as demonstrated by the transformation of **101** to **102** upon heating

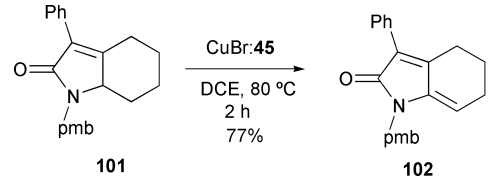


Scheme 43

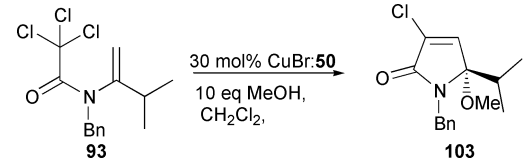
with 1 equivalent CuBr–**45** (Scheme 44).[38] Attempts to trap out the postulated acyliminium ion with nucleophiles have met with limited success. Hence, reaction of **93** with CuCl–**52a** in the presence of MeOH furnished the lactam **103**, albeit in only low yield (30%) (Scheme 45).

10 Synthesis of β-lactams

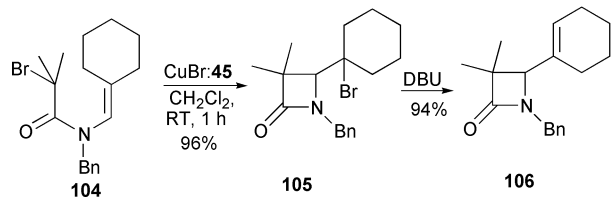
Enamides substituted only at the terminal end of the alkene group undergo rapid ATRC to furnish β-lactams in high yield.[39,40] Cyclisation of **104** using 30 mol% CuBr–**45** in CH_2Cl_2 at room temperature furnished the desired atom transfer product **105** in 94% yield after only 1 hour.[39] Facile elimination of the tertiary bromide to furnish the alkene **106** was possible by reaction with DBU (Scheme 46). Cyclisation of secondary monobromide **107** required heating for 24 hours. Under these conditions the alkene **108** was obtained directly as a 2.1 : 1 ratio of diastereomers (Scheme 47). Presumably initial atom transfer is followed by rapid elimination at the elevated temperature of the reaction. The regiochemical outcome of cyclisation had been reported to be solvent and ligand dependent.[40] Thus heating **109** with 0.5 equivalents of CuCl–bipy in toluene led to only 9% of the β-lactam **110** and 86% of the corresponding γ-lactams **111** (Scheme 48). However, when the reaction was repeated using CuCl–bipy or CuCl–TMEDA in acetonitrile as solvent only the β-lactam was produced. The change in regioselectivity can be explained by the differences in the solubilities of the copper catalysts. Thus because the CuCl–bipy catalyst is relatively insoluble in toluene, rapid trapping of the initial kinetically produced 4-*exo* cyclised radical is inefficient and this radical has time to undergo ring opening and thermodynamic 5-*endo* ring closure. However in acetonitrile (where the catalyst system is much more soluble) the initial kinetically produced radical undergoes highly efficient trapping leading to the β-lactam only.



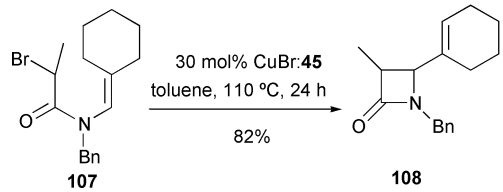
Scheme 44



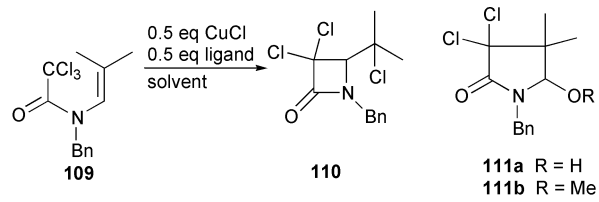
Scheme 45



Scheme 46



Scheme 47



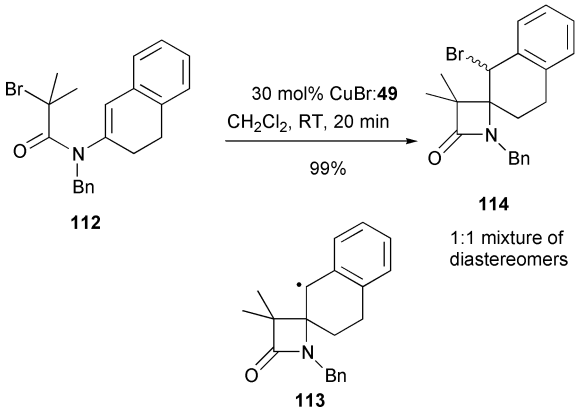
Bipy, reflux toluene then MeOH, yield **110** = 9%, **111** = 86% **111 a:b** = 1:1
Bipy, reflux MeCN or TMEDA, reflux MeCN, yield **110** = 85-86%

Scheme 48

4-*exo* Cyclisation has also been observed in systems where the cyclised radical is particularly stabilised.[26] Hence, 4-*exo* cyclisation of **112** gives the benzylic radical **113** which upon atom transfer furnished the bromofunctionalised β-lactam **114** in 99% yield as a 1 : 1 mixture of diastereomers (Scheme 49).

11 Concluding remarks

The last decade has seen the emergence of copper mediated atom transfer radical cyclisation reactions as a useful tool in the construction of cyclic molecules. Cyclisation of a range of substrates is possible furnishing a versatile array of ring sizes (4–18 membered rings), often in high yields. The development of activated complexes that mediate the cyclisation of monohalo substrates at room temperature or below, coupled with ability to sequence both intra- and intermolecular additions has broadened the scope of this technology. In particular, the development of solid supported/polymer bound reagents as well perfluorinated complexes makes the new processes relatively attractive towards industrial applications. Future investigations



Scheme 49

into the use of dendritic reagents, and the application of ATRC in 'environmentally friendly' solvents (such as water or ionic liquids) will further increase the attractiveness of this technology. The recent development of radical–polar crossover reactions (particularly in 5-*endo* processes) is particularly valuable. The potential to sequence both radical reactions and cationic reactions increases the number of possible synthetic applications of this methodology.

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