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Atom transfer radical cyclisations of activated and unactivated *N*-allylhaloacetamides and *N*-homoallylhaloacetamides using chiral and non-chiral copper complexes

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Activated *N*-tosyl-2,2,2-trichloroacetamide **6a**, *N*-benzyl-2,2,2-trichloroacetamide **6d**, 2,2-dichloroacetamides **6b**–**c** and **6e**–**f** and 2-monohaloacetamides **11a**–**g** undergo efficient 5-*exo* atom transfer radical cyclisations at room temperature mediated by CuCl or CuBr in the presence of tris(*N*,*N*-dimethylaminoethylene)amine **3** (trien-Me_6). The efficiency and stereoselectivity of these cyclisations was found to be greater than existing published atom transfer procedures based upon CuCl(bipyridine), $RuCl_2(PPh_3)_3$ and $CuCl(TMEDA)_2$. The product distribution for the cyclisation onto alkyne **11g** was found to be solvent dependent. Attempts to make larger ring sizes by *endo* cyclisation of *N*-tosylacetamides **19a**–**c** led to a competing 5-*exo ipso* aromatic substitution into the *N*-tosyl group followed by re-aromatisation and loss of SO_2 to furnish an amidyl radical. Cyclisation of *N*-homoallylacetamides **25a**–**d** proceeded smoothly to give δ-lactams with a range of catalysts based upon ligands **2** and **26**. The stereoselectivity of cyclisation to give γ lactams could be somewhat influenced by using chiral enantiopure copper complexes **28**–**30** suggesting that the reactions may involve metal-complexed radicals.

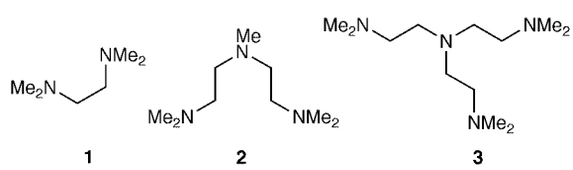
Introduction

In recent years, transition metal mediated free radical processes have gained in importance.[1] In particular the atom transfer radical cyclisation reactions (ATRC) of 2,2,2-trichlorinated carbonyl compounds have been reported with a range of metal catalysts, *e.g.* $RuCl_2(PPh_3)_3$,[2] $FeCl_2(P(OEt)_3)_3$,[3] CuCl(bipy),[4] $CuCl(TMEDA)_2$,[5] and CuCl(*N*,*N*,*N*′,*N*′,*N*″-pentamethyldiethylenetriamine).[6] However, even with these catalysts both high temperatures 60–160 °C and activated carbon–halogen bonds (*e.g.* 2,2,2-trihaloacetyl or 2,2-dihaloacetyl groups) are generally required as initiators. The cyclisation of *N*-allyl-*N*-(4-tolylsulfonyl)-2,2,2-trichloroacetamides by CuCl(bipy)[7] (bipy = 2,2′-bipyridine) has been shown to be an efficient process occurring at room temperature and has been recently extended to the sequencing of both intramolecular and intermolecular reactions.[8] Ghelfi and co-workers[5] reported the use of $CuCl(TMEDA)_2$ [*e.g.* $CuCl(\mathbf{1})_2$] in the cyclisation of *N*-allyl-*N*-benzyl-2,2-dichloro-2-alkylacetamides at room temperature and claimed it to be superior to that of $RuCl_2(PPh_3)_3$ and CuCl(bipy). While it was possible to mediate cyclisations using $CuCl(TMEDA)_2$ at room temperature, conversions were often low and diastereoselectivity was relatively poor.[5c] In addition cyclisations onto triple bonds failed[5b] and only cyclisations of 2,2,2-trihaloacetamides or 2,2-dihaloacetamides were described. We recently reported that *N*-alkyl-2-pyridylmethanimines could act as versatile tuneable alternative to bipyridine as ligands in ATRC[9] and ATRP[10] reactions. In fact a range of 2,2,2-trihaloacetamides or 2,2-dihaloacetamides could be reacted with high efficiency at room temperature with 2-haloacetamides requiring elevated temperatures. We report in this paper a versatile improved procedure which allows for the generation of radicals not only from 2,2,2-trihaloacetamide and 2,2-dihaloacetamide derivatives but also from the less activated 2-monohaloacetamide derivatives at room temperature. Both the yields and stereoselectivities are superior to those reported for similar substrates with either CuCl(bipy),[7] homogeneous and silica supported CuCl(*N*-pentyl-2-pyridylmethanimine)[9] or $CuCl(TMEDA)_2$[5] at room temperature. In addition, cyclisation onto alkynes and 6-*exo* cyclisations to give δ-lactams are reported as well as attempts to mediate 8 to 12-*endo* cyclisations at room temperature. The effect of chiral catalysts on the stereoselectivity of cyclisation of a range of substrates is also reported.

Results and discussion

Screening of multidentate amine ligands

We speculated that the origin of the reported improvement in the activity of $CuCl(TMEDA)_2$ relative to CuCl(bipy) in ATRC reactions was due to the fact that simple copper(amine) complexes have lower redox potentials than copper(bipyridine) complexes.[11] Ghelfi and co-workers reported that the optimum ratio of **1** to copper halide was 2:1, indicating that two



1 **2** **3**

bidentate ligands were required for the preparation of the active catalyst.[5] As a consequence, we recently screened a variety of multivalent amine ligands (**1**–**3**) in atom transfer reactions and discovered that CuBr(**2**) and CuBr(**3**) were substantially more active than $CuBr(\mathbf{1})_2$ in the cyclisation reaction of the bromide

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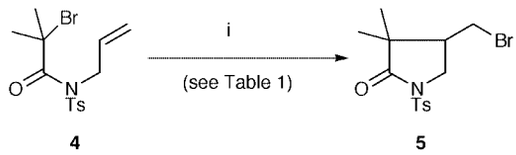
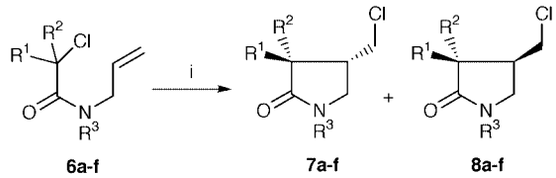


Scheme 1 *Reagents and conditions*: i, 30 mol% CuBr, ligand (see Table 1), CH_2Cl_2, 30 minutes, rt.



Scheme 2 *Reagents and conditions*: i, 30 mol% CuCl, 30 mol% **3**, CH_2Cl_2, rt.

4 (Table 1, Scheme 1).[9b] Repeating the reactions with CuBr(**2**) and CuBr(**3**) at lower catalyst loadings and lower concentrations (for two hours) allowed us to determine that the tetradentate ligand (trien-Me_6) **3** was at least ten times faster at mediating the cyclisation of **4** than the tridentate ligand (PMDETA) **2**. A similar conclusion was reached recently by Matyjaszewski and co-workers[12] who compared the series of multidentate ligands **1**–**3** with bipyridine in copper mediated atom transfer radical polymerisation of styrene. He discovered that catalysts derived from tridentate **2** or tetradentate **3** ligands were more active than those derived from TMEDA **1** or bipyridine ligands. With this information in hand we examined the cyclisation reactions of a variety of substrates in order to compare the efficiency of the new ligand system to that of the published systems using CuCl(**1**) and $RuCl_2(PPh_3)_3$.

We initially chose to evaluate the efficiency and stereoselectivity of the 1 : 1 complex of CuCl and **3** in atom transfer radical cyclisation of acetamides **6a**–**f**. Initial experiments involved comparison of the efficiency of this catalyst CuCl(**3**) with that of the previously reported catalysts for the cyclisation of acetamides **6a**–**f**, those being CuCl(bipyridine),[7] CuCl(TMEDA)$_2$[5] and $RuCl_2(PPh_3)_2$.[2] The substrates **6a**–**f** were prepared by the previously reported literature methods.[2b,5a,b] Ligand **3** was synthesised according to the standard literature procedure.[13] The active catalyst, CuCl(**3**) was prepared by the reaction of a 1 : 1 ratio of CuCl with the ligand **3** in CH_2Cl_2. The catalyst (30 mol%) was then added to the trichloroacetamide substrates **6a** and **6d** (Scheme 2). It was not necessary to use rigorously dried solvents or glassware or to use an inert atmosphere in order to carry out the reactions. After the reactions were complete the crude reaction mixture was passed through a short silica plug (eluted with CH_2Cl_2) and the solvent was evaporated to furnish the atom transfer products in high yield (92–98%). In both cases the reactions proceeded cleanly with only products arising from cyclisation being detected. While cyclisations of both **6a** and **6d** using CuCl(bipyridine)[7] at room temperature have been reported to take 15 minutes and 1 hour respectively, with our catalyst system the reactions were over in less than 30 seconds and 5 minutes respectively (Table 2). No advantage was found in running the reactions at low concentrations, and all reactions were consequently run at 0.12 M in substrate (identical to that reported for the $RuCl_2(PPh_3)_3$ mediated cyclisation of **6a**).[2b,c] While the reactions of the 2,2,2-trichloroacetamide derivatives **6a** and **6d** were over rapidly at room temperature, the less activated dichloroacetamide substrates **6b** and **6c** took approximately 2 h and 30 minutes respectively. Both reactions furnished mixtures of diastereomers with **6b** giving the *cis* isomer **8b** as the major product (ratio **7b** : **8b** = 17 : 83) while **6c** gave the *trans* isomer **7c** as the major product (ratio **7c** : **8c** = 85 : 15). Stereochemical assignments were confirmed by comparison of the NMR data of the products with those of authentic samples already published.[2b] The selectivities of these processes were greater than those reported for the $RuCl_2(PPh_3)_3$ mediated reactions with the added advantage that the reactions were carried out at room temperature while the ruthenium mediated processes required 80–100 °C. Interestingly, the sense of induction in the cyclisation of **6b** was opposite to that observed for the related $RuCl_2(PPh_3)_3$ mediated reaction. The reason for this outcome is unclear.

The effect of catalyst loading on the efficiency of the cyclisation of **6c** was briefly investigated. Hence, **6c** was reacted with either 10, 5, 1 or 0.5 mol% of catalyst at rt over a 24 h period. While the reactions with 10 and 5 mol% of catalyst proceeded to completion (by NMR) within the 24 h period, the reactions with loadings of 1 or 0.5 mol% of catalyst proceeded to give 57 and 33% conversions respectively. While the results indicated that it was possible to mediate the cyclisations at room temperature with lower catalyst loadings for the rest of the work, we continued to utilise 30 mol% of catalyst in order to keep the reaction times conveniently low. Having shown that the CuCl(**3**) catalyst was superior to $RuCl_2(PPh_3)_3$ for the cyclisation of *N*-tosylacetamides, we next compared its efficiency to that of CuCl(TMEDA)$_2$ in the cyclisation of the *N*-benzyl compounds **6e**–**f**. While Ghelfi reported that the cyclisation of **6f** with CuCl(TMEDA)$_2$ required 20 hours at room temperature and proceeded to give a 51 : 49 mixture of *cis* : *trans* isomers, we were delighted to find that using CuCl(**3**) the reaction was over in 2 hours giving a superior 9 : 1 ratio of products. For **6e**, selectivity was marginally greater using the CuCl(**3**) catalyst system. The sense of the diastereoselectivity in both examples was identical to that reported by Ghelfi and co-workers.[5a–c]

Table 1 Screening of ligands

Ligand	Equiv.	Conversion (%)[a]	Mass balance (%)
1	1	5	98
1	2	37	98
2	1	100	92
3	1	100	92
2	1	<2[b]	90
3	1	20[b]	94

[a] 30 mol% CuBr, CH_2Cl_2, 0.12 M, rt, 30 min. [b] 10 mol% CuBr, CH_2Cl_2, 0.03 M, rt, 30 min.

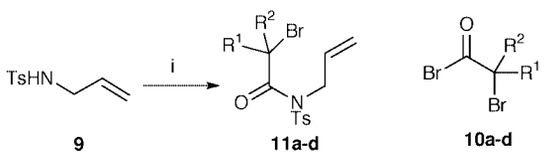
Table 2 Cyclisation of substrates **6a**–**f**

6	R^1	R^2	R^3	Time/min	Yield (%)	Diastereoselectivity (%)[a]
a	Cl	Cl	Ts	<0.5	92	—
b	Cl	H	Ts	<120	96	66 (56)[b]
c	Cl	Me	Ts	<30	98	70 (46)[b]
d	Cl	Cl	Bn	<5	94	—
e	Cl	H	Bn	240	90	62 (44)[c]
f	Cl	Me	Bn	120	88	80 (2)[d]

[a] Ratio determined by 250 MHz ^{1}H NMR. [b] Ratio in brackets from $RuCl_2(PPh_3)_3$ cyclisation at 100 °C.[2b,c] [c] Ratio from CuCl(TMEDA)$_2$ cyclisation at 80 °C.[5b] [d] Ratio from CuCl(TMEDA)$_2$ cyclisation at rt.[5c]

Cyclisation of monohaloacetamide substrates

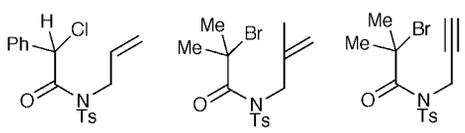
Having shown that activated trihaloacetamides and dihaloacetamides underwent atom transfer reactions at room temperature in a more efficient manner than $CuCl(TMEDA)_2$, we next investigated the reactions of the less activated monohaloacetamides **11a**–**g**. Cyclisation of these unactivated systems with CuBr(bipyridine), $CuBr(TMEDA)_2$ or $RuCl_2(PPh_3)_3$ had not been reported previously. However we recently reported the cyclisation of **11a**,**b** and **11e**,**f** at elevated temperatures using a silica supported *N*-pentyl-2-pyridylmethanimine catalyst.[9c] Hence, reaction of the lithium amide of **9** with the various acid bromides **10a**–**d** at −78 °C for 2 hours furnished the 2-haloacetamides **11a**–**d** in good yields (Scheme 3). The remaining cyclisation precursors **11e**–**g** were prepared from their corresponding lithium amides using the same approach.



9 **11a-d** **10a-d**

11a, R^1 = Me, R^2 = Me, 72%
11b, R^1 = Me, R^2 = H, 70%
11c, R^1 = H, R^2 = H, 64%
11d, R^1 = Pr^i, R^2 = H, 64%

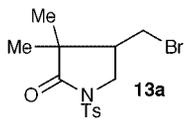
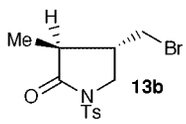
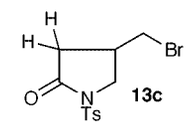
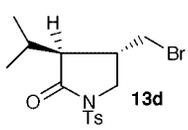
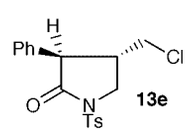
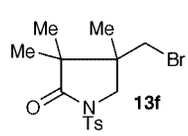
Scheme 3 *Reagents and conditions*: i, a) BuLi, THF, −78 °C, 30 min; b) **10a**–**d**, 2 h.



11e 65% **11f** 75% **11g** 76%

The five bromo precursors **11a**–**d** and **11f** underwent cyclisation with 30 mol% of CuBr(**3**) to furnish the expected cyclisation products **13a**–**d** and **13f** respectively, (Table 3). It was discovered that as the degree of substitution at the α-carbon decreased, the rate of the cyclisation reactions slowed markedly. Hence, cyclisation of the tertiary precursors **11a** or **11f** proceeded with the fastest rate and were over after a few hours at room temperature while cyclisation of the primary halide **11c** required heating (100 °C, sealed tube) over an extended period of time (24 hours). Under these conditions **11c** furnished a mixture of products with the cyclised product **13c** being obtained in low yield (18%). A significant amount of deacetylated product *N*-allyl-*N*-toluene-4-sulfonamide **9** was also detected. In this case cleavage of the amide bond was the major reaction pathway indicating that the use of high temperatures is not applicable to this methodology. While the reaction of **11c** was not very efficient the result is significant in that Nagashima *et al.*[7] reported that CuCl(bipyridine) failed to cyclise the related *N*-allyl-*N*-benzyliodoacetamide.[7] Atom transfer cyclisation of the secondary bromoacetamides **11b**, **11d** and **11e** furnished the expected 5-*exo* products **13b**, **13d** and **13e** as mixtures of diastereomers. The major products in all cases were determined to be the *trans* diastereomers based upon comparison with authentic samples[9c,14] and NOE evidence. The high *trans* selectivity can be rationalised by examining the potential transition states of cyclisation (Fig. 1). Transition states (TS) for pathways leading to *cis* and *trans* products were computed using MOPAC.[15] The calculations indicated that cyclisation *via* the *trans* pathway TS was lower in energy than that for the *cis* pathway (ΔE = 4.0 kJ mol^{-1}). Cyclisation of the *N*-(2-methylallyl)-*N*-(4-tolylsulfonyl)amide derived precursor **11f** furnished the 5-*exo* cyclisation product **13f** exclusively with no 6-*endo* product being detected in the crude NMR spectrum.

Table 3 Cyclisation of substrates **11a**–**11f**

Entry	Substrate	Product	Yield (%) (*cis*:*trans*)[a,b]
1	**11a**	 **13a**	92
2	**11b**	 **13b**	92 (12:88)[c]
3	**11c**	 **13c**	18[d]
4	**11d**	 **13d**	95 (6:94)
5	**11e**	 **13e**	86 (6:94)[e]
6	**11f**	 **13f**	96

[a] 30 mol% CuBr, 30 mol% ligand **3**, in CH_2Cl_2 at rt (0.12 M). [b] Determined by 300 MHz ^{1}H NMR of the crude mixture. [c] Ratio using silica supported *N*-pentyl-2-pyridylmethanimine at 80 °C (18:82). [d] Reaction carried out at 100 °C in $ClCH_2CH_2Cl$ in a sealed tube for 24 h. [e] Ratio using silica supported *N*-pentyl-2-pyridylmethanimine at 80 °C (17:83).

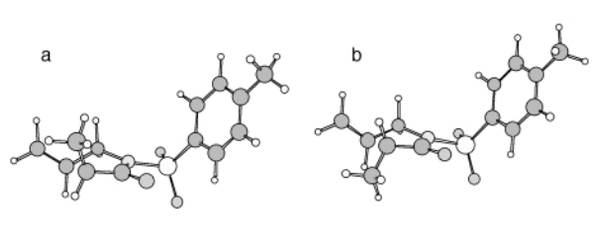
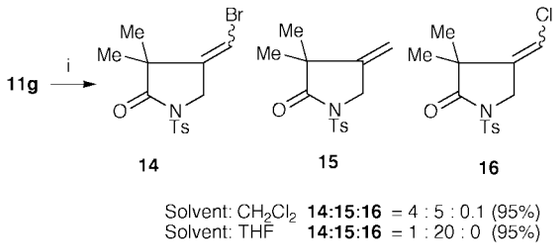


Fig. 1 Transition states for pathways leading to a) *cis* and b) *trans* compounds.

Cyclisation onto alkynes

The report that $CuCl(TMEDA)_2$ failed to mediate the cyclisation of radicals onto alkynes[5b] prompted us to investigate the cyclisation of the propargylic† acetamide **11g**. Reaction with 30 mol% CuBr(**3**) in CH_2Cl_2 at room temperature gave a mixture of products (Scheme 4). Analysis of the crude reaction mixture indicated that the expected bromoalkene derivatives **14** (3:1 mixture of (*E*)- and (*Z*)-isomers) had been formed along with a significant amount of the reduced alkene **15** (ratio **14**:**15** = 1:1). In addition, a trace amount (<2%) of a mixture of

† The IUPAC name for propargylic is prop-2-ynyl.

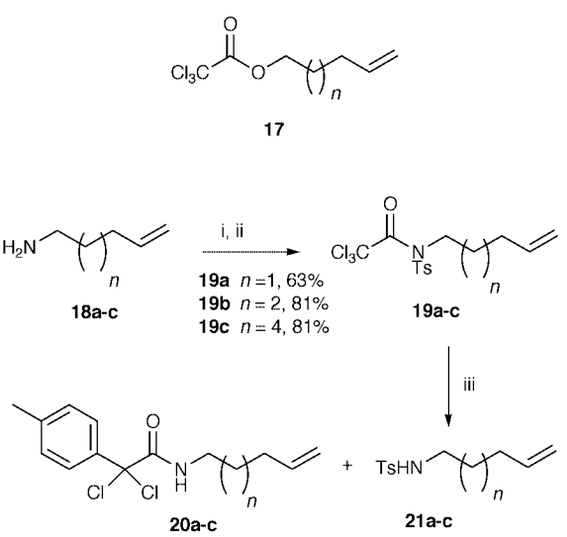


Scheme 4 *Reagents and conditions*: i, 30 mol% CuBr, 30 mol% **3**, solvent, rt.

compounds, tentatively assigned as the chloroalkene derivatives **16**, was also detected. The products **16** and **15** presumably arise from chlorine atom and hydrogen atom abstraction from the solvent (CH_2Cl_2) respectively. Repeating the reaction using tetrahydrofuran as solvent (a better hydrogen atom donor than CH_2Cl_2) furnished the reduced product **15** almost exclusively in high yield (90%) even though a catalytic amount (30 mol%) of CuBr(**3**) was used. In this case it is unclear whether the tetrahydrofuranyl radical formed by the reduction of the intermediate vinyl radical can facilitate cleavage of the carbon–bromine bond in the precursor **11g** thus completing the chain reaction. These competing abstraction reactions were not observed for any of the other cyclisations reported here. This can be rationalised in terms of the greater reactivity of the intermediate vinyl radical arising from the reaction of **11g** with respect to the primary radicals arising from the cyclisation of the substrates **11a**–**f**.

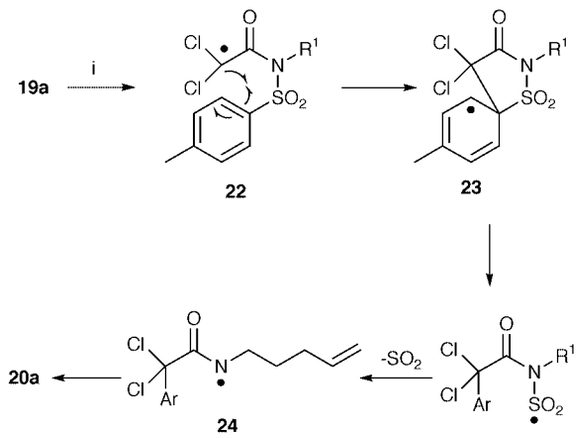
Attempts to mediate macrocyclisations

Recently we have shown that medium ring lactones could be prepared by 8-, 9- and 10-*endo* atom transfer radical macrocyclisation of trichloro esters **17** at elevated temperatures.[6] No reports of the cyclisation to furnish medium ring lactams were reported in this work. In order to evaluate the tetradentate catalyst system **3** with respect to the synthesis of larger ring lactams we prepared the acetamides **19a**–**c** (Scheme 5). Acetamides **19a**–**c** were prepared in good overall yield by tosylation of the corresponding amines **18a**–**c** followed by acylation with trichloroacetyl chloride.



Scheme 5 *Reagents and conditions*: i, TsCl, Et_3N, CH_2Cl_2; ii, BuLi, THF, −78 °C CCl_3COCl; iii, 30 mol% CuCl, 30 mol% **3**, CH_2Cl_2, rt.

Attempts to facilitate 8-*endo* cyclisation of acetamide **19a** at room temperature failed with the main products being the rearranged product **20a** (30%) and the toluenesulfonamide **21a** (16%) formed by amide bond cleavage. In addition, a large amount of starting material was recovered (53%). The unexpected formation of the amide **20a** can be explained by a competing 5-*exo ipso* aromatic radical substitution of initial radical **22** to give **23** (Scheme 6). This new radical can then undergo re-aromatisation followed by C–S bond cleavage and ultimately loss of SO_2 to furnish the observed product **20a**. The intermediate amidyl radical **24** in theory could undergo a 5-*exo* cyclisation reaction. However, no product arising from this pathway was detected in the crude mixture. We have recently reported that the cyclisations of amidyl radicals of type **24** with hindered secondary or tertiary groups appended to the carbonyl are extremely slow[16] and, as a consequence, in this example the amidyl radical is likely to be competitively trapped by a H atom from the solvent to furnish the observed amide. The competitive migration of arylsulfonyl groups in relatively slow radical cyclisations mediated by tributyltin hydride has been observed before[17] and has been exploited by Motherwell and co-workers to develop a new approach to substituted biphenyls.[18] In our case the relatively slow rate of 8-*endo* cyclisation allows competitive migration to be observed under atom transfer conditions. The observed yield of only 30% of the rearranged product **20a** suggests that the copper complex is not regenerated in the reaction and that it is not acting as a "catalyst". Attempts to mediate macrocyclisation of the other two precursors **19b**,**c** using stoichiometric amounts of copper reagents (100 mol%) also led to no observable macrocyclisation products. As before, varying amounts of the products tentatively assigned as **20b**,**c** were detected (**20b** = 49%, **20c** = 37%, based upon NMR spectra) although these could not be isolated pure from the crude reaction mixture.



Scheme 6 *Reagents and conditions*: 30 mol% CuCl, 30 mol% **3**, CH_2Cl_2, rt.

Cyclisation to give δ-lactams

Functionalised δ-lactams are valuable intermediates for the synthesis of six-membered heterocyclic compounds. During the last ten years there has been much interest in their synthesis due to their biological activity against ophthalmic infections,[19] gastric carcinogenesis,[20] blood contamination[21] or digestive tract cancer.[22] Surprisingly, only a few methods are reported in the literature for the synthesis of these compounds. Most approaches have relied on ionic chemistry that involves nitrogen–carbon bond formation. Radical cyclisation involving carbon–carbon bond formation is an alternative route, but this methodology has received little attention in contrast with the manifold applications for the synthesis of γ-lactams. Consequently, we prepared the trichloroacetamides **25a**–**d** in 40–93% yields from the corresponding *N*-substituted alkenyl amines, by direct trichloroacetylation at 0 °C in dichloromethane.

We screened a variety of copper complexes including the

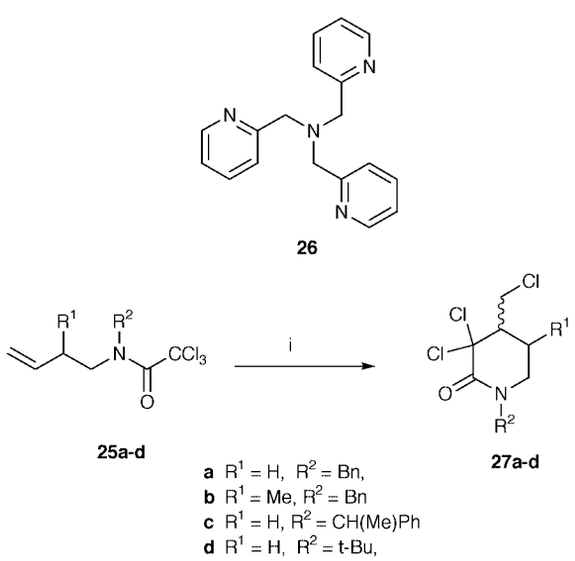
Table 4 Synthesis of γ- and δ-lactams using ligands **2** and **26**

Entry	Substrate	Catalyst (mol%)	Time/h	Temp/°C	Product	Yield (%)
1	**6a**	CuCl·bipy (30)	2	25	**7**	95
2	**6a**	CuCl·**2** (30)	2	25	**7**	99
3	**6a**	CuCl·**26** (30)	3	25	**7**	99
4	**6a**	CuCl·**2** (5)	18	80	**7**	92
5	**6a**	CuCl·**26** (30)	18	80	**7**	97
6	**25a**	CuCl·bipy (30)	72	25	**27a**	60
7	**25a**	CuCl·**2** (30)	72	25	**27a**	30
8	**25a**	CuCl·**26** (30)	72	25	**27a**	40
9	**25a**	CuCl·**2** (30)	2	80	**27a**	92
10	**25a**	CuCl·**26** (30)	2	80	**27a**	90
11	**25d**	CuCl·bipy (10)	18	80	**27d**	99
12	**25d**	CuCl·**2** (10)	18	80	**27d**	98
13	**25d**	CuCl·**26** (10)	18	80	**27d**	96

Table 5 Effect of chiral catalysts on diastereoselectivity of cyclisation

Entry	Substrate	Ligand	Time/h	Temp/°C	Product	Diastereomer ratio (Yield %)[a]
1	**31**	**2**	18	80	**32**	43:57 (97)
2	**31**	**28**	18	80	**32**	42:58 (86)
3	**31**	**29**	18	80	**32**	44:56 (85)
4	**31**	**30**	18	80	**32**	49:51 (85)
5	**31**	**2**	96	25	**32**	42:58 (78)
6	**31**	**28**	96	25	**32**	27:73 (21)
7	**31**	**29**	18	25	**32**	40:60 (61)
8	**31**	**30**	18	25	**32**	43:57 (77)
9	**25c**	**2**	18	80	**27c**	54:46 (78)
10	**25c**	**29**	18	80	**27c**	56:44 (95)
11	**25c**	**29**	18	25	**27c**	54:46 (6)
12	**25c**	**30**	18	80	**27c**	55:45 (96)

[a] Diastereomeric ratio determined by GC, stereochemistry of major isomer not determined.

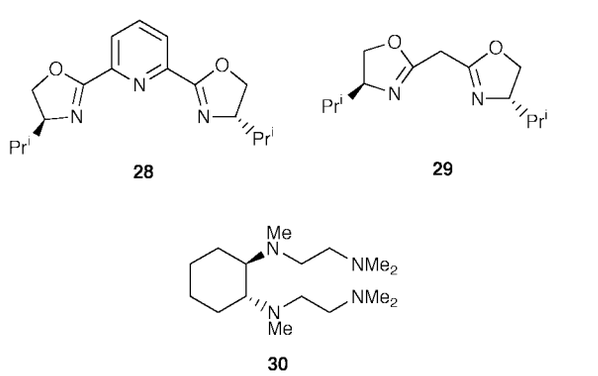


Scheme 7 *Reagents and conditions*: i, 30 mol% CuCl, 30 mol% ligand **2** or **26**, 25–28 °C, 1,2-dichloroethane.

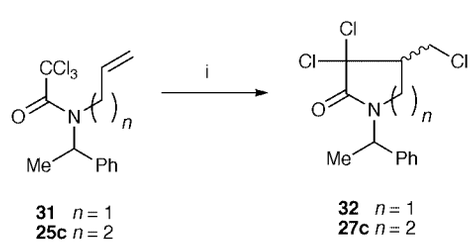
complexes derived from CuCl and the ligands **2** and **26**[6] in the cyclisation both of **25a** and **25d** (Scheme 7) as well as of **6a**. Cyclisation proceeded at 25–80 °C in moderate to excellent yields (see Table 4) in 1,2-dichloroethane (0.1 M) under an argon atmosphere. We observed that 1:1 Cu(I) complexes with ligands **2** and **26** are as active as the previously reported CuCl(bipy) catalyst in the case of the cyclisation of substrates **6a** (entries 1–5) and **25d** (entries 11–13). Surprisingly, the introduction of a *tert*-butyl protecting group onto the nitrogen of **25d** does not impede the reaction. Whichever ligand was employed, only *exo* cyclisation products were obtained.

Modification of stereoselectivity of cyclisations mediated by chiral copper(I) complexes

We next prepared a range of chiral enantiopure ligands (**28**–**30**)[23–25] and investigated their effect on the diastereoselectivity



of cyclisation of a range of substrates. Hence, initial work focussed on the cyclisation of the trichloracetamides **31** and **25c** (Table 5, Scheme 8).



Scheme 8 *Reagents*: 10 mol% CuCl, 10 mol% ligand, $ClCH_2CH_2Cl$.

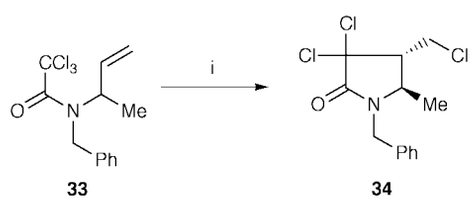
Table 6 Effect of chiral catalysts on diastereoselectivity of cyclisation

Entry	Substrate	Ligand	Time/h	Temp/°C	Product	Diastereomer ratio (Yield %)[a]
1	**33**	bpy	18	25	**34**	10:90 (54)
2	**33**	**2**	18	80	**34**	14:86 (99)
3	**33**	**28**	18	80	**34**	25:75 (94)
4	**33**	**29**	18	80	**34**	20:80 (92)
5	**33**	**30**	18	80	**34**	16:84 (100)
6	**33**	**2**	72	25	**34**	8:92 (97)
7	**33**	**29**	96	25	**34**	19:81 (100)
8	**33**	**30**	18	25	**34**	10:90 (65)
9	**25b**	**2**	96	80	**27b**	15:85 (88)
10	**25b**	**2**	96	25	**27b**	5:95 (15)
11	**25b**	**29**	96	80	**27b**	15:85 (83)
12	**25b**	**30**	18	80	**27b**	15:85 (87)

[a] Diastereomeric ratio determined by GC, stereochemistry of major isomer not determined.

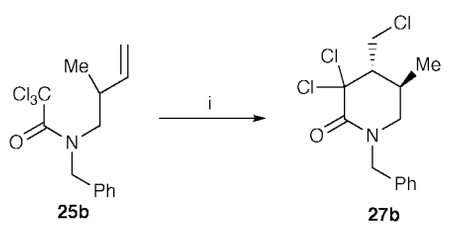
As the majority of the enantiopure copper(I) complexes used in this study were very oxygen sensitive, their reactions were performed after rapid degassing of the reaction vessel with nitrogen. The effect of the α-methylbenzylamine substituent on the outcome of cyclisation of both **31** and **25c** remained low even at room temperature. However, the diastereoselectivity for **31** was dependent upon the chirality of the ligand, particularly at room temperature (compare entries 5 and 6), although the low yield for this reaction means the result should be treated with caution. However, it does provide some evidence that it should be possible to induce stereochemical control in a cyclisation by utilising chiral copper complexes (*i.e.* by matching the ligand with the substrate). In addition it suggests that enantioselective cyclisations may be possible using chiral copper complexes (*i.e.* the chiral copper complex is involved in the TS for cyclisation perhaps by complexing to the radical and thus the reactions may not be truly "free radical" in nature).

Finally, we investigated the effect of the different chiral ligands on the stereochemical outcome of cyclisation of the substrates **33**[7] and **25b** where the stereochemistry is provided by the alkenyl side-chain (Schemes 9, 10). The use of the ligands **2**



33 **34**

Scheme 9 *Reagents*: 10 mol% CuCl, 10 mol ligand, $ClCH_2CH_2Cl$.



25b **27b**

Scheme 10 *Reagents*: 10 mol% CuCl, 10 mol ligand, $ClCH_2CH_2Cl$.

and **28**–**30** resulted in the formation of *trans* γ- and δ-lactams predominantly with very high conversions. Substrate **25b** was converted quantitatively even at ambient temperature in the presence of 10 mol% of catalyst derived from ligand **29**. In all the experiments the resulting diastereomeric ratio (Table 6) is as good as previously reported by Nagashima *et al.*[7] with the 2,2′-bipyridine complex and it seems to be slightly dependent upon the ligand at low temperature but not as greatly as for **31**.

Conclusions

In conclusion, we have shown that the use of CuX [X = Br or Cl] with ligands **2**, **3** or **26** will successfully mediate atom transfer radical cyclisation reactions of a range of haloacetamides in excellent yields at room temperature to give γ- or δ-lactams. The selectivity of these processes was greater than that reported for related $RuCl_2(PPh_3)_3$ and $Cu(TMEDA)_2$ mediated cyclisations. While the previous procedures have described the cyclisation of activated 2,2,2-trichloroacetamides or 2,2-dichloroacetamides at elevated temperatures we have shown that it is possible to cyclise not only these activated systems but also less activated 2-bromoacetamides at ambient temperatures. Cyclisation onto alkynes is also possible, in contrast to the reported $CuCl(TMEDA)_2$ procedure. For relatively slow cyclisations, *N*-(4-tolylsulfonyl)acetamides undergo competing rearrangement reactions under the reaction conditions. The greater activity of the new catalyst system CuX(**3**) relative to $CuCl(TMEDA)_2$ should allow studies into chiral induction by chiral *N*-groups in cyclisations to be optimised by carrying out these reactions at low temperatures. Finally, we have shown that by using chiral ligands in conjunction with chiral substrates it is possible to alter slightly the diastereoselectivity of cyclisation (matched or mismatched) suggesting that enantioselective cyclisations may be possible using chiral copper complexes. This suggests that the cyclisations are not truly "free radical" in character and that the copper complex may be intimately involved in the TS for cyclisation either by a templating effect[4] or by the direct involvement of metal complexed radicals.

Experimental

Melting points were recorded on a Stuart Scientific SMP1 melting point apparatus and are uncorrected. Accurate mass determinations were performed either on a Kratos MS80 at the University of Warwick or on a LC-MS SSS at Knoll Pharmaceuticals. Microanalyses were recorded on a Leeman Labs Inc. CE440 Elemental Analyser. Infra-red spectra were recorded in a solution cell, as Nujol mulls or neat, as stated in the text, on a Perkin-Elmer 1720X Fourier transform spectrometer. ^{1}H NMR spectra were recorded at either 250, 300, or 400 MHz on a Bruker ACF250, Bruker DPS300 or Bruker ACP400 instrument respectively. Chemical shifts are quoted in parts per million (ppm) and referenced to the appropriate solvent peak; coupling constants are given in Hz. ^{13}C NMR spectra were recorded at 62.9, 75 and 100.6 MHz. Chemicals used were obtained from either Lancaster or Sigma–Aldrich at the highest grade available. All solvents were purchased from Fisons Scientific Equipment at SLR grade and purified, when needed, by literature methods. Flash chromatography was carried out on silica gel (Merck Kieselgel $60F_{254}$, 230–400 mesh). TLC was

carried out using aluminium backed plates precoated with silica (0.2 mm, $60F_{254}$). $[\alpha]_D$ has units of 10^{-1} deg cm^2 g^{-1}.

Preparation of substrates

Tris(*N*,*N*-dimethylaminoethylene)amine **3**, *N*-allyltoluene-4-sulfonamide, *N*-(2-methylprop-2-enyl)toluene-4-sulfonamide, *N*-allyl-*N*-benzylamine, *N*-allyl-*N*-(4-tolylsulfonyl)-2,2,2-trichloroacetamide **6a**, *N*-allyl-*N*-(4-tolylsulfonyl)-2,2-dichloroacetamide **6b**, and *N*-allyl-*N*-(4-tolylsulfonyl)-2,2-dichloro-2-methylacetamide **6c**, *N*-allyl-*N*-benzyl-2,2,2-trichloroacetamide **6d**, *N*-allyl-*N*-benzyl-2,2-dichloroacetamide **6e**, and *N*-allyl-*N*-benzyl-2,2-dichloro-2-methylacetamide **6f** were prepared according to literature procedures.[2b,c,5a–c] *N*-(4-tolylsulfonyl)-4-chloromethyl-3,3-dichloropyrrolidin-2-one **7a**, *cis*- and *trans*-*N*-(4-tolylsulfonyl)-4-chloromethyl-3-chloropyrrolidin-2-one **7b** and **8b**, *cis*- and *trans*-*N*-(4-tolylsulfonyl)-4-chloromethyl-3-chloro-3-methylpyrrolidin-2-one **7c** and **8c**, *N*-benzyl-4-chloromethyl-3,3-dichloropyrrolidin-2-one **7d**, *cis*- and *trans*-*N*-benzyl-4-chloromethyl-3-chloropyrrolidin-2-one **7e** and **8e**, and *cis*- and *trans*-*N*-benzyl-4-chloromethyl-3-chloro-3-methylpyrrolidin-2-one **7f** and **8f** exhibited spectroscopic data identical to those previously published.[2b,c,5a–c] *N*-Allyl-*N*-(4-tolylsulfonyl)-2-bromo-2-methylpropionamide **11a**, *N*-allyl-*N*-(4-tolylsulfonyl)-2-bromopropionamide **11b**, 4-bromomethyl-3,3-dimethyl-1-(4-tolylsulfonyl)pyrrolidin-2-one **13a**, and *trans*-4-bromomethyl-3-methyl-1-(4-tolylsulfonyl)pyrrolidin-2-one **13b** exhibited spectroscopic data identical to those previously published.[9c,14]

General procedure for the preparation of toluene-4-sulfonamide cyclisation precursors

A solution of BuLi (2.24 cm^3, 2.5 M in hexanes, 5.6 mmol) was added dropwise over 5 minutes to a stirred solution of *N*-alkyltoluene-4-sulfonamide (2.4 mmol) in dry tetrahydrofuran (30 cm^3) at −78 °C under nitrogen and the mixture was stirred for 30 minutes at this temperature. The acid halide (6.2 mmol) was added and the mixture stirred for 2 h at −78 °C. The reaction was quenched with ammonium chloride (5 cm^3) and allowed to warm to room temperature. The mixture was extracted with diethyl ether (2 × 30 cm^3) and washed with saturated sodium bicarbonate (2 × 30 cm^3). The organic extracts were dried over $MgSO_4$ and the solvent evaporated under reduced pressure to give the products. The crude compounds were purified by column chromatography on silica using hexane–ethyl acetate (4 : 1) as eluent.

***N*-Allyl-*N*-(4-tolylsulfonyl)bromoacetamide 11c.** Yield 62%, as a white crystalline solid, mp 89–90 °C (from ethyl acetate) (Found: C, 43.7; H, 4.1; N, 3.9. $C_{12}H_{14}BrNO_3S$ requires C, 43.4; H, 4.25; N, 4.2%); ν_{max} ($CHCl_3$)/cm^{-1} 2923, 1694, 1648, 1593, 1356, 1167, 838 and 717; δ_H(250 MHz; $CDCl_3$) 7.80 (2 H, d, *J* 8.5, *Ar*), 7.32 (2 H, d, *J* 8.5, *Ar*), 5.89–5.73 (1 H, m, C*H*=CH$_2$), 5.26–5.16 (2 H, m, CH=C*H*$_2$), 4.43 (1 H, dt, *J* 5.4 and 1.5, C*H*$_2$CH=CH$_2$), 4.18 (2 H, s, C*H*$_2$Br), and 2.41 (3 H, s, *Me*); δ_C(67.8 MHz; $CDCl_3$) 166.1 (s), 146.0 (s) 136.0 (s), 132.4 (d), 130.3 (2 × d), 128.5 (2 × d), 119.1 (t), 49.6 (t), 29.4 (t) and 22.1 (q); *m*/*z* (EI) 330.9887 (M$^+$, $C_{12}H_{14}Br^{79}NO_3S$ requires 330.9877), 331 (4%, M$^+$), 162 (80), 155 (65), 91 (100) and 65 (70).

***N*-Allyl-*N*-(4-tolylsulfonyl)-2-bromo-3-methylbutanamide 11d.** Yield 64%, as a clear viscous oil (Found: C, 48.55; H, 5.5; N, 3.7. $C_{15}H_{20}BrNO_3S$ requires C, 48.1; H, 5.4; N, 3.7%); ν_{max} (neat)/cm^{-1} 2922, 1706, 1597, 1462, 1376, 1172 and 928; δ_H(300 MHz; $CDCl_3$) 7.82 (2 H, d, *J* 8.5, *Ar*), 7.32 (2 H, d, *J* 8.5, *Ar*), 5.90–5.80 (1 H, m, C*H*=CH$_2$), 5.32–5.22 (2 H, m, CH=C*H*$_2$), 4.65 (1 H, ddt, *J* 17.1, 5.2 and 1.5, C*H*HCH=CH$_2$), 4.48 (1 H, d, *J* 9.2, C*H*Br), 4.35 (1 H, ddt, *J* 17.1, 5.5 and 1.2, CH*H*-CH=CH$_2$), 2.42 (3 H, s, *Me*), 2.26 (1 H, m, C*H*Me$_2$), 1.06 (3 H, d, *J* 6.7, CH*Me*Me) and 0.86 (3 H, d, *J* 6.7, CHMe*Me*); δ_C(75 MHz; $CDCl_3$) 169.3 (s), 145.6 (s) 136.2 (s), 132.9 (d), 130.1 (2 × d), 128.5 (2 × d), 118.6 (t), 53.2 (d), 49.1 (t), 36.6 (d), 22.1 (q), 20.9 (q) and 20.2 (q); *m*/*z* (EI) 373.0347 (M$^+$, $C_{15}H_{20}Br^{79}NO_3S$ requires 373.0347), 373 (8%, M$^+$), 294 (13), 204 (86), 155 (80), 91 (100) and 65 (45).

***N*-Prop-2-enyl-*N*-(4-tolylsulfonyl)-2-chloro-2-phenylacetamide 11e.** Yield 65%, as a white crystalline solid, mp 70–71 °C (from ethyl acetate) (Found: C, 59.2; H, 5.0; N, 3.75. $C_{18}H_{18}ClNO_3S$ requires C, 59.4; H, 5.0; N, 3.85%); ν_{max} ($CHCl_3$)/cm^{-1} 2925, 1702, 1593, 1375, 1161 and 919; δ_H(250 MHz; $CDCl_3$) 7.69 (2 H, d, *J* 8.2, *Ar*), 7.37–7.25 (7 H, m, *Ar*), 6.13 (1 H, s, C*H*Ph), 5.86–5.71 (1 H, m, C*H*=CH$_2$), 5.24–5.16 (2 H, m, CH=C*H*$_2$), 4.50–4.27 (2 H, m, NC*H*$_2$) and 2.43 (3 H, s, *Me*); δ_C(75 MHz; $CDCl_3$) 162.7 (s), 145.6 (s) 135.9 (s), 132.3 (d), 130.7 (d), 129.8 (d), 129.4 (2 × d), 128.9 (2 × d), 128.6 (d), 119.0 (t), 58.8 (d), 49.1 (t) and 22.1 (q); *m*/*z* (EI) 363.0684 (M$^+$, $C_{18}H_{18}Cl^{35}NO_3S$ requires 363.0696), 362 (5%, M$^+$), 328 (34), 155 (100), 125 (82), 91 (83) and 69 (20).

***N*-(2-Methylprop-2-enyl)-*N*-(4-tolylsulfonyl)-2-bromo-2-methylpropanamide 11f.** Yield 75%, as a white crystalline solid, mp 112–113 °C (from ethyl acetate) (Found: C, 48.2; H, 5.4; N, 3.4. $C_{15}H_{20}BrNO_3S$ requires C, 48.1; H, 5.35; N, 3.7%); ν_{max} ($CHCl_3$)/cm^{-1} 2936, 1680, 1597, 1353, 1169 and 924; δ_H(300 MHz; $CDCl_3$) 7.78 (2 H, d, *J* 8.5, *Ar*), 7.21 (2 H, d, *J* 8.5, *Ar*), 4.95 (1 H, br s, CMe=C*H*$_2$), 4.73 (2 H, br s, C*H*$_2$), 2.32 (3 H, s, *Me*) and 1.72 (6 H, s, 2 × *Me*); δ_C(75 MHz; $CDCl_3$) 170.8 (s), 145.1 (s) 140.9 (s), 136.2 (s), 129.5 (2 × d), 129.1 (2 × d), 112.4 (t), 58.0 (s), 53.7 (t), 32.4 (2 × q), 22.1 (q) and 20.7 (q); *m*/*z* (EI) 373 (2%, M$^+$), 309 (34), 202 (82), 155 (82) and 91 (100).

***N*-Prop-2-ynyl-*N*-(4-tolylsulfonyl)-2-bromo-2-methylpropionamide 11g.** Yield 76%, as a white crystalline solid, mp 92–93 °C (from ethyl acetate) (lit.,[26] 92–93 °C) (Found: C, 47.3; H, 4.55; N, 3.9. $C_{14}H_{16}BrNO_3S$ requires C, 46.9; H, 4.5; N, 3.9%); ν_{max} ($CHCl_3$)/cm^{-1} 2925, 1692, 1593, 1376 and 1165; δ_H(300 MHz; $CDCl_3$) 7.91 (2 H, d, *J* 8.5, *Ar*), 7.23 (2 H, d, *J* 8.5, *Ar*), 5.05 (2 H, d, *J* 2.5, C*H*$_2$CH=CH$_2$), 2.40 (1 H, t, *J* 2.5, C*H*), 2.35 (3 H, s, *Me*) and 1.87 (6 H, s, 2 × *Me*); δ_C(75 MHz; $CDCl_3$) 170.0 (s), 145.3 (s) 136.0 (s), 129.6 (4 × d), 79.1 (s), 74.3 (d) 57.1 (s), 38.2 (t), 32.1 (2 × q) and 22.1 (q); *m*/*z* (CI) 358.0127 (MH$^+$ $C_{14}H_{17}Br^{79}NO_3S$ requires 358.0113), 358 (39%, MH$^+$), 280 (100), 216 (45), 189 (32) and 124 (55).

***N*-(4-tolylsulfonyl)-pent-4-enamine 21a.** Yield 16% (Found: C, 60.45; H, 7.0; N, 5.8. $C_{12}H_{17}NO_2S$ requires C, 60.2; H, 7.2; N, 5.85%); ν_{max} (Nujol)/cm^{-1} 3280, 2927, 1640, 1598, 1162, 1095 and 914; δ_H(400 MHz; $CDCl_3$) 7.72 (2 H, d, *J* 8.2, *Ar*), 7.26 (2 H, d, *J* 8.2, *Ar*), 5.66 (1 H, m, C*H*=CH$_2$), 5.05 (1 H, br s, N*H*), 4.91 (2 H, m, CH=C*H*$_2$), 2.89 (2 H, t, *J* 7.2, C*H*$_2$NHTs), 2.38 (3 H, s, *Me*), 1.99 (2 H, m, C*H*$_2$CH=CH$_2$) and 1.52 (2 H, quintet, *J* 7.2, CH$_2$C*H*$_2$CH$_2$); δ_C(75 MHz; $CDCl_3$) 143.7 (s), 137.6 (d), 137.3 (s), 130.1 (2 × d), 127.5 (2 × d), 115.9 (t), 43.0 (t), 31.0 (t), 29.0 (t) and 21.9 (q); *m*/*z* (CI) 240 (30%, MH$^+$), 184 (65), 155 (100) and 91 (94).

***N*-Pent-4-enyl-*N*-(4-tolylsulfonyl)-2,2,2-trichloroacetamide 19a.** Yield 77%, as a white crystalline solid, mp 70–71 °C (from ethyl acetate) (Found: C, 43.7; H, 4.2; N, 3.5. $C_{14}H_{16}Cl_3NO_3S$ requires C, 43.7; H, 4.2; N, 3.6%); ν_{max} (Nujol)/cm^{-1} 2924, 1713, 1661, 1368, 1371, 1173 and 1086; δ_H(400 MHz; $CDCl_3$) 7.89 (2 H, d, *J* 8.4, *Ar*), 7.32 (2 H, d, *J* 8.4, *Ar*), 5.79 (1 H, m, C*H*=CH$_2$), 5.06 (2 H, m, CH=C*H*$_2$), 4.18 (2 H, m, C*H*$_2$N), 2.43 (3 H, s, *Me*) and 2.11 (4 H, m, C*H*$_2$C*H*$_2$); *m*/*z* (EI) 383.9975 (MH$^+$, $C_{14}H_{16}Cl_3NO_3S$ requires 383.9994), 382 (<1%, M$^+$), 321 (5), 214 (27), 155 (95) and 91 (100).

***N*-Hex-5-enyl-*N*-(4-tolylsulfonyl)-2,2,2-trichloroacetamide 19b.** Yield 81%, as a white crystalline solid, mp 73–74 °C (from ethyl acetate) (Found: C, 44.8; H, 4.6; N, 3.15. $C_{15}H_{18}Cl_3NO_3S$ requires C, 45.2; H, 4.55; N, 3.50%); ν_{max} (Nujol)/cm^{-1} 2924, 1712, 1551, 1368, 1371, 1173 and 1086; δ_H(400 MHz; $CDCl_3$) 7.89 (2 H, d, *J* 8.4, *Ar*), 7.32 (2 H, d, *J* 8.4, *Ar*), 5.78 (1 H, m, C*H*=CH$_2$), 5.06–4.96 (2 H, m, CH=C*H*$_2$), 4.18 (2 H, m, C*H*$_2$N), 2.44 (3 H, s, *Me*), 2.14 (2 H, m, C*H*$_2$), 2.00 (2 H, m, C*H*$_2$) and 1.49 (2 H, m, C*H*$_2$); *m*/*z* (EI) 397.0085 (M$^+$, $C_{15}H_{18}Cl_3NO_3S$ requires 397.0090).

***N*-Oct-7-enyl-*N*-(4-tolylsulfonyl)-2,2,2-trichloroacetamide 19c.** Yield 81%, (Found: C, 48.0; H, 5.2; N, 3.0. $C_{17}H_{22}Cl_3NO_3S$ requires C, 47.8; H, 5.2; N, 3.2%); ν_{max} (Nujol)/cm^{-1} 2924, 1714, 1610, 1551, 1368, 1371, 1173 and 1086; δ_H(400 MHz; $CDCl_3$) 7.48 (2 H, d, *J* 8.4, *Ar*), 7.32 (2 H, d, *J* 8.4, *Ar*), 5.78 (1 H, m, C*H*=CH$_2$), 5.02–4.92 (2 H, m, CH=C*H*$_2$), 4.15 (2 H, m, C*H*$_2$N), 2.44 (3 H, s, *Me*), 2.00 (4 H, m, 2 × C*H*$_2$) and 1.42–1.29 (6 H, m, 3 × C*H*$_2$); *m*/*z* CI (426, 100%, MH$^+$), 358 (47), 155 (90), 108 (83) and 91 (72).

General procedure for atom transfer cyclisation reactions

To the substrate (2 mmol) in dry CH_2Cl_2 (2 cm^3) under nitrogen at room temperature was added either CuCl (0.6 mmol) or CuBr (0.6 mmol) and tri(*N*,*N*-dimethylaminoethylene)amine **3** (0.6 mmol). The reaction was followed by TLC. After complete reaction the mixture was passed through a small silica plug. The silica plug was washed with dichloromethane (50 cm^3) and the solvent removed *in vacuo* to give the crude products. Chromatography using hexane–ethyl acetate furnished the pure cyclised compounds.

4-Bromomethyl-1-(4-tolylsulfonyl)pyrrolidin-2-one 13c. Cyclisation gave an inseparable mixture of *N*-allyl-*N*-toluene-4-sulfonamide[5b] and 4-bromomethyl-1-(4-tolylsulfonyl)-pyrrolidin-2-one **13c**[26] (ratio 1:3). Discernible data for 4-bromomethyl-1-(4-tolylsulfonyl)pyrrolidin-2-one: δ_H(250 MHz; $CDCl_3$) 7.92 (2 H, d, *J* 8.5, *Ar*), 7.34 (2 H, d, *J* 8.5, *Ar*), 4.06 (1 H, dd, *J* 10.2 and 7.6, C*H*HN), 3.66 (1 H, dd, *J* 10.2 and 6.0, CH*H*N), 3.45 (2 H, m, C*H*$_2$Br), 2.78, (1 H, m, C*H*CH$_2$Br), 2.62, (1 H, dd, *J* 17.4 and 8.5, CH*H*CO), 2.43 (3 H, s, *Me*) and 2.35 (1 H, dd, *J* 17.4 and 6.8, CH*H*CO).

4-Bromomethyl-3-isopropyl-1-(4-tolylsulfonyl)pyrrolidin-2-one 13d. Yield 95%, as an inseparable mixture of diastereomers (ratio 87:13) (Found: C, 48.3; H, 5.4; N, 3.75. $C_{15}H_{20}BrNO_3S$ requires C, 48.1; H, 5.4; N, 3.7%); ν_{max} ($CHCl_3$)/cm^{-1} for mixture 2964, 1734, 1367, 1172 and 917; δ_H(250 MHz; $CDCl_3$) 7.88 (2 H major + 2 H minor, d, *J* 8.3, *Ar*), 7.31 (2 H major + 2 H minor, d, *J* 8.3, *Ar*), 3.98 (1 H major, dd, *J* 10.5 and 8.5, C*H*HN), 3.62 (1 H major, dd, *J* 10.5 and 5.6, C*H*HN), 3.44 (1 H major, dd, *J* 10.2 and 4.9, CH*H*Br), 3.31 (1 H major, dd, *J* 10.2 and 7.4, C*H*HBr), 2.78 (1 H minor, m, C*H*CH$_2$Br), 2.54 (1 H major, m, C*H*CH$_2$Br), 2.42 (3 H major, s, *Me*), 2.26 (1 H major, dd, *J* 6.0 and 4.2, C*H*), 2.10 (1 H major, m, C*H*Me$_2$), 1.84 (1 H minor, m, C*H*Me$_2$), 0.99 (3 H minor, d, *J* 6.3, *Me*), 0.95 (3 H minor, d, *J* 6.6, *Me*), 0.92 (3 H major, d, *J* 6.7, *Me*) and 0.8 (3 H major, d, *J* 4.5, *Me*); *m*/*z* (CI) 374.0422 (M$^+$ + H, $C_{15}H_{21}Br^{79}NO_3S$ requires 374.0425), 374 (11%, M$^+$), 296 (27), 279 (32) and 142 (10).

4-Chloromethyl-3-phenyl-1-(4-tolylsulfonyl)pyrrolidin-2-one 13e. Yield 86%, as a clear oil (Found: C, 59.3; H, 4.9; N, 3.6. $C_{18}H_{18}ClNO_3S$ requires C, 59.4; H, 5.0; N, 3.85%); ν_{max} ($CHCl_3$)/cm^{-1} for mixture 2923, 1737, 1596, 1453, 1361, 1171, 1088 and 963; δ_H(250 MHz; $CDCl_3$) 7.96 (2 H, d, *J* 8.5, *Ar*), 7.34–7.24 (5 H, m, *Ar*), 7.06 (2 H, d, *J* 8.5, *Ar*), 4.20 (1 H, dd, *J* 10.2 and 7.7, C*H*HN), 3.71 (1 H, dd, *J* 9.8 and 8.7, C*H*HN), 3.64 (1 H, dd, *J* 11.6 and 3.5, CH*H*Cl), 3.58 (1 H, d, *J* 10.5, C*H*Ph), 3.50 (1 H, dd, *J* 11.6 and 6.6, C*H*HCl), 2.75–2.84 (1 H, m, C*H*CH$_2$Cl) and 2.44 (3 H, s, *Me*); δ_C(75 MHz, $CDCl_3$) 172.3 (s), 145.9 (s), 135.3 (s), 133.2 (s), 130.2 (2 × d), 129.9 (d), 129.0 (2 × d), 128.9 (2 × d), 128.8 (2 × d), 53.0 (t), 48.4 (s), 44.3 (s), 43.2 (t) and 22.1 (q); *m*/*z* (EI) 363.0683 (M$^+$, $C_{18}H_{18}ClNO_3S$ requires 363.0696), 363 (5%, M$^+$), 328 (23), 265 (17), 155 (80) and 91 (100).

4-Bromomethyl-3,3,4-trimethyl-1-(4-tolylsulfonyl)pyrrolidin-2-one 13f. Yield 96%, as a white crystalline solid, mp 175–176 °C (from ethyl acetate) (Found: C, 48.4; H, 5.5; N, 3.6. $C_{15}H_{20}BrNO_3S$ requires C, 48.1; H, 5.35; N, 3.7%); ν_{max} ($CHCl_3$)/cm^{-1} 2936, 1738, 1367 and 1174; δ_H(300 MHz; $CDCl_3$) 7.88 (2 H, d, *J* 8.3, *Ar*), 7.31 (2 H, d, *J* 8.3, *Ar*), 3.83 (1 H, d, *J* 10.7, C*H*HN), 3.54 (1 H, d, *J* 10.7, CH*H*N), 3.06–3.27 (2 H, m, C*H*$_2$Br), 2.41 (3 H, s, *Me*), 1.06 (3 H, s, *Me*), 1.02 (3 H, s, *Me*) and 0.94 (3 H, s, *Me*); δ_C(75 MHz, $CDCl_3$); 177.4 (s), 145.7 (s), 135.3 (s), 130.1 (2 × d), 128.3 (2 × d), 54.5 (t), 48.9 (s), 43.0 (s), 38.9 (t), 22.1 (q), 21.3 (q), 19.5 (q) and 18.9 (q); *m*/*z* (EI) 374 (1%, M$^+$), 309 (100), 230 (46), 155 (51), 133 (70) and 91 (86).

3,3-Dimethyl-4-methylene-1-(4-tolylsulfonyl)pyrrolidin-2-one 15,[26] (*E*)-4-bromomethylene-3,3-dimethyl-1-(4-tolylsulfonyl)-pyrrolidin-2-one (*E*)-14,[26] and (*Z*)-4-bromomethylene-3,3-dimethyl-1-(4-tolylsulfonyl)pyrrolidin-2-one (*Z*)-14.[26] Yield 95%, as an inseparable mixture of compounds, ν_{max} (Nujol)/cm^{-1} 1740, 1670, 1365 and 1170; Discernible data for **15**, δ_H(400 MHz; $CDCl_3$) 7.92 (2 H, m, *Ar*), 7.33 (2 H, m, *Ar*), 5.08 (1 H, m, C=CH*H*), 5.04 (1 H, m, C=CH*H*), 4.44–4.37 (2 H, m, C*H*$_2$), 2.43 (3 H, s, *Me*) and 1.14 (6 H, s, 2 × *Me*); discernible data for (*E*)-**14** and (*Z*)-**14** (ratio 3:1), 7.94 (2 H, m, *Ar*), 7.30 (2 H, m, *Ar*), 6.17 (1 H (*E*), t, *J* 2.1, C=C*H*Br), 6.14 (1 H (*Z*), t, *J* 2.6, C=C*H*Br), 4.44–4.37 (2H (*E*) and (*Z*), m, C*H*$_2$), 2.37 (3 H (*E*) and (*Z*), s, *Me*) 1.38 (3 H (*E*), s, *Me*) and 1.20 (3 H (*Z*), s, *Me*); *m*/*z* LC-MS (AP$^+$) 4.70 minutes 280 (MH$^+$) 280.1022 (MH$^+$, $C_{14}H_{18}NO_3S$ requires 280.1001), 5.20 minutes 358 (M$^+$), 358.0098 (M$^+$, $C_{14}H_{17}Br^{79}NO_3S$ requires 358.0112), 215 (60%), 149 (46), 91 (100) and 81 (75).

General procedure for trichloroacetylation of benzylamines

To a solution of trichloroacetyl chloride (0.037 mol) in dichloromethane (80 cm^3) at 0 °C was added dropwise benzylamine (0.034 mol). Triethylamine was then added dissolved in dichloromethane (20 cm^3) and the reaction left for two hours at 0 °C. At this temperature, dilute HCl was added (2 M, 50 cm^3) and the organic phase was washed with saturated brine and water, dried over $MgSO_4$ and evaporated *in vacuo* to give the crude amide. Chromatography using petroleum ether–ethyl acetate (80:20) furnished the purified compounds.

***N*-Benzyl-*N*-but-3-enyltrichloroacetamide 25a.** Yield 41%, as a clear oil (Found: C, 50.8; H, 4.6; N, 4.5; Cl, 34.2. $C_{13}H_{14}Cl_3NO$ requires C, 50.9; H, 4.6; N, 4.6; Cl, 34.7%); ν_{max} (Nujol)/cm^{-1} 1678; δ_H(250 MHz; $CDCl_3$) 7.29 (5 H, m, *Ar*), 5.88 (1 H, m, C*H*=CH$_2$), 4.98 (2 H, m, CH=C*H*$_2$), 4.77 (2 H, s, C*H*$_2$Ph), 3.65 (2 H, m, C*H*$_2$) and 2.41 (2 H, m, C*H*$_2$); δ_C(62.9 MHz; $CDCl_3$) 160.4 (s), 137.3 (s), 134.5 (d), 128.8 (2 × d), 127.9 (2 × d), 126.8 (d), 115.5 (t), 92.3 (s), 53.4 (t), 47.7 (t) and 31.6 (t); *m*/*z* (EI) 305 (4%, M$^+$), 235 (12), 203 (100), 160 (27) and 90 (23).

***N*-Benzyl-*N*-(2-methylbut-3-enyl)trichloroacetamide 25b.** Yield 76% (Found: C, 52.9; H, 5.0; N, 4.35; Cl, 32.8. $C_{14}H_{16}Cl_3NO$ requires C, 52.4; H, 5.0; N, 4.4; Cl, 33.2%); ν_{max} (CH_2Cl_2)/cm^{-1} 1678; δ_H(200 MHz; $CDCl_3$) 7.26 (5 H, m, *Ar*), 5.63 (1 H, m, C*H*=CH$_2$), 4.68–5.04 (4 H, m, CH=C*H*$_2$ and C*H*$_2$Ph), 3.22 (2 H, m, C*H*$_2$), 2.64 (1 H, m, C*H*) and 0.92 (3H, d, *J* 7.0, *Me*); δ_C(50.3 MHz; $CDCl_3$) 162.5 (s), 140.5 (s), 135.1

(d), 128.4 (2 × d), 127.4 (2 × d), 126.6 (d), 115.2 (t), 93.5 (s), 53.4 (t), 52.7 (t), 35.8 (d) and 17.3 (q).

(*S*)-(*N*-α-Methylbenzyl)-*N*-but-3-enyltrichloroacetamide 25c. Yield 67%, $[a]_D^{22}$ −20 (Found: C, 52.1; H, 4.9; N, 4.35; Cl, 33.0. $C_{10}H_{16}Cl_3NO$ requires C, 52.4; H, 5.0; N, 4.4; Cl, 33.2%); ν_{max} (CH_2Cl_2)/cm^{-1} 1673; δ_H(200 MHz; $CDCl_3$) 7.23 (5 H, m, *Ar*), 5.73 (1 H, m, C*H*=CH_2), 5.48 (1 H, m, CH), 4.82 (2 H, m, CH=CH_2), 3.25 (1 H, m, NCH*H*), 2.74 (1 H, m, NCH*H*), 2.22 (2 H, m, CH_2) and 1.60 (3H, d, *J* 7.0, *Me*); δ_C(50.3 MHz; $CDCl_3$) 161.2 (s), 140.0 (s), 135.7 (d), 129.6 (2 × d), 128.7 (2 × d), 127.9 (d), 117.7 (t), 95.3 (s), 57.6 (d), 47.2 (t), 33.1 (t) and 18.7 (q); *m*/*z* (EI) 319 (4%, M^+), 284 (97), 214 (100) and 104 (10).

***N*-*tert*-Butyl-*N*-but-3-enyltrichloroacetamide 25d.** Yield 62%, as a clear oil (Found: C, 44.12; H, 6.0; N, 5.15; Cl, 38.6. $C_{10}H_{16}Cl_3NO$ requires C, 44.0; H, 5.9; N, 5.5; Cl, 39.0%); ν_{max} (CH_2Cl_2)/cm^{-1} 1684; δ_H(250 MHz; $CDCl_3$) 5.42–5.25 (1 H, m, C*H*=CH_2), 4.80–4.60 (2 H, m, CH=CH_2), 3.41 (2 H, m, CH_2), 2.15 (2 H, m, CH_2) and 1.23 (9H, s, *t*-Bu); δ_C(62.9 MHz; $CDCl_3$) 161.2 (s), 133.2 (d), 116.9 (t), 95.1 (s), 59.8 (s), 45.7 (t), 35.4 (t) and 27.8 (3 × q).

***N*-Benzyl-3,3-dichloro-4-chloromethylpiperidin-2-one 27a.** Yield 90%, as a clear oil (Found: C, 51.0; H, 4.5; N, 4.6; Cl, 34.4. $C_{13}H_{14}Cl_3NO$ requires C, 50.9; H, 4.6; N, 4.6; Cl, 34.7%); ν_{max} (CH_2Cl_2)/cm^{-1} 1676; δ_H(250 MHz; $CDCl_3$) 7.40–7.20 (5 H, m, *Ar*), 4.80 (1 H, d, *J* 14.5, C*H*HPh), 4.45 (1 H, d, *J* 14.5, C*H*HPh), 4.16 (1 H, dd, *J* 11.1 and 2.8, C*H*HCl), 3.58 (1 H, dd, *J* 11.1 and 10.1, C*H*HCl), 3.33 (2 H, m, NCH_2), 2.75 (1 H, m, C*H*), 2.36 (1 H, ddd, *J* 14.2, 3.6 and 3.0, C*H*H) and 1.94 (1 H, ddd, *J* 14.2, 12.3 and 9.0, C*H*H); δ_C(62.9 MHz; $CDCl_3$) 165.7 (s), 134.5 (s), 129.1 (2 × d), 128.4 (2 × d), 128.2 (d), 84.3 (s), 51.6 (d), 47.9 (t), 47.3 (t) and 41.1 (t); *m*/*z* (EI) 305 (3%, M^+), 270 (3), 235 (14), 201 (100) and 90 (6).

***N*-Benzyl-3,3-dichloro-4-chloromethyl-5-methylpiperidin-2-one 27b.** Yield 88% for mixture (Found: C, 52.85; H, 5.0; N, 4.4; Cl, 32.8. $C_{14}H_{16}Cl_3NO$ requires C, 52.4; H, 5.0; N, 4.4; Cl, 33.2%); ν_{max} (CH_2Cl_2)/cm^{-1} 1677; data for *trans* compound, δ_H(250 MHz; $CDCl_3$) 7.40–7.20 (5 H, m, *Ar*), 4.82 (1 H, d, *J* 14.5, C*H*HPh), 4.44 (1 H, d, *J* 14.5, C*H*HPh), 4.16 (1 H, dd, *J* 12.1 and 1.0, C*H*HCl), 3.69 (1 H, dd, *J* 12.1 and 5.9, C*H*HCl), 3.23 (1 H, dd, *J* 12.6 and 5.4, NCH*H*), 3.02 (1 H, dd, *J* 12.6 and 10.6, NCH*H*), 2.56 (1 H, ddd, *J* 11.1, 6.2 and 1.7, C*H*CH_2Cl), 2.33 (1 H, m, C*H*Me) and 1.18 (3 H, d, *J* 6.9, *Me*); δ_C(62.9 MHz; $CDCl_3$) 163.9 (s), 135.9 (s), 128.9 (2 × d), 128.2 (2 × d), 128.1 (d), 87.6 (s), 57.9 (d), 52.8 (t), 51.5 (t), 43.2 (t), 30.8 (d) and 16.4 (q): data for *cis* compound, δ_H(250 MHz; $CDCl_3$) 7.40–7.20 (5 H, m, *Ar*), 4.73 (1 H, d, *J* 14.5, C*H*HPh), 4.57 (1 H, d, *J* 14.5, C*H*HPh), 4.05 (1 H, dd, *J* 11.6 and 3.1, C*H*HCl), 3.91 (1 H, dd, *J* 11.6 and 8.4, C*H*HCl), 3.45 (1 H, dd, *J* 12.6 and 5.1, NCH*H*), 3.19 (1 H, dd, *J* 12.6 and 5.2, NCH*H*), 2.93 (1 H, m, C*H*CH_2Cl), 2.33 (1 H, m, C*H*Me) and 1.06 (3 H, d, *J* 7.4, *Me*); δ_C(62.9 MHz; $CDCl_3$) 163.8 (s), 135.7 (s), 128.4 (2 × d), 128.0 (2 × d), 127.9 (d), 87.3 (s), 56.2 (d), 53.8 (t), 52.8 (t), 41.9 (t), 26.7 (d) and 13.2 (q); *m*/*z* (EI) for mixture 319 (64%, M^+), 284 (35), 249 (100), 214 (22) and 91 (18).

***N*-(1-α-Methylbenzyl)-3,3-dichloro-4-chloromethylpiperidin-2-one 27c.** Yield 96%, as a clear oil, for mixture (Found: C, 53.0; H, 5.1; N, 4.3. $C_{14}H_{16}Cl_3NO$ requires C, 52.4; H, 5.0; N, 4.4%); ν_{max} (CH_2Cl_2)/cm^{-1} 1667; δ_H(250 MHz; $CDCl_3$) 7.40 (5 H, m, *Ar*), 6.03 (1 H, m, C*H*Me), 4.20 (0.5 H, m, CH*H*Cl), 4.14 (0.5 H, m, CH*H*Cl), 3.58 (1 H, m, CH*H*Cl), 3.16–3.28 (1 H, m, CH*H*N), 3.08 (0.5 H, m, CH*H*N), 2.80–2.60 (1 H, m, C*H*), 2.68 (0.5 H, m, CH*H*N), 2.24–2.41 (1.5 H, m, C*H*H), 2.24–2.41 (0.5 H, m, C*H*H), 1.56 (1.5 H, d, *J* 8.3, *Me*) and 1.60 (1.5 H, d, *J* 8.3, *Me*); δ_C(62.9 MHz; $CDCl_3$) 165.4 (s), 165.2 (s), 138.4 (s), 138.6 (s), 128.7 (2 × d), 128.8 (2 × d), 127.7 (2 × d), 127.6 (2 × d), 127.0 (d), 127.1 (d), 86.5 (s), 86.3 (s), 52.6 (d), 52.5 (d), 52.2 (d), 52.0 (d), 44.1 (t), 44.0 (t), 40.6 (t), 40.4 (t), 22.9 (t), 22.8 (t), 15.2 (q) and 14.8 (q); *m*/*z* (EI) for mixture 319 (100%, M^+), 284 (41), 249 (100), 214 (30) and 105 (88).

***N*-*tert*-Butyl-3,3-dichloro-4-chloromethylpiperidin-2-one 27d.** Yield 99%, as a clear oil (Found: C, 44.05; H, 5.9; N, 5.05; Cl, 39.2. $C_{10}H_{16}Cl_3NO$ requires C, 44.1; H, 5.9; N, 5.1; Cl, 39.0%); ν_{max} (CH_2Cl_2)/cm^{-1} 1674, δ_H(250 MHz; $CDCl_3$) 4.14 (1 H, dd, *J* 11.2 and 4.9, CH*H*Cl), 3.52 (1 H, m, CH*H*N), 3.52 (1 H, dd, *J* 11.2 and 10.1, CH*H*Cl), 3.27 (1 H, m, CH*H*N), 2.63 (1 H, m, C*H*), 2.35 (1 H, m, C*H*H), 1.75–1.95 (1 H, m, C*H*H) and 1.43 (9H, s, *t*-Bu); δ_C(62.9 MHz; $CDCl_3$) 163.4 (s), 87.2 (s), 59.4 (s), 52.2 (d), 44.5 (t), 43.4 (t), 27.9 (3 × q) and 23.8 (t).

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