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A green way to γ-lactams through a copper catalyzed ARGET-ATRC in ethanol and in the presence of ascorbic acid

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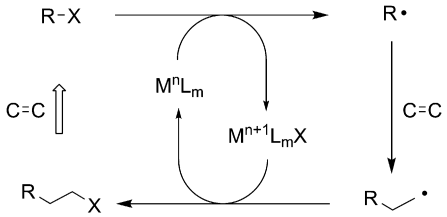
ABSTRACT

A 'green' ARGET-ATRC, for the CuCl[PMDETA] catalysed *cyclo*-isomerization of *N*-allyl-α-polychloroamides to γ-lactams is described. The process works efficiently (yields 78–96%), uses a bio-solvent, as ethanol, and exploits the reducing feature of ascorbic acid to limit, at a low level (2–4%), the amount of catalyst. To preserve the efficacy of the catalytic cycle, addition of Na_2CO_3 is essential, which quenches the HCl released during the CuCl[PMDETA] regeneration step. Profitable features of the process are: mild reaction temperatures (25–37 °C), relatively short reaction times (usually 5 h) and low solvent volumes (2 mmol of substrate/mL of ethanol). The method, upon stoichiometric adjustment, was also used for the synthesis of α,β-unsaturated-γ-lactams from *N*-(2-chloroallyl)-α-polychloroamides, via a tandem process involving an ATRC and a reductive [1,2]-elimination.

1. Introduction

The addition of C-radicals, obtained by C–X bond homolysis, to the olefinic C=C double bond has nowadays become a standard technique in synthetic organic chemistry.[1] Two common strategies that can be adopted to accomplish this goal are: (1) the method of Giese, where metal hydrides (generally tin hydrides) are used[2] and (2) the atom transfer radical addition (ATRA).[3] The second alternative is not only safer (as toxic tin compounds are excluded), but it is synthetically more appealing, since the reaction products recover the versatile halogen functionality that is present in the starting material.[4]

From the seminal studies of Kharash,[5] where the ATRA was carried out with the help of peroxide initiators, the technique has substantially improved with the introduction of transition metal complexes, which behave as 'single electron transfer' redox catalysts.[6] The recognized mechanism for the transition metal catalyzed ATRA (TMC-ATRA) consists of three elementary steps (Scheme 1).[7] First the metal complex M^nL_m, in its reduced state, abstracts (reversibly) a halogen atom from the halo-precursor, generating a radical species and thereby increasing the oxidation state of the metal by one ($M^{n+1}L_mX$). The radical intermediate, in the next step, adds to the olefinic substrate yielding a new radical. Finally, the adduct radical is quenched by halogen transfer from $M^{n+1}L_mX$ (the metal complex in its oxidized state), regenerating the active form of the catalyst (M^nL_m) and affording the reaction product. The atom transfers to and from the metal complex follow a concerted mechanism, via an inner-sphere electron transfer process.[7,8]



Scheme 1. Atom transfer radical addition mechanism.

The effectiveness and high selectivity of the TMC-ATRA is due to the capability of the system to maintain the radical species at a low concentration, guaranteeing that undesired radical side reactions

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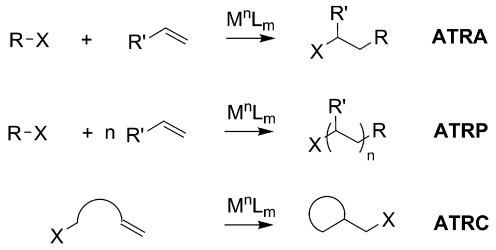
are minimal. Three variations of the method are known (Scheme 2): (1) the inter-molecular ATRA,[9] (2) the atom transfer radical polymerization (ATRP)[10] and (3) the atom transfer radical cyclization (ATRC).[11]



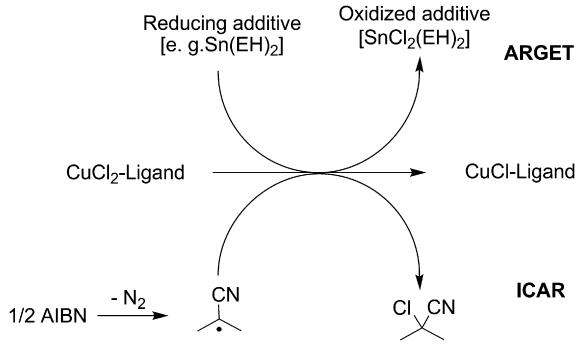
Scheme 2. Basic types of atom transfer radical reactions.

In the ATRA the halo-reagent (R-X) is usually employed in excess in comparison with the radicophilic partner (C=C), to ensure a complete conversion of the alkene and, at the same time, help to control the parasitic oligomerization process. The opposite is true for the ATRP. Here, on the contrary, the alkene is present in very large excess, the target being now the generation of a polymeric material. An even different situation is encountered for the ATRC, where the radical precursor and radicophilic components are tethered. Notwithstanding the similar reaction mechanisms, these differences mean that the experimental conditions cannot simply be translated among the three ATRA types, but instead require them to be adjusted. For example, it can be inferred from the literature that the amount of the same redox catalyst has to be substantially increased (with respect to the halo-precursor) moving from ATRA to ATRC,[12a,b] from ATRC to ATRP[12c–e] and from ATRA to ATRP;[12f–h] a few exceptions are reported, though.[13]

Although ATRP is the youngest among the ATRA methods, being discovered independently by Matyjaszewski[14a] and Sawamoto,[14b] only 15 years ago, it is by far the most studied and applied ATRA method, since it allows the preparation of polymers with well defined compositions, architectures and functionality.[10] This is the result of the controlled nature of this process, which is an example of 'living polymerization'.

The most significant advances, regarding the structure of the redox catalysts and of the variables, which influence their activity, are essentially due to researchers operating in the field of ATRP.[10] Recently, many efforts have been devoted to the development of 'green' methods, mainly targeted to the containment of the amount of catalyst required for controlling the polymerization.[10c–e] The addition of a reducing agent to these systems appeared the most effective solution. The catalytic cycle continues in the presence of a reducing agent as this reduces the metal complex in its oxidized state, which, otherwise, progressively builds up, because of 'parasitical' side reactions: radical-radical couplings or radical reductions. Regeneration of the catalyst can be achieved in two ways (Scheme 3).[10c–e] In one case, known as 'initiator for continuous activator regeneration' (ICAR)-ATRP, free radicals are slowly and steadily fed to the polymerizing mixture by the decomposition of conventional radical initiators, e.g., azoisobutyronitrile (AIBN). These interact with the $M^{n+1}L_mX$, which is accumulating, and reduce it into the active form M^nL_m.[15] In the other case, more common and named 'activators regenerated by electron transfer' (ARGET)-ATRP, non-radical reducing reagent are used,[10c–e] typically Sn(ethylhexanoate)$_2$ [Sn(EH)$_2$],[16a–f] although ascorbic acid[16g,h] or aliphatic tertiary amines have found some use.[16i,j]

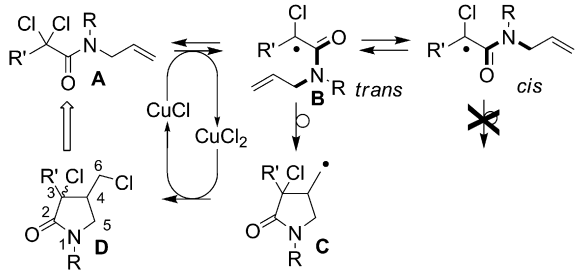
Although these techniques have been fully incorporated into the ATRP dominion, their adoption in the companion fields of ATRA or



Scheme 3. Methods for the regeneration of the active form of the catalyst.

ATRC can be considered, on the contrary, occasional.[7] The only examples, reported thus far, involve, for the ARGET-ATRA, the employment of Mg^0, as reducing reagent, with a Ru(II)[12a,13a,17] or Os (II)[17c] catalyst, and for the ICAR-ATRA, the use of the radical initiators AIBN or 2,2′-azobis(4-methoxy-2,4-dimethylvaleronitrile) (V-70) with Cu(I) or Ru(II) redox complexes.[18] Moving on to ATRC, the picture is even more sparse and we retrieved only five examples from the literature; four concerned the ARGET method,[12a,b,13a,17c] with Ru(II) or Os(II)/Mg^0 systems, and only one the ICAR approach, with CuCl complexes/AIBN.[19]

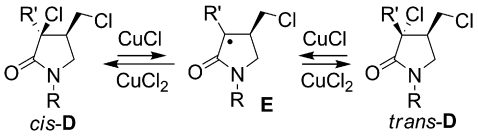
γ-Lactams are central structures in organic chemistry[20] either for their biological properties[21a,b] or as intermediates in synthesis.[21c–e,22g–i] Their assembly through a copper catalyzed ATRC (Scheme 4) of *N*-allyl-α-polichloroamides **A** has become nowadays one of the most valuable methods of preparation.[11,22]



Scheme 4. Copper catalyzed ATRC of *N*-allyl-α-polychloroamides to γ-lactams (in bold are highlighted the cis and trans conformation around the amide bond).

Main features of the process are: (i) the mild reaction conditions, (ii) easy execution and work-up, (iii) high yields, (iv) use of a catalytic amount of copper and, last but not least, (vi) the preservation of all the starting C–Cl functionalities in the heterocyclic skeleton. Notwithstanding ruthenium(II) complexes have found some use in the TMC-ATRC, cuprous halide complexes with polydentate nitrogen ligands are by far the preferred catalysts,[7,11,22a] because they are both cheap and easy to prepare. Moreover they are versatile since the redox features can be simply adjusted by changing the ligand.[12e,23] When using particularly reactive amides or a nucleophilic solvent, like DMF, the ligand can be left out.[22a]

Two pivotal points of the TMC-ATRC of amides **D** are of note. First, the presence of a substituent R (cyclization auxiliary) on the N atom of the amide **A** is an essential structural requisite, since it allows **B** to adopt the correct conformation for the cyclization (Scheme 4).[22,24] Second, the C-3 stereogenic center of **D** is configurationally unstable under the reaction conditions, and is epimerized by the same ATRC catalyst (Scheme 5).[22b,c,25]



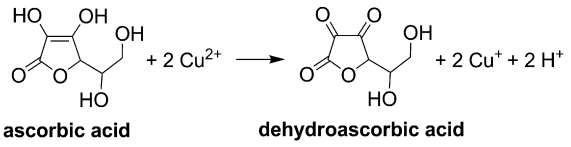
Scheme 5. Epimerization of the C-3 center of γ-lactams **D**.

Currently no real 'environmental friendly' ATRC procedures are available for the preparation of γ-lactams. The use of unsafe solvents, such as acetonitrile, CH_2Cl_2, sym-dichloroethane and toluene pose environmental concerns particularly on scale-up. Neither the published ARGET[12a,b,13a] or ICAR[19] ATRC of *N*-allyl-α-halogenoamides can be regarded as a viable solution, although the catalyst amount was substantially reduced. Fatal flaws are: (i) the use of expensive catalysts [CuCl–(Me_6-tren), CuCl–TPA or $RuCl_2Cp\cdot(PPh_3)$] at a relatively high level (1–5 mol %), (ii) the utilization of CH_2Cl_2 or toluene, as solvents, (iii) the low concentration of substrate in the reaction mixture (0.15 M) and (iv) the high percentage of the reducing additives, which increase from 5 mol % for AIBN (toxic) to even 3000–4000 mol % for Mg^0.

We thus resolved to develop a greener and sustainable TMC-ATRC procedure to obtain γ-lactams. In this article we show that this can be successfully accomplished with a copper catalysed ARGET-ATRC, using ascorbic acid (AA) as reducing agent, in ethanol. The method can be also used for the synthesis of α,β-unsaturated 4-chloromethyl-γ-lactams from *N*-(2-chloroallyl)-α-polichloroamides.

2. Results and discussion

The ARGET technique is a good starting point for the development of an environmentally friendly ATRC process, especially if coupled with a safe reductant like AA. Since we are working with redox catalysts based on Cu(I) complexes, we must take into account that in the oxidation of AA with cupric ions, 2 equiv of Cu(II) are expended and 2 equiv of H^+ concurrently released (Scheme 6).[26] Unfortunately the occurrence of acidity in the system destabilizes the catalytic complex,[15b] prejudicing its activity and, as a consequence, the running of the catalytic cycle.[22g,27] We succeeded to overcome the drawback, complementing the reaction mixture with an inorganic carbonate.[27] As one molecule of AA regenerates two cupric complexes, it is clear that the carbonate to add has to be at least equimolecular with AA.

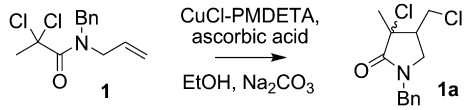


Scheme 6. Oxidation of ascorbic acid by cupric ions.

The work of Shalmashi, who studied the AA solubility in a number of solvents at different temperatures,[28] helped us to identify the appropriate reaction solvent. Because the activity of a reducing reagent is more effective in a homogeneous phase, water, methanol and ethanol appeared the most suitable solvents, however water cannot solubilise the substrate and methanol is toxic. The remaining option was thus ethanol, but luckily this is a safe and biodegradable solvent that can be produced by fermentation from renewable natural resources.

As for the redox catalyst, CuCl-*N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylentriamine (PMDETA) was preferred, being fairly active[12e,23] and as a tripodal ligand is cheap and commercially available.

The reaction conditions of the green ARGET-ATRC with the catalytic system CuCl[PMDETA]/AA/Na_2CO_3 were tested using *N*-allyl-*N*-benzyl-2,2-dichloropropanamide **1** (Scheme 7), and Table 1 shows the most significant results we obtained.



Scheme 7. ARGET-ATRC of the *N*-allyl-2,2-dichloroamide **1**.

Table 1
ARGET-ATRC of **1**[a]

No.	**1** (mmol)	CuCl/L[b] (mol %)	AA/Na_2CO_3 (mol %)	*T* (°C)	*t* (h)	Conv[c] (%)	**1a**[c,d] (%)
1	4	4/4	5/5.5	rt	2	100	95 (81/19)
2	4	4/4	0/0	rt	2	35	31 (53/47)
3	4	14/14.7	0/0	31	6	100	89 (78/22)
4	4	4/4	5/0	rt	2	57	54 (52/48)
5	4	4[e]/4	5/5.5	rt	2.5	35	29 (52/48)
6	8	2/2	2.5/2.75	rt	7	98	94 (59/41)
7	8	2/4[f]	2.5/2.75	31	6	53	50 (57/43)

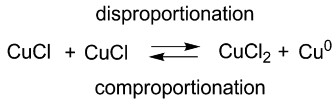
[a] All reactions were carried out in absolute EtOH (2 mL), under argon.
[b] L=PMDETA.
[c] Yields and conversions are determined on isolated material.
[d] In round brackets, cis/trans ratios (by ^{1}H-NMR spectroscopy) are quoted.
[e] Cu^0 powder replaces CuCl.
[f] L=TMEDA.

In the presence of AA and Na_2CO_3, respectively, at 2.5–5 mol % and 2.75–5.5 mol %, the ATRC proceeded smoothly with the cuprous complex at 2–4 mol % (Table 1, No. 1 and 6). The new catalytic system is so active that conversion of **1** was completed in only 2–7 h at room temperature, while with a standard redox catalyst in acetonitrile the same substrate required 20 h ca.[22i,j] Furthermore, the reaction was carried using a high concentration of substrate (2–4 mmol of substrate/mL of ethanol). On replacing PMDETA with *N*,*N*,*N*′,*N*′-tetramethylethylendiammine (TMEDA), another commercially available and cheap ligand we have widely used, however resulted in an unsatisfactory performance (Table 1, No. 7).

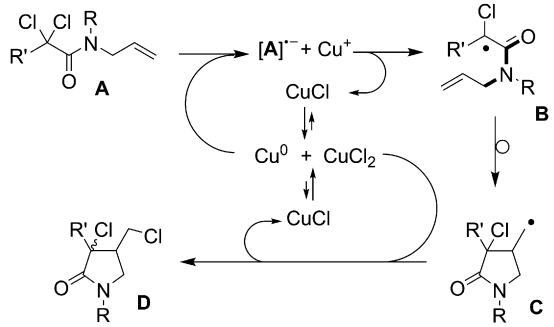
The role played by the couple AA/Na_2CO_3 is crucial. Indeed, when excluding the reductant and base in the reaction mixture, the efficiency of CuCl[PMDETA] was impaired (Table 1, No. 2), and only on trebling of the mol % of the redox complex, it was possible to arrive at a total conversion of **1** (Table 1, No. 3).

As expected, the use of ascorbic acid alone was unable to ensure an effective ATRC (Table 1, No. 4). Its acidity and the H^+ released, during the reduction of Cu(II) to Cu(I) (Scheme 6), affect the stability of the complex, interfering with the interaction between the basic nitrogen ligand and the metal cation.[27] The addition of Na_2CO_3 is thus required for safeguarding the integrity of the catalyst.

Since it is known that cuprous salts or complexes can be prone, mostly in protic solvents, to disproportionation[29] (Scheme 8), the mechanism of the ATRC may not involve the generation of the intermediate *N*-allylcarbamoylmethyl radical from amide **1**, through direct abstraction of an α-Cl by the cuprous complex (Scheme 4). Instead, as Percec proposed for the single electron transfer-living radical polymerization (SET-LRP),[29] the homolytic cleavage of the carbon halogen bond might entail a SET process, carried out by Cu^0 (Scheme 9).



Scheme 8. Disproportionation/comproportionation equilibrium.



Scheme 9. SET mechanism for the copper(I) catalysed ATRC of a generic *N*-allyl-α-chloroamide **A**.

Even though we did not observe the formation of copper powder inside the reaction mixture, this cannot exclude disproportionation and the Persec's mechanism, since the nascent Cu^0 might be rapidly oxidized by the substrate. As a consequence a test, wherein CuCl was replaced by an equivalent amount of Cu^0 powder, was conceived (Table 1, No. 5). Under these conditions, formation of the γ-lactam **1a** was accompanied by a significant amount of 1-benzyl-4-(chloromethyl)-3-methylpyrrolidin-2-one, a side-product arising from the hydro-de-chlorination of **1a** (the ratio of **1a**/side-product was 1/5, whereas in the transformations catalyzed by CuCl it was 1/49). This evidence is not supportive of the SET mechanism, although it is not totally convincing. More convincingly, the hypothetical alternative mechanism pathway, depicted in Scheme 9, was rejected, when a blank test (no added substrate) in ethanol was compared to another test reaction in water. Under these conditions, if dismutation were active, Cu^0 has to build up in the reaction mixture, as no oxidizing reagent (in our case, the amide **1**) is present. Only in water did we observe the formation of copper metal (virtually immediately), whereas in ethanol, even after 48 h, no change was detected. Clearly under our reaction conditions, the cuprous complex CuCl[PMDETA] is quite stable and unable to dismutate.

The method was than extended to a number of *N*-allyl-dichloroacetamides **2**–**4**, *N*-allyl-2,2-dichloroamides **5**–**8** and *N*-allyl-trichloroacetamides **9**–**11** (Fig. 1). The results are summarised in Table 2. In all reactions we recovered the expected γ-lactams (Fig. 2), generally in good yields (78–96%).

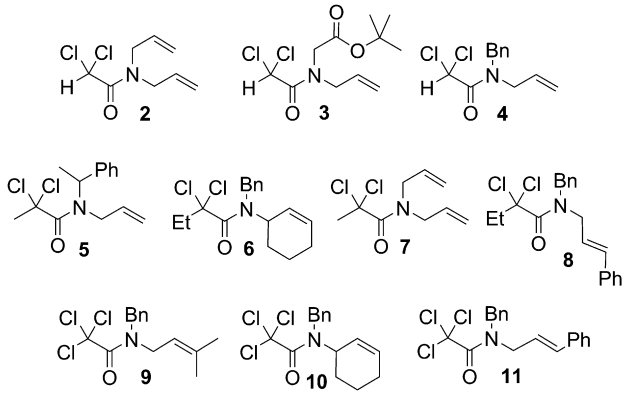


Fig. 1. Amides precursors for the ARGET-ATRC.

Table 2
ARGET-ATRC of amides **1**–**11**[a]

No.	Sub. (mmol)	CuCl/L[b]/AA/Na_2CO_3 (%)	*t* (h)	Conv[c] (%)	Products[c,d] (%)
1	**1** (4)	4/4/5/5.5	1	100	**1a** [91 (81/19)]
2	**1** (8)	2/2/2.5/2.75	6	99	**1a** [96 (61/39)]
3	**2** (4)	4/4/5/5.5	5	100	**2a** [88 (23/77)], **12**[e] [6]
4	**2** (8)	2/2/2.5/2.75	7	100	**2a** [87 (25/75)], **12**[e] [6]
5	**3** (4)	4/4/5/5.5	5	100	**3a** [89 (21/79)], **13**[e] [4]
6	**4** (4)	4/4/5/5.5	4	100	**4a** [91 (25/75)], **14**[e] [8]
7[f]	**5** (4)	4/4/5/5.5	20	100	**5a** [92 (69/31)]
8	**6** (4)	4/4/5/5.5	4	100	**6a** [92 (72/28)][g]
9	**7** (4)	4/4/5/5.5	4	100	**7a** [87 (82/18)]
10	**7** (8)	2/2/2.5/2.75	4	100	**7a** [88 (82/18)]
11	**8** (4)	4/4/5/5.5	5	100	**8a** [94 (89/11)][h]
12	**9** (4)	4/4/5/5.5	5	89	**9a** [83]
13[i]	**10** (4)	4/4/5/5.5	5	81	**10a** [63]
14[i]	**10** (4)	7.6/7.6/9.5/10.5	4	100	**10a** [83]
15	**11** (4)	4/4/5/5.5	4	89	**11a** [78]

[a] All reactions were carried out in absolute EtOH (2 mL) at 37 °C, under Argon.
[b] L=PMDETA.
[c] Yields and conversions are determined on isolated material.
[d] In round brackets are the cis/trans ratios, from ^{1}H NMR excepting **3a** (GC value).
[e] *N*,*N*-Diallyl-2-chloroacetamide (**12**), *tert*-butyl 2-(*N*-allyl-2-chloroacetamido)-acetate (**13**), *N*-allyl-*N*-benzyl-2-chloroacetamide (**14**).
[f] *T*=55 °C.
[g] Cis and trans isomers are mixtures of two diastereomers in the ratios 74/26 and 68/32, respectively (GC values).
[h] Cis and trans isomers are mixtures of two diastereomers in the ratios 92/8 and 90/10, respectively (GC values).
[i] EtOH (4 mL).

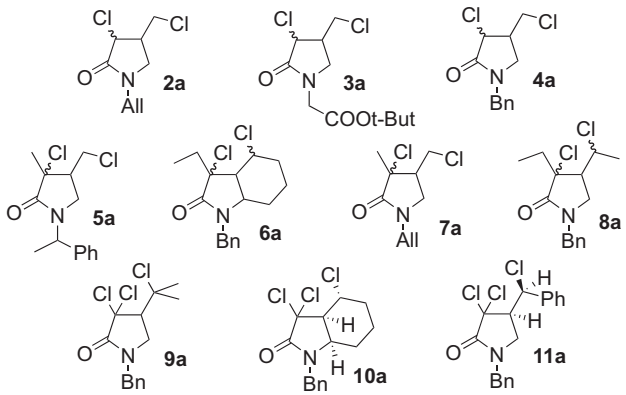


Fig. 2. γ-Lactam products from the ARGET-ATRC of amides **2**–**11**.

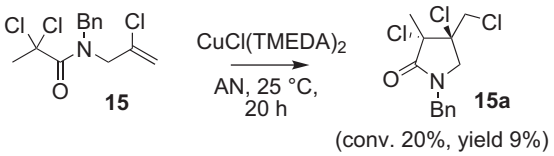
Quite surprisingly, the lower product yields (63–83%) were derived from tricloroacetamides **9**–**11** (Table 2, No. 12, 13 and 15), which otherwise gave higher yields (90–100%) in standard ATRC conditions.[4a] Moreover the conversions were incomplete (80–90%), indicating that these molecules were the less reactive. This is surprising since the trichloroacetamides are typically amongst the most reactive substrates.[22a] It is likely that the partial conversion is a consequence of an early degradation of the catalyst. Evidence for this hypothesis was the complete reaction of **10**, when the amounts of each constituent of the catalytic system were doubled (Table 2, No. 14).

Despite the mild reaction conditions, even the less reactive 2,2-dichloroacetamides **2**–**4**[22a] were completely converted into cyclic products, which emphasizes the high reactivity of the new catalytic system. The expected γ-lactams **2a**–**4a** were recovered in high yield, but along with some α-chloroacetamides (4–8%) (**12**–**14**). These adducts originated evidently from the hydro-de-halogenation of the starting materials **2**–**4**. It means that the equilibrium between the cis and trans rotamers of the intermediate radical **B**

was not fast enough (Scheme 4). As a result the cyclization is relatively slow and so the electrophilic *N*-allylcarbamoylmethyl **B** has time to be reduced by the catalytic system.

The diastereoselectivity of γ-lactams **1a**–**8a** is in line with that reported in the literature, for the most effective catalytic systems.[4a,22a] Besides, when using a chiral cyclization auxiliary, like the (*R*)-1-phenyl-1-ethyl group, a negligible chiral induction at positions C-3 and C-4 was found in **5a**, which is similar to that observed for the same transformation catalyzed by CuCl[TMEDA]$_2$ in acetonitrile.[22j]

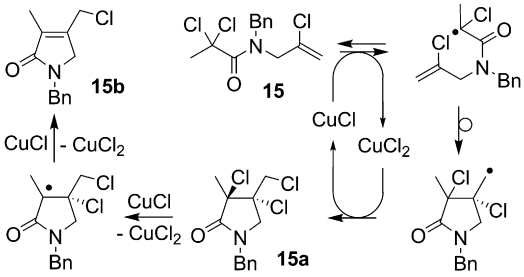
Some years ago we were interested in the ATRC of **15**. The reaction, promoted by either CuCl[TMEDA]$_2$ or CuCl[bipyridine]$_2$, gave the γ-lactam **15a** in low yields (Scheme 10).[22h] The discouraging outcome was a direct consequence of the modest conversion, which we ascribed to the instability of **15a**; indeed, **15a** was able to block the ATRC of *N*-allyl-α-polychloroamides, otherwise capable of reacting.



Scheme 10. ATRC of the *N*-benzyl-2,2-dichloro-*N*-(2-chloroallyl)propanamide **15**.

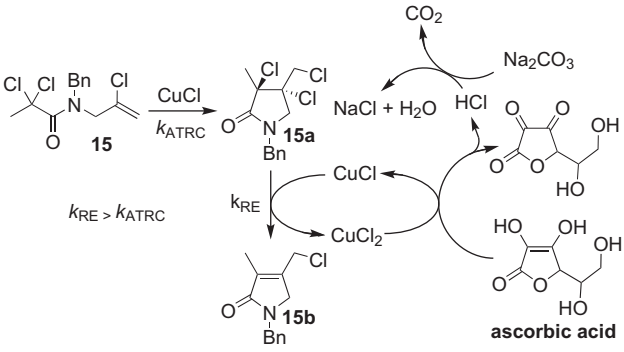
As aforementioned, the redox catalyst can epimerize the C-3 stereogenic center of α-chloro γ-lactam **D** through the reversible generation of a 3-pyrrolidin-2-onyl radical **E** (Scheme 6). Nagashima studied the activation of this peculiar α-Cl function and applied it in intra-[12d,25a,30a] and inter-molecular[25a,30b] ATRA.

We deemed that radical generation at C-3 might explain the poor efficacy of the redox complex in the *cyclo*-isomerization of **15**. The intermediate 3-pyrrolidin-2-onyl radical has a β-Cl-function, which should be liable to elimination, furnishing the α,β-unsaturated γ-lactam **15b** (Scheme 11). A radical mechanism, with loss of a Cl atom (β-fragmentation),[31] or a stepwise ionic path, with release of a chloride anion, after reduction of the radical center to give a carbanion, can be assumed.[32] Whatever happens, the elimination consumes 2 equiv of cuprous complex, leading a breakdown of the catalytic cycle.



Scheme 11. *cyclo*-Isomerization of **15** to **15a** followed by the elimination.

Since formation of **15b** is expected to follow a two-step process, wherein the initial ATRC, and the subsequent reductive [1,2]-elimination (RE) are mediated by the same redox complex, we surmised that, simply by adjusting the amounts of AA and Na_2CO_3, the new method could promote the efficient transformation of **15** into **15b** (Scheme 12). As far we are aware only two other examples of tandem ATRC-RE are known, but both involve [1,3]-eliminations.[13a,32]



Scheme 12. Mechanism of the sequential ATRC/[1,2]-RE using CuCl[PMDETA]/AA/Na_2CO_3.

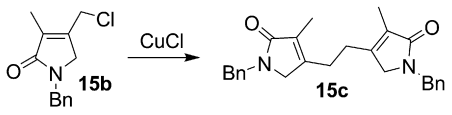
With great satisfaction we verified that our hypothesis was correct. After a series of tests, the optimal **15**/AA/Na_2CO_3 ratio was determined as 4/4.1/4.2 (Table 3, No. 1). To allow an easy stirring of the reaction mixture, the amount of ethanol was increased to 5 mL/4 mmol of substrate. Glucose was also tried as reductant,[33] but this proved unsuccessful. In addition, reaction temperatures above 60–70 °C have to be carefully avoided, since, otherwise, a third reaction, the ethoxy-de-halogenation of the allylic chlorine, is appended to the [1,2]-RE. The formation of trichloro γ-lactam **15a** was always detected, even at short reaction times, in minimal amounts (<2%), indicating that the RE step is faster than ATRC.

Table 3
ATRC-ER of amides **16**–**20**[a]

No.	Substrate	*T* (°C)	*t* (h)	Conv.[b] (%)	**b**[b] (%)	**c**[b] (%)
1	**15**	25	4	100	83	8
2	**16**	25	4	90	73	11
3	**17**	25	4	100	—[c]	—
4	**18**	25	4	100	59	—
5	**19**	25	4	100	27	—
6	**20**	25	4	57	—	10

[a] All reactions were carried out in absolute EtOH (5 mL), substrate (4 mmol), CuCl-PMDETA (5 mol %), AA (4.1 mmol), and Na_2CO_3 (4.2 mmol), under Argon.
[b] Yields and conversions are determined on isolated material.
[c] *N*-Benzyl-2-chloro-*N*-(2-chloroallyl)acetamide (**22**) was quantitatively obtained.

A dimeric species, **15c**, was also isolated, albeit in low yield (8%). This is derived from a formal reductive homo-coupling of **15b**, by linking the two allylic carbons C_{exo} (Scheme 13), a further reaction most likely mediated by the cuprous complex. Clearly, the remaining allylic C–Cl function is still fairly reactive.



Scheme 13. Reductive homo-coupling of **15b**.

To study the extension of the tandem ATRC-RE, a range of *N*-(2-chloroallyl)-α-polychloroamides (Fig. 3, substrates **16**–**20**) was prepared.

Table 3 summarises the results we obtained, while Fig 4 shows the structures of the products isolated. Disappointingly, the method was lacking in general applicability. Indeed, we did never observe a selectivity better than the one registered for **15**. On the contrary it just seems that each of the amides **16**–**20** exhibits a peculiar behaviour.

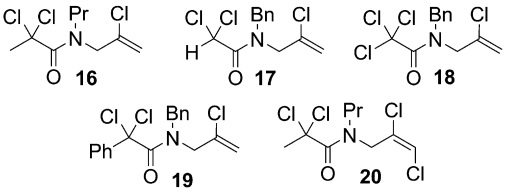


Fig. 3. Precursor amides for the tandem ATRC-RE.

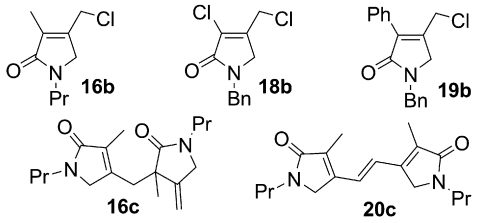
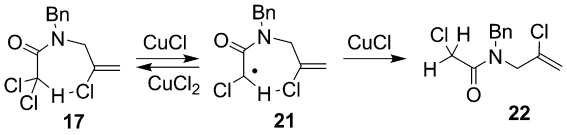


Fig. 4. Products from the tandem ATRC-RE of amides **16**–**20**.

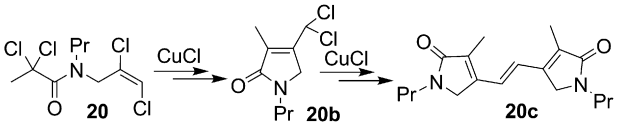
Even though the α,β-unsaturated γ-lactam **16b** (Table 3, No. 2) was attained in a good yield (73%) from **16**, the conversion was partial (90%), despite attempts at optimization. Moreover the dimer by-product **16c**, secured in 11% yield, was unexpectedly derived from a connection between C_{exo} and C_{endo} carbons of the two allylic precursors.

From **17**, instead, we quantitatively recovered the *N*-benzyl-2-chloro-*N*-(2-chloroallyl)acetamide **22** (Scheme 14) (Table 3, No. 3). The result indicates that the intermediate α-amide radical, derived from chlorine abstraction from **17**, has no tendency to cyclise, unlike the dichloroacetamides **2**–**4**. Instead, even on increasing the reaction temperature to 70 °C, it is gradually reduced to **22** (Scheme 14). Perhaps this may be explained by formation of an inter-molecular hydrogen bond between the α-H (of the amide moiety), and the vinylic chlorine (in the allylic moiety), which forces the amide **17**, and the intermediate carbamoylmethyl radical **21**, to adopt a conformation unsuitable for the cyclization.



Scheme 14. Hydro-de-halogenation of the amide **17**.

Substrates **18** and **19** (Table 3, No. 4 and 5) afforded the expected unsaturated γ-lactams: **19b** in poor yields (27%) and **18b** with a fairly better outcome (59%). Both transformations were not clean and it was impossible for us to isolate any dimer. Finally, the only important product isolated from the reaction with the tetrachloroamide **20**, although in a small amount (10%), was **20c** (Table 3, No. 6). The molecule is a symmetric dimer, where the heterocyclic rings are joined by a vinylene bridge, likely arising from the presumed ATRC intermediate **20b** through a tandem reductive homo-coupling/[1,2]-RE process (Scheme 15).



Scheme 15. Transformation of the amide **20** into the dimer **20c**.

3. Conclusions

This work has shown that a 'green' ARGET-ATRC, for the CuCl-PMDETA catalysed *cyclo*-isomerization of *N*-allyl-α-polychloroamides into γ-lactams, proceeds efficiently (yields between 78 and 96%). The catalytic system works in ethanol, a safe solvent obtainable from renewable bio-resources, and exploits the reducing features of ascorbic acid to limit the amount of the redox complex to only 2–4 mol %. To preserve the efficacy of the catalytic cycle, it is essential that Na_2CO_3 is added. It neutralises the HCl released during the regeneration of the active cuprous form of the redox catalyst. Other advantages of the method are: mild reaction temperatures (25–37 °C), relatively short reaction times (usually 5 h) and low solvent volumes (2 mmol of substrate/mL of ethanol). These features altogether make the reaction attractive for an eventual scale-up.

The method does have some limitations, when using the *N*-allyl-2,2-dichloroamides and the *N*-allyl-trichloroacetamides. In the first case some reduction of the starting amides was noted and, in the other case, conversions were incomplete, unless to increase the amount of CuCl[PMDETA]/AA/Na_2CO_3. We have also ascertained that, under our conditions, the reaction proceeds with a typical inner-sphere mechanism, propelled by CuCl, whereas the hypothetical SET mechanism, based on Cu^0, cannot be operative.

The method, upon stoichiometric adjustment of the reagents, looked also suitable for the synthesis of α,β-unsaturated 4-chloromethyl-γ-lactams from *N*-(2-chloroallyl)-α-polychloroamides, via a tandem process involving an ATRC and a reductive [1,2]-elimination. Unfortunately, this second application is not general. In fact, each of the experienced amides (**16**–**20**) investigated exhibited a peculiar behaviour, although satisfactory results were achieved with substrates **15** and **16**. Product **18b**, even if isolated in only 59% yield, is quite appealing as it carries both a vinylic and an allylic chloro function. Finally, the isolation of dimeric products, in these reactions, means that the allylic chlorine atom of the α,β-unsaturated 4-chloromethyl-γ-lactams is somewhat reactive.

4. Experimental part

4.1. General

Reagents and solvents were standard grade commercial products, purchased from Aldrich, Acros, Fluka or RdH, and used without further purification. The silica gel used for flash chromatography was Silica Gel 60 Merck (0.040–0.063 mm). The starting amides **1**–**11** and **15**–**20** were obtained through amino-dechlorination of acyl chlorides with allyl amines (all prepared by *N*-alkylation of amines, adapting the Shipman's method)[34] following typical procedures.[4a,14] The 2,2-dichloropropanoyl and 2,2-dichlorobutanoyl chlorides were, respectively, prepared from 2,2-dichloropropanoic and 2,2-dichlorobutanoic acids[35] by halo-de-hydroxylation with $(COCl)_2$, following the literature.[22] Products **2a**,[22a] **4a**,[22a] **5a**,[22h] **6a**,[4a] **7a**,[22a] **8a**,[4a] **9a**,[4a] **10a**[4a] and **11a**[4a] are known compounds. NMR spectra were recorded on a 'Bruker DPX 200' and a 'Varian 500 MHz' spectrometer. The relative configuration of **3a** was determined by NOESY experiments. IR and MS spectra were recorded, respectively, on a 'Perkin Elmer 1600 Series FT-IR' and 'HP 5890 GC–HP 5989 AMS Engine'. Only for **15b** was the MS spectra obtained on an 'LC–$MS_{(n)}$ Ion Trap 6310A Agilent Technologies'. Elemental analysis was performed on the 'EA 1110 Carlo Erba'.

4.2. Typical procedure for the cyclization of amides 1–11: reaction of *tert*-butyl 2-(*N*-allyl-2,2-dichloroacetamido) acetate (3)

CuCl (0.16 mmol, 16 mg), ascorbic acid (0.2 mmol, 35 mg), Na_2CO_3 (0.22 mmol, 23 mg) and amide **3** (4 mmol, 1.129 g) were weighed in

a Schlenk tube fitted with a pierceable septum (blocked by a screw cap) and a magnetic stirring bar. Absolute ethanol (2 mL) was then added under argon. The reaction mixture (only in this case) was heated to a moderate extent until all the substrate was dissolved. Afterwards PMDETA (0.16 mmol, 36 μL) was injected through the septum with a microsyringe and the Schlenk tube promptly immersed in a water bath at 37 °C. The reaction mixture was stirred for 5 h and then diluted with water (8 mL), acidified with HCl 10% w/v and extracted with ethyl acetate (3×6 mL). The combined organic layers were concentrated and the crude product was purified by flash chromatography on silica gel, eluting with a petroleum ether (PE: bp 40–60 °C)/diethyl ether (Et_2O) gradient (from 100/0 to 0/100). This gave the 2-pyrrolidinone **3a** (1.005 g, colourless oil, 89%), as an inseparable mixture of *cis*/*trans* diastereomers (21/79, ^{1}H NMR) [found: C, 47.0; H, 6.2; N, 5.1. $C_{11}H_{17}Cl_2NO_3$ requires 46.82; H, 6.07; N, 4.96] and **13** (0.040 g, colourless oil, 4%).

*4.2.1. tert-Butyl 2-[3-chloro-4-(chloromethyl)-2-oxopyrrolidin-1-yl] acetate (**3a**).* ν_{max} (liquid film) 1740 and 1717 cm^{-1}; δ_H cis (500 MHz, $CDCl_3$) 1.47 (9H, s, CMe_3), 2.99 (1H, m, H-4), 3.44 (1H, dd, *J* 9.7, 7.9, H-5), 3.61 (1H, dd, *J* 9.7, 7.0, H-5), 3.82 (2H, m, CH_2Cl), 3.96 and 4.03 (2H, *J* 17.5, pseudoq AB, CH_2CO), 4.49 (1H, d, *J* 6.4, CHCl); δ_H trans 1.47 (9H, s, CMe_3), 2.91 (1H, m, H-4), 3.64 (1H, dd, *J* 9.6, 7.9, H-5), 3.47 (1H, dd, *J* 9.6, 7.0, H-5), 3.76 (2H, ddd, *J* 11.5, 6.6, 4.8, CH_2Cl), 3.87 (1H, d, *J* 17.5, part A of an AB, CHCO), 4.14 (1H, d, *J* 17.5, part B of an AB, CHCO), 4.38 (1H, d, *J* 7.8, H-3); δ_C *cis* (125.68 MHz, $CDCl_3$) 27.8, 40.6, 41.8, 44.7, 48.8, 56.7, 82.6, 166.6, 168.9; δ_C *trans* 27.8, 43.1, 44.9, 47.9, 55.9, 82.6, 166.6, 168.9; *m*/*z* (EI, 70 eV) 225 [12 (M−56)$^+$], 208 (12), 190 (5), 181 (18), 180 (43), 146 (55), 57 (100%).

*4.2.2. tert-Butyl 2-(N-allyl-2-chloroacetamido)acetate (**13**).* *m*/*z* (EI, 70 eV) 191 [23 (M−56)$^+$], 174 (11), 146 (60), 114 (22), 70 (92), 57 (100), 41 (52%). This MS spectrum is identical to the one of an original sample of **13**, prepared by reaction of 2-chloropropionyl chloride with *tert*-butyl 2-(allylamino)acetate.

4.3. Reaction of *N*-benzyl-2,2-dichloro-*N*-(2-chloroallyl) propanamide (15)

CuCl (0.2 mmol, 0.020 g), ascorbic acid (4.1 mmol, 0.722 g), Na_2CO_3 (4.2 mmol, 0.445 g) and amide **15** (4 mmol, 1.227 g) were weighed in a Schlenk tube fitted with a pierceable septum (blocked by a screw cap) and a magnetic stirring bar. Absolute ethanol (5 mL) was then added under argon and the Schlenk tube immersed in a water bath at 25 °C. After 10′, PMDETA (0.2 mmol, 41 μL) was injected through the septum with a microsyringe. The reaction mixture was stirred for 4 h and then diluted with ethyl acetate (50 mL), acidified with HCl 10% w/v and washed with water (3×20 mL). The organic layer was concentrated and the crude product was purified by flash chromatography on silica gel, eluting with a gradient from PE/Et_2O (100/0) to Et_2O/MeOH (95/5). This gave the α,β-unsatured-γ-lactam **15b** (0.782 g, 83%), as a white solid [found: C, 66.5; H, 6.1; N, 6.0. $C_{13}H_{14}ClNO$ requires C, 66.24; H, 5.99; N, 5.94], R_f (50% PE/Et_2O) 0.075, and the dimer **15c** (0.063 g 8%), as a slightly brownish solid [found: C, 77.8; H, 7.1; N, 7.0. $C_{26}H_{28}N_2O_2$ requires C, 77.97; H, 7.05; N, 6.99], R_f (95% Et_2O/MeOH) 0.27.

*4.3.1. 1-Benzyl-4-(chloromethyl)-3-methyl-1H-pyrrol-2(5H)-one (**15b**).* Mp 91–93 °C; ν_{max} (KBr) 1718 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.92 (3H, s, CH_3), 3.85 (2H, s, C(5)H_2), 4.30 (2H, s, CH_2Cl), 4.63 (2H, s, N−CH_2), 7.18–7.40 (5H, m, Ph); δ_C (50.32 MHz, $CDCl_3$) 9.1, 38.9, 47.7, 51.8, 124.7, 125.3, 125.8, 133.8, 138.6, 144.7, 171.1; *m*/*z* (EI, 70 eV) 235 (25, M$^+$), 200 (100), 91 (73%).

*4.3.2. 4,4′-(Ethane-1,2-diyl)bis[1-benzyl-3-methyl-1H-pyrrol-2(5H)-one] (**15c**).* Mp 117–120 °C; ν_{max} (KBr) 1672 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.76 (4H, s, CH_2CH_2), 2.43 (6H, s, CH_3), 3.58 (4H, s, 2×C(5)H_2), 4.58 (4H, s, 2×N−CH_2), 7.11–7.39 (10H, m, 2×Ph); δ_C (50.32 MHz, $CDCl_3$) 8.8, 26.3, 46.1, 51.8, 127.5, 127.9, 128.7, 129.8, 137.3, 147.7, 172.1; *m*/*z* (ESI-Ion Trap) 423.2 [4 (M+Na)$^+$], 401.2 [100% (M+H)$^+$].

4.4. Reaction of 2,2-dichloro-*N*-(2-chloroallyl)-*N*-propylpropanamide (16)

Following the procedure, used for **15**, **16** (4 mmol, 1.034 g) gave, after flash-chromatography of the crude product on silica gel, using a PE/Et_2O gradient (from 100/0 to 0/100), the α,β-unsaturated-γ-lactam **16b** (0.548 g, 73%), as a slightly brown oil [found: C, 57.4; H, 7.5; N, 7.4. $C_9H_{14}ClNO$ requires C, 57.60; H, 7.52; N, 7.46], R_f (50% PE/Et_2O) 0.096, and the dimer **16c** (0.070 g 11%), as a colourless oil [found: C, 71.2; H, 9.3; N, 9.1. $C_{18}H_{28}N_2O_2$ requires C, 71.02; H, 9.27; N, 9.20], R_f (Et_2O) 0.075.

*4.4.1. 1-Propyl-4-(chloromethyl)-3-methyl-1H-pyrrol-2(5H)-one (**16b**).* ν_{max} (liquid film) 1681 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 0.89 (3H, t, *J* 6.9, CH_2CH_3), 1.58 (2H, sext, *J* 6.9, CH_2CH_3), 1.85 (3H, s, CH_3), 3.38 (2H, t, *J* 6.9, N−CH_2), 3.93 (2H, s, C_5H_2), 4.32 (2H, s, CH_2−Cl); δ_C (50.32 MHz, $CDCl_3$) 9.0, 11.2, 21.8, 37.6, 44.0, 51.5, 133.1, 143.2, 171.2; *m*/*z* (EI, 70 eV) 187 (38, M$^+$), 158 (100), 152 (47%).

*4.4.2. 3-Methyl-4-((3-methyl-4-methylene-2-oxo-1-propylpyrrolidin-3-yl)methyl)-1-propyl-1H-pyrrol-2(5H)-one (**16c**).* ν_{max} (liquid film) 1682, 1654 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.87 and 0.88 (6H, 2×t, 2×CH_3CH_2), 1.32 (3H, s, CH_3−C), 1.52 (4H, m, 2×CH_3CH_2), 1.78 (3H, s, CH_3C=C), 2.63 and 2.76 (2H, *J* 13.6, app. q AB, exocyclic tethering CH_2), 3.26 (2H, t, N−CH_2), 3.32 (2H, m, N−CH_2), 3.59 and 3.60 (2H, AB, *J* 16.2, app. q N−CH_2−C=C), 3.74 (1H, td, *J* 2.0, 14.3, part A of an ABXX′, N−C*H*−C=CH_2) 3.91 (1H, td, *J* 2.3, 14.3 Hz, part B of an ABXX′, N−C*H*−C=CH_2), 5.14 (2H, ddd, *J* 2.0, 2.5, 4.2, part X and X′, CH_2=C); δ_C (125.68 MHz, $CDCl_3$) 9.5, 11.1, 11.2, 20.3, 21.8, 25.5, 37.2, 43.6, 43.8, 48.9, 50.6, 53.7, 108.8, 131.8, 145.0, 146.1, 172.0, 176.5; *m*/*z* (EI, 70 eV) 275 [1, (M−29)$^+$], 152 (100%).

4.5. Reaction of *N*-benzyl-2,2,2-trichloro-*N*-(2-chloroallyl) acetamide (18)

Following the procedure, used for **15**, **18** (4 mmol, 1.308 g) gave, after flash-chromatography of the crude product on silica gel, using a PE/Et_2O gradient (from 100/0 to 0/100), 1-benzyl-4-(chloromethyl)-3-chloro-1*H*-pyrrol-2(5*H*)-one (**18b**) (0.604 g, 59%), as a slightly brown solid [found: C, 56.1; H, 4.3; N, 5.5. $C_{12}H_{11}Cl_2NO$ requires C, 56.27; H, 4.33; N, 5.47], R_f (50% PE/Et_2O) 0.18; mp 96–98 °C; ν_{max} (KBr) 1708 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.94 (2H, s, C_2H_5), 4.37 (2H, s, CH_2Cl), 4.65 (2H, s, N−CH_2), 7.15–7.43 (5H, m, Ph); δ_C (50.32 MHz, $CDCl_3$) 36.66, 47.12, 50.41, 127.08, 128.00, 128.20, 128.94, 136.15, 143.94, 165.00; *m*/*z* (EI, 70 eV) 255 (20, M$^+$), 220 (100), 91 (88).

4.6. Reaction of *N*-benzyl-2,2-dichloro-*N*-(2-chloroallyl)-2-phenyl-acetamide (19)

Following the procedure, used for **15**, **19** (4 mmol, 1.475 g) gave, after flash-chromatography of the crude product on silica gel, using a PE/Et_2O gradient (from 100/0 to 30/70), 1-benzyl-4-(chloromethyl)-3-phenyl-1*H*-pyrrol-2(5*H*)-one (**19b**) (0.322 g, 27%), as a yellow oil [found: C, 72.7; H, 5.5; N, 4.8. $C_{18}H_{16}ClNO$ requires C, 72.60; H, 5.42; N, 4.70], R_f (70% PE/Et_2O) 0.092; ν_{max} (KBr) 1684 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 4.03 (2H, s, C(5)H_2), 4.44 (2H, s, CH_2Cl), 4.72 (2H, s, N−CH_2), 7.20–7.60 (10H, m, Ar); δ_C (50.32 MHz, $CDCl_3$) 38.63, 46.53, 50.97, 127.73, 128.26, 128.56, 128.72, 129.16, 130.38, 135.61, 136.98, 128.83, 144.99, 169.87; *m*/*z* (EI, 70 eV) 297 (24, M$^+$), 262 (51), 248 (10), 91 (100).

4.7. Reaction of 2,2-dichloro-*N*-(2,3-dichloroallyl)-*N*-propylpropanamide (20)

Following the procedure, used for **15**, **20** (4 mmol, 1.172 g) gave, after flash-chromatography of the crude product on silica gel, using a gradient from PE/Et_2O (100/0) to Et_2O/MeOH (95/5), (*E*)-4,4′-(ethene-1,2-diyl)bis(3-methyl-1-propyl-1*H*-pyrrol-2(5*H*)-one) (**20c**) (0.121 g, 10%), as yellowish solid [Found: C, 71.8; H, 8.7; N, 9.3. $C_{18}H_{26}N_2O_2$ requires C, 71.49; H, 8.67; N, 9.26], R_f (95% Et_2O/MeOH) 0.22; mp 169–171 °C; ν_{max} (KBr) 1680 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 0.91 (6H, t, *J* 6.8, 2×CH_2CH_3), 1.62 (4H, sext, *J* 6.8, 2×CH_2CH_3), 1.95 (6H, s, 2×CH_3), 3.44 (4H, t, *J* 6.8, 2×N–CH_2), 4.06 (4H, s, 2×C_5H_2), 6.68 (2H, s, 2× =CH); δ_C (50.32 MHz, $CDCl_3$) 9.41, 11.26, 21.80, 44.06, 50.15, 122.17, 133.39, 142.96, 171.79; *m*/*z* (EI, 70 eV) 302 (51, M^+), 273 (100).

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