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Efficient and Green Route to γ-Lactams by Copper-Catalysed Reversed Atom Transfer Radical Cyclisation of α-Polychloro-*N*-allylamides, using a Low Load of Metal (0.5 mol%)

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Abstract: The cyclisation of *N*-allyl-*N*-substituted-α-polychloroamides is efficiently obtained through a copper-catalysed activators regenerated by electron transfer–atom transfer radical cyclisation process, with a metal load of only 0.5 mol%. The redox catalyst is introduced in its inactive form as copper(II) chloride/[nitrogen ligand] complex, and continuously regenerated to the active copper(I) chloride/[nitrogen ligand] species by ascorbic acid. To preserve the catalyst integrity, the hydrochloric acid, released after each regeneration cycle, has been quenched by carbonate. The choice of the solvent is critical, the best performance being observed in ethyl acetate-ethanol (3:1).

Keywords: atom transfer radical cyclization; ATRC; copper; cyclisation; γ-lactams; radicals

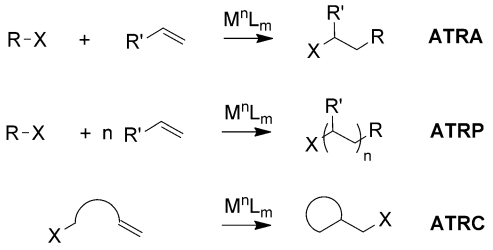
Introduction

The insertion of an olefinic C=C function between the components of a C–X (X = Cl, Br, I) bond through a radical chain process, named *atom transfer radical addition* (ATRA) or Kharasch addition, has become a standard technique in synthetic organic chemistry.[1]

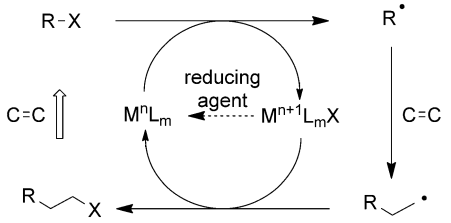
Originally the ATRA was carried out with the help of radical initiators and was limited to substrates with a quite weak C–X bond.[1] Nowadays the scope of the reaction has been considerably enlarged with the help of transition metal complexes (TMC).[2] Three variants of the method are known (Scheme 1): (i) the intermolecular ATRA,[3] (ii) the atom transfer radical polymerisation (ATRP)[4] and (iii) the atom transfer radical cyclisation (ATRC).[5]

All these processes feature a common mechanism (Scheme 2).[3–5] First the metal complex M^nL_m, in its reduced state (active form or activator), abstracts (reversibly) a halogen atom from the halo precursor, generating a radical species and increasing its oxidation state by one unit ($M^{n+1}L_mX$). The radical intermediate then adds to the olefinic substrate yielding a new radical. Finally, the second adduct radical is quenched by halogen transfer from $M^{n+1}L_mX$ (the metal complex in its oxidised state or inactive form or deactivator), 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.[6]

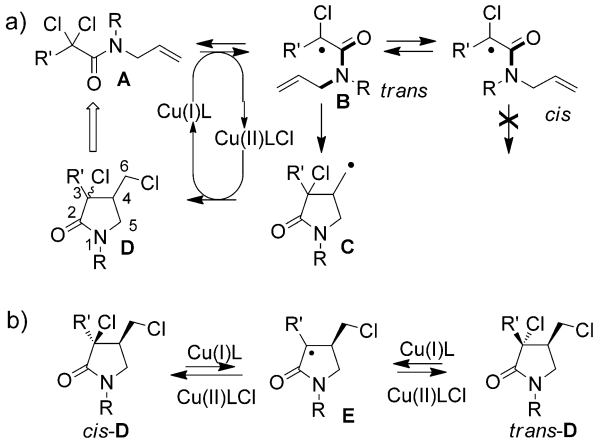
Even though ATRP is the youngest among the ATRA methods,[7] it is certainly the most studied and applied, allowing the controlled preparation both of polymers with complex architectures and of hybrid



Scheme 1. Types of atom transfer radical reactions.



Scheme 2. Atom transfer radical addition mechanism (if a reducing agent is added to the reaction mixture, as in the ICAR or ARGET processes, catalyst regeneration occurs *via* the dotted arrow, see text); in the case of ATRP the activation/deactivation/addition cycle is repeated many times resulting in polymer formation.



Scheme 3. a) Typical copper-catalysed ATRC of *N*-allyl-α-polychloroamides (the *cis* and *trans* conformations around the amide bond are highlighted in bold); b) copper-catalysed epimerisation of the C-3 centre of γ-lactams **D**.

materials.[4] Redox catalysts based on copper are usually preferred and thanks to these investigations, major achievements, regarding their structure and the variables, which influence their activity, were accomplished.[4a,c,6a,b,8]

Many efforts have been devoted to the containment of the amount of copper required for controlling the ATRP process.[9] This has been achieved by complementing the catalytic system with a "reducing agent" that re-establishes the catalytic cycle, regenerating the active metal complex from the inactive oxidised form, which, otherwise, because of termination reactions, progressively builds up. There are three methods of choice to this end: (i) the "*initiator for continuous activator regeneration*" protocol (ICAR)-ATRP, where free radicals, slowly and steadily fed to the polymerising mixture by decomposition of conventional radical initiators (e.g., AIBN), interact with the $M^{n+1}L_mX$ species,[10] (ii) the "*activators regenerated by electron transfer*" process (ARGET)-ATRP, which uses non-radical reducing reagents, such as Sn(ethyl hexanoate)$_2$ [Sn(EH)$_2$],[11] ascorbic acid,[12] aliphatic tertiary amines,[13] or zerovalent metals [Cu(0) above all][14] and (iii) the recently reported electrochemical (*e*)-ATRP, where the reduction is realised through the intake of electrons from an electrode.[15] These techniques have found some application[16] in the companion field of ATRA,[17] but their implementation in the ATRC area is still in its infancy.[17f–i,18]

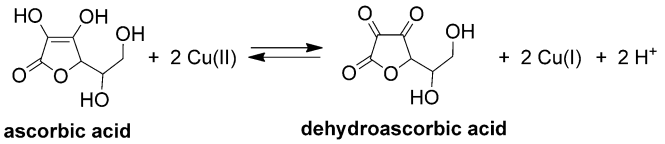
One of the most popular ATRCs is the cycloisomerisation to γ-lactams of *N*-allyl-α-haloamides.[19a] Copper(I),[19] ruthenium(II)[20] or sporadically iron(II)[19t,21] are the typical metal ions used to catalyse these transformations. A number of interesting natural and unnatural products, have been prepared by this method,[19a] and useful domino processes, involving ATRC, have also been developed.[17g,19a,k,q,u,20a,c,e]

Two pivotal aspects of the TMC-ATRC of amides need to be highlighted. First, the presence of a substituent R (cyclization auxiliary) on the N atom of the starting amide **A** is essential, since it allows the α-amide radical intermediate **B** to adopt the correct conformation for the cyclisation (Scheme 3a).[19a,22] Second, when the C-3 stereogenic centre of the lactam **D** carries a halo function, it becomes configurationally unstable under the reaction conditions, and can be epimerised by the same ATRC catalyst (Scheme 3b).[19a,b,f,h,q,20i] The best stereochemical results are thus achievable when the thermodynamic control is fully operative, the preferred products being those in which the substituents Cl and CH_2Cl stay on the same face of the ring.

Recently we have proposed a "green" ARGET-ATRC of *N*-allyl-α-polychloroamides.[18a] The process, catalysed by CuCl/PMDETA,[23] worked efficiently (yields 78–96%) in ethanol, using ascorbic acid (AA) (2.5–5 mol%) as regenerating agent (2–4 mol%);[18a] AA was also used in few copper-catalysed ARGET-ATRA.[17l,m,p]

Previously the activator in the ATRC of unsaturated amides was regenerated through an ICAR process in CH_2Cl_2, using CuCl/TPMA (1 mol%)/AIBN (10 mol%),[18b] or through an ARGET process in toluene, based on Ru(II) or Os(II) (1–5 mol%)/Mg(0) (3000–4000 mol%).[17f–i] More recently an ARGET process exploiting the system $CuSO_4$/TPMA-KBH_4 has been also issued.[18c] It uses methanol as solvent, and the typical load of catalyst is around 1–2.5 mol%, while that of the reducing agent is 10–50 mol%. The expensive nature of the Ru or Os catalysts, the excessive load of reducing agents, the toxicity of AIBN and the low concentration of substrate in the reaction mixture make these methods unappealing for large-scale preparations.

Our green ARGET alternative, however, has also some disadvantages: (i) substrate solubility in ethanol is not always good, (ii) metal loading is still too high (2–4 mol%) and (iii) unsatisfactory results are



Scheme 4. Reduction of cupric cation by ascorbic acid.

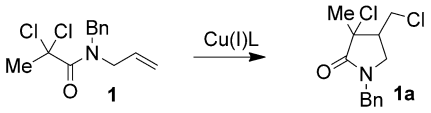
achieved with polychloroacetamides.[18a] Here, we now report how these problems have been solved.

Results and Discussion

The system ascorbic acid/Cu(II)/Cu(I)/dehydroascorbic acid in water and under anaerobic conditions is coarsely drawn in Scheme 4.[24] It is important to note that the oxidation of one equivalent of AA restores two equivalents of Cu(I), but concurrently releases two equivalents of H^+.[24] Unfortunately, the production of acidity destabilises the catalytic complex,[9c] undermining its activity.[19n,25] For this reason a base (e.g., Na_2CO_3) has to be added to the reaction mixture.[18a,25]

In order to identify a better solvent than ethanol and the most appropriate reaction conditions for the amide substrates, wherein the redox system CuCl/PMDETA-AA-Na_2CO_3 can work at the maximum of its capability, we chose to study as archetypal reaction, the ATRC of the *N*-allyl-2,2-dichloropropanamide **1** (Scheme 5). At first we examined the cycloisomerisation of **1** in a number of solvents, fixing arbitrarily the catalyst load to 1 mol%.

We observed (Table 1) the best reactivity in ethanol, but in AcOEt, THF and DME the cycloisomerisation gave also interesting results (conversions around 80%). Astonishingly, the conversion was very low in DMF, notwithstanding the complete solubility of AA in this solvent. Considering also that at 35 °C the mol fraction of AA in AcOEt is $0.23 \cdot 10^{-3}$ while in EtOH it is $3.85 \cdot 10^{-3}$,[26] it is clear that the solubility of AA in the reaction medium is not a very crucial feature in the choice of the solvent. Moreover Matyjaszewski observed that controlled ARGET-ATRP with AA was possible only if the solubility of the reducing agent was limited through the adoption of heterogeneous conditions[12e] or through its slow feeding into the reaction mixture.[12f] We also tried (unreported results) the more lipophilic ascorbyl-6-palmitate as reducing agent, but without success: it always gave



Scheme 5. Cycloisomerisation of amide **1** to γ-lactam **1a**.

Table 1. Effect of solvent on the ARGET-ATRC of **1**.[a]

Entry°	Solvent[b] [mL]/[mmol] of **1**	Conversion[c] [%]	Products[c,d] [%]
1	AcOEt (0.5)	83	81 (59:41)
2	THF (0.5)	82	78 (59:41)
3	DME (0.5)	79	77 (59:41)
4	AN (0.5)	20	20 (53:47)
5	toluene (0.5)	14	14 (58:42)
6	DMF (0.5)	39	38 (55:45)
7	EtOH (0.5)	100	99 [93][e] (60:40)

[a] All reactions were carried out under argon: substrate 8 mmol, CuCl/PMDETA 1 mol%, AA 2 mol%, Na_2CO_3 4 mol%, *T* 35 °C, *t* 4 h.
[b] AcOEt (ethyl acetate), THF (tetrahydrofuran), DME (1,2-dimethoxyethane, AN (acetonitrile), DMF (*N*,*N*-dimethylformamide, EtOH (ethanol).
[c] GC value.
[d] In round brackets are the *cis*/*trans* ratios (GC).
[e] Yields determined on isolated material.

much lower conversions than AA. The diastereomeric ratio (*cis*/*trans*) of **1a** was practically the same in all solvents, about 60:40. Since the *cis* isomer has a more interesting reactivity than its *trans* counterpart, being able to be smoothly dehydrohalogenated, the C-3−Cl and the C-4−H can, in fact, easily achieve the antiperiplanar conformation required for the elimination,[19a,d,f,h] its modest prevalence makes these transformations globally not very attractive.

Owing to its favourable properties, such as: better solubility for our substrates, environmental sustainability and adequate reactivity of the ARGET-ATRC system, AcOEt was considered for further tests (Table 2).[27] The necessity of the simultaneous presence of AA and carbonate to attain the best catalyst performance was confirmed (Table 2, entries 1–3). Unfortunately, the reactivity did not improve increasing the temperature; longer reaction time was the only solution to get a higher conversion. In any case the diastereomeric ratio remained stable at around 60:40 (Table 2, entries 3–5).

At this point we investigated the application of tetradentate tripodal nitrogen ligands, such as Me_6TREN and TPMA (Figure 1). Although expensive, these ligands are widely exploited in all the fields of ATRA reactions, since they give rise to more reducing and active Cu(I) complexes than PMDETA. It was indeed observed that, in the same solvent, there exists an excellent correlation between the $E_{1/2}$ of Cu(I)X[nitrogen ligand] species and the K_{ATRP} (ATRP equilibrium constant), a parameter used to rank the activity of the catalysts.[4a,8a,f,19s,28]

The first trial (Table 2, entries 6 and 7) with these more active catalysts, however left us dismayed: conversions were quite low, much less than in the case of PMDETA. What was happening? As the reaction

Table 2. Setting of the best conditions for the ARGET-ATRC of **1** in AcOEt.[a]

Entry°	Ligand	CuCl/L-AA/Na_2CO_3 [mol%]	*T*/*t* [°C]/[h]	Conversion[b] [%]	Products[b,c] [%]
1	**A**	1/0/0	35/4	15	15 (58:42)
2	**A**	1/2/0	35/4	50	50 (59:41)
3	**A**	1/2/4	35/4	83	81 (59:41)
4	**A**	1/2/4	55/4	85	85 (60:40)
5	**A**	1/2/4	35/20	96	95 [87][d] (60:40)
6	**B**	1/2/4	35/4	5	5 (59:41)
7	**C**	1/2/4	35/4	13	13 (59:41)
8[e]	**A**	1/2/4	35/4	99	99 [95][d] (83:17)
9[e]	**B**	1/2/4	35/4	100	99 [95][d] (84:16)
10[e]	**C**	1/2/4	35/4	100	99 [94][d] (85:15)

[a] All reactions were carried out under argon: substrate 8 mmol and AcOEt 4 mL.
[b] GC value.
[c] In round brackets are the *cis*/*trans* ratios (GC).
[d] Yields determined on isolated material.
[e] Reaction performed in 4 mL of AcOEt/EtOH 3/1.

mixture did not take any hue, but instead coloured particles were observed, we concluded that the reactivity problem had to be attributed to the insolubility of the new copper complexes in AcOEt. We thought to bypass the problem by adding EtOH as cosolvent. Unbelievably with this trivial adjustment, the reactivity of all the complexes was increased in AcOEt/EtOH 3/1. Not only did we observe total conversions and high yields, but also the diastereomeric ratio increased, reaching the highest values (Table 2, entries 8–10).

These achievements opened the door to a further lowering of the catalyst load (Table 3). The less expensive ligand PMDETA was considered first.

Moreover, since the amount of catalyst to be used began to be really small, we also decided to adopt the more practical reversed protocol for the ATRC (reversed means that the catalyst is added to the reaction system in its higher oxidation state), thus copper was weighed as $CuCl_2$. The percentage of AA was concurrently changed (and the Na_2CO_3 with it) to maintain

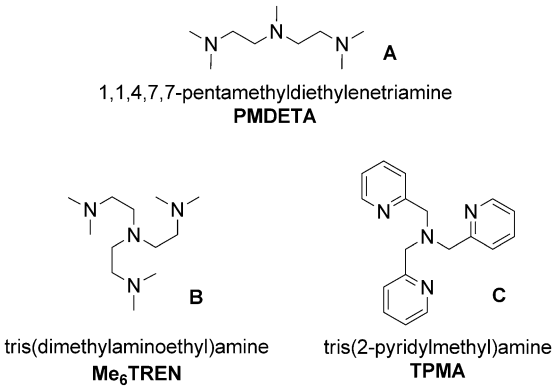


Figure 1. Polydentate nitrogen ligands used in this work.

the same reducing capacity of the reactions reported in Table 2.

Halving the load of $CuCl_2$/PMDETA to 0.5 mol% did not show any performance drop (Table 3, entry 3 and Table 2, entry 8). Under these conditions, the effect of the AcOEt/EtOH ratio on the reaction outcome was very interesting. In neat ethanol the efficiency collapsed, but when the AcOEt/EtOH ratio was brought to 2/2 the catalyst activity was partially recovered (Table 3, entries 1 and 2). In fact, while both conversion and yield were excellent, the diastereomeric ratio was disappointing. A further increase of the AcOEt/EtOH ratio to 3/1 gave an even better result both in terms of conversion and yield, and *cis*/*trans* ratio (Table 3, entry 3). No extra improvement was noted when the AcOEt/EtOH ratio was raised from 3/1 to 3.5/0.5 (Table 3, entry 4). Clearly the redox system is the more reactive, the lower the fraction of protic solvent in the solvent mixture is, and this up to the limit of an amount of EtOH around 12–25%.

Confident of the good results attained, we took a further step forward, and the catalyst load was decreased to 0.1 mol%, but the conversion of **1**, even with the more active complexes, was not complete (Table 3, entries 5–7). Believing that at such low concentrations the *in situ* formation of the complex, between $CuCl_2$ and the nitrogen ligand, did not proceed smoothly, we thought to employ preformed cupric complexes in ethanol. The results were indeed better but not as much as hoped for: only $CuCl_2$/TPMA gave a satisfactory 96% conversion (Table 3, entry 10), although the diastereomeric ratio still remained unsatisfactory.

Efforts to improve the result by rising the temperature were in vain. Counter intuitively, the process efficiency progressively declined when the temperature

Table 3. Setting of the best conditions for the reversed ARGET-ATRC of **1** in AcOEt/EtOH.[a]

Entry°	$CuCl_2$ [mol%]	Ligand [mol]	AcOEt/ EtOH	*T*/*t* [°C]/[h]	Conversion[b] [%]	Products[b,c] [%]
1	0.5	**A** (0.5)	0/4	35/8	63	60 (55:45)
2	0.5	**A** (0.5)	2/2	35/8	100	98 [93][d] (65:35)
3	0.5	**A** (0.5)	3/1	35/8	100	99 [95][d] (84:16)
4	0.5	**A** (0.5)	3.5/0.5	35/8	100	99 [95][d] (84:16)
5	0.1	**A** (0.1)	3/1	35/24	32	30 (57:43)
6	0.1	**B** (0.1)	3/1	35/24	48	45 (57:43)
7	0.1	**C** (0.1)	3/1	35/24	86	84 (60:40)
8[e]	0.1	**A** (0.1)	3/1	35/24	47	44 (58:42)
9[e]	0.1	**B** (0.1)	3/1	35/24	55	52 (58:42)
10[e]	0.1	**C** (0.1)	3/1	35/24	96	91 [85][d] (61:39)
11[e]	0.1	**C** (0.1)	3/1	40/24	91	89 (60:40)
12[e]	0.1	**C** (0.1)	3/1	45/24	91	88 (60:40)
13[e]	0.1	**C** (0.1)	3/1	55/24	82	80 (59:41)
14[e]	0.1	**C** (0.1)	3/1	25/24	100	98 [92][d] (66:34)
15[e]	0.1	**C** (0.1)	3/1	15/24	73	71 (59:41)

[a] All reactions were carried out under argon and with $CuCl_2$ complexes: substrate 8 mmol, solvent 4 mL, AA 2.5 mol% and Na_2CO_3 5.0 mol%.
[b] GC value.
[c] In round brackets are the *cis*/*trans* ratios (GC).
[d] Yields determined on isolated material.
[e] The catalyst system Cu/ligand is preformed.

Table 4. Effect of the AA and Na_2CO_3 percentage on the reversed ARGET-ATRC of **1** in AcOEt/EtOH 3/1.[a]

Entry	Complex [mol%]	AA/Na_2CO_3 [mol%]	w/w %[b]	Conversion[c] [%]	Products[c,d] [%]
1	$CuCl_2$**A**$^{-1}$ (0.5)	2.5/5.0	4.1 (0.013)	100	99 [93] (86:14)
2	$CuCl_2$**A**$^{-1}$ (0.5)	1.5/3.0	2.7 (0.009)	100	99 [95] (85:15)
3	$CuCl_2$/**C** (0.5)	2.5/5.0	4.3 (1.044)	100	99 [93] (84:16)
4	$CuCl_2$/**C** (0.5)	1.5/3.0	2.9 (1.040)	100	99 [96] (85:15)
5	CuCl/**A** (3)	0/0	–	73	73 (59:41)
6	CuCl/**A** (5)	0/0	5.0 (0.032)	98	98 [94] (57:43)

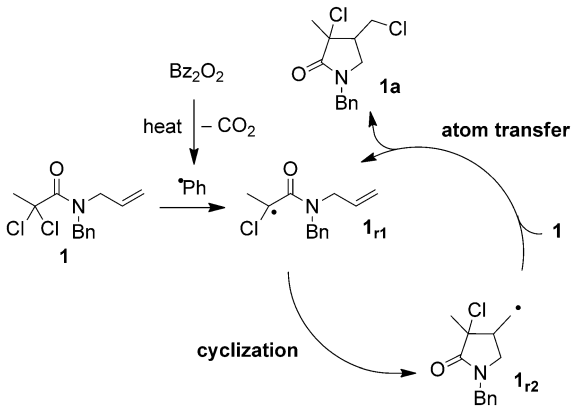
[a] All reactions were carried out, under argon, with preformed complexes: substrate 8 mmol, solvent 4 mL, *T* 35 °C, *t* 8 h.
[b] Catalytic system load in weight % and in parentheses its cost in €.
[c] GC value.
[d] In round brackets are the *cis*/*trans* ratios (GC), and in square brackets the yields determined on isolated material.

was just slightly raised (Table 3, entries 10–13). It seems that at higher temperatures the catalyst somehow suffers from a premature "degradation" or a larger dissociation (more appreciable at such low concentration levels). On the contrary the best result (conversion 100% and yield 92%) was achieved under milder conditions, at 25 °C (Table 3, entry 14), but with an unacceptably low diastereomeric ratio. A further decrease of the reaction temperature substantially deteriorated the performances of the process (Table 3, entry 15).

With the best combination between $CuCl_2$, ligand and solvent ratio (Table 3, entry 3) in hand, we considered the possibility of diminishing the load of AA/Na_2CO_3. Indeed, working with 1.5/3.0 mol% of AA/Na_2CO_3 gave, both with PMDETA and TPMA, results that were indistinguishable from those recorded with the usual load of 2.5/5.0 mol% (Table 4, entries 1–4).

As a comparison, two "normal" ATRCs of **1**, catalysed by an amount of CuCl/PMDETA with the same global reducing capacity of the two previous ARGET systems (Table 4, entries 1-4), were also carried out (Table 4, entries 5 and 6). The results of the comparison unambiguously indicate that the redox catalyst works more efficiently in the reversed ARGET-ATRC mode.

The global catalytic system load was also expressed in [w/w %] (weight of the catalyst/weight of substrate %), an industrially more revealing parameter. The percentages (Table 4, column 4; values in parentheses) are attractive and are even lower than that for



Scheme 6. Metal-free ATRC of **1**.

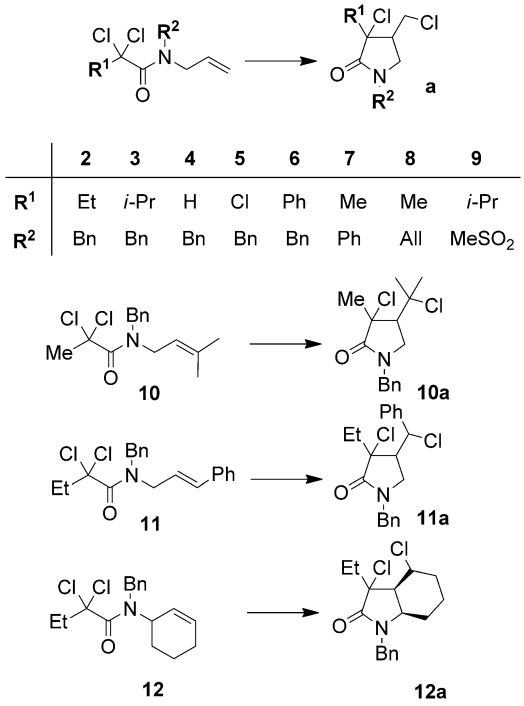
a typical ATRC. Finally cost analysis shows that, efficiency being equal, the redox system, based on $CuCl_2$/PMDETA, is to be preferred, as it is by far the cheapest one.

To exclude any overlapping of the copper-catalysed cyclisation (Scheme 3a) with the hypothetical free radical chain process, outlined in Scheme 6, we tried to trigger the ATRC of **1** with a typical radical initiator. Thus a solution of the amide **1** (8 mmol) in AcOEt/EtOH 3/1 (4 mL) was heated at 90 °C in the presence of Bz_2O_2 (2–4 mol%).

The absence of **1a** and of any cyclisation product (conversion was virtually zero) means that the phenyl radical (BDE_{Ph-Cl} is 95 kcal mol^{-1} and $k_{25°C}$ for the extraction of Cl from CCl_4 is 6.0×10^6 M^{-1} s^{-1})[29] and the less reactive primary radical $\mathbf{1_{r2}}$ (BDE stays between BDE_{Bn-Cl} 74 kcal mol^{-1} and BDE_{Me-Cl} 83 kcal mol^{-1}, while $k_{25°C}$ for the extraction of Cl from CCl_4 by RCH_2• is 7.2×10^3 M^{-1} s^{-1})[29] were unable to displace the α-Cl from **1**. Besides, even if some initiation could occur under these conditions, the complete failure of the metal-free ATRC points to the same deduction, i.e., the primary radical $\mathbf{1_{r2}}$ is unable to sustain the propagation step. We can thus confidently exclude that **1a** can originate through a classic chain process, during the metal-catalysed ATRC.

To explore the scope of the method, we prepared a variety of amides with different cyclisation auxiliaries, allyl moieties or groups bound to the CCl_2 unit (Scheme 7). Tests were carried out taking $CuCl_2$/PMDETA as the reference redox complex, and turning to $CuCl_2$/TPMA, only when a highly active catalyst was really required. A selection of the best results obtained, under the cheapest conditions, is reported in Table 5.

The new method appears robust and reliable, always providing excellent yields (except with **6**, see below), and the highest possible diastereomeric ratios yet reported,[18a] the preferred isomer being always, as expected, the thermodynamic one. Generally this is the *cis*-adduct, but in the case of **4a**, where only two



	2	3	4	5	6	7	8	9
R^1	Et	*i*-Pr	H	Cl	Ph	Me	Me	*i*-Pr
R^2	Bn	Bn	Bn	Bn	Bn	Ph	All	$MeSO_2$

Scheme 7. Substrates and products used to test the scope of the method.

groups are bound to the C-3–C-4 bond, the opposite is true. The weak selectivity observed for **10a**, is instead typical of substrates that carry bulky groups at C-4, which, for steric reasons, have difficulty to distinguish between geminal methyl and Cl substituents at C-3.[19b,o]

The excellent outcomes with dichloroacetamide **4** and trichloroacetamide **5** deserve comment. In our previous study with CuCl/PMDETA-AA-Na_2CO_3 at a load ranging between 2/2.5/2.75 and 4/5/5.5 mol%, these compounds suffered partial hydrodehalogenation and incomplete conversion, respectively.[18a] Both phenomena have a common cause: the catalyst is too reactive and/or its concentration is too high.

In the case of acetamide **4** the rotation around the amide bond in the radical **4B** (Scheme 3a) is not as fast as in other radicals of the series. Hence the cyclisation becomes relatively slow and the electrophilic *N*-allylcarbamoylmethyl radical **B** could be reduced by the catalytic system. Amides, like **5**, and their cyclisation products are on the other hand quite reactive,[19c] and are likely to undergo parasitic reactions that bring about a premature catalyst depletion.

As reported in the ATRP field, all these side reactions are second order and can be controlled through a drastic reduction of the concentration of the catalyst active form.[8a,l] In our new catalytic system this condition is fully accomplished: $CuCl_2$ is the starting redox component, its concentration is low (0.5 mol%) and the AA is much less soluble in AcOEt/EtOH 3/1 than

Table 5. Reversed ARGET-ATRC of amides **2**–**12**.[a]

Entry	Substrate/ Method[b]	AA/base [mol%]	*t* [h]	Conversion[c] [%]	Products[d,e] [%]
1	**2**/I	2.5/5.0	8	100	94 (87:13)
2	**3**/I	2.5/5.0	8	100	93 (99:1)
3	**4**/II	2.5/5.0	8	100	95 (26:74)
4	**5**/I	2.5/5.0	8	100	93
5	**7**/I	2.5/5.0	8	100	96 (87:13)
6	**8**/I	1.5/3.0	8	100	94 (84:16)
7	**9**/I	1.5/3.0	8	100	96 (96:4)
8	**10**/I	2.5/5.0	8	100	95 (58:42)
9	**11**/II	2.5/5.0	8	100	96 [97(84/16):3(100/0)]
10	**12**/II	2.5/5.0	8	100	96 [82(59/41):18(76/24)]

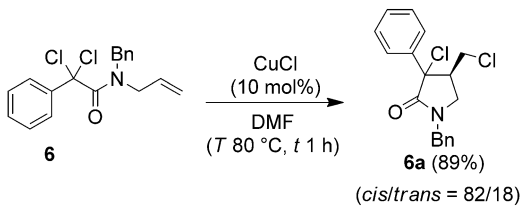
[a] All reactions were carried out, under argon: substrate 8 mmol, preformed $CuCl_2$/L 0.5 mol%, AcOEt/EtOH 3/1 4 mL, *T* 35 °C, *t* 8 h.
[b] Method I, L = PMDETA; method II, L = TPMA.
[c] GC value.
[d] Yields determined on isolated material.
[e] In brackets are the *cis*/*trans* ratios (GC or ^{1}H NMR).

in neat ethanol. The ensuing drop of the rate of the parasitic phenomena improved selectivity and efficiency of **4** and **5** cycloisomerisations.

On the contrary, ATRC of substrate **6**, notwithstanding our efforts, never gave acceptable conversions. Moreover, the selectivity was always disappointing. It was as if the substrate **6** and its product **6a** were incompatible with the catalytic system. ATRP has already come across situations of this type.[14d,30] When this occurs, less active systems have to be used. Indeed, when **6** was reacted with CuCl under ligand free-like conditions,[19c] the cyclisation proceeded smoothly (Scheme 8), yielding a result analogous to the one we obtained previously with the less reducing complex CuCl/TMEDA.[19t]

Preformed cupric complexes with variable shelf life (from a few hours to 1 month) were used in our tests, without consequences on the reaction performances. This well matches with the data reported in Table 6, which show that for both complexes the shelf life has no effect on the redox properties of the catalyst; variation of $E_{1/2}$ with time is in fact negligible.

From a thermodynamic point of view, the ATRP equilibrium constant (K_{ATRP}) was conveniently split into four elementary thermodynamic contributions (Scheme 9): C–X bond homolysis (K_{BH}), oxidation of



Scheme 8. Ligand free-like ATRC of amide **6**.

Table 6. $E_{1/2}$ measured for $CuCl_2$ complexes in different mixture of AcOEt/EtOH.[a]

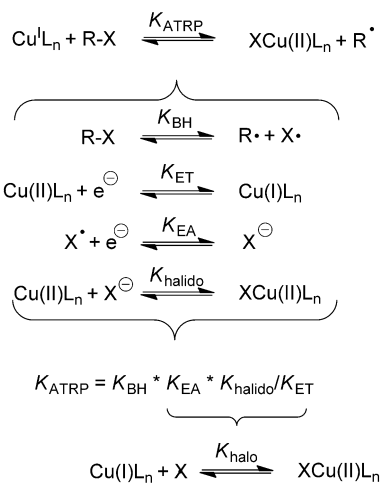
Entry	Ligand	AcOEt/ EtOH	$E_{1/2}$ (1 d)[b] [V]	$E_{1/2}$ (10 d)[b] [V]	$E_{1/2}$ (20 d)[b] [V]
1	PMDETA	0/4	−0.082	−0.086	−0.078
2	PMDETA	1/3	−0.110	−0.106	−0.110
3	PMDETA	2/2	−0.130	−0.141	−0.124
4	PMDETA	3/1	−0.169	−0.176	−0.158
5	TPMA	0/4	−0.226	−0.226	−0.228
6	TPMA	1/3	−0.245	−0.256	−0.258
7	TPMA	2/2	−0.283	−0.286	−0.290
8	TPMA	3/1	−0.313	−0.308	−0.318

[a] All measurements were carried out, under argon, in the presence of 0.1 M $(C_2H_5)_4NBF_4$, $[CuCl_2] = [ligand] = 0.01$ M, *T* 35 °C, potentials are referred to the ferrocenium/ferrocene.
[b] In parentheses the time after which the measurement was taken.

the metal complex (or equilibrium of electron transfer, $1/K_{ET}$), electron affinity of X atom (K_{EA}) and association of the halide ion to the catalyst in its higher oxidation state (or halidophilicity, K_{halido}).[8a,e,f,i,l]

Since ATRP and ATRC are inherently similar processes, considerations from the ATRP thermodynamic model of Scheme 9 can be useful to rationalise the solvent effect that we observed on the reaction outcome (Table 3, entries 1–4).

Now it is well known that solvent affects at the same time K_{ET}, K_{EA} and K_{halido},[8f] which altogether define the halogenophilicity (K_{halo}) of the catalyst, i.e., the process of formation of the Cu(II)–X bond (Scheme 9).[8a,e] We attribute tentatively the observed dependence of reactivity on solvent composition



Scheme 9. Factorisation of the ATRP equilibrium in 4 elementary contributions.

(Table 3, entries 1–4) to its strong action on K_{halido}.[8f] In fact, since halidophilicity is low in protic solvents, it is clear that increasing the percentage of EtOH in the solvent mixture triggers a progressive K_{halido} drop (particularly marked as the halide at issue is Cl^-). As a consequence the ratio K_{halido}/K_{ET} should decrease, and with it the K_{halo} (side by side with K_{ATRP}) too, notwithstanding the predictable increase of K_{EA}.[8f]

Interestingly, the standard potential of the ClCu(II)L/ClCu(I)L couple has shown a significant dependence of the solvent composition. In order to show correctly the solvent effect on $E_{1/2}$, we used the ferrocenium/ferrocene couple as reference system, instead of the conventional aqueous saturated calomel electrode, which would introduce an inter-solvent potential that varies with the composition of the solvent. As can be seen in Table 6, $E_{1/2}$ becomes more negative upon increasing the percentage of AcOEt (a moderately polar but low coordinating solvent) in the reaction mixture. The measured potentials, however, have to be related to the $K^{app}{}_{halido}/K_{ET}$ parameter ($K^{app}{}_{halido}$ means apparent halidophilicity), since they also take into account the Cu(I)L halidophilicity.[8f] In any case $K^{app}{}_{halido}/K_{ET}$ also correlates well to K_{ATRP}.[8f] For similar solvent variations (e.g., from ethanol to acetone or propylene carbonate)[8f] the shift of $E_{1/2}$ to more negative potentials raises $K^{app}{}_{halido}/K_{ET}$, and with it the K_{ATRP}, notwithstanding the decrease of K_{EA}.[8f] Thus, as envisaged, the drop of the protic features of the solvent mixture improves the process performance, in terms of both conversion and selectivity (Table 3), because the catalyst, becoming more reducing, increases the reaction rate of the starting material, as well as the rate of interconversion of the two diastereomeric products.

Conclusions

We have described a highly efficient ARGET-ATRC for the cycloisomerisation of *N*-allyl-*N*-substituted-α-polychloroamides to γ-lactams. The catalytic system is based on the combination of copper complexes (as redox catalysts), ascorbic acid (as safe regenerating agent) and Na_2CO_3 (as acidity quencher). Thanks to the individualisation of a more appropriate solvent (AcOEt/EtOH 3/1), the efficacy of this catalytic system was boosted, allowing a drop of the metal load to 0.5 mol%.

For the first time the protocol, to which we adhere, was of the reversed type, since the catalyst was more conveniently added to the reaction mixture as preformed cupric complex (the inactive form of the redox pair): $CuCl_2$/PMDETA or $CuCl_2$/TPMA.

The new process showed to be robust and worked reliably with all the substrates we tested, polychloroacetamides included, allowing the highest stereoselectivities compatible with the thermodynamic control.

The only severe exception was the *N*-allyl-*N*-benzyl-2,2-dichloro-2-phenylacetamide. This arose from the incompatibility of this highly reactive substrate with our catalytic system.

Mild reaction conditions, low load of catalyst and additives, handling of stable cupric complexes, use of "natural" solvents and high substrate concentrations (2 mmol mL^{-1} of solvent) make this process really attractive for scale-up or large-scale preparations.

Experimental Section

General Remarks

Reagents and solvents were standard grade commercial products and used without further purification. For the catalytic systems we employed: CuCl Fluka (≥97%), $CuCl_2$ Riedel-de Haën (≥97%), PMDETA Acros (+99%), TPMA Aldrich (98%), Me_6TREN Aldrich (≥88%), AA Sigma (> 99.5%) and Na_2CO_3 Carlo Erba (≥99.5%). Silica gel for the flash chromatography was the Silica Gel 60 Merck (0.040–0.063 mm). The screw-capped Schlenck tube, fitted with a rotaflow valve, had a capacity of 25 mL and an external diameter of 2.5 cm. An oval stirring bar ($l = 1$ cm, $d = 0.5$ cm) was used. The 2,2-dichloroacyl chlorides (apart from dichloroacetyl chloride and trichloroacetyl chloride, which were purchased) were prepared, on our mini-pilot plant, by chlorination of acyl chlorides with Cl_2 in the presence of tetrabutylammonium chloride.[31] The starting amides **1**–**8** and **10**--**12** were obtained through standard aminodechlorination of acyl chlorides with allylic amines (all prepared by *N*-alkylation of amines, adapting Shipman's method[32]). The sulphonamide **9** was assembled by acylation of the lithium salt of *N*-allylmethanesulphonamide.[19a] All the amides were thoroughly purified! Products **1a**,[19c] **3a**,[19t] **4a**,[19c] **5a**,[19c] **6a**,[19t] **8a**,[19c] **10a**,[19] **11a**[19d] and **12a**[19d] are known compounds, which were all obtained through copper-catalysed

ATRC reactions. NMR spectra were recorded on a "Varian 500 MHz" spectrometer. The relative configurations were determined by NOESY experiments. IR and mass spectra were recorded on a Perkin-Elmer 1600 Series FT-IR and HP 5890 GC - HP 5989 AMS Engine, respectively. Elemental analyses were performed on the EA 1110 Carlo Erba. Cyclic voltammetric experiments were carried out in a three-electrode cell with a glassy carbon disc ($d=3$ mm, Bioanalytical Instruments) working electrode, a Pt wire counter-electrode and an $Ag|AgI|I^-$ reference electrode. The potential of the reference electrode was always calibrated at the end of the experiment *versus* the ferrocenium/ferrocene (Fc^+/Fc) couple. All potentials in the paper are reported *versus* Fc^+/Fc.

Typical Procedure: Cyclization of *N*-Allyl-*N*-benzyl-2,2-dichlorobutanamide (2)

In an oven-dried Schlenk tube (previously rinsed with a solution of NH_3 and plenty of water in sequence) were weighed ascorbic acid (0.2 mmol, 35.2 mg), Na_2CO_3 (0.4 mmol, 42.4 mg) and amide **2** (8 mmol, 2.290 g). After 3 cycles of vacuum/argon (globally 10 min, approximately 8.50 min for vacuum and 1.50 min under argon) AcOEt (3 mL) and – when the substrate was fully solubilized – the preformed solution of $CuCl_2$/PMDETA 0.04 M in absolute ethanol (1 mL) were added under argon. The reaction mixture was promptly immersed in a water bath at 35 °C and stirred (700 rpm). After 8 h the Schlenk tube was opened (a little pressure due to CO_2 released during the reaction) and the reaction mixture was diluted with water (8 mL), acidified with HCl 10% w/v and extracted with CH_2Cl_2 (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 **2a** as a colourless oil; yield: 2.156 g [94%, an inseparable mixture of *cis*/*trans* diastereomers (87:13, ^{1}H NMR]; anal. found: C 58.57, H 6.01, N 4.87; $C_{14}H_{17}Cl_2NO$ requires: C 58.75, H 5.99, N 4.89; R_f (70% PE/Et_2O) 0.65.

1-Benzyl-3-chloro-4-(chloromethyl)-3-ethylpyrrolidin-2-one **(2a):** IR (liquid film): $\nu_{max}=1710$ cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, *cis*): $\delta=1.06$ (t, $J=7.9$ Hz, 3H, CH_3CH_2), 2.21 (2H, m, CH_2CH_3), 2.72 (1H, m, H-4), 3.05 (1H, dd, $J=$ 9.0, 10.0 Hz, H-5), 3.39 (1H, dd, $J=7.1$, 10.0 Hz, H-5), 3.63 (1H, dd, $J=9.7$, 11.1 Hz, C*H*HCl), 3.79 (1H, dd, $J=4.9$, 11.1 Hz, C*H*HCl), 4.41 and 4.49 (2H, AB system, $J=$ 14.6 Hz, CH_2Ph), 7.24–7.37 (5H, m, ArH); ^{13}C NMR (125 MHz, $CDCl_3$, *cis*): $\delta=9.5$, 30.6, 42.6, 43.0, 46.9, 47.6, 72.9, 127.95, 128.9, 135.45, 170.7; ^{1}H NMR (500 MHz, $CDCl_3$, *trans*): $\delta=1.16$ (t, $J=7.9$ Hz, 3H, CH_3CH_2), 1.77 and 2.12 (1H each, m, CH_2CH_3), 2.88 (1H, m, H-4), 3.15 (1H, dd, $J=4.9$ and 10.4 Hz, H-5), 3.34 (1H, t, $J=10.8$ Hz, C*H*HCl), 3.54 (1H, dd, $J=6.4$, 10.4 Hz, H-5), 3.68 (1H, dd, $J=4.0$, 10.8 Hz, C*H*HCl), 4.44 and 4.59 (AB system $J=$ 14.6 Hz, 2H, CH_2Ph), 7.24–7.37 (5H, m, ArH); ^{13}C NMR (125 MHz, $CDCl_3$, *trans*): $\delta=8.6$, 26.6, 41.9, 47.0, 47.1, 47.65, 72.6, 128.0, 128.9, 135.5, 170.5; MS (ESI-ion trap): $m/z=286$ $[(M+H)^+]$, 308 $[(M+Na)^+]$.

Cyclization of *N*-Allyl-*N*-phenyl-2,2-dichloropropanamide (7)

Following the same procedure as described for **2**, **7** (8 mmol, 2.066 g) gave, after flash-chromatography on silica gel, using a PE/Et_2O gradient (from 100/0 a 0/100), the lactam **7a** as a colourless oil; yield: 1.980 g [96%, a mixture of *cis*/*trans* diastereomers (87:13, ^{1}H NMR)]; anal. found: C 55.74, H 5.07, N 5.41; $C_{12}H_{13}Cl_2NO$ requires: C 55.83, H 5.08, N, 5.43; R_f (70% PE/Et_2O) 0.60 *cis*-**7a** and 0.46 *trans*-**7a**.

3-Chloro-4-(chloromethyl)-3-methyl-1-phenylpyrrolidin-2-one **(7a):** IR (liquid film): $\nu_{max}=1695$ cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, *cis*): $\delta=1.87$ (3H, s, CH_3), 2.73 (1H, m, H-4), 3.68 (1H, dd, $J=9.5$, 10.0 Hz, H-5); 3.80 (1H, dd, $J=$ 9.3, 11.3 Hz, CHCl), 3.91 (1H, dd, $J=5.2$, 11.3, CHCl); 4.00 (1H, dd, $J=7.0$, 10.0 Hz, H-5), 7.21 (1H, m, ArH), 7.40 (2H, m, ArH), 7.64 (2H, m, ArH); ^{13}H NMR (125 MHz, $CDCl_3$, *cis*): $\delta=25.0$, 42.0, 47.1, 49.4, 69.8, 120.1, 125.4, 129.0, 138.5, 169.7; ^{1}H NMR (500 MHz, $CDCl_3$, *trans*): $\delta=$ 1.73 (3H, s, CH_3), 3.08 (1H, m, H-4), 3.54 (1H, dd, $J=9.7$, 11.2 Hz, C*H*HCl); 3.74 (1H, dd, $J=4.8$, 10.3 Hz, H-5), 3.84 (1H, dd, $J=4.5$, 11.2, C*H*HCl); 4.17 (1H, dd, $J=7.0$, 10.3 Hz, H-5), 7.21 (1H, m, ArH), 7.40 (m, 2H, ArH), 7.64 (2H, m, ArH); ^{13}C NMR (125 MHz, $CDCl_3$, *trans*): $\delta=21.5$, 42.2, 47.7, 48.9, 68.7, 120.1, 125.5, 129.0, 138.5, 169.8; MS (ESI-ion trap): $m/z=244$ $[M\text{-}HCl+Na]^+$, 280 $[M+Na]^+$.

Cyclization of *N*-Allyl-*N*-methylsulphonyl-3-methyl-2,2-dichlorobutanamide (9)

Following the same procedure as described for **2**, **9** (8 mmol, 2.306 g) gave, after flash-chromatography on silica gel, using a PE/Et_2O gradient (from 100/0 a 0/100), the lactam **9a** as a white solid; yield: 2.218 g [96%, a mixture of *cis*/*trans* diastereomers (96:4, ^{1}H NMR)]; anal. found: C 37.70, H 5.23, N 4.90, S 11.17; $C_9H_{15}Cl_2NO_3S$ requires: C 37.51, H 5.25, N 4.86, S 11.13; R_f (70% PE/Et_2O) 0.25.

3-Chloro-4-(chloromethyl)-3-isopropyl-1-(methylsulphonyl)pyrrolidin-2-one **(9a):** mp 57–8 °C; IR (nujol): $\nu_{max}=$ 1745 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, *cis*): $\delta=1.11$ and 1.19 [3H each, d, $J=6.7$ Hz, $(CH_3)_2CH$], 2.50 [1H, septet, $J=6.7$ Hz, $(CH_3)_2CH$], 2.91 (1H, m, H-4), 3.29 (3H, s, SO_2CH_3), 3.53 (1H, dd, $J=8.7$, 10.1, H-5), 3.69 (1H, dd, $J=$ 9.0, 11.2, CH*H*Cl), 3.84 (1H, dd, $J=4.1$, 11.2 Hz, C*H*HCl), 4.21 (1H, dd, $J=7.3$, 10.1 Hz, H-5); ^{13}C NMR (125 MHz, $CDCl_3$, *cis*): $\delta=17.3$, 18.2, 34.7, 39.8, 40.7, 42.9, 47.4, 76.1, 170.1; ^{1}H NMR (500 MHz, $CDCl_3$, *trans*): $\delta=1.13$ and 1.35 [3H each, d, $J=6.3$ Hz, $(CH_3)_2CH$], 2.25 [sept, 1H, $J=$ 6.3 Hz, $(CH_3)_2CH$], 2.93 (1H, overlapped to the signal at 2.91 relative to H-4 *trans*, H-4), 3.53 (1H, overlapped overlapped to the signal at 3.53 relative to H-4 *trans*, CH*H*Cl), 3.78 (1H, dd, $J=3.5$, 11.5 Hz, C*H*HCl), 3.95 (1H, dd, $J=$ 2.0, 10.5 Hz, H-5), 4.09 (1H, dd, $J=6.0$, 10.5 Hz, H-5); ^{13}C NMR (*trans*): sample concentration too low; MS (EI, 70 eV): $m/z=245$ [42, $(M-42)^+$], 196 (100), 79 (18).

Cyclization of *N*-Allyl-*N*-benzyl-2,2-dichloro-2-phenylacetamide (6)

CuCl (50 mg, 0.5 mmol) and 2,2-dichloroamide **6** (1.672 g, 5 mmol) were weighed in a Schlenk tube fitted with a piercable septum (blocked by a screw cap) and a magnetic stirring bar. DMF (2.5 mL) was then added under argon. The mix-

ture was stirred at 80 °C and after 1 h was diluted with H_2O (30 mL), acidified with HCl 10% w/v, and extracted with CH_2Cl_2 (4×5 mL). The combined organic layers were concentrated and the crude product was purified by flash chromatography on silica gel, eluting with PE/Et_2O gradient. This gave the 2-pyrrolidinone **6a** as a red oil; yield: 1.486 g red oil [89%, inseparable mixture of *cis*/*trans* diastereomers (82:18, ^{1}H NMR)]; anal. found: C 64.74, H 5.13, N 4.20; $C_{18}H_{17}Cl_2NO$ requires: C 64.68, H 5.13, N 4.19; R_f (70% PE/Et_2O) 0.40.

***1-Benzyl-3-chloro-4-(chloromethyl)-3-phenylpyrrolidin-2-one* (6a):** IR (liquid film): $\nu_{max=}$1709 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, *cis*): δ=2.98 (1H, m, H-4), 3.25 (1H, dd, J=8.9, 10.1 Hz, H-5), 3.56 (1H, dd, J=6.9, 10.1 Hz, H-5), 3.75 (2H, m, CH_2Cl), 4.50 and 4.72 (2H, AB system, J 14.0 Hz, CH_2Ph), 7.29–7.44 (8H, m, ArH), 7.54 (2H, m, ArH); ^{13}C NMR (125 MHz, $CDCl_3$, *cis*): δ=41.7, 47.4, 47.7, 49.1, 73.7, 127.2, 128.3, 128.65, 129.0, 135.4, 137.1, 170.6; ^{1}H NMR (500 MHz, $CDCl_3$, *trans*): δ=2.78 (1H, t, J=10.6 Hz, CHCl), 3.12–3.22 (3H, overlapped signals, H-4 and H-5, CHCl), 3.65 (1H, dd, J=6.0, 9.8 Hz, H-5), 4.62 and 4.73 (2H, AB system, J=14.0 Hz, CH_2Ph); 7.29–7.44 (10H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$, *trans*): δ=42.9, 47.1, 47.6, 50.4, 72.6, 128.1, 128.6, 128.8, 128.85, 129.05, 134.8, 135.3, 170.2; MS (EI, 70 eV): m/z=298 [40, $(M-35)^+$], 297 (38), 262 (7), 248 (20), 242 (9), 151 (46), 115 (47), 91 (100%).

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