Radical Cyclization of Trichloroacetamides: Synthesis of Lactams
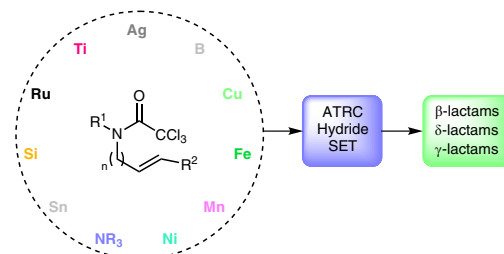
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Abstract Trichloroacetamides can act as radical precursors to synthesize nitrogen-containing heterocycles in a variety of processes, mainly involving atom transfer radical cyclizations (ATRC), mediated by Cu(I) or Ru(II) catalysts, and the hydride reductive method, employing either Bu_3SnH or $(Me_3Si)_3SiH$, or recently $NaBH_3CN$. Additionally, amine-mediated single-electron transfer cyclizations, as well as radical processes promoted by Ni, Fe, Mn, Ti, and Ag, have been developed.

Key words radical reactions, lactams, cyclization, nitrogen heterocycles, hydrides, atom transfer, reduction, haloacetamides

1 Introduction

Radical cyclization reactions comprise three basic steps: selective radical generation, radical cyclization, and after the formation of one or more carbon–carbon bonds, conversion of the new radical into the final stable product (Figure 1).
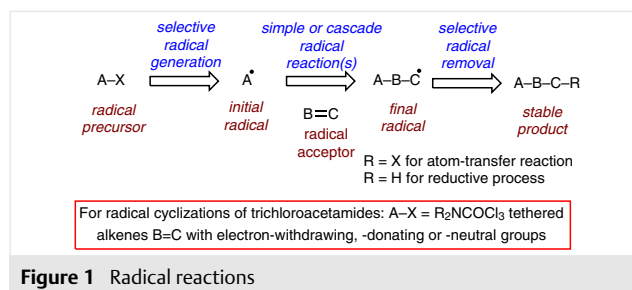

Figure 1 Radical reactions

Trichloroacetamides have been used since the 1980s for the synthesis of nitrogen-containing heterocycles such as γ-lactams, as well as β- and δ-lactams, in a variety of radical processes (e.g., atom transfer and hydride transfer). The usefulness of trichloroacetamides as radical precursors relies on the generation of an electrophilic carboradical. Indeed, the two chlorine atoms and carbamoyl moiety act as an electron-withdrawing group, which makes the dichloromethylcarbamoyl radical able to react with any type of alkene as a radical acceptor (Figure 2). In non-reductive conditions, in addition to the formation of the corresponding heterocycle, the process allows the introduction of chlorine atom(s), which can be further functionalized.

This review is focused on the utilization of trichloroacetamides in the synthesis of nitrogen-containing compounds via radical intermediates. The different ring-closing methods have been grouped according to whether the radical process involves a transition-metal-mediated atom

Figure 2 The electrophilic character of the dichloromethylcarbamoyl radical allows an ambiphilic reactivity
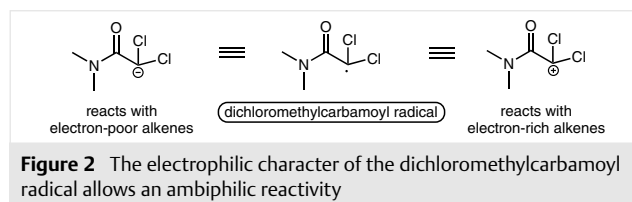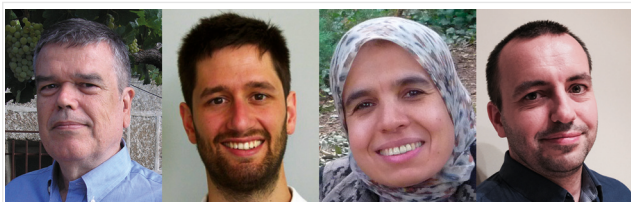
Josep Bonjoch (left) was born in Barcelona (Catalonia, Spain) in 1952. He received his Ph.D. (1979) under the supervision of Professor Joan Bosch at the University of Barcelona, Faculty of Chemistry. He then moved to the Faculty of Pharmacy at the same university, where he became Full Professor of Organic Chemistry in 1992. His main research involves the synthesis of complex nitrogen-containing natural products, and the concomitant development of new synthetic methodology. The main methodological areas in which his group is involved are organocatalysis and radical chemistry. He has described for the first time the total synthesis of twenty natural products, including indole alkaloids (melinonine, echitamidine *inter alia*), some aeruginosin-type peptides (aeruginosin 298-A), terpenes (nakamurol, xylarenal A, anominine), and phlegmarine alkaloids (cermizine B, serratezomine E). He has published more than 150 papers and supervised 30 Ph.D. theses.

Guilhem Coussanes (second left) was born in Sète, France, in 1989. After receiving his master's degree (2013) in biomolecular chemistry and his engineering degree (2013) in organic chemistry from the National School of Chemistry of Montpellier, he joined the research group of Professor Bonjoch at the Faculty of Pharmacy of the University of Barcelona, where he is completing his Ph.D. working on the total synthesis of calyciphylline A-type alkaloids.

Faïza Diaba (second right) studied chemistry at the University of Constantine, Algeria, and obtained her Ph.D. with Dr. Micheline Grignon-Dubois at Bordeaux I University, France. She then moved to the University of Barcelona to take up a postdoctoral position with Professor Josep Bonjoch and pursued her scientific career as a Lecturer until 2009 when she was promoted to Associate Professor. Her research interests are focused on developing new synthetic methodologies for the synthesis of nitrogen-containing compounds based on radical processes.

Xavier Vila (right) was born in Hostalric, Spain, in 1976. He graduated in pharmacy in 1999 and received his Ph.D. in 2004 from the University of Barcelona, where he investigated the total synthesis of natural products using radical reactions under the supervision of Professors Josefina Quirante and Josep Bonjoch. After a postdoctoral stay at École Polytechnique (Palaiseau, France) with Professor Samir Z. Zard, working on new radical methodologies using xanthates, he joined the pharmaceutical company Uriach, where he worked as a process chemist, and since 2013 as a project manager.

transfer[2] or a reductive radical cyclization,[3] and the reagents required in each case. A section about nickel-promoted cyclizations and single-electron transfer (SET) processes[4] has also been included.[5]

The trichloroacetamides used as starting materials in these processes are easily synthesized from the corresponding amines by treatment with trichloroacetyl chloride in the presence of triethylamine or pyridine in dichloromethane at 0 °C.[6] They can also be obtained by an Overman rearrangement of trichloroacetimidates obtained by condensation between an allylic alcohol and a trichloroacetonitrile.[7]

2   Atom Transfer Radical Cyclizations (ATRC)

An atom transfer radical reaction, also known as the Kharasch reaction, consists of a metal-catalyzed radical addition of a carbon–halogen bond to an alkene.

2.1   Copper-Mediated Reactions

The Stauffer Chemical Company[8] was the first to report a copper-mediated ATRC of trichloroacetamides, e.g., **1a** to afford the potential herbicide γ-lactam **2a** (Scheme 1). The reaction was carried out in toluene at reflux using Cu_2O:pyridine.
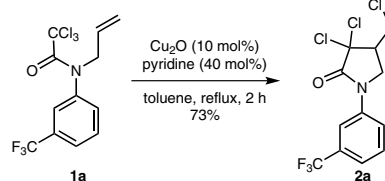
Scheme 1 First example of the radical cyclization of a trichloroacetamide

2.1.1   CuCl

The first use of CuCl to promote a chlorine transfer radical cyclization in the trichloroacetamide field was described in 1984 by Itoh for the synthesis of γ-lactams **2** by cyclization of *N*-allyltrichloroacetamides **1**, as shown in
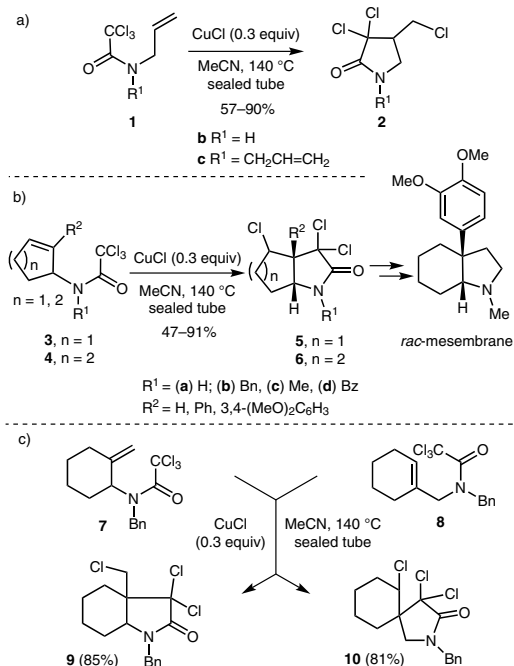
**Scheme 2** Synthesis of γ-lactams and bicyclic lactams

Scheme 2 (a).[6] The process required a sub-stoichiometric amount of the catalyst and high temperatures (acetonitrile in a sealed tube). This method was extended to the synthesis of bicyclic lactams, starting from trichloroacetamides **3** and **4**[9] to afford *cis*-octahydrocyclopenta[*b*]pyrroles **5** and *cis*-octahydroindoles **6**, embedding the bicyclic core of mesembrine alkaloids (Scheme 2, b). Moreover, from trichloroacetamides **7** and **8**, bicyclic lactams **9** and **10** were synthesized (Scheme 2, c).

In 1987, Yamazaki applied the same reaction conditions to *N*-trichloroacetyltetrahydroisoquinoline **11**. Through a 6-*exo* radical cyclization, benzo[*a*]quinolizine **12** (Scheme 3), the azatricyclic fragment of emetine alkaloids, was obtained in an excellent yield.[10]
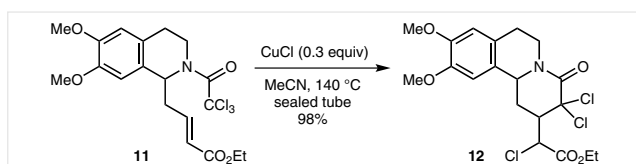
Scheme 3 Synthesis of a benzo[*a*]quinolizine

The same reaction conditions were employed to synthesize the pyrrolizidine alkaloids, pseudoheliotridane and trachelantamidine, starting from trichloroacetamide **13** derived from L-proline via the indolizidine **14** (Scheme 4).[11]
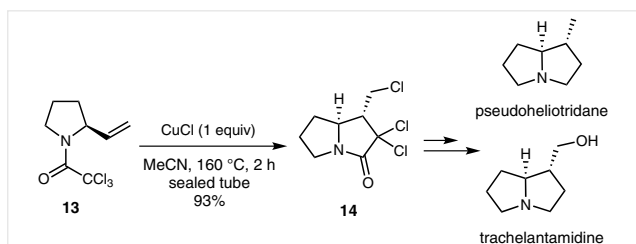

Scheme 4 Synthesis of pyrrolizidine alkaloids

In 2010, Ghelfi optimized the reaction conditions of 'ligand-free-like' ATRC (**1d** → **2d**) by changing the solvent to DMF, which acts as a ligand. This allowed a reduction of the temperature to 60 °C and the catalyst loading to 10 mol% (Scheme 5).[12] In a similar process, the *N*-methylsulfonyl compound **1e** led to **2e** when using acetonitrile as the solvent, and after warming in DMF elimination of HCl afforded **15** (Scheme 5).[13] The process can be run stepwise or sequentially, but the stepwise process was preferred due to cleaner reactions.

2.1.2 CuCl and Bidentate Ligands

Early on, Itoh discovered that CuCl employed with bidentate amine ligands such as bipyridine (bpy) allowed the radical reactions to take place at lower temperatures
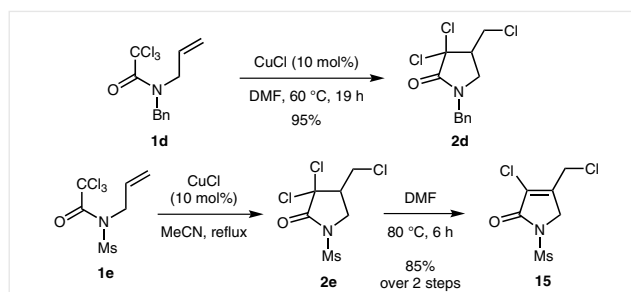

Scheme 5 A sequential ATRC/elimination process

and in a shorter time.[14] The cyclization does not occur if there is a free NH group in the substrate, as it reacts with the Cu catalyst to form an inactive Cu–amide species. As shown in Scheme 6, *cis*- and *trans*-β,γ-dialkyl γ-lactams **17** were stereoselectively prepared from *N*-substituted *N*-allyl-trichloroacetamides **16**, using CuCl:bpy in dichloromethane. The diastereoselection depended on the *N*-substituent and the temperature. When Z = Bn, the *trans* diastereomer **17a** was obtained in a ratio from 95:5 at –15 °C, whereas with an EWG (Z = Ts, Cbz, Boc) at the nitrogen atom, the *cis* isomers **17b** were obtained in a ratio from 20:80 to 10:90 at –70 °C or –15 °C. The lower the temperature, the more diastereoselective the reaction.
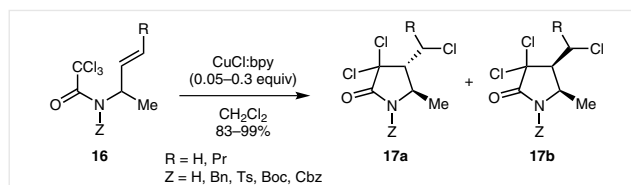

Scheme 6 Low-temperature process in *N*-substituted amides

The CuCl:bpy system was used to synthesize *cis*-3a-aryl-octahydroindole **19** from trichloroacetamide **18**,[15] a useful compound for the synthesis of mesembrane and crinane alkaloids (Scheme 7). Nagashima postulated that the introduction of an EWG at the *N*-allyltrichloroacetamide facilitates the cyclization by lowering the LUMO of the trichloroacetyl moiety, therefore favoring the abstraction of a Cl by the Cu(I) complex via electron transfer. Moreover, for relatively large acyl substituents (e.g., CCl₃), the barrier for N–(CO) amide bond rotation is moderate, enabling an easier cyclization process from the advantageous *E*-rotamer.[15,16]

In 1999, Nagashima's group introduced a procedure for the α-functionalization of α,α,γ-trichlorinated γ-lactams obtained by a CuCl:bpy-mediated cyclization of *N*-allyltrichloroacetamides.[17] The reaction can be stepwise, the formation of the γ-lactam followed by the reaction with an olefin, or sequential, as the γ-lactam bearing two chlorine atoms at the α-position of the carbonyl group is less reactive than the trichlorinated starting material. As depicted in Scheme 8, the reaction of α,α,γ-trichlorinated γ-lactams **2d,f** with allyltrimethylsilane provided **20**, which after

Scheme 7 Synthesis of *cis*-3a-aryloctahydroindoles
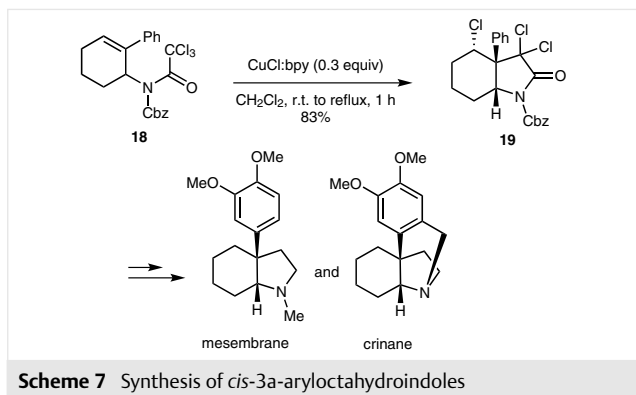
treatment with silica gel gave α-alkylated γ-lactam **21** as an epimeric mixture. *N*-Benzyl compounds needed a higher amount of catalyst to afford comparable yields, as they are less reactive than *N*-tosyl compounds (*vide supra*). In a one-pot procedure, trichloroacetamide **1f** was treated with allyltrimethylsilane and heated in dichloroethane, giving allylated lactam **21** in 80% yield (Scheme 8).


Scheme 8 ATRC-intermolecular/allylation reactions
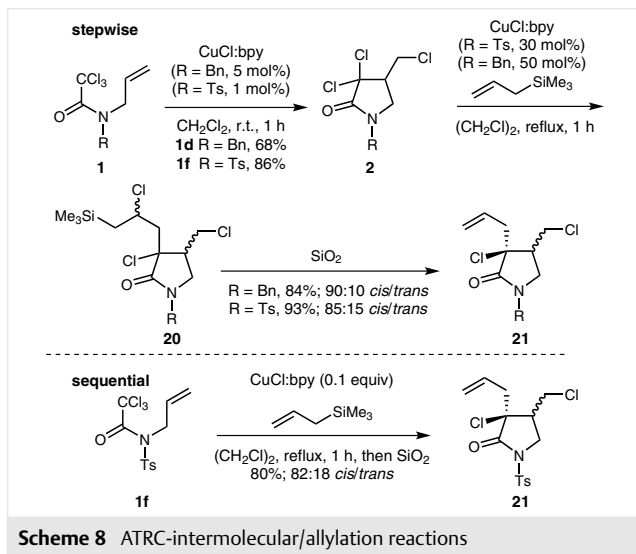
It is noteworthy that a domino process[18] was also developed, involving two sequential intramolecular ATRCs starting from trichloroacetamide **22** to afford **23** in good yield, in

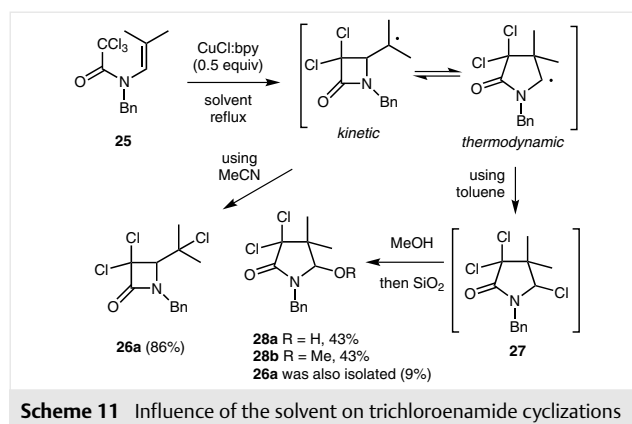**Scheme 9** One-pot biscyclization
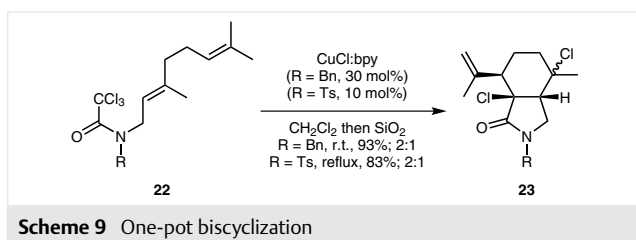
which a second intramolecular alkylation took place from an α,α-dichlorolactam (Scheme 9).[17] Thus, a catalytic Cu(I)-radical-triggered biscyclization was accomplished.

Using the catalytic system CuCl:bpy in toluene at reflux, Parsons and co-workers developed an efficient synthesis of unsaturated pyrrolidinones by 5-*endo* cyclization of *N*-cyclohexenyltrichloroacetamide **4b**. The first step consists of an ATRC, followed by a thermal elimination of HCl to afford **24a** (Scheme 10).[19]


Scheme 10 Synthesis of unsaturated bicyclic pyrrolidinones
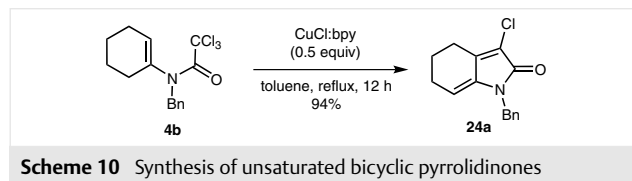
In addition, β- or γ-lactams were obtained from trichloroenamides, depending on whether a 4-*exo* or 5-*endo* cyclization took place (Scheme 11).[20] Besides the structure of the compound, the solvent used played a significant role in the selectivity of the reaction. In the depicted example, when the reaction was carried out in toluene from **25**, the major product was produced by a 5-*endo* cyclization, whereas if it was performed in acetonitrile, β-lactam **26a** was obtained exclusively. This is because CuCl is soluble in acetonitrile, and the kinetic 4-*exo* cyclization is followed by a rapid oxidation of the resulting tertiary radical to afford the β-lactam product (i.e., **26a**). On the contrary, the catalyst is less soluble in toluene, and as a consequence the rate of oxidation is expected to be slower. This allows equilibration to the more stable radical (5-*endo* thermodynamic product) to take place prior to oxidation, thus leading to a predominance of γ-lactam **27**. Treatment of this unstable γ-lactam with methanol and silica afforded the γ-lactams **28**.


Scheme 11 Influence of the solvent on trichloroenamide cyclizations

This methodology was extended to the synthesis of the anti-epileptic drug gabapentin marketed by Pfizer,[21] in which the key step is a CuCl:bpy-mediated 5-*endo* cyclization of trichloroenamide **29** leading to **30a**, as depicted in

Scheme 12. Removal of the three chlorine atoms led to the hydroxy-pyrrolidinone **30b**, which arose from the hydrolysis of the intermediate acyl iminium. Unlike the previous results (Scheme 11), the 5-*endo* pathway is preferred to the 4-*exo* due to the bulkiness generated by the cyclohexane ring.


Scheme 12   Synthesis of gabapentin
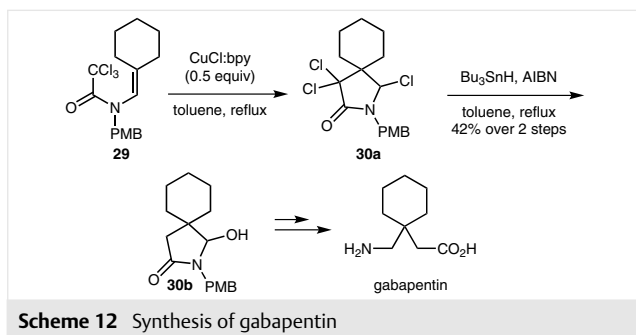
Ghelfi and Parsons decided to introduce TMEDA, a cheaper ligand than bipyridine but just as efficient.[22] Starting from *N*-allyltrichloroacetamides **1d** and **16**, and using only 10 mol% of CuCl:TMEDA in acetonitrile, γ-lactams **2d** and **17** were afforded, respectively, in excellent yields (Scheme 13).

**Scheme 13**   Synthesis of γ-lactams using the CuCl:TMEDA system
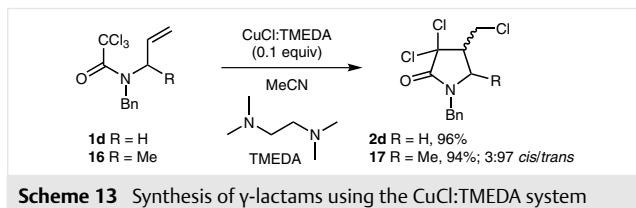
Subsequently, a CuCl:TMEDA-mediated cyclization of *N*-dimethylamino-*N*-allyltrichloroacetamides was developed to afford *N*-dimethylaminopyrrolidones (**1g** → **2g**) (Scheme 14).[23] The dimethylamino group was introduced because it was easier to remove from the cyclic compounds compared to a benzyl moiety. It was also envisaged that it would form a complex with the CuCl, which could lead to cyclization in the absence of TMEDA. However, without TMEDA, only the starting material was recovered, which emphasized that a bidentate rather than a monodentate amine ligand was required.


Scheme 14   ATRC of trichloroacetylhydrazines
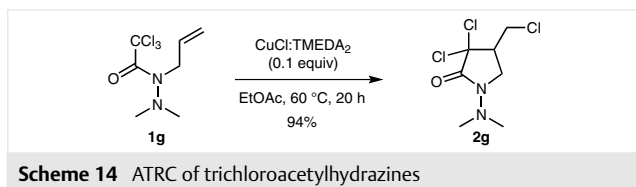
Another application of this ligand for Cu(I) was the ATRC of *N*-α-perchloroacyl-ketene-*N,S*-acetal **31**, which after oxidation afforded the disubstituted maleic anhydride **32** (Scheme 15).[24]

Scheme 15   Synthesis of disubstituted maleic anhydrides
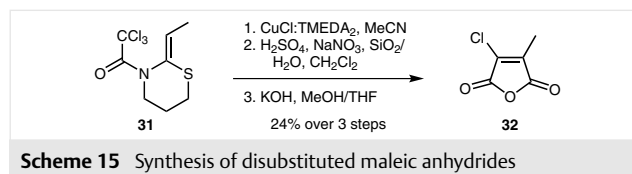
Stevens et al. used the CuCl:TMEDA methodology for the synthesis of spiroindoles (Scheme 16),[25a] consisting of an intramolecular 5-*exo* radical cyclization of the tether indole trichloroacetamide **33a** to **34**. No product of a 6-*endo* cyclization was detected. As an extension, a domino 5-*exo*- and 6-*endo*-trig cyclization from **33b** was developed to access diazatetracyclic compound **35**, obtained in moderate yield.[25b]


Scheme 16   Synthesis of spiroindoles
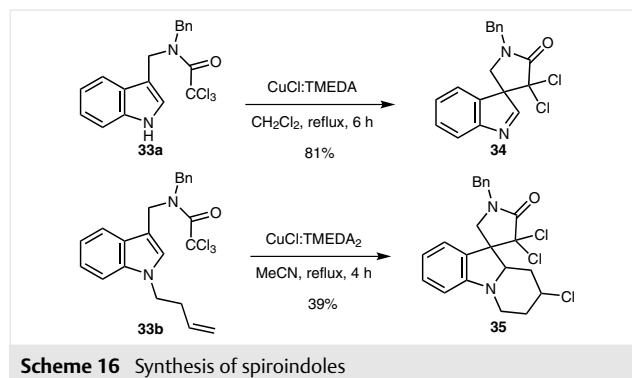
Clark worked on the development of supported multi-dentate imine ligands such as **A**, derived from *N*-alkyl-2-pyridylmethanimines (Scheme 17),[26] which complexed Cu(I). These ligands were found to be effective in catalyzing the radical cyclization of *N*-allyltrichloroacetamides to furnish pyrrolidinones. The polymeric support was shown to have very little effect on the reaction, whereas the nature of the ligand was crucial. These catalysts can be reused several times, albeit with a drop in activity due to copper leaching.

**Scheme 17**   ATRC with a solid-supported amine ligand
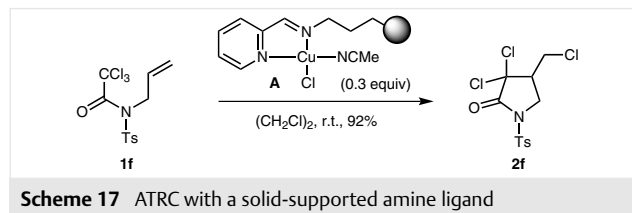
A similar ligand **B** was used in homogeneous conditions to synthesize unsaturated pyrrolidinones and bicyclic pyr-

rolidinones by a 5-*endo* radical cyclization of trichloro-enamides (**4b → 24a**) (Scheme 18).[27]
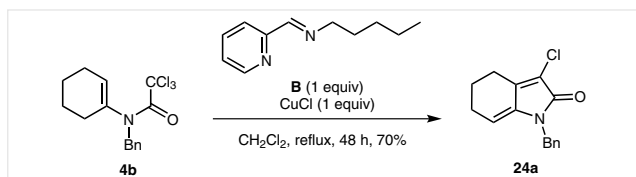

Scheme 18   Synthesis of unsaturated bicyclic pyrrolidinones

The electronic and steric environment of ligand **C** was modified to assess the effects on the 5-*exo* radical cyclization of trichloroacetamide **1f** (Scheme 19).[28] Substitution at C-6 led to a drop in ligand activity due to steric hindrance, but this was overcome by the electronic effect of a substituent at C-5. The experiment showed that activity was reduced by an inductively withdrawing group such as a methoxy group and slightly improved by an inductively donating group such as methyl.
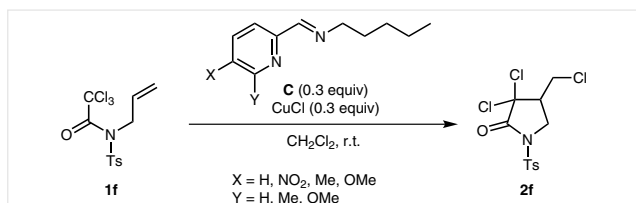
**Scheme 19**   Ligand optimization for homogeneous catalysis

Nagashima developed a Cu:bpy system encapsulated in polysiloxane gel.[29] This system showed faster reactivity and a higher total turnover number compared to the non-encapsulated system for 4-*exo* and 5 *exo*-trig cyclizations {[Cu:bpy]@Si (0.45 mol%); TON = 220 vs CuCl:bpy (1 mol%); TON = 66} (Scheme 20).
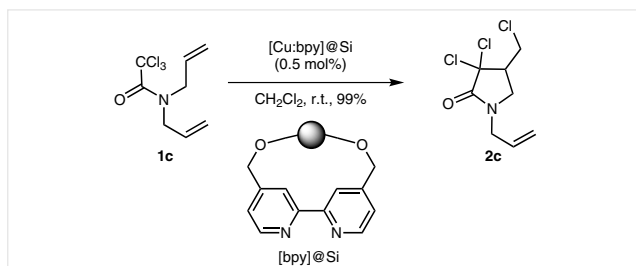
**Scheme 20**   ATRC with Cu/bpy encapsulated in polysiloxane gel

2.1.3   CuCl and Multidentate Ligands

Additionally, multidentate amine ligands such as PMDETA and TPMA were used by Clark et al., and shown to be efficient in the synthesis of γ- and δ-lactams. Arising from *N-tert*-butylamide **36**, compound **37** is one of the few examples of a 2-piperidone obtained by ATRC (Scheme 21).[30]
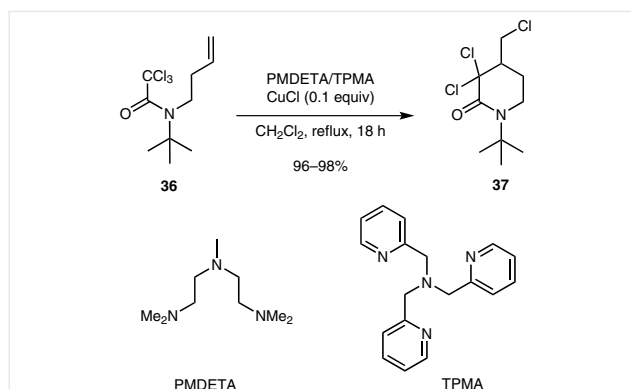
Scheme 21   Synthesis of δ-lactams using multidentate amine ligands

When using the CuCl:TPMA system for the radical cyclization of 1-substituted enamides, the substituent was able to stabilize the cyclized radical to force the 5-*endo* process.[31] Thus, from enamide **38a**, the hydroxylated products **39** were isolated, which probably arose from an oxidation of a radical intermediate by $CuCl_2$:TPMA, giving an acyl iminium that reacted with water upon work-up. The related compound **38b** followed a different pathway, providing the indigoid derivative **40** of unknown configuration in low yield (Scheme 22). In both cases, a high catalyst loading was
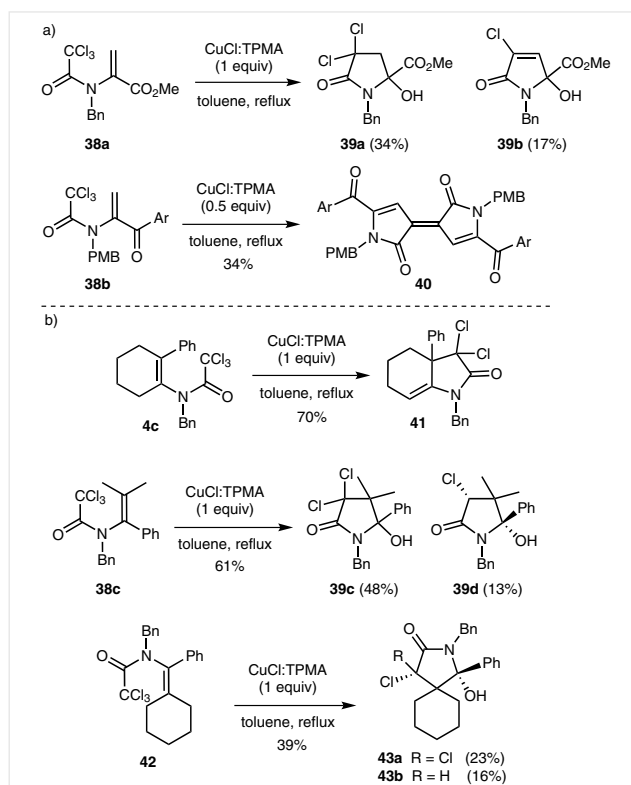

Scheme 22   Enamides to γ-lactams via a 5-*endo* radical-polar crossover process

necessary, and only moderate yields were achieved, as the generation of HCl deactivated the catalyst system.

Recently, in an extensive study of the substituent effects and rotation barriers (*N*-alkenyl and NCO bonds) in enamide cyclization,[16c] 5-*endo* radical-polar crossover reactions from highly substituted enamides (e.g., **4c**, **38c**, and **42**) using CuCl:TPMA (1 equiv) were reported, leading to the isolation of polyfunctionalized lactams such as **41** and **43** (Scheme 22, b).

The regiochemistry of the dienamides was studied under ATRC conditions using CuCl:TPMA.[32] For 3-substituted dienamide **44a**, the 4-*exo* cyclization prevailed to afford β-lactam **45a** in a moderate yield. For 2-substituted dienamide **46**, the 5-*exo* cyclization took preference over the 6-*endo* pathway to afford compound **47** in good yield (Scheme 23). From trienamide **44b**, using the catalytic system CuCl:TPMA, only the 4-*exo* cyclization compound **45b** was isolated in poor yield.[31]
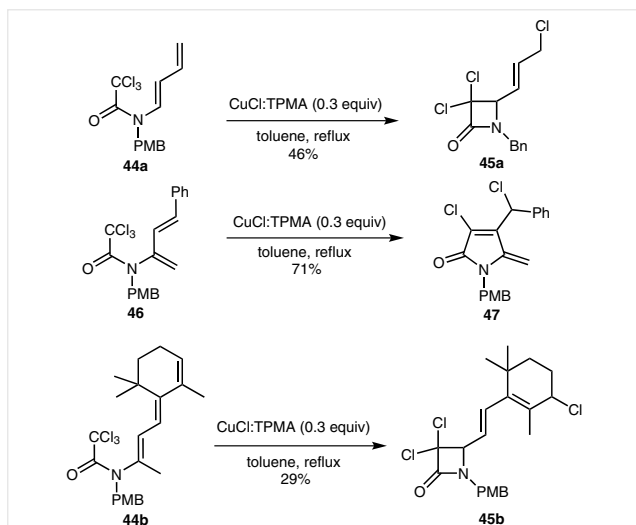
**Scheme 23** Regiochemistry study of dienamides and trienamides

Recently, a different type of trichloroacetylhydrazine, i.e., **48**, was introduced to achieve tetrahydropyridazinones (e.g., **49**) through an ATRC (Scheme 24). The less favored 7-*endo* cyclization gave minor amounts of a diazepanone when the starting alkene was monosubstituted.[33]
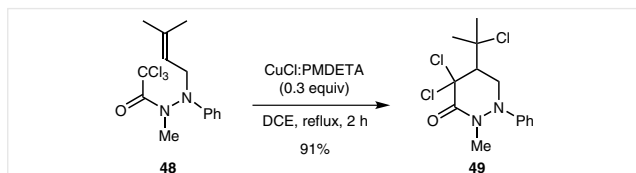
Scheme 24 ATRC of trichloroacetylhydrazines

2.1.4 NHC Ligands

The use of CuCl:NHC complexes to perform ATRC was introduced by Quayle.[34] At reflux in dichloroethane, only a slow conversion of **1d,f** into γ-lactams **2d,f** was observed, but the yields were drastically improved when using microwave irradiation at 110 °C (Scheme 25).
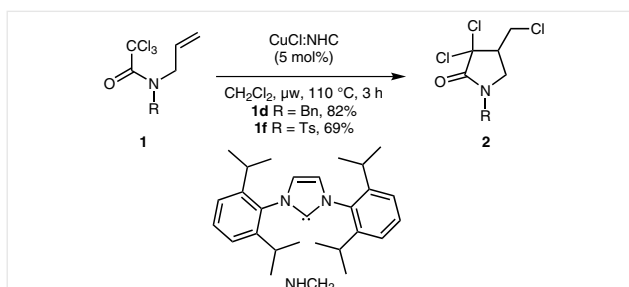
Scheme 25 ATRC using NHC ligands

2.1.5 Radical Addition to the Aromatic Ring

When a secondary *N*-arylsulfonyltrichloroacetamide (e.g., **50**) without an alkene as the radical acceptor was treated with a stoichiometric amount of CuCl:PMDETA or CuCl:trien-Me$_6$, a 5-*exo-ipso*-cyclization followed with loss of SO$_2$ was observed. The formation of the resulting *N*-alkyldichlorophenylacetamide **51** (Scheme 26)[30,35] involved a 1,4-aryl migration through a Smiles-type rearrangement.
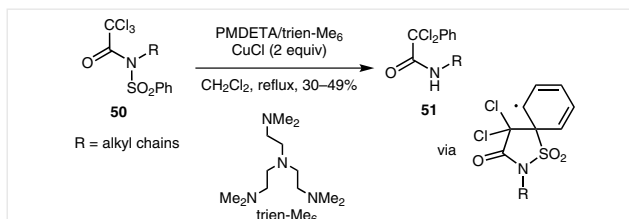

Scheme 26 Aryl migration under ATRC conditions

Treatment of *N*-benzyltrichloroacetamides **52** with Cu(I) in 'free-ligand' reaction conditions under microwave irradiation in acetonitrile at 80 °C led to the spirocyclohexadiene **53a** with a labile allylic chlorine atom. The latter was replaced with a hydroxy or other groups by quenching with water, methanol or allylamine, leading to **53b–d** (Scheme 27).[36] The yields were higher when the bulkiness of the R group was increased.

2.1.6 Improvements in Copper-Mediated ATRC

In recent years, several improvements have increased the efficiency of atom transfer radical polymerization processes.[37] In ATRC of trichloroacetamides catalyzed by Cu(I), reducing agents have been applied to lower the catalyst
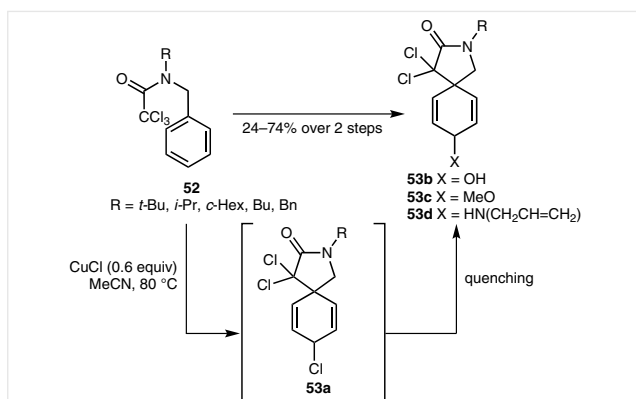
Scheme 27 Dearomatization process under ATRC conditions

load.[38] Thus, cyclization of **1d,f** using a system combining ethanol, ascorbic acid (AA) and Na$_2$CO$_3$ with CuCl:PMDETA allows the catalyst amount to be reduced to 0.5 mol%, affording γ-lactams **2d,f** in excellent yields (Scheme 28).[39] This constitutes an example of ATRC in which the activator is regenerated by electron transfer (ARGET protocol).
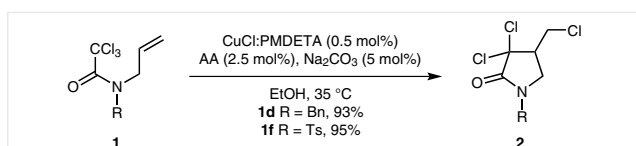

**Scheme 28** ARGET–ATRC: Ascorbic acid is used as a reductant

Another protocol involves the use of AIBN as an 'Initiator for Continuous Activator Regeneration' (ICAR–ATRC process). Starting from electron-deficient, -neutral, and -rich alkenes **54**, a series of functionalized morphan systems **55** was generated using CuCl:TPMA (10 mol%) in dichloroethane (Scheme 29).[40] Using a 2 mol% catalyst loading of Tp$^{t\text{-Bu}}$Cu(NCMe) and AIBN (10 mol%) as a reducing agent, the cyclization of **54** with the cyano group embedded took place in high yield.

This methodology has been applied in the synthesis of the ABC fragment of calyciphylline A type alkaloids. Thus, enol acetate **56** underwent ATRC in high yield to give a mixture of the dichloro and monochloro derivatives **57a** and **57b**, which after hydrogenation afforded morphan **57c** *en route* to the targeted azatricyclic core of the calyciphylline A alkaloid.[40b]

Recently, Ghelfi and Clark developed a 'Supplementary Activator and Reducing Agent' (SARA–ATRC) process using Cu(0) (wire), the ligand TPMA, and Na$_2$CO$_3$.[38] They were able to lower the ligand loading to 0.5 mol% to afford γ-lactam **2h** from **1h** in good yield (Scheme 30). The role played by Na$_2$CO$_3$ in the ligand reduction is still not understood.
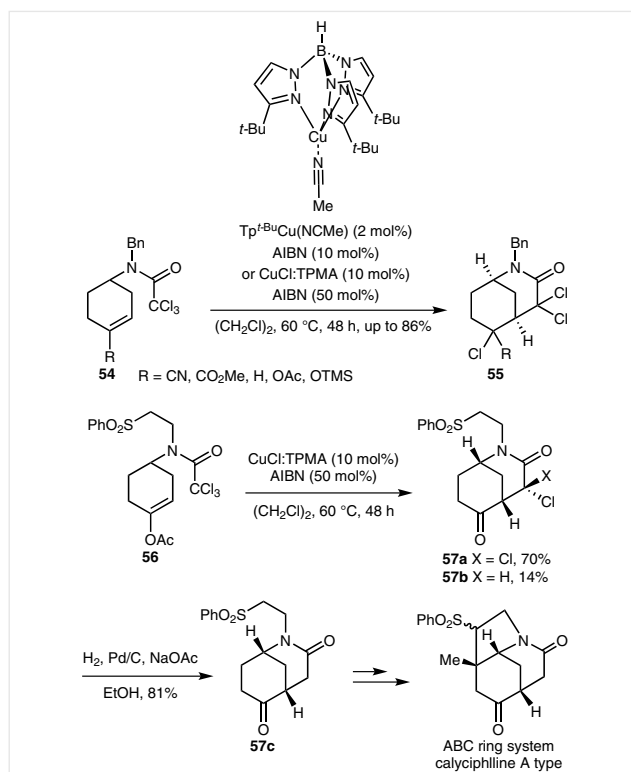

Scheme 29 ICAR–ATRC: AIBN in morphan synthesis
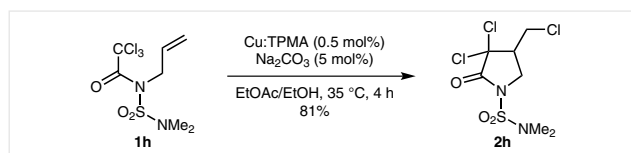
Scheme 30 SARA–ATRC: Cu(0) as the copper source

2.2 Ruthenium(II)-Mediated Reactions

2.2.1 RuCl$_2$(PPh$_3$)$_3$

Itoh and, later on, Slough, reported the first examples of ATRC upon trichloroacetamides mediated by RuCl$_2$(PPh$_3$)$_3$. Several pyrrolidinones **17**, spirocyclic γ-lactams and hexahydroindoles **5** and **6** were obtained in good yields in spite of the harsh conditions used (benzene or xylenes at 140 °C in a sealed tube), starting from *N*-allyltrichloroacetamides **16** and the related cyclic trichloroacetamides **3** and **4** (Scheme 31).[6,9,14,41,42]

In parallel to his work with CuCl, Parsons developed a RuCl$_2$(PPh$_3$)$_3$-mediated ATRC toward the synthesis of β- or γ-lactams starting from *N*-vinylic trichloroacetamides (**25** or **58**). As depicted in Scheme 11, the use of CuCl:bpy in toluene led preferentially to the 5-*endo* cyclization product (kinetic product) thanks to the lower solubility of CuCl in this solvent. On the other hand, the use of RuCl$_2$(PPh$_3$)$_3$ in toluene afforded the 4-*exo* cyclization product (Scheme 32)

Scheme 31 Ru(II)-mediated synthesis of γ-lactams
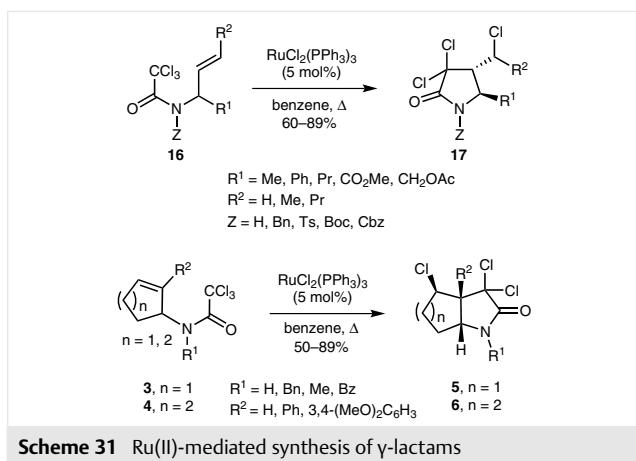
due to its higher solubility, causing the intermediate β-lactam radical to rapidly oxidize.[20] Starting from the more sterically hindered amide **58**, the 5-*endo* pathway was favored, and pyrrolones **59** embedding the structure of the alkaloid pulchellalactam were obtained.[21]

**Scheme 32** Ru(II)-mediated cyclization of trichloroenamides
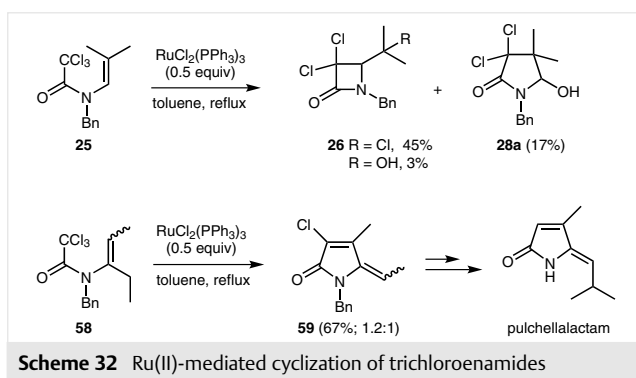
Sutherland, starting from the enantiopure MOM-ether **60**, developed a synthetic sequence involving an Overman rearrangement to achieve trichloroacetamide **61**. Ring-closing metathesis (RCM) of the latter gave **62**, and an ATRC, employing RuCl$_2$(PPh$_3$)$_3$, achieved enantiopure bicyclic γ-lactam **63** in good yield (Scheme 33).[43]


Scheme 33 Ru(II)-mediated synthesis of an enantiopure γ-lactam
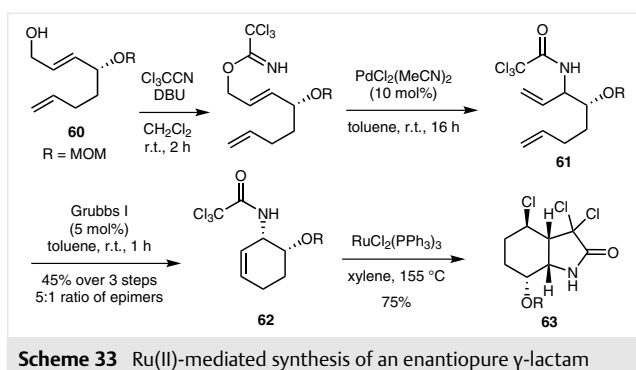
Recently, Shi also employed these conditions as the key step in building the morphan ring system (**64 → 65**) of aspidophylline A (Scheme 34).[44] Notably, both applications constitute scarce examples of the cyclization of monosubstituted trichloroacetamides (NH in the structure), whose Z-rotamer at room temperature is unsuitable for cyclization.

Scheme 34 Synthesis of aspidophylline A
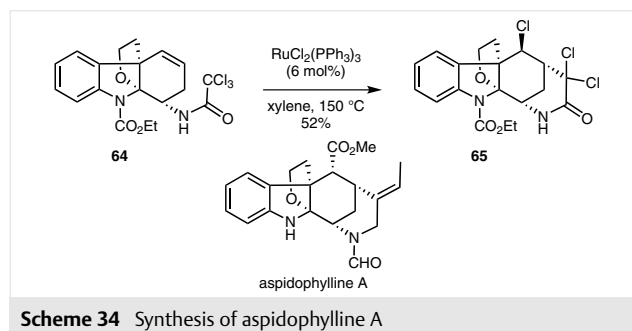
2.2.2 Other Ruthenium(II) Catalysts

Nagashima developed a novel organoruthenium amidinate {(η^5-C$_5$Me$_5$)RuCl[η-i-PrN=C(Me)N-i-Pr]} (**D**) that, unlike RuCl$_2$(PPh$_3$)$_3$, catalyzes the ATRC of N-vinyltrichloroacetamides and N-allyltrichloroacetamides at room temperature to afford pyrrolidinones, β-lactams and pyrrolizidines in good yields (Scheme 35).[45]

Scheme 35 ATRC-mediated by a novel organoruthenium amidinate
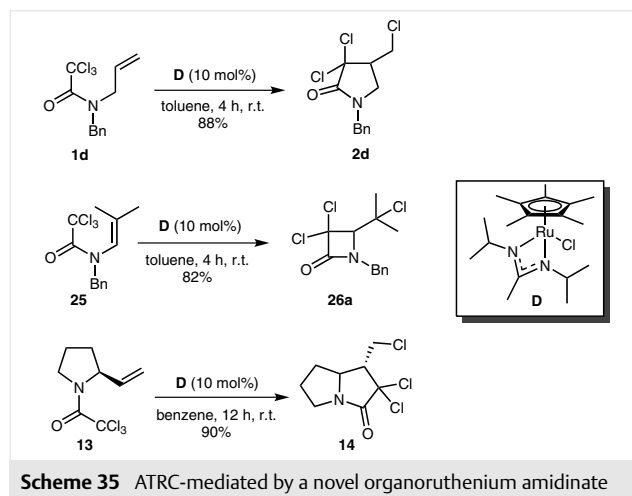
Severin developed a series of bridged ruthenium complexes (**E** and **F**) able to perform ATRC at room temperature in toluene to afford γ-lactam **2i** (Scheme 36).[46]

The use of Grubbs' catalysts, known to perform Atom Transfer Radical Addition (ATRA),[47] was extended by Quayle's group to access γ-lactams from N-allyltrichloroacetamides (Scheme 37).[48]
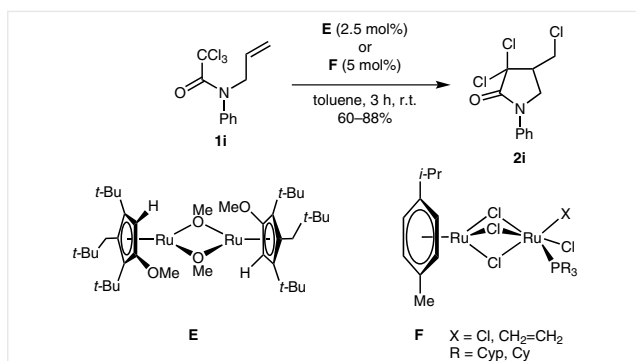
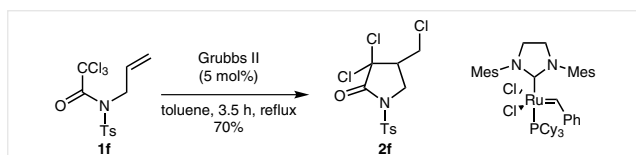**Scheme 36** ATRC-mediated by bridged Ru(II)–Ru(II) and Ru(II)–Ru(III) complexes

Scheme 37 ATRC promoted by Grubbs' catalyst

Following their work on copper-mediated ATRC (Schemes 27 and 29), Bonjoch's group obtained access to the morphan compound **57** and 2-azaspiro[4.5]decane **67** using ATRC-mediated by the Grubbs II catalyst (Scheme 38).[49] In these reactions a possible SET leading to an oxonium intermediate, instead of an atom-transfer process, may be involved.
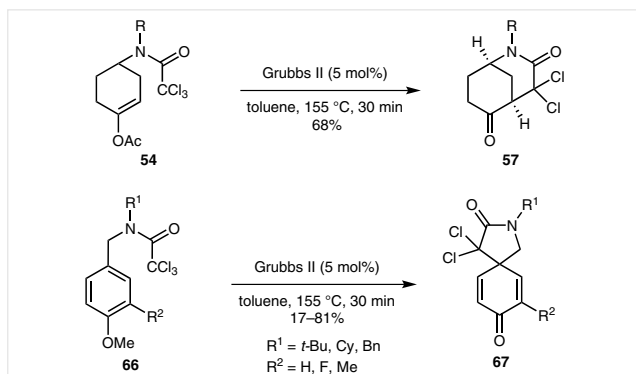

Scheme 38 ATRC of trichloroacetamides mediated by the Grubbs II catalyst

2.2.3 Tandem Processes

In 2005, Snapper developed a tandem ruthenium-catalyzed olefin ring-closing metathesis (RCM)–ATRC.[50] The starting trichloroacetamide **68** was first treated with the Grubbs I catalyst at room temperature to allow the metathesis to take place, then the temperature was raised to 110 °C to perform the radical cyclization, leading to γ-lactams **5** and **6**. Using the same principle, the tandem reaction

was extended to an RCM–ATRC–ATRA, involving styrene in the last step to generate γ-lactam **69**. These processes constitute one of the high points in the field so far (Scheme 39).
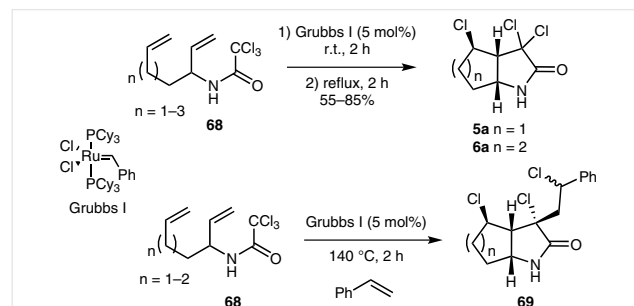
Scheme 39 Bicyclic lactams obtained by RCM–ATRC and RCM–ATRC–ATRA

Quayle later showed that the Grubbs II catalyst was also able to perform sequential ATRC–ATRA (**1i** → **70**) and RCM–ATRC (**68a** → **5a**) (Scheme 40).[51]
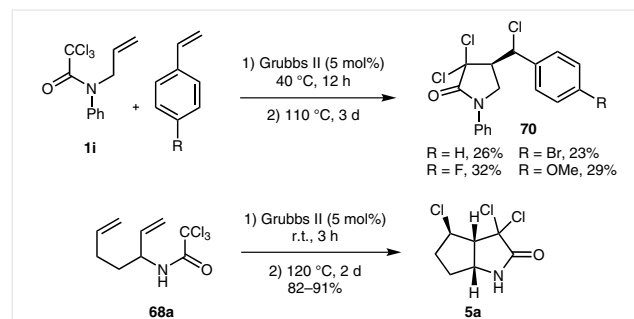
Scheme 40 Synthesis of γ-lactams by ATRC–ATRA and RCM–ATRC

Delaude developed a homobimetallic ruthenium–indenylidene complex **G**, which was able to perform an intramolecular sequential RCM–ATRC from dienes **68** to give octahydroindoles **6** in good yields (Scheme 41).[52]
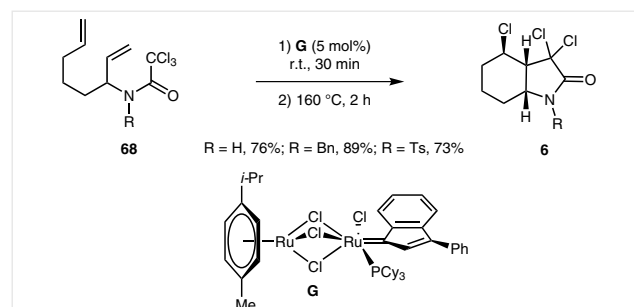
Scheme 41 A new catalyst for the synthesis of γ-lactams by RCM–ATRC

Sutherland developed a one-pot procedure starting from allylic alcohols **71** to afford bicyclic γ-lactams **73**. The process involved a Pd(II)-mediated Overman rearrange-

ment leading to trichloroacetamide **72**, followed by a sequential RCM–ATRC mediated by the Grubbs I catalyst (Scheme 42).[53]

Scheme 42 Synthesis of lactams by an Overman rearrangement–RCM–ATRC process
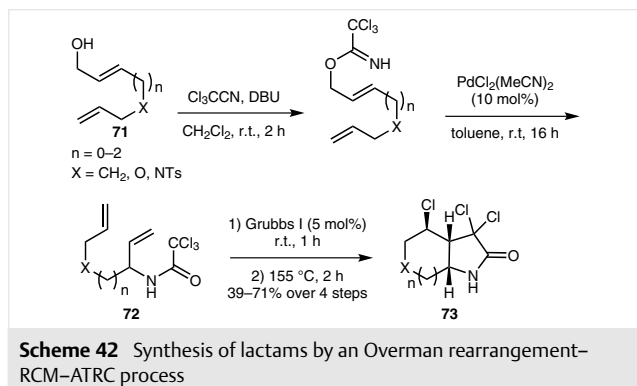
2.3 ATRC Promoted by Other Metals

2.3.1 Iron-Mediated ATRC

Metals other than copper or ruthenium have been seldom used in atom transfer reactions from trichloroacetamides. As in the case of copper (Scheme 1), the Stauffer Chemical Company were the first to report an iron-mediated ATRC to form a trichloroacetamide.[54] Using $FeCl_2 \cdot 4H_2O$, **1i** was heated at reflux in diglyme to afford γ-lactam **2i** (Scheme 43).

Scheme 43 Iron-mediated ATRC of trichloroacetamides

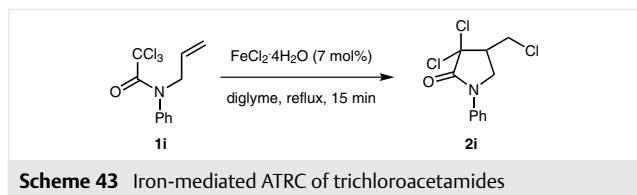Ghelfi published the cyclization of *N*-allyltrichloroacetamide **1d** using an Fe–FeCl₃ system to generate 2-pyrrolidinone **2d** in good yield.[55] There are also a few examples of the intermolecular radical addition of *N*-methyltrichloroacetamide onto non-activated alkenes using Fe(0) to generate acyclic amides **74** in moderate yield (Scheme 44).[56]

Scheme 44 Iron-catalyzed radical reactions of trichloroacetamides
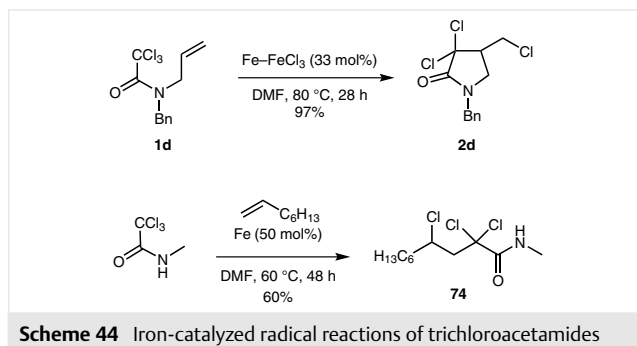
2.3.2 Manganese-Mediated ATRC

Parsons studied the cyclization of trichloroacetamide **1j** to generate pyrrolidinones **75** and **76a** using $Mn_2(CO)_{10}$ as a radical promoter and light as a radical initiator (Scheme 45).[57] The radical ·Mn(CO)₅ is able to abstract halogen atoms from organohalides bearing weak carbon–halogen bonds. The radical formed after the cyclization can be trapped by TEMPO, or reduced by a hydrogen donor such as isopropanol.

Scheme 45 Mn-catalyzed cyclizations of trichloroacetamides
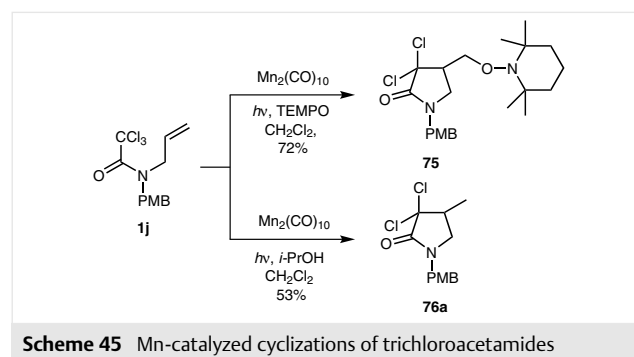
3 Photocyclization Reactions

Another cyclization process from trichloroacetamides through a SET reaction was reported by Moody and co-workers.[58] Witkop photocyclization[59] of *N*-trichloroacetyl tryptophan (**77**) and related indoles led to azocinoindoles (e.g., **78**) (Scheme 46).[58]

Scheme 46 Photocyclization processes
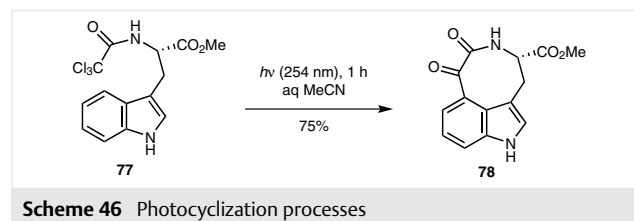
4 Reductive Cyclization via Single-Electron Transfer (SET) Processes

4.1 Ni/AcOH-Promoted Cyclizations

Zard introduced metallic nickel in combination with acetic acid, a very weak reducing system, to perform radical cyclization and trapping. These reaction conditions allow the reduction of trichloroacetamides to a transient radical anion, which rapidly expels a chloride anion to generate the dichloromethylcarbamoyl radical that undergoes a cyclization reaction.

The 5-*exo* cyclization of *N*-allyltrichloroacetamides **1d** enabled the construction of γ-lactams, the resulting radical being trapped in numerous ways: hydrogen abstraction from the solvent, or trapping with diphenyl diselenide or cyanide leading to lactams **76b**, **79**, and **80**, respectively (Scheme 47).[60]
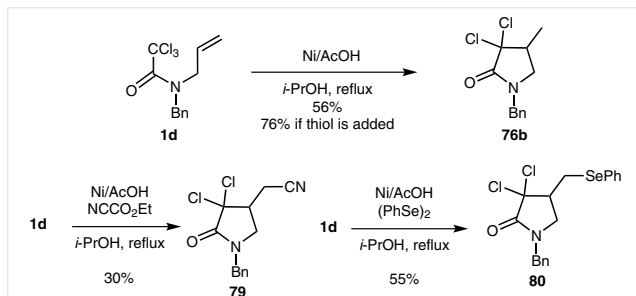
Scheme 47 Ni/AcOH-mediated cyclization of trichloroacetamides

Formation of β-lactams using a radical process is usually reversible, requiring the introduction of a fast irreversible step, such as a fragmentation followed by a cyclization, to force their formation. In the depicted example in Scheme 48, the irreversible step consists of the 4-*exo* cyclization of allylic sulfide **81**, followed by elimination of the benzenethiyl radical to afford β-lactams **82** i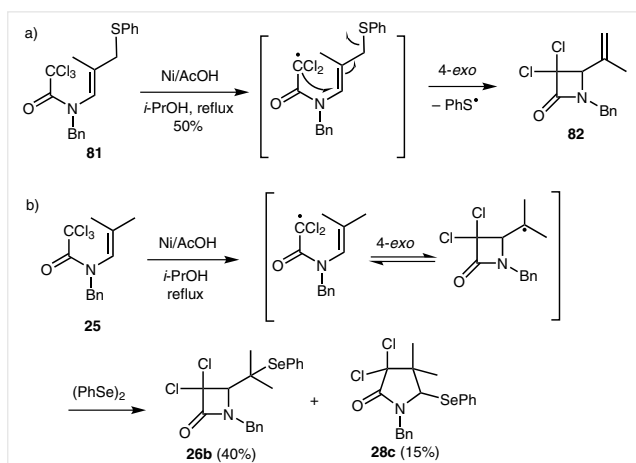n moderate yield.[61a] Alternatively, it can consist of a fast intermolecular capture of the tertiary radical intermediate by diphenyl diselenide to give **26b**,[61b] together with small amounts of the 5-*endo* product **28c**.

**Scheme 48** Ni/AcOH-mediated cyclization of trichloroenamides

When no trap was added, the only product obtained from trichloroacetamide **25** arose from the 5-*endo* cyclization. The radical formed after the cyclization step was easily oxidized to form an acyliminium salt, which was quenched by a chlorine anion and then displaced by the solvent. A

further reduction by the Ni/AcOH system removed one of the chlorine atoms α to the carbonyl to afford monochlorolactam **83** in moderate yield (Scheme 49).[61b]
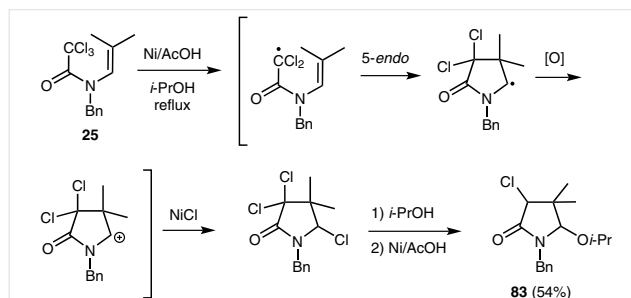
Scheme 49 Synthesis of γ-lactams from trichloroenamides

This methodology can be extended to disfavored 5-*endo* cyclizations of *N*-alkenyltrichloroacetamides **4** to afford unsaturated bicyclic γ-lactams in moderate to good yields (Scheme 50).[61b] In an attempt to trap the product of 4-*exo* cyclization using diphenyl diselenide, no β-lactams were observed. The formation of the unsaturated compounds **24a,b** and **85a,b** could be explained by oxidation of the intermediate radical to a cation, followed by a proton elimination.
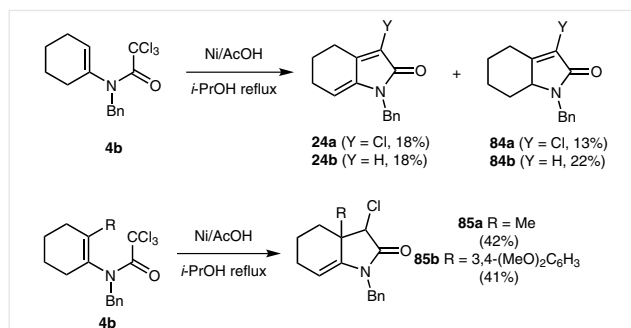
Scheme 50 Synthesis of unsaturated γ-lactams

Beyond the initial hypothesis that the oxidizing agent of these α-amido radicals (see Scheme 49) could be the starting trichloroacetamide, Zard demonstrated that cupric ions may have contaminated the nickel batches and could therefore be the source of the oxidation process. In order to confirm this new hypothesis, Cu(OAc)$_2$ was incorporated into the Ni/AcOH system and was found to control the oxidation level of the cyclization products of vinylic (5-*endo*) or allylic (5-*exo*) trichloroacetamides.[62] As depicted in Scheme 51, oxidation of trichloroacetamide **86** using the Ni/AcOH system yielded the reduced bicyclic lactam **24b**, whereas addition of Cu(OAc)$_2$ to the reducing system yielded the monochloro derivative **24a**.
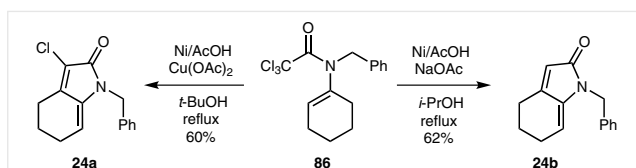
Scheme 51   Oxidation control of bicyclic γ-lactams

The use of Ni/AcOH increases the lifetime of the radical by avoiding its premature reduction. It therefore allowed the 5-*exo* cyclization of *N*-aryltrichloroacetamides **87** (Scheme 52) to afford substituted indolones **88** in good yields.[63] The latter are far more difficult to synthesize using classical radical conditions such as tin chemistry.
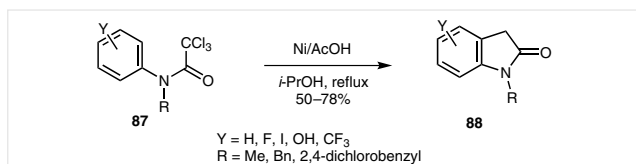
Scheme 52   Ni-promoted trichloromethylanilide cyclization

Taking advantage of the increased lifetime of the radical, the spirocyclization of *N*-benzyltrichloroacetamides **52** was explored (Scheme 53).[64] By increasing the bulkiness of the group on the nitrogen, the yields were improved.

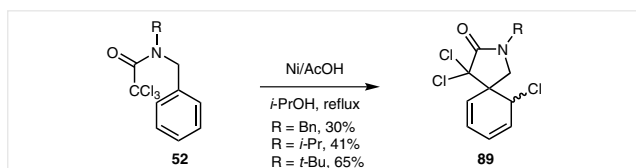**Scheme 53**   Ni/AcOH-mediated dearomative spirocyclization

This methodology was successfully applied to the total synthesis of erythrina[65] and lycorane[66] alkaloids, through the cyclizations **90 → 91** and **4 → 92**, respectively, as key steps (Scheme 54).

Interestingly, in sharp contrast with compound **93a**, which gave lactam **94**, reaction of **93b** under the same conditions afforded enamide **95** (Scheme 55).[67] Its formation could be explained by a [1,4]-hydrogen atom transfer (HAT)[68] leading to a stabilized allylic radical, which could further react with diphenyl diselenide.

4.2   Titanocene(III)-Catalyzed Reactions

Recently, biscyclopentadienyltitanium(III) chloride (Cp$_2$TiCl),[69] was introduced to generate dichloromethylcarbamoyl radicals, e.g., for **96a**, under mild conditions to afford fully reduced lactam **28f** (Scheme 56).[70] Mn dust and
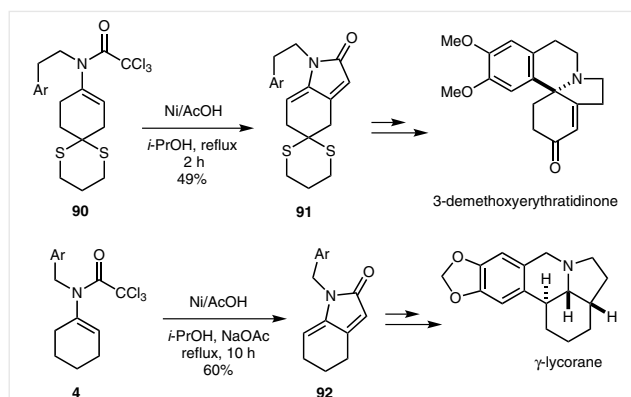
Scheme 54   Synthesis of erythrina and lycorane alkaloids
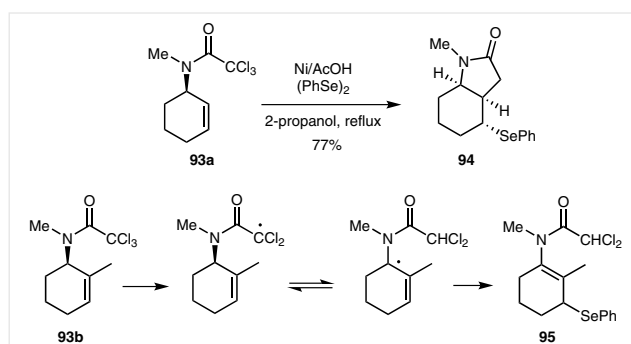
Scheme 55   Effect of steric hindrance on the mode of cyclization

TMSCl/2,4,6-collidine were used to regenerate the titanocene(III) species. The proton source was assumed to be the THF.[71]
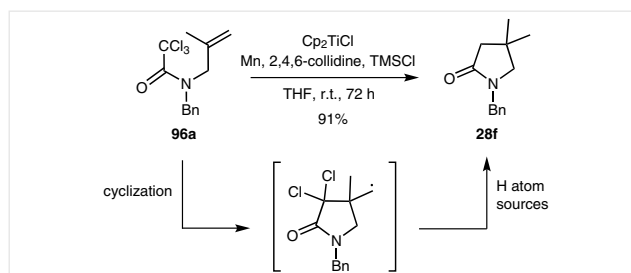
Scheme 56   Ti(III)-mediated radical cyclization

4.3   Silver Acetate Mediated Reactions

Also recently, Ueda showed that AgOAc in THF was able to generate radicals to cyclize trichloroacetamide **1c** to afford γ-lactam **76c** in moderate yield (Scheme 57).[72] It was shown that Ag(I) was reduced to Ag(0), which would act as a radical initiator, and THF was again assumed to be the proton source.
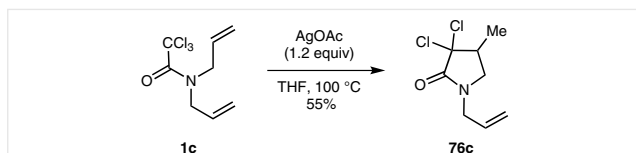
Scheme 57 Ag(0)-mediated radical cyclization

4.4 Amine-Mediated Single-Electron Transfer

Following Naito's work,[73] in which DBU in acetonitrile was found to perform a reductive dechlorination of trichloroacetamides via SET, Ishabashi carried out an extensive screening of amines and found that 1,4-dimethylpiperazine (1,4-DMP) was the best amine to undergo a SET process.[74] Heating 1,4-dimethylpiperazine and *N*-allylic or *N*-vinylic trichloroacetamides **96b** and **4b** yielded substituted pyrrolidinones **28**, and bicyclic γ-lactams **97** (Scheme 58).
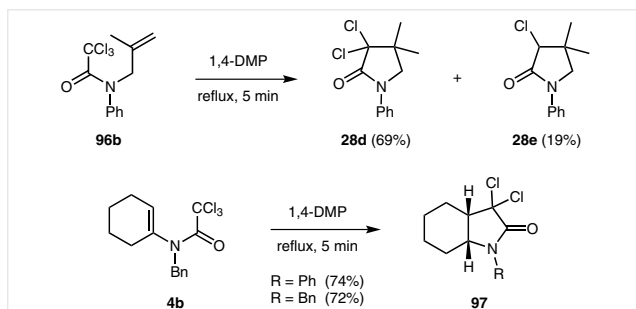
Scheme 58 1,4-DMP-mediated trichloroacetamide cyclization

Cyclization of the electron-rich trichloroacetamide **98** using the 1,4-DMP-mediated radical cyclization afforded pyrrolizidinone **99**, a key intermediate toward the total synthesis of trachelantamidine (Scheme 59).[75]

Scheme 59 Synthesis of trachelantamidine

Treatment of *o*-ethenyltrichloroacetanilide **100** with 1,4-DMP afforded the unique product **101**, through a 6-*exo* cyclization (Scheme 60).[76] This methodology showed a higher regioselectivity compared to the Bu₃SnH-mediated reaction (see below).

Scheme 60 SET-mediated cyclization of trichloroacetanilides
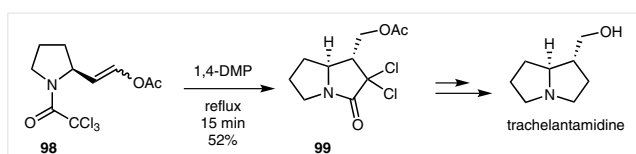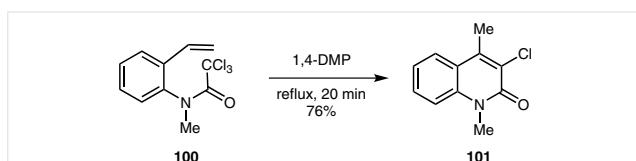
As when using copper (Scheme 26), Clark employed 1,4-DMP to demonstrate that in sulfonamides **50**, in the absence of a radical acceptor, 1,4-aryl transfer took place leading to *N*-alkyldichloroarylacetamides **51** (Scheme 61).[35a]
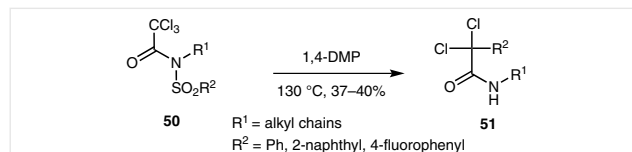
Scheme 61 1,4-DMP-mediated aryl migration

When tackling the problem of reproducibility, Ishibashi and co-workers figured out that water plays a key role in the SET process.[77] When distilled 1,4-DMP was used, the reaction worked poorly, resulting mainly in the decomposition of **102**. By adding up to five equivalents of water, the reproducibility of the cyclization was recovered to afford **103** (Scheme 62). Adding additional water led to a drop in the yield.
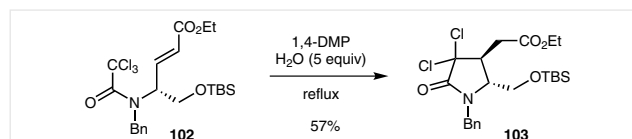
Scheme 62 Effect of water on the 1,4-DMP-mediated radical cyclization

5 Cyclization Involving M–H Hydrogen Atom Donors (M = Sn, Si, B)

5.1 Bu₃SnH-Mediated Reactions

Yamazaki's group described the first example of piperidine ring formation by a radical reductive procedure in the synthesis of benzo[*a*]quinolizidine **104**. The starting material, trichloroacetamide **11**, bore an alkene with an electron-withdrawing group as the radical acceptor (Scheme 63).[10]
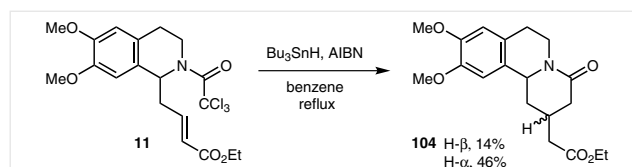
Scheme 63 Tin-mediated piperidine formation

Parsons studied the 5-*exo* cyclization of serine-derived trichloroacetamides **105** and obtained trisubstituted pyrrolidinones **106** as intermediates toward the synthesis of kainoid amino acids (Scheme 64).[78]

Scheme 64 Toward kainoid amino acids
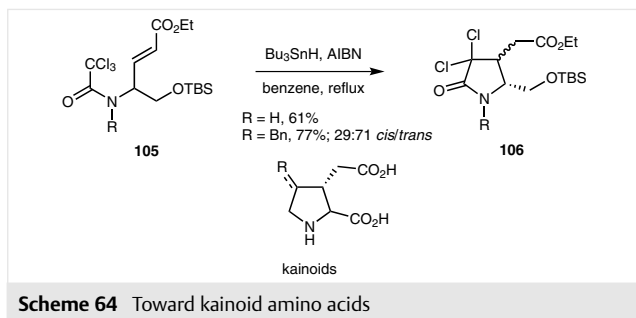
The 4-substituted pyroglutamate **107** was obtained in a disfavored 5-*endo* tin-mediated cyclization of serine-derived *N*-trichloroacetamido dehydroalanine **38a** (Scheme 65).[79]

Scheme 65 Synthesis of pyroglutamates
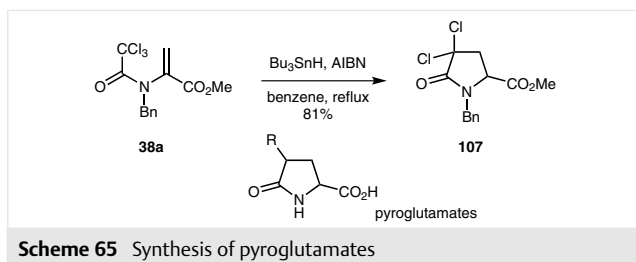
Ishibashi et al. studied the factors influencing the cyclization mode (4-*exo* or 5-*endo*) of trichloroacetamide **108**.[80] The 4-*exo* process was predominant when the *N*-vinylic bond was substituted with a phenylthio group, which increased the stability of the formed radical. However, the main factor influencing the course of the reaction was the temperature. As depicted in Scheme 66, when the cyclization of trichloroacetamide **108** was carried out at reflux in toluene, the only isolated product was the γ-lactam **24a**, whereas at room temperature (with triethylborane as the radical initiator), the 4-*exo* product **109** was obtained, albeit in low yield. At low temperatures (kinetic conditions), the dichloromethylcarbamoyl radical cyclizes predominantly in a 4-*exo* fashion. However, at a high temperature, ring opening occurs rapidly and the resulting radical cyclizes in a 5-*endo* manner. When the enamide was substituted by a phenyl (i.e., **4b**) instead of a thiophenyl group, no product of 4-*exo* cyclization was detected because the intermediate radical was insufficiently stabilized by the aromatic π-system due to its free rotation (Scheme 66, b).[80b]

Interestingly, the trichloroacetamide **111**, upon treatment with Bu₃SnH (1.2 equiv) and AIBN, gave the aromatized product **112**, whereas the dichloroacetamide (not shown) provided th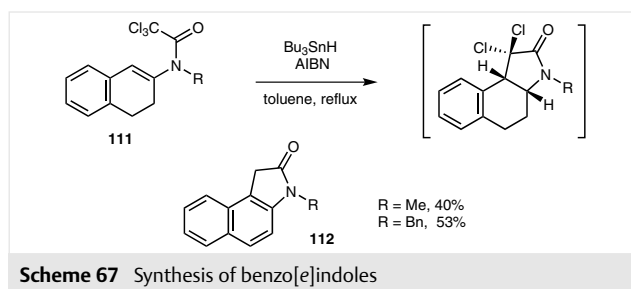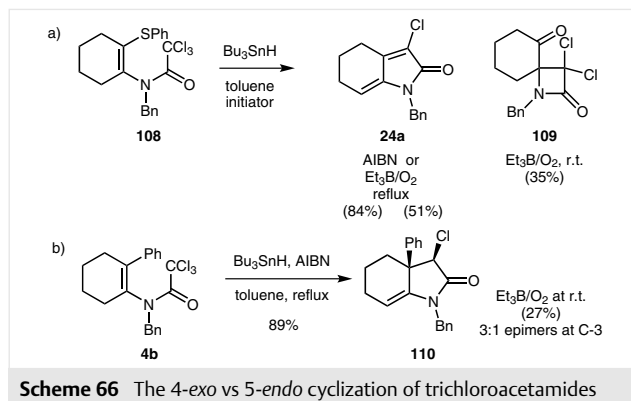e β-lactam.[80c] It was assumed that the aromatization took place by a non-radical process involving dehydrochlorination from an initially formed dichlorolactam (Scheme 67).

Scheme 66 The 4-*exo* vs 5-*endo* cyclization of trichloroacetamides

Scheme 67 Synthesis of benzo[*e*]indoles

In 1997, a series of studies on the synthesis of 2-azabicyclo[3.3.1]nonanes via reductive radical-triggered 6-*exo-trig* carbocyclizations was carried out by Bonjoch's group (see section 5.2). Using Bu₃SnH methodology to perform 6-*exo* cyclization upon electron-rich alkenes **54** afforded morphans **113** (Scheme 68).[81]

Scheme 68 Synthesis of morphans
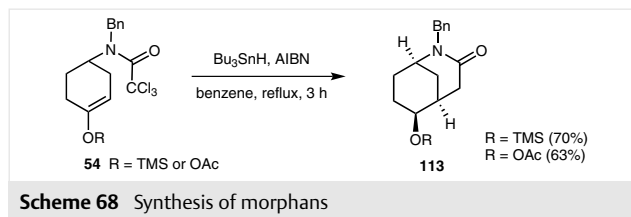
The enantiopure trichloroacetamides **114** were submitted to a tin-mediated radical cyclization to afford the desired morphans **115** together with the normorphans **116** in a stereospecific manner (Scheme 69).[82] The formation of the normorphans could be explained by 1,4-HAT[68] with memory of chirality (MOC)[83] due to the high activation barrier for rotation of the C–N single bond, which preserves its absolute chirality during the course of the reaction. Latterly, the radical cyclization has been studied using CuCl/TMPA/AIBN (as in Scheme 29), with similar results.[84]

Another intramolecular tin-mediated 6-*exo* radical cyclization occurred using trichloroacetamides **117** with an α,β-unsaturated ketone as a radical acceptor to generate
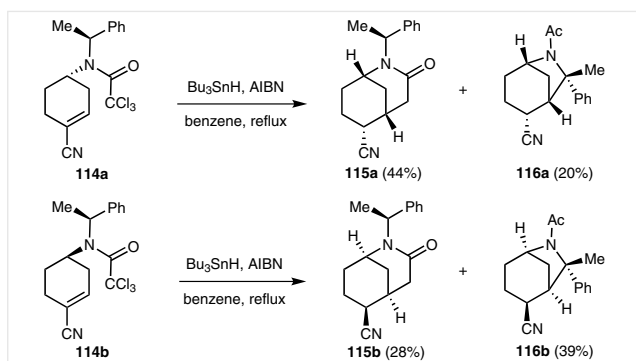
Scheme 69 Synthesis of enantiopure morphans

cis-hydroisoquinolines **118** (Scheme 70).[85] Comparable yields for this radical cyclization were found using (Me$_3$Si)$_3$SiH (see section 5.2).
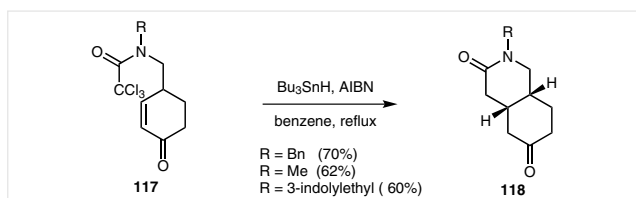
Scheme 70 Tin-mediated synthesis of cis-hydroisoquinolines

Trichloroacetamide **119**, bearing a cyclohexenylmethyl substituent, was cyclized in a 5-exo fashion to afford spiro-lactam **120** (Scheme 71).[86]
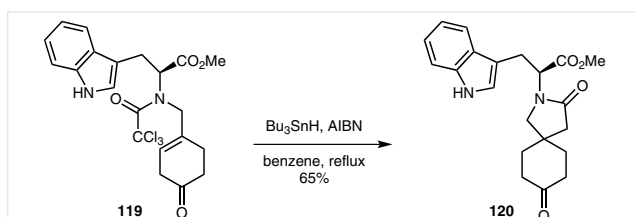
Scheme 71 Tin-mediated synthesis of spirolactams

Ishibashi studied the Bu$_3$SnH-mediated cyclization of o-ethenyltrichloroacetanilide **100**, which led to a mixture of 6-exo cyclization products **121** and **122** (Scheme 72).[76] Formation of the latter was assumed to go through a neophyl rearrangement of a radical intermediate and not through a 7-endo cyclization process.
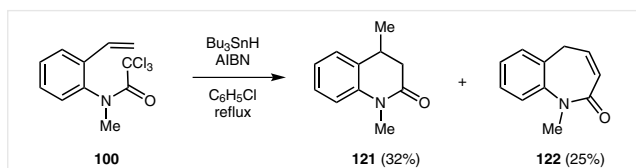
Scheme 72 Tin-mediated cyclization of o-ethenyltrichloroacetanilides

5.2 (Me$_3$Si)$_3$SiH (TTMSS)-Mediated Reactions

Bonjoch's group introduced (Me$_3$Si)$_3$SiH to generate di-chloromethylcarbamoyl radicals. These underwent cyclization onto non-activated (R = H),[87] electron-rich (R = OAc, OTMS)[81,88] or electron-poor (R = CN, CO$_2$Me)[89] alkenes **54**, affording morphans **123** and **124** (Scheme 73). The wide scope of this reaction is explained by the ambiphilic character of the dichloromethylcarbamoyl radical, which acts as a nucleophile with electron-poor alkenes, behaving as an equivalent of a β-aminocarbanion. On the other hand, with electron-rich alkenes, it acts as an electrophile, serving as an equivalent of a β-aminocarbocation. Together with the benzo[a]quinolizidine synthesis previously described by Yamazaki[10] (Scheme 63), these results expanded the scope of six-membered ring formation using trichloroacetamides with a reductive method.
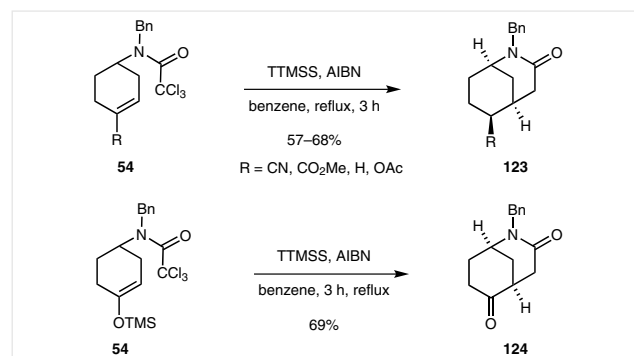
Scheme 73 Synthesis of 6-functionalized morphans

This methodology was applied in the synthesis of the alkaloids melinonine E and strychnoxanthine (Scheme 74).[90] In a one-pot procedure, trichloroacetamide **125**, embodying all the carbon atoms of the targeted alkaloids, was treated with (Me$_3$Si)$_3$SiH to perform the radical cyclization, followed by the addition of Bu$_3$SnH to reduce the remaining chlorine atoms, leading to amide **126**.
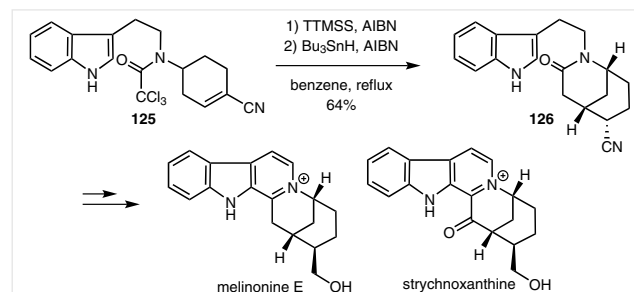
Scheme 74 Total synthesis of melinonine E and strychnoxanthine

In the depicted example (Scheme 75), silyl enol ethers **127**[82b,91] were submitted to the (Me$_3$Si)$_3$SiH-mediated radical cyclization to afford enantiopure morphans **128** togeth-

▼
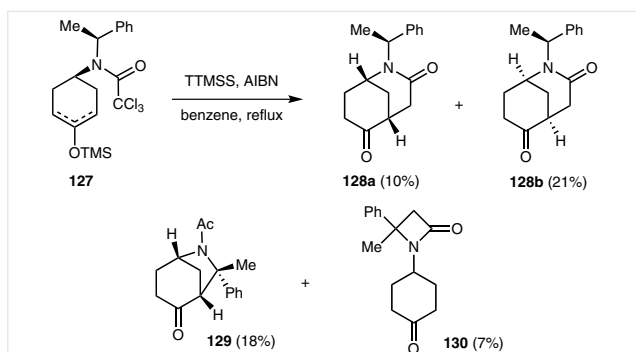
Scheme 75 Synthesis of enantiopure morphans

Scheme 77 NaBH₃CN-mediated radical cyclization

er with two by-products, normorphan **129** and β-lactam **130**.

Recently, Bonjoch and co-workers described a radical cyclization of trichloroacetamide-tethered ketone **131** using pyrrolidine, AIBN and TTMSS under microwave activation, leading to 2-azabicyclo[3.3.1]nonan-3,6-dione **124**. In a five-minute one-pot process, after the generation of an enamine, intramolecular addition of a dichloromethylcarbamoyl radical, and oxidation of the α-aminoalkyl radical intermediate, the resulting iminium salt evolved into the corresponding enamine and, after work-up, into ketone **124** (Scheme 76).[92]

Scheme 76 One-pot radical cyclization of a trichloroacetamide via an enamine

5.3 Borohydride-Mediated Radical Cyclizations

Following the early work of Barltrop[93] and the more recent studies of Ryu,[94] Bonjoch's group investigated the use of NaBH₃CN for radical cyclization involving trichloroacetamides. In an initial synthesis of the morphan ring system **132**, the 6-*exo-trig* radical cyclization proceeded smoothly in *tert*-butanol using AIBN as the radical initiator and sodium cyanoborohydride as the source of hydrogen to trap the radical intermediate after the radical cyclization step. The BH₂CN radical anion also allows the radical chain mechanism through a carbon–chlorine homolytic cleavage in the starting trichloroacetamide **54**. Thus, after an additional reduction, the morphan **132** was isolated in 85% yield (Scheme 77).[95] It should be noted that the cyanoborane radical anion (BH₂CN•⁻) did not reduce the last chlorine atom.

6 Concluding Remarks

The chemistry associated with trichloro derivatives as a source of C-centered radicals is more extensive than the trichloroacetamide-based research covered here and studies on trichloroethylamines,[96] trichloromethyl ketones,[9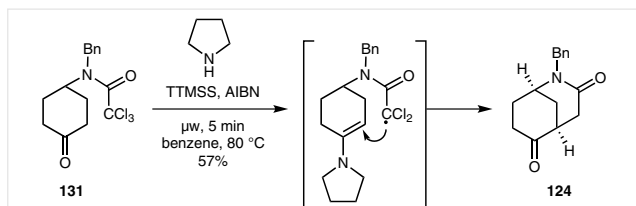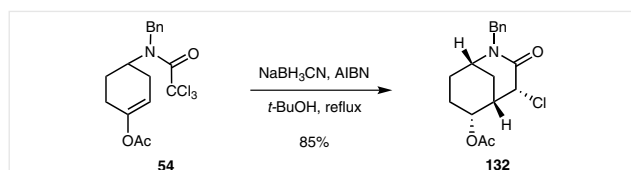7] and trichloroacetates[98] have been reported. Moreover, the use of dichloro- and monochloroacetamides, also well established, gives different results compared with their trichloro analogs reported here.

In conclusion, trichloroacetamides are radical precursors that allow a wide range of radical cyclizations in a vast array of procedures, including atom transfer, single-electron transfer and hydride-mediated reactions. The efficiency of trichloroacetamides in these radical processes could be related with the electrophilicity of the carbamoyldichloromethyl radical and a low energy barrier for the rotation around the C–N amide bond.

The radical cyclization of trichloroacetamides represents a unique approach for lactam formation with the generation of a C–C bond. Despite its simplicity, this reaction is important in terms of its synthetic applications. Among the resulting compounds, which are either polychlorinated or fully reduced, are β-, γ-, and δ-lactams. These represent highly useful building blocks in the synthesis of nitrogen-containing natural products and bioactive molecules.

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