Atom Transfer Radical Reactions as a Tool for Olefin Functionalization – On the Way to Practical Applications

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Transition-metal-catalyzed atom transfer radical reactions of halogenated compounds with olefins constitute a versatile tool in organic synthesis within the area of C–C bond forming transformations. The inter- or intramolecular versions, atom transfer radical addition (ATRA) or cyclization (ATRC), respectively, lead to the atom-economic, useful synthesis of compounds that can be further functionalized. This contribution summarizes the recent developments in this area in terms of catalyst design as well as the applicability of this methodology in sequential, domino, or tandem reactions.

Introduction

In 1937, during their investigations of the regioselectivity of the addition of HBr to unsymmetrical alkenes in the presence of peroxides (the so-called *peroxide effect*),

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Kharasch and co-workers observed[1] the formation of the anti-Markovnikov adduct. They proposed that such products were formed by means of a free radical mechanism in which the peroxides acted as free-radical initiators (Scheme 1).

A few years later, Kharasch extended his investigations to the addition of polyhalogenated compounds to olefins. This transformation, known as Kharasch addition,[2] occurred in the presence of free-radical precursors or light (Scheme 2). However, the reaction competes with radical-mediated olefin polymerization, mainly as a result of the
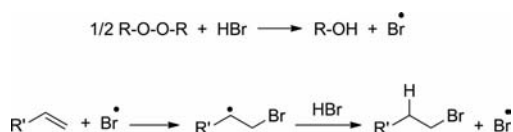
José María Muñoz-Molina (1979) graduated in Chemistry at the Universidad de Sevilla (2005) and obtained his Ph.D. from the Universidad de Huelva (2010) under the supervision of Prof. Tomás R. Belderrain and Prof. Pedro J. Pérez. His research has been focused on the development of copper-based catalysts for ATRA, ATRAC, and ATRP reactions.

Tomás R. Belderrain (1966) graduated in Chemistry in 1989 in Sevilla. He received his Ph.D. degree in Chemistry (1994) from the Universidad de Sevilla, under the supervision of Prof. Ernesto Carmona. He continued his scientific education as a postdoctoral fellow with Professor Claudio Bianchini (1995) in Florence, Italy, and Professor Robert H. Grubbs, at Caltech, Pasadena, USA (1996–97). In 1997 he moved to the Universidad de Huelva (Spain), where he became a lecturer in 2000. His research interests are related to processes in which carbon–carbon bond formation occurs: copper-mediated ATRA and ATRP reactions, and palladium complexes as potential catalysts in olefin functionalization reactions.

Pedro J. Pérez (1965) graduated in Chemistry in 1987 and received his Ph.D. degree in Chemistry (1991) at the Universidad de Sevilla, under the direction of Prof. Ernesto Carmona. As a Fulbright Scholar, he then joined Prof. Brookhart's group at UNC-Chapel Hill (USA). In 1993 he moved to a new university founded in Huelva, as an Assistant Professor (1993–1995), later becoming Lecturer (1995), and finally Professor of Inorganic Chemistry (2005). The general research interest of his group is related to the development of late-transition-metal complexes for their use as catalysts in transformations with hydrocarbons as substrates.

$$1/2 \ R\text{-}O\text{-}O\text{-}R + HBr \longrightarrow R\text{-}OH + \overset{\bullet}{Br}$$

$$R' \diagup + \overset{\bullet}{Br} \longrightarrow R' \diagdown Br \overset{HBr}{\longrightarrow} R' \diagdown Br + \overset{\bullet}{Br}$$

Scheme 1. Addition of hydrogen bromide to unsymmetrical alkenes in the presence of peroxide initiators.

high k_p/k_a ratio of CCl_4 and $CHCl_3$ with the majority of olefins. Because of this, the reaction has found limited application in organic synthesis.

$$CXCl_3 \xrightarrow{\text{Initiator}} \bullet CXCl_2$$
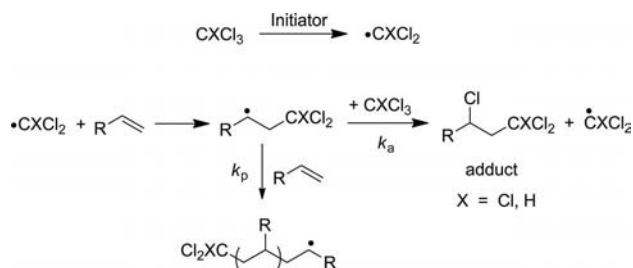
Scheme 2. The Kharasch addition of polyhalogenated compounds to olefins in the presence of an initiator.

In the middle of the past century, Minisci and co-workers discovered, during their studies of acrylonitrile polymerization in halogenated solvents (CCl_4 and $CHCl_3$), the formation of considerable amounts of the addition product of the halomethane to the olefin.[3] They realized that iron species originating from corrosion in the reactor were responsible for the catalytic process, and they therefore proposed a mechanism in which iron chlorides increased the addition rate constant k_a.[4] These seminal findings constituted a breakthrough, and they can be considered as the beginning of the transition-metal-catalyzed Kharasch reaction, also called atom transfer radical addition (ATRA).

The commonly accepted mechanism for ATRA reactions begins with the activation step in which the carbon–halogen bond is homolytically dissociated by the metal center, yielding a carbon-centered radical and a metal halide. The former species interacts with the olefin to afford another radical, inducing the abstraction of the halogen from the metal halide in the deactivation step. The metal is reduced to the initial oxidation state, and the desired addition product is formed (Scheme 3).
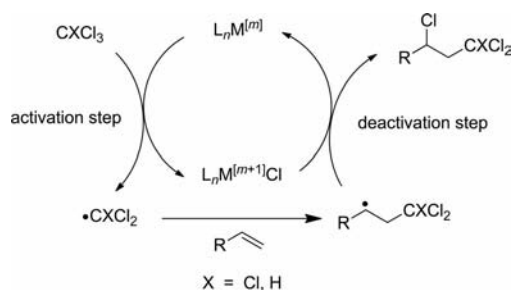
Scheme 3. General mechanism for atom transfer radical addition.

In spite of the potential use of ATRA reactions as an effective synthetic tool for the formation of carbon–carbon bonds in organic synthesis, the interest in this methodology declined over the years.

It was not until the mid 1990s when its importance emerged again due to pioneering, separate reports of Sawamoto and Matyjaszewski[5] on a related reaction, atom transfer radical polymerization (ATRP). In fact, the ATRP process begins with an atom transfer radical addition (ATRA).[6] ATRP reactions, mainly catalyzed by copper complexes, provide a simple route to well-defined polymers and copolymers with predetermined molecular weight and a narrow molecular weight distribution. Thus, in the last 15 years ATRP has become one of the most powerful synthetic methods to obtain polymers. As the leader in the field, Matyjaszewski has reviewed this issue recently.[7] On the other hand, the intramolecular version of ATRA reactions, the so-called atom transfer radical cyclization (ATRC) has found a number of synthetic applications. This reaction constitutes a useful tool for the synthesis of valuable cyclic compounds and also provides an alternative for the environmentally unfriendly organotin hydride methodology (Scheme 4). The most successful catalysts for ATRC reactions have been copper complexes that have induced the formation of an array of ring sizes (4–18 membered rings). This topic was reviewed by Clark in 2002.[8]
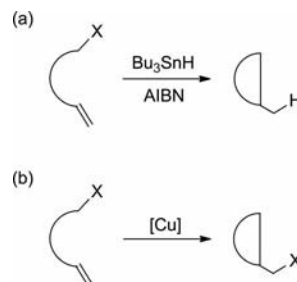
Scheme 4. (a) Reductive cyclization with Bu_3SnH. (b) Copper-catalyzed atom transfer radical cyclization (ATRC).

Since the discovery of ATRA reactions, many efforts have been focused on making this reaction in a valuable method in organic synthesis and increasing its relevancy. Several metals have been described to catalyze this transformation. Among them, ruthenium-, copper- and nickel-based catalysts have provided the best results. The atom economy and control of the product selectivity have been improved even for easily polymerizable olefins such as styrene, alkyl acrylates, and acrylonitrile. Furthermore, the reaction has been carried out by employing a wide variety of halogenated compounds[9] and it has been improved by reduction of the large excess of the halogen compound traditionally used. Highly efficient catalysts have been developed in the recent years, which have allowed the reactions to be run with low catalyst loading. With the same aim, in situ catalyst regeneration by reduction has lately attracted much attention.[10] In many systems, some of the catalyst is deactivated because of side reactions (radical homocoupling) that leave some of it in the higher oxidation state.

The presence of a reducing agent as an additive to help the metal to recover its initial oxidation state has achieved ATRA reactions with catalyst loadings at the ppm level (Scheme 5).

Scheme 5. Catalyst regeneration in metal-mediated ATRA reactions.

Catalyst recycling is another important issue in ATRA systems. The design of solid-supported catalysts[11] (Figure 1) and also their use in aqueous media[12] have contributed to eliminate the tedious and environmentally unfriendly catalyst separation steps. Clark and co-workers have described a range of copper catalysts bearing pyridinemethanimine or polyamine ligands and supported on silica, polystyrene, or JandaJel resin for ATRC reactions (Figure 1c).[13]
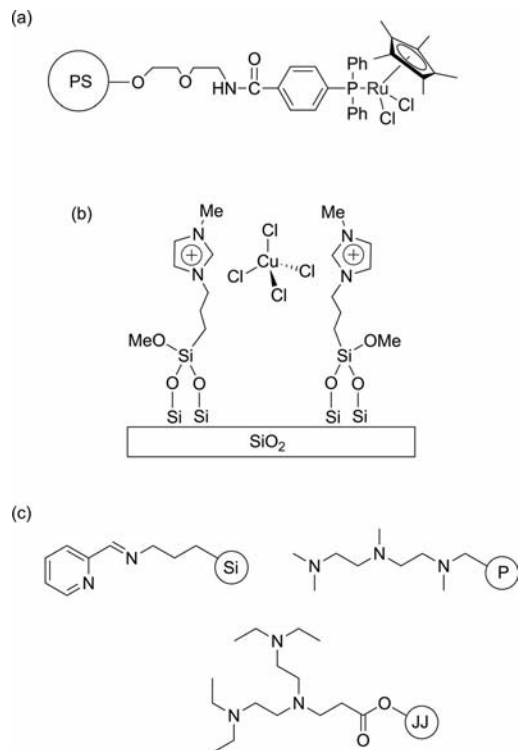

Figure 1. (a) Silica-supported copper-ion-containing ionic liquid ATRA catalysts. (b) Heterogeneous aqueous ruthenium ATRA catalyst supported by polystyrene-polyethylene glycol (PS-PEG) resin. (c) Some examples of solid-supported ligands employed in copper-catalyzed ATRC reactions.

Atom Transfer Radical Addition

Copper-Based Catalysts

Until recently, the use of copper complexes was mainly restricted to ATRC reactions.[8] However, three decades ago

Hajek and co-workers reported the use of several in situ generated Cu^I complexes for the addition of halogenated compounds to olefins.[14] The maximum conversions were about 90%, but temperatures of 80 °C or higher were required. More recently, another Cu^I system, described by Zazybin et al., required heating at 120 °C to add CCl_4 to alkenes with moderate yields.[15] In 2007, we reported the use of Cu^I complexes containing tris(pyrazolyl)borate ligands to efficiently catalyze ATRA reactions of CCl_4 or $CHCl_3$ with olefins under mild conditions (30 °C).[16] These neutral complexes are soluble in common organic solvents. We found that the more active catalysts were those with hindered as well as electron-donating Tp^x ligands (Figure 2). The addition of coordinating additives, such as acetonitrile, was also investigated. No conversion was observed when the reaction was carried out with CH_3CN as solvent. However, the addition of 20 equiv. of acetonitrile induced an enhancement of yields and selectivity, although reaction rates decreased. This methodology applied with [$Tp^{tBu}Cu$ (NCMe)] as catalyst led us to achieve efficient and selective ATRA reactions of CCl_4, CBr_4, TsCl (Ts = tosyl), or Cl_3CCO_2Et with activated olefins (styrene, methyl methacrylate, n-butyl methacrylate, tert-butyl methacrylate) in the absence of any reducing agent with low catalyst loadings.[17] In addition, copper homoscorpionate complexes have been proved as efficient catalysts for ATRP of several methacrylates.[18]
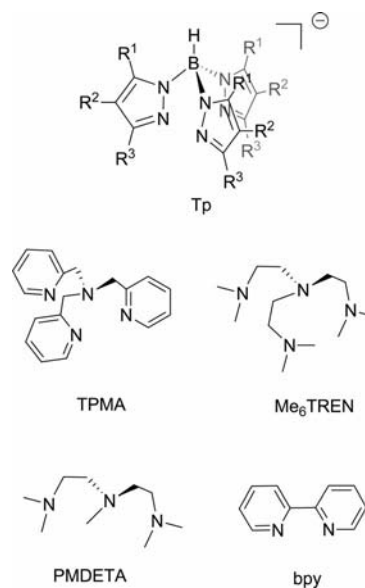

Figure 2. Ligands commonly used for ATRA reactions catalyzed by copper complexes.

The main drawback of the metal-catalyzed ATRA reactions is the radical–radical termination reactions that cause the accumulation of the metal complex in the higher oxidation state (Scheme 6), consequently decreasing the efficiency and selectivity of the catalytic system. A solution to this problem has been elucidated on the basis of the so-called ARGET-ATRP (activators regenerated by electron transfer ATRP),[19] which consists of the addition of a re-

ducing agent to continuously regenerate the lower oxidation state of the metal. Pintauer and co-workers applied this idea to ATRA by employing azobis(isobutyronitrile) (AIBN) as a reducing agent with cationic copper complexes (Figure 2).[20] The reactions with AIBN required heating at 60 °C in order to make it an efficient radical source. However, the use of the room-temperature radical initiator 2,2-azobis(4-methoxy-2,4-dimethylvaleronitrile), known as V-70, as the reducing agent, provided efficient ATRA reactions with α-olefins with only 0.005 mol-% catalyst loading.[21] The main disadvantage of this strategy is that AIBN or V-70 also promote the generation of free radicals, which function as efficient chain-transfer agents, in the case of the more reactive monomers such as styrene, methyl acrylate, or methyl methacrylate. Recently, the efficacy and versatility of ascorbic acid as a reducing agent (Scheme 7) in copper-catalyzed ATRA reactions has been demonstrated:[22] the addition of 7–20 mol-% ascorbic acid relative to alkene has led to the selective formation of the monoadduct with a catalyst loading of as low as 5×10^{-3} mol-%.
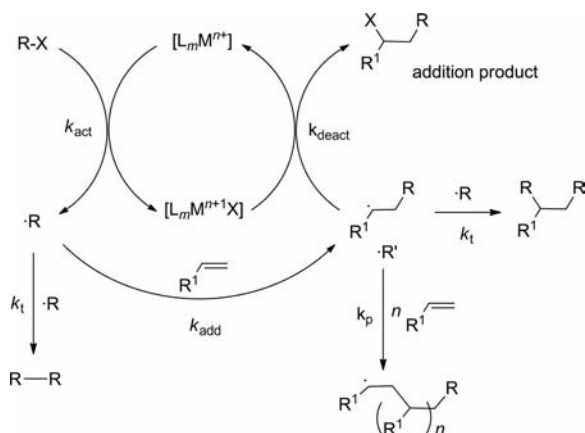
Scheme 6. ATRA mechanism showing byproducts that are not desired.
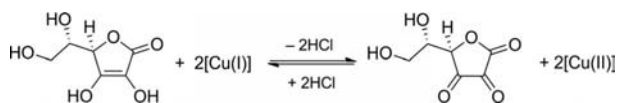
Scheme 7. Proposed mechanism for the copper complex reduction in the presence of ascorbic acid.

Ruthenium-Based Catalysts

Catalytic systems based on ruthenium have been described by far as the most active and efficient for the ATRA reaction of halogenated compounds with olefins. The first active ruthenium catalyst described for such processes was [RuCl$_2$(PPh$_3$)$_3$],[23] and ever since many others have been developed. This issue has been previously reviewed by Demonceau and Noels.[24] In that contribution, ruthenium-based catalysts were classified into three main families: Grubbs-type complexes,[25] half-sandwich ruthenium complexes,[26] and ruthenium complexes bearing anionic carborane–phosphane and dicarbollide ligands (Figure 3).[27]
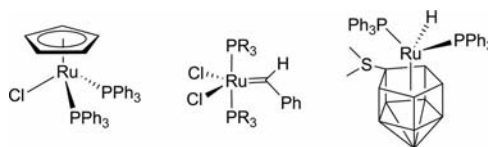

Figure 3. Representative examples of ruthenium catalyst for ATRA reactions.

The development of new ruthenium complexes as well as new applications for ATRA reactions has had a great impact in this field over the last few years. For example, Quayle and co-workers have studied the ability of first-generation Grubbs' catalysts to promote either ring closing metathesis (RCM) or ATRC reactions and the conditions necessary for these transformations.[28] Demonceau and co-workers reported that the exchange of tricyclohexylphosphane [RuCl$_2$(p-cymene)(PCy$_3$)] with p-substituted triarylphosphane ligands enhanced the catalytic activity of these complexes for the ATRA of carbon tetrachloride to unactivated α-olefins.[29] In addition, the reactivity was improved by microwave irradiation.[30] The use of ruthenium di- and tetranuclear complexes as catalysts for ATRA reactions has been described by Severin and co-workers (Scheme 8). For example, complex [{RuCl$_2$(1,3,5-C$_6$H$_3$iPr$_3$)}$_2$] and PCy$_3$ were efficiently used to catalyze ATRA of CHCl$_3$ to aromatic olefins with yields up to 80% at 40 °C.[31] Heterometallic di- and tetranuclear complexes involving rhodium and ruthenium also catalyzed ATRA reactions (Figure 4): [Cp*Rh(μ-Cl)$_3$RuCl(PPh$_3$)$_2$] and [{(tcp)Rh(μ-Cl)$_3$Ru-(dcypb)}$_2$(μ-N$_2$)] complexes promoted the ATRA of CCl$_4$ to styrene with an initial TOF of 1200 h^{-1}.[32]
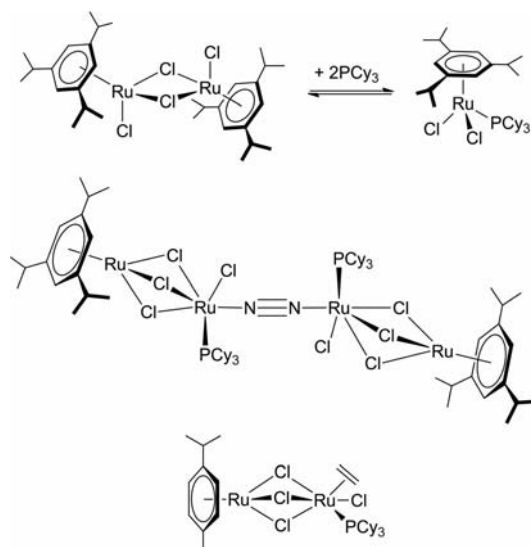
Scheme 8. Di- and tetranuclear ruthenium complexes used as catalysts in ATRA reactions.

Ruthenium half-sandwich complexes such as [Cp*Ru-(PPh$_3$)$_2$(CH$_3$CN)][OTf] (Cp* = η^5-C$_5$Me$_5$, OTf = SO$_3$CF$_3$) were described by Severin et al. as catalysts for ATRA reactions.[33] Their studies showed that the simple modification of the neutral chlorido complex into a cationic acetonitrile
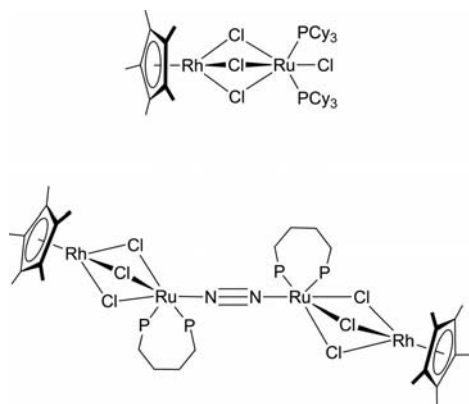
Figure 4. Di- and tetranuclear heterometallic complexes used as catalysts in ATRA reactions.

complex results in a significant increase in the stability of the catalyst. In addition, Severin and co-workers proposed a methodology to improve the catalytic activity of ruthenium half-sandwich complexes, which consisted of the addition of the radical initiator AIBN as cocatalyst.[34] Such additives continuously regenerate the lower oxidation state of the [Cp*RuCl(PPh$_3$)$_2$] complex. As a result, an exceptional increase in yields was observed. Such methodology has been successfully employed in the case of a series of [LRu(PR$_3$)(PPh$_3$)Cl] catalysts, with L = Cp*, Dp, Ind, Cp, Tp and PR$_3$ = PTA, PMe$_3$, or PPh$_3$, as well as other Ru-based complexes supported by *P,N*-substituted indene or indenide ligands.[35] Unfortunately, as already mentioned, the use of AIBN involves some drawbacks: (i) it can act as a radical initiator for polymerizations; (ii) its decomposition products have to be separated from the reaction products; and (iii) the reactions cannot be performed at ambient temperature. These limitations were overcome by using elemental magnesium instead of AIBN as the cocatalyst. The metal can be easily separated by filtration, and reductions take place at ambient temperature. The [Cp*RuCl$_2$(PPh$_3$)] complex in combination with magnesium allowed to perform ATRA reactions with very low catalyst loadings under mild conditions with high efficiency.[36] Mechanistic studies of these reactions catalyzed by the latter complexes in the presence and in the absence of magnesium[37] showed that the oxidation state of the catalyst in the resting state is +3 and that the reaction is zero-order with respect to the halogenated compound. In addition, the kinetic data suggested that the metal catalyst is not directly involved in the rate-limiting step of the reaction.

Nickel-Based Catalysts

Nickel complexes containing carbonyl or phosphane ligands (e.g. [NiCl$_2$(PPh$_3$)$_2$]) showed limited activity in promoting ATRA reactions.[23] However, van Koten and co-workers described the use of nickel complexes bearing N,C,N-tridentate pincer ligands (Figure 5).[38] They found that the electron-donating *para* substituent on the aryl ligand facilitates the oxidation to Ni^{III}. In addition, there

existed a good correlation between the reaction rate and the Ni^{II}/Ni^{III} redox potentials. These data, together with subsequent mechanistic studies, demonstrated that the formation of nickel(III) species occurs by a single-electron halide transfer from the halogenated compound in an inner-sphere complex.[39] The organic radical generated is supposed to stay in the coordination sphere of the metal, where it reacts with the alkene. This proposal is in good accord with the decrease in the reaction rate with an increase in the bulkiness of the ligand.
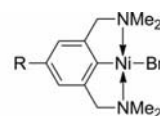
R = H, NO$_2$, NH$_2$, Cl, OMe, etc.

Figure 5. Square-planar arylnickel complexes [Ni^{II}{C$_6$H$_2$(CH$_2$-NMe$_2$)$_2$-2,6-R-4}Br].

Later, van Koten et al. extended their investigations to catalyst heterogenization using several supports, with the aim to improve catalyst separation from the product-containing solution.[40] Nickel complexes were incorporated onto polysiloxane polymers or grafted onto silica particles. The main problem with this methodology was to control both the number and the location of the metal sites. In order to overcome this limitation, they designed and tested dendrimer-based nickel catalysts. Well-defined polysilane dendrimers were synthesized and functionalized at their periphery with nickel active sites (Figure 6). These materials were tested in ATRA reactions without significant leaching of the nickel catalyst. Subsequent studies showed that the catalytic activity was affected by the irreversible formation of Ni^{III} sites on the periphery due to the accumulation and
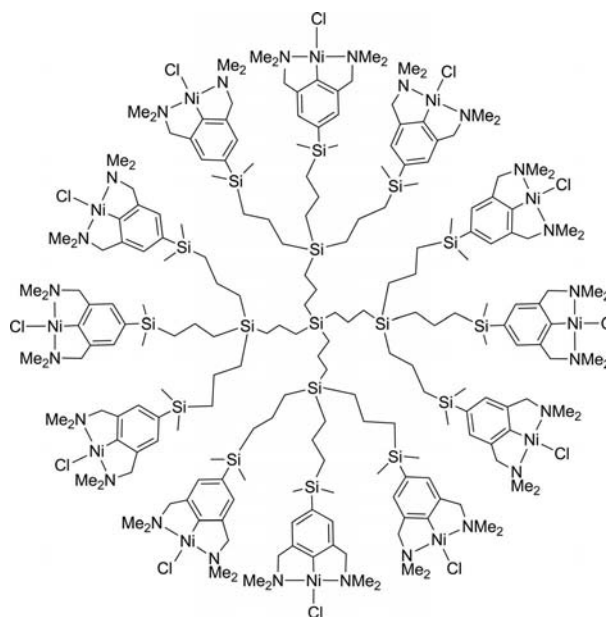

Figure 6. Nickel-centered carbosilane dendrimer.

proximity of the nickel active sites. The separation of macromolecular catalysts from the product was achieved by using ultrafiltration membrane technology.

Synthetic Applications

Although ATRC reactions are an emerging tool in both inter- and intramolecular versions,[41] there does not exist a significant number of reports published on their use in target-oriented synthesis.[42] Among others, ATRC reactions have provided access to 2-oxabicyclo[4.3.0]nonanes present in terpenes such as eunicellin (Scheme 9a) or functionalized γ-butyrolactones (Scheme 9b).
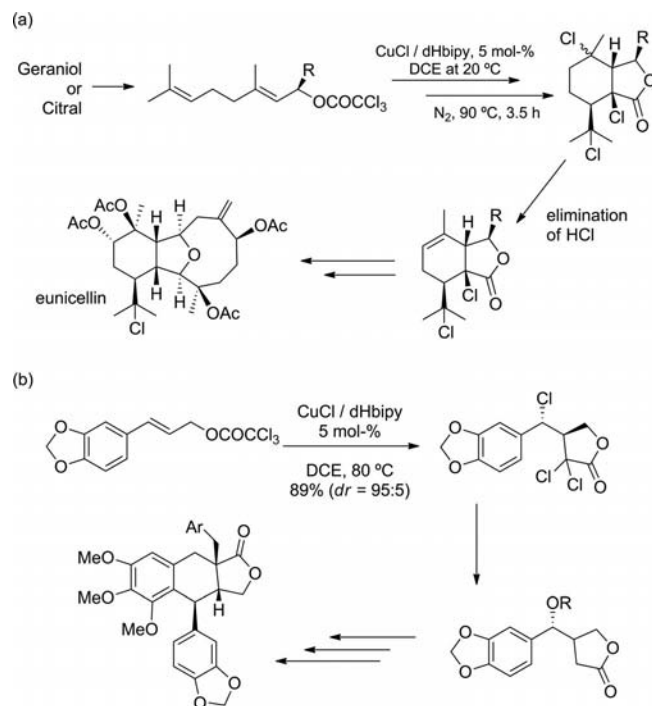
Scheme 9. (a) Sequential ATRC reactions followed by elimination of HCl involved in the total synthesis of eunicellin. (b) Functionalized γ-butyrolactones synthesized by ATRC reactions and subsequent cyclolignan total synthesis.

One interesting feature of these reactions is that the products display several halogenated carbon centers that can be subsequently functionalized (Scheme 10).[43] Cyclic systems such α-pyrones, halogenated pyridines, cyclopropane carboxylic acids, or cyclic amides of glutamic acid can be potentially formed by this strategy. Thus, hydrolysis of the styrenyl-derived ATRA products leads to enals or enones, whereas in the case of acrylate-derived products, substituted γ-hydroxybutenolides can be obtained by hydrolysis. Recently, Severin and co-workers have reported a novel, interesting procedure for the synthesis of substituted cyclopropanes by ATRA or ATRC reactions followed by a dechlorination reaction.[44] The first step consists of the ATRA reaction of 1,1′-dichlorides with several olefins catalyzed by the [Cp*RuCl₂(PPh₃)] complex. In a second, and mechanistically still uncertain step, the transformation of

the 1,3-dichloride adducts into cyclopropanes takes place by reductive coupling, in a process accelerated by the ruthenium center.
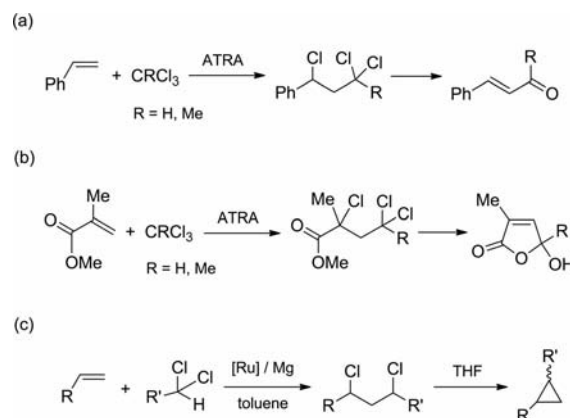
Scheme 10. (a) Synthesis of enals or enones by hydrolysis of styrenyl-derived ATRA products. (b) Synthesis of γ-hydroxybutenolides by hydrolysis of the acrylate-derived ATRA products. (c) Synthesis of substituted cyclopropanes by ATRA reactions followed by a dechlorination reaction.

Atom transfer radical reactions can also be combined with other useful synthetic reactions in a sequential fashion by using the same catalytic system. Pintauer and co-workers have very recently described the use of [Cu(TPMA)X][X] {X = -Br or -Cl, TPMA = tris(2-pyridylmethyl)amine} complexes, in the presence of ascorbic acid as a reducing agent, as catalysts for sequential azide–alkyne [3+2] cyclo-addition and ATRA reactions (Scheme 11).[45]
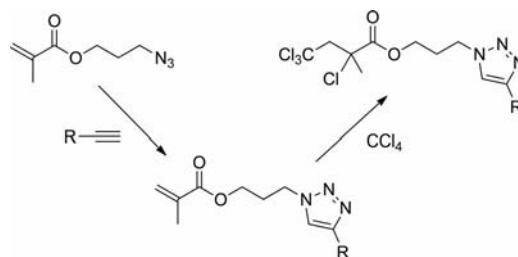

Scheme 11. Copper-catalyzed azide–alkyne [3+2] cycloaddition followed by ATRA.

Sequential ATRA or ATRC Reactions

ATRA and ATRC reactions can be sequentially performed to yield molecules with a certain degree of complexity.[46] Severin and co-workers reported the synthesis of linear 1,5-dichlorides by double, sequential ATRA reactions of activated dichlorides with olefins catalyzed by [Cp*RuCl₂(PPh₃)] in the presence of Mg (Scheme 12a).[47] A variant has been reported by the Nagashima et al., showing that the synthesis of trichlorinated γ-lactams can be achieved by an ATRC reaction of N-allyltrichloroacetamides in the presence of CuCl and bipyridine at room temperature, followed by a second ATRA with 1-hexene (Scheme 12b).[48] The double ATRC–ATRC version is also

known, exemplified by the synthesis of bicyclic lactams (Scheme 12c).[48] With the same CuCl/bipyridine system, *N*-tosyl-*N*-geranyl trichloroacetamide is converted into the corresponding bicyclic lactam in a one-pot reaction. The monocyclic lactam can be isolated as a 2:1 mixture of diastereomers, proving that the reaction is sequential.
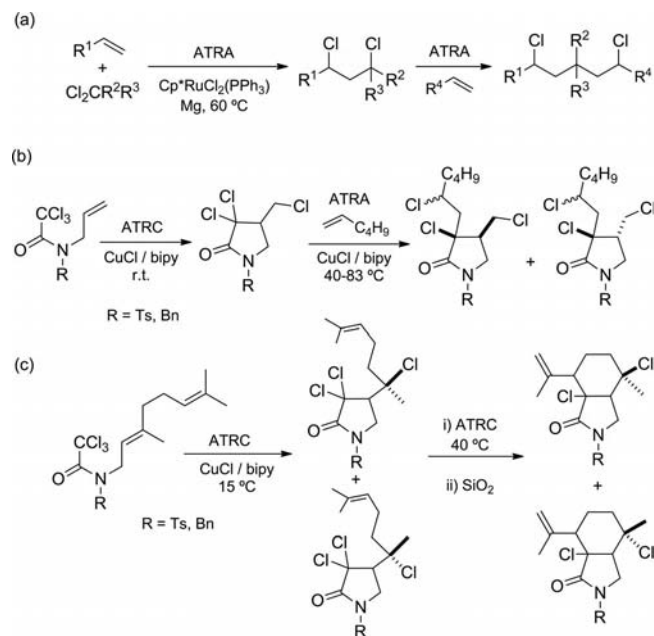

Scheme 12. Various combinations of sequential atom transfer radical addition (ATRA) and cyclization (ATRC) reactions.

## Domino Atom Transfer Radical Reactions

Domino reactions are defined as "*a process involving two or more bond-forming transformations (usually C–C bonds) which take place under the same reaction conditions without adding additional reagents and catalysts, and in which the subsequent reactions result as a consequence of the functionality formed in the previous step*".[49] Thus, in some cases, both inter- and intramolecular atom transfer radical reactions can be combined into one radical-domino catalytic reaction. An interesting transformation is that leading to the formation of 1,2-disubstituted cyclopentanes by domino atom transfer radical addition–cyclization (ATRAC) of CCl$_4$ to 1,6-heptadienes (Scheme 13). The reaction usually affords a mixture of *cis* and *trans* isomers, along with the linear addition products. Our group has recently reported the first example of the use of copper in such transformations.[50] The use of [Tp^{x}Cu(NCMe)] complexes along with magnesium as a reducing agent has led to nearly quantitative conversions, under mild conditions. The process involves the intermolecular addition of CCl$_4$ to the diene followed by a 5-*exo-trig* cyclization reaction, resulting in the formation of the *cis*-3-chloromethyl-4-(2,2,2-trichloroethyl)-cyclopentane isomers in a highly regiospecific and stereospecific manner. The regioselectivity between closed and linear products was found to be catalyst-dependent, whereas the isomer ratio did not vary with the array of cata-

lyst employed. Pintauer and co-workers have reported the use of complex [Cu(TPMA)Cl][Cl] as catalyst for such transformations in the presence of AIBN, V-70, or ascorbic acid as a reducing agent. Very high activity was observed when using catalyst loadings as low as 100 ppm.[51]
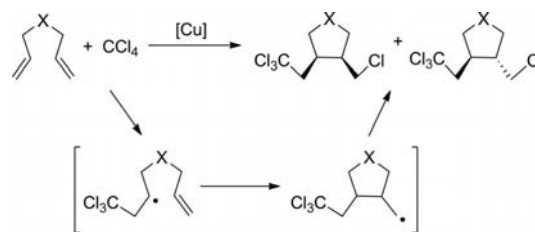
Scheme 13. Synthesis of 1,2-disubstituted cyclopentanes from 1,6-dienes by copper-catalyzed domino atom transfer radical addition–cyclization of CCl$_4$ to 1,6-heptadienes.

Multicyclic systems with high complexity can be obtained by combining two or more ATRC steps in a domino process. Stevens and co-workers described the copper-catalyzed synthesis of benzospiro-indolizidinepyrrolidinones by domino ATRC reactions[52] by using CuCl/TMEDA as the catalyst. As shown in Scheme 14a, the process involves a 5-*exo-trig* followed by a 6-*endo-trig* cyclization. However, when the *N*-indole was substituted with an allyl group, only the spiro-cyclization took place (Scheme 14b). According to the Baldwin rules,[53] a 5-*endo-trig* cyclization would be disfavored, whereas the favored 4-*exo-trig* cyclization would suffer from considerable ring strain due to the formation of the four-membered ring.
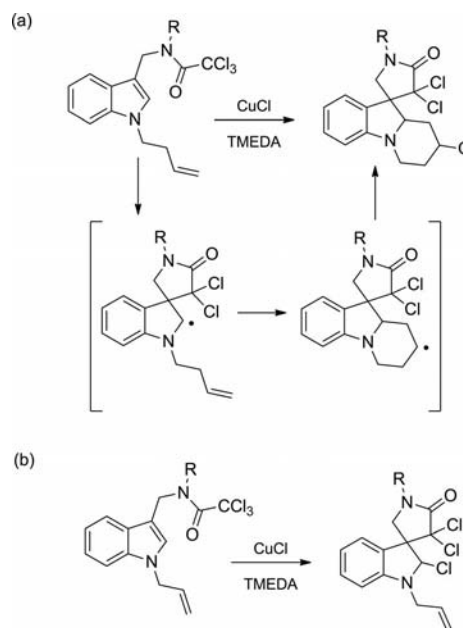
Scheme 14. (a) Synthesis of benzospiro-indolizidinepyrrolidinones by domino ATRC reactions. (b) Simple ATRC.

Another example of domino-type ATRC reactions were also studied by Yang and co-workers using α-dichlorinated-β-keto esters as precursors (Scheme 15).[54] The process takes place by a 6-*endo*-trig followed by a 5-*exo*-trig cycliza-

tion, with the concomitant formation of four stereocenters. The reaction was performed at 80 °C with CuCl/bipyridine as catalyst, leading to the formation of a mixture of 6,5-*cis* isomers (1:2.3 ratio) in 61 % total yield.
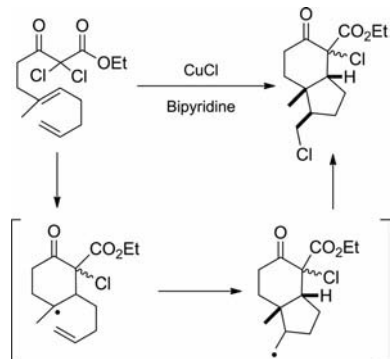

Scheme 15. Synthesis of bicyclic compounds by domino ATRC reaction.

Tandem Atom Transfer Radical Reactions

Denmark has defined tandem reactions as a domino reaction in which the intermediate or intermediates are isolable entities.[55] From a catalytic reaction point of view, tandem reactions should include two or more transformations mediated by the cooperative action of two or more catalytic cycles with different mechanisms operating in a serial arrangement. In this context, atom transfer radical reactions can be combined with other processes, just one metal complex being responsible for the whole transformation along the different catalytic cycles.

In 2005, Snapper and co-workers developed a remarkable tandem process in which Grubbs' ruthenium alkylidene complex, $[(Cy_3P)_2Cl_2Ru = CHPh]$, was employed to catalyze tandem olefin ring-closing metathesis (RCM)/ATRC
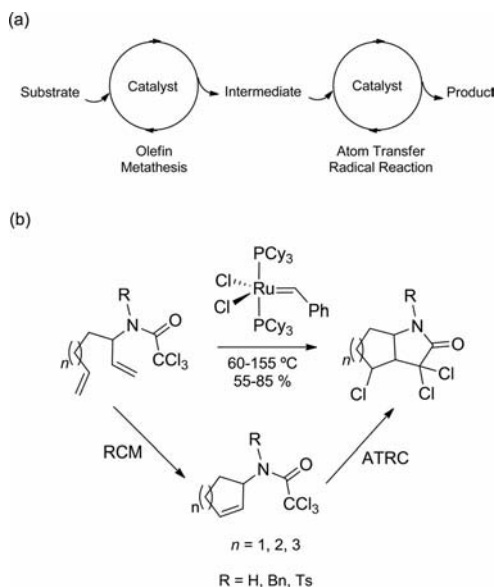
Scheme 16. Tandem RCM/ATRC reactions.

reactions (Scheme 16a).[56] The process created in a one-pot procedure several C–C and C–Cl bonds, leading to the facile preparation of polycyclic compounds from functionalized acyclic precursors (Scheme 16b).

This group has also described further functionalization of the latter bicyclic ring systems by sequential ATRA reactions. However, this process does not strictly match with the definition of a tandem reaction. Quayle[57] described the cross metathesis (CM) reaction of two alkenes followed by an ATRC reaction (Scheme 17). Similarly, Delaude et al. described the use of a homobimetallic ruthenium–indenylidene complex as catalyst for tandem metathesis/ATRC reactions.[58]
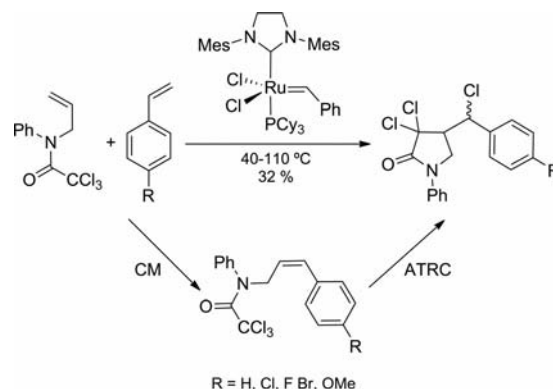
Scheme 17. Tandem CM/ATRC reactions.

Conclusions

Active metal-catalyzed atom transfer radical addition systems based on ruthenium, nickel, or copper have been developed in the last decade. Many of those catalytic systems are quite stable in terms of handling; they are also inexpensive and easy to prepare. Although they were initially applied to model olefins, the time for a wider application as a tool in organic synthesis has come. Particularly attractive is the development of polycyclic molecules by successive ring closing, with the added value of the availability of C–Cl bonds in the final products that are conducive to further functionalization. For future work, the effective asymmetric version[59] of such transformations are yet to be developed. Furthermore, new approaches have to be found to tackle the problem of separating the products from the catalyst.

Acknowledgments

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