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# 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 halogen compounds to olefins constitute a versatile tool in organic synthesis within the area of C-C bond forming transformations. The inter- or intramolecular versions, respectively atom transfer radical addition (ATRA) or cyclization (ATRC), lead to the atom economic, valuable 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*), Kharasch and co-workers observed[1] the formation of the anti-Markovnikov adduct. They proposed that such product was formed by means of a free radical mechanism in which the peroxides acted as free-radical initiators (Scheme 1).
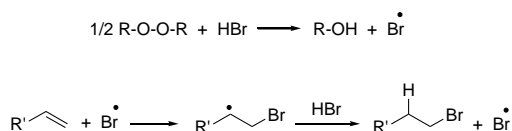

Scheme 1. Addition of hydrogen bromide to unsymmetric alkenes in the presence of peroxide initiators.

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 the radical-mediated olefin polymerization, mainly due to the 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.

In the mid 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 originated by corrosion in the reactor were responsible of the catalytic process, a mechanistic proposal being therefore proposed in which iron chlorides increased the addition rate constant k_a.[4] These seminal findings constituted a breakthrough and can be considered as the beginning of the transition-metal-catalyzed Kharasch reaction, also called atom-

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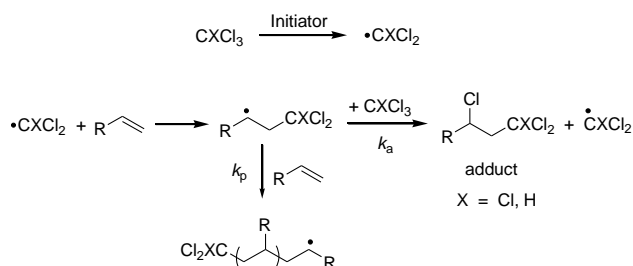
Scheme 2. The Kharasch addition of polyhalogenated compounds to olefins in the presence of an initiator.

transfer radical addition (ATRA).

The commonly accepted mechanism for ATRA reactions initiates 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. This supposes the metal reduction to the initial oxidation state and the
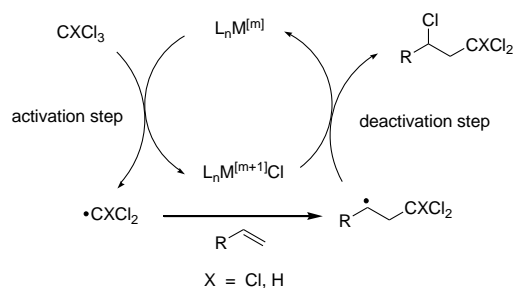
Scheme 3. General Mechanism for Atom Transfer Radical Addition.

formation of the desired addition product (Scheme 3).

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.

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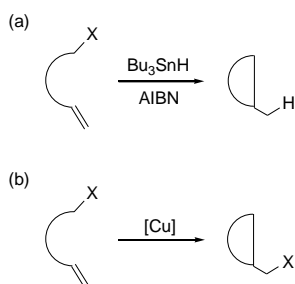
Tomás R. Belderrain (1966) graduated in Chemistry in 1989 in Sevilla. He received his Ph.D. degree in Chemistry (1994) from the Universidad de Sevilla, under the supervision of Prof. Ernesto Carmona. He continued his scientific education as a postdoctoral fellow with Professor Claudio Bianchini (1995), 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 the processes where carbon-carbon bond formation occurs: copper mediated ATRA and ATRP reactions, and palladium complexes as potential catalysts in olefin functionalization reaction.

Pedro J. Pérez (1965) graduated in Chemistry in 1987 and received his Ph.D. degree in Chemistry (1991) in 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

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It was not until the mid-90s when its importance emerged again due to pioneering, separate reports of Sawamoto and Matyjazewski[5] on the related reaction atom transfer radical polymerization (ATRP). In fact, ATRP process initiates 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 narrow molecular weight distribution. Thus, in the last 15 years ATRP has become one of the most powerful polymer synthetic methods. As the leader in the field, Matyjaszewski has reviewed this field 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 environmental unfriendly organotin hydrides methodology (Scheme 4). The most successful catalysts for ATRC

reactions have been copper complexes that has induced the formation of an array of ring sizes (4-18 membered rings). This topic was reviewed by Clark in 2002.[8]

Since the discovery of ATRA reactions, many efforts have been focused to make this reaction in a valuable method in organic synthesis and increase 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 reaction atom-economy and the 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 employing a wide variety of halogenated compounds[9] and improved reducing the large excess of the halogen compound traditionally used. Highly efficient catalysts have been developed in the recent years which have allowed to run the reactions 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 deactivates due to side reactions (radical homocoupling), leaving some of it in the higher oxidation state. The presence of a reducing agent as an additive to help the metal to recover the initial oxidation state, achieving ATRA reactions using catalyst loadings at the ppm levels (Scheme 5).

Scheme 4. (a) Reductive cyclization using Bu₃SnH. (b) Copper-catalyzed atom transfer radical cyclization (ATRC).

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 environmental unfriendly catalyst separation steps. Clark and co-workers have described a range of silica, polystyrene, or JandaJel resin supported copper catalysts bearing pyridinemethanimine or polyamine ligands for ATRC reactions (Figure 1 c).[13]
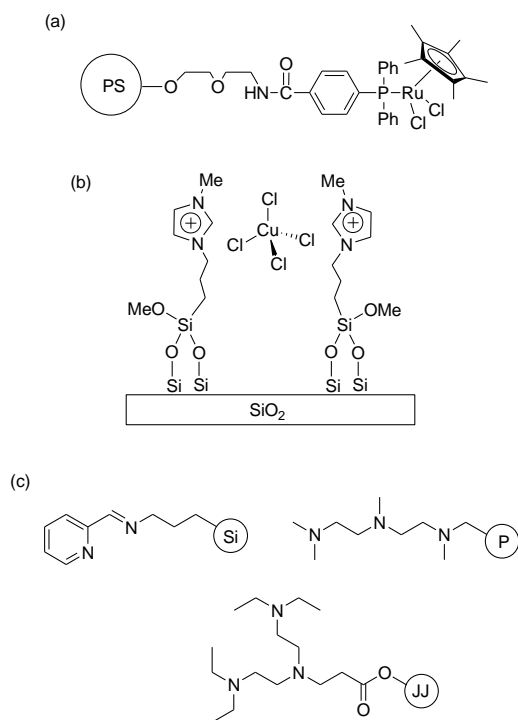

Figure 1. (a) Silica supported copper ion-containing ionic liquid ATRA catalysts. (b) Heterogeneous aqueous polystyrene-polyethylene glycol (PS-PEG) resin-supported ruthenium ATRA catalyst. (c) Some examples of solid-supported ligands employed in copper-catalyzed ATRC reactions.

Atom Transfer Radical Addition

Copper-based Catalyst

Until recently, the use of copper complexes has been mainly restricted to ATRC reactions.[8] However, three decades ago Hajek and co-workers had reported the use of several in situ generated Cu(I) complexes for the addition of halogen 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 trispyrazolylborate ligands efficiently catalyze ATRA reactions of CCl_4 or $CHCl_3$ to 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 eq. of acetonitrile induced an enhancement of yields and selectivity, although reaction rates decreases. This methodology applied with $[Tp^{tBu}Cu(NCMe)]$ as catalyst led us to achieve efficient and
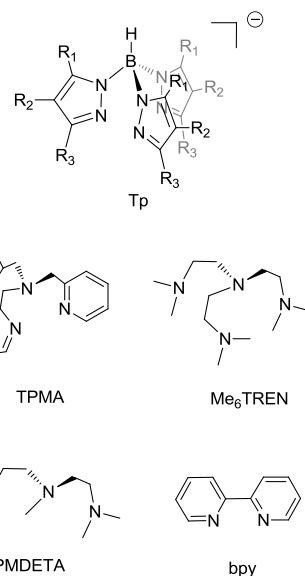

Figure 2. Ligands commonly used for ATRA reactions catalyzed by copper complexes.

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]

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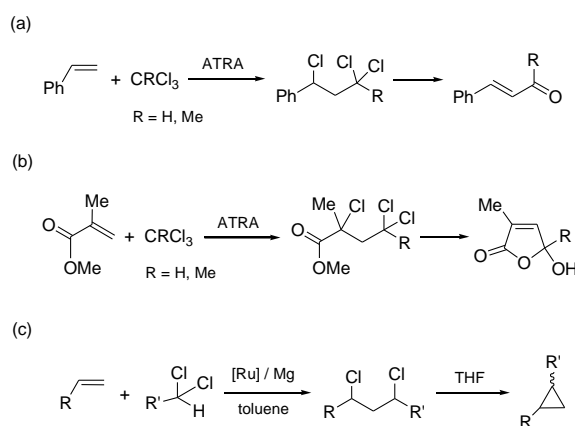
Scheme 6. ATRA Mechanism showing nondesired byproducts.

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-dimethyl valeronitrile), known as V-70, as the reducing agent, provided efficient ATRA reactions with α-olefins with only 0.005 mol % of 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, they have demonstrated the efficacy and versatility of ascorbic acid as a reducing agent (Scheme 7) in
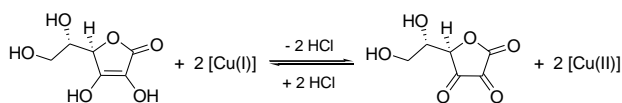
Scheme 7. Proposed mechanism for the copper complex reduction in the presence of ascorbic acid.

copper-catalyzed ATRA reactions:[22] the addition of 7-20 mol% of ascorbic acid relative to alkene, the selective formation of the monoadduct with a catalyst loading of as as low as 5×10^{-3} mol% was observed.

Ruthenium-based Catalyst

Catalytic systems based on ruthenium have been described by far as the most active and efficient for the ATRA reaction of halogenated compounds to 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-phosphine and dicarbollide ligands (Figure 3).[27]
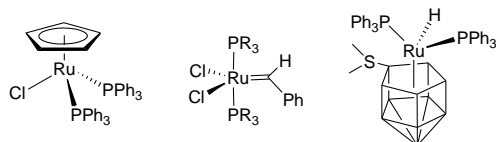

Figure 3. Representative examples of ruthenium catalyst for ATRA reactions.

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 and the reaction conditions of the first generation of Grubbs' catalyst to promote either ring closing metathesis (RCM) or ATRC reactions.[28] Demonceau and co-workers reported that the exchange of tricyclohexylphosphine [RuCl$_2$(p-cymene)(PCy$_3$)] with p-substituted triarylphosphine 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 did 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 initial TOF of 1200 h^{-1}.[32]
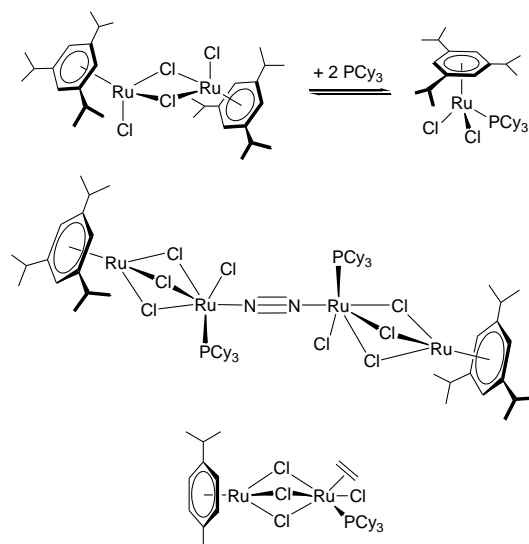
Scheme 8. Di- and tetranuclear ruthenium complexes used as catalysts in ATRA reactions.
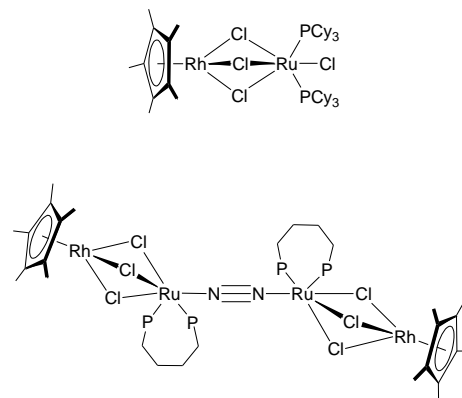

Figure 4. Di- and tetranuclear heterometallic complexes used as catalysts in ATRA reactions.

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's group as catalysts for ATRA reactions.[33] Their studies showed that the simple modification of the chloro neutral complex into a cationic acetonitrile complex result in a significant increase of the catalyst stability. In addition, Severin and co-workers have proposed a methodology to improve the catalytic activity of ruthenium half-sandwich complexes, which consisted in the addition of the radical initiator azobis(isobutyronitrile) (AIBN) as cocatalyst.[34] Such additive continuously regenerates the lower oxidation state of the [Cp*RuCl(PPh$_3$)$_2$] complex. As a result, an exceptionally increase in yields were observed. Such methodology have 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 another 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 could be easily separated by filtration, and reductions take place at ambient temperature. The [RuCl$_2$Cp*(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 Catalyst

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*
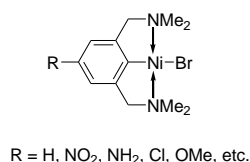

R = H, NO$_2$, NH$_2$, Cl, OMe, etc.

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

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 on the reaction rate with an increase in the bulkiness of the ligand.

Later, van Koten's group extended their investigations to catalyst heterogenization using several supports, with the aim to improve
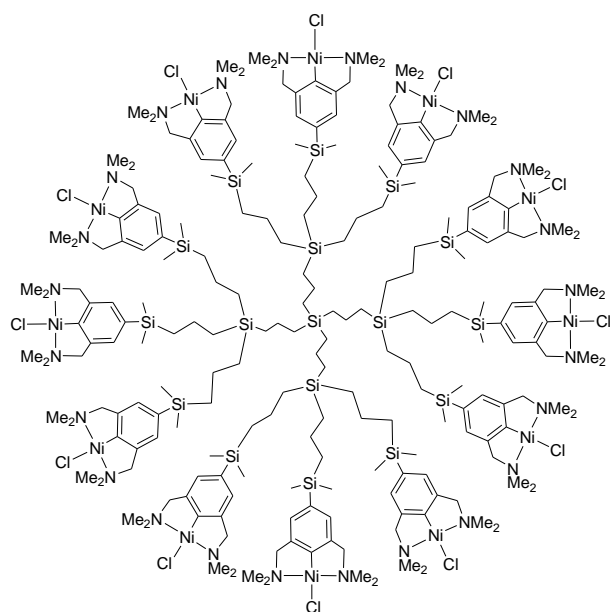

Figure 6. Nickel-centered carbosilane dendrimer.

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

Synthetic Applications

Although an emerging tool in both inter- or intramolecular versions,[41] there no exist a significant number of reports published concerning their use in target-oriented.[42] Among them ATRC reactions have provided access to 2-oxabicyclo[4.3.0]nonanes present in terpenes such as eunicellin (Scheme 9 *a*) or functionalized γ-butyrolactones (Scheme 9 *b*).

(a)

(b)
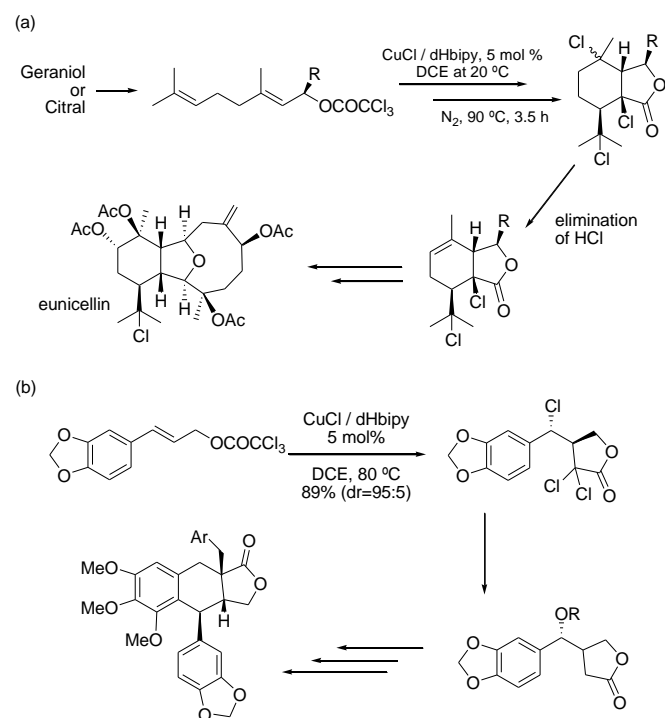
Scheme 9. (a) Sequential ATRC reactions followed by elimination of HCl involved in the total synthesis of eunicellin. (b) Functionalized γ-butyrolactones synthetized by ATRC reactions and subsequent cyclolignan total synthesis.

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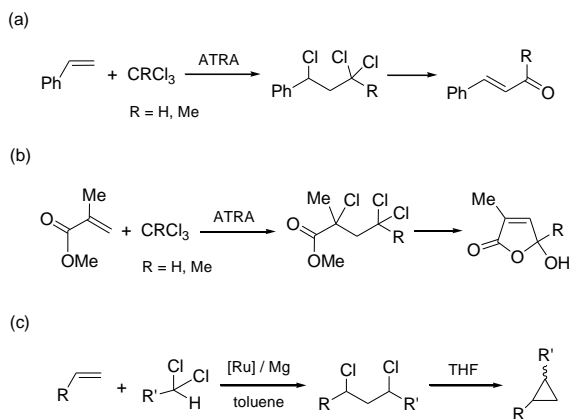
Scheme 10. (a) Synthesis of enals or enones by hydrolysis of styrenyl-derived ATRA products. (b) Synthesis the γ-hydroxybutenolides by hydrolysis of the acrylate-derived ATRA products. (c) Synthesis of substituted cyclopropanes by ATRA reactions followed by dechlorination reaction.

Atom transfer radical reactions can also be combined with other synthetic useful reactions in a sequential fashion 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] cycloaddition and ATRA reactions (Scheme 11).[45]
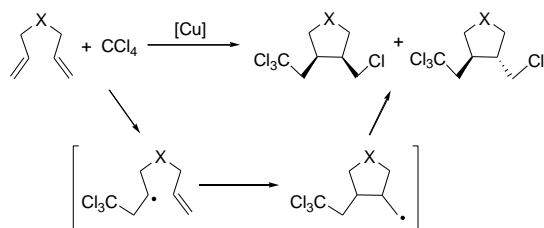

Scheme 11. Copper-catalyzed azide–alkyne [3+2] cycloaddition followed by atom transfer radical addition.

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 have reported the synthesis of linear 1,5-dichlorides by double, sequential ATRA reactions of activated dichlorides to olefins catalyzed by [Cp*RuCl2(PPh3)] in the presence Mg (Scheme 12 a).[47] A variant has been reported by the group of Nagashima, 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 12 b).[48] The double ATRC-ATRC version is also known, exemplified by the synthesis of bicyclic lactams (Scheme 12 c).[48] With the same CuCl/bipyridine system, N-tosyl-N-geranyl trichloroacetamide converted into the corresponding bicyclic lactam in a one-pot reaction. The monocyclic lactam can be isolated as a 2:1 mixture of diastereomers, probing that the reaction is sequential.
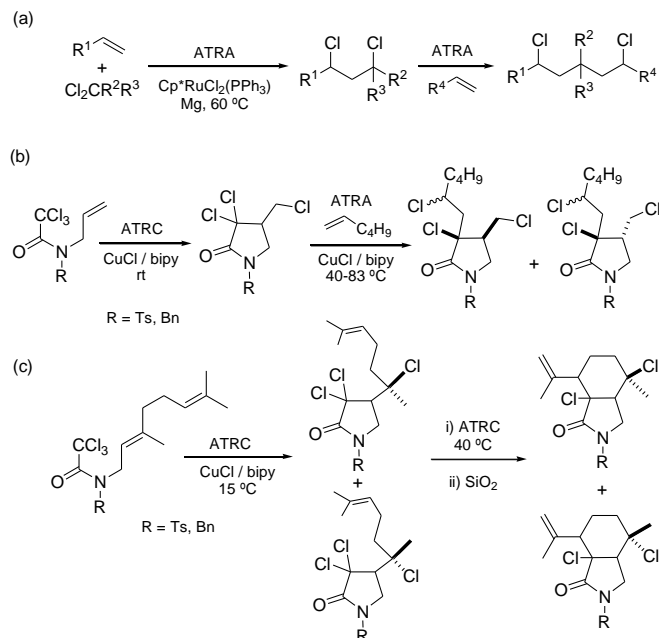
Scheme 12. Various combinations of sequential atoms transfer radical addition (ATRA) and cyclization (ATRC) reactions.

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- or 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 via domino atom transfer radical addition-cyclization (ATRAC) of CCl4 to 1,6-heptadienes (Scheme 13). The
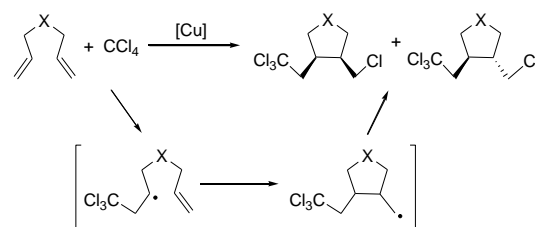

Scheme 13. Synthesis of 1,2-disubstituted cyclopentanes from 1,6-dienes via copper-catalyzed domino atom transfer radical addition-cyclization of CCl4 to 1,6-heptadienes.

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 catalyst employed. Pintauer and co-workers have reported the use of [Cu(TPMA)Cl][Cl] complex as catalyst for such transformations in the presence of AIBN, V-70 or ascorbic acid as a reducing agent. Very high activity were observed using as low as 100 ppm of catalyst loading.[51]

Multi-cyclic systems with high complexity can be afforded by combining two or more ATRC steps in a domino process. Thus, Stevens and co-workers have described the copper-catalyzed synthesis of benzospiro-indolizidinepyrrolidinones by domino ATRC reactions,[52] using CuCl/TMEDA as the catalyst. As shown in Scheme 14 *a*, the process involves a 5-*exo-trig* followed by a 6-
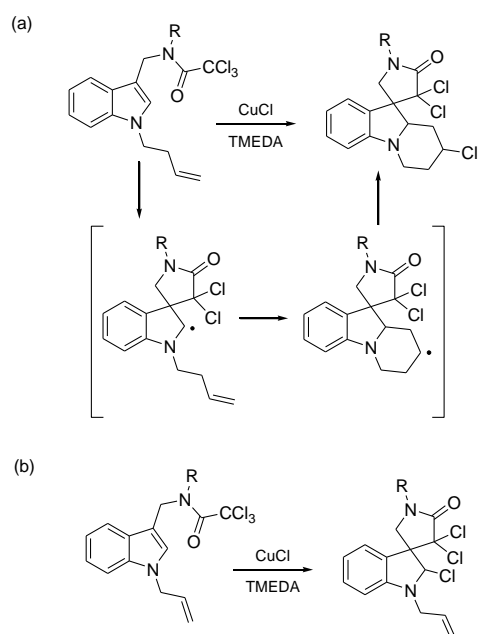
Scheme 14. (a) Synthesis of benzospiro-indolizidinepyrrolidinones by domino ATRC reactions. (b) Simple ATRC.

endo-trig cyclization. However, when the *N*-indole was substituted with an allyl group, only the spiro-cyclization took place (Scheme 14 *b*). According to the Baldwin rules[53] a 5-*endo-trig* cyclization
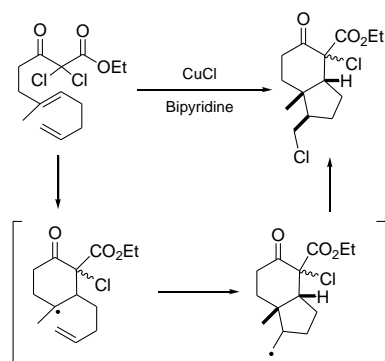
Scheme 15. Synthesis of bicyclic compounds by domino ATRC reaction.

would be disfavoured, whereas the favoured 4-*exo-trig* cyclization would suffer of a considerable ring strain due to the four-membered ring formation.

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 via 6-*endo*-trig followed by a 5-*exo*-trig cyclization, with the concomitant formation of four stereocenters. The reaction was performed at 80 ºC using CuCl / bipyridine as catalyst, leading to the formation of a mixture of 6,5-cis isomers (1:2.3 ratio) in 61% total yield.

Tandem Atom Transfer Radical Reactions

Denmark has defined tandem reactions as a domino reaction in which 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 others processes with just one metal complex being responsible of 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$_3$P)$_2$Cl$_2$Ru=CHPh], was employed to catalyze tandem olefin ring-closing metathesis (RCM)/ATRC reactions (Scheme 16 *a*).[56] The process originated 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 16 *b*).
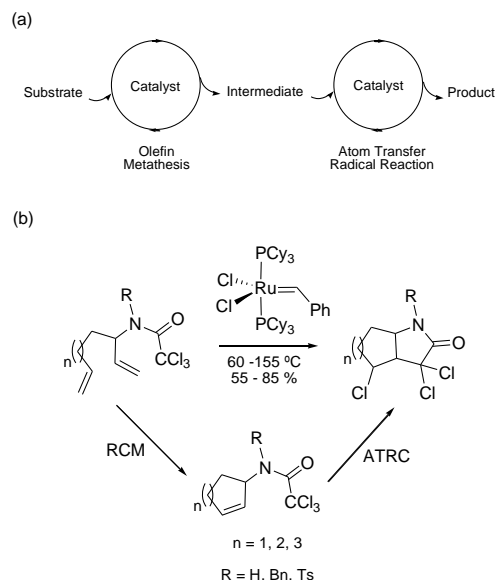
Scheme 16. Tandem RCM / ATRC reactions.

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] has described the cross metathesis (CM) reaction of two alkenes followed by the an ATRC reaction (Scheme 17). Similarly, Delaude's group has described the use of

homobimetallic ruthenium-indenylidene complex as catalyst for tandem metathesis / ATRC reactions.[58]
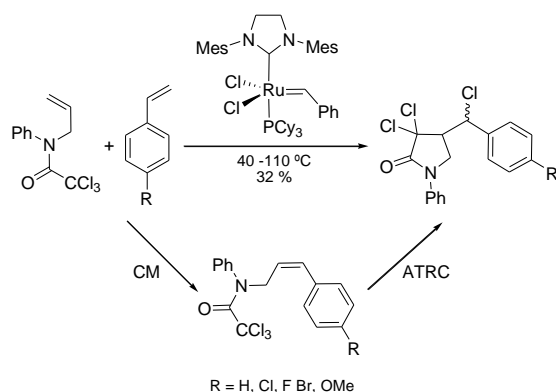
Scheme 17. Tandem CM / ATRC reactions.

Conclusions

Active metal-catalyzed Atom Transfer Radical Addition systems based in ruthenium, nickel or copper have been developed in the last decade. Many of those catalytic systems are quite stable in terms of handling, as well as inexpensive and easy to prepare. Initially applied to model olefins, the time for a wider application as a tool in organic synthesis has come. Particularly attracting 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 susceptible of further functionalization. As a future work, the effective asymmetric version[59] of such these transformations are yet to be developed as well as the approaches to tackle the problem of the products separation from the catalyst.

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Active metal-catalyzed Atom Transfer Radical Addition systems based in ruthenium, nickel or copper have been developed in the last two decades. Many of those catalytic systems are quite stable in terms of handling, as well as inexpensive and easy to prepare. Initially applied to model olefins, the time for a wider application as a tool in organic synthesis has come.

Atom Transfer Radical Reactions

Ru Cu Ni
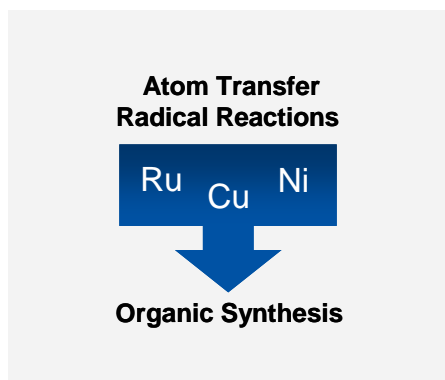
Organic Synthesis

José María Muñoz-Molina, Tomás R. Belderrain,* and Pedro J. Pérez*

Atom Transfer Radical Reactions as a Tool for Olefin Functionalization: On the way to Practical Applications in Organic Synthesis