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Catalyst Regeneration in Transition-Metal-Mediated Atom-Transfer Radical Addition (ATRA) and Cyclization (ATRC) Reactions

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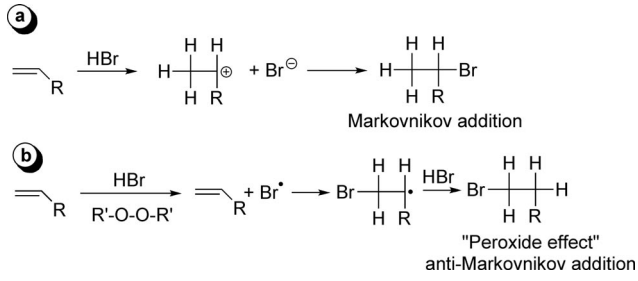
Transition-metal-catalyzed atom-transfer radical addition (ATRA) and cyclization (ATRC) are considered fundamental reactions in organic chemistry for the formation of C–C bonds using free-radical means. Until recently, both processes were plagued by the large amounts of catalysts needed to achieve high selectivity towards the desired target compound (as high as 30 mol-%). The principal problem was the accumulation of the transition metal complex in the higher oxidation state as a result of unavoidable radical-radical termination reactions. In this article, recent advanced in the area of catalyst regeneration in transition-metal-mediated ATRA and ATRC reactions in the presence of free-radical diazo initiators or magnesium as reducing agents are reviewed. The role of the reducing agent in both systems is to continuously regenerate the activator (transition metal complex in the lower oxidation state) from the deactivator (transition metal complex in the higher oxidation state). As a result, ATRA and ATRC reactions can be conducted using very small concentrations of metal catalysts, making this methodology a "greener" alternative to currently available synthetic processes for such organic transformations.

Introduction and Background

The Origins of Atom Transfer Radical Addition

The origins of atom transfer radical addition (ATRA) can be traced back to 1937 when Kharasch and co-workers discovered "the peroxide effect", or anti-Markovnikov addition of HBr to unsymmetrical alkenes in the presence of peroxide initiators (Scheme 1).[1] At the time, these findings were rather unexpected because of the known fact that hydrogen halides react with alkenes via an electrophilic addition mechanism, giving rise to a Markovnikov product. Subsequent work showed that peroxides acted as free-radical initiators in this reaction, generating bromine radicals by homolytic cleavage of the HBr bond. The addition of bromine radicals to an alkene occurred at the least substituted carbon atom producing more stable secondary alkyl radicals, which were in turn irreversibly trapped by hydrogen atom from HBr molecule, giving rise to anti-Markovnikov addition product.



Scheme 1. Addition of hydrogen bromide to unsymmetrical alkene in the absence (a) and presence (b) of free-radical peroxide initiators.

Soon after the discovery of the "peroxide effect" it was recognized that a variety of substrates such as hydrocarbons, polyhalogenated alkanes, alcohols, ethers, amines, aldehydes, ketones, aliphatic acids and esters, and com-

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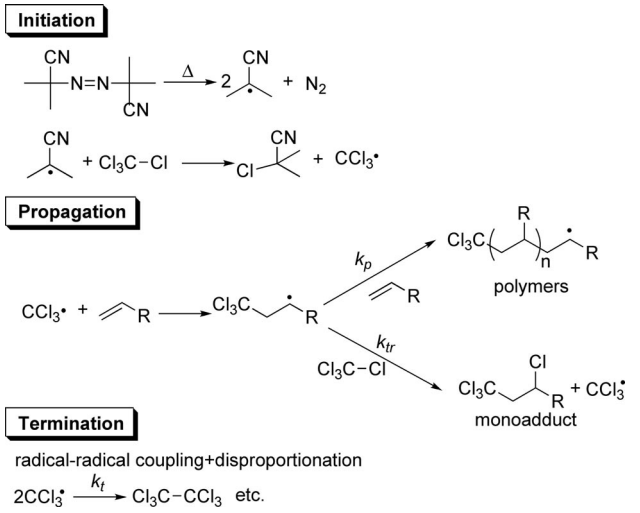
pounds of sulfur, phosphorus, silicon, tin and germanium can be used in the radical addition to alkenes. In particular, Kharasch investigated the addition of polyhalogenated alkanes to alkenes in the presence of free-radical initiators or light (Scheme 2), in a reaction that is today widely referred to as the *Kharasch addition* or *atom transfer radical addition* (*ATRA*).[2,3] Very high yields of the monoadduct were obtained in the case of simple α-olefins such as 1-hexene and 1-octene, but were significantly decreased for more reactive alkenes (styrene, methyl acrylate and methyl methacrylate).

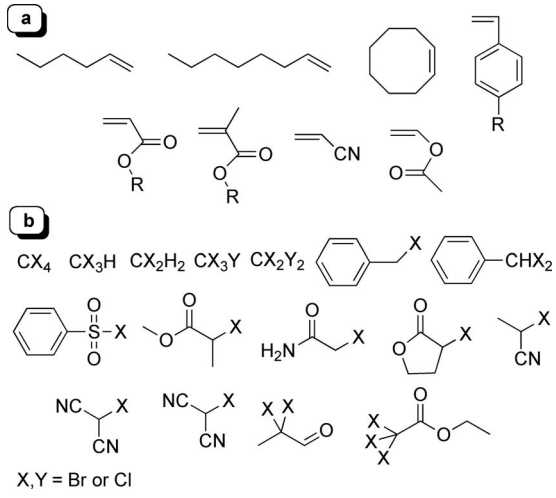


Scheme 2. Kharasch addition of CCl_4 to alkene in the presence of free-radical diazo initiator AIBN.

For alkenes that are highly active in free-radical polymerization, the decreased yield of the monoadduct was mostly the result of radical-radical termination reactions and repeating radical additions to alkene to generate oligomers and polymers. In theory, radical termination reactions by disproportionation and coupling could be suppressed by decreasing the radical concentration (rate of termination $\propto$ [radicals]^2). However, telomerization reactions, which result in the formation of oligomers and polymers, could not be avoided due to the low chain-transfer constant (k_{tr}/k_p, Scheme 2). For example, the reported value of k_{tr}/k_p for CCl_4 and acrylonitrile is 8.65×10^{-5}.[4] This indicates that in ATRA of CCl_4 to acrylonitrile the rate of transfer (k_{tr}[CCl_4]) will approach the rate of free-radical polymerization (k_p[alkene]) when as much as 11560 equiv. of CCl_4 are used relative to acrylonitrile. Even under such conditions, statistically we should expect only 50% yield of the monoadduct. Clearly, the search for a better halogen atom transfer agents was needed.

Fundamentals of Transition-Metal-Catalyzed Atom Transfer Radical Addition

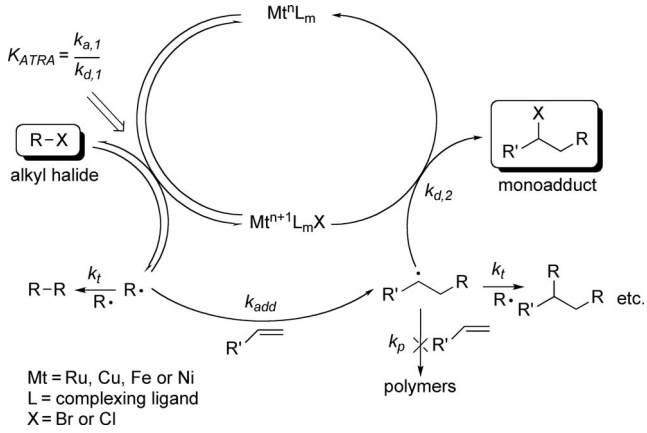
In 1956, Minisci et al. attempted thermal polymerization of acrylonitrile in carbon tetrachloride and chloroform in a steel autoclave.[5] Surprisingly, these reactions yielded considerable amounts of monoadduct (CCl_3–CH_2–CHClCN with CCl_4 and $CHCl_2$–CH_2–CHClCN with $CHCl_3$).[5] As discussed above, these results were unexpected because the chain transfer constants (k_{tr}/k_p) for CCl_4 and $CHCl_3$ are not high enough to prevent polymerization of acrylonitrile. In 1961, a mechanism was proposed in which iron chlorides (arising from corrosion of the autoclave) played a major role in this process by increasing the chain transfer constant.[6–11] This reaction marked the beginning of *transition-metal-catalyzed ATRA* (*TMC ATRA*). Since the initial discovery, a number of transition metals have been found to catalyze ATRA. In particular, complexes of Cu, Ru, Fe and Ni[12–17] were found to be the most effective in not only controlling the product selectivity for highly active alkenes such as styrene, alkyl acrylates and acrylonitrile, but also in catalyzing ATRA reactions utilizing a variety of halogenated compounds (alkyl and aryl halides,[10,18,19] *N*-chloroamines,[10] alkylsulfonyl halides[20–25] and polyhalogenated compounds,[20,25–27] Scheme 3). Therefore, TMC ATRA became broadly applicable synthetic tool.[13–15,28,29]



Scheme 3. Alkenes (a) and alkyl halides (b) commonly used in transition-metal-catalyzed ATRA.

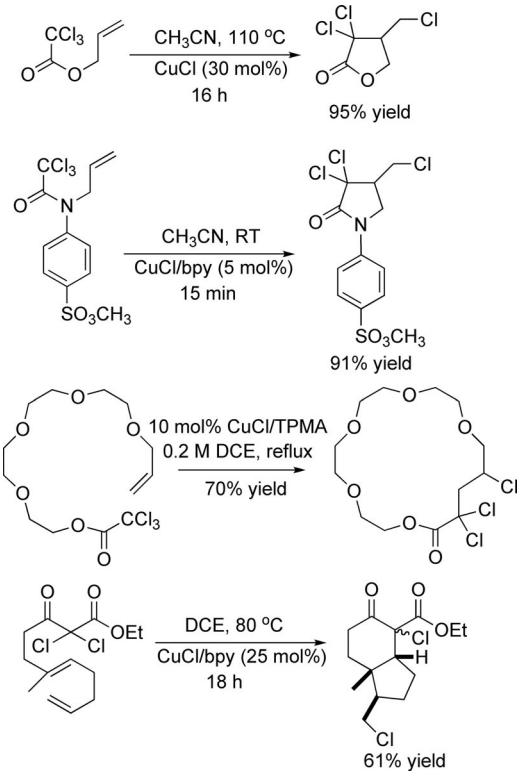
Based on chemo-, regio-, and stereoselectivity, it is generally accepted that the mechanism of TMC ATRA involves free-radical intermediates.[10,20] The proposed mechanism is shown in Scheme 4. The catalytic cycle starts with a homolytic cleavage of an alkyl halide bond by a transition metal complex in the lower oxidation state (Mt^nL_m) to generate an organic radical and the corresponding metal complex in the higher oxidation state ($Mt^{n+1}L_mX$). In the next step, the radical adds to an alkene to form more stable secondary radical, which is irreversibly trapped by the transition metal complex in the higher oxidation state to generate the desired monoadduct. This last step also regenerates the transition metal complex in the lower oxidation state and therefore completes the catalytic cycle. As indicated in Scheme 4, the side reactions that compete with the formation of monoadduct in TMC ATRA include radical termination reactions by coupling or disproportionation and repeating radical addition to alkene resulting in oligomerization/polymerization. There are several guidelines that

should be followed in order to increase chemoselectivity of the monoadduct. Firstly, the radical concentration in the system must be low in order to suppress radical termination reactions (rate constants of activation [$k_{a,1}$ and $k_{a,2}$] << rate constants of deactivation [$k_{d,1}$ and $k_{d,2}$]). Secondly, further activation of the monoadduct should be avoided ($k_{a,1} >> k_{a,2}$, ideally $k_{a,2} \approx 0$). Lastly, formation of oligomers/polymers should be suppressed, indicating that the rate of deactivation ($k_{d,2}$[$Mt^{n+1}L_mX$]) should be much larger than the rate of propagation (k_p[alkene]).



Scheme 4. Proposed mechanism for transition-metal-catalyzed ATRA.

TMC ATRA reactions can also be conducted intramolecularly when alkyl halide and alkene functionalities are part of the same molecule. Intramolecular TMC ATRA or atom transfer radical cyclization (ATRC) is a very attractive synthetic tool because it enables the synthesis of functionalized ring systems that can be used as starting materials for the preparation of complex organic molecules.[15,30] Furthermore, halide functionality in the resulting product can be very beneficial because it can be easily reduced, eliminated, displaced, converted to a Grignard reagent, or if desired serve as a further radical precursor. The use of TMC ATRC in organic synthesis has been reviewed recently.[15,29–32] Some examples showing the formation of lactones, lactams, cyclic ethers and bicyclic compounds (as a result of radical cascade reaction) in copper-catalyzed ATRC are illustrated in Scheme 5.



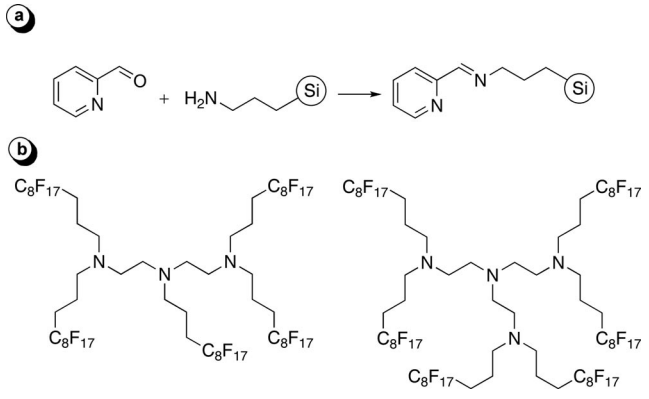
Scheme 5. Examples of copper-catalyzed ATRC reactions.

"Greening" of Transition-Metal-Catalyzed Atom Transfer Radical Processes

TMC ATRA and ATRC reactions are versatile tools for the synthesis of small organic molecules starting from alkyl halides and alkenes.[14,15,28,33–37] However, these methods for carbon–carbon bond formation are still not fully utilized in free-radical synthesis, and are by far much less represented in literature than standard tin hydride mediated radical addition to olefins[38] and iodine atom transfer radical reactions.[39] The principal reason for small participation of TMC ATRA and ATRC reactions in organic synthesis until recently remained the large amount of metal catalyst needed to achieve high selectivity of the desired monoadduct (typically between 5 and 30 mol-% relative to substrate). Such large amounts of catalyst were required in these transformations in order to compensate for the accumulation of the deactivator or transition metal complex in the higher oxidation state, as a result of unavoidable and often diffusion controlled radical termination reactions ($k_t \approx 2.0 \times 10^9$ $M^{-1} s^{-1}$). To emphasize this point a little further, one needs to take into account that the activation of alkyl halide ($k_{a,1}$) and deactivation of the resulting radical ($k_{d,1}$) in TMC ATRA are in equilibrium ($K_{ATRA} = k_{a,1}/k_{d,1}$, Scheme 4). Increasing the concentration of alkyl halide relative to activator (transition metal complex in the lower oxidation state) results in the shift of the ATRA equilibrium towards its right hand side. Since the radical concentration in the system increases, so does the rate of radical termination. Every termination step further shifts the ATRA equilibrium towards deactivator (transition metal complex in the higher oxidation state), until essentially deactivator remains the only species in the reaction mixture. Without activator, the homolytic cleavage of carbon-halide bond cannot occur, and the ATRA reaction will reach only limited conversions.

Until recently, relatively high amount of transition metal catalysts in ATRA made this methodology rather unsuitable for fine chemical synthesis because of lengthy procedures needed to remove the catalyst from the reaction mixture. Also, on the other hand, the process was generally considered non-atom-economic because it required relatively large excess of alkyl halide, environmentally un-

friendly and expensive. From the early stages, researchers have recognized these limitations of TMC ATRA and various methodologies have been developed to overcome these problems. In particular, catalyst removal in TMC ATRA was addressed through the design of solid supported catalysts,[15,40,41] as well as the use of biphasic systems containing fluorous solvents (Scheme 6).[42–45] Additionally, particularly in the case of copper, various highly active nitrogen based complexing ligands have been developed that enable homogeneous ATRA reactions to be conducted using much smaller amounts of metal.[46,47] However, by far, the most attractive method that solves the above issues in TMC ATRA reactions involves catalyst regeneration in the presence of environmentally benign reducing agents.[36,48–53] As will be discussed in the following sections of this article, this new methodology enables the synthesis of single addition adducts in ATRA and ATRC using ppm levels of the catalyst.



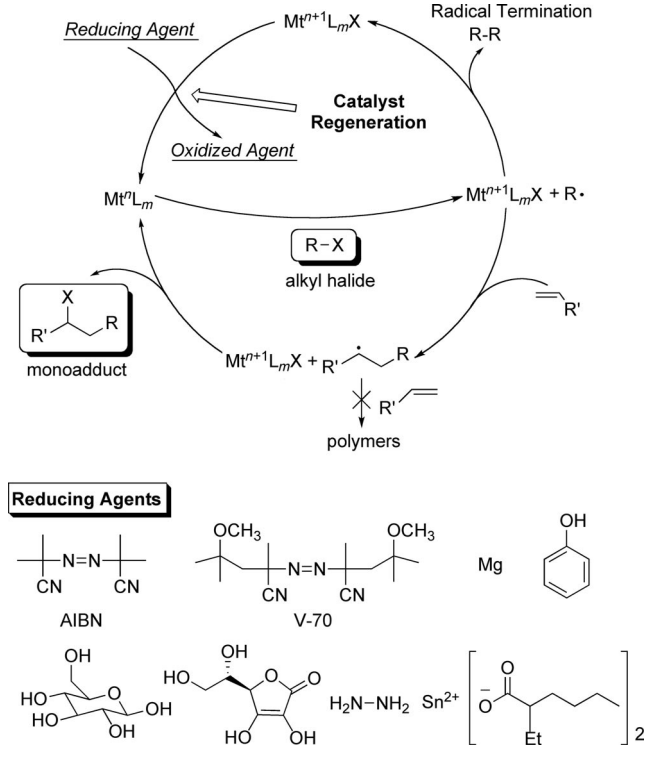
Scheme 6. Synthesis of solid supported nitrogen based ligands for copper-catalyzed ATRA and ATRC (a) and perfluorous ligands commonly used in biphasic systems (b).

Highly Efficient Transition-Metal-Catalyzed ATRA and ATRC Reactions in the Presence of Reducing Agents

Catalyst Regeneration in the Presence of Reducing Agents

As aforementioned, the principal reason for the need of high catalyst concentration in TMC ATRA under standard reaction conditions ($[Mt^nL_m]_o$:$[RX]_o$:$[alkene]_o$ = (5–30):400:100) is the fact that radical termination reactions lead to the irreversible accumulation of the persistent radical or deactivator (transition metal complex in the higher oxidation state). Consequently, lowering catalyst concentration in the system relative to alkyl halide will result in only limited conversions of alkene and small yields of the desired monoadduct.

Originally, the solution to this problem has been found for copper-catalyzed atom transfer radical polymerization (ATRP).[36,48–51,54–57] ATRP is mechanistically similar to ATRA, with the exception that the structure of alkyl halide is modified in such a way that more than one activation/deactivation cycle can occur. As a result, polymers with predetermined molecular weights and narrow molecular weight distribution can be synthesized. Subsequently, this methodology was then applied first to ruthenium[53] and then copper-catalyzed[52] ATRA reactions. In all of these processes, the activator (transition metal complex in the lower oxidation state) is continuously regenerated from deactivator (transition metal complex in the higher oxidation state) in the presence of reducing agents such as phenols, glucose, ascorbic acid, hydrazine, tin(II) 2-ethylhexanoate, magnesium, and free-radical initiators (Scheme 7). Such regeneration compensates for unavoidable radical termination reactions, enabling a significant reduction in the amount of metal catalyst. When applied to ATRA of CCl_4 to alkenes catalyzed by $Cp^*Ru^{III}Cl_2(PPh_3)$ complex in the presence of AIBN, TONs as high as 44500 were obtained.[53] Even more impressive TONs were achieved with CBr_4 and [Cu^{II}-(TPMA)Br][Br] [TPMA = tris(2-pyridylmethyl)amine] complex (as high as 160000), enabling efficient ATRA reactions in the presence of as low as 5 ppm of copper.[58] Previous TONs for copper-catalyzed ATRA ranged between 0.1 and 10.[15,36] Since the initial reports by our,[52] and the research group of Severin,[53] this method of catalyst regeneration in ATRA has been utilized in a series of organic transformations, with particular emphasis on detailed structural and mechanistic understanding of this process.[36,59–82] This, in turn, could be a visible indicator that this methodology is on a potential trajectory to become a "greener" alternative to currently available synthetic processes for such organic



Scheme 7. Proposed mechanism for catalyst regeneration in ATRA in the presence of reducing agents.

transformations.[35–37] The following sections describe synthetic applications and kinetic features of this novel catalytic system.

Highly Efficient TMC ATRA Reactions in the Presence of Reducing Agents

Ruthenium and copper complexes are among the most active catalysts for ATRA and ATRC reactions of (poly)-halogenated compounds to alkenes.[12,14,15,17,35–37,46] However, as discussed above, excessive catalyst loadings are required in order to achieve high yields of the monoadduct. Since radical termination reactions in these systems result in accumulation of the transition metal complex in the higher oxidation state, in principle, it should be possible to increase the lifetime of the catalyst by the addition of a reagent that could regenerate the metal complex in the lower oxidation state.

This was first realized in TMC-catalyzed ATRA reactions using [Cp*$Ru^{III}Cl_2(PPh_3)$][53] (Figure 1) and [Cu^{II}-(TPMA)X][X][52,58] [TPMA = tris(2-pyridylmethyl)amine, X = Br or Cl, Figure 2] complexes in conjunction with free-radical diazo initiator AIBN [2,2′-azobis(2-methylpropionitrile)] as a reducing agent. The results are summarized in Tables 1 and 2. For ruthenium-catalyzed ATRA, unprecedented turn over numbers (TONs) were obtained in the addition of CCl_4 to simple α-olefins such as 1-hexene (44500) and 1-decene (23300). However, more reactive alkenes (styrene and methyl acrylate) required higher catalyst loadings [1:1000<$(Ru^{III})_o$:(alkene)$_o$<1:15000]. The principal reason was not inefficient catalyst regeneration or further activation of the monoadduct, but rather competing free-radical polymerization initiated by AIBN. The potential solution to this problem is to utilize reducing agents that do not generate free radicals such as magnesium.[65] As indicated in Table 1, higher catalyst loadings were required when Mg was used to regenerate the active ruthenium(II) complex. However, generally, higher product selectivity was achieved. Furthermore, the heterogeneous nature of this system makes it relatively easy to separate the addition product from unreacted magnesium and $MgCl_2$ by simple filtration.

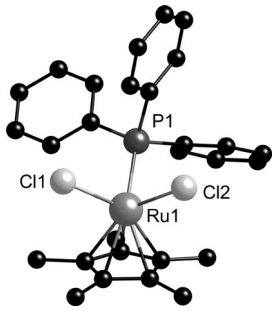


Figure 1. Molecular structure of [Cp*$Ru^{III}Cl_2(PPh_3)$]. H-atoms and co-crystallized solvent molecules have been omitted for clarity.[65]

Similarly to ruthenium, copper-catalyzed ATRA using [Cu^{II}(TPMA)X][X] (X = Cl and Br) complexes was also very successful in the presence of AIBN as a reducing agent

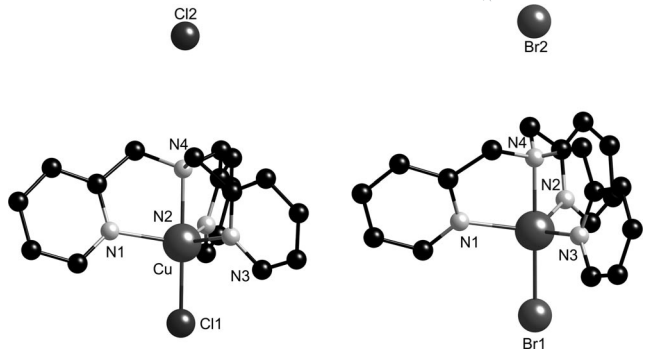


Figure 2. Molecular structures of [Cu^{II}(TPMA)Cl][Cl] and [Cu^{II}-(TPMA)Br][Br] complexes. H-atoms have been omitted for clarity.[52,58]

Table 1. ATRA of polychlorinated compounds and *p*-tosyl chloride to alkenes catalyzed by complex [Cp*$Ru^{III}Cl_2(PPh_3)$] in the presence of reducing agents.[53,65]

Alkene	R–Cl	Reducing agent	$[Alk]_o/[Ru^{III}]_o$	Yield [%]
Styrene	CCl_4	AIBN[a]	15000:1	88 (82)[b]
		Mg[c]	5000:1	97
	$CHCl_3$	AIBN	1500:1	88 (85)[b]
		Mg	2000:1	92
	CCl_3CO_2Et	AIBN	1000:1	95
		Mg	1000:1	94
	CCl_2HCO_2Et	AIBN	1000:1	96
		Mg	5000:1	90
	*p*TsCl	AIBN	1000:1	98
		Mg	1000:1	98
α-Methylstyrene	CCl_4	AIBN	10000:1	98
		Mg	5000:1	93
	$CHCl_3$	Mg	1000:1	26
	CCl_3CO_2Et	Mg	1000:1	82
	CCl_2HCO_2Et	Mg	1000:1	94
	*p*TsCl	AIBN	1000:1	96
		Mg	1000:1	97
p-Cl-Styrene	CCl_4	Mg	5000:1	95
	$CHCl_3$	AIBN	1500:1	88
		Mg	2000:1	89
	CCl_3CO_2Et	Mg	1000:1	91
	CCl_2HCO_2Et	Mg	1000:1	95
	*p*TsCl	AIBN	1000:1	95
1-Hexene	CCl_4	AIBN	50000:1	89
1-Decene	CCl_4	AIBN	25000:1	93 (87)[b]
		Mg	5000:1	81
	$CHCl_3$	Mg	500:1	21
Methyl methacrylate	CCl_2HCO_2Et	AIBN	1000:1	94
		Mg	1000:1	84
	CCl_3CO_2Et	Mg	1000:1	67
	*p*TsCl	Mg	1000:1	69
	CCl_4	Mg	10000:1	86
	$CHCl_3$	Mg	500:1	48

[a] Reactions with AIBN were conducted at 60 °C. [b] Isolated yield after column chromatography. [c] Reactions with Mg were conducted at ambient temperature.

(Table 2).[52,58] In the case of [Cu^{II}(TPMA)Cl][Cl], the addition of CCl_4 to simple α-olefins proceeded efficiently with the catalyst to alkene ratio as low as 1:10000, resulting in TONs of 7200 for 1-hexene and 6700 for 1-octene.[52] However, significantly higher catalyst loadings were required for methyl acrylate and styrene, due to competing free-radical

Table 2. ATRA of polyhalogenated compounds to alkenes catalyzed by [Cu^{II}(TPMA)X][X] (X = Cl or Br) complexes in the presence of reducing agent.[52,58]

Alkene	R–Cl	Red. agent	$[Alk]_o/[Cu^{II}]_o$	Yield [%]
[Cu^{I}(TPMA)Cl] or [Cu^{II}(TPMA)Cl][Cl]				
1-Hexene	CCl_4	AIBN[a]	10000:1	72
		V-70[b]	2000:1	85
	$CHCl_3$	AIBN	1000:1	56
1-Octene	CCl_4	AIBN	10000:1	67
			5000:1	87
		V-70	2000:1	84
	$CHCl_3$	AIBN	500:1	49
Styrene	CCl_4	AIBN	250:1	85
		V-70	500:1	51
	$CHCl_3$	AIBN	1000:1	58
Methyl acrylate	CCl_4	AIBN	1000:1	60
		V-70	1000:1	84
	$CHCl_3$	AIBN	1000:1	63
Methyl methacrylate	CCl_4	V-70	1000:1	66
Vinyl acetate	CCl_4	V-70	1000:1	94
[Cu^{II}(TPMA)Br][Br]				
1-Hexene	CBr_4	V-70	50000:1	93
1-Octene	CBr_4	V-70	50000:1	93
1-Decene	CBr_4	V-70	50000:1	88
Methyl acrylate	CBr_4	AIBN	200000:1	81 (76)[c]
			100000:1	94
		V-70	10000:1	82
	$CHBr_3$	AIBN	500:1	66
		V-70	1000:1	48
Styrene	CBr_4	AIBN	200000:1	95 (86)[c]
		V-70	2000:1	57
	$CHBr_3$	AIBN	5000:1	77
		V-70	1000:1	70
Methyl methacrylate	CBr_4	V-70	10000:1	71
Vinyl acetate	CBr_4	V-70	2000:1	87

[a] Reactions with AIBN were conducted at 60 °C. [b] Reactions with V-70 were conducted at ambient temperature. [c] Isolated yield after column chromatography.

polymerization initiated by AIBN. Even more impressive results were obtained in ATRA of polybrominated compounds to alkenes catalyzed by [Cu^{II}(TPMA)Br][Br] complex in the presence of AIBN.[58] This selection of the catalyst and alkyl halide should result in a significant improvement in the catalytic activity because Cu–Br and C–Br bonds are much weaker than the corresponding chloride analogues. Indeed, as shown in Table 2, the activity of [Cu^{II}(TPMA)Br][Br] complex in ATRA of polybrominated compounds to alkenes in the presence of AIBN, based on catalyst loadings, conversion of alkene, and the yield of monoadduct, was approximately 10 times higher than the activity of [Cu^{II}(TPMA)Cl]Cl]. Also, for comparable monomers and alkyl halides, its activity exceeded the activity of [Cp*$Ru^{III}Cl_2(PPh_3)$] complex.[53] [Cu^{II}(TPMA)Br][Br], in conjunction with AIBN, effectively catalyzed ATRA reactions of polybrominated compounds to alkenes with concentrations between 5 and 100 ppm, which was by far the lowest number achieved in any metal mediated ATRA.[15,29,35–37,83–86] As discussed above, the use of magnesium as a reducing agent in ruthenium-catalyzed ATRA eliminates free-radical polymerization commonly associated with free-radical initiator such as AIBN. Alternatively, this competing side reaction can be minimized by utilizing low temperature free-radical diazo initiators such as V-70 [2,29-azobis(4-methoxy-2,4-dimethyl valeronitrile)].[67] V-70 can be utilized at room temperature and easily, together with radical decomposition products, removed from the reaction mixture. From the results summarized in Table 2, it is evident that this free-radical initiator enables selective formation of the monoadduct at ambient temperatures with α-olefins and highly active alkenes such as methyl acrylate, methyl methacrylate and vinyl acetate using as low as 0.002 mol-% of copper.

So far, we have demonstrated that reducing agents enable a significant reduction in the amount of ruthenium or copper complexes in ATRA of polyhalogentated compounds to alkenes. Another advantage of this methodology, apart from low catalyst loadings, is the fact that air stable and easy to handle metal complexes in the higher oxidation state (deactivators) can be utilized. Lastly, free-radical initiators as reducing agents can also be used to consume oxygen from the reaction mixture and therefore eliminate deoxygenation step.

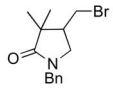
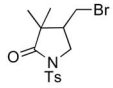
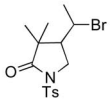
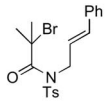
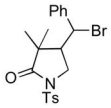
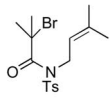
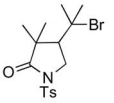
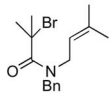
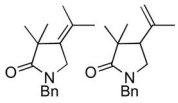
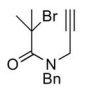
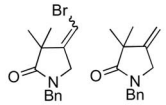
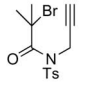
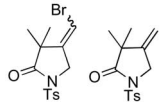
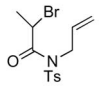
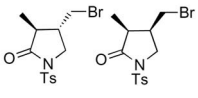
Highly Efficient TMC/ATRC Reactions in the Presence of Reducing Agents

Reducing agents such as free-radical diazo initiators and magnesium have been shown to be particularly effective in decreasing concentrations of ruthenium and copper complexes in intermolecular ATRA of polyhalogenated compounds to alkenes.[36,52,53,58,65,67,75] The logical extension of this methodology is to conduct intramolecular ATRA, also commonly known as atom transfer radical cyclization (ATRC). ATRC reactions are synthetically more attractive because they enable the synthesis of functionalized ring systems that can be used as starting materials in the preparation of complex organic molecules.[15]

The methodology used to regenerate activator in ATRA originally developed for Ru[53] and Cu[52,58] catalysts has been successfully utilized in a range of 5-*exo*-*trig* and 5-*exo*-*dig* ATRC reactions of bromoacetamides using 0.1–1 mol-% of Cu^{I}(TPMA)Br or [Cu^{II}(TPMA)Br][Br] complexes (Table 3).[68] The presence of AIBN as a reducing agent enabled a 30–300 fold reduction in the amount of catalyst previously reported for such cyclizations.[15,41,87–90] In a related study, [Cp*$Ru^{III}Cl_2(PPh_3)$] complex, in conjunction with magnesium as a reducing agent, was also shown to be effective in ATRC reactions producing lactones, lactams and furans in excellent yields (Table 4).[65] *N*-allyldichloroacetamides are generally considered less reactive substrates for ATRC and when standard catalysts, such as $Cu^{I}Cl$/bpy[91] (bpy = 2,2′-bipyridine) or [$RuCl_2(PPh_3)_3$][92] are used, high catalyst loadings and/or elevated reaction temperatures are required. Although some ruthenium catalysts have been reported to catalyze ATRC reactions with these substrates at ambient temperatures and relatively low catalyst loadings, the main drawback of these complexes is their high air and moisture sensitivity.[91,93] As indicated in

Table 4, *N*-allyl-*N*-tosyldichloroacetamide successfully undergoes ATRC using as low as 5 mol-% of air stable [Cp*$Ru^{III}Cl_2(PPh_3)$] complex, in combination with Mg, yielding 94% of the corresponding γ-butyrolactam after 4 h at room temperature.

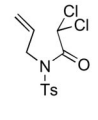
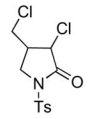
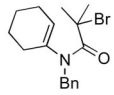
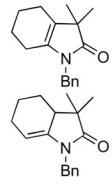
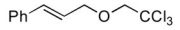
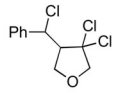
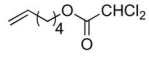
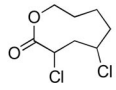
Table 3. ATRC of bromoacetamides catalyzed by copper complexes with TPMA ligand in the presence of AIBN.[68]

Substrate[a]	Product	Solvent	*T* [°C]	Yield [%]
		CH_2Cl_2	50	84
		CH_2Cl_2	50	97[b]
		toluene	110	87
		CH_2Cl_2	50	95
		CH_2Cl_2	50	100
		CH_2Cl_2	50	99
		CH_2Cl_2	50	99
		CH_2Cl_2	50	13[b]
		toluene	110	88(1:2)[b]
		CH_2Cl_2	50	30(3:2)
		toluene	110	51(1:1)
		CH_2Cl_2	50	33(1:2)
		toluene	110	67(1:1)
		toluene	110	80(1:1)[b]
		toluene	110	90(4:1)

[a] Reactions were performed with [substrate]$_o$:[Cu^I or Cu^{II}]$_o$:[AIBN]$_o$ = 1:0.01:0.10 for 24 h. [b] $CuBr_2$/TPMA complex was used instead.

The 5-endo cyclization reaction of α-bromo enamides has been investigated by Clark et al.[15,40,88,89] Tertiary bromo enamides can be cyclized at room temperature using 30 mol-% of Cu^IBr/Me_6TREN complex {Me_6TREN = tris[2-(*N*,*N*-dimethylamino)ethyl]amine} in a reaction that proceeds through a radical-polar crossover mechanism with elimination of HBr.[88] Using the same ruthenium complex and Mg, instead of Cu^IBr/Me_6TREN, the catalyst concentration can be reduced to 0.05 mol-% without compromising the yield of the reaction (Table 4).

Table 4. ATRC reactions catalyzed by [Cp*$Ru^{III}Cl_2(PPh_3)$] in the presence of Mg.[65]

Substrate[a]	Product(s)	[Ru]$_o$ [mol-%]	*T* [°C]	*t* [h]	Yield [%][b]
		5	r.t.	4	94
	(87:13)				
		0.05	r.t.	9	94
	(37:63)				
		0.5	r.t.	9	89
	(92:8)				
		1	60	48	67
	(86:14)				

[a] The reactions were performed in the presence of activated Mg powder with [substrate]$_o$ = 0.14 M. [b] Isolated yield.

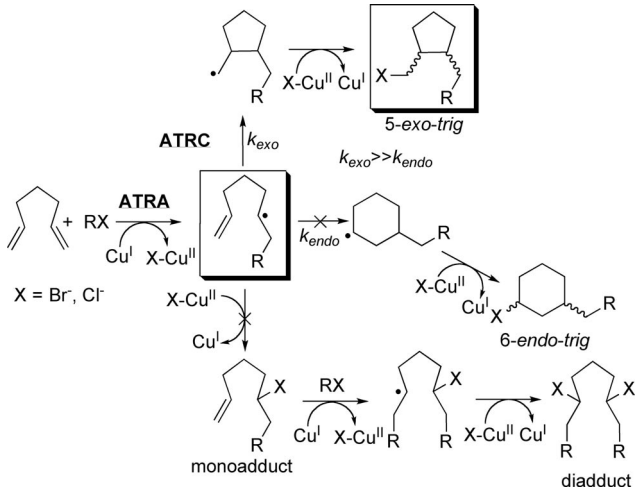
The last two examples in Table 4 indicate that Mg is also effective reducing agent in ruthenium-catalyzed ATRC reactions of ethers and dichloroesters. The ATRC of 2,2,2-trichloroethyl ethers has been previously studied by Ram and Charles.[94] However, efficient cyclizations were achieved at 80 °C using as much as 30 mol-% of Cu^ICl/bpy complex. Similar catalyst loadings were also required for ATRC of dichloroesters to yield medium-sized lactones.[43,44,95]

Atom Transfer Sequential Radical Addition/Cyclization Processes

The principal advantages of the methodology for catalyst regeneration in atom transfer sequential radical addition/cyclization reactions are two fold. On one hand, the presence of reducing agents enables a significant reduction in the amount of metal catalyst. Such reduction is very beneficial because it increases the radical annulation efficiency by decreasing the rate of radical trapping by the deactivator (transition metal complex in the higher oxidation state), compared to the rate of radical ring closure. On the other

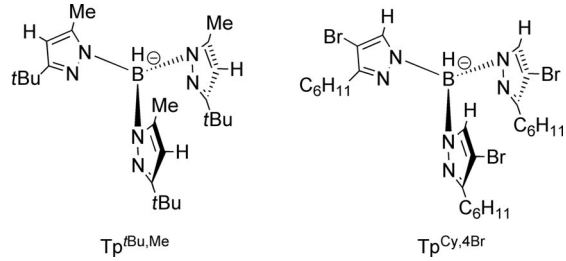
hand, the rate constant of deactivation can be further controlled through the choice of complexing metal or ligand design.

1,6-Dienes are excellent candidates to further expand the methodology for catalyst regeneration originally developed for ATRA,[52,53,58] because the addition of radicals generated from alkyl halides results in a formation of 5-hexenyl radicals, which are known to undergo very fast and selective 5-*exo-trig* mode of cyclization ($k_{exo-trig} \approx 10^5$ s^{-1} and $k_{exo-trig}/k_{endo-trig} \approx 100$).[96] To demonstrate this point a little further, let us consider the rate constant of deactivation ($k_{d,1}$, Scheme 4) for copper(II) complexes with highly active TPMA ligand. In a recent study for ATRA of CCl_4 to various alkenes, these rate has been estimated to be on the order of 10^8 M^{-1} s^{-1}.[71] Assuming that the initial concentration of diene in the system is 1.0 M, the rate of radical ring closure (resulting in 5-*exo-trig* cyclic product) will approach the rate of radical trapping (resulting in the formation of halogen terminated open chain monoadduct and diadduct) at copper(II) concentrations on the order of 1.0×10^{-3} M (0.1 mol-% relative to diene). These ATRA/ATRC pathways are illustrated in Scheme 8. Statistically, under such conditions, equal amounts of the cyclic product and monoadduct and/or diadduct are expected to form. Therefore, in theory, the selective formation of 5-*exo-trig* cyclic product could be obtained using even lower copper(II) concentrations, provided that a reducing agent is present in the system The reducing agent continuously regenerates copper(I) from copper(II) complex. The latter accumulates in the system as a result of unavoidable radical-radical termination reactions, especially under ATRA conditions that utilize large excess of alkyl halide relative to copper catalyst.



Scheme 8. ATRA/ATRC pathways in the addition of alkyl halides to 1,6-heptadiene catalyzed by copper complexes.

The results for ATRA followed by sequential ATRC of CCl_4 to various 1,6-dienes catalyzed by [Cu^{II}(TPMA)Cl][Cl][70] and Cu^{I}Tp^{X}[69] (X = *t*Bu,Me or Cy,4Br, Scheme 9) complexes in the presence of free-radical diazo initiators (AIBN or V-70) and Mg as reducing agents are summarized in Table 5. AIBN- or V-70-initiated ATRA of carbon tetrachloride to 1,6-heptadiene in the absence of a catalyst resulted in approximately 20% yield of the 5-*exo-trig* product, which formed as a result of simple Kharasch addition. For all other dienes investigated, no cyclic products were observed. However, when [Cu^{II}(TPMA)Cl][Cl] complex was used in combination with the free-radical diazo initiator, truly remarkable results were obtained. In the presence of AIBN at 60 °C, cyclic products derived from the addition of CCl_4 to 1,6-heptadiene, diallyl ether and *N*,*N*-diallyl-2,2,2-trifluoroacetamide were synthesized in nearly quantitative yields using as low as 0.02 mol-% of the catalyst (relative to diene). On the other hand, excellent results with *tert*-butyl-*N*,*N*-diallylcarbamate and diethyl diallylmalonate were also achieved using even smaller amounts of the catalyst (0.01 mol-%). Cyclizations were also very efficient at ambient temperature using V-70 as a reducing agent, although slightly higher catalyst loadings were required (0.04–0.1 mol-%).



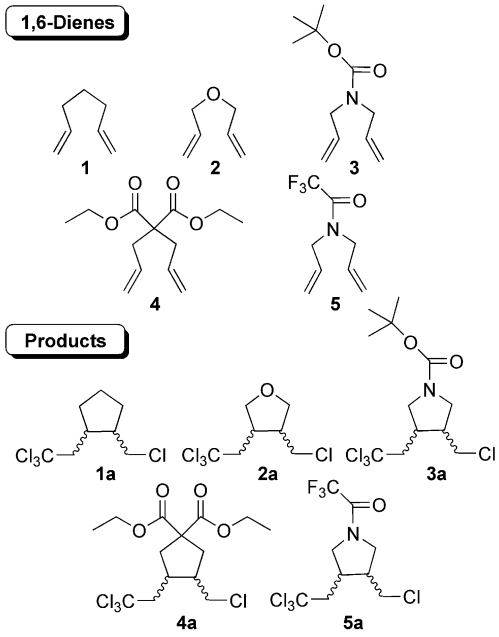
Scheme 9. Monoanionic homoscorpionate ligands (Tp^{X}) for copper-catalyzed ATRA followed by sequential ATRC.[69]

Similarly, neutral copper(I) homoscorpionate complexes also required higher catalyst loadings at 30 °C (1 mol-%).[69] However, these complexes have been shown to be quite promising in ATRA reactions in the absence of any reducing agents.[97,98] The catalytic mechanism is presently not very well understood, however, it appears that the equilibrium between copper(I) and copper(II) species in these systems is controlled through the addition of ancillary ligand such as acetonitrile, which in turn suppresses radical termination reactions. The data presented in Table 5 also indicate that regardless of the choice of diene, catalyst, reaction temperature or reducing agent, 1,2-disubstituted cyclopentanes showed a strong preference for the formation of the *cis* product, which was also observed in similar free-radical cyclizations that do not utilize transition metal complexes as halogen atom transfer agents.[99–101]

Sequential Organic Transformations Involving ATRA or ATRC

So far, we have demonstrated that reducing agents can be successfully utilized to reduce the amount of ruthenium and copper catalysts in a variety of ATRA and ATRC reactions.[35–37,52,53,58,65,67,69–71,77,78,97,98] This new methodology for catalyst generation was also successfully applied to the one pot synthesis of cyclopropanes via sequential atom transfer radical addition-dechlorination reactions in the

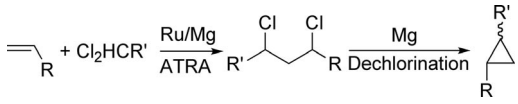
Table 5. ATRA of CCl_4 to 1,6-dienes followed by sequential ATRC catalyzed by copper(I) homoscorpionate ($Cu^{I}Tp^{X}$) and [Cu^{II}(TPMA)Cl][Cl] complexes in the presence of free-radical diazo initiators and Mg as reducing agents.[69,70]



Product	Ligand[a]	*T* [°C]	Red. agent	$[Cat.]_o$ [mol-%]	Yield [%]	*cis*:*trans*
1a	$Tp^{tBu,Me}$	30	/	1.0[b]	59	87:13
	$Tp^{Cy,4Br}$	30	/	1.0	62	84:16
	TPMA	60	AIBN	0.02	95 (83)[c]	84:16
		30	V-70	0.04	92	85:15
		room temp.[d]	V-70	0.04	87	86:14
2a	$Tp^{tBu,Me}$	30	Mg	1.0	>99	86:14
	$Tp^{Cy,4Br}$	30	Mg	1.0	>99	82:18
	TPMA	60	AIBN	0.05	89 (70)[c]	80:20
		30	V-70	0.1	91	79:21
		room temp.	V-70	0.1	80	82:18
3a	$Tp^{tBu,Me}$	30	Mg	1.0	95	87:13
	$Tp^{Cy,4Br}$	30	Mg	1.0	90	83:17
	TPMA	60	AIBN	0.02	96	74:26
		60	AIBN	0.01	91 (75)[c]	66:34
		30	V-70	0.02	87	64:36
		room temp.	V-70	0.02	77	56:44
4a	$Tp^{tBu,Me}$	30	Mg	1.0	>99	93:7
	$Tp^{Cy,4Br}$	30	Mg	1.0	>99	90:10
	TPMA	60	AIBN	0.02	>99	86:14
		60	AIBN	0.01	89 (80)[c]	84:16
		30	V-70	0.02	90	91:9
		room temp.	V-70	0.02	81	86:14
5a	TPMA	60	AIBN	0.02	90 (77)[c]	81:19
		60	AIBN	0.01	73	84:16
		30	V-70	0.1	95	73:27
		room temp.	V-70	0.1	87	73:27

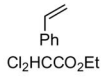
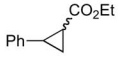
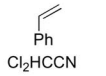
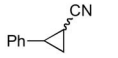
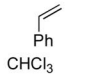
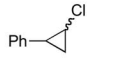
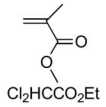
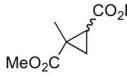
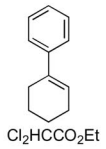
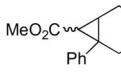
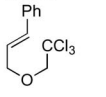
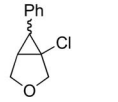
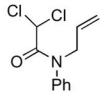
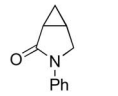
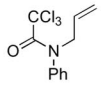
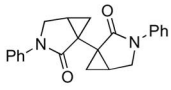
[a] Reactions with [Cu^{II}(TPMA)Cl][Cl] were performed in CH_3OH for 24 h with $[CCl_4]_0$:$[diene]_0$:[AIBN or V-70]$_0$ = 1.25:1:0.05, $[diene]_0$ = 1.0 M. Reactions with $Cu^{I}Tp^{X}$ were performed in [D_6]benzene for 24 h with $[diene]_0$:$[CCl_4]_0$ = 100:400. The yield is based on the formation of 5-*exo*-*trig* product (*cis* and *trans*) and was determined by ^{1}H NMR using toluene or 1,4-dimethoxybenzene as internal standard (relative errors are ±15%). [b] Mol percent of catalyst relative to diene. [c] Isolated yield after column chromatography for the large scale reaction. [d] Room temp. = 22 ± 2 °C.

presence of [$Cp^*Ru^{III}Cl_2(PPh_3)$] complex and magnesium.[78] In this organic transformation, magnesium not only regenerates the active Ru^{II} species needed for ATRA and ATRC, but also acts as a dechlorination reagent. The reaction sequence is depicted in Scheme 10. Alkenes are first reacted with 1,1′-dichlorides in ruthenium-catalyzed ATRA process. The resulting 1,3-dichlorides are then directly converted into cyclopropanes by reductive coupling with magnesium. Shown in Table 6 are some representative examples for this transformation.



Scheme 10. Synthesis of cyclopropanes via sequential ATRA/dechlorination reactions catalyzed by Ru in the presence of Mg.[78]

Table 6. Sequential ATRA(ATRC)/dechlorination reactions catalyzed by [Cp*$Ru^{III}Cl_2(PPh_3)$] complex in the presence of Mg.[78]

Substrate(s)[a]	Product	t_1 [h]	t_2 [h]	Yield[b]	*cis*/*trans*[c]
ATRA					
		6	1	74	1:3.0
		24	2	70	1:2.8
		24	2	71	1:2.3
		8	3	60	1:2.9
		48	0.5	51	1:12.6
ATRC					
		3	1	67	1:11.7
		4	0.5	65	/
		2	24	61	/

[a] ATRA reactions were performed in toluene with $[alkene]_0$ = 0.33 M, $[Cl_2HR]_0$ = 0.33 M and $[alkene]_0/[Mg]_0$ = 1:40 with 1 mol-% of Ru catalyst. ATRC reactions were performed in toluene with $[alkene]_0$ = 0.16 M and $[alkene]_0/[Mg]_0$ = 1:40 with 1 or 2 mol-% of Ru catalyst. After the time t_1 at 60 °C, the reaction mixture was diluted with 2.5 times the volume of THF and then stirred for time t_2 at either 0 °C or 25 °C. [b] Isolated yield. [c] *cis*/*trans* ratio was determined by ^{1}H NMR analysis.

As evident from Table 6, sequential ATRA/dechlorination reactions are applicable to a variety of alkenes (styrene, methyl methacrylate and cyclohexenylbenzene), as well as alkyl halides (dichloroacetate, chloroform and dichloroacetonitrile). The corresponding yields of the cyclopropanes are relatively high, with the *trans* isomer being slightly preferred. Also, the reactions can be conducted in an intramolecular fashion to yield the corresponding bicyclic cyclopropanes. This has been demonstrated in the case of trichlorinated allyl ethers and di- and tri-chlorinated *N*-allylacetamides (Table 6). Cyclopropanes were isolated in yields between 57 and 67% using 1–2 mol-% of [Cp*$Ru^{III}Cl_2(PPh_3)$] complex in conjunction with 40 equiv. of Mg (relative to substrate). It is interesting to note that ATRA/dechlorination of *N*-allyl-2,2-dichloroacetamindes yielded the corresponding 3-azabicyclo[3.1.0]hexan-2-one derivatives, which are precursors of *cis*-2-amino-methylcyclopropanecarboxylic acid (CAMP), a pharmacologically active analogue of γ-aminobutyric acid (GABA). Furthermore, in some cases trichloroacetamides yielded a complete dechlorination product in which two 3-azabicyclo[3.1.0]hexan-2-one fragments were bridged through a carbon–carbon bond. It is quite remarkable that such a complex molecule can be obtained with high diastereoselectivity in a simple one-pot reaction.

Conclusions and Future Outlook

In conclusion, recent advances in the area of catalyst regeneration in transition metal mediated atom transfer radical addition (ATRA) and cyclization (ATRC) reactions were reviewed. Both processes utilize reducing agents such as free-radical diazo initiators and magnesium to regenerate the activator (transition metal complex in the lower oxidation state) from the deactivator (transition metal complex in the higher oxidation state). The latter accumulates in the system as a result of unavoidable and often diffusion controlled radical-radical termination reactions. The presence of reducing agents in these systems enables a significant reduction in the amount of metal catalyst, making this new methodology environmentally friendly and inexpensive. Apart from mechanistic understanding of this novel catalytic process, several examples were presented which demonstrate its usefulness in organic synthesis of highly functionalized substrates via ruthenium or copper-catalyzed ATRC, ATRA followed by sequential ATRC, and ATRA or ATRC followed by sequential dehalogenation. It is envisioned that this methodology of catalyst regeneration is on a potential trajectory to become a "greener" alternative to currently available synthetic processes for such organic transformation. As such, it could also have a potential impact on the large-scale industrial synthesis of complexes molecules, including biologically active compounds, pharmaceutical drugs and natural products.

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