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Atom Transfer Radical Addition in the Presence of Catalytic Amounts of Copper(I/II) Complexes with Tris(2-pyridylmethyl)amine

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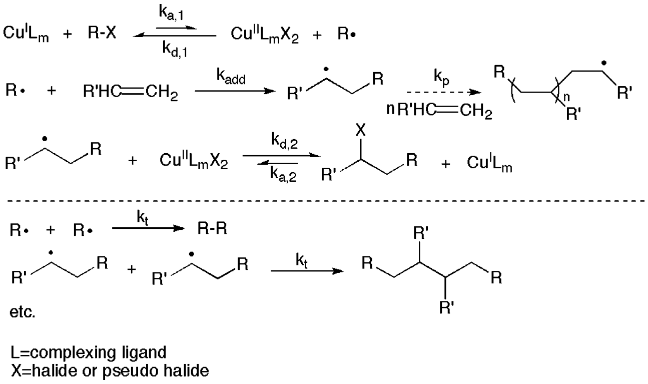
Highly efficient atom transfer radical addition of polyhalogenated compounds to alkenes catalyzed by copper(I/II) complexes with tris(2-pyridylmethyl)amine in the presence of a radical initiator [2,2′-azobis(2-methylpropionitrile)] was reported.

The addition of halogenated compounds to carbon−carbon double (or triple) bonds through a radical process is one of the fundamental reactions in organic chemistry.[1] It was first reported in the early 1940s in which the halogenated methanes were directly added to olefinic bonds.[2] The process was initiated by small amounts of diacyl peroxides or by light. This reaction became known as the Kharasch addition or atom transfer radical addition (ATRA).[3] However, soon after its discovery, it was realized that the use of the Kharasch addition reaction was rather limited because of radical−radical couplings to form alkanes and repeating radical addition to alkene to generate oligomers and polymers. The research was thus shifted in a direction of finding a means to selectively control the product distribution. This was achieved by utilizing transition-metal complexes, which are much more effective halogen transfer agents than alkyl halides. A number of species were found to be particularly effective, and they included the complexes of ruthenium, iron, copper, and nickel.[4−7]

It is generally accepted that the mechanism of copper-catalyzed ATRA involves free-radical intermediates (Scheme 1).[8,9] Homolytic cleavage of the alkyl halide bond (R−X) by the copper(I) complex generates an alkyl radical R$^\bullet$ and the corresponding copper(II) complex. The radical R$^\bullet$ adds across the double bond of an olefin, terminates by radical coupling or disproportionation, or abstracts the halogen from the copper(II) complex. The key to increasing the chemoselectivity of the monoadduct lies in the radical-generating step. In order to achieve high selectivity, the following guidelines need to be met: (a) the radical concentration must be low in order to suppress radical termination reactions [rate constant of activation ($k_{a,1}$ and $k_{a,2}$) $\ll$ rate constant of deactivation ($k_{d,1}$ and $k_{d,2}$)], (b) further activation of the monoadduct should be avoided ($k_{a,1} \gg k_{a,2}$), and (c) the formation of oligomers/polymers should be suppressed [rate of transfer ($k_{d,2}[\mathrm{Cu^{II}L}_m\mathrm{X}]$) $\gg$ rate of propagation (k_p[alkene])].

Scheme 1. Proposed Mechanism for Copper-Catalyzed ATRA



L=complexing ligand
X=halide or pseudo halide

Although transition-metal-catalyzed ATRA can be applied to a variety of halogenated substrates and alkenes, the principal drawback of this useful synthetic tool is the large amount of catalyst required to achieve high selectivity toward the monoadduct. In copper-catalyzed ATRA, the amount of catalyst typically ranges from 10 to 30 mol % relative to alkene and/or a halogenated compound.[7] As a result, the separation of the catalyst from the reaction mixture is often tedious and difficult.

The solution to this problem has recently been found through atom-transfer radical polymerization (ATRP),[10,11] which originated from ATRA. This new process, termed initiators for continuous activator regeneration (ICAR),[12]

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utilizes copper(II) complexes that are continuously reduced to copper(I) complexes in the presence of phenols, glucose, hydrazine, and radical initiators. With ICAR ATRP, controlled synthesis of poly(styrene) and poly(methyl methacrylate) can be implemented with a catalyst concentration between 10 and 50 ppm. This technique has recently been utilized with great success in ATRA reactions catalyzed by the $[\mathrm{Cp^{*}Ru^{III}Cl_2(PPh_3)}]$ complex.[13] However, to the best of our knowledge, it has never been applied to copper-mediated ATRA.

In this article, we report on the characterization and high activity of the $\mathrm{Cu^{I}Cl}$ and $\mathrm{Cu^{II}Cl_2}$ complexes with tris(2-pyridylmethyl)amine (TPMA) in ATRA reactions of polyhalogenated compounds to alkenes in the presence of 2,2′-azobis(2-methylpropionitrile) (AIBN).

Tetradentate nitrogen-based ligand TPMA was chosen for this study because its complexation to $\mathrm{Cu^{I}X}$ (X = Br or Cl) results in the formation of one of the most active catalysts in copper-mediated ATRP.[14−16] Despite the fact that the $\mathrm{Cu^{I}Cl}$/TPMA complex is a highly active catalyst in ATRP, the conversion of only 2% was observed after 24 h at 60 °C in ATRA of $\mathrm{CCl_4}$ to 1-hexene when the ratio of the catalyst to olefin was 1:10000. This result is not surprising because the low catalyst-to-$\mathrm{CCl_4}$ ratio resulted in complete deactivation of the catalyst. In other words, because of the irreversible radical coupling reactions (Scheme 1), the $\mathrm{Cu^{I}Cl}$/TPMA complex was converted to $\mathrm{Cu^{II}Cl_2}$/TPMA. In the absence of $\mathrm{Cu^{I}Cl}$/TPMA, 3% conversion of 1-hexene was observed, resulting in the formation of oligomers/polymers.

This situation can be changed by the addition of an external radical source such as AIBN. The slow decomposition of AIBN provides a constant source of radicals, which continuously reduce the $\mathrm{Cu^{II}Cl_2}$/TPMA complex to $\mathrm{Cu^{I}Cl}$/TPMA (Supporting Information).[12] Indeed, when the above reaction was conducted in the presence of 5.0 mol % AIBN (relative to the olefin), 88% conversion of 1-hexene was observed after 24 h, with the main product being the desired monoadduct (yield = 72%, entry 1, Table 1). Increasing the catalyst concentration (entry 2), under the same reaction conditions, resulted in a complete conversion of 1-hexene and an increase in the yield of monoadduct (98%). Similar results were also obtained with 1-octene (entries 3 and 4). The turnover numbers (TONs) in these experiments ranged between 4900 and 7200 (1-hexene) and between 4350 and 6700 (1-octene) and are the highest so far obtained for copper-catalyzed ATRA of $\mathrm{CCl_4}$ to olefins. Previously reported TONs ranged between 0.1 and 10.[7,17] The efficient regeneration of the copper(I) complex by AIBN suggests that ATRA reactions can also be conducted using the $\mathrm{Cu^{II}Cl_2}$/TPMA complex, which we have confirmed experimentally. In the case when the starting catalyst is $\mathrm{Cu^{II}Cl_2}$/TPMA, the process can be termed reverse ATRA, in analogy with the well-known reverse ATRP developed by Xia and Matyjaszewski.[11,18]

Table 1. ATRA of Polychlorinated Compounds to Alkenes Catalyzed by $\mathrm{Cu^{I}(TPMA)Cl}$ in the Presence of AIBN[a]

entry	alkene	RCl	$[\mathrm{alkene}]_0/[\mathrm{Cu^{I}}]_0$	yield (%)	TON
1	1-hexene	$\mathrm{CCl_4}$	10000:1	72	7200
2			5000:1	98	4900
3	1-octene	$\mathrm{CCl_4}$	10000:1	67	6700
4			5000:1	87	4350
5	styrene	$\mathrm{CCl_4}$	1000:1	42	420
6			500:1	54	270
7			250:1	85	212
8	methyl acrylate	$\mathrm{CCl_4}$	1000:1	60	600
9	1-hexene	$\mathrm{CHCl_3}$	1000:1	56	560
10	1-octene	$\mathrm{CHCl_3}$	500:1	49	245
11	styrene	$\mathrm{CHCl_3}$	1000:1	58	580
12	methyl acrylate	$\mathrm{CHCl_3}$	1000:1	63	630

[a] All reactions were performed in toluene at 60 °C for 24 h with $[\mathrm{R\text{-}Cl}]_0/[\mathrm{alkene}]_0 = 4.0$. The yield is based on the formation of a monoadduct and was determined by ^{1}H NMR using toluene as the internal standard or column chromatography. The conversion of alkene for all substrates ranged from 85 to 100%.

To test the applicability of this new methodology for copper(I) regeneration in ATRA, additional experiments were conducted using other alkenes as well as alkyl halides. Relatively high yields of monoadduct were obtained in ATRA of $\mathrm{CCl_4}$ to styrene (entries 5−7) and methyl acrylate (entry 8) but with much higher catalyst loadings. At a $\mathrm{Cu^{I}Cl}$/TPMA-to-styrene ratio of 1:250 (entry 7), complete conversion of styrene was observed after 24 h and monoadduct was obtained in 85% yield. A further increase in the ratio of styrene to $\mathrm{Cu^{I}Cl}$/TPMA (entries 5 and 6) still resulted in quantitative conversion of styrene; however, a more pronounced decrease in the yield of monoadduct was observed. The decrease in the yield of monoadduct was mostly due to the formation of oligomers/polymers. Similar results were also obtained for methyl acrylate. The experiments with a less active $\mathrm{CHCl_3}$ substrate also worked reasonably well. Relatively high yields were obtained for all alkenes investigated at $[\mathrm{alkene}]_0$-to-$[\mathrm{Cu^{I}}]_0$ ratios between 500 and 1000 (entries 9−12).

The catalytic activity of the $\mathrm{Cu^{I}Cl}$/TPMA complex in AIBN-mediated ATRA reported in this study is lower than the activity of recently reported ruthenium(II) and ruthenium(III) complexes, which were capable of catalyzing ATRA reactions of $\mathrm{CCl_4}$ to olefins with TONs as high as 44 500.[13] However, despite the superiority of ruthenium in intermolecular ATRA reactions,[13,19,20] we believe that the success of this new methodology for catalyst regeneration can be applied to atom-transfer radical cyclization (ATRC) reactions, which are predominantly conducted using copper(I) complexes.[7]

The structural features of highly ATRP- and now ATRA-active $\mathrm{Cu^{I}X}$/TPMA (X = Cl and Br) complexes are still not

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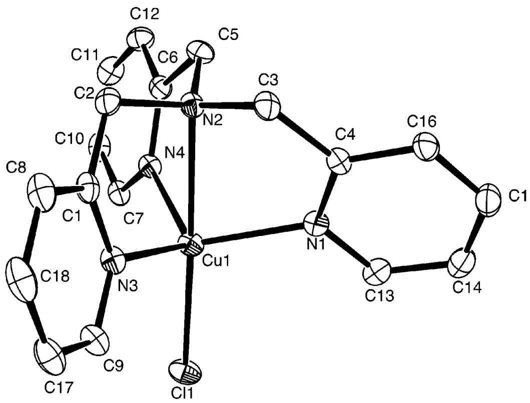

Figure 1. Molecular structure of Cu^{I}(TPMA)Cl, shown with 30% probability displacement ellipsoids. H atoms have been omitted for clarity.

fully understood.[21] Typically, TPMA coordinates to the copper(I) complex in a tetradentate fashion,[22] similarly to structurally related tris[2-(*N*,*N*-dimethylamino)ethyl]amine (Me$_6$TREN). However, the role of the halide counterion in these complexes is also very unclear. For example, in the case of the Cu^{I}Br/Me$_6$TREN complex, extended X-ray absorption fine structure studies have indicated several possible structures in the solution, which included [Cu^{I}(Me$_6$TREN)][Br], [Cu^{I}(Me$_6$TREN)][Cu^{I}Br$_2$], and [Cu^{I}(Me$_6$TREN′)Br] (Me$_6$TREN′ denotes a tricoordinated Me$_6$TREN).[21,23] These structures were based on the validated assumption that the maximum coordination number of copper(I) should not exceed four.[24]

Shown in Figure 1 is the molecular structure of the Cu^{I}(TPMA)Cl complex, which was obtained by slow crystallization of Cu^{I}Cl/TPMA from THF/EtOH at −35 °C. Surprisingly, the geometry of the complex is distorted trigonal-bipyramidal. The Cu^{I} ion is coordinated by four N atoms with bond lengths of 2.0704(11), 2.0833(11), and 2.0888(11) Å for the equatorial Cu−N bond and 2.4366(11) Å for the axial Cu−N bond and a Cl atom with a bond length of 2.3976(4) Å. Furthermore, the Cu^{I} atom lies 0.534(6) Å below the least-squares plane derived from N1, N3, and N4, toward the Cl^{-} ion.

The corresponding deactivator [Cu^{II}(TPMA)Cl][Cl] can be synthesized from Cu^{II}Cl$_2$ and TPMA, or alternatively Cu^{I}(TPMA)Cl and a large excess of a halogenated compound (CCl$_4$, CHCl$_3$, etc.). In [Cu^{II}(TPMA)Cl][Cl] (Figure 2), the Cu^{II} atom is coordinated by four N atoms [Cu^{II}−N$_{eq}$ = 2.0759(8) Å and Cu^{II}−N$_{ax}$ = 2.0481(14) Å] from the TPMA ligand and a Cl atom [Cu^{II}−Cl = 2.2369(4) Å]. The overall geometry of the complex is distorted trigonal bipyramidal, and the Cu^{II} atom is positioned 0.335(3) Å below the least-squares plane derived from the equatorial N atoms in TPMA. The molecule possesses crystallographic 3-fold symmetry with respect to the Cu−Cl1 or Cu−N1 vector. The structures of Cu^{I}(TPMA)Cl and [Cu^{II}(TPMA)Cl][Cl], from the point of view of TPMA coordination, are very similar. In the Cu^{I}(TPMA)Cl complex, the average Cu^{I}−N$_{eq}$ bond length is approximately 0.0050 Å longer than that in [Cu^{II}(TPMA)Cl][Cl]. The angles in the plane N$_{ax}$−Cu−N$_{ax}$ are slightly smaller in Cu^{I}(TPMA)(Cl) [111.13(4)−116.60(4)°] than in [Cu^{II}(TPMA)Cl][Cl] [117.447(12)°], while the N$_{ax}$−Cu−N$_{eq}$ angles are very similar. The only more pronounced difference in the TPMA coordination to the copper center can be seen in the shortening of the Cu−N$_{ax}$ bond length on going from Cu^{I}(TPMA)Cl [2.4366(11) Å] to [Cu^{II}(TPMA)Cl][Cl] [2.0481(14) Å]. From the structural point of view, we believe that the high activity of the TPMA ligand in ATRA/ATRP can be explained by the fact that the minimum entropic rearrangement is required when the Cu^{I}(TPMA)Cl complex homolytically cleaves the R−Cl bond to generate the corresponding [Cu^{II}(TPMA)Cl][Cl] complex. At the present moment, it is unclear what the role of Cl^{-} coordination to the [Cu^{I}(TPMA)]$^{+}$ cation [Cu^{I}−Cl = 2.3976(4) Å] is. The most reasonable explanation is that activation in the ATRA/ATRP process proceeds with either prior dissociation of Cl^{-} from the Cu^{I}(TPMA)Cl complex or dissociation of Cl^{-} from the corresponding Cu^{II}(TPMA)Cl$_2$ to generate the deactivator [Cu^{II}(TPMA)Cl][Cl]. Both possibilities are currently under investigation.

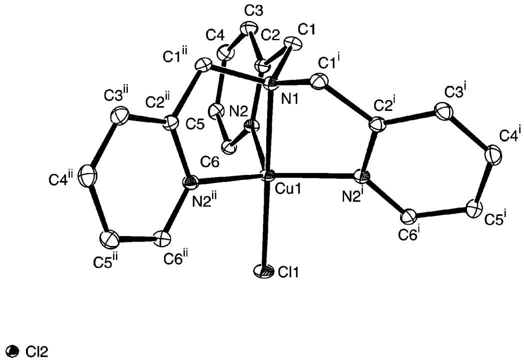

Figure 2. Molecular structure of [Cu^{II}(TPMA)Cl][Cl], shown with 30% probability displacement ellipsoids. H atoms have been omitted for clarity.

In summary, the characterization and high activity of the Cu^{I}Cl and Cu^{II}Cl$_2$ complexes with TPMA in ATRA of polyhalogenated compounds to alkenes were reported. This methodology utilized AIBN, which provided an external source of radicals for continuous regeneration of the copper(I) complex. The TONs for 1-hexene (7200) and 1-octene (6700) are the highest so far reported for copper-catalyzed ATRA of CCl$_4$ to olefins. The outlined procedure can potentially be used to decrease the amount of copper catalyst in other ATRA and ATRC reactions.

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Supporting Information Available: Synthetic procedures and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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