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Highly Efficient Ambient-Temperature Copper-Catalyzed Atom-Transfer Radical Addition (ATRA) in the Presence of Free-Radical Initiator (V-70) as a Reducing Agent

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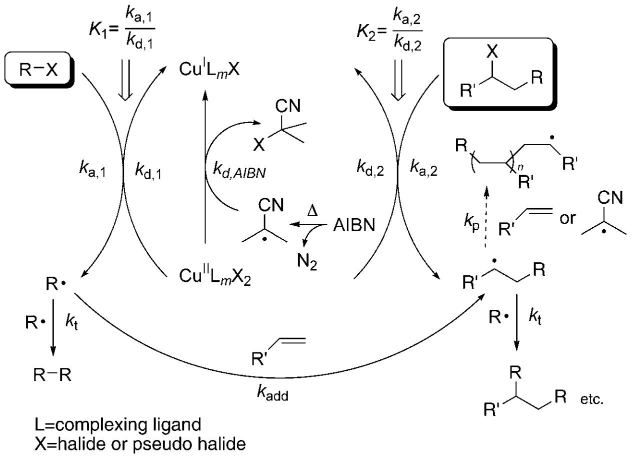
The addition of halogenated compounds to carbon–carbon double (or triple) bonds through a radical process is one of the fundamental reactions in organic chemistry.[1] It was first reported in the mid 1940s in a reaction in which halogenated alkenes were directly added to olefinic bonds in the presence of free-radical initiators or light.[2] Today, this reaction is known as the Kharasch addition or atom-transfer radical addition (ATRA), and it is typically catalyzed by transition-metal complexes of Ru, Fe, Ni, and Cu.[3–6] Transition-metal-catalyzed ATRA, despite being discovered nearly 40 years before the widely used tin-mediated radical addition to olefins[7] and iodine atom-transfer radical addition,[8] is still not fully utilized as a technique in organic synthesis. Until recently, the principal reason for small participation of ATRA in complex molecule and natural product syntheses remained the large amount of transition metal needed to achieve high selectivity towards the desired target compound (typically 5–30 mol% relative to alkene).[3,9] This obstacle caused serious problems in product separation and catalyst regeneration, making the process environmentally unfriendly and expensive.

Originally, the solution to this problem has been found for copper-catalyzed atom-transfer radical polymerization (ATRP),[3,10,11] and was subsequently applied first to ruthenium-[12] and then copper-catalyzed[13,14] 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 1).[3]



Scheme 1. Proposed mechanism for copper(I) regeneration in the presence of reducing agent (AIBN) during ATRA process.

When applied to ATRA of CCl_4 to alkenes catalyzed by $[Ru^{III}Cp^*Cl_2(PPh_3)]$ (Cp^* = pentamethylcyclopentadiene) complex in the presence of AIBN (azobisisobutyronitrile), turnover numbers (TONs) as high as 44500 were obtained.[12] 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 little as 5 ppm of copper.[13] Since the seminal reports by our research group[14] as well as Severin's,[12] this method of catalyst regeneration in ATRA has attracted considerable academic interest,[15–22] and was even successfully applied to intramolecular ATRA or atom-transfer radical cyclization (ATRC) reactions.[21–23]

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In our initial studies, AIBN was successfully utilized as a reducing agent in copper-catalyzed ATRA of polyhalogenated compounds to alkenes at 60 °C.[13,14] Excellent results were obtained in the case of simple α-olefins (1-hexene, 1-decene, and 1-octene), as well as methyl acrylate and styrene. However, this method of catalyst regeneration was not very successful for monomers with high propagation rate constants, such as methyl methacrylate ($k_{p,60} = 6.3 \times 10^2\,\text{M}^{-1}\,\text{s}^{-1}$), vinyl acetate ($k_{p,60} = 2.3 \times 10^3\,\text{M}^{-1}\,\text{s}^{-1}$), and acrylonitrile ($k_{p,60} = 1.9 \times 10^3\,\text{M}^{-1}\,\text{s}^{-1}$).[24] ATRA of these monomers in the presence of AIBN at 60 °C yielded significant amounts of polymers/telomers unless high copper loadings and/or large excess of alkyl halide (4 equiv relative to alkene) were used. The principal reason for the difficulty in controlling the formation of single addition adduct was not inefficient catalyst regeneration or further activation of the monoadduct, but rather competing polymerization initiated by the presence of AIBN (Scheme 1). The potential solution to this problem is to utilize redox-reducing agents that do not generate free radicals, such as magnesium.[21] However, the presence of magnesium as a reducing agent is less desired, because it increases the total metal concentration in the system. An alternative solution is to utilize low-temperature free-radical initiators that could be used at ambient temperatures and be easily removed from reaction mixtures together with radical decomposition products. At ambient temperatures, free-radical polymerization of highly active monomers ($3.0 \times 10^2\,\text{s}^{-1} < k_p[\text{alkene}] < 1.8 \times 10^3\,\text{s}^{-1}$), as a result of decrease in propagation rate constants ($k_{p,25}(\text{MMA}) = 1.9 \times 10^2\,\text{M}^{-1}\,\text{s}^{-1}$, $k_{p,25}(\text{VA}) = 1.0 \times 10^3\,\text{M}^{-1}\,\text{s}^{-1}$ and $k_{p,25}(\text{AN}) = 9.3 \times 10^2\,\text{M}^{-1}\,\text{s}^{-1}$))[24] is expected to compete with a halide transfer ($1.8 \times 10^3\,\text{s}^{-1} < k_{d,2}[\text{Cu}^{\text{II}}\text{L}_m\text{X}_2] < 1.8 \times 10^5\,\text{s}^{-1}$) to a much lesser extent.[25] Consequently, provided efficient regeneration of the copper(I) complex, substantially higher yields of the desired monoadduct could be obtained.

In this article, we report on highly efficient, ambient-temperature, copper-catalyzed ATRA of polyhalogenated compounds to alkenes in the presence of free radical initiator 2,2′-azobis(4-methoxy-2,4-dimethyl valeronitrile) (V-70) as a reducing agent.

The addition of polyhalogenated compounds (in particular CBr_4 and CCl_4) to alkenes could proceed only in the presence of free-radical initiator, because of their known ability to function as very efficient chain-transfer agents.[26,27] As indicated in Table 1 (entries 3, 7, and 11), ambient-temperature, V-70-initiated Kharasch addition reactions in the presence of one equivalent of alkyl halide proceeded with reasonably high yields only in the case of CBr_4 and simple α-olefins. However, the obtained yields of the monoadduct (53–64 %) were significantly lower than the yields obtained at 60 °C in the presence of AIBN (96–100 %).[13] Furthermore, the formation of monoadduct was observed in the V-70-initiated free-radical addition of CBr_4 to styrene (entry 15), methyl acrylate (entry 19), and vinyl acetate (entry 27) and $CHBr_3$ to methyl acrylate (entry 20) and methyl methacrylate (entry 24), albeit with much smaller yields. For these highly active monomers, the discrepancies between the alkene conversion and percent yield were mostly due to competing free-radical polymerization.

Table 1. Ambient-temperature Kharasch addition of polyhalogenated compounds to alkenes in the presence of V-70.

Entry[a]	Alkene	RX	% Conv.	% Yield[b]
1	1-decene	CCl_4	5	0
2		$CHCl_3$	3	0
3		CBr_4	55	53
4		$CHBr_3$	3	0
5	1-octene	CCl_4	8	0
6		$CHCl_3$	1	0
7		CBr_4	57	56
8		$CHBr_3$	5	0
9	1-hexene	CCl_4	4	0
10		$CHCl_3$	3	0
11		CBr_4	66	64
12		$CHBr_3$	4	0
13	styrene	CCl_4	18	1
14		$CHCl_3$	26	0
15		CBr_4	32	29
16		$CHBr_3$	37	0
17	methyl acrylate	CCl_4	88	0
18		$CHCl_3$	83	0
19		CBr_4	96	38
20		$CHBr_3$	51	37
21	methyl methacrylate	CCl_4	86	0
22		$CHCl_3$	83	0
23		CBr_4	91	8
24		$CHBr_3$	96	14
25	vinyl acetate	CCl_4	18	16
26		$CHCl_3$	11	0
27		CBr_4	30	27
28		$CHBr_3$	6	0

[a] All reactions were performed in CH_3CN at 22 ± 2 °C for 24 h with $[\text{RX}]_0$:$[\text{alkene}]_0$:$[\text{V-70}]_0 = 1$:1:0.05, except reactions for entries 1–4 which were performed in 1,2-dichloroethane. [b] Yield is based on the formation of monoadduct and was determined by ^{1}H NMR spectroscopy using anisole (styrene) or 1,4-dimethoxybenzene (all other alkenes) as internal standards.

When $[\text{Cu}^{\text{II}}(\text{tpma})\text{X}][\text{X}]$ ($\text{X} = \text{Cl}^-$ (for RCl) or Br^- (for RBr)) was added to the reaction mixture at ambient temperature, truly remarkable results were obtained (Table 2). For ATRA of CCl_4 to α-olefins (1-decene, 1-octene, and 1-hexene) using stoichiometric amounts of both reagents, excellent yields of the monoadduct were obtained with Cu^{II} to alkene ratio of 1:1000 (entries 1, 8, and 15). Further decrease in catalyst loading to 1:2000 (0.05 mol %) still resulted in high conversions and excellent yields of the monoadduct. Even more impressive results were obtained in ATRA of CBr_4 to 1-decene (entries 4–6), 1-octene (entries 11–13), and 1-hexene (entries 18–20) using concentrations of copper as low as 0.002 mol % (20 ppm relative to alkene) (Figure 1). On the other hand, $CHCl_3$ and $CHBr_3$ were found to be quite inactive in ATRA reactions with α-olefins at ambient temperatures, at catalyst loadings as high as 10 mol %.

Table 2. Ambient-temperature ATRA of polyhalogenated compounds to alkenes catalyzed by $[Cu^{II}(tpma)X][X]$ ($X = Cl^-$ and Br^-) in the presence of free-radical initiator V-70 as a reducing agent.

Entry[a]	Alkene	RX	$[Alk]_0:[Cu^{II}]_0$[b]	Conv. [%]/ Yield[c] [%]	TON[d]
1	1-decene	CCl_4	1000:1 (0.1)	93/93	930
2		CCl_4	2000:1 (0.05)	81/80	1600
3		$CHCl_3$	10:1 (10)	1/0	0
4		CBr_4	10000:1 (0.01)	~100/99	4600
5		CBr_4	20000:1 (0.005)	96/89	7200
6		CBr_4	50000:1 (0.002)	92/88	17500
7		$CHBr_3$	100:1 (1)	2/2	2
8	1-octene	CCl_4	1000:1 (0.1)	99/97	970
9		CCl_4	2000:1 (0.05)	87/84	1680
10		$CHCl_3$	10:1 (10)	2/0	0
11		CBr_4	10000:1 (0.01)	~100/~100	4400
12		CBr_4	20000:1 (0.005)	96/94	7600
13		CBr_4	50000:1 (0.002)	92/93	18500
14		$CHBr_3$	100:1 (1)	3/2	2
15	1-hexene	CCl_4	1000:1 (0.1)	96/96	960
16		CCl_4	2000:1 (0.05)	86/85	1700
17		$CHCl_3$	10:1 (10)	4/0	0
18		CBr_4	10000:1 (0.01)	~100/98	3400
19		CBr_4	20000:1 (0.005)	98/96	6400
20		CBr_4	50000:1 (0.002)	96/93	14500
21		$CHBr_3$	100:1 (1)	4/4	4
22	styrene	CCl_4	500:1 (0.2)	54/51	255
23		CCl_4	1000:1 (0.1)	33/31	310
24		CCl_4	2000:1 (0.05)	22/24	480
25		$CHCl_3$	100:1 (1)	60/48	48
26		$CHCl_3$	200:1 (0.5)	51/39	78
27		CBr_4	200:1 (0.5)	96/91	124
28		CBr_4	2000:1 (0.05)	64/57	560
29		CBr_4	10000:1 (0.01)	49/46	1700
30		$CHBr_3$	1000:1 (0.1)	86/70	700
31		$CHBr_3$	2000:1 (0.05)	82/61	1220
32	methyl acrylate	CCl_4	1000:1 (0.1)	~100/84	840
33		CCl_4	2000:1 (0.05)	~100/62	1240
34		CBr_4	10000:1 (0.01)	~100/82	4400
35		CBr_4	20000:1 (0.005)	~100/70	6400
36		CBr_4	50000:1 (0.002)	~100/63	12500
37		$CHBr_3$	1000:1 (0.1)	64/48	480
38		$CHBr_3$	2000:1 (0.05)	47/39	780
39	methyl methacrylate	CCl_4	1000:1 (0.1)	~100/66	660
40		CCl_4	2000:1 (0.05)	87/44	880
41		CBr_4	10000:1 (0.01)	~100/71	6300
42		CBr_4	20000:1 (0.005)	~100/44	7200
43		$CHBr_3$	1000:1 (0.1)	94/8	0
44		$CHBr_3$	2000:1 (0.05)	96/5	0
45	vinyl acetate	CCl_4	1000:1 (0.1)	96/94	780
46		CCl_4	2000:1 (0.05)	80/70	1220
47		CBr_4	1000:1 (0.1)	95/88	610
48		CBr_4	2000:1 (0.05)	87/87	1200
49		CBr_4	5000:1 (0.02)	80/77	2500
50		$CHBr_3$	100:1 (1)	7/6	6
51		$CHBr_3$	200:1 (0.5)	3/3	6

[a] All reactions were performed in CH_3CN at ambient temperature (22±2 °C) for 24 h with $[RX]_0:[alkene]_0:[V\text{-}70]_0 = 1:1:0.05$, except reactions for entries 1–7, which were performed in 1,2-dichloroethane. [b] mol% of copper relative to alkene. [c] Yield is based on the formation of monoadduct and was determined by ^1H NMR spectroscopy using anisole (styrene) or 1,4-dimethoxybenzene (all other alkenes) as internal standards. [d] TONs were calculated taking into account the percent yield of monoadduct for ATRA reactions conducted in the absence of $[Cu^{II}(tpma)X][X]$ (see Table 1).

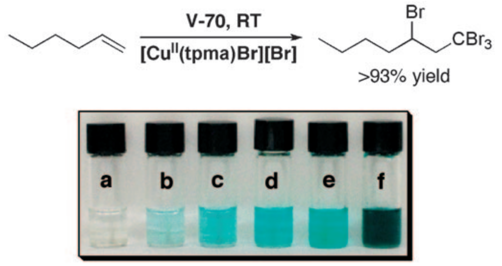

Figure 1. $[Cu^{II}(tpma)Br][Br]$ catalyzed ATRA of CBr_4 to 1-hexene in the presence of V-70 at 22±2 °C with a) 0.002, b) 0.01, c) 0.05, d) 0.1, e) 1.0, and f) 10 mol% of copper. For all experiments, the conversion of 1-hexene was ~100% and the yield of monoadduct >93%.

As mentioned above, ATRA of polyhalogenated compounds to monomers that are highly active in free-radical polymerization was not very successful at 60 °C when AIBN was used as radical initiator. As a result of very high propagation rate constants for monomers such as methyl acrylate, methyl methacrylate, acrylonitrile, or vinyl acetate, copper-catalyzed ATRA in the presence of AIBN as a reducing agent at 60 °C required high catalyst loadings and/or large excess of alkyl halide. The results at ambient temperatures using V-70 as a reducing agent and stoichiometric amounts of alkene and alkyl halide were quite different. In ATRA of CCl_4 (entry 22) to styrene, the monoadduct was obtained in 51% yield using 0.2 mol% of copper catalyst. On the other hand, nearly quantitative yield was observed with CBr_4 (entry 27) using 0.5 mol% of copper. ATRA reactions with styrene were also quite successful with less active $CHCl_3$ (entries 25, 26) and $CHBr_3$ (30, 31). Similarly, dramatic improvements were also observed in ATRA of CCl_4 and CBr_4 to methyl acrylate (entries 32, 33 and 34, 36) and methyl methacrylate (entries 39, 40 and 41, 42). For both monomers, ATRA of CCl_4 and CBr_4 proceeded very efficiently at ambient temperature using catalyst loadings as low as 0.1 and 0.005 mol%, respectively. As evident from Table 2 (entries 37, 38) ATRA of $CHBr_3$ to methyl acrylate also yielded the desired monoadduct with 0.1 and 0.05 mol% of copper. Furthermore, $CHBr_3$ was quite inactive alkyl halide in copper-catalyzed ATRA of methyl methacrylate (entries 43, 44). Although high monomer conversions were obtained, they were mostly attributed to polymer formation.

The methodology for catalyst regeneration in copper-mediated ATRA in the presence of V-70 as a reducing agent also worked very well in the addition of CCl_4 and

CBr_4 to highly active vinyl acetate. For CCl_4 (entries 45, 46) and CBr_4 (entries 47–49), very high yields of the monoadduct were obtained using as little as 0.1 and 0.05 mol% of copper catalyst, respectively. However, similarly to methyl methacrylate, ATRA of $CHBr_3$ to vinyl acetate (entries 50, 51) was also quite unsuccessful even when high copper concentrations were used (0.5–1.0 mol%).

In summary, highly efficient, ambient-temperature ATRA of polyhalogenated compounds to alkenes catalyzed by $[Cu^{II}(tpma)X][X]$ ($X = Br^-$ and Cl^-) complexes in the presence of 2,2′-azobis(4-methoxy-2,4-dimethyl valeronitrile) (V-70) is reported. V-70 has been shown to be very effective reducing agent for this process, enabling selective formation of the monoadduct with α-olefins and highly active monomers such as methyl acrylate, methyl methacrylate, and vinyl acetate.

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Keywords: atom-transfer radical addition · catalysis · copper · halogens · radical initiators

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[1] D. P. Curran, *Comprehensive Organic Synthesis*, Pergamon, New York, **1992**.

[2] M. S. Kharasch, E. V. Jensen, W. H. Urry, *Science* **1945**, *102*, 128.

[3] T. Pintauer, K. Matyjaszewski, *Chem. Soc. Rev.* **2008**, *37*, 1087.

[4] R. A. Gossage, L. A. Van De Kuil, G. Van Koten, *Acc. Chem. Res.* **1998**, *31*, 423.

[5] J. Iqbal, B. Bhatia, N. K. Nayyar, *Chem. Rev.* **1994**, *94*, 519.

[6] K. Severin, *Curr. Org. Chem.* **2006**, *10*, 217.

[7] B. Giese, *Angew. Chem.* **1985**, *97*, 555; *Angew. Chem. Int. Ed.* **1985**, *24*, 553.

[8] D. P. Curran, M.-H. Chen, K. Dooseop, *J. Am. Chem. Soc.* **1986**, *108*, 2489.

[9] A. J. Clark, *Chem. Soc. Rev.* **2002**, *31*, 1.

[10] K. Matyjaszewski, W. Jakubowski, K. Min, W. Tang, J. Huang, W. A. Braunecker, N. V. Tsarevsky, *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 15309.

[11] J.-S. Wang, K. Matyjaszewski, *J. Am. Chem. Soc.* **1995**, *117*, 5614.

[12] L. Quebatte, K. Thommes, K. Severin, *J. Am. Chem. Soc.* **2006**, *128*, 7440.

[13] W. T. Eckenhoff, S. T. Garrity, T. Pintauer, *Eur. J. Inorg. Chem.* **2008**, 563.

[14] W. T. Eckenhoff, T. Pintauer, *Inorg. Chem.* **2007**, *46*, 5844.

[15] A. G. Blackman, *Eur. J. Inorg. Chem.* **2008**, 2633.

[16] A. E. Díaz-Alvarez, P. Crochet, M. Zablocka, C. Duhayon, V. Cadierno, J. P. Majoral, *Eur. J. Inorg. Chem.* **2008**, 786.

[17] Y. Iizuka, Z. M. Li, K. Satoh, M. Karnigaito, Y. Okamoto, J. Ito, H. Nishiyama, *Eur. J. Org. Chem.* **2007**, 782.

[18] R. J. Lundgren, M. A. Rankin, R. McDonald, M. Stradiotto, *Organometallics* **2008**, *27*, 254.

[19] D. Maiti, A. A. N. Sarjeant, S. Itoh, K. D. Karlin, *J. Am. Chem. Soc.* **2008**, *130*, 5644.

[20] Y. Oe, Y. Uozumi, *Adv. Synth. Catal.* **2008**, *350*, 1771.

[21] K. Thommes, B. Icli, R. Scopelliti, K. Severin, *Chem. Eur. J.* **2007**, *13*, 6899.

[22] J. Wolf, K. Thommes, O. Brie, R. Scopelliti, K. Severin, *Organometallics* **2008**, *27*, 4464.

[23] A. J. Clark, P. Wilson, *Tetrahedron Lett.* **2008**, *49*, 4848.

[24] G. Odian, *Principles of Polymerization*, 4th ed., Wiley, New York, **2004**.

[25] Values were calculated assuming $[alk]_0 = 1.8\,\text{M}$, $1.8\times10^{-5}\,\text{M}$ (0.001 mol%) $< [Cu]_0 < 1.8\times10^{-3}\,\text{M}$ (0.01 mol%) and $k_d = 1.0\times10^8\,\text{M}^{-1}\text{s}^{-1}$.

[26] J. Brandrup, E. H. Immergut, E. A. Gulke, *Polymer Handbook*, Wiley-Interscience, New York, **1999**.

[27] G. C. Eastmond in *Comprehensive Chemical Kinetics, Vol. 14 A* (Eds.: C. H. Bamford, C. F. H. Tipper), American Elsevier, New York, **1976**.

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