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An Efficient, Selective, and Reducing Agent-Free Copper Catalyst for the Atom-Transfer Radical Addition of Halo Compounds to Activated Olefins

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Efficient and selective ATRA reactions of CCl_4, CBr_4, TsCl (Ts = tosyl), or Cl_3CCO_2Et with activated olefins (styrene, methyl methacrylate, *n*-butyl methacrylate, *tert*-butyl methacrylate) using the $Tp^{tBu}Cu(NCMe)$ complex as a catalyst have been achieved in the absence of any reductant and with low catalyst loadings.

Introduction

The transition-metal-catalyzed Kharasch reaction,[1] so-called atom-transfer radical addition (ATRA),[2] constitutes a promising synthetic tool in organic synthesis. Several metals such as Fe,[3] Ru,[4] Ni,[5] or Cu[6] are known to promote this transformation either in the inter- or intramolecular version (Scheme 1a).[7] The commonly accepted mechanism for this radical process is shown in Scheme 1b. The metal complex reacts with an R−X (X = halide) bond to generate the radical ·R and a metal halide complex. The former radical species may react with the olefin to give radical R′ (addition step) or, alternatively, with another radical (·R or ·R′) in nonproductive side reactions (termination steps). Following the addition, the resulting radical recovers the halide from the metal in the deactivation step, the metal center being reduced to the initial oxidation state to be ready to restart the catalytic cycle. It is worth mentioning that radical ·R′ can also react with another olefin molecule to start a polymerization route.

The main drawback of the metal-catalyzed ATRA reactions is the formation of the side products, which not only decrease the yield in the desired addition products but also induce the accumulation of M^{n+1}, affecting the $[M^{n+}]/[M^{n+1}]$ ratio and, finally, bringing the catalytic reaction to the end. A methodology envisaged to solve this problem was introduced by Severin and co-workers with Ru-based catalysts and consisted of the addition of a reducing agent (magnesium powder) to continuously regenerate the lower oxidation state of the metal at room temperature ($[L_mM^{n+}]$ in Scheme 1b).[8] The main advantage of this strategy is that magnesium does not generate free radicals; however, the total metal concentration increases in the system.[9] Also, the groups of Severin[10] and Pintauer[11]

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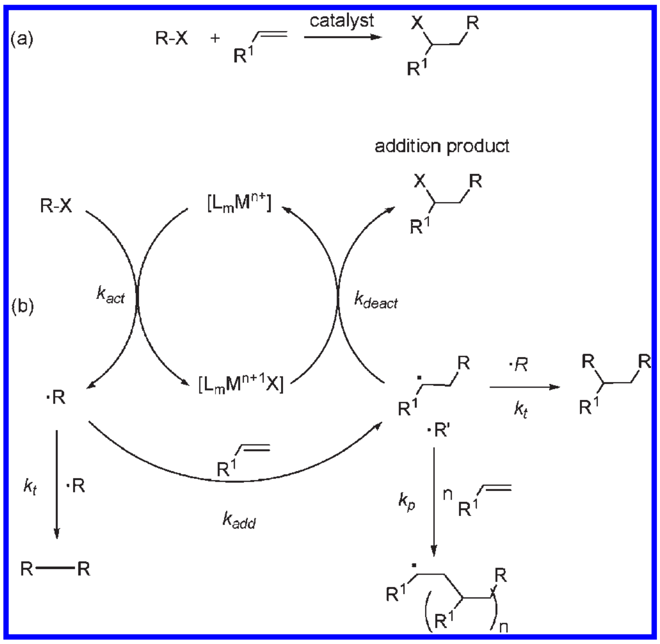
Scheme 1. (a) Atom-Transfer Radical Addition Reaction and (b) the Commonly Accepted Mechanism for the ATRA Reaction Also Showing Nondesired Byproducts



have independently reported azobis(isobutyronitrile) (AIBN) as the reducing agent in ATRA catalyzed by ruthenium and copper complexes. These reactions needed heating at 60 °C in order to make AIBN an efficient radical source.

As an alternative to the above methods, Pintauer and coworkers have very recently described the use of 2,2′-azobis(4-methoxy-2,4-dimethyl valeronitrile), a room-temperature radical initiator known as V-70, as the reducing agent.[9] Such an additive has provided efficient ATRA reactions with α-olefins with 0.005 mol % of catalyst loading. However, it was not that efficient with the more reactive monomers such as styrene, methyl acrylate, or methyl methacrylate probably due to their low k_{deact}/k_p ratio (Scheme 1).[12] In the above cases, AIBN or V-70 also promote the generation of free radicals, which would lead to competing termination or free-radical polymerization due to their known ability to function as efficient chain-transfer agents, against the atom economy of the ATRA reactions. Therefore, the current state of the art indicates that the best catalytic systems reported require an additive as a reducing agent, and that for the most reactive olefins this strategy is not yet very efficient.

Results and Discussion

We have previously reported that Cu(I) complexes containing trispyrazolylborate ligands (Tp^xCu) catalyze the ATRA of polyhalogenated alkanes to various olefins under mild conditions,[6i] the best catalyst being the complex $Tp^{tBu,Me}Cu(NCMe)$ (**1**). With the idea in mind of avoiding the use of such additives and the functionalization of the more reactive olefins, we checked the catalytic capabilities of the related $Tp^{tBu}Cu(NCMe)$[13] (**2**) complex, which only differs from our previous report in the methyl group located at R^1 (eq 1). As a probe reaction, we carried out the experiment with styrene, CCl_4 in C_6D_6 at 30 °C, monitoring the disappearance of the olefin with **1** and **2** in separate experiments. As shown in Figure 1, complex **2** provided nearly quantitative conversions into the addition product, whereas in the case of **1** the reaction was not completed.

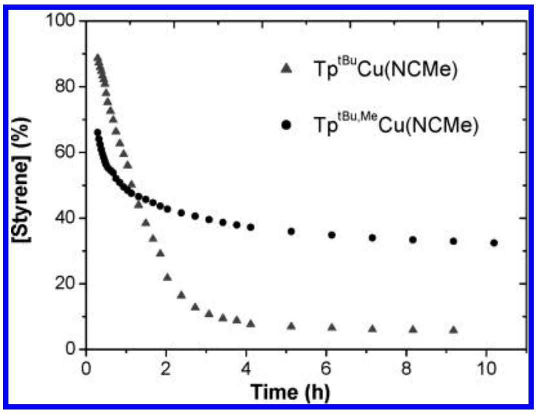
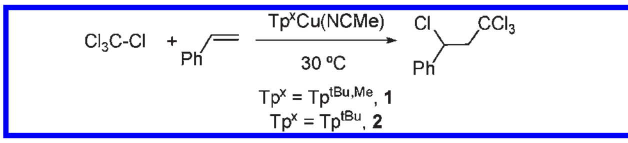
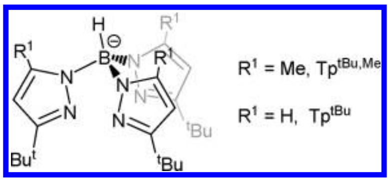


Figure 1. Kinetic monitoring (^{1}H NMR, 30 °C, C_6D_6) of the consumption of styrene in the reaction with CCl_4 using complexes **1** or **2** as the catalysts. Reactions performed at 30 °C; [Cu]/[styrene]/[CCl_4] = 1:500:2000. Rate constants: (a) **1** as catalyst, $k_{obs} = 2.01 \times 10^{-4}$ s^{-1}; (b) **2** as catalyst, $k_{obs} = 1.76 \times 10^{-4}$ s^{-1}.



(1)



After that finding, we also studied the effect of added acetonitrile on the reaction rate. Such a study is based in our previous mechanistic proposal[6i] (Scheme 2) in which the presence of a coordinating substrate, that is, MeCN, would reduce the amount of the Tp^xCu species and therefore would control the free-radical concentration (·R), slowing down the radical homocoupling side reaction. Furthermore, MeCN is also proposed[6i] to favor the formation of a pentacoordinated Cu(II) species that would prevent the accumulation of the Tp^xCuCl species and the subsequent formation of $(Tp^x)_2Cu$ species that would suppose a dead-end in the catalytic cycle. Consequently, the addition of acetonitrile should slow down reaction rates but would lead to an enhancement of yields and selectivity. Three experiments with 0, 20, and 40 equiv of MeCN with respect to the initial amount of complex **2** were carried out to evaluate the reaction rate. As shown in Figure 2, the reaction in the presence of 20 equiv of MeCN yielded 90% of the product after 24 h (entry 2), whereas only 69% or 80% yield were obtained when no or 40 equiv were added, respectively, as the result of catalyst deactivation.

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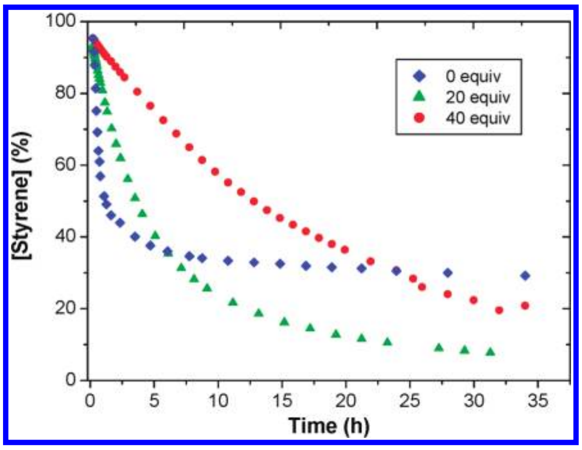
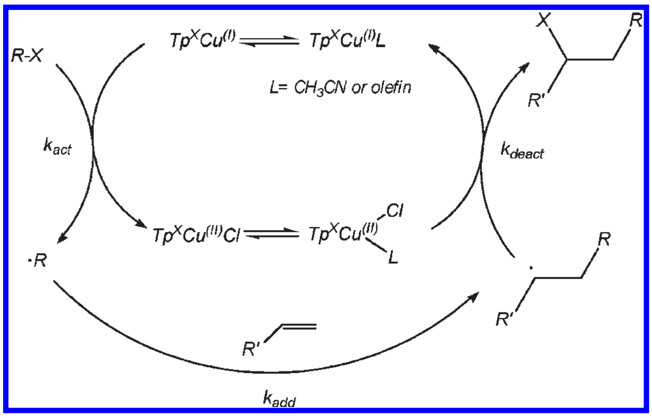


Figure 2. Consumption of styrene with time in the ATRA reaction of CCl_4 to styrene catalyzed by complex **2**, in the presence of different amounts of MeCN. Reactions performed at 30 °C with a [Cu]/[styrene]/[CCl_4] ratio of 1:2000:4000. Rate constants: (a) no MeCN added, $k_{obs} = 7.79 \times 10^{-5}\ s^{-1}$; (b) 20 equiv of MeCN added, $k_{obs} = 4.97 \times 10^{-5}\ s^{-1}$; 40 equiv of MeCN added, $k_{obs} = 1.38 \times 10^{-5}\ s^{-1}$.

Scheme 2. Mechanistic Proposal for ATRA Reactions Catalysed by Tp^xCu Complexes



Once the ability of complex **2** to induce the ATRA of CCl_4 to styrene was established, we carried out a study of its use in ATRA reactions of CCl_4 and CBr_4 to various olefins[14] in the presence of 20 equiv of MeCN. In a typical procedure, a solution (C_6D_6) of **2**, containing 20 equiv of MeCN, 2000 equiv of the olefin, and 4000 equiv of CCl_4 or CBr_4, was heated at 30 °C and the conversion monitored with time by ^1H NMR. As shown in Table 1, remarkable results were obtained for the more reactive olefins. Thus, the addition of CCl_4 to styrene (entries 1 and 2) proceeded with excellent yield and selectivity for the addition product, using 0.05 mol % of the copper catalyst. Similarly, nearly quantitative yields were observed for the addition of CCl_4 to methacrylates (entries 7, 12, and 13) with that catalyst loading. The results shown in Table 1 exceed those reported with other copper-based catalysts that, in addition, required the presence of a reducing agent, in contrast with the lack of such an additive in the system reported herein. The decrease in conversion when 1:5000 [catalyst]/[olefin] was used can be explained in terms of a decrease in the concentration of the active species Tp^xCu due to the formation of significant amounts of Tp^xCuL (L = olefin). On the other hand, this catalytic system was not very successful with less activated α-olefins (entries 14−16). The use of CBr_4 did not induce significant changes in the conversion when styrene was used (entries 4 and 5), although in the case of methyl methacrylate a decrease in the activity was observed (entries 9−11). In addition, low selectivity was obtained with acrylates (entries 17 and 18), probably due to their well-known high propagation rate constant (MA: $k_{p,25} = 5.8 \times 10^2\ M^{-1}\ s^{-1}$; MMA: $k_{p,25} = 1.9 \times 10^2\ M^{-1}\ s^{-1}$).[12]

Table 1. Atom Transfer Radical Addition (ATRA) of CCl_4 to Various Olefins Catalyzed by $Tp^{tBu}Cu(NCMe)$[a]

entry	alkene	R−X	[Cu]/[Olefin]	time (h)	conv/yield (%)[b]
1	styrene	CCl_4	1:2000	24	90/90
2			1:2000	48	>99/>99
3			1:5000	24	38/38
4		CBr_4	1:2000	24	84/83
5			1:2000	48	94/92
6			1:5000	24	68/66
7	MMA	CCl_4	1:2000	24	98/95
8			1:5000	24	33/33
9		CBr_4	1:2000	24	47/45
10			1:2000	48	60/57
11			1:5000	24	37/33
12	BuMA	CCl_4	1:2000	24	>99/>99
13	^{t}BuMA	CCl_4	1:2000	24	>99/97
14	1-hexene	CCl_4	1:2000	48	42/42
15	1-octene	CCl_4	1:2000	48	40/40
16	1-decene	CCl_4	1:2000	48	38/38
17	MA	CCl_4	1:2000	24	36/22
18	BA	CCl_4	1:2000	24	35/17

[a] All reactions were performed in the presence of 20 equiv of MeCN; temperature = 30 °C; [Olefin]/[R−X] = 1:2, except entries 3, 6, 8, and 11, [Olefin]/[R−X] = 1:1.2. Solvent is benzene-d_6. [b] The conversions and yields were determined by ^1H NMR spectroscopy after the desired times.

Table 2. ATRA Reaction of Polychlorinated Esters and Sulfonyl Chlorides to Olefins Catalyzed by Complex **2**[a]

entry	alkene	R-X	[Cu]/[Olefin]	time (h)	conv/ yield (%)[b]
1	Styrene	TsCl	1:300	24	>99/>99
2		Cl_3CCO_2Et	1:1000	24	>99/>99
3	MMA	TsCl	1:300	24	99/98
4		Cl_3CCO_2Et	1:1000	48	68/65

[a] All reactions were performed in the presence of 20 equiv of MeCN; temperature = 30 °C; [Olefin]/[R−X] = 1:2 for entries 2 and 4; [Olefin]/[R−X] = 1:1.2 for entries 1 and 3. Solvent is benzene-d_6. [b] The conversions and yields were determined by ^1H NMR spectroscopy after the desired times.

In order to extend the use of our catalytic system to synthetically interesting reactions, we decided to use other halide compounds instead of carbon tetrahalides, employing sulfonyl chloride or ethyl trichloroacetate. The radical addition of sulfonyl chlorides to olefins catalyzed by copper catalysts was previously, and independently, reported by the groups of Suzuki and Percec.[15] Typically, these reactions were carried out with CuCl (1−2 mol %) in the presence of Et_3NHCl at 80−100 °C. In a similar manner, Severin and co-workers used Ru-based catalysts[8] for this transformation (0.1 mol %, 48 h, room temperature, Mg as the reducing agent). In our case, when complex **2** was used as a catalyst, *p*-toluenesulfonyl chloride (TsCl) was efficiently added to

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(14) Olefins used: styrene (Sty), methyl methacrylate (MMA), *n*-butyl methacrylate (BMA), tert-butyl methacrylate (^{t}BMA), methyl acrylate (MA), butyl acrylate (BA), 1-hexene, 1-octene, and 1-decene.

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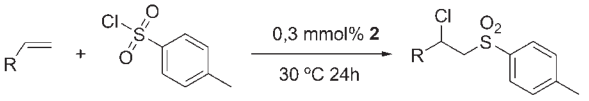
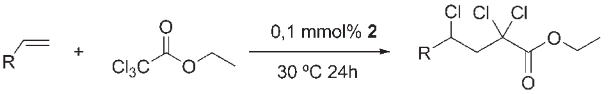
styrene or methyl methacrylate at 30 °C (eq 2, Table 2). The use of an olefin/Cu ratio of 300:1 led to the addition products in quantitative yields after 24 h at 30 °C (Table 2, entries 1 and 3). It should be noted that, for example, the 1:1 addition product between *p*-toluenesulfonyl chloride (TsCl) and styrene (1-[(2-chloro-2-phenylethyl)sulfonyl]-4-methylbenzene) can be easily transformed into (*E*)-*β*-(*p*-toluenesulfonyl)styrene in the presence of NBu_3.



(2)

On the other hand, the ATRA reactions of polychlorinated esters to olefins (eq 3) are synthetically interesting since the resulting products are precursors of lactones.[16] As shown in Table 2 (entries 2 and 4), complex **2** (0.1 mol %) catalyzes the addition of Cl_3CCO_2Et to olefins at 30 °C. After 24 h, the monoadducts were obtained in good yields without the assistance of reducing agents. These results are, at least, as good as those reported for others catalytic systems. For example, the addition of Cl_3CCO_2Et to styrene at room temperature gave 94% yield with the Ru/Mg system,[8] in good agreement with similar conversions obtained with **2** as a catalyst. However, it is worth mentioning that this copper-based system does not require the use of a reducing agent to achieve the conversions described with other systems that do need such an additive.



(3)

In conclusion, we have described a catalytic system for the ATRA reactions of halo compounds to olefins that does not need the presence of reducing agents and takes place with high efficiency and selectivity under mild conditions. Experimental and theoretical studies aiming to understand the effect of the Tp^x ligand are currently underway in our laboratory.

Experimental Section

General Information. All preparations were carried out in a glovebox. Starting materials and reagents were purchased from Aldrich. Olefins (styrene, methyl methacrylate, *n*-butyl methacrylate, *tert*-butyl methacrylate, methyl acrylate, butyl acrylate, 1-decene, 1-octene, and 1-hexene) were filtered on alumina columns prior to use. The homoscorpionate ligand was prepared according to literature methods as well as the complexes $Tp^{tBu,Me}Cu(NCMe)$ (**1**) and $Tp^{tBu}Cu(NCMe)$ (**2**). NMR experiments were run on a Varian Mercury 400-MHz spectrometer.

General Procedure for the ATRA of CCl_4 to Olefins. The desired amount of a stock solution of the copper complex in benzene-d_6, an appropriate amount of MeCN, and the corresponding amount of the olefin and CCl_4 were dissolved in the required amount of C_6D_6 to arrive at a total volume of 1.1 mL. The initial concentrations were [catalyst] = 0.94 mM, [MeCN] = 18.8 mM, [olefin] = 1.88 M, and $[CCl_4]$ = 3.76 M. The solution was transferred into a NMR pressure tube and sealed with a Teflon screw cap. The tube was removed from the glovebox and placed in an oil bath at 30 °C. The conversions were monitored by ^1H NMR spectroscopy at the desired times.

General Procedure for the ATRA of CBr_4 to Olefins. The procedure was identical to that described above for CCl_4. All reactions were performed with an appropriate amount of a stock solution of the copper complex, MeCN, olefin, CBr_4, and C_6D_6 to reach a final volume of 1.5 mL. The initial concentrations were [catalyst] = 0.69 mM, [MeCN] = 13.8 mM, [olefin] = 1.38 M, and $[CBr_4]$ = 1.66 M.

General Procedure for the ATRA of TsCl to Olefins. The procedure was identical to that described above for CCl_4. All reactions were performed with an appropriate amount of a stock solution of the copper complex, MeCN, olefin, TsCl, and C_6D_6 to reach a final volume of 1.5 mL. The initial concentrations were [catalyst] = 4.33 mM, [MeCN] = 86.6 mM, [olefin] = 1.30 M, and [TsCl] = 1.56 M.

General Procedure for the ATRA of Cl_3CCO_2Et to Olefins. The procedure was identical to that described above for CCl_4. All reactions were performed with an appropriate amount of a stock solution of the copper complex, MeCN, olefin, Cl_3CCO_2Et, and C_6D_6 to reach a final volume of 1.5 mL. The initial concentrations were [catalyst] = 1.38 mM, [MeCN] = 27.6 mM, [olefin] = 1.38 M, and $[Cl_3CCO_2Et]$ = 2.76 M.

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Supporting Information Available: NMR data for the products, NMR spectra of reaction mixtures, and kinetic plots. This material is available free of charge via the Internet at http://pubs.acs.org.

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