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Generation of Halomethyl Radicals by Halogen Atom Abstraction and Their Addition Reactions with Alkenes

Robynne K. Neff,[‡,a] Yong-Liang Su,[‡,a] Siqi Liu,[b] Melina Rosado,[a] Xinhao Zhang,[*,c] Michael P. Doyle[*,a]

a. Department of Chemistry, The University of Texas at San Antonio, San Antonio, Texas 78249, United States

b. College of Chemistry and Molecular Engineering, Peking University, Beijing 100871, China

c. Lab of Computational Chemistry and Drug Design, State Key Laboratory of Chemical Oncogenomics, Peking University Shenzhen Graduate School, Shenzhen 518055, China

ABSTRACT: α-Aminoradicals undergo halogen atom abstraction to form halomethyl radicals in reactions initiated by the combination of *tert*-butyl hydroperoxide, aliphatic trialkylamine, halocarbon, and copper(I) iodide. The formation of the α-aminoradical circumvents preferential hydrogen atom transfer in favor of halogen atom transfer, thereby releasing the halomethyl radical for addition to alkenes. The resulting radical addition products add the *tert*-butylperoxy group to form α-peroxy-β,β-dichloropropylbenzene products that are convertible to their corresponding β,β-dichloro-alcohols and to novel pyridine derivatives. Computational analysis clearly explains the deviation from traditional HAT of chloroform and also establishes formal oxidative addition/reductive elimination as the lowest energy pathway.

INTRODUCTION

Radical addition reactions of alkenes with dissociable molecular species (X-Y) provide convenient access to vicinal disubstituted products with increased molecular and functional complexity (Figure 1a). The initiation of these reactions effects atom transfer that forms radical Y which adds to the carbon-carbon double bond to form a carbon radical that abstracts X from X-Y to enter the catalytic cycle. In one of the most notable examples of these reactions, Kharasch reported in 1945 the acetyl peroxide-induced Markovnikov addition of Cl and CCl_3 from CCl_4 to alkenes.[1] The Kharasch reaction has been extensively investigated,[2,3] and numerous examples of atom-transfer radical addition using transition metal catalysts to initiate CCl_3 radical generation have been reported.[4-7] However, when this process was applied with chloroform (Figure 1b), the initiation step generated the CCl_3 radical by H atom transfer (HAT), rather than form the dichloromethyl radical by chlorine atom transfer.[1] In fact, the dichloromethyl radical can be generated by a HAT from CH_2Cl_2,[8] albeit indirectly via an aryl radical formed from a boronic acid or an aryldiazonium salt, and a catalytic methodology has been reported to utilize the chloroform analog $CHCl_2Br$ in the presence of stoichiometric amounts of tri- and tetra-tertiary amines as an alternative.[9] Transition metal compounds, especially those of low valent platinum,[10] are well known to undergo oxidative addition with halocarbon solvents, but there has not been a report of a catalytic process through which the dichloromethyl radical has been generated from chloroform. We wish to report an effective indirect methodology for preferential chlorine atom abstraction from chloroform and its application to the regioselective addition of $CHCl_2$ and the *tert*-butylperoxy radical to styrenes, resulting in α-peroxy-β, β-dichloropropylbenzene products in moderate to high yields (Figure 1c), and their conversion to the corresponding β,β-dichloro-alcohols and novel pyridine derivatives. Experimental data along with DFT calculations demonstrate the essential role of the α-aminoradical that changes the preference of atom extraction from $CHCl_3$. A excellent correlation is found to be valuable for selecting appropriate radical and a general mechanism are also proposed.

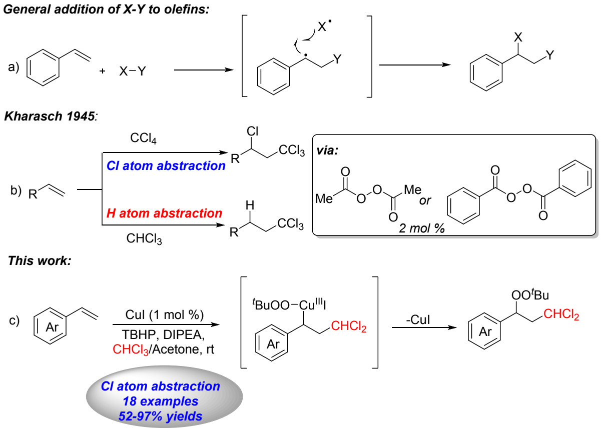


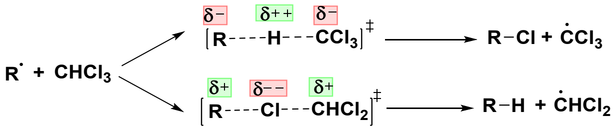
Figure 1. (a) General approach to functionalize olefins by dissociable molecular species. (b) Kharasch's first examples of halogen atom abstraction from carbon tetrachloride and HAT from chloroform. (c) Selective chlorine atom abstraction from chloroform to form α-peroxy-β,β-dichloropropylbenzenes.

RESULTS AND DISCUSSION

We envisioned that generation of the dichloromethyl radical from chloroform would be a function of the relative energies for C-Cl versus C-H homolytic bond cleavage from various radical initiators. Those atom transfer agents that have been reported (^{t}BuOO, ^{t}BuO, OH, and Ar) favor C-H bond cleavage,[8a,11] but this list is limited.[12] As shown in Scheme 1, we expected that reversing radical polarity would lead to free radical species that could favor C-Cl bond cleavage and thereby provide a viable pathway for the generation of halogenated carbon radicals.

A search for appropriate radicals were initiated with examining adiabatic ionization potentials (IPs) of carbon radicals.[13] The calculated IPs and differences in free energy barriers of hydrogen atom transfer (HAT) vs. chlorine atom transfer (CAT) $(\Delta G_{H\neq} - \Delta G_{Cl\neq})$ are listed in Table 1 and plotted in Figure 2.

Scheme 1. Different polar effects of atom transfer reaction.



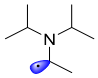
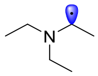
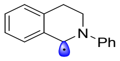
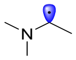
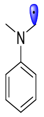
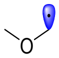
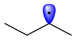
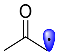
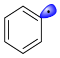
Indeed, the IPs indicate the potential of releasing an electron and a good correlation between IP and the preference of HAT vs. CAT was found. Results in Table 1 and Figure 2 suggested that α-amino radicals would favor C-Cl homolytic cleavage to generate the dichloromethyl radical.[14] More specifically, α-amino radicals were indicated to have the highest potential to undergo chlorine atom abstraction with energy differences greater than those of α-alkoxy carbon radicals (Table 1, entries 1-6). Alkyl, α-carbonyl, and phenyl radicals, in contrast, have a higher preference for C-H bond homolytic cleavage (Table 1, entries 7-9).

Table 1. Calculated Gibbs free energy barrier ($\Delta G_{X^{\neq}}$)/energy differences ($\Delta G_{H^{\neq}}$-$\Delta G_{Cl^{\neq}}$) of various radicals

$R^{\bullet} + H\text{-}CX_3 \xrightarrow{\Delta G^{\ddagger}_H} R\text{-}H + \dot{C}X_3 \quad R^{\bullet} + X\text{-}CHX_2 \xrightarrow{\Delta G^{\ddagger}_X} R\text{-}X + \dot{C}HX_2$

$\Delta G^{\ddagger}_H$ (kcal/mol) for free energy barriers of hydrogen atom transfer

$\Delta G^{\ddagger}_X$ (kcal/mol) for free energy barriers of halogen atom transfer

Entry	Radical	IP	$\Delta G_{H^{\neq}}$	$\Delta G_{Cl^{\neq}}$	$\Delta G_{H^{\neq}}$-$\Delta G_{Cl^{\neq}}$
1		4.7	17.4	9.2	8.2
2		4.9	12.9	6.7	6.2
3		5.3	24.2	17.9	6.3
4		5.1	12.9	7.8	5.1
5		5.6	14.7	12.8	1.9
6		7	14.6	13.6	1.0
7		7.1	13.3	15.8	-2.5
8		8.3	17.2	21.9	-4.7
9		8.1	5.4	10.7	-5.3

On this basis we searched for those reactants that preferentially form an intermediate radical capable of undergoing chlorine atom abstraction from chloroform to produce the $CHCl_2$ radical.[15] Tertiary amines were surveyed, but with the caveat that generation of α-amino radicals is subject to the oxidation potential of the amine. Specifically, electron transfer (ET) is the initial step in the catalytic oxidation of *N*,*N*-dialkylanilines to their corresponding iminium ions by *tert*-butyl hydroperoxide (TBHP),[16] whereas hydrogen atom transfer (HAT) occurs preferentially as the initial step in the similar oxidation of tetrahydroquinolines.[17]

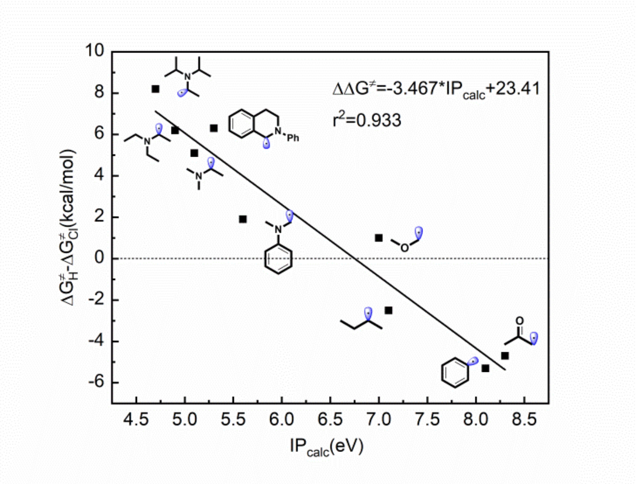


Figure 2. A correlation between IPs and the difference in free energy barrier of HAT vs. CAT.

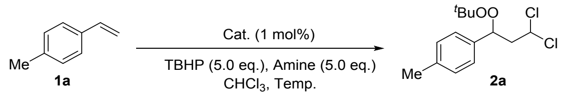
Because of their demonstrated suitability for free radical addition reactions, styrenes were selected as the target substrates.[18] Reactions were performed in various solvents containing excess chloroform, amines capable of HAT, and selected catalysts known to form the *tert*-butylperoxy radical. Table 2 provides an abbreviated selection of various screening parameters (see Supporting Information for full screening parameters). As expected, trialkylamine bases performed well under the reaction conditions in the presence of $Rh_2(cap)_4$ (Table 2, entries 1-3). When 3□ benzylamines and anilines were used, no conversion of the styrene reactant to product was observed (Table 2, entries 4-5). $Rh_2(OAc)_4$ was ineffective at room temperature or 65 °C, and silver based catalysts showed moderate product formation (Table 2, entries 7-8). However, use of CuI gave nearly quantitative formation of the desired product (Table

2, entry 9). No significant drop in yield was observed at ambient temperature, although the low solubility of CuI in organic solvents led to inconsistent initiation/yields. To overcome this problem acetone was used as a co-solvent, and this change provided high reproducibility to these reactions (Table 2, entry 10). Furthermore screening of the amine and the copper catalyst showed that the DIPEA and CuI provide the best result (Table 2, entries 11-16). No product could be detected without both 3° aliphatic amine and CuI (Table 2, entries 17-18 and SI).[18]

The optimum catalyst, amine, and reaction conditions were applied to substituted styrenes, and the results obtained showed generality for this transformation (Scheme 1). Styrenes with both electron-rich and electron-deficient substituents at the para-, meta-, and ortho-positions of the phenyl moiety furnished product in moderate to high yields (**2a - 2k**). Furthermore, substitution at the α-position of styrene also gave product with good yields (**2l - 2m**), and 1-vinylnaphthalene and 2-vinylnaphthalene were also compatible with this catalytic process (**2n - 2o**). In reactions with vicinal disubstituted alkenes, however, an additional 3.0 eq. of TBHP were necessary to obtain higher yields (**2p - 2q**). Cumyl peroxide was also compatible under the reaction conditions (**2r**). However, di-*tert*-butylperoxide (DTBP) and benzoyl peroxide were unreactive.

Other perhalogenated compounds that could undergo hydrogen atom abstraction were also found to be selective for halogen atom abstraction (Table 3, except entry 1, 5 and 6). Several methodologies undergo similar addition of alkyl halides but often times are limited to substrates wherein α-halogens are excluded.[19] Under our standard reaction conditions where mixed halogenated compounds were used, selectivity for I > Br > Cl > F removal was observed (Table 3, entries 1-3) in moderate to high yields. Carbonyl substrates containing α-halogenated esters also underwent addition in good yields (Table 3, entries 4-5). Finally, while reactivity remained high for chloroform derivatives and bromoform (Table 3, entry 7) and for chlorine atom transfer from tetrachloromethane (Table 3, entry 6), iodoform (Table 3, entry 8) consistently led to lower conversions, possibly due to subsequent reactions.

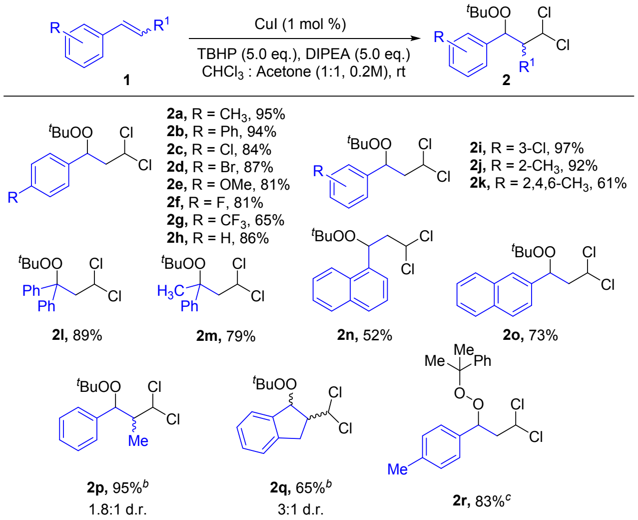
Table 2. Optimization of reaction conditions for dichloromethyl radical addition[a]



Entry	Amine	Catalyst	Yield[b]
1	NEt_3	$Rh_2(cap)_4$	71%
2	NCy_2Me	$Rh_2(cap)_4$	71%
3	DIPEA	$Rh_2(cap)_4$	87%
4	$N(Bn)_3$	$Rh_2(cap)_4$	0%
5	$PhNMe_2$	$Rh_2(cap)_4$	0%
6	DIPEA	Rh_2OAc_4	0%
7	DIPEA	AgOTf	55%
8	DIPEA	AgOAc	61%
9	DIPEA	CuI	97%
10[c]	DIPEA	CuI	95%
11[c]	NEt_3	CuI	62%
12[c]	NCy_2Me	CuI	67%
13[c]	$N(Hex)_3$	CuI	36%
14[c]	DIPEA	CuOAc	74%
15[c]	DIPEA	CuBr	82%
16[c]	DIPEA	$Cu(ACN)_4PF_6$	82%
17[c]	DIPEA	-	0%
18[c]	-	CuI	0%

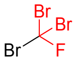
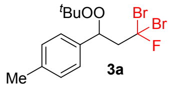
[a]Reaction conditions: unless indicated otherwise, the reaction of **1a** (1.0 mmol), catalyst (1 mol%), TBHP (5.0 eq.), amine (5.0 eq.) was carried out in $CHCl_3$ (5.0 mL) at 65 °C. [b]Isolated yield. [c]$CHCl_3$:acetone were used in a 1:1 ratio as co-solvents (5.0 mL) at rt.

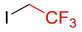
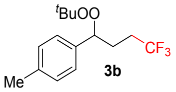
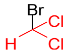
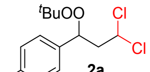
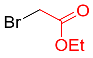
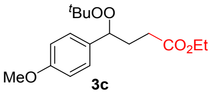
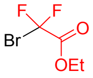
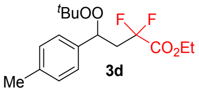
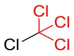
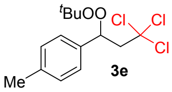
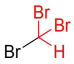
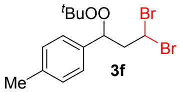
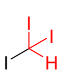
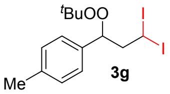
Scheme 2. Substrate scope of alkenes for dichloromethyl radical addition[a]



[a]Reaction conditions: unless indicated otherwise, reactions of **1** (1.0 mmol), CuI (1 mol%), TBHP (5.0 eq.), DIPEA (5.0 eq.) were carried out in $CHCl_3$/acetone (1:1, 5.0 mL) at rt. [b]After 30 minutes, an additional 3.0 eq. of TBHP were added. [c]Cumyl hydroperoxide was used as an alternative to TBHP, and an additional 3.0 eq. of cumyl hydroperoxide were added after 30 minutes.

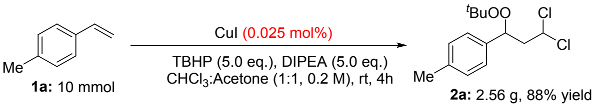
Table 3. Substrate scope of alkyl halide for addition to aryl alkenes[a]

Entry	Alkyl Halide	Product	Yield[b]
1		 **3a**	81%

2		 **3b**	83%
3		 **2a**	53%
4		 **3c**	69%
5		 **3d**	71%
6		 **3e**	91%
7		 **3f**	73%
8		 **3g**	43%

[a]Reaction conditions: unless indicated otherwise, the reaction of **1** (1.0 mmol), R-X (5.0 eq.), CuI (1 mol%), TBHP (5.0 eq.), DIPEA (5.0 eq.) was carried out in acetone (5.0 mL) at rt. [b]Isolated Yields.

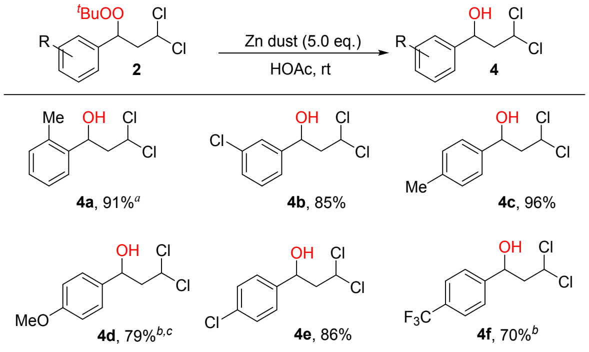
Moreover, the dichloromethyl addition reaction could be carried out on a gram scale with high product yield using only 0.025 mol% of CuI (eq 1). Considering that the reaction does not give **2a** without the CuI catalyst (Table 2, entry 17), we conclude that CuI is very efficient but also essential. Furthermore, without the 3° aliphatic amine the reaction takes an entirely different course.



(1)

The synthetic utility of the peroxide products was studied next.[20] Different from "Russell mechanism" where the alcohol is a derived in a 1:1 mixture with their corresponding carbonyl products,[21] the peroxide products can be easily converted to their alcohol counterparts by a rarely applied reduction that occurs in acetic acid with zinc dust (Scheme 3).[22] In all cases, once starting material was consumed a simple basic aqueous work up led to the desired product with no need for additional purification. For the *p*-methoxyphenyl substrate, the main product was the alcohol **4d,** but 10% of acylated **4d´** was also isolated.

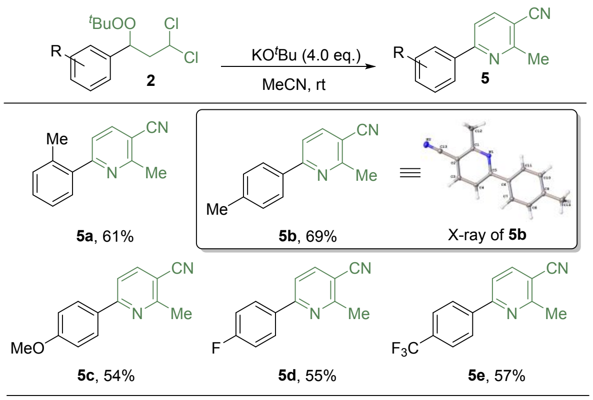
Scheme 3. Transformation of peroxide products to benzyl alcohols



[a]After 48 hours an additional 3.0 eq. of Zn dust was added. [b]After 48 hours, an additional 5.0 eq. of Zn dust was added. [c]Product yield includes 10% acetate ester.

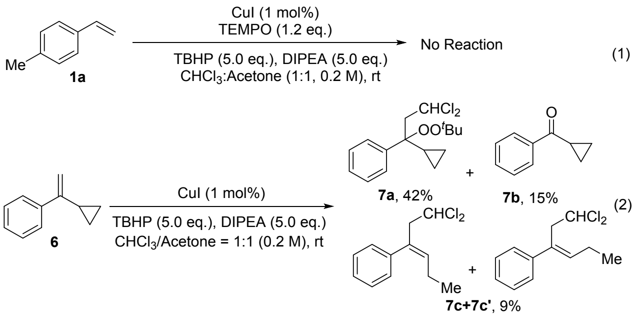
A further example of the utility of the dichloromethyl addition process is evident in the conversion of the addition products to substituted pyridine derivatives, a recent example of which is a palladium-catalyzed condensation of acetonitrile with homopropargylic alcohols.[23] We were delighted to observe that formation of substituted pyridines occurred in moderate yields in the presence of KO^{t}Bu in acetonitrile (Scheme 4). A similar process, known as the Thorpe-Ziegler reaction, is used in the self-condensation reactions of aliphatic nitriles that results the synthesis of enamines that provides ketone products after acid hydrolysis.[24] The X-ray structure of **5b** was obtained for full characterization. A full study of this reaction and its implications is ongoing.

Scheme 4. Transformation of peroxide products into substituted pyridines.



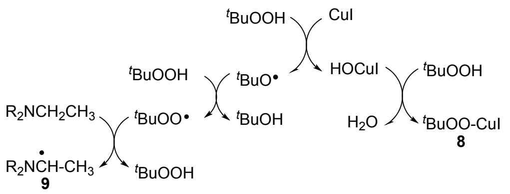
The radical nature of the transformation is suggested by the reaction conditions that have been employed, but additional experimentation confirms this inference (Scheme 5). Reaction of **1a** under standard reaction conditions along with TEMPO as an additive provided no conversion of the starting material (Scheme 5, eq 1). Additionally, using vinylcyclopropane **6** as the substrate to ascertain the fate of the initially-formed reaction intermediate and its lifetime, several products were formed in addition to **7a**: ketone **7b** and ring opening products **7c** and **7c´**(Scheme 5, eq 2). Major product **7a** is consistent with the overall addition process from which products **7c** and **7c´** are formed and whose yields suggest the relative rates for capture by the *tert*-butylperoxy radical versus ring opening/hydrogen atom transfer.[25] The formation of cleavage product **7b** is due to the initial addition of the *tert*-butylperoxy radical to **6**, and its formation in reactions with O_2 or H_2O_2 as the oxidant has been reported.[26]

Scheme 5. Mechanistic experiments to probe the radical pathway.



From a mechanistic standpoint, the most likely initiation of this reaction is by TBHP and CuI to form the *tert*-butylperoxy radical by hydrogen atom transfer from TBHP to the initially formed *tert*-butoxy radical[27] (Scheme 6). This process has been extensively studied.[28] The Cu^{II} species produced by this oxidative reaction, (HO)CuI, is proposed to be in equilibrium with ICu-OO^{t}Bu (**8**).[29] A HAT of the *tert*-butylperoxy radical with the trialkylamine generates the α-aminoradical (**9**) that is the key intermediate which preferentially undergoes chlorine atom abstraction from chloroform. The $CHCl_2$ radical generated from chloroform adds regioselectively to the terminal carbon of styrene to generate the benzyl radical.

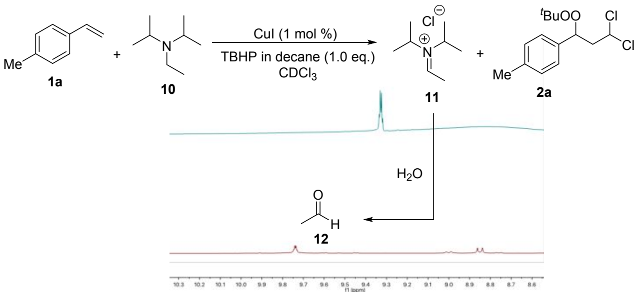
Scheme 6. Initiation of the process leading to the dichloromethyl radical through formation of α-aminoradical 9.



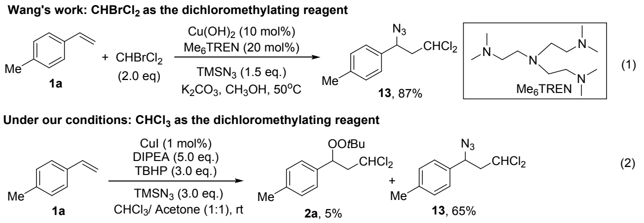
That the α-aminoradical is the key intermediate is not only inferred from the calculations reported in Table 1, but its involvement is strongly supported by the direct observation of iminium ion **11** using ^{1}H NMR spectral analysis under the standard conditions (Scheme 7). Addition of H_2O sequestered the intermediate quantitatively to acetaldehyde **12**. The reaction was also monitored by ^{1}H NMR under the standard reaction conditions, and acetaldehyde was observed to ultimately form in a 1:1 ratio to the peroxide product (see Supporting Information).

Hydrogen atom abstraction from tertiary amine bases is key to understanding the formation of the dichloromethyl radical from chloroform, and may also contribute to understanding recently published copper(II) hydroxide catalyzed generation of the dichloromethyl radical from $CHCl_2Br$ whose transformations are dependent on the stoichiometric uses of tertiary amine bases (Scheme 8, eq 1)[9]. The requirement for amines may also indicate that the amine plays an important role in the generation of the dichloromethyl radical rather than being only a ligand or base. Under our conditions with CuI, TBHP, and DIPEA, reaction with TMS-azide produces the same azide addition product as was reported by Wang and coworkers [in competition with formation of **2a** (Scheme 8, eq 2)]; and increasing the stoichiometric amount of $TMSN_3$ also increases the yield of the azide **13** relative to **2a** (see Supporting Information); this outcome suggests that the indirect methodology makes possible a broad spectrum of radical oxidative addition processes.

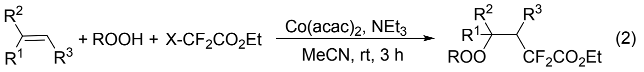
Scheme 7. ^{1}H NMR spectral observation of iminium ion 11 and acetaldehyde 12 in the standard reaction.



Scheme 8. Copper-catalyzed dichloromethylazidation of alkene using $CHBrCl_2$ or $CHCl_3$ as the dichloromethylating reagent.



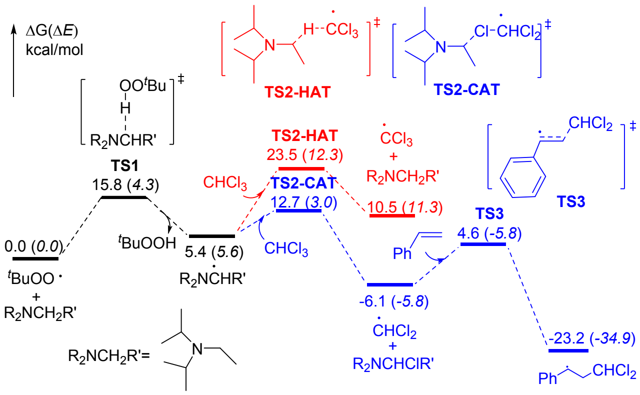
As we were submitting this manuscript for publication, Li and coworkers reported the use of cobalt(II) acetylacetonate as a catalyst and triethylamine as a base for difluroalkylation-peroxidation of arylalkenes (eq 2).[15d] In their survey of applicable halogenation reagents they reported one example using chloroform in which the dichloromethyl product **2h** was formed in 41% yield, and we have confirmed this result. The role of trimethylamine was proposed to be solely that of a base to neutralize acid formation, but the results that we report suggests that the tertiary amine is essential for halogen atom abstraction.



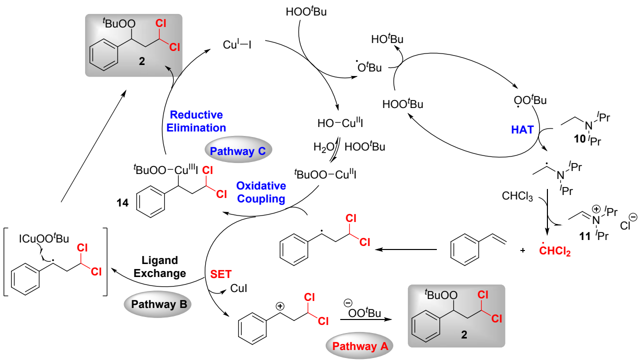
The selectivity of CAT versus HAT for the generation and oxidative addition of the dichloromethyl radical was subjected to DFT analysis (Scheme 9). Hydrogen atom abstraction from the α-position of DIPEA to the *tert*-butylperoxy radical occurs with a relatively low activation barrier of 15.8 kcal/mol. The HAT from chloroform to the DIPEA radical was calculated to have a higher energy barrier (23.5 kcal/mol) than the CAT from chloroform to the DIPEA radical (12.7 kcal/mol). This preference is sufficiently great to direct the reaction exclusively to the dichloromethyl radical.

The formation of peroxide products **2** and **3** in relatively high yields narrows the possible outcomes to three distinct pathways (Scheme 10). In Pathway A a single electron transfer (SET) by Cu^{II} would yield a benzyl carbocation which could be intercepted by TBHP or, in theory, by other suitable nucleophiles, including water in T-HYDRO. However, when the reaction was conducted in the presence of alternative nucleophiles, no deviation in product selectivity for **2** was observed (i.e., with MeOH, NaOH/H_2O, indole). In Pathway B the formation of **2** occurs through a two-step outer sphere ligand transfer between ICu-OO^tBu and the benzyl radical. Alternatively, in Pathway C addition of Cu^{II} to the benzyl radical, resulting in Cu^{III} species **14**, followed by reductive elimination regenerates the catalyst and affords the observed product. This pathway has been used to explain other copper catalyzed addition reactions involving TBHP,[30] but there has not been experimental evidence for this pathway, and asymmetric induction from the use of chiral ligands for copper(I) (and, alternatively, for dirhodium(II) carboxamidates) offered an attractive experiment that might distinguish this Pathway from Pathway B. However, only borderline enantioselectivity was observed in the presence of chiral ligands (see Supporting Information), possibly due to ineffective metal-ligand coordination. Since the lack of enantioselectivity does not fully discredit this particular pathway, we turned to DFT calculations to further distill the key reaction intermediates as well as which route was more plausible.

Scheme 9. Computed free energy diagram for α-amino radical mediated reactions with chloroform. Calculations were at the B3LYP-D3 level.

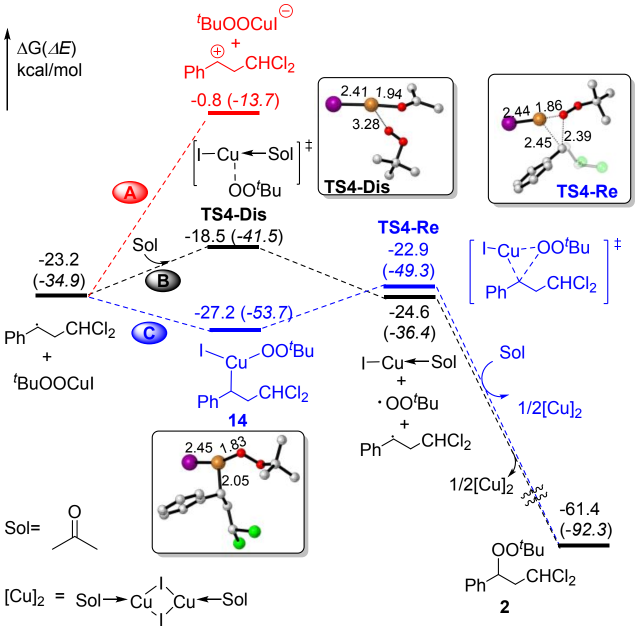


Scheme 10. Three possible mechanistic pathways for product formation



The three pathways for C-O bond formation were probed (Scheme 11). A single electron transfer to form the benzylic carbocation was calculated to have the highest energy profile (Pathway A) which explains why no product loss due to the presence of other nucleophiles is observed. The direct outer sphere ^tBuOO ligand transfer had the next highest energy barrier (**TS4-Dis** in Pathway B) whereas the formal oxidative addition of copper to styrene followed by reductive elimination (**TS4-Re** in Pathway C) was calculated to have the lowest activation free energy for the two steps and, so, is considered to be the most favorable pathway. The Cu—C and O—C distances (2.45Å and 2.39Å) in **TS4-Re** are much longer than the reported enantioselective cases.[31] Such ineffective coordination accounts for the experimental observation of the lack of enantioselectivity (see Supporting Information).

Scheme 11. Computed free energy diagram for C-O bond formation. Calculations were at the B3LYP-D3 level and distances are in Å.



CONCLUSIONS

In conclusion, a previously unrealized chlorine atom transfer from chloroform was achieved by an indirect process through which catalytic TBHP-induced formation of an α-aminoradical causes chlorine atom transfer from chloroform forming the dichloromethyl radical that undergoes regioselective addition to the carbon-carbon double bond of styrenes. This process was optimized to form various substituted α-peroxy-β,β-dichloropropylarene products and was also suitable for halogen atom abstraction of additional alkyl halides to form diverse α-peroxy-β-substituedethylbenzene products. An excellent correlation between IPs and the difference in free energy barrier of HAT vs. CAT was found. The correlation provides a general method to select appropriate radical for halogen atom transfer reaction. Furthermore, the mechanism for halogen atom transfer involving α-aminoradical intermediates unifies disparate reports and establishes a cohesive framework for further advances. A detailed computational investigation clearly demonstrated the deviation from traditional HAT of chloroform and also established a formal oxidative addition/reductive elimination as being the lowest energy pathway. The *tert*-butylperoxide products formed by this methodology are reducible to their corresponding alcohols under mild conditions and are also convertible to highly substituted pyridine derivatives in acetonitrile.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website. General experimental procedures and detailed optimization and product analyses, experimental procedures for mechanistic analyses, computational details, references, and NMR spectra. CIF file for **5b**.

AUTHOR INFORMATION

Corresponding Author

*Email: michael.doyle@utsa.edu

Author Contributions

R. K. N. and Y.-L. S. contributed equally.

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