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Metal-Free, Radical Addition to Alkenes *via* Desulfitative Chlorine Atom Transfer

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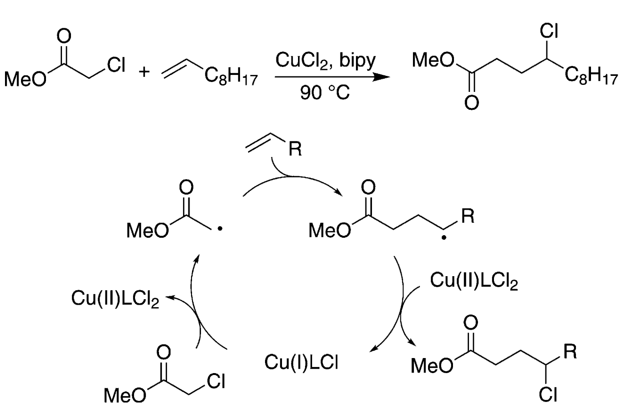
Abstract: An efficient method for radical additions to unactivated alkenes *via* desulfitative chlorine-atom transfer is described. The reaction is based on the use of readily available sulfonyl chlorides as starting materials and cheap radical initiators such as azobisisobutyronitrile (AIBN), di-*tert*-butyldiazene (DTBD), and dilauroyl peroxide (DLP). No transition metal catalyst is required and the reaction takes place under mild conditions at temperatures ≤85 °C.

Keywords: amides; atom-transfer radical addition (ATRA) reaction; chlorine atom transfer; desulfitation; esters; radical reaction; sulfonyl chloride; trichloromethyl radical

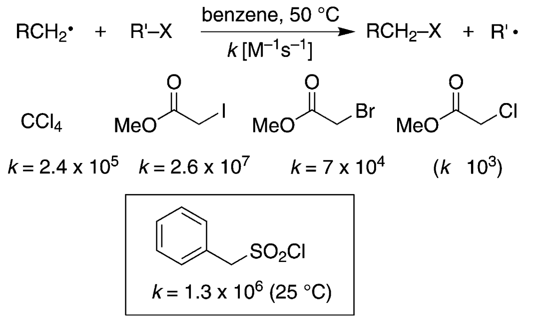
Introduction

The development of mild and selective methods for carbon-carbon bond formation *via* radical pathway has attracted the interest of many synthetic chemists during the last decades.[1] Among various types of radical processes, halogen atom-transfer radical addition (ATRA) reactions, pioneered by Kharasch[2] and further developed by Curran and others,[3] have received considerable attention because of their atom-economic nature and high efficiency.[4] Despite the instability of the starting iodides, iodine atom transfer processes represent a powerful method for C–C bond formation. Bromine atom transfers were among the earliest examples of atom transfer processes,[2a] however, they are restricted to a limited number of cases involving highly reactive bromides such as bromotrichloromethane and bromomalonitrile.[5–7] Due to the high C–Cl bond dissociation energy, the chlorine ATRA reaction is less common. It is mainly limited to polychlorinated substrates and it requires catalysis by transition metal complexes.[8] The use of monochlorinated species is still highly challenging despite the early report by Julia about the addition of ethyl chloroacetate to 1-decene in the presence of a $CuCl_2$-bipyridine catalyst system (Scheme 1).[9]

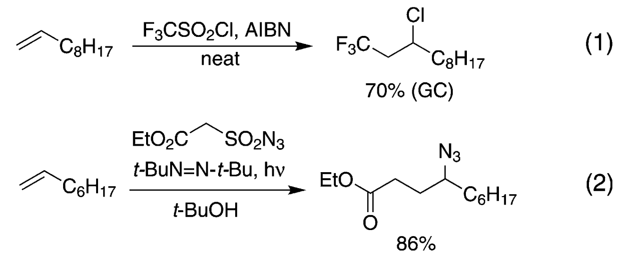
Due to their stability and long-term storage properties, chlorides are very attractive synthetic intermediates. An efficient method for chlorine ATRA reaction that does not rely on a transition metal catalyst would clearly be of high interest for preparative applications. Interestingly, sulfonyl chlorides are excellent radical chorinating agents. For instance, the rate constant for the chlorination of primary alkyl radicals has been measured to be $k = 1.3 \times 10^6\ M^{-1}s^{-1}$ at 25 °C.[10] This value is one order of magnitude smaller than the rate constant reported for iodine atom transfer between primary alkyl radicals and methyl iodoacetate, one order of magnitude higher than the rate constant reported for chlorine atom transfer with CCl_4 and two order of magnitudes higher than the rate of bromine atom transfer reported from methyl bromoacetate (Scheme 2).[11] As a consequence, sulfonyl chlorides



Scheme 1. Copper-catalyzed chlorine atom transfer process.[9]



Scheme 2. Rate constants for halogen atom transfer involving primary alkyl radicals.[10,11]

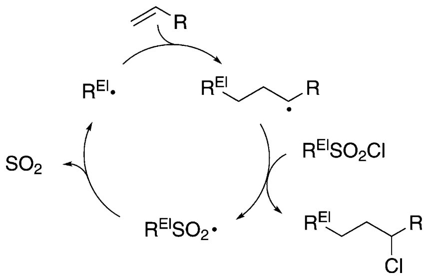


Scheme 3. Desulfitative chlorine[18] and azide transfer reactions.[19]

are very attractive precursors for chlorine ATRA reactions. However, so far these reactions are mostly restricted to the addition of arenesulfonyl radicals to alkenes[12–14] and in most cases a transition metal catalyst is needed.

The formation of carbon-centered radicals by α-scission of sulfonyl radicals is a well-established process that has been used to generate alkyl radicals involved in chain reactions.[15] Trifluoromethanesulfonyl chloride (CF_3SO_2Cl) and trichloromethanesulfonyl chloride (Cl_3CSO_2Cl) have been employed as radical precursors in desulfitative chlorine ATRA reactions by Kamigata under ruthenium(II) catalysis.[16] Cobalt(II) was also shown to catalyze reactions involving tricholoromethyl radicals.[17] Roques discovered that chlorine ATRA reactions involving perfluorinated sulfonyl chlorides could be performed under solvent-free conditions with azobisisobutyronitrile (AIBN) as a radical initiator [Scheme 3, Eq. (1)].[18] Recently, we reported an efficient metal-free desulfitative azide transfer reaction involving various electrophilic C-centered radicals [Scheme 3, Eq. (2)].[19]

Based on these results, we hypothesized that the metal-free desulfitative chlorine ATRA reaction could become a general approach applicable to various types of electrophilic radicals (Scheme 4). We report here our study of the scope and limitations of this approach that demonstrates its generality.

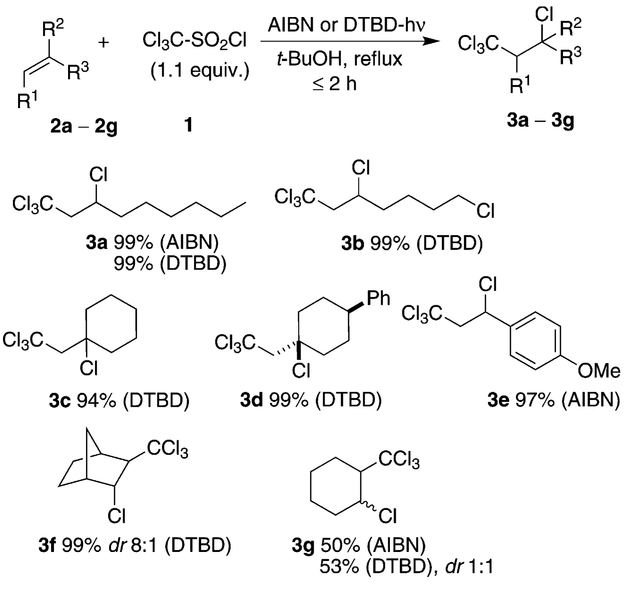


Scheme 4. General mechanism for the desulfitative chlorine ATRA to alkenes (R^{El} = radical with electrophilic character).

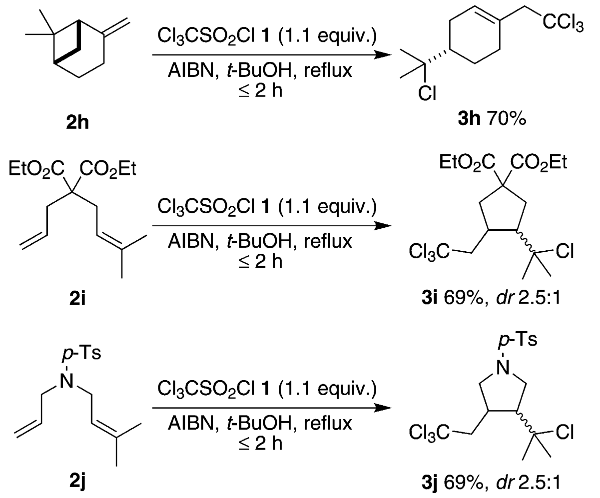
Results and Discussion

Reactions with Trichloromethanesulfonyl Chloride

The desulfitative chlorine ATRA reaction with commercially available Cl_3CSO_2Cl **1** was investigated first. Under the neat conditions reported by Roques,[18] low to moderate yields were obtained due to the formation of a polymeric material. In a rapid screening of solvents, *tert*-butanol, a solvent of low toxicity, gave the best results in terms of yield and cleanness of the reaction (Scheme 5). Both AIBN and di-*tert*-butyldiazene (DTBD) can efficiently initiate the reaction. Reaction of Cl_3CSO_2Cl with monosubstituted terminal alkenes **2a** and **2b** and methylenecyclohexane derivatives **2c** and **2d** afforded the products of the desulfitative chlorine ATRA reaction **3a**–**3d** in excellent yields. Interestingly, *para*-methoxystyrene **2e** reacted with Cl_3CSO_2Cl in almost quantitative yield demonstrating that the chlorination of benzylic radicals can



Scheme 5. Chlorine ATRA reactions of trichloromethanesulfonyl chloride **1**.



Scheme 6. Ring-opening and ring-closing reactions involving desulfitative chlorine ATRA reactions of trichloromethanesulfonyl chloride **1**.

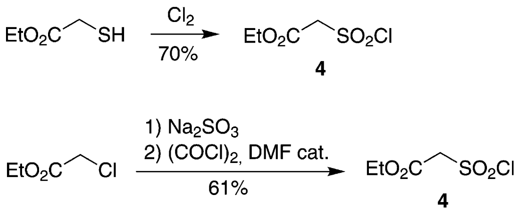
be achieved very efficiently with this reagent. Reaction with an internal cyclic olefin such as norbornene **2f** gave **3f** in almost quantitative yield. As expected for a radical reaction, the less reactive cyclohexene **2g** afforded **3g** in only 50–53% yield as a mixture of stereomers.

The radical nature of the process is demonstrated by the opening of the cyclobutane ring observed with (−)-β-pinene **2h** that afforded **3h** (Scheme 6). Similarly, dienes **2i** and **2j** gave products **3i** and **3j** resulting from a 5-*exo*-trig radical cyclization in 69% yield (Scheme 6).

The chlorine ATRA reaction of trichloromethanesulfonyl chloride and that of CCl_4 afford identical products. The advantages of the sulfonyl chloride-mediated process over the CCl_4-mediated one are the absence of a metal catalyst [the reaction with CCl_4 requires a metal catalyst (Cu, Ru, etc.) to achieve high efficiency] and the reduced dangerousness of trichloromethanesulfonyl chloride (corrosive) relative to the volatile CCl_4 (highly hepatotoxic and possibly carcinogenic). The CCl_4 method is slightly superior in terms of cost and atom efficiency despite the fact that a substochiometric amount of a reducing species is necessary to regenerate the catalyst.[20]

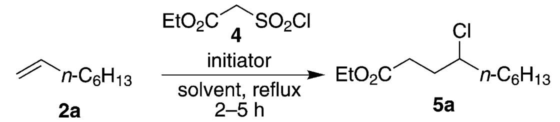
Reaction with Ethyl 2-(Chlorosulfonyl)acetate (4)

The results obtained with Cl_3CSO_2Cl incited us to investigate some other sulfonyl chlorides. Despite the high synthetic potential of ATRA reactions involving chloroacetates, they remain extremely difficult to run even under transition metal catalysis.[9] Since ethyl 2-(chlorosulfonyl)acetate **4** is easily prepared either by chlorination of ethyl thioglycolate[21] or by treatment of ethyl chloroacetate with sodium sulfite and oxalyl chloride[22] (Scheme 7), it was of interest to test its reactivity in desulfitative chlorine ATRA reactions.



Scheme 7. Preparation of ethyl 2-(chlorosulfonyl)acetate **4**.[20,21]

Table 1. Optimization of the reaction conditions for the desulfitative chlorine ATRA reaction of **4** to 1-octene **2a**.



Entry	4 (equiv.)	Initiator (equiv.)	Solvent	5a Yield[a]
1	1.2	DTBD (0.2)[b]	benzene	55%
2	2	DTBD (0.2)[b]	benzene	72%
3	2	AIBN (0.2)	benzene	70%
4	2	DLP (0.2)	benzene	91%
5	2	DLP (0.2)	$ClCH_2CH_2Cl$	90%

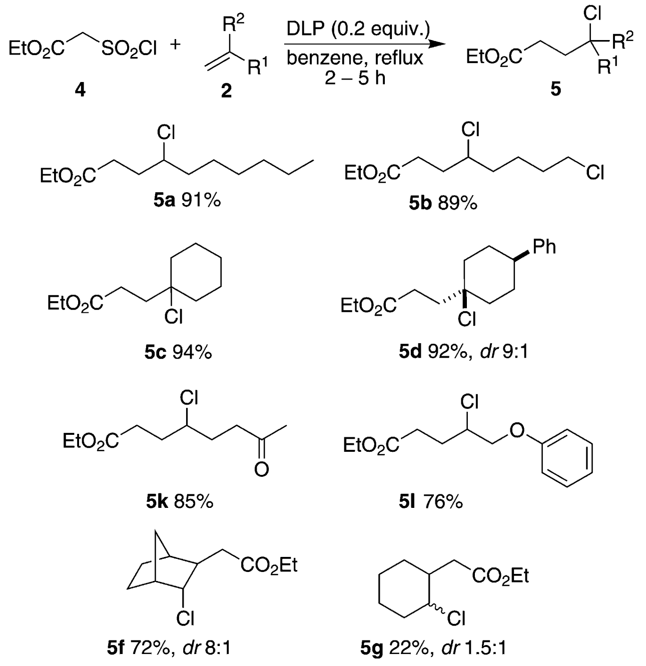
[a] Isolated yield.

[b] 300 W sun lamp irradiation was used.

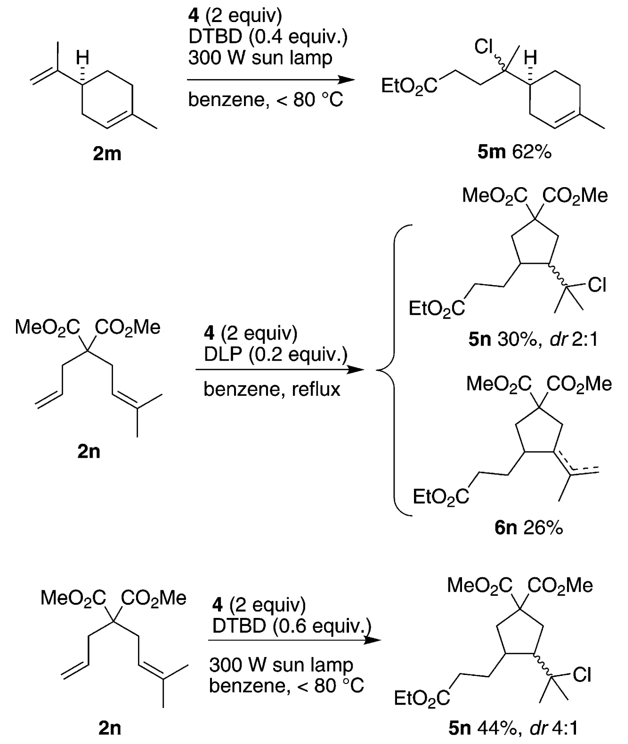
The reaction was optimized with 1-octene **2a** and the results are summarized in Table 1. A moderate yield was obtained with 1.2 equivalents of **4** and DTBD/sun lamp irradiation to initiate the process. A better yield was obtained with 2 equivalents of the sulfonyl chloride under the same initiation conditions. Initiation with AIBN did not enhance the yield. Finally, dilauryl peroxide (DLP) as an initiator in benzene or 1,2-dichlorethane gave the best results in a very reliable manner (Table 1, entries 4 and 5).

The scope of the chlorine ATRA reaction of **4** was then examined with different terminal alkenes (Scheme 8, compounds **5a**–**5d**, **5k**–**5l**). The products were obtained in good to excellent yields. Under these conditions, the tertiary chlorides **5c** and **5d** are stable and were isolated in high yields, other tertiary chlorides proved to be more prone to elimination (*vide infra*). Reactions with non-terminal alkenes were also examined and as expected only strained systems such as norbornene **2f** gave a good yield of **5f**. Internal alkenes such as cyclohexene **2g** afforded the chlorine ATRA product **5g** in 22% yield.

Reaction of **4** with different dienes was attempted next (Scheme 9). When (*S*)-limonene **2m** was used, the chlorine ATRA product **5m** was formed in low



Scheme 8. Chlorine ATRA reactions of ethyl 2-(chlorosulfonyl)acetate **4**.



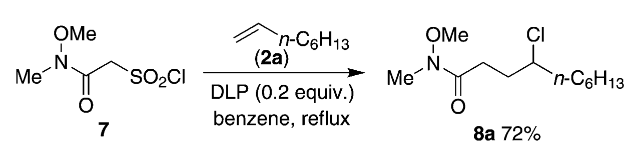
Scheme 9. Desulfitative chlorine ATRA reactions of ethyl (2-chlorosulfonyl)acetate **4** with dienes.

yield under the optimized DLP-initiated reaction conditions. Decomposition products were obtained resulting most probably from processes involving cationic intermediates. Traces of lauric acid generated from DLP could also be at the origin of the low efficiency of the ATRA reaction. Therefore, another radical initiator that allows running the reaction under strict non-acidic conditions and at lower temperature was tested. When DTBD (sun lamp irradiation, <80°C) was used, product **5m** was isolated in 62% yield. As expected, the reaction takes place exclusively at the terminal alkene. Interestingly, when the iodine ATRA reaction using ethyl iodoacetate was attempted, none of the expected tertiary iodides were isolated. Reaction of **4** with the 1,6-diene **2n** was then examined. Under the standard DLP procedure, the desired cyclized product **5n** was obtained in 30% yield, together with 26% of HCl elimination products **6n** (mixture of isomers). Using the DTBD/irradiation initiation procedure, the expected product **5n** was obtained in 44% yield and the diastereoselectivity was increased from 2:1 to 4:1.

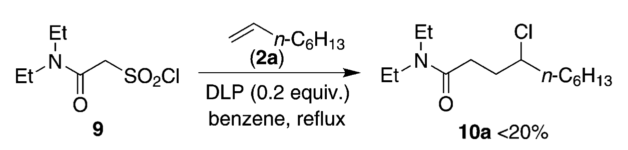
Reaction with *N*-Methoxy-*N*-methyl-2-(chlorosulfonyl)acetamide

Since radicals derived from Weinreb amides are know to react efficiently with terminal alkenes,[23] sulfonyl chloride **7** was prepared and tested. The chlorine ATRA reaction of **7** with 1-octene **2a** afforded **8a** in 72% yield (Scheme 10) demonstrating further that Weinreb amides are excellent reagents for intermolecular radical addition to terminal alkenes.

To test its limitations, the chlorine ATRA reaction involving an *N,N*-dialkylamide was attempted next. This system is of interest since iodine ATRA reactions of *N,N*-dimethyliodoacetamide do not afford the expected iodine atom transfer products but rather lactones resulting from nucleophilic substitution of the iodide by the ester group.[24] These reactions proceed inefficiently under standard atom-transfer conditions and the use of 0.5 equiv. $(Bu_3Sn)_2$ and 3.5 equiv. EtI is required to reach acceptable yields. To test the desulfitative chlorine ATRA reaction, *N,N*-diethyl-2-(chlorosulfonyl)acetamide **9** was prepared and its reaction with 1-octene was examined (Scheme 11). The



Scheme 10. Chlorine ATRA reaction of Weinreb amide **7**.



Scheme 11. Chlorine ATRA reaction of amide **9**.

desired chlorine atom transfer product **10a** was obtained but the yield was low. Optimization of the reaction conditions did not allow us to improve significantly the yield. This result demonstrates that the desulfitative chlorine ATRA reaction offers an advantage over the iodine ATRA reaction in terms of product stability (the chloride product does not undergo an intramolecular nucleophilic substitution) but, as anticipated, the limitation due to the lack of reactivity (electrophilicity) of the intermediate radical is not alleviated.

Conclusions

The desulfitative chlorine atom transfer radical addition reaction has shown to be a general strategy for the formation of carbon-carbon bonds under metal-free conditions. Sulfonyl chlorides are easily prepared by simple and cheap procedures. They are stable radical precursors that can be stored for months without decomposition. The reaction can be performed in a variety of solvents such as *tert*-butanol, 1,2-dichloroethane, and benzene. Commercially and easily available radical initiators have been used with success to trigger the reaction.

Experimental Section

ATRA Reactions of Cl_3CSO_2Cl (AIBN Initiation)

In a two-necked, flame-dried flask equipped with a reflux condenser, the alkene (1.0 equiv.), Cl_3CSO_2Cl (1.1 equiv.), and AIBN (0.05 equiv.) were weighed. After purging with N_2, the solvent was added, and the reaction mixture was heated to reflux and monitored by TLC. At the end of the reaction time (typically 0.5–2 h), the mixture was concentrated and the crude product was purified by flash chromatography using silica gel.

ATRA Reactions of Cl_3CSO_2Cl (DTBD Initiation)

In a quartz round-bottomed flask equipped with a reflux condenser, the alkene (1.0 equiv.) and DTBD (0.5 equiv.) were added to a stirred solution of sulfonyl chloride (2.0 equiv.) in *tert*-butanol. The reaction mixture was irradiated by a sunlamp (300 W) and heated to reflux. At the end of the reaction time (typically 2 h), the crude product was purified by flash chromatography using silica gel.

ATRA Reactions of Ethyl 2-(Chlorosulfonyl)acetate

In a two-necked flask, equipped with a reflux condenser and charged with ethyl 2-(chlorosulfonyl)acetate **4** (2.0 equiv.), alkene (1.0 equiv.) and benzene was added DLP (0.2 equiv.) under an N_2 atomosphere. The reaction mixture was heated to reflux and monitored by TLC. At the end of the reaction time (typically 2–5 h), the mixture was concentrated and the crude product was purified by flash chromatography using silica gel.

The preparation of sulfonyl chlorides and detailed characterization of all compounds can be found in the Supporting Information.

Acknowledgements

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