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Atmospheric Oxygen Mediated Radical Hydrothiolation of Alkenes

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Abstract: A mild, metal-free, atmospheric oxygen-mediated radical hydrothiolation of alkenes (and alkyne) is reported. A variety of sulfur containing motifs including alkanethiols, thiophenols and thioacids undergo an atmospheric oxygen-mediated radical hydrothiolation reaction with a plethora of alkenes in good yield with excellent functional group compatibility, typically with short reaction times to furnish a range of functionalised products. Biomolecules proved tolerant to the conditions and the procedure is robust and easily executable requiring no specialised equipment. Concise mechanistic studies confirm the process proceeds through radical intermediates in a thiol-ene reaction manifold. The methodology offers an efficient 'green' approach for thiol-ene mediated 'click' ligation and a milder alternative to thermally initiated hydrothiolation processes.

The increasing prevalence of sulfur within pharmaceuticals and compounds of biological interest has driven the search for improved methodologies and strategies enabling mild C-S bond formation.[1-3] The addition of thiols to alkenes (hydrothiolation) has proven a highly attractive strategy in these endeavors due to the overall atom-economy of this process and the availability and low-cost of alkenes, many of which are by-products of the petroleum industry.[4-5]

Towards this goal, several important synthetic approaches have been pursued. One approach focuses on the utilization of transition metal catalysts to forge C-S bonds, which in some instances allows for enantioselective hydrothiolation or the regioselective functionalization of polyenes.[6-10] Another route focuses on the use of Lewis acids to catalyze this transformation.[11] An alternative strategy focuses on the generation of thiyl radicals and subsequent anti-Markovnikov addition onto an alkene (thiol-ene reaction).[12-14] This latter strategy is highly effective and has seen widespread application. Indeed, the efficiency of this process renders it suitable as a "click" reaction and thus the thiol-ene reaction has seen applications in fields ranging from materials science to glycoscience and protein labelling. [15-28]

There are a wide variety of reported approaches for the formation of thiyl radicals, however the most frequently utilized are: (i) hydrogen atom abstraction (HAA) from a thiol and; (ii) homolytic cleavage of weak S-X bonds (X = halide, S, Se, etc.). A plethora of reagents and initiation strategies have been reported for the HAA step, with the photodecomposition of photoinitiators under UV mediated conditions frequently employed, as well as the generation of photoexcited metal complexes by visible light irradiation and electrochemical radical generation (Figure 1a).[29-43] Furthermore, thermal initiators may also be employed (Figure 1b).[44] In most instances external additives are required which often demand strenuous work-up and purification for their removal. A highly desirable protocol for thiol-ene ligation would involve a thermal reaction under atmospheric conditions, since this would greatly simplify both the reaction set-up and purification. Furthermore, it would represent another 'green chemistry' approach to thiol-ene 'click' ligation with numerous, diverse applications.

The seminal report on the addition of thiols to alkenes by Posner in 1905 was performed without the addition of external additives, although the radical nature of the process was unknown at that time.[45] Since then, a small number of 'additive free' thiol-ene reactions have been reported.[46-47] However, these processes typically involve solvent-free conditions, high temperature (often >100 °C), or extended, multi-day reaction times. The mechanism of initiation of such 'dark' systems is intriguing and Metzger and co-workers have postulated a Molecule-Assisted Homolysis (MAH) initiation for the thermal generation of thiyl radicals in the absence of any other initiator in which the thiol and alkene form an electron-donor/-acceptor (EDA) complex, albeit these reactions were run in the absence of solvent at 118 °C.[48-49] Though elegant, this approach is yet to see widespread use within the synthetic community. With this in mind, we sought to develop a simplified protocol for thiyl radical initiation that is compatible with organic solvents, while maintaining efficient hydrothiolation applicable in the context of the thiol-ene reaction manifold.[50-51]

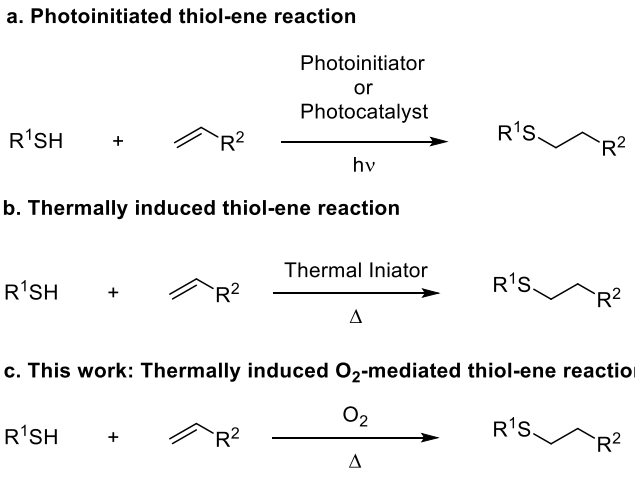

Figure 1. Approaches for thiyl radical formation from thiols.

We envisioned that molecular oxygen may function in the initial abstraction of a hydrogen atom from thiols or thioacids, thereby generating a thiyl radical which could undergo addition to

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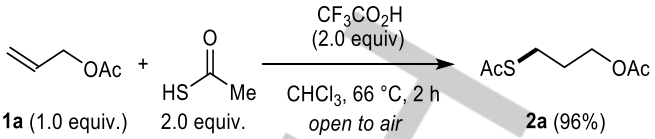
an alkene furnishing a thioether (sulfide) or thioester linkage (Figure 1c). Early studies of the aerobic copolymerization of thiols and alkenes by Kharasch have shown that triplet oxygen is capable of generating thiyl radicals.[52] Indeed, this mode of reactivity is proposed for the thiol-olefin cooxidation reaction (TOCO).[12, 53-54] Furthermore, it has previously been observed that at elevated temperatures, the presence of atmospheric oxygen can promote thiophenols to cyclize onto a pendent alkene *via* a thiyl radical intermediate as opposed to through a thiophenolate in a 6-*exo*-*trig* manner, however this reactivity has yet to be elaborated to deliver a general route to hydrothiolation.[55-56] Recently, the role of atmospheric oxygen as a radical initiator in the cyclative hydrothiolation of alkynes has been postulated.[57] To the best of our knowledge this approach has not been applied the general hydrothiolation of alkenes (thiol-ene reaction).

Allyl acetate (**1a**), was chosen as the test substrate due to the often difficult reaction of allyl substrates.[58] To test the viability of the proposed process in an intermolecular context **1a** was stirred vigorously (900-1250 RPM) with thioacetic acid (CH_3COSH/HSAc) in an open flask at room temperature. A small amount of the desired thioester was formed. After optimization of the reaction it was found that optimal conditions required reflux of the alkene in $CHCl_3$ with 2 equiv. of both the thioacid and trifluoroacetic acid (CF_3CO_2H/TFA), cleanly affording a quantitative yield of the thiol-ene product. Gratifyingly, the use of atmospheric oxygen as the oxygen source proved suffucient without the requirement for the addition of exogenous oxygen (as is often required for the TOCO process). It is worthy of note that despite the use of oxygen to mediate this reaction its concentration in solution remained adequately low that no TOCO products (α-hydroxyl sulfoxide or α-hydroperoxy sulfide) were deteced.

Although the presence TFA was not essential, it appeared to have an accelerating effect on the reaction, allowing the developed hydrothiolation to proceed on a comparable timescale (~2 h) to the photomediated thiol-ene reaction (Table 1 entry 1). The role of the the acid within the reaction is intriguing and is currently under investigation. Firstly, it ensures that the thioacid remains protonated, allowing HAA to occur. Moreover, it is likely that the presence of TFA in the reaction facilitates hydrogen bonding to the thioacid or thiol motif (*vide infra*), thereby lowering the BDE and expediating HAA.[59-61] The efficiency of the thiol-ene radical chain typically circumvents the neccessity for constant reinitiation.[14] To gain further insight into this reaction process a series of parameters were varied. It was found that solvent may not be required (entry 2), though in this instance a MAH pathway is likely operative. However, in solution heating has an exceptional acceleratory effect on the reaction with very little product being formed at room temperature (entry 3). We next sought exclude an ionic mechanism. Substitution of HSAc with KSAc led to low yield of **2a** (entry 4) likely due to the generation of a small amount of HSAc by protonation of KSAc. Thus, we eliminated the possibility of a thiocarboxylate intermediate in the reaction. Furthermore, when TFA was replaced with aqueous HCl no alkene hydration or hydrochlorination products were observed (entry 5) ruling out a cationic intermediate. The addition of TEMPO (entry 6) induced a mild decrease in the yield whilst the addition of Et_3SiH drastically diminished the yield (entry 7) suggesting the formation of a thiyl radical intermediate (no alkene hydrogenation or hydration products were observed). Exclusion of all light sources did not affect the yield suggesting that photochemical initiation is not involved. When efforts were made to exclude air the reaction was severely compromised. Reflux under argon led to some product formation (entry 9), which may be attributed to a small amount of air seeping into the reaction setup, however conducting the reaction in a sealed tube led to minimal product formation which may be attributed to the presence of oxygen, or an MAH reaction (entry 10).

Table 1. Deviations from standard conditions



1a (1.0 equiv.) 2.0 equiv. **2a** (96%)

Entry	Deviations from Above	Yield (%)[a]
1	None	Quant. (96)
2	Neat	Quant.
3	rt	3
4	KSAc instead of HSAc	8
5	37% HCl in water instead of CF_3CO_2H	Quant.
6	1.1 equiv. TEMPO	76
7	1 equiv. Et_3SiH	17
8	Dark	Quant.
9	Degassed solvent under argon	42
10	Sealed tube	9[b]

[a] 0.1 mmol scale, yield determined by ^1H NMR using mesitylene as an internal standard. [b] As part of a complex mixture. Yields in parentheses are isolated yields.

With optimized conditions in hand, we investigated the scope of the hydrothiolation reaction. Firstly, we examined the capability of monosubstituted alkenes (Scheme 1A) to undergo acyl thiol-ene (ATE) reaction.[62] Our conditions were found to be efficient for effecting hydrothiolation of simple alkenes (**B2**) in excellent yield, allowing for the potential upvaluing of byproducts of the petroleum industry. Esters proved compatible with the conditions (**B1**, **B3**, **B4**, and **B5**), even labile esters such as trichloromethyl ester **B6** which was afforded in 57% yield. The reaction proved scalable with **B1** being prepared in near quantitative yield on a 10 mmol scale. Aryl ether **B7** was afforded in 52%. Nitrogenous substituents on aryl esters were well tolerated (**B8** and **B9**) as were halides (**B10-B12**) allowing for the potential further functionalization of these compounds. Gratifyingly substrates possessing a carboxylic acid or an amide motif proved compatible with the hydrothiolation process (**B14**, **B16**, **B19**, **B22**, and **B25**). It was observed that the carboxylic acid containing substrates required the shortest reaction times to go to complete conversion, lending credence to our posited role of acid within the reaction.

A styrenyl-type ester and carboxylic acid underwent hydrothiolation in 84% and 87% yield, respectively (**B23** and **B24**). No deprotection of benzyl ether **B26** was observed under the reaction conditions, although a small amount of transacylation was observed during the formation of the hydroxyl containing thioester **B27**. Thioesters containing a wide variety of functional groups, including ketones and aldehydes, were all afforded in excellent yield under these conditions (**B31-37**). Notably, **B32** could be prepared without homolytic fragmentation of the allyl thioester being observed. Furthermore, biomolecule derivatives such as menthol derivative **B37**, vanillin derivative **B38**, and estrone derivative **B39** were all formed without any decomposition products being observed, highlighting the potential use of the protocol for the preparation and modification of biologically and/or pharmaceutically relevant compounds.

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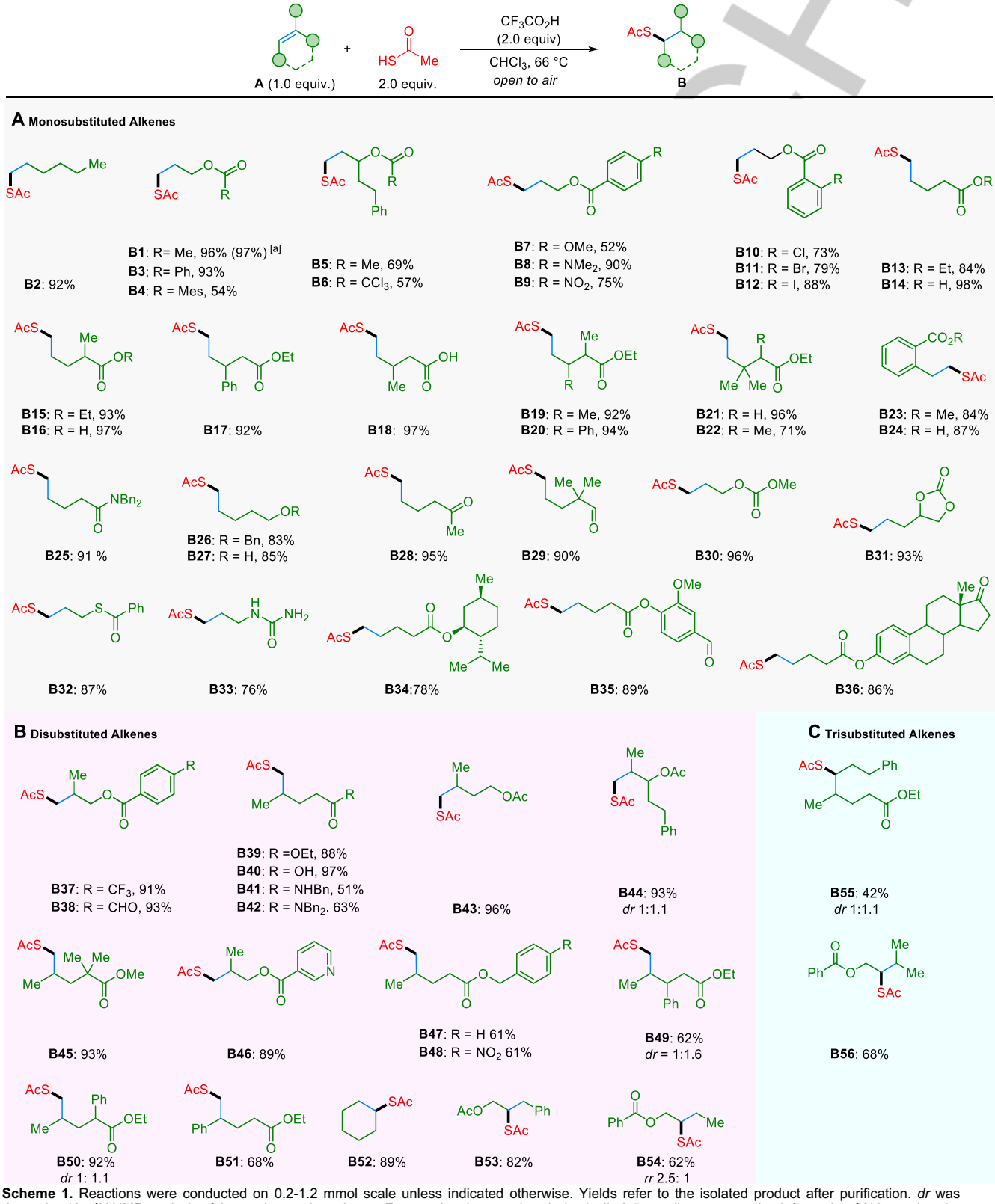
A broad range of geminal disubstituted alkenes also proved compatible with the hydrothiolation process, affording **B37-B51** in good to excellent yield. The medicinally relevant CF_3 group was tolerant of these conditions (**B37**), as were a range of other functional groups including primary and secondary amides **B41** and **B42**, as well as pyridine containing compound **B46**.[63] Unfortunately only moderate diastereoselectivity was imparted when a substituent was placed at the α-position to the alkene (**B49**, *dr* 1:1.6), however, and somewhat unsurprisingly, relocation of this substituent to the β-position essentially removed any diastereocontrol from the reaction furnishing **B50** in 92% yield with a *dr* of 1:1.1.

1,2-Disubstituted olefins were also investigated. Cyclohexene furnished thioester **B52** in 89% yield. Employing a sterically bulky group at one position of the alkene can drive the reaction to form a single regioisomer, as was seen with the



Scheme 1. Reactions were conducted on 0.2-1.2 mmol scale unless indicated otherwise. Yields refer to the isolated product after purification. *dr* was determined by ^{1}H NMR analysis of the crude reaction mixture. For reaction times and scale (typically 0.5 mmol) see supporting information. [a]10 mmol scale.

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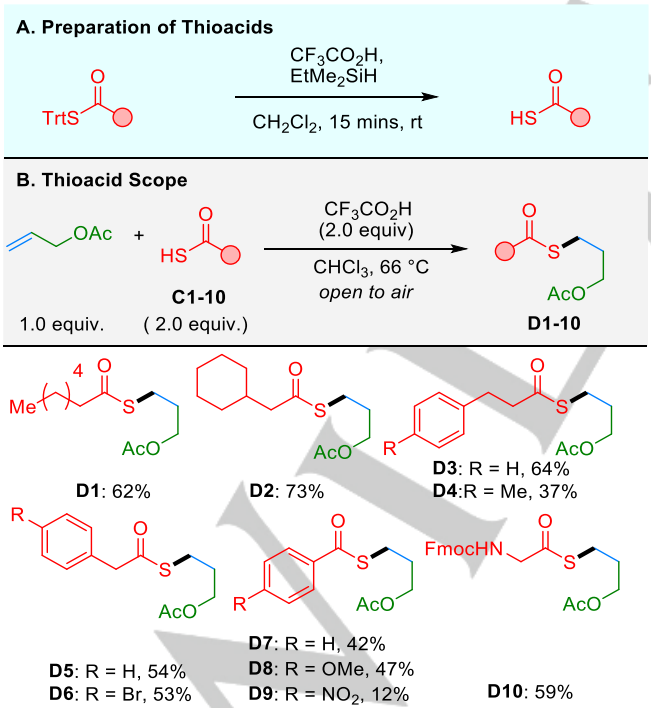
reaction of cinnamyl acetate to afford **B53**. However, sterically unbiased alkenes give mixtures of regioisomers as was the case with the hydrothiolation of crotyl benzoate in which radical addition occurred at both positions of the alkene giving **B54** in a 2.5:1 isomeric ratio and a combined yield of 62%.

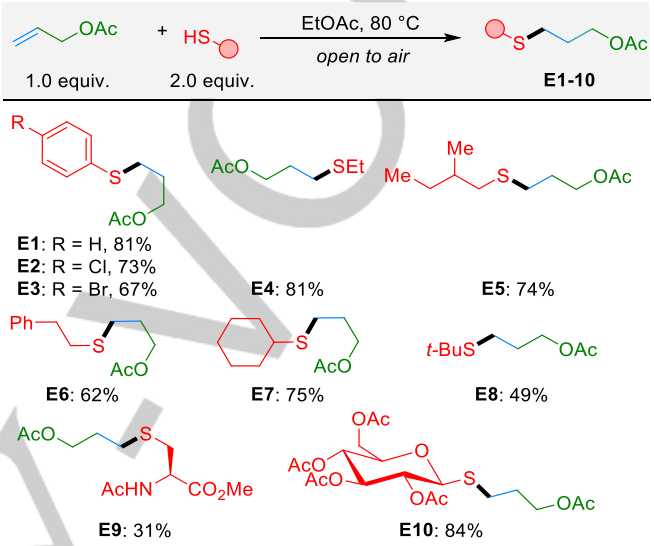
Trisubstituted alkenes also proved compatible but furnished reduced yields compared to mono- or disubstituted alkenes. Extended reaction times were also required, and this afforded only moderate yield of thioesters **B55-56**. Furthermore, no diastereoselectivity was observed for hydrothiolation of these substrates (**B55**).

Following our evaluation of alkenes scope, we next examined the scope of thioacids for the oxygen-mediated ATE reaction. Thioacids (**C1-6** and **C8-10**) were prepared via Steglich coupling of the corresponding carboxylic acids with triphenymethanethiol (TrtSH), to give Trt-thioesters which were subsequently deprotected under acidic conditions as previously reported by Crich and co-workers.[64] Simple alkyl thioacids furnished the thioester derivatives (**D1-4**) in moderate to good yield across the two steps (up to 74% yield). Benzylic thioacids also underwent hydrothiolation reactions, without dethiocarboxylation being observed under conditions of elevated temperature (**D5-6**). Benzoyl-type thioacids proved less efficient at hydrothiolation under these conditions with **D7-9** formed in relatively low yields (<50% yield). However, these thioacids proved more capable coupling partners with non-biased alkenes (see ESI). Interestingly, electron-poor nitro group containing thioacid **C9** required extended reaction time to furnish a small amount of thioester **D9**. The use of thioacids and the salts thereof have attracted increasing attention of late within the field of peptide and protein chemistry.[64-69] To our delight, amino acid derived thioacid **C10** furnished hydrothiolation product **D10** in 59% yield, without any deprotection of the amine being observed, highlighting the potential use of this methodology for the functionalization of peptides.



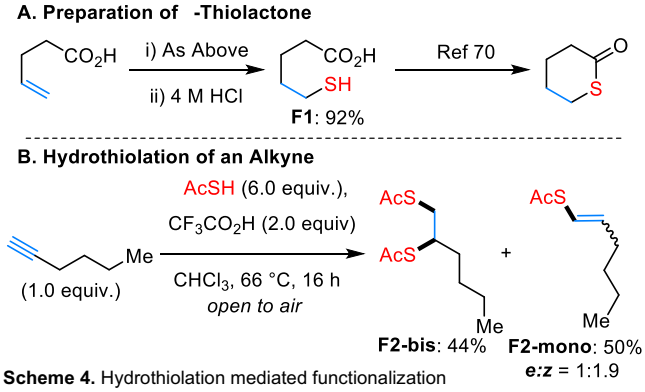
Scheme 2. Preparation of thioacids and examination of the thioacid scope of the O_2 mediated hydrothiolation. Reactions were conducted on 2 mmol of thioacid. Yields refer to the isolated product after purification. For reaction times see ESI.

Thiols (thiophenols and alkanethiols) proved less reactive than thioacids under the original reaction conditions, likely due to their lesser ability to undergo hydrogen-bonding and afforded poor conversion upon subjection to the initial reaction conditions. However, it was found that by substituting the solvent and increasing the reaction temperature, the thiol-ene reaction could occur in good yield. Thiophenols provided the thioether derivatives (**E1-3**) in good yield. Simple alkanethiols also proved compatible with the reaction conditions (**E4-7**). *Tert*-Butyl thiol afforded **E8** in a somewhat diminished yield of 49%, likely due to steric factors. Although affording **E9** in only 31% yield, it was found that cysteine could be functionalized under our reaction conditions. Furthermore, thioglycoside **E10** was furnished in excellent yield exclusively as the β-anomer, again highlighting applications in biomolecular synthesis and bioconjugation.



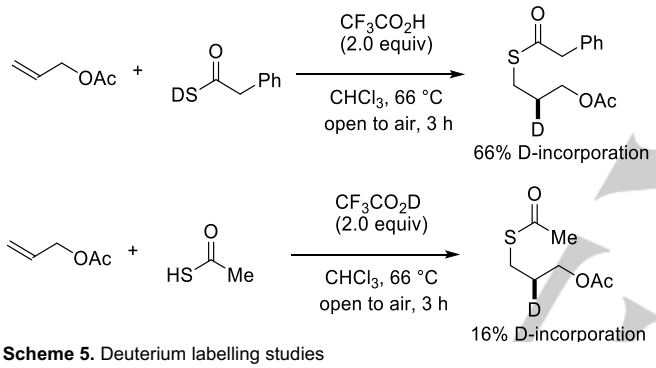
Scheme 3. Hydrothiolation of alkenes with thiophenols and alkanethiols. Reactions were conducted on 2 mmol of thiol/thiophenol. Yields refer to the isolated product after purification. For reaction times see supporting information.

To demonstrate the utility of this methodology we performed a number of functionalization reactions. Recognizing that by incorporation of a thioester, we are introducing a thiol in protected form, we were able to transform **A13** to 5-mercaptopentanoic acid (**F1**) by subjecting the product of the hydrothiolation reaction to an acidic workup and affording the free thiol in 92% yield (Scheme 4A). This thiol can then easily be converted to a δ-thiolactone by Steglich thiolactonization, delivering a class of compound important in numerous fields.[17-18, 70-76] In addition to this, we also attempted the hydrothiolation of an alkyne (thiol-yne reaction).[77-78] It was found that under slightly modified condition (6 equiv. of AcSH and extended reaction time) that the bis-thioester **F2-bis** and the vinyl thioester **F2-mono** were formed in a 1:1.1 ratio (determined by ^{1}H NMR analysis of the crude reaction mixture) and were isolated in 44% and 50% yield, respectively (Scheme 4B). It is not uncommon for such systems to furnish the mono-hydrothiolated adduct.[79-80] Interestingly for mono hydrothiolation substitution occurred exclusively at the alkyne terminus, though the product was obtained in 1:1.9 stereomeric ratio, with the kinetically favoured *Z*-vinyl sulfide predominating.[12]



Scheme 4. Hydrothiolation mediated functionalization

To provide further evidence in support of the proposed radical mediated mechanism, we performed deuterium labelling experiments (Scheme 5). It was found than when the reaction is performed with a deuterothioacid (prepared by deprotection of the corresponding trityl thioester with TFAD) there is 66% D-incorporation in the product at the internal position of the alkene, congruous with radical addition. The somewhat lower than expected labelling may be accounted for by the rapid H/D exchange of thiols.[81] However, when the reaction is performed using a regular thioacids (AcSH) and TFAD, only 16% D-incorporation was observed. These findings help to further exclude the possibility of an ionic mechanism. The high level of D-incorporation for the deuterothioacid suggests that the reaction involves a hydrogen atom abstraction step by a carbon-centered radical following thiyl radical addition, as opposed to protonation of the alkene or a carbanion as the bond dissociation energy for an S-H bond is far lower than that of an O-H.[12, 82-83] Furthermore, TFA is several orders of magnitude more acidic than AcSH and very little D-incorporation would be expected if protonation were occurring.[84] In the second instance some D-incorporation was observed and this is likely the consequence of D/H exchange between AcSH and TFAD. The smooth formation of thioesters under our conditions in the presence of a pendent nucleophile, such as **B27** without the observation cyclized products further corroborates our claim.



Scheme 5. Deuterium labelling studies

A postulated mechanism is depicted in a somewhat simplified manner in Figure 2. It is likely that triplet O_2, the diradical, abstracts the hydrogen atom of the thiol, thereby generating a thiyl radical and a hydroperoxyl radical (**A**).[85] The thiyl radical undergoes reversible additions to an alkene in an anti-Markovnikov manner generating a carbon-centered radical (**B**) which abstracts a hydrogen atom from a thiol, thus generating the desired hydrothiolated product and generating another thiyl radical, thus propagating a radical chain reaction (**C**).

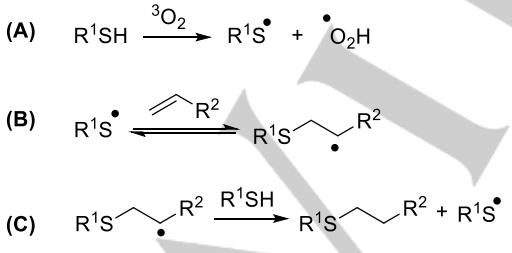


Figure 2 The postulated mechanism for the atmospheric O_2-mediated hydrothiolation.

In summary we have developed a highly versatile, metal-free, air-mediated radical hydrothiolation of alkenes. This approach allows for the circumvention of the use of radical initiators, many of which are toxic and/or explosive, and which are often difficult to remove from the product. Furthermore, this approach obviates the requirement for specialized equipment (i.e. UV/visible light sources). The reaction is general, with a broad substrate scope and allows for the functionalization of biomolecules with complete anti-Markovnikov regioselectivity. This approach can readily be applied to thioacids, thiophenols and alkanethiols and has proven scalable. Further studies on the reaction mechanism are ongoing.

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Keywords: Thiol-ene • Radical • Hydrothiolation • Initiation • Green chemistry

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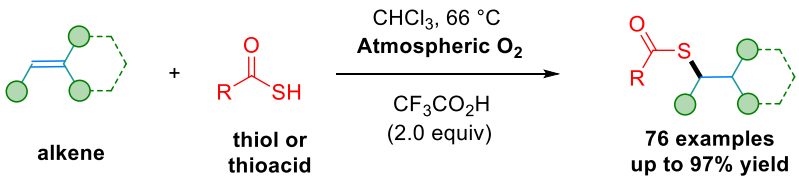

A mild, metal-free, atmospheric oxygen-mediated radical hydrothiolation of alkenes is reported. A variety of sulfur containing motifs undergo thiol-ene reaction with a plethora of alkenes in good yield with excellent functional group compatibility. Mechanistic studies confirm the process proceeds through radical intermediates. The methodology offers an efficient 'green' approach for thiol-ene mediated 'click' ligation.

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