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A Divergent Strategy for Site-Selective Radical Disulfuration of Carboxylic Acids with Trisulfide 1,1-Dioxides

Zijun Wu and Derek A. Pratt*[a]

Dedicated to Professor Ilhyong Ryu, in recognition of his contributions to radical chemistry, on the occasion of his 70th birthday.

Abstract: *The direct conversion of carboxylic acids to disulfides is described. The approach employs oxidative photocatalysis for the base-promoted decarboxylation of the substrate, which yields an alkyl radical that engages a trisulfide dioxide by homolytic substitution. The trisulfide dioxides are easily prepared via a newly described approach. Each of 1°, 2° and 3° carboxylic acids with varied substitution are good substrates, including amino acids and substrates with highly activated C-H bonds. Trisulfide dioxides are also used to achieve γ-C(sp³)–H disulfuration of amides via radical relay. In both reactions, the sulfonyl radical that results from substitution propagates the reaction. Factors governing the selectivity of substitution at S2 vs S3 of the trisulfide dioxides are explored.*

Disulfide moieties, which frequently occur in both natural and synthetic products, have significant roles in biological and pharmaceutical contexts due to their unique redox equilibrium with thiols.[1] Indeed, this equilibrium is generally exploited in their synthesis; a symmetric disulfide is prepared via oxidation of a thiol to a symmetric disulfide and then one half is exchanged for another to access the disulfide.[2] Of course, given this equilibrium, achieving a single unsymmetric disulfide product directly can be challenging and/or wasteful (**Figure 1A**). The emerging role of disulfides in redox-sensitive therapeutics, imaging agents, chemical probes and various other applications[3] has therefore prompted the development of strategies for direct disulfuration (i.e. where both sulfur atoms are introduced via the same reagent).[4] These approaches generally involve nucleophilic substitution between appropriately activated disulfuration reagents and electrophilic substrates[4a,b,f-i] or transition metal-catalyzed cross-coupling to aryl boronic acids (**Figure 1B, left**).[4b-d]

We recently demonstrated that disulfides could be accessed quite conveniently by homolytic substitution on tetrasulfides.[5] This approach relies on the weak central S-S bond in tetrasulfides and the fact that the highly stabilized perthiyl radical (RSS•) which results from substitution simply combines with another under the reaction conditions to yield more starting tetrasulfide.[6] In principle, any alkyl or aryl radical source could be utilized, but in practice, we found the scope and utility of the approach to be most easily illustrated using radicals obtained by photolysis of Barton esters or energy transfer photocatalysis[7] utilizing O-acyl oximes (**Figure 1B, right**). From the outset we sought to use carboxylic acids directly as substrates,[8] but the tetrasulfide was destroyed under

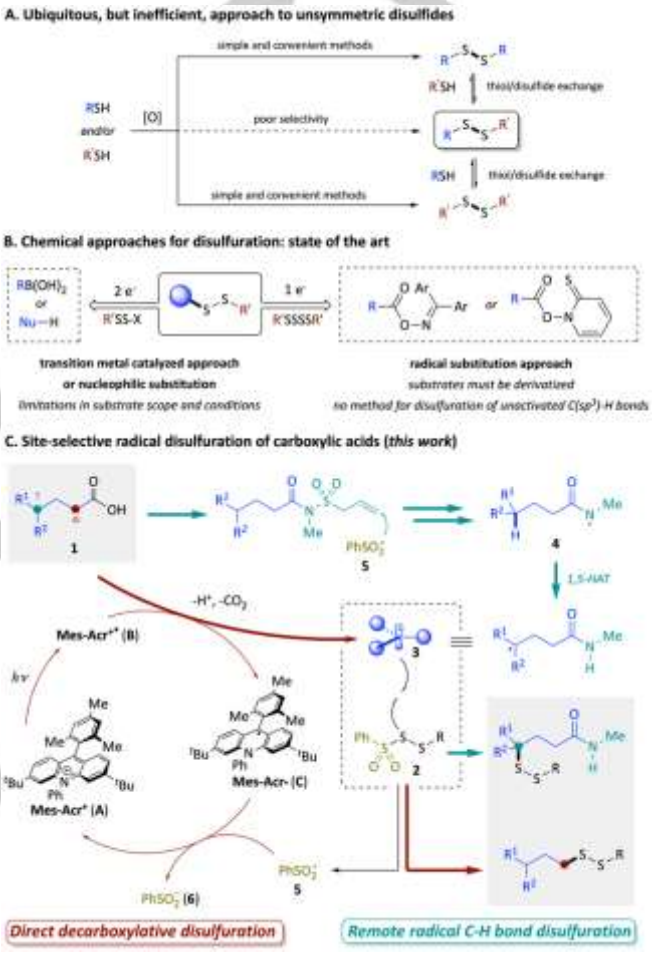

Figure 1. (**A**) Thiol oxidation and thiol-disulfide exchange are typical means of accessing unsymmetric disulfides – by chemistry and in nature. (**B**) Despite recent advances in selective disulfuration, direct functionalization of readily available subtrates remains elusive. (**C**) A summary of the divergent, site-selective radical disulfuration of carboxylic acids presented in this work.

Hunsdiecker-type conditions[9] and more contemporary oxidative photocatalysis conditions[10] yielded only trace disulfide. We surmised that the perthiyl radical liberated upon substitution on the tetrasulfide under the photocatalytic conditions was not capable of re-oxidizing the photocatalyst and wondered if a disulfurating reagent RSS-X that would yield a more oxidizing radical X• upon substitution might enable the direct conversion of carboxylic acids to disulfides (**Figure 1C**). Of course, even if a suitable reagent could be identified, both it and the product must be stable to the conditions of decarboxylative radical generation,[8a,10] which is a challenge in of itself given the lability of disulfides to oxidants, reductants, nucleophiles and electrophiles.

In earlier work on organosulfur antioxidants, we had found that trisulfide-1-oxides undergo homolytic substitution with

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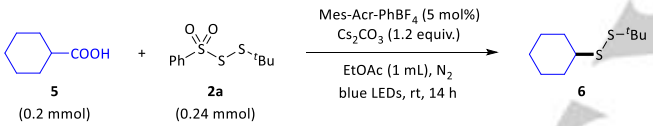
peroxyl radicals,[6a] so we initially considered them as disulfuration reagents. However, we found them to be unstable to heat or light. Although the weak S-S bond in trisulfide-1-oxides is stronger than that in tetrasulfides (e.g. 36.3 kcal/mol in *t*-BuS(O)–SS*t*-Bu[6b] *vs.* 30.0 kcal/mol in *t*-BuSS–SS*t*-Bu[6a]), thermal or photochemical cleavage of the central S-S bond in tetrasulfides is fully reversible (even in the presence of O_2[6b]). In contrast, the trisulfide-1-oxides photolyze/thermolyze irreversibly to form tetrasulfide and thiosulfonate.[6b] Given that sulfonyl radicals are less stable than sulfinyl radicals (the O-H BDEs in sulfinic and sulfenic acids are *ca.* 78 and 70 kcal/mol, respectively[11]) we anticipated that trisulfide dioxides would be more stable. Indeed, CBS-QB3 calculations[12] predict that the *t*-BuS(O)$_2$–SS*t*-Bu BDE is 12 kcal/mol stronger than in *t*-BuS(O)–SS*t*-Bu. Moreover, sulfonyl radicals are capable oxidants (e.g. $PhSO_2$•/$PhSO_2Na$, $E_{1/2}^{red}$ = + 0.50 V vs SCE[13]), implying that they may recycle reduced photocatalyst in an oxidative photoredox cycle. Indeed, vinyl sulfones have been used by MacMillan to achieve photoredox α-vinylation of α-amino acids.[10g] As such, we prepared the trisulfide dioxide **2a** and were delighted to see that when combined with carboxylic acid **5** ($E_{1/2}^{red}$(hexanoate) = +1.16 V vs SCE[14]) in the presence of an acridinium salt (Mes-Acr-$PhBF_4$, $E_{1/2}^{red}$*(Mes-Acr-Ph^{+}*/Mes-Acr-Ph^{+}) = +2.15 V vs SCE[15]) and base (Cs_2CO_3) in EtOAc the desired unsymmetric disulfide **6** was produced in 69% yield.

Table 1. Optimization of the reaction conditions[a]



Entry	Deviation from above conditions	Yield (%)[b]
1	^{t}BuSSSS^{t}Bu as disulfuration reagent	trace
2	none	69
3	with ^{t}BuOMe as solvent	54
4	with TBME as solvent	64
5	with CH_3CN as solvent	37
6	with DCE as solvent	27
7	with DMF as solvent	38
8	with $KHCO_3$ as base	60
9	with K_2HPO_4 as base	49
15[c,d]	Without base	NP
16[c,d]	Without light	NP
17[c,d]	Without Mes-Acr-$PhBF_4$	NP

[a]Reaction conditions: **5** (0.2 mmol), **2a** (0.24 mmol), photocatalyst (5 mol%) and base (0.24 mmol), blue LEDs, N_2 atmosphere, room temperature, 14 h. [b]Yields were determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard. [c]**2a** (0.30 mmol), CsF as base. [d]EtOAc (0.1 M). [e]Isolated yield.

In an effort to boost the yield of the reaction, a variety of reaction conditions were surveyed (**Table 1** and **Supporting Information**). Unsurprisingly, photocatalysts with a less oxidizing excited state (e.g. [Ir(dF(CF_3)ppy)$_2$(dtbbpy)]PF_6 and [Ru(bpy)$_3$]PF_6) were found to be either inferior or ineffective. Although the reaction could be carried out in a wide variety of solvents (entries 3-7), EtOAc proved optimal. The identity of the base was found to have a dramatic effect on the yield. Exchanging Cs_2CO_3 for less basic options ($KHCO_3$, K_2HPO_4, NaOAc) resulted in a progressive decrease in yield (entries 8-10). The stronger, but also nucleophilic ^{t}BuOK also gave a poor yield (entry 11, 32%). Overall, CsF proved to be most effective, presumably due to the high stability towards oxidation of the fluorine anion, delivering the product in 78% yield (entry 12). Boosting the concentration of **2a** from 1.2 to 1.5 equivalents improved the yield to 83% (entry 13) and decreasing the reaction concentration to 0.1 M improved things further to 85% yield (entry 14), presumably due to improved solubility of the cyclohexanoate. Control experiments confirmed the essentiality of each of the base, photocatalyst and irradiation to successful decarboxylative disulfuration (entries 15-17).

With optimal reaction conditions identified, we sought to explore the substrate scope in both carboxylic acid and trisulfide dioxide. Trisulfide dioxides, known more precisely as sulfenic sulfonic thioanhydrides,[16a] are generally prepared from the reaction of a thiosulfonate salt and a sulfenyl chloride.[16] The sulfenyl chloride can be obtained by halogenation of a thiol or treating a disulfide with sulfonyl chloride.[17] The latter route was recently taken by Dong in a one-pot preparation of *p*TolS(O)$_2$SS*t*-Bu, which was subsequently utilized to produce unsymmetric disulfides ArSS*t*-Bu in Cu-catalyzed couplings with aryl boronic acids.[4b] We were able to prepare several simple alkyl- and phenyl-substituted trisulfide dioxides **2a–2f** using this method (**Figure 2A**). However, we anticipated that the requirement of SO_2Cl_2 to convert disulfide to sulfenyl chloride may limit the application of this method and designed a new strategy involving substitution of $PhSO_2Na$ on easily accessible phthalimidyl persulfides (sometimes referred to as the Harpp reagent),[4g,18] exemplified by

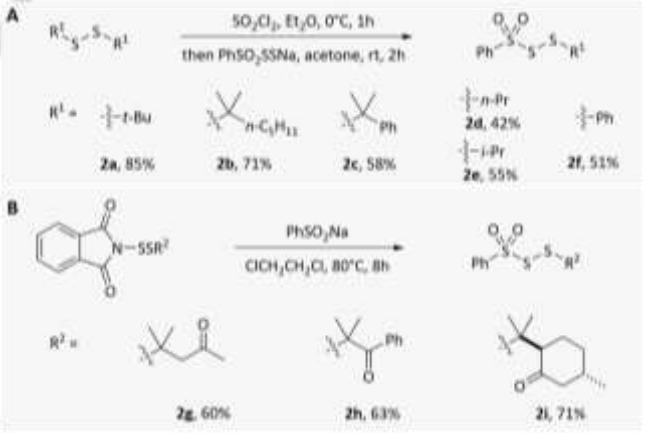


Figure 2. Construction of benzenesulfonodithioperoxoates (trisulfide dioxides).

those containing methyl isobutyl ketone (**2g**), propiophenone (**2h**) and pulegone (**2i**) scaffolds (**Figure 2B**).

Equipped with optimized reaction conditions and a set of trisulfide dioxides, the generality of this direct decarboxylative disulfuration of carboxylic acids was explored. A range of primary (**7**−**18**), secondary (**19**, **20**, **22**) and tertiary (**21**, **26**) carboxylic acids were efficiently transformed into the corresponding (**7**−**18**)

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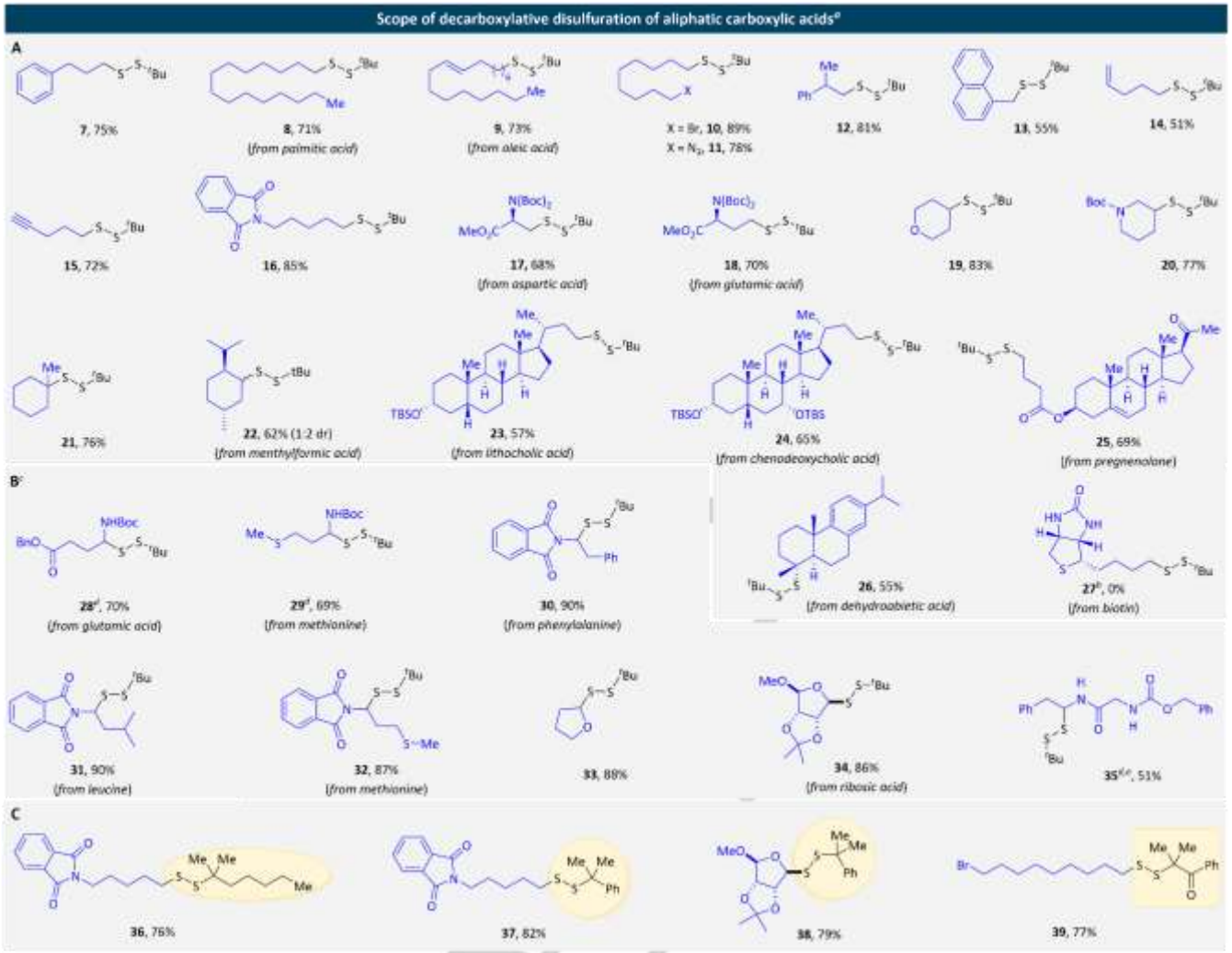

Figure 3. **Scope of the decarboxylative disulfuration of carboxylic acids.** [a]Reaction conditions: carboxylic acid (0.2 mmol), **2** (0.3 mmol), photocatalyst (Mes-Acr-PhBF$_4$, 5 mol%) and CsF (0.24 mmol), blue LEDs, N_2 atmosphere, room temperature, 14 h. Isolated yields are reported. [b]Various solvents (DMF, DMSO, CH_3CN/H_2O, EtOAc/DMF), bases (CsF and Cs_2CO_3) and photocatalysts gave the same result. [c]10 h. [d]Dioxane was used as solvent. [e][Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ (1 mol%) was used as the photocatalyst.

disulfides. Substrates possessing bromide (**10**), azide (**11**), alkene (**14**), alkyne (**15**), ether (**19**) and protected amine (**16**, **20**) functionalities were all well accommodated (**Figure 3A**). Tolerance of azides, bromides and alkynes are expected to be particularly useful in applications of this chemistry in (bio)conjugation chemistry, but are versatile functional handles, in general. Although alkenes did not interfere in the radical chemistry *per se*, internal olefins (e.g. oleic acid) were found to isomerize under the reaction conditions (**9**).[19] Disulfides from amino acids aspartate (**17**) and glutamate (**18**), derivatives of lithocholic acid, chenodeoxycholic acid and pregnenolone (**23**−**25**), menthylformic acid (**22**), and dehydroabietic acid (**26**) were all easily accessed. We were excited to try biotin as a substrate since disulfides are often used as redox sensitive linkers to biotinylated conjugates, but were dismayed to find no disulfide **27.** Extensive screening of reaction conditions proved fruitless. Interestingly, when biotin was added to the prototype reaction of **2a** and **5** none of disulfide **6** was observed,[20] suggesting that biotin quenches the excited state of the photocatalyst, precluding decarboxylation of the substrate.

Further investigations revealed that a variety of α-amino acids could undergo this transformation, giving the corresponding disulfides **28**-**32** (**Figure 3B**). It should be noted that Boc-protected amines consistently afforded lower yields than when amines were protected as phthalimides – presumably due to the greater lability of the of α-amino disulfide products. Improved yields for these substrates (**28**, **29**) were obtained using a lower polarity solvent (dioxane). It is of note that α-O-silyl-disulfides have been described to release reactive sulfur species by pH control,[21] and as such, these α-amino disulfides have the potential to be developed as hydropersulfide precursors. Similarly, α-ether acids, such as 2-tetrahydrofuroic acid and a ribosic acid derivative, were good substrates (88% for **33**, 86% for **34**). Although messy mixtures were observed on oxidizable peptide substrates under the standard reaction conditions, by adopting [Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ as photocatalyst ($E_{1/2}^{red*}$ ((Ir^{IV}/Ir^{III}) =

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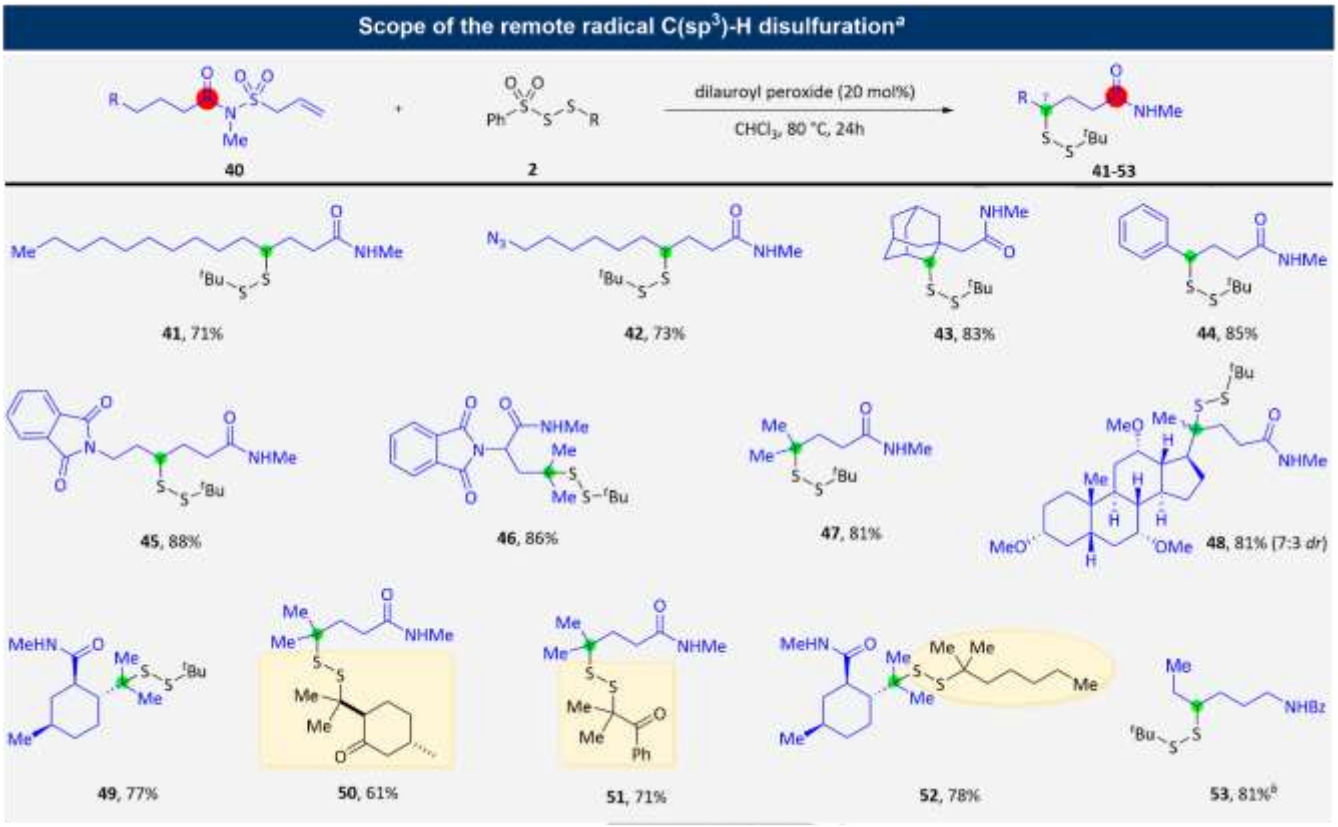

Figure 4. **Scope of the remote radical C(sp^3)–H disulfuration.** [a]Reaction conditions: N-allylsulfonamide (0.2 mmol), **2** (0.4 mmol), dilauroyl peroxide (20 mol%) and $CHCl_3$ (0.5 mL), N_2 atmosphere, 80 °C, 24 h. Isolated yield reported. [b]*N*-(allylsulfonyl)-*N*-hexylbenzamide was used instead of an *N*-allylsulfonamide.

+1.69 V vs SCE in CH_3CN[22]), synthetically useful yields could be obtained (i.e. 51% for **35**). Trisulfide dioxides with longer alkyl chains (**2b**), phenyl (**2c**) or phenone (**2h**) substitution could be exchanged for **2a**, affording the desired products **36**−**39** in 76%−82% yield (**Figure 3C**).

Late-stage C–H functionalization has emerged as a powerful tool for the diversification of medicinal compound libraries.[23] Although there are now many radical-mediated C–H functionalization strategies (for oxidation, amination, sulphuration, fluorination, chlorination, bromination, cyanation, alkenylation and alkylation, etc.)[24], there is no protocol for the disulfuration of unactivated C(sp^3)–H bonds, which would be *very* useful given the limitations of previous reported disulfide formation strategies. Inspired by Studer's remote site-selective C–H functionalization[24j] using amidyl radicals formed from *N*-allylsulfonamides,[25] we surmised that the sulfonyl radicals formed upon substitution on the trisulfide dioxides could be engaged in a chain reaction to achieve a remote site-selective C-H disulfuration. Thus, the sulfonyl radical would add to the termination carbon of an *N*-allylsulfonamide, liberating an amidyl radical that could undergo a 1,5–hydrogen atom transfer to generate an alkyl radical at the γ-site of the amide.[24b,26] Since the *N*-allylsulfonamide can be readily prepared from a carboxylic acid,[24j,25] this would enable access to another selective disulfuration from the same starting materials as above. Indeed, following a short screening of reaction conditions (see the **Supporting Information** for details), the envisioned γ-C(sp^3)–H disulfuration was feasible as a radical chain reaction using lauroyl peroxide as the initiator. As summarized in **Figure 4**, the disulfide moiety could be selectively installed on long aliphatic chains (**41**, **42**, **44**) and carbocycles (**43**, **49**), tolerating a range of functionalities, including azide (**42**), protected amine (**45**, **46**) and ether (**48**, from chenodeoxycholic acid). Again, exchanging trisulfide dioxide **2a** with those incorporating pulegone, propiophenone and longer sidechains were competent reagents, providing the γ-C(sp^3)–H disulfuration products in good yield (**50**–**52**). Finally, and perhaps most notably, alkylamine-derived sulfonamides were selectively disulfurated at the δ-position of the amine (**53**).

During the course of our studies, we surprisingly obtained sulfides **56** and **57** when trisulfide dioxides featuring *n*-propyl- and phenyl substitution on the terminal sulfur were reacted with **54** under the standard decarboxylative reaction conditions (**Figure 5A**). This result suggested that steric hinderance was responsible for the successful disulfuration chemistry observed until that point (the corresponding *t*-butyl trisulfide dioxide gave the disulfide **16** exclusively in 85% yield upon reaction with **54**). Given that no sulfide products were observed in radical substitutions on tetrasulfides *regardless of their structure*, we investigated further. Upon moving to a trisulfide dioxide with an *i*-propyl substituent at the terminal sulfur atom as the reaction partner for **54**, a mixture of disulfide and sulfide was isolated (**55**, **Figure 5A**). The contribution of steric effects to the selectivity of substitution was further evident from the results of a series of reactions with the tertiary carboxylic acid **58**; the phenyl substrate yielded sulfide, the *n*-propyl substrate yielded a mixture of sulfide and disulfide whereas the *i*-propyl and *t*-butyl substrates yielded disulfides

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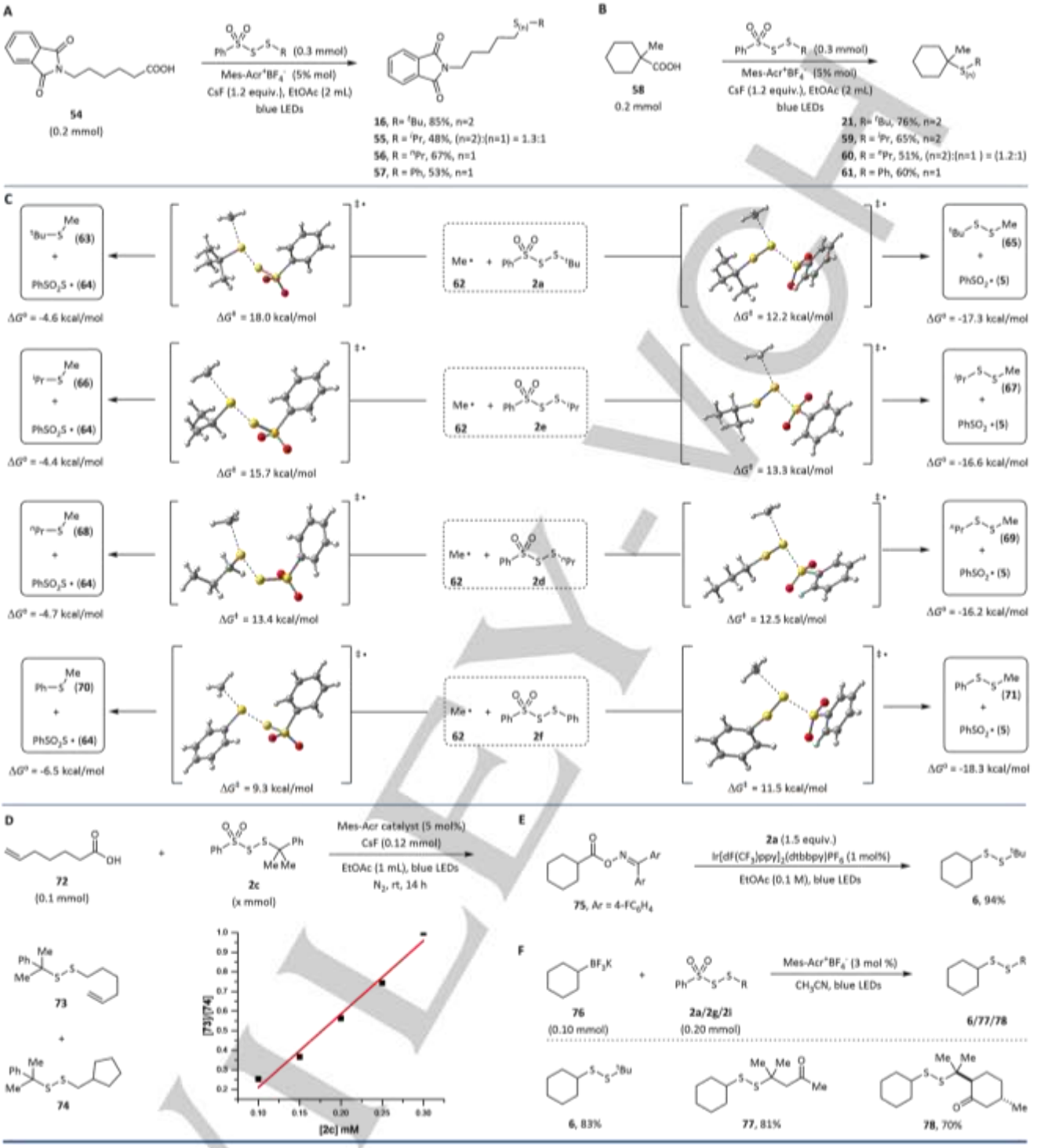

Figure 5. Steric effects on homolytic substitution, competition kinetics and use of additional radical precursors. (**A** and **B**) Steric effects on disulfide/sulfide product distribution. (**C**) Lowest energy transition state structures and corresponding reaction energetics determined by CBS-QB3 for homolytic substitution by a model alkyl (methyl) radical on phenyl trisulfide dioxides bearing differing substitution on the terminal sulfur atom. (**D**) Radical clock experiment provides k_{sub} = 6.5 ×10^5 M^{-1}s^{-1} for the reaction of a primary alkyl radical with trisulfide dioxide **2c**. (**E, F**) Reaction of trisulfide dioxides with cyclohexyl radicals generated from either an acyl oxime using energy transfer photocatalysis or from an alkyltrifluoroborate using oxidative photocatalysis.

exclusively. Computations[12] revealed that the barrier to substitution at S2 to afford the disulfide is essentially independent of the substituent on the terminal sulfur ($\Delta G^{\ddagger}$ ~ 12-13 kcal/mol), whereas the barrier to substitution at S3 to afford the sulfide is strongly dependent on its substituent, with $\Delta G^{\ddagger}$ increasing from 9.3 to 18.0 kcal/mol along the series Ph < *n*-Pr < *i*-Pr < *t*-Bu. We were surprised that sulfide formation was preferred to disulfide formation for the less hindered substrates since the driving force

for disulfide formation is significantly greater than for sulfide formation (*ca.* -17 kcal/mol *vs* -5 kcal/mol) owing to the greater stability of the departing sulfonyl radical compared to the thiosulfonyloxyl radical (CBS-QB3 predicts the S-H BDE in $PhS(O)_2SH$ to be 86.9 kcal/mol and the O-H BDE in $PhSO_2H$ to be 77.2 kcal/mol[11]). Evidently, a significant polar effect in the transition state for substitution at S3 to yield the sulfide must be at play. Indeed, although the pK_a of phenylthiosulfonic acid has not been reported, its gas phase acidity is calculated (by CBS-QB3) to be 14 kcal/mol lower than that of phenylsulfinic acid.

Since reactions at S1 and S2 of the tetrasulfides have similar thermodynamics (the displaced RSS• and RSSS• have similar stabilities[6a]), and the polar effects are expected to be similar in each of the transition states, the preference for disulfide formation observed in our previous work[5] must originate from small steric effects on substitution. Indeed, we calculate increasing barriers for substitution of a methyl radical on S1 of *n*-PrSSS*n*-Pr (11.3 kcal/mol), *i*-PrSSS*i*-Pr (14.0 kcal/mol) and *t*-BuSSS*t*-Bu (17.1 kcal/mol), while the barrier to substitution at S2 is comparatively invariant (10.3-11.7 kcal/mol) (see **Supporting Information**).[32] Thus, the same steric effects that drive the inherent preference for substitution at S2 in tetrasulfides must be leveraged to overcome the inherent preference for substitution at S1 of the trisulfide dioxides in order for efficient disulfuration to take place.

To provide some insight on the absolute kinetics of radical substitution on the trisulfide dioxides and enable comparison to the same process on the tetrasulfide, we carried out radical clock experiments using the cyclization of the 5-hexenyl radical derived from **72** as the calibrated unimolecular rearrangement (k_{cyc} = 2 × 10^5 s^{-1}).[27] Thus, the ratio of the linear product **73** derived from substitution by the unrearranged 5-hexenyl radical and the cyclized product **74** formed from substitution by the rearranged cyclopentylcarbinyl radical rearrangement were determined by GC-MS as a function of the concentration of **2c** (see **Figure 5D** and the **Supporting Information**). The data yield a rate constant of 6.5 × 10^5 M^{-1} s^{-1} for substitution of the primary alkyl radical on trisulfide dioxide **2c**. The fact that this rate constant is slightly larger than the value we determined for *t*-BuSSSS*t*-Bu using the same methodology (5.8 × 10^5 M^{-1} s^{-1})[5] despite the fact that the reaction is ~6 kcal/mol less exergonic again speaks to the greater polarization in the transition state for substitution for the sulfonyl radical over the perthiyl radical; consistent with the lower pK_a of $PhSO_2H$ (~3)[28] relative to *t*-BuSSH (~7).[29] The strikingly similar rate constants prompted us to reconsider our proposed mechanism; could the trisulfide dioxide simply be a source of tetrsulfide that reacts with alkyl radicals? Indeed, we found that the decomposition of trisulfide dioxide **2c** could deliver the tetrasulfide under the standard disulfuration reactions conditions. However, after 14 hours (the time for which the foregoing preparative reactions have been run), less than 0.15 equivalents of tetrasulfide were observed in the reaction mixture,[30] indicating that it cannot be the principal disulfuration reagent in the reactions of the trisulfide dioxides. This was reinforced by a direct competition experiment utilizing differently substituted tetrasulfide and trisulfide dioxide that give rise to unique disulfide products upon substitution. In each case, the predominant product observed was derived from alkyl radical substitution on the trisulfide dioxide (see the **Supporting Information** for the details).

To round out our investigations, we also evaluated the capacity of the trisulfide dioxides to deliver disulfides in conjunction with other radicals sources.[31] Use of **2a** with oxime ester **75** under the energy transfer photocatalytic conditions which we employed in our report on tetrasulfides yielded disulfide **6** in 94% yield – besting the 87% yield obtained with *t*-BuSSSS*t*-Bu (**Figure 5E**). Likewise, alkyltrifluoroborates reacted with the trisulfide dioxides shown in **Figure 5F** by oxidative photocatalysis to afford the corresponding disulfide products in good yield. It is noteworthy that the base-free deboronative disulfuration conditions enabled us to access the β-perthioketone products **77** and **78**, which cannot be obtained from the (basic) decarboxylative disulfuration due to the elimination of perthiolate.

In summary, the use of trisulfide dioxides in place of tetrasulfides has enabled the development of a practical photocatalytic protocol for the *direct* disulfuration of (aliphatic) carboxylic acids. In addition, we have also presented the first C(sp^3)–H bond disulfuration strategy to install disulfide moieties onto the γ-site of amides. These strategies should find widespread applications in late-stage disulfuration given their operationally simple procedures, broad substrate scope and wide functional group tolerance.

Acknowledgements

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Keywords: disulfides • alkyl radicals • homolytic substitution • photocatalysis • C-H functionalization

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COMMUNICATION

Trisulfide-1,1-dioxides are shown to undergo rapid homolytic substitution by alkyl radicals, which has enabled the development of an oxidative photocatalytic approach for the direct conversion of carboxylic acids to disulfides and a related approach for installation of a disulfide moiety by remote C-H functionalization.

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