Synthetic exploration of sulfinyl radicals using sulfinyl sulfones

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Abstract

Sulfinyl radicals – one of the fundamental classes of S-centered radicals – have eluded synthetic application in organic chemistry for over 60 years, despite their potential to assemble valuable sulfoxide compounds. Here we report the successful generation and use of sulfinyl radicals in a dual radical addition / radical coupling with unsaturated hydrocarbons, where readily-accessed sulfinyl sulfones serve as the sulfinyl radical precursor. The strategy provides an entry to a variety of previously inaccessible linear and cyclic disulfurized adducts in a single step, and demonstrates excellent tolerance to an extensive range of hydrocarbons and functional groups. Experimental and theoretical mechanistic investigations suggest that these reactions proceed through sequential sulfonyl and sulfinyl radical addition.

Main Text

Organosulfur compounds are of fundamental importance in synthetic and biological chemistry. They are widespread in molecules such as natural products, proteins and pharmaceuticals, playing a central role in biology as structural elements and key mediators of biological processes[1-4], and providing vital tools for organic synthesis[5-10]. Many methodologies and sulfur sources have been developed to install a variety of sulfur functionalities into organic molecules[11-14]. Among these, the use of sulfur-centered radicals to access sulfur-containing compounds has attracted considerable attention due to their ease of generation and efficiency of reaction[15-20]. However, in contrast to the popularity of sulfonyl and thiyl radicals, the utilization of sulfinyl radicals in synthetic chemistry has remained unexplored. This is due to the challenges of the inherent properties of sulfinyl radicals: their additions to π-systems are typically reversible, because of the relatively high stability of the sulfinyl radical[21], and they also readily undergo homodimerization to form thiosulfonates (Fig. 1A)[22]. We hypothesized that a dual radical addition / radical coupling strategy might overcome these issues and open up possibilities for the application of sulfinyl radicals in organic synthesis, not least by providing a new means to access sulfoxides, which are one of the most important classes of organosulfur compounds[23-25]. Specifically, the coupling of a sulfinyl radical with an *in situ* generated highly reactive carbon-centered radical could suppress the homo-coupling of the sulfinyl radical, and also avoid generation of a radical at the β-position to the sulfinyl group, thus preventing the undesired β-elimination of the sulfinyl group. Key to the implementation of this strategy is a suitable reagent that under mild conditions can simultaneously release a sulfinyl radical and another radical species of higher reactivity.

Sulfinyl sulfones (Fig. 1B), which are high-valent analogues of disulfides, have been known for over a century[26]. However, their structure and reactivity has only been sporadically investigated[27-30]; the perception that sulfinyl sulfones are unstable, hard-to-handle materials, along with a lack of reliable methods for their synthesis, has deterred research and restricted their occasional use as electrophilic sulfur sources[31-33]. A single report suggested that their thermal decomposition might proceed via homolytic fission, generating two distinct sulfur-centered radicals- a sulfinyl radical and a sulfonyl

radical[34]. As sulfonyl radicals are known to undergo facile addition to π-bonds[17-19], sulfinyl sulfones appeared to be well suited for our envisioned strategy. Here we describe the successful generation and use of sulfinyl sulfones in radical addition / radical coupling reactions with a wide variety of unsaturated hydrocarbons (Fig. 1C). This chemistry offers a new strategy for the synthesis of sulfoxide-containing molecules, which are of widespread utility throughout organic synthesis. Moreover, this reaction provides a simple and efficient method to access high value disulfurized products, the synthetic utility of which is demonstrated by selective transformation of either the sulfonyl or sulfinyl group into a variety of other building blocks in a controllable fashion.

We hypothesized that these disulfide derivatives might be prepared by nucleophilic attack of a sulfinate anion on a suitably activated S-electrophile, and questioned whether sulfinate salts might serve as the source of both species. After significant efforts, we found that sulfinyl sulfone **1** could indeed be directly prepared by the reaction of sodium *p*-toluenesulfinate with acetyl chloride in chloroform under a nitrogen atmosphere (72% yield, Fig. 1D). The identity of **1** was confirmed by single-crystal X-ray diffraction analysis, which revealed a S–S bond length of 2.230 Å; this is significantly longer than the S–S bond lengths of other disulfide derivatives[35-38], and may explain the lability of sulfinyl sulfones: while **1** can be stored without decomposition at -18 °C for over four months under a nitrogen atmosphere as solid or as solution in deuterated chloroform, it is sensitive to air and to temperatures above 25 °C (Fig. S1). We next tested sulfinyl sulfone **1** as a sulfinyl radical source for reaction with phenylacetylene. When **1** was reacted with phenylacetylene at 40 °C within 30 minutes, a disulfurized adduct **2** was obtained in nearly quantitative yield, the regio- and stereoselectivity of addition being confirmed through single-crystal X-ray diffraction (Fig. 1D).

We further questioned whether the synthesis of a sulfinyl sulfone and its subsequent reaction with an unsaturated hydrocarbon could be achieved directly from the sodium sulfinate salt. This indeed turned out to be the case, as reaction of sodium toluenesulfinate, acetyl chloride, and a variety of alkynes for 30 min under mild heating afforded the corresponding *E*-β-sulfinyl vinylsulfones **2**–**40** in high yield (Fig. 2A). Terminal (cyclo)alkyl alkynes provided additional products **3**–**13** in good yield, whereas the reaction with aryl alkynes resulted in near-quantitative yield, regardless of the steric and electronic properties of the substituents (**14**–**29**), with the possible exception of 4-nitrophenylacetylene (**23**, 75%). Equally productive were a naphthyl and two thienyl alkynes (**30**–**32**). A conjugated enyne was chemoselectively converted into product **33** with the alkene moiety untouched; however, alkynes featuring functional groups sensitive to acetyl chloride (hydroxyl, amino, carboxyl, amide) required the use of preformed sulfinyl sulfone **1** (**12**, **13**, **27**, and **28**).

While the regioselectivity of the reaction with terminal alkynes is dictated by the obvious difference in sterics, for internal alkynes the control on regiochemistry of the products is typically challenging. After ascertaining that our method can deliver a tetrasubstituted disulfurized alkene in good yield, as demonstrated with the *E*-2-butenyl product **34**, the reaction protocol was tested with aryl alkyl alkyne substrates, delivering alkenes **35**–**40** in high yield and exceptional regioselectivity for the product featuring the sulfinyl group positioned adjacent to the aromatic ring, irrespective of the nature of the

functional groups on the arene or alkyl chain. In particular, bromoalkene **40**, further amenable for functionalization, was obtained as a single isomer. In all cases, the exquisite *Z*-stereoselectivity remained confirmed.

We next turned our attention to the disulfurization of monosubstituted alkene, and obtained products **42**–**47** with high efficiency and regioselectivity. Even ethylene gas could be converted to sulfinyl sulfone **41** at atmospheric pressure in good isolated yield. Equally successful was the methodology with a range of acyclic and (hetero)cyclic 1,1-disubstituted alkenes, resulting in products **48**–**63**. The structural determination of **49** by single-crystal X-ray diffraction confirmed the regioselectivity of addition, in analogy to what observed with terminal alkynes and arylalkyl alkynes. As small carbocyclic and heterocyclic rings have been increasingly included in the design of pharmaceutical interest for their favorable physicochemical properties, as opposed to sp^2-hybridized scaffolds[39-41], disulfurized products such as **49** and **53**–**55** could be attractive building blocks in medicinal chemistry, especially in consideration of the potential further derivatization of the two distinct sulfur-based moiety, as discussed later. 1,2-Disubstituted linear and cyclic alkenes were also suited to the transformation, delivering adducts **64**–**69** in generally high yield. However, for almost all terminal alkenes and unsymmetric internal alkenes, the sulfinylsulfonation products exhibit poor stereoselectivity. Finally, even 1,3- and 1,2-dienes (allenes) underwent the addition with complete regiocontrol, affording the respective 1,4-addition products **70**–**72** with up to 6:1 *E*/*Z* selectivity, and allylic sulfones **73**–**78**, respectively, in moderate to good yield.

As a consequential development for our sulfinylsulfonylation methodology, we questioned whether it could be adopted in radical cascade cyclizations of 1,*n*-enynes, which notoriously enable the preparation of a variety of carbo- and heterocyclic compounds[42]. Such approach would inevitably present the challenge of controlling the site-selectivity of addition of either sulfur component onto the enyne moiety. When tested with our protocol, a few probe enyne substrates successfully undertook the targeted radical cascade reaction, delivering products with chemo- and regioselectivity that strictly depended on the substitution pattern of the substrate (Fig. 2B). In particular, the cyclization of 1,6-enynes with a trisubstituted double bond and capped by a phenyl group on the alkyne yielded six-membered endocyclic vinyl sulfones as single regioisomers (**79**–**81**). The structure of compound **79** was confirmed by single-crystal X-ray diffraction. Conversely, the regioselectivity of addition was completely reversed for 1,6-enynes with terminal alkynes, giving five-membered exocyclic vinyl sulfones (**82**–**84**). A complete switch in chemoselectivity was observed for 1,6-enynes with a methylidene moiety, whereby the sulfonyl group added to the alkene, and the sulfinyl substituent to the alkyne. Phenyl alkynes delivered five-membered exocyclic vinyl sulfoxides (**85**–**87**), while terminal alkynes reversed the regioselectivity of the cyclization, affording six-membered endocyclic vinyl sulfoxides (**88**–**90**). Overall, this new radical cascade enables the efficient formation of one C–C bond and two C–S bonds in one step, and offers a powerful means for the construction of sulfur-containing carbo- and heterocycles with exceptional control over both ring size and substituent regioselectivity.

Arynes are a class of highly reactive intermediates, generated in situ from certain precursors such as the most commonly used 2-(trimethylsilyl)phenyl triflates, and have rich reactivity including multi-component

reaction, aryne relay reaction, σ-bond insertion, cylcoaddition, and so on.[43] However, the radical reaction of arynes is quite rare, probably due to the low concentration and the high reactivity of both aryne and radical species generated in situ in the reaction system.[44] We therefore examined the tolerance of arynes as an unsaturated hydrocarbon in our methodology. In order to minimize the interference of reactants, the sulfinyl sulfone **1** was prepared separately and then employed in the reaction with 2-(trimethylsilyl)aryl triflates in the presence of CsF and 18-crown-6. We were pleased to find that both benzyne and naphthalyne precursors smoothly underwent the sulfinylsulfonation reaction to afford the corresponding disulfurized aromatics **91**-**99**, **101**, and **103** in good-to-excellent yield. The structure of **91** was confirmed with the help of single-crystal X-ray diffraction. The unsymmetric aryne precursors resulted in a 1:1 ratio of regioisomer mixture, which could be normalized through the oxidation leading to vicinal disulfone compounds **100**, **102**, and **104**.

Further investigation of the reaction scope with respect to the sulfinate revealed that alkylsulfinates as well as arylsulfinates with either electron-donating or electron-withdrawing groups were readily converted into adducts **105**–**119** in excellent yield (Fig. 4A). Alkyl sulfoxides and alkyl sulfones are widely found in drugs, such as tinidazole, apremilast, armodafinil, armodafinil, and fulvestrant.[1,3] In general, these moieties are prepared by oxidation of sulfides; the disadvantage of this method is that it can be difficult to control the oxidation state of organosulfurs - a mixture of sulfoxides and sulfones is often obtained, and there is a risk of undesired oxidation of other functional groups.[3] Our method avoids these problem by directly accessing desulfurized compounds containing alkyl sulfinyl and alkyl sulfonyl groups without the need for redox manipulations. Application of the sulfinylsulfonation methodology to the functionalization of alkyne functionality in selected natural products afforded disulfurized products **120**-**125** in high yield (Fig. 4B). Further, the sulfinylsulfonation of intrinsic alkyne functionality in drug such as erlotinib and clodinafop-propargyl ester also proved to be suitable and afforded the corresponding adducts **126** and **127** in high yield (Fig. 4C). These results demonstrate the utility of the sulfinylsulfonation method in functionalizing pharmaceutically relevant molecules.

Our sulfinylsulfonation protocol can be easily scaled up more than a 100-fold, as demonstrated by the uneventful preparation of a multigram quantity of compound **2** in 85% yield after recrystallization (Fig. 5). β-Sulfinyl vinylsulfones are newly synthesized compounds and the synthetic utility of these now readily accessible disulfurized products was showcased by a large number of transformations. For instance, the selective functionalization of either the sulfonyl or sulfinyl motif in **2** was first explored. Treatment of **2** with sodium hydride (NaH) results in an acetylenic sulfone **128** by eliminating the sulfinyl group. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) as the base affords a product **129** by the selective reduction of the sulfonyl group. Reaction of **2** with SmI_2 in THF selectively leads to the desulfinated product **131**, whereas SmI_2 in HMPA induces desulfonation and give product **130**. Nucleophilic addition / elimination reactions of the sulfinyl group in **2** with amines, azide, and alkoxides give products **135**–**140**, whereas sulfide and selenide ions displace the sulfonyl group to give compounds **132**–**134**. In both cases, inversion of stereochemistry is observed at the double bond (as confirmed by ^1H-^1H NOESY analysis of **132** and **135**). Use of Grignard reagent (EtMgBr) as the nucleophile results in the nucleophilic substitution of the sulfinyl

group to give compounds **131** and **141**, whereas an eliminative coupling product **142** is produced in the presence of $Ni(acac)_2$. Oxidation of the vinyl sulfoxide with *m*-CPBA gives disulfone **143**. The sulfinyl group reacts with benzyne affording a rearrangement product **144** via [2+2] cycloaddition / S-O-vinyl migration cascade.[45] Treatment of **2** with trifluoromethanesulfonic anhydride in acetonitrile leads to a product **145** by [3,3]-sigmatropic rearrangement reaction.[46] Note that some core structures of these products are present in drug and natural products, for example, the 1,2-disulfonylehene moiety in **143** is the key structure of dimethipin, the 1,3-butadiyne unit in **142** is found as the core structure in natural products such as bupleurotoxin, lobetyolin, enanthotoxin, etc., and the β-sulfonyl enamine in **135**-**137** is observed in adociaquinones.

A proposed mechanism for the sulfinylsulfonation is shown in Fig. 6A, which begins with activation of the sulfinate salt with acetyl chloride to form intermediate (**I**). This intermediate undergoes reaction with a further equivalent of the sulfinate to give the sulfinyl sulfone **1**. No reaction with phenyl acetylene was observed in the absence of acetyl chloride, confirming its essential role as an activator. Homolytic fission of the S–S bond in **1** generates sulfonyl radical **A** and sulfinyl radical **B**. The formation of these two radicals was confirmed by electron paramagnetic resonance (EPR) experiments with the addition of free-radical spin-trapping agent 5,5-dimethyl-1-pyrroline *N*-oxide (DMPO) (Fig. S2). In addition, we also found thiosulfonate as a byproduct by the result of sulfinyl radical homocoupling. Based on our experimental observations of regioselectivity, the more electrophilic radical **A** is proposed to undergo addition to the unsaturated hydrocarbon, leading to the (more stable) carbon-centered radical **II**, which is then captured by the sulfinyl radical **B** to afford the product **2**. In support of the proposal of a radical process, the sulfinylsulfonation of phenylacetylene was completely suppressed in the presence of TEMPO, whereas the use of cyclopropylethylene as substrate led to ring-opened product **146** (52%).

The proposed mechanism was studied using Density Functional Theory (DFT) calculations at the SMD-B3LYP/6-31+G(d,p) level of theory (Fig. 6B; for additional detail see Figs. S3–6). After a mildly endergonic cleavage of the S–S bond in reagent **1**, the addition of the sulfonyl radical **A** to phenylacetylene via **TS1** ($\Delta G^{\ddagger}$ = 7.6 kcal·mol^{-1}) is favored by $\Delta\Delta G^{\ddagger}$ = 10.7 kcal·mol^{-1} over addition of the sulfinyl radical **B**, which would proceed via **TS1'** ($\Delta G^{\ddagger}$ = 18.3 kcal·mol^{-1}) - a highly endergonic and reversible process to give radical **II' (**ΔG^{0} = +17.1 kcal·mol^{-1}). The expected higher electrophilicity of **A** is reflected by the higher charge on the sulfur atom in **A** (1.27, calculated by Natural Population Analysis, NPA), in contrast to **B** (0.61), thus favoring the attack of **A** over **B** on the alkyne, to give the stabilized radical **II**. The approach of the sulfinyl radical **B** to **II** is sterically directed to give the (*E*)-disulfurized product **2** via **TS2**, $\Delta G^{\ddagger}$ = 18.5 kcal·mol^{-1}, a lower energy pathway than that leading to (*Z*)-disulfurized product **2-1** via **TS6,** $\Delta G^{\ddagger}$ = 22.4 kcal·mol^{-1}, in agreement with the experimental findings that where no (*Z*)-disulfurized product has ever been detected.

In conclusion, we have described a new strategy for the utilization of sulfinyl radicals in organic synthesis, overcoming the known tendency to undergo homo-coupling and β-cleavage. Reaction of unsaturated hydrocarbons by a radical mechanism with *in situ* generated sulfinyl sulfones revealed the

potential to harness these compounds as source of disulfurized organic molecules. The reaction scope spanned from cascade processes to derivatization of scaffolds found in natural products, affording a wide range of novel organosulfur compounds, which have broad potential use in organic synthesis, pharmaceutical, and materials research. In addition, this dual radical addition / radical coupling concept for the generation and use of sulfinyl radicals can serve as a general model for the development of other novel sulfur reagents.

Declarations

Data availability

Crystallographic data for the structures reported have been deposited at the Cambridge Crystallographic Data Centre, under deposition numbers CCDC 1994377 (**1**), 1864547 (**2**), 2003800 (**49**), 2003798 (**79**), 2058384 (**91**) and 1907354 (**119**). Complete experimental procedures and compound characterization data are available in the Supplementary Information, or from the corresponding author upon request.

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Author contributions

Z.W. and Z.Z. contributed equally to this work. Z.W. and X.B. conceived the strategy, designed the investigation, analyzed the data, and together with E.A.A., G.Z. and P.S. discussed the results and drafted this manuscript. Z.W., Z.Z., W.Z., P.S., Y.W. performed the experiments and the calculations.

Competing interests

The authors declare no competing interests.

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Figures

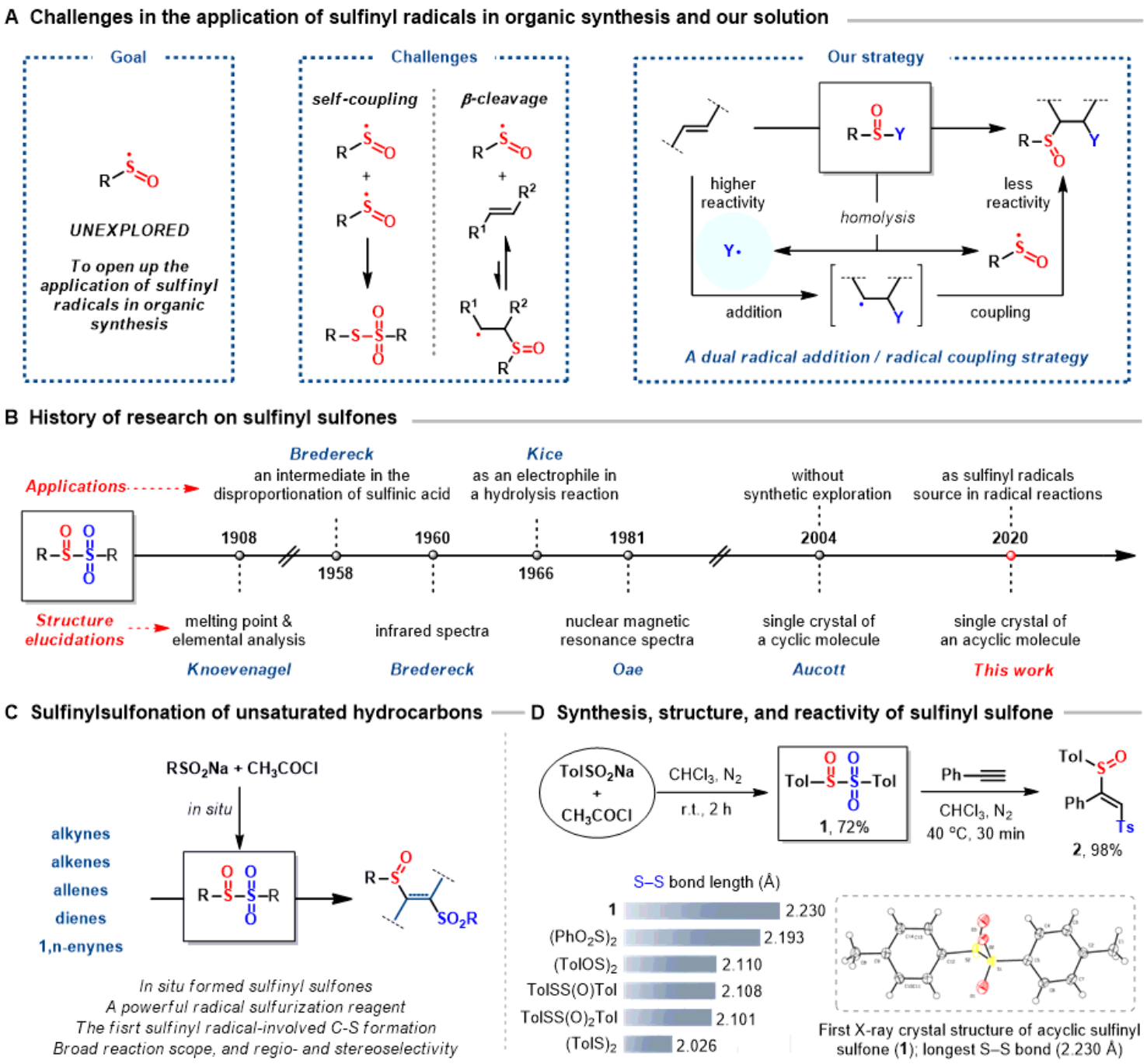

Figure 1

(A) Design of a new strategy for the application of sulfinyl radicals in organic synthesis; (B) The discovery history of sulfinyl sulfones, with emphasis on the limited synthetic access and applications; (C) Sulfinylsulfonation of various unsaturated hydrocarbons with in situ formed sulfinyl sulfones; (D) The synthesis, single crystal X-ray structure of sulfinyl sulfone 1, comparison of the S–S bond length (Å) with that of other analogous compounds, and the sulfinylsulfonation of phenylacetylene.

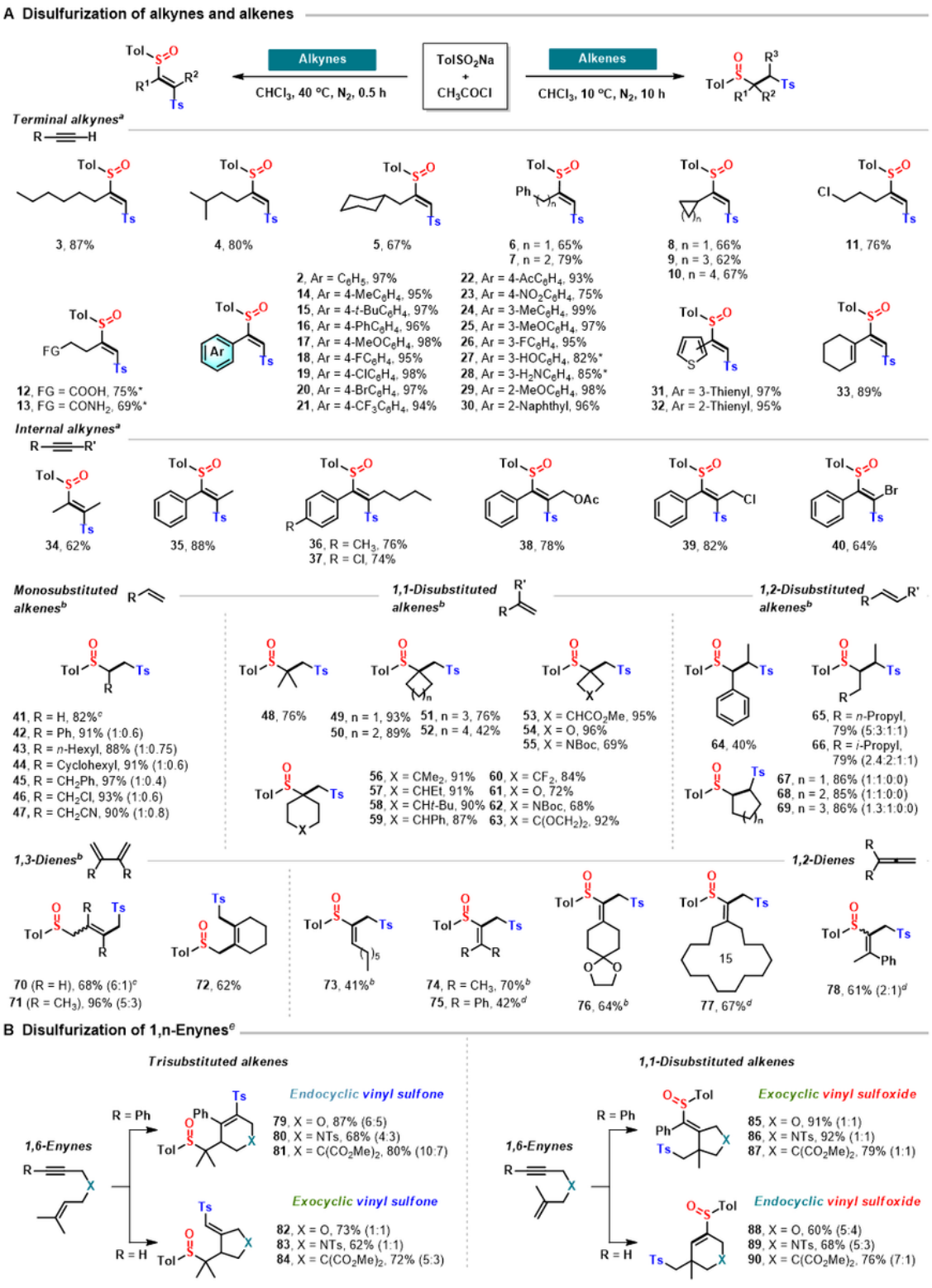

Figure 2

A) Sulfinylsulfonation of alkynes and alkenes; (B) Cascade sulfinylsulfonation of enynes. All yields are isolated yields. Diastereomeric ratios are shown in parentheses where appropriate. Amounts of reagents and solvent: alkyne/alkene/enyne (0.3 mmol), TolSO2Na (1.8 mmol), CH3COCl (1.2 mmol), 0.1 M in CHCl3, N2. a 40 °C, 30 min. b 10 °C, 10 h. c Reaction conditions for gaseous olefins: TolSO2Na (1.8 mmol), CH3COCl (1.2 mmol), CHCl3 (3 mL), 10 °C, 20 h, ethylene/1,3-butadiene (1 atm); the yield of

product was calculated using TolSO2Na as the standard. d 40 °C, 5 h. e room temperature, 8 h. * Reaction conditions for the synthesis of 12, 13, 27, and 28: alkyne (0.3 mmol), 1 (0.45 mmol), 0.1 M in CHCl3, N2, 40 oC, 0.5 h.

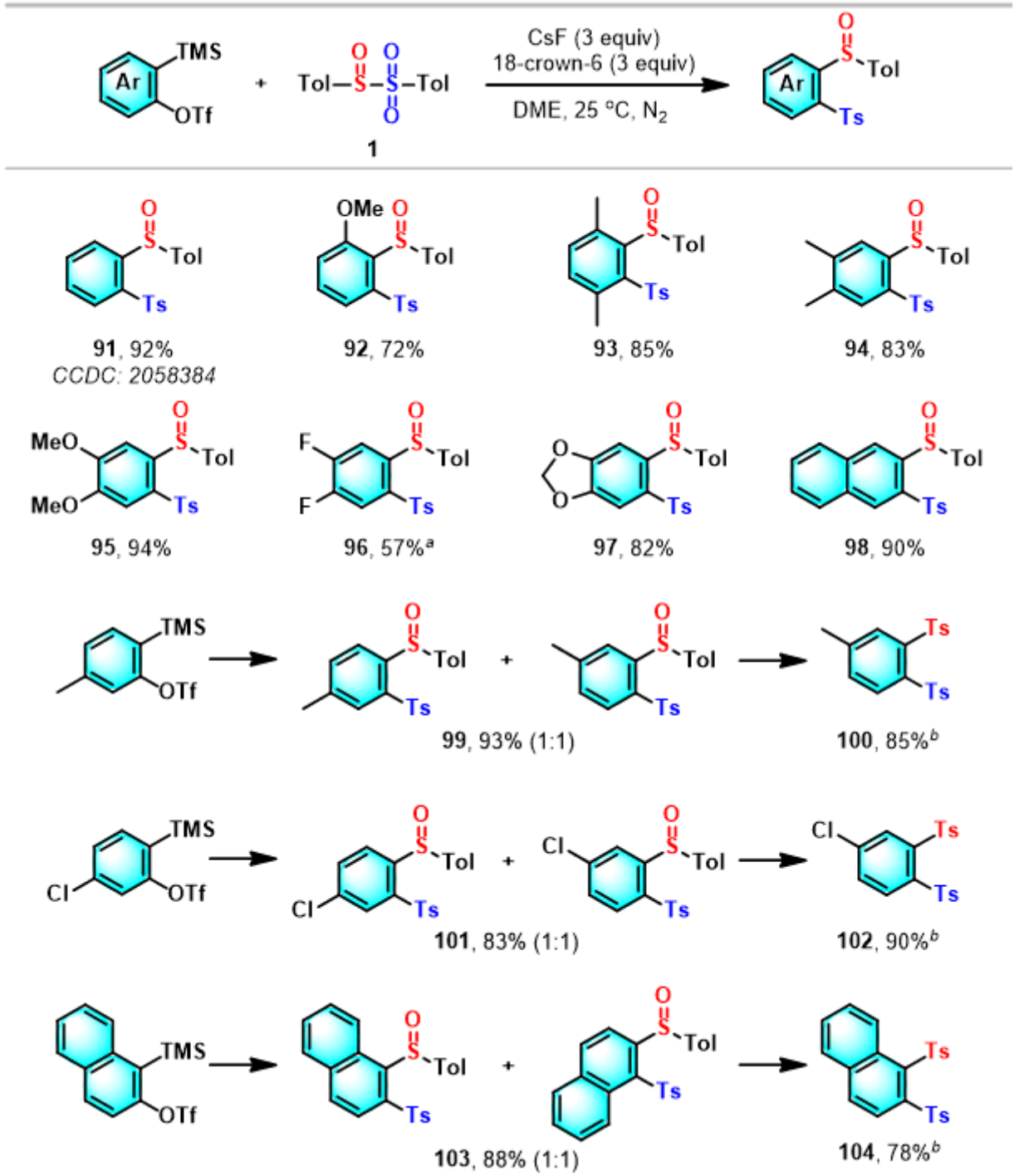

Figure 3

The sulfinylsulfonation of arynes. Reaction conditions: arynes (0.5 mmol), 1 (0.5 mmol), CsF (1.5 mmol), 18-crown-6 (1.5 mmol), DME (3 mL), 25 oC, N2, 3 h. a 0 oC, N2, 1 h. b 99, 101, or 103 (0.5 mmol), m-CPBA (0.75 mmol), DCM (3 mL), 25 oC, 1 h.

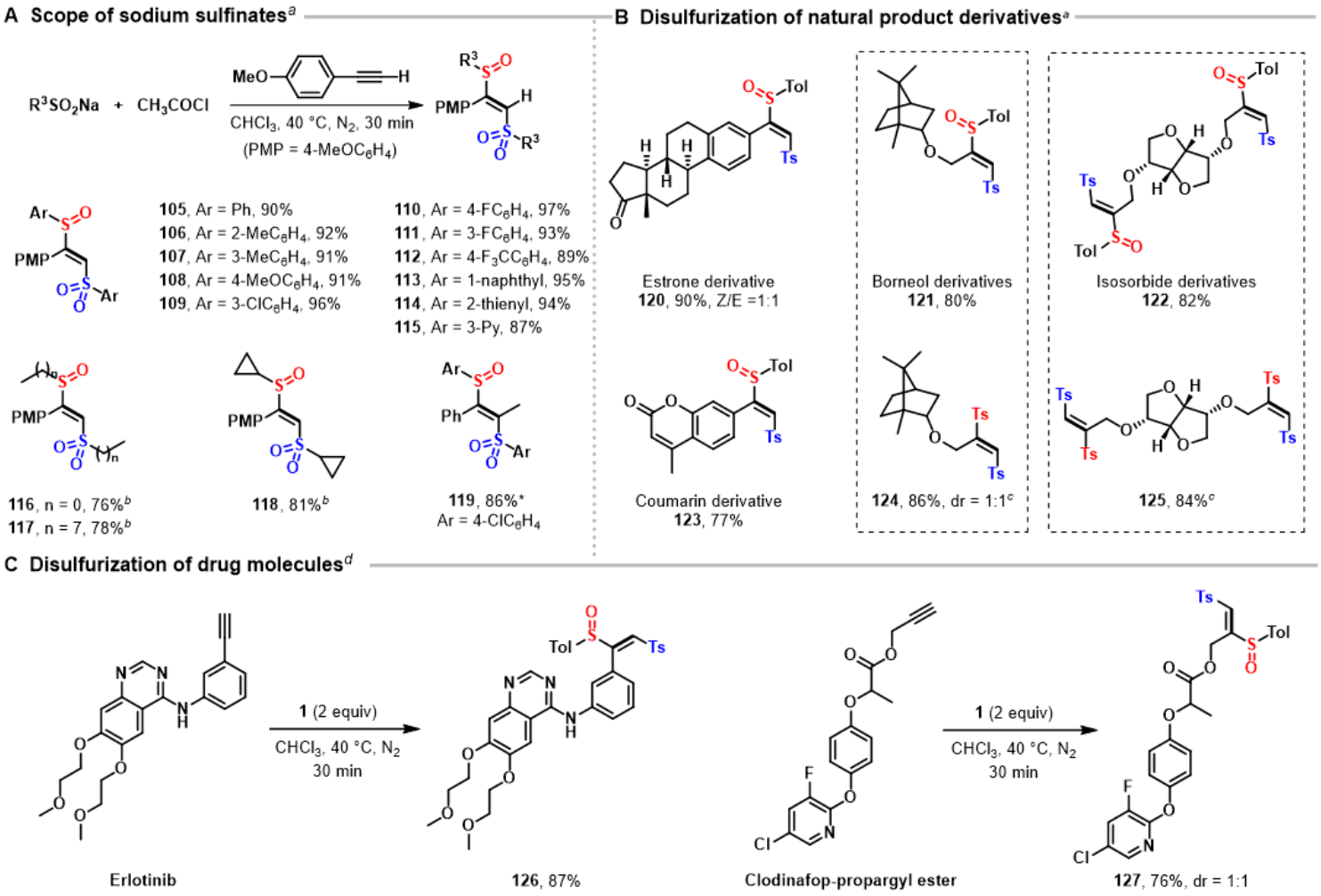

Figure 4

(A) Variation of the sodium sulfinate. * Prop-1-yn-1-ylbenzene was used as the substrate; (B) Disulfurization of natural product derivatives; (C) Disulfurization of drug molecules. All yields are isolated yields. Reaction conditions for the synthesis of 105-123: alkyne (0.3 mmol), sodium sulfinate (1.8 mmol), acetyl chloride (1.2 mmol), 0.1 M in CHCl3, N2. a 40 °C, 30 min. b 10 °C, 12 h. c 121 or 122 (0.5 mmol), m-CPBA (0.75 mmol), DCM (10 mL), room temperature, 1 h. d Erlotinib or Clodinafop-propargyl ester (0.5 mmol), 1 (1.0 mmol), CHCl3 (3.0 mmol), 40 oC, N2, 0.5 h.

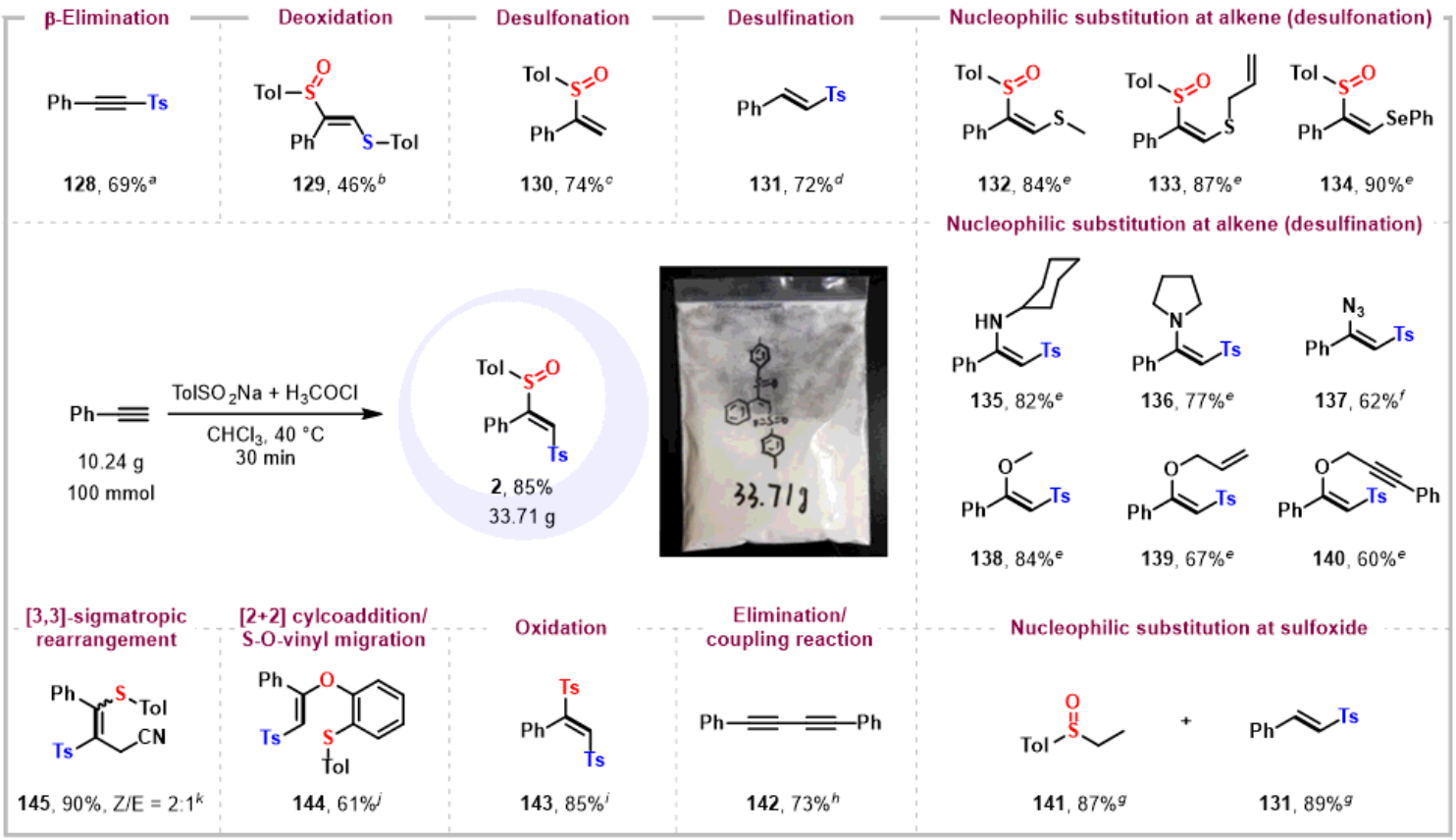

Figure 5

Large scale synthesis and further transformations. All yields are isolated yields. The amount of 2 is 0.5 mmol. a NaH (0.75 mmol), CH3CN (3.0 mL), 25 oC, 6 h. b DBU (5.0 mmol), toluene (3 mL), 100 oC, 6 h. c Methanol (5.0 mmol), hexamethylphosphoric triamide (HMPA, 2.5 mmol), SmI2 in THF (0.1 M, 25 mL), THF (1 mL), -20 oC, N2, 2 h. d SmI2 in THF (0.1 M, 25 mL), methanol/THF (v/v = 1/1, 1 mL), 25 oC, N2; then, 60 oC, 3 h. e NaH (0.75 mmol), RXH (0.75 mmol), CH3CN (3 mL), 25 oC, 5 h. f NaN3 (5.0 mmol), DMSO (3 mL), 25 oC, 0.5 h. g EtMgBr (1.0 mmol), THF (3 mL), 25 oC, N2, 3 h. h EtMgBr (1.0 mmol), Ni(acac)2 (0.005 mmol) THF (3 mL), 25 oC, N2, 3 h. i m-CPBA (0.75 mmol), DCM (10 mL), 25 oC, 1 h. j CsF (3.0 mmol), 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (1.5 mmol), CH3CN (5 mL), 55 oC, 12 h. k Tf2O (1.0 mmol), DABSO (1.25 mmol), CH3CN (5 mL), -30 oC, 2 h.

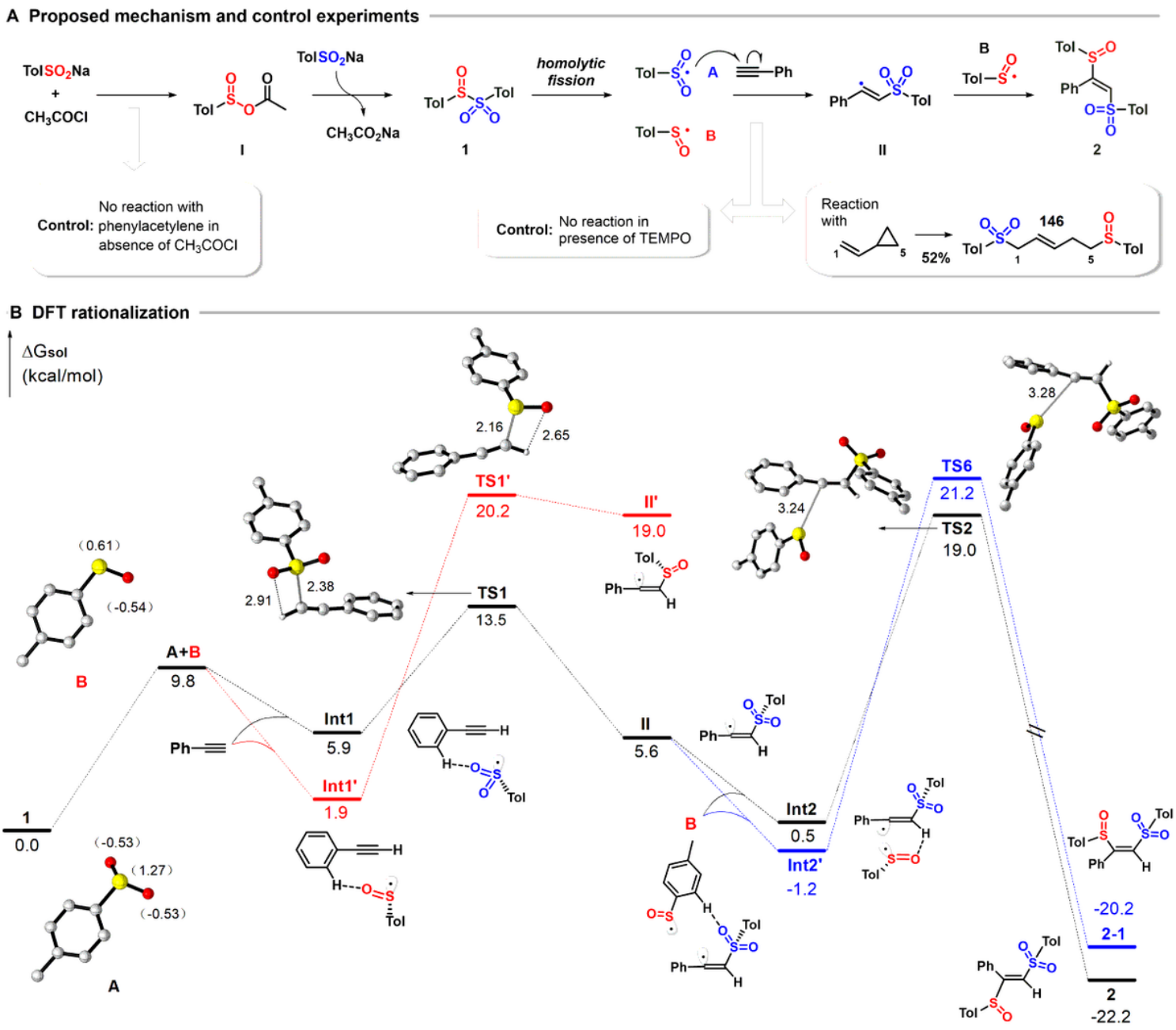

Figure 6

(A) Proposed mechanism and experimental support for a radical pathway; (B) DFT calculations and graphical reprentation of the proposed mechanistic pathway. The energies are in kcal·mol-1 and represent the relative free energies calculated at the SMD-B3LYP/6-31+G(d,p) level in chloroform.

Supplementary Files

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- SupplementaryInformation01311.docx