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To be cited as: *Chem. Eur. J.* **2025**, e202501384

Link to VoR: <https://doi.org/10.1002/chem.202501384>

Oxidative Thiolated Aromatization of Terpenes for Divergent Construction of Organosulfur Compounds

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Abstract: Synthetic transformation of terpenoids represents a long-standing research topic in organic synthesis. Due to the presence of multiple oxidation states and isomers in naturally abundant terpenoids, their separation and efficient utilization pose challenges. Convergent transformations of various terpenes can circumvent these issues. We herein developed a convergent and divergent strategy for control of oxidation states, enabling the construction of sulfur-containing terpenoid derivatives using various terpenes. This protocol features broad substrate scope, good functional compatibility, and high redox-selectivity. Convergent synthesis strategy was implemented smoothly by using drug and plant extracts. The synthesis of sulfoxide and sulfone products was further achieved by modulating the oxidation conditions, respectively. Additionally, the products can undergo an array of elaborate transformations, which highlight the potential applications of this strategy.

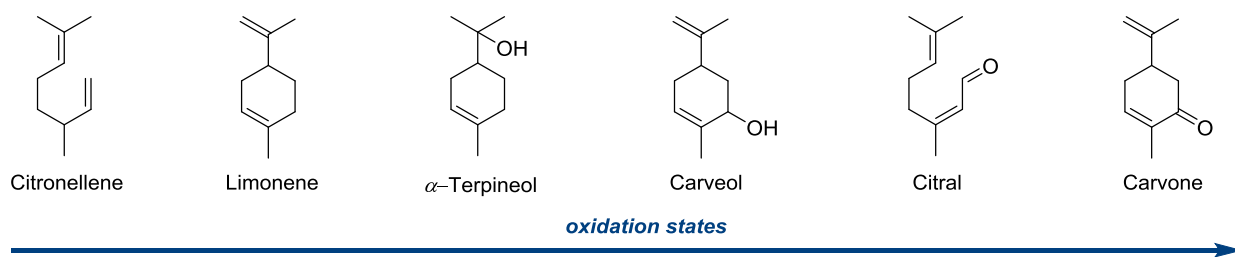
Introduction

Terpenoids are the largest group of natural products and are widely distributed in plants, animals, and microorganisms. Monoterpenes are a class of terpenoids consisting of two isoprene units, which mainly originate from the secretion system of plants^[1]. Owing to their unique physicochemical properties, monoterpenes with different oxidation states have been widely applied in medicine, food, and cosmetics (Figure 1a)^[2]. For instance, limonene^[3] has medical applications in the treatment of biliary diseases. α -Terpineol^[4] can be used as flavors, preservatives, and antioxidants in food processing. Meanwhile, citral^[5] can be used as a raw material for the synthesis of Vitamin A.

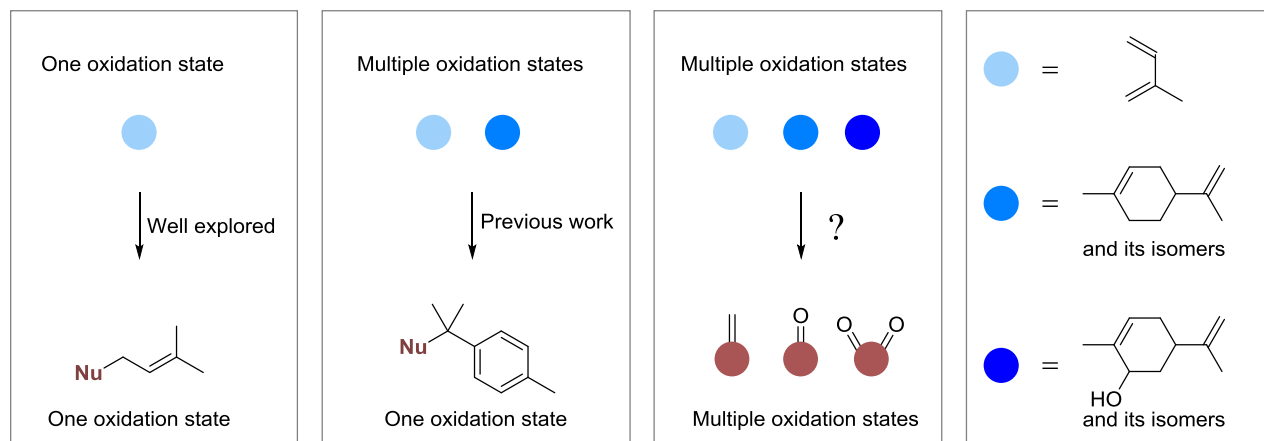
Since monoterpenes have the advantages of wide source and inexpensive, achieving high value-added conversion of existing monoterpenes has attracted much attention in chemistry community for a long time^[6]. However, natural terpenes are frequently found as complex mixtures containing various oxidation states and isomers, making it challenging to separate and purify them, thus leading to decreased utilization efficiency. If these terpenes with multiple oxidation states can be used uniformly, their utilization efficiency will undoubtedly be greatly improved. Currently, majority of research studies focus on the transformation of raw material with a single oxidation state to a single oxidation state product (Figure 1b)^[7]. For instance, the reaction between isoprene and a nucleophile yields a prenylated product. Our group has previously reported an example of using multiple oxidation terpenes to generate a single oxidation state product^[6f]. Presently, the transformation of terpenes with multiple oxidation states to multiple oxidation states derivatives still faces challenges. This constraint hinders the versatile

application of terpenes. Due to the varying functions associated with different oxidation states, it is highly important to streamline the conversion of mixed terpenes into products with multiple oxidation states for the efficient and diversified utilization of terpenes.

a) Representative terpenes with various oxidation states in natural products



b) Utilization of terpenes and oxidation states control



c) This work: Convergent oxidative thiolated aromatization of terpenes for divergent construction of organosulfur compounds

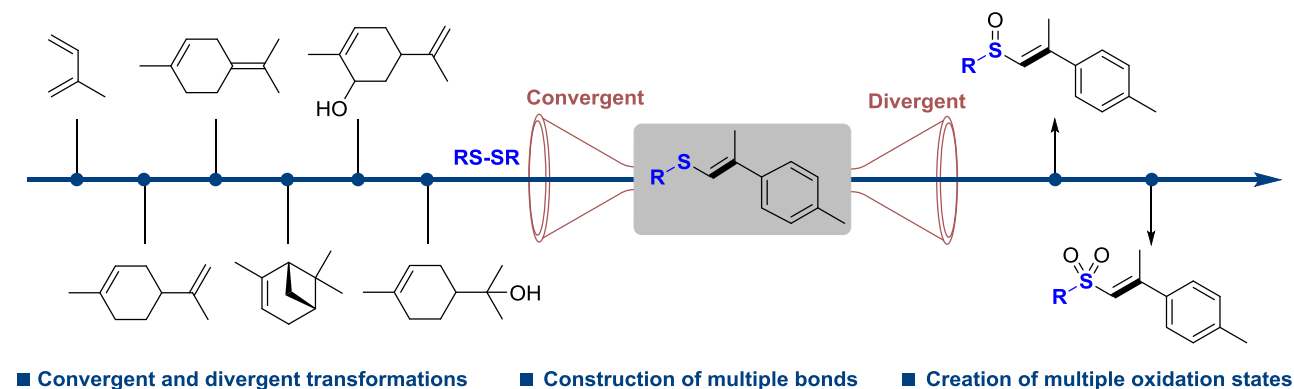


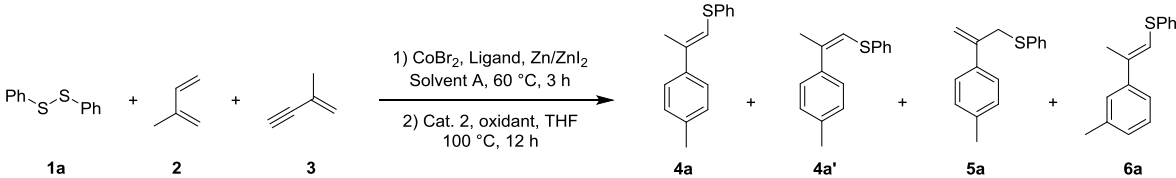
Figure 1. Terpenoids with various oxidation states and their utilizations.

In addition, organic sulfur-containing compounds also have multiple oxidation states^[8]. Due to the diverse oxidation states of sulfur atoms, sulfur-containing compounds have greatly enriched their applications in the fields such as medicine, pesticides, and materials, etc^[9]. For example, the representatives of sulfide compound penicillin G^[10], sulfoxide compound esomeprazole^[11], and sulfone compound tazobactam^[12] have been used in clinical therapeutic applications. Furthermore, sulfur-containing drugs account for 57 of the top 200 small molecule drugs in terms of sales in 2023^[13]. Currently, constructing C-S bonds through olefins has also attracted widespread attention as a practical strategy^[14].

Given the significance of controlling the oxidation states of terpenes and sulfur-containing compounds, we have developed a unified protocol utilizing oxidation state convergence and divergence to effectively harness terpenes and selectively generate sulfur-containing compounds in various oxidation states (Figure 1c). This method enables efficient transformation of mixed terpenes from plants, demonstrating significant application value in biomass utilization.

Results and Discussion

Table 1. Optimization of Reaction Conditions



Entry	Ligand	Cat. 2	Oxidant	Solvent A	4a (%)	4a' (%)	5a (%)	6a (%)
1	dppe	I ₂	K ₂ S ₂ O ₈	DCM	4	-	-	-
2	dppe	I ₂	K ₂ S ₂ O ₈	MeCN	3	-	-	1
3	dppe	I ₂	K ₂ S ₂ O ₈	Dioxane	26	3	trace	2
4	dppe	I ₂	Na ₂ S ₂ O ₈	Dioxane	27	2	1	2
5	dppe	I ₂	H ₂ O ₂	Dioxane	24	3	1	1
6	dppe	I ₂	DMSO	Dioxane	51	5	37	1
7	dppe	I₂	BQ-1	Dioxane	84	5	2	3
8	dppp	I ₂	BQ-1	Dioxane	72	5	8	8
9	dppb	I ₂	BQ-1	Dioxane	-	-	-	-
10	bpy	I ₂	BQ-1	Dioxane	-	-	-	2
11 ^a	dppe	NIS	BQ-1	Dioxane	81	6	4	4
12 ^a	dppe	HI	BQ-1	Dioxane	75	5	1	3
13	dppe	-	BQ-1	Dioxane	-	-	-	-
14 ^b	dppe	I ₂	BQ-1	Dioxane	48	3	23	2
15 ^c	dppe	I ₂	BQ-1	Dioxane	-	-	-	-
16 ^d	dppe	I ₂	BQ-1	Dioxane	-	-	-	-

Conditions. Step I: **2** (0.40 mmol), **3** (0.40 mmol), [Co]/ligand (0.01 mmol), Zn/ZnI₂ (0.04 mmol), solvent A (0.5 mL), 60 °C, 3 h; Step II: **1a** (0.10 mmol), I₂ (0.08 mmol), oxidant (0.60 mmol), THF (0.5 mL), 100 °C, 12 h. Yields and selectivities were determined by GC-FID analysis with mesitylene as the internal standard. ^aCat. 2 (0.16 mmol); ^b60 °C for the second step; ^cWithout **2**; ^dWithout **3**. dppe: 1,2-bis(diphenylphosphino)ethane, dppp: 1,3-bis(diphenylphosphino)propane, dppb: 1,4-Bis(diphenylphosphino) butane, bpy: 2,2'-bipyridine, BQ-1: 2,5-di-*tert*-butyl-1,4-benzoquinone.

Due to its unique structure and abundance, isoprene as the simplest hemiterpene is unquestionably the most economically efficient and directly option for preparing various terpene derivatives. The coupling of isoprene with disulfides was first

attempted to synthesize sulfur-containing terpene derivatives (Table 1). Under cobalt/iodine cascade catalysis, an investigation was conducted on the reaction solvents initially, revealing that the reaction efficiency was superior in 1,4-dioxane (26%) compared to dichloromethane (4%) and acetonitrile (3%) (entries 1-3). Subsequently, different oxidants were tested for this reaction (entries 4-7). Sodium persulfate and hydrogen peroxide exhibited a similar reaction effect (entries 4-5). When using dimethyl sulfoxide as an oxidant, the target product **4a** could be obtained with a yield of 51%. Meanwhile, 37% of the olefin isomerization side-product **5a** was detected (entry 6). It was worth noting that 2,5-di-tert-butyl-*p*-benzoquinone (BQ-1) could yield the target product **4a** with 84% yield (entry 7). The ligand examination suggested that dppe was optimal for this process (entries 8-10). Although NIS and HI could catalyze the reaction, their catalytic effects were somewhat inferior (entries 11 and 12). In the absence of an iodine source, this reaction could not proceed (entry 13). It was found that a lower temperature (60 °C) favors the generation of side-product **5a** (entry 14). The reaction could not proceed in the absence of either isoprene **2** or enyne **3** (entries 15 and 16). Due to compatibility issues, corresponding product could not be obtained through a direct one-pot reaction.

With the optimized conditions in hand, the scope of disulfide ethers **1** was investigated. A wide range of substituted disulfides was applied and transformed to target products (Figure 2). It showed that both electron-donating and electron-withdrawing groups at the *para*-position of phenyl ring, had no significant impact on the reactions and the desired products were obtained in 72-85% yields (**4b-4k**). It's noteworthy that the halogen groups, which could offer useful handles for further synthetic manipulations, were also applicable to this reaction (**4g-4i**). In addition, the configuration of **4i** was unambiguously determined by single-crystal X-ray crystallography (CCDC: 2355771)^[15]. Substituents at *meta*-position of the phenyl ring were amenable to the transformation as well (**4l-4p**, 71-82%). Notably, the reaction also applied to thioethers where the *ortho*-position on the benzene ring were substituted (**4q-4t**, 31-78%). Although the reactions of *ortho* amide and nitro substituted substrates were inhibited, it still delivered the desired products in acceptable yields (**4r**, **4t**). The structure of **4r** was confirmed by single-crystal X-ray crystallography (CCDC: 2351121)^[15]. Additionally, 3,5-dimethyl and 3,5-difluoro substituted aryl sulfide were also found as good substrates in the reaction, affording the desired products (**4u**, **4v**) in 80% and 73% yields. Pleasingly, highly functionalized trichloro phenyl sulfide also reacted smoothly under standard conditions to produce oxidative coupling product **4w** in decent yield. Furthermore, alkyl sulfides were suitable for this reaction with slightly lower yields (**4x-4ab**, 48-70%) than aryl sulfides, where the large steric hindrance isopropyl and cyclohexyl sulfides also gave the desired products (**4y**, **4aa**) in moderate yields.

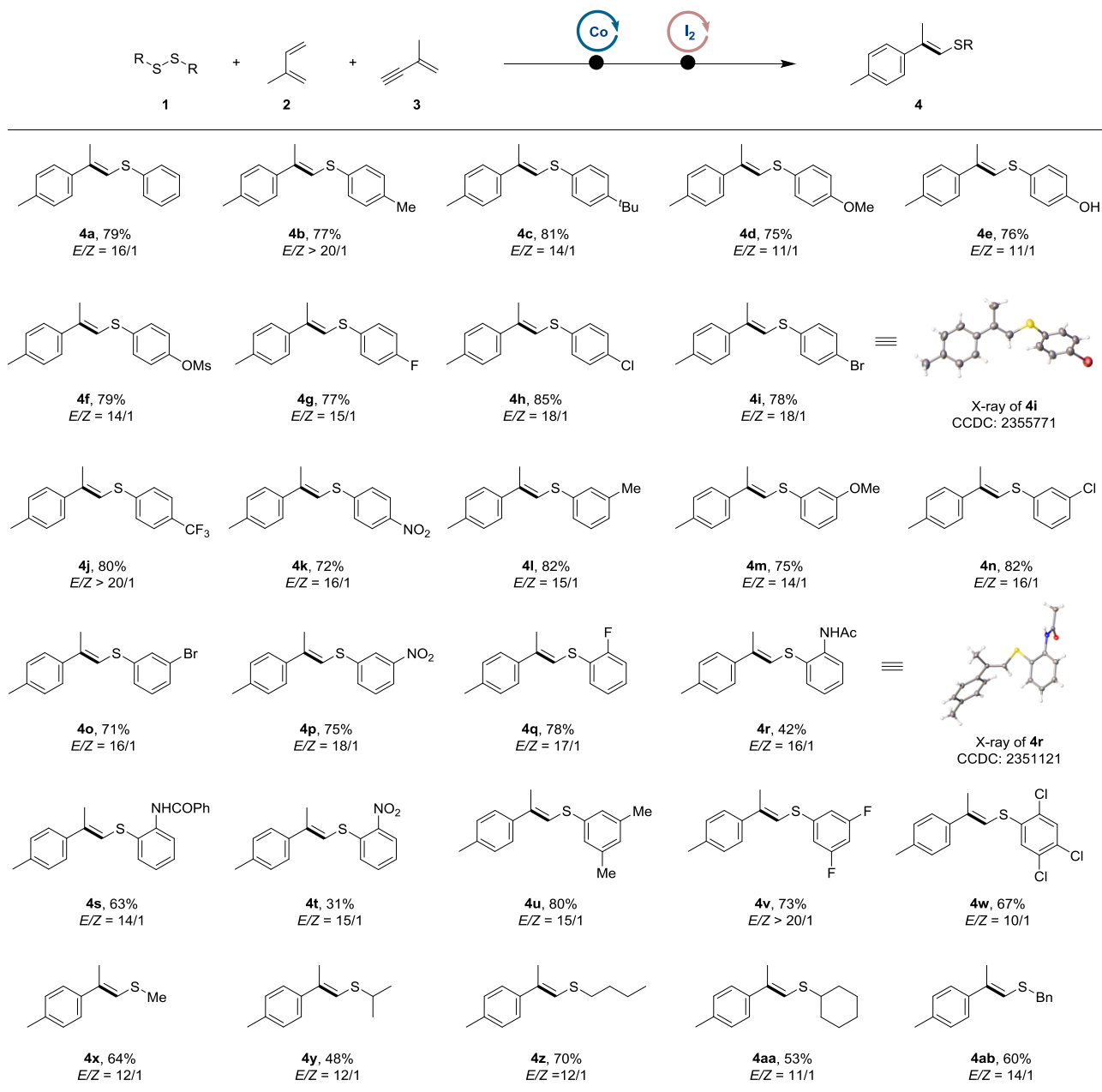


Figure 2. Substrate scope of disulfide ethers. Reaction condition: Step I: **2** (0.40 mmol), **3** (0.40 mmol), CoBr₂ (0.01 mmol), dppe (0.01 mmol), Zn (0.04 mmol), ZnI₂ (0.04 mmol), 1,4-dioxane (0.5 mL), 60 °C, 3 h; Step II: **1** (0.10 mmol), I₂ (0.08 mmol), BQ-1 (0.60 mmol), THF (0.5 mL), 100 °C, 12 h; E/Z of products were determined by ¹H NMR, and the yields of E isomer were given.

Limonene is an important naturally occurring monoterpene that is abundant in citrus peels. Using limonene instead of isoprene and alkyne for the reaction with sulfide ethers, the substrate compatibility of sulfide ethers with different substituents was investigated (Figure 3a). Different substituents, including *tert*-butyl, halogen, methoxyl, nitro, and methanesulfonic acid, were involved in the reaction with good yields. In addition, di-substituted 3,5-dimethyl phenyl sulfide and alkyl sulfide (**4u**, **4z**) also showed good compatibility under the reaction conditions.

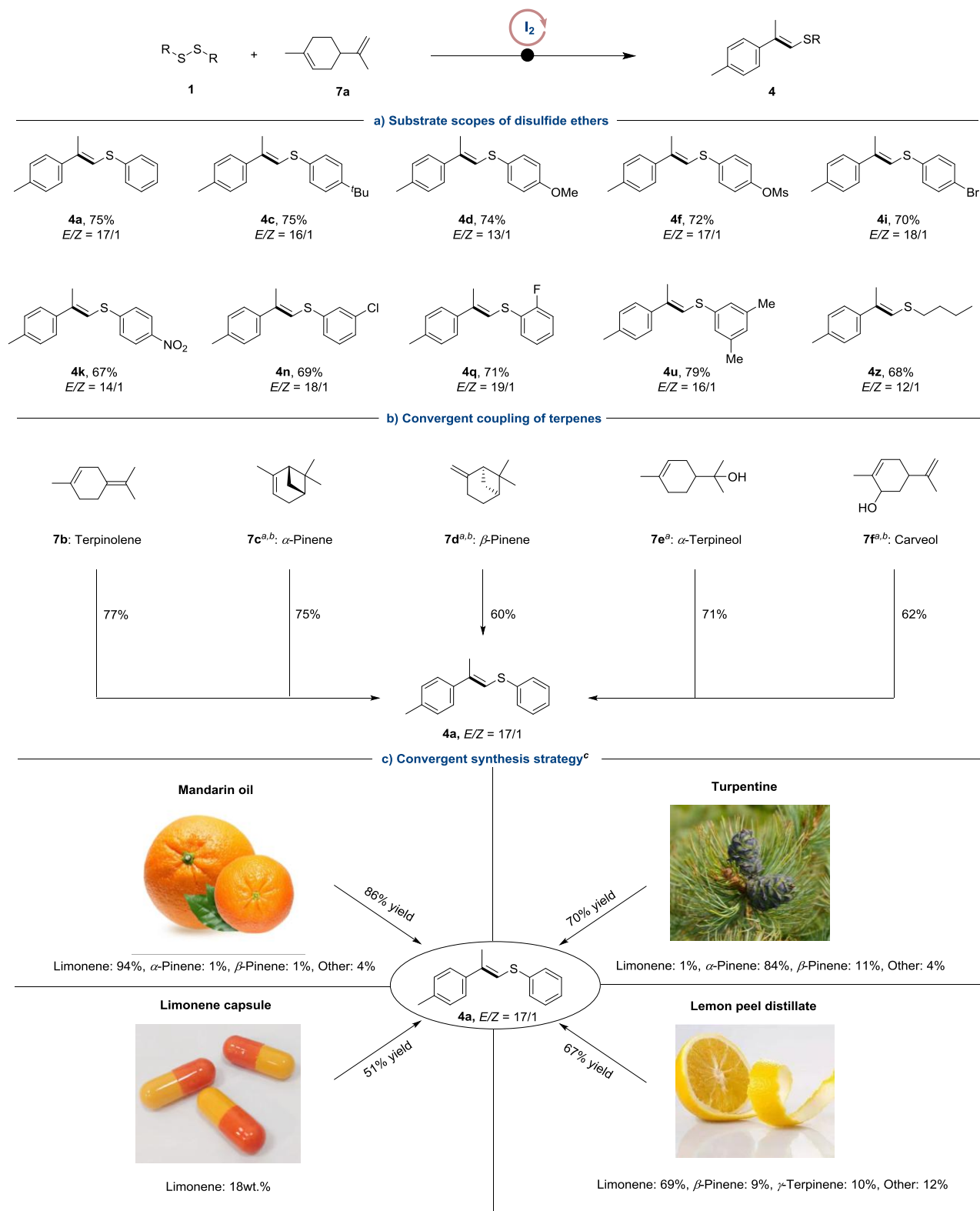


Figure 3. Substrate scope of terpenes. Reaction condition: **1** (0.10 mmol), **7** (0.30 mmol), I_2 (0.04 mmol), BQ-1 (0.60 mmol), THF (1.0 mL), 100 °C, 18 h. *E/Z* of products were determined by 1H NMR, and the yields of *E* isomer were given. ^a**7** (0.40 mmol), BQ-1 (0.80 mmol); ^b I_2 (0.08 mmol); ^cThe proportion of each component was determined by the analysis of GC-FID.

In addition to limonene, various other natural terpenes^[16] with diverse oxidation states are capable of producing product **4a** (Figure 3b). Being derived from the essential oil of cypress plants, terpinolene could be converted into the target product **4a** with a yield of 77%. α -Pinene and β -pinene, which are mainly derived from the resin secretion of pine plants, could also undergo coupling with disulfides with good efficiency. α -Terpineol is an oxygen-containing terpene that is industrially produced from turpentine and is widely used in the preparation of food flavors. It was also capable of producing sulfur-containing terpene derivative **4a** in 71% yield. Carveol, a terpene with a different oxidation state from α -terpineol, generated an identical product **4a** with a yield of 62%. These results suggest that the convergent coupling strategy has the ability to unify the utilization of terpenes in different oxidation states, thereby circumventing the difficulties associated with the separation and purification of natural terpenes.

To further demonstrate the practicality of this protocol, a convergent synthetic strategy for constructing target product **4a** using mixture of terpenes derived from natural sources has been developed (Figure 3c). Mandarin oil is an important food additive extracted from the peel of citrus, which could be used directly to produce the target product **4a** in good yield (86%). Turpentine is an important industrial raw material, which is mainly extracted from the resin of the pinaceae. Using turpentine as a terpene source could give the target product in 70% yield. Being clinically used for the treatment of cholecystitis, dyspepsia, etc, limonene capsule could deliver product **4a** in moderate yield. The use of lemon peel distillate could achieve the synthesis of product **4a** with 67% yield (Please see Supplementary Figure S2 for details). These convergent synthetic strategies fully demonstrate that this protocol holds significant advantages in the efficient utilization of various oxidative states of terpene mixtures.

Given the distinct functionalities of substances with varying oxidation states, the ability to manipulate the oxidation state of the coupled product would significantly broaden the utility of this approach. Moreover, sulfoxide and sulfone compounds play an important role in natural molecules and serve as valuable building blocks in organic synthesis. Hence, the synthesis of sulfur-containing compounds in the various oxidation states has been attempted (Figures 4a, b). After careful evaluation of the reaction parameters, it was found that the sulfoxide product **8a** could be achieved by using *m*-CPBA as the oxidant and dichloromethane as the reaction solvent. Subsequently, the compatibility of reaction substrates for synthesizing sulfoxide compounds was investigated. Aryl sulfides containing both an electron-withdrawing group (-Cl) and an electron-donating group (-OMe) could be efficiently converted to sulfoxides with good yields (**8b**, **8c**). The structure of **8b** was confirmed by single-crystal X-ray crystallography (CCDC: 2445323)^[15]. Strong electron-withdrawing group (-NO₂) at the *meta* position of phenyl ring was also suitable (**8d**). Aryl sulfoxide bearing fluorine was synthesized with 76% yield by slightly increasing the amount of oxidant (**8e**). On the other hand, when using oxone as the oxidant and ethanol as the reaction solvent, the sulfide compound **4a** could be oxidized to sulfone product **9a**. The substrate tolerance investigation showed that sulfides with either electron-donating or electron-withdrawing substituents on the phenyl ring were effective partners, resulting in the formation of corresponding products **9b-9e** in 61-74% yields. The configuration of **9a** was unambiguously determined by single-crystal X-ray crystallography (CCDC: 2337996)^[15].

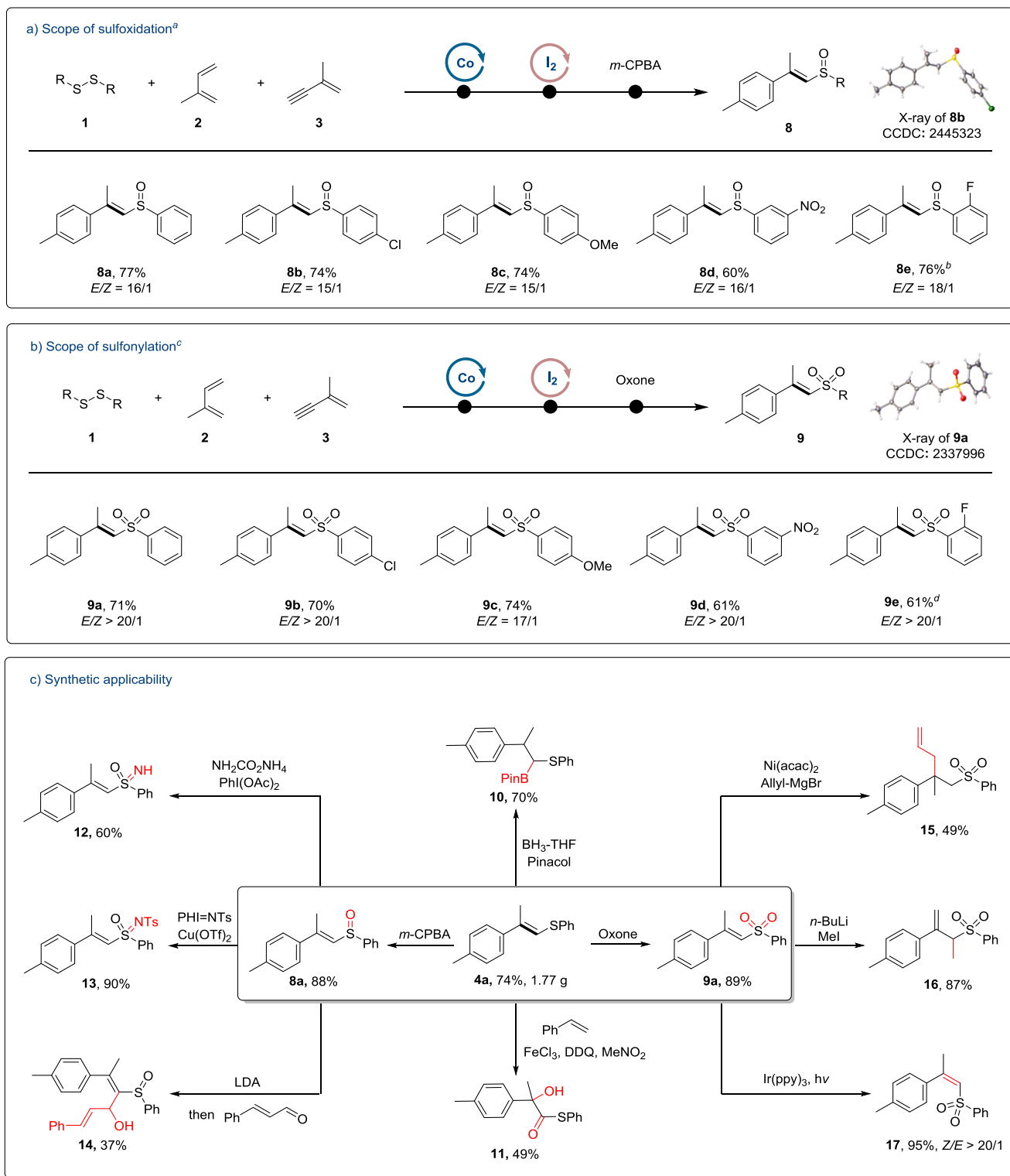


Figure 4. Synthesis of sulfoxides, sulfones, and transformations. Reaction condition: Step I: **2** (0.40 mmol), **3** (0.40 mmol), CoBr₂ (0.01 mmol), dppe (0.01 mmol), Zn (0.04 mmol), ZnI₂ (0.04 mmol), 1,4-dioxane (0.5 mL), 60 °C, 3 h; Step II: **1** (0.10 mmol), I₂ (0.08 mmol), BQ-1 (0.60 mmol), THF (0.5 mL), 100 °C, 12 h; The ratio (*E/Z*) of products were determined by ¹H NMR, and the yields of *E* isomer were given. ^aStep III: *m*-CPBA (0.24 mmol), DCM (1.5 mL), 0 °C, 30 mins; ^b*m*-CPBA (0.28 mmol); ^cStep III: Oxone (0.60 mmol), EtOH (1.5 mL), 70 °C, 12 h; ^dOxone (1.00 mmol).

To further demonstrate the synthetic applicability of this divergent protocol, a gram-scale (5.0 mmol) reaction of phenyl disulfide and limonene was performed (Figure 4c). Under standard conditions, product **4a** was obtained in 74% yield (1.77 g) smoothly. Subsequently, further synthetic transformations of **4a** were carried out. The vinyl group of **4a** could undergo hydroboration to give compound **10** (70% yield)^[14g]. In addition, in the presence of styrene, FeCl₃, DDQ, and MeNO₂, the vinyl group of **4a** could undergo oxidation to furnish thioester **11**. Oxidative amidation of sulfoxide **8a** with hypervalent iodine reagents could afford sulfoximine **12**^[17] or **13**^[18], which are also universal structural motifs in bioactive molecules and drugs. The deprotonation of sulfoxide **8a** with LDA for the subsequent nucleophilic addition onto *trans*-cinnamaldehyde gave highly functionalized olefin **14**^[19]. Furthermore, the nickel-catalyzed hydroallylation of compound **9a** was successfully conducted, delivering the desired sulfone **15** in 49% yield^[20]. The deprotonation of alkenyl sulfone **9a** with *n*-butyllithium and a subsequent alkylation with methyl iodide resulted in the formation of methyl-substituted allylic sulfone **16** with a yield of 87%^[21]. In the presence of Ir(ppy)₃ and blue LEDs, the stereo configuration of **9a** motif could undergo flipping to furnish product **17** with 95% yield (*Z/E* > 20/1) through a photochemical *E/Z* isomerization process^[22].

Mechanistic Studies

To gain insights into the reaction mechanism, some preliminary mechanistic experiments have been performed. Firstly, radical quenchers were added to the reaction system to verify the presence of free radicals during the reaction process. BHT (2,6-di-*tert*-butyl-4-methyl-phenol) did not have a significant inhibitory effect on the reaction. But when TEMPO (2,2,6,6-tetramethyl-piperidine-*N*-oxyl) was used as a free radical quencher, no desired product **4a** was detected. Additionally, the product of TEMPO binding to phenyl sulfur radical was detected by HRMS (SI, Figure S4). These results indicate that a radical pathway might be involved in the reaction (Figure 5a). To demonstrate the involvement of a three-member thiaranium ion intermediate in the reaction process, another component of nucleophile reagent was added to the standard reaction system of sulfide and terpene (Figure 5b). The three-component reaction product **19a** was obtained in 47% yield using methanol as the nucleophile reagent. Subsequently, using styrene instead of isoprene **2** and 2-methyl-1-buten-3-yne **3**, corresponding products (**19b** and **19c**) of the three-component reaction were obtained, respectively. When an equivalent amount of iodine was added to the reaction of **1a** and **22**, the molecular weight of thiiranium ion intermediate was observed by HRMS (SI, Figure S4). These results suggest the presence of three-membered thiiranium ion intermediate in the reaction process^[23].

The kinetic profiles for the second step of the reaction under standard conditions were obtained through GC monitoring. As depicted in Figure 5c, a rapid accumulation of **22** was observed in the initial period (ca. 5 min), followed by a gradual decay in the rest of the reaction. On the other hand, the process accompanied a slower but steady growth in the amount of the oxidative coupling product **4a**. These results indicate that the compound **22** may serve as a crucial intermediate for the coupling reaction. In addition, the kinetic studies also showed that *Z*-type product **4a'** was formed in the early stage of the reaction and remained a stable yield. The production of another side-product **5a** exhibited a rising trend during the initial period, followed by a gradual decrease until it reached near depletion. It suggests that the side-product **5a** might be converted to the target product **4a** through a process of olefinic isomerization. To gain more details of the transformations, several control experiments were

conducted. When the temperature of the second step was decreased to 60 °C, 48% yield of product **4a** and 23% yield of side-product **5a** were obtained. Subsequently, when the reaction temperature was raised to 100 °C and the reaction was allowed to proceed for 6 hours, the yield of product **4a** increased to 73% with only 3% yield of side-product **5a** remaining. The control conversion experiment of **5a** in the presence of iodine further supported that side-product **5a** could be converted into desired product **4a** during the reaction (Figure 5d).

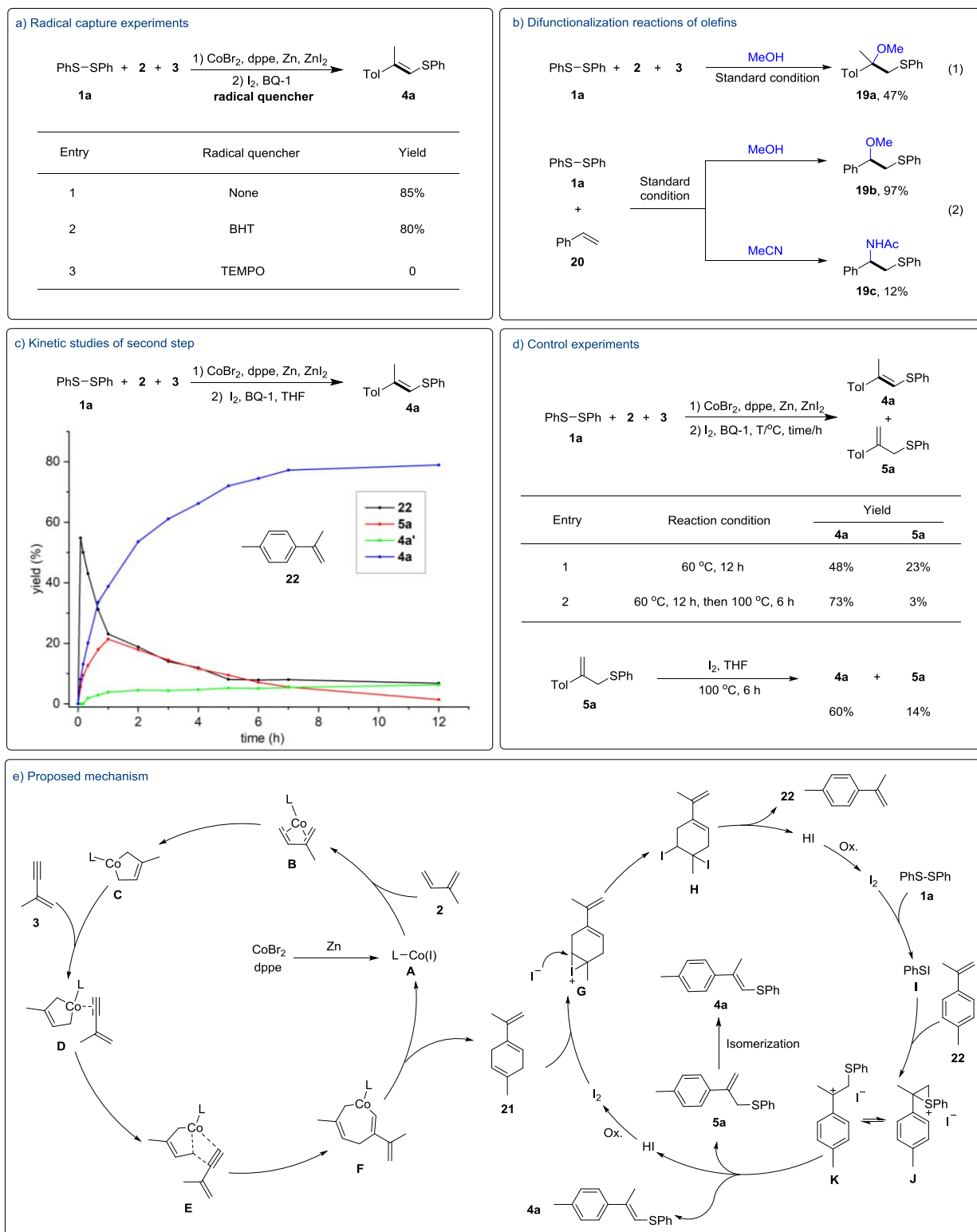


Figure 5. Mechanistic studies and proposed mechanism

Based on these results and previous reports, a possible reaction pathway is shown in Figure 5e. Firstly, in the presence of zinc powder, Co (II) is reduced to give Co (I) species **A**^[24], which then coordinates with one molecule isoprene **2** to generate the complex **B**. Subsequently, Co complex **B** undergoes oxidative cyclometallation to give a five-membered cobalt cycle **C**. Through the coordination with enyne **3**, complex **D** proceeds with a migratory insertion to furnish a seven-membered cobalt cycle **F** via the transition state **E**. With the formation of a new C-C bond, reductive elimination of Co (III) complex **F** yields the terpene **21** and active Co (I) species **A**. Subsequently, iodonium species **G** is initially obtained from terpene **21** with the help of I₂. Through a nucleophilic attack by iodide, vicinal diiodide intermediate **H** is generated, which gives the aromatized terpene **22** smoothly by elimination of HI. Then HI undergoes oxidation to regenerate I₂, which subsequently reacts with disulfide **1** to yield PhSI via radical coupling. Finally, sulfonium ion intermediate **J** is generated by the reaction of aromatized terpene **22** and PhSI. The desired product **4a** is formed through the isomerization of intermediate **J** to intermediate **K**, followed by the elimination of HI. Additionally, the desired product **4a** can also be obtained via the isomerization of side-product **5a**.

Conclusions

In conclusion, a convergent coupling of terpenes with various oxidation states and disulfide has been developed under the cobalt/iodine catalysis. The method exhibits a notable substrate scope with tolerance towards sulfides of various functional groups, providing plentiful sulfide derivatives. The efficient conversion of naturally abundant terpene mixtures is achieved by the convergence of their oxidation states. Additionally, sulfur-containing compounds with varying oxidation states can be obtained through the divergent synthesis strategies. Meanwhile, mechanistic studies suggest that the reaction involves a three-membered cycle thiiranium ion intermediate. It is expected that this protocol may be of broad interest in chemistry community pursuing the transformation of terpenes and constitutes a practical alternative to the synthesis of natural products and pharmaceuticals.

Acknowledgements

Financial support from the National Natural Science Foundation of China (22071239 and 22371275) is acknowledged.

Supporting Information

The Supporting Information is available from the Wiley Online Library or from the author.

Experimental procedures, characterization data, and NMR spectra (PDF).

Notes

The authors declare no competing financial interest.

Keywords

Cascade Catalysis • Terpenes • Oxidative Thiolation • Aromatization • Organosulfur Compound

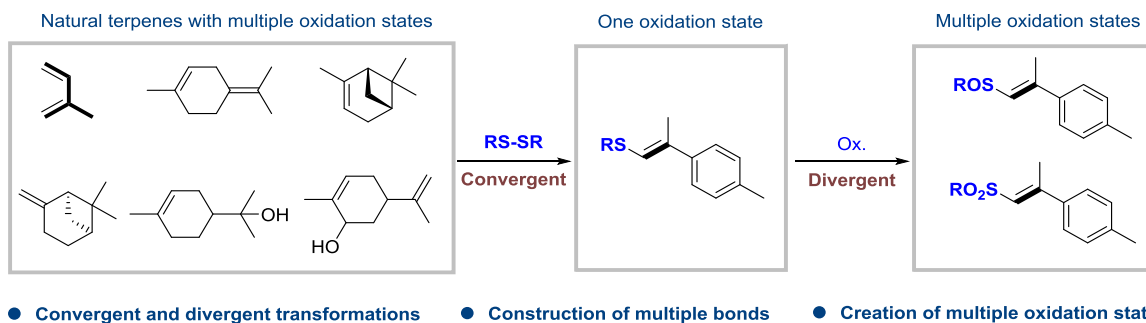
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TOC



A convergent and divergent strategy has been developed for the construction of sulfur-containing terpenoid derivatives using various terpenes with different oxidation states. It is expected that this protocol may be of broad interest in chemistry community pursuing the transformation of terpenes and constitutes a practical alternative to the synthesis of natural products and pharmaceuticals.