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Cobalt-catalyzed hydrothiolation of alkynes for the diverse synthesis of branched alkenyl sulfides

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Alkenyl sulfides have gained increasing prominence in medicinal chemistry and materials. Hydrothiolation of alkynes for the diverse synthesis of alkenyl sulfides is an appealing method. Herein, we report a cobalt-catalyzed Markovnikov hydromethylthiolation of alkynes to afford branched alkenyl methylsulfanes with good yields and high regioselectivity. This method also enables the diverse synthesis of branched alkenyl sulfides. The reaction shows good functional group tolerance and could be scaled up. The mechanistic studies including control experiments, deuterium-labeling experiments, and Hammett plot indicated alkynes insertion followed by electrophilic thiolation pathway.

Alkenyl sulfides have important applications in antibiotic drugs, analytical detection, and functional materials (Fig. 1A), driving continuous developments in synthetic methods for their preparation[1–5]. The use of readily available and cost-effective alkynes as starting materials for hydrothiolation represents an appealing method (Fig. 1B)[6–10]. It should be noted that the synthetic methods for branched configuration products are still limited. Representative examples include transition metal-catalysis, such as Pd[11–15], Rh[16–20], Th[21,22], Zr[23], Ni[24–27], and photocatalysis[28], using thiols or thiophenols as raw materials. Although the methylthio group is recognized for its utility in modifying drug properties by enhancing solubility and altering metabolic pathways[4,29,30], the hydromethylthiolation of alkynes with methanethiol is rarely explored[31–33], due to the high toxicity, low boiling point (279 K at 1 atm), repugnant odor, and strong coordination with transition metal catalysts (as an example, the bond energy of Pd–SMe (92–99 kcal/mol) is much higher than that of C_{Ar}–SMe (82–85 kcal/mol), making the reduction elimination process difficult)[34]. Furthermore, hydrothiolation reactions are significantly influenced by the groups of alkynes and sulfur sources[14], and there is still no protocol applicable to four types of hydrothiolation (reactions between alkyl, aryl alkynes and alkyl, aryl sulfur sources), so the development of more versatile protocols for the diversity hydrothiolation of alkynes remains desirable.

While significant progress has been made in developing masked sulfurizing reagents for the green synthesis of sulfur-containing compounds[31,35–39], to the best of our knowledge, metal-catalyzed regioselective hydrothiolation of alkynes with masked sulfurization reagents has not been reported. The intrinsic challenge of regioselective hydrothiolation involves addressing the issues of chemoselectivity (the masked sulfurizing reagents could be reduced to deliver side products, such as thiols and disulfides), regioselectivity (branched versus linear alkenyl sulfides), and potential metal poisoning[40,41]. Here, we report a cobalt-catalyzed Markovnikov hydromethylthiolation of alkynes with masked sulfurizing reagents, which also enables diverse reactions between alkyl, aryl alkynes and alkyl, aryl sulfur sources (Fig. 1C).

Results

Reaction optimization

The investigation was initiated by examining the hydromethylthiolation of 1-ethynyl-4-methoxybenzene (**1a**) with sulfur electrophile (**2a**). After screening various masked sulfurizing reagents, it was observed that using **L1** as the ligand, OMTS (1,1,1,3,5,7,7,7-octamethyltetrasiloxane) as the silane, and lithium methoxide as the base, **3a** could be obtained with excellent yield (90%) and excellent regioselectivity (*b*/*l* = 97/3) (Table 1, entry 1). However, with phthalimide, methanethio, or methanesulfonyl masked sulfurizing reagents, the reactions afforded **3a** in 5–15% yields (entries 2–4), demonstrating the substantial influence of the masks. Employing **L2** and **L3** as ligands although the yields were reduced, products are predominantly afforded in the

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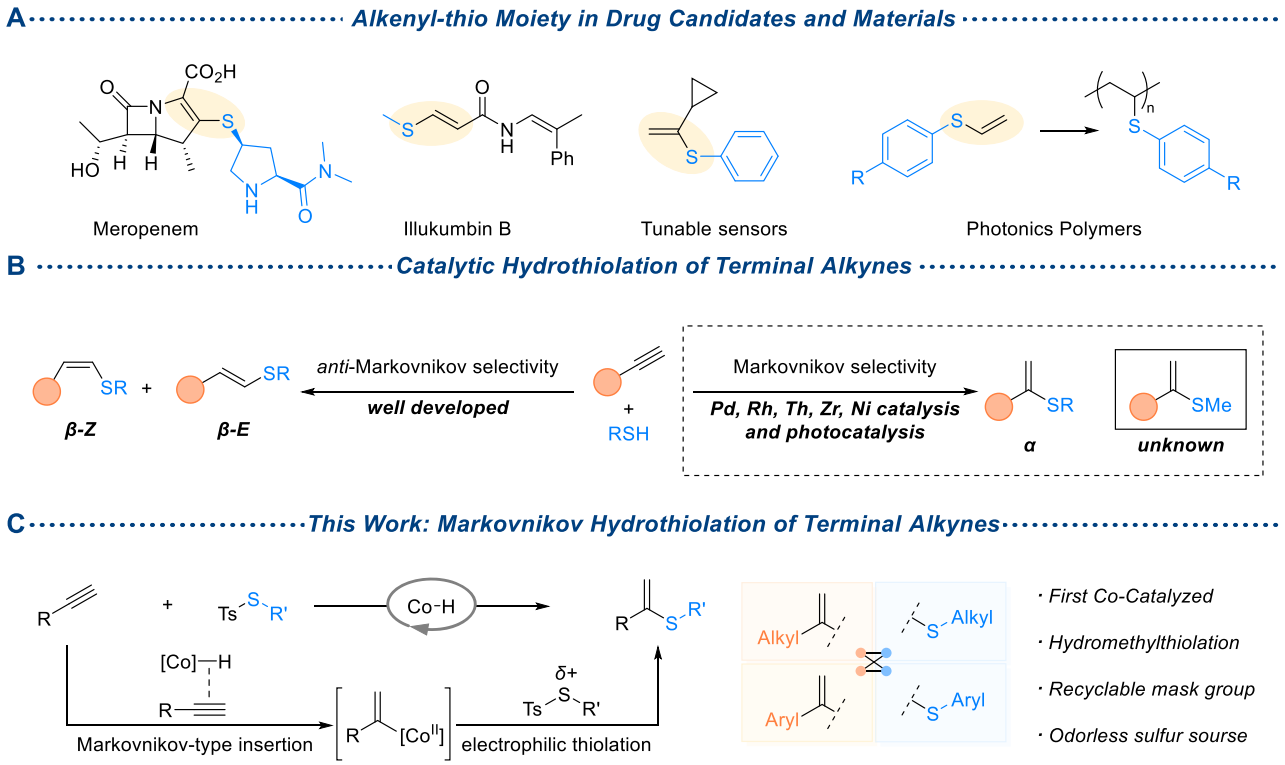
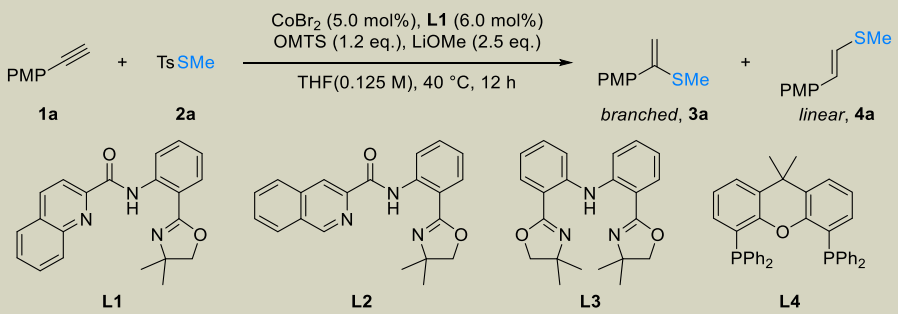


Fig. 1 | Introductions to methylthio moiety and hydromethylthiolation. A Alkenyl-thio moiety in drug candidates and materials. **B** Catalytic hydrothiolation of terminal alkynes. **C** This work: Markovnikov hydrothiolation of terminal alkynes.

Table 1 | Optimization of reaction conditions and control experiments.[a]



Entry	Variation	Yield of 3a (%)[b]	b/l [b]
1	None	90	97/3
2[c]	PhthN-SMe instead of TsSMe	5	–
3[c]	MeSSMe instead of TsSMe	5	–
4[c]	MsSMe instead of TsSMe	15	94/6
5	**L2** instead of **L1**	58	99/1
6	**L3** instead of **L1**	16	84/16
7	**L4** instead of **L1**	0	–
8	Ph_2SiH_2 instead of OMTS	86	96/4
9	$PhSiH_3$ instead of OMTS	29	96/4
10	TMDSO instead of OMTS	67	96/4
11	NaOMe instead of LiOMe	4	–
12	LiO*t*Bu instead of LiOMe	14	86/14
13	CsF instead of LiOMe	9	–
14[c]	45 °C	91	96/4

[a]In glove box, **1a** (0.50 mmol), **2a** (0.25 mmol), $CoBr_2$ (5 mol%), **L1** (6 mol%), OMTS (1,1,1,3,5,7,7,7-octamethyltetrasiloxane, 1.2 eq.), LiOMe (2.5 eq.), THF (2.0 mL), 40 °C for 12 h.
[b]Determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard.
[c]**L1**•CoBr (5 mol%) was used instead of $CoBr_2$ and **L1**.

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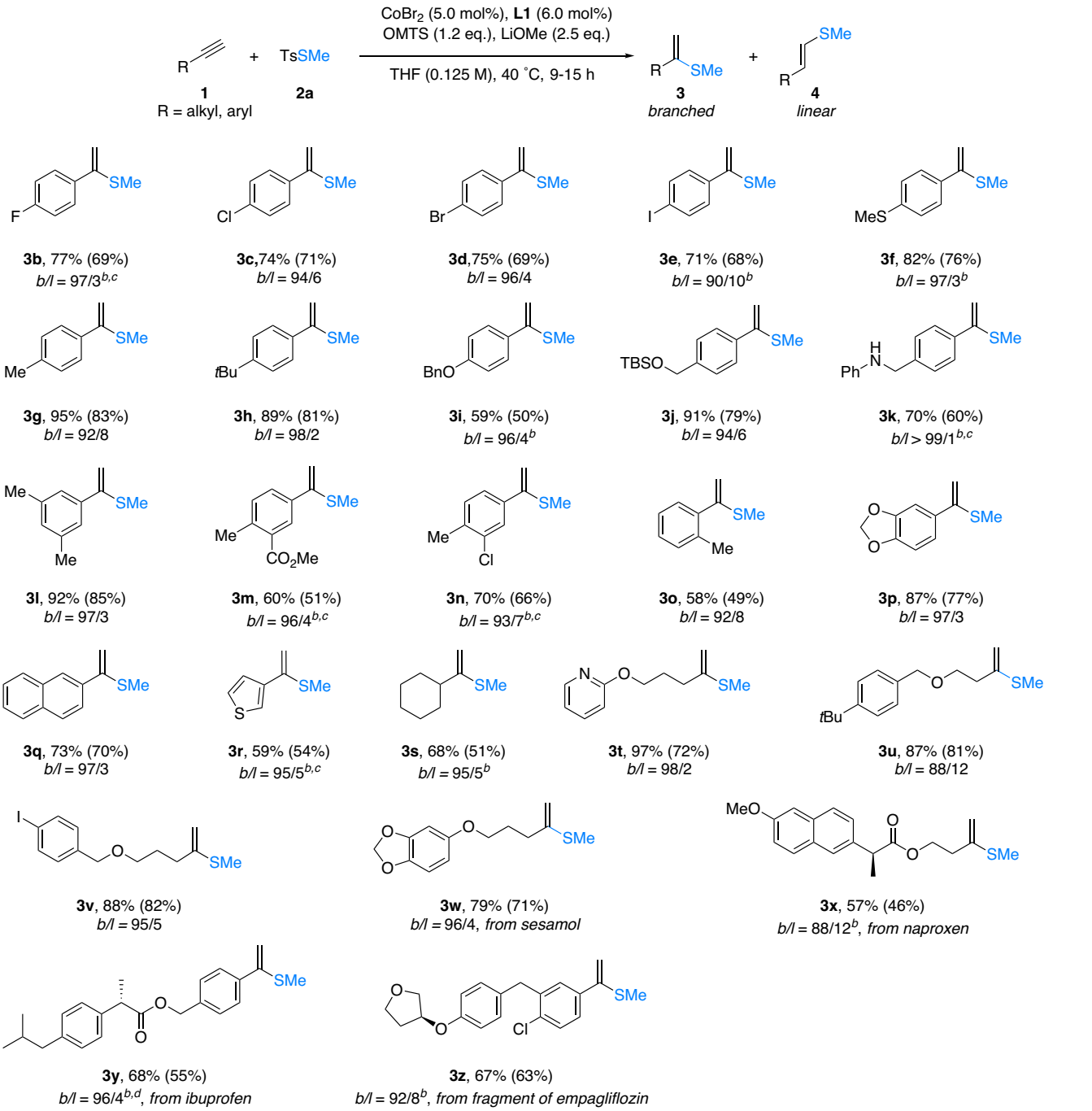

Fig. 2 | Substrate scope for branched alkenyl methylsulfane.[a] [a]**1** (0.50 mmol), **2** (0.25 mmol), $CoBr_2$ (5 mol%), **L1** (6 mol%), OMTS (1.2 eq.), LiOMe (2.5 eq.), THF (2.0 mL), 40 °C for 12 h, yields were determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane or 1,3,5-trimethoxybenzene as an internal standard, isolated yields are shown in parentheses. [b]**L1**•CoBr (5 mol%) instead of $CoBr_2$ and **L1**. [c]At 45 °C. [d]At 35 °C.

branched configuration; however, the bisphosphine ligand **L4** did not facilitate this reaction (entries 5–7). Other bases such as sodium methoxide, lithium *tert*-butoxide or CsF significantly reduced the yield of **3a** (entries 11–13). Finally, the pre-catalyst complex was used instead of the in situ catalyst to control the reaction, and the similar yield and selectivity of **3a** were obtained (entry 14).

Substrate scope

After optimizing the reaction conditions, a series of alkynes as substrates were investigated (Fig. 2). Due to the instability of branched alkenyl sulfides in air, all separation steps were carried out in a nitrogen atmosphere whenever possible. The electron-donating and electron-withdrawing groups on the phenyl ring were tolerated to afford **3b**-**3k** in 50–83% yields with 90/10– > 99/1 *b*/*l*. Particularly, Csp^2–Br (**3d**), Csp^2–I (**3e**) and phenylamino (**3k**) were well compatible, providing more chances for further molecule cross-linkage. *Meta*-substituted and *ortho*-substituted alkynes **1l**–**1o** could also participate in the reaction to afford **3l**–**3o** in 49–85% yields with 92/8–97/3 *b*/*l*. The alkynes containing a polycyclic ring or heterocycle, such as piperonyl (**1p**), 2-naphthyl (**1q**), and 3-thienyl (**1r**), could be converted to the corresponding products **3p**–**3r** in 54–77% yields with 95/5–97/3 *b*/*l*. Notably, aliphatic alkynes were also applicable to the reaction. Ethynylcyclohexane (**1 s**) could participate to deliver the hydromethylthiolation product **3 s** in 51% yield with 95/5 *b*/*l*. The linear aliphatic alkynes

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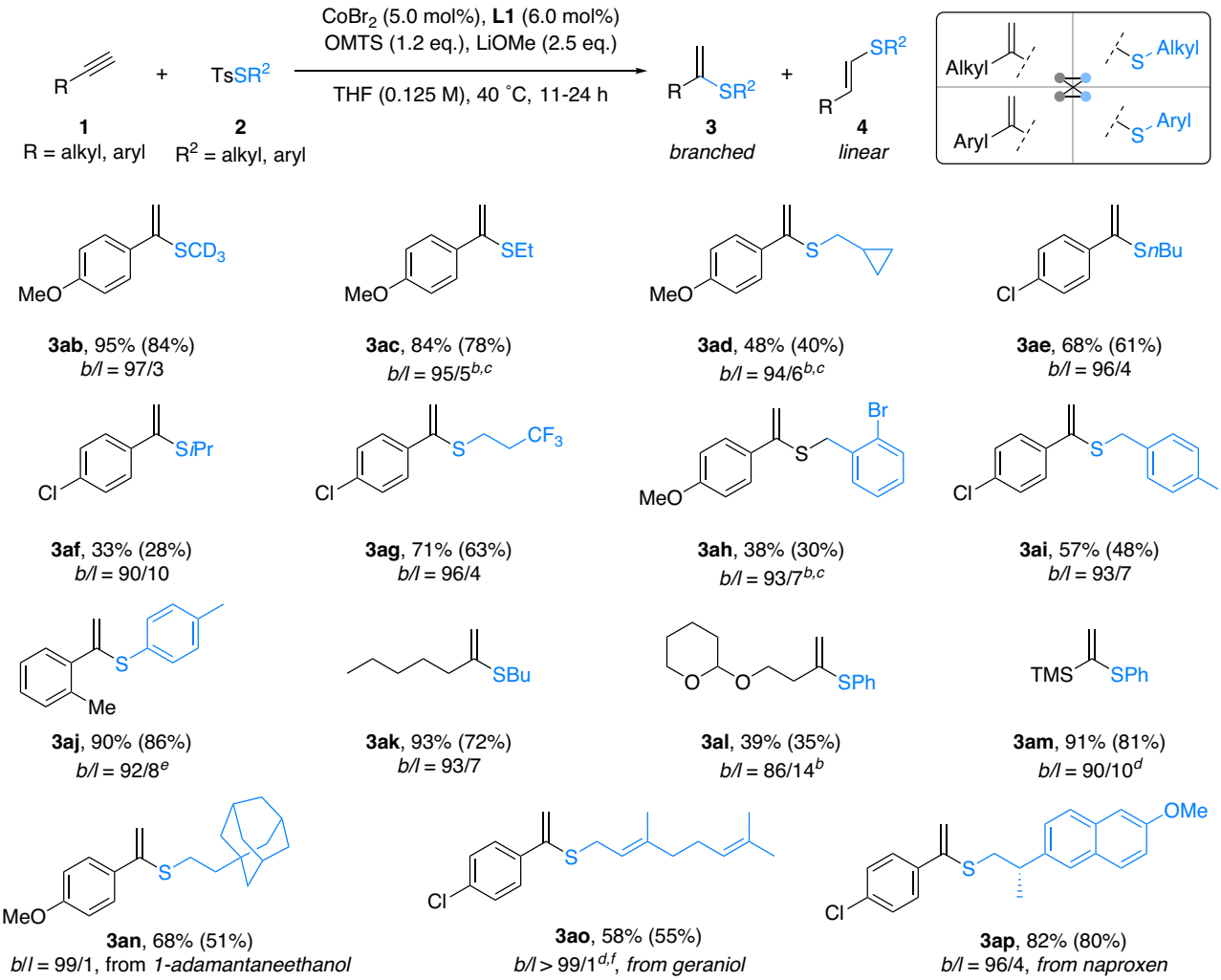

Fig. 3 | Substrate scope for branched alkenyl sulfides.[a] [a]**1** (0.50 mmol), **2** (0.25 mmol), $CoBr_2$ (5 mol%), **L1** (6 mol%), OMTS (1.2 eq.), LiOMe (2.5 eq.), THF (2.0 mL), 40 °C for 12 h, yields were determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane or 1,3,5-trimethoxybenzene as an internal standard, isolated yields are shown in parentheses. [b]**L1**•CoBr (5 mol%) was used instead of $CoBr_2$ and **L1**. [c]At 45 °C. [d]At room temperature. [e]59 h. [f]Ph_2SiH_2 instead of OMTS.

(**1t**–**1v**) could be reacted to afford **3t**–**3v** in 72–82% yields with 88/12–98/2 *b*/*l*. Additionally, alkynes that incorporate bioactive molecules, such as sesamol (**1w**), naproxen (**1x**), ibuprofen (**1y**), and the fragment of empagliflozin (**1z**), could be employed to deliver the corresponding products **3w**-**3z** in 46–71% yields with 88/12–96/4 *b*/*l*, further demonstrating the utilities of the approach.

Inspired by the effectiveness of thiol-ene and thiol-yne reactions in connecting two molecular structures through the robust creation of carbon-sulfur bonds[42–47], the diverse synthesis based on this protocol has been conducted (Fig. 3). The sulfur source available for this protocol can be easily obtained from alcohols, halides, and disulfides. Aryl alkynes could undergo hydrothiolation with aliphatic sulfurizing reagents such as deuterated methyl (**2ab**), ethyl (**2ac**), cyclopropylmethyl (**2ad**), butyl (**2ae**), isopropyl (**2af**), and trifluoropropyl (**2ag**), obtaining the corresponding products (**3ab**–**3af**) in 28–84% yields with 90/10–97/3 *b*/*l*. Sulfurizing reagents bearing substituted benzyl groups (**2ah, 2ai**), could also be transformed into the desired products (**3ah, 3ai**). To our delight, the reaction between **1aj** and **2aj** resulted in **3aj** in 86% yield and 92/8 *b*/*l*, proving the suitability of aryl alkynes with aryl sulfurizing reagents. The reaction between alkyl alkynes and alkyl or aryl sulfurizing reagents is also suitable to obtain the corresponding products (**3ak**–**3am**) in 35–81% yields with 86/14–93/7 *b*/*l*. Masked sulfurizing reagents derived from 1-adamantaneethanol (**2an**), geraniol (**2ao**), and naproxen (**2ap**), successfully reacted with alkynes to obtain **3an**–**3ap** in 51–80% yields with 96/4– > 99/1 *b*/*l*, confirming the universality of diverse synthesis.

Gram-scale reaction and synthetic applications

The reaction could be smoothly conducted on a 10 mmol scale, yielding 1.34 grams of the methyl(1-phenylvinyl)sulfane **3aa** with an impressive 89% yield (Fig. 4a), facilitating subsequent derivatization with ease. The Ts- group utilzied in the reaction can be efficiently recovered in the form of lithium 4-methylbenzenesulfinate (**5**) and regenerated into the starting material (**2a**) through a two-step conversion. This capability showcases the remarkable recyclability and sustainability of the employed protocol. To showcase the utility of the branched alkenyl sulfides, further transformations of **3aa** were investigated (Fig. 4b). The product **3aa** could undergo nickel-catalyzed Kumada coupling with methylmagnesium bromide to obtain 1,1-dialkene (**6**) in 80% yield[18,48]. With copper catalysis, **3aa** could proceed hydroboronation to deliver compound **7** in 95% yield[49,50]. The double bond of **3aa** could be reduced with *p*-toluenesulfonyl hydrazide to obtain *α*-methylthioethylbenzene (**8**) in 90% yield[51]. The [2 + 1] cycloaddition reaction of difluorocarbene to **3aa** could give difluorocyclopropane (**9**) in 87% yield[52]. Additionally, given that selenium belongs to the same chalcogen family as sulfur and has a similar

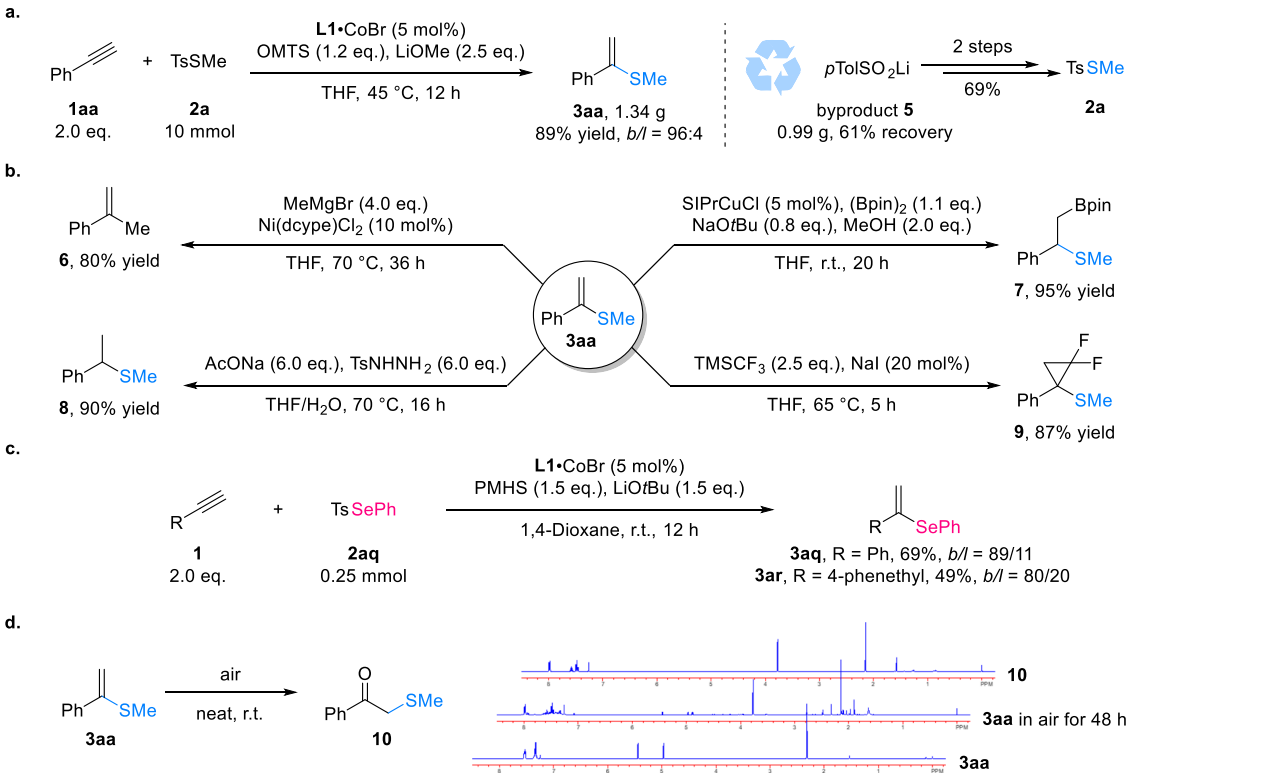

Fig. 4 | Gram-scale reaction and synthetic applications. a Gram-scale reaction and recycling of byproduct. **b** Synthetic applications of the product. **c** Hydroselenation of alkynes. **d** Aerobic oxidation of the product in air.

electronegativity, Markovnikov hydroselenation of alkynes was likewise found to be a viable reaction pathway (Fig. 4c)[53].

Unlike linear alkenyl sulfides, branched alkenyl sulfides are highly sensitive to air (Fig. 4d). Exemplified by **3aa**, it could readily undergo oxidation in the presence of air, transforming into 2-(methylthio)-1-phenylethan-1-one (**10**). This reactivity explains why **3aa** can be easily stained with (2,4-dinitrophenyl)hydrazine on thin-layer chromatography plates. To our knowledge, this phenomenon has never been reported. However, upon scrutinizing the supporting information from prior works on the synthesis of branched alkenyl sulfides, traces of oxidized products can be observed in the ^{1}H NMR spectra. A possible mechanism involving radical addition has been proposed (see SI). The sensitivity of branched alkenyl sulfides to oxygen provides insights into the potential applications in ROS probes[54]. It should be emphasized that branched alkenyl sulfides are quite stable in a nitrogen-filled glove box, with no oxidation products observed after six months of storage.

Mechanistic investigation

To elucidate the reaction mechanism, a range of comparative experiments were undertaken. The addition of 2.0 equivalents of radical scavengers to the reaction system did not obstruct the course of the reaction (Fig. 5a). Introduction of deuterated phenylacetylene or deuterated diphenylsilane into the reaction elucidated the emergence of two identical deuterated ratio at the β-position of the product (Fig. 5b). To excluded the possibility of the possibility of the process that β-H elimination followed by branched alkenyl methylsulfanes inserting into Co–H pathway, **3aa** was added to the reaction with deuterated diphenylsilane, and no significant deuterium substitution was observed in the recovered **3aa**. To ruled out the possible H-D exchange between terminal alkynes and silanes, 1,2-diphenylacetylene was used as a raw material for the reaction, resulting in **11** in equivalent yield with $E/Z = 1/4$ (Fig. 5c). The observations suggest the conceivable occurrence of a Crabtree-Ojima isomerization process. When **L1**•CoOMe was used as catalyst, the targeted product was obtained in 84% yield. When lithium methoxide was removed, only trace of product was obtained (Fig. 5d). This means that in this system, despite being classified as a cobalt oxide species, the coordination between the toluenesulfonate anion and the central metal was relatively robust, making it impossible to regenerate cobalt hydride species from silane. The reaction exhibited an induction period before reaching maximum yield approximately after eight hours (see SI). An in-depth analysis of the influence of different substituents on phenylacetylene on the reaction kinetics facilitatedthe construction of a Hammett plot (Supplementary Data 1), which unveiled a positive slope. The observation implies that the turnover-limiting step is dominated by negative charge accumulation, providing valuable insights into the reaction mechanism (Fig. 5e).

Based on these mechanistic experiments and previous literatures[55–64], a possible reaction mechanism is proposed (Fig. 6). The initial steps involve cobalt bromide species undergoing ligand exchange with lithium methoxide to obtain cobalt hydride species **II** upon interaction with silane. Subsequent alkyne coordination is followed by cobalt hydride insertion, resulting in the formation of an alkenyl cobalt intermediate **IV**. This species further undergoes reaction with the masked sulfurizing reagent, proceeding through a five-membered ring pathway. Ultimately, the branched alkenyl sulfide and cobalt *p*-toluenesulfonate **V** are obtained[65]. Then **V** undergoes ligand exchange with lithium methoxide, initiating the subsequent catalytic cycle.

Discussion

In summary, a cobalt-catalyzed hydromethylthiolation reaction of alkynes have been developed, which also enables the diverse synthesis of branched alkenyl sulfides and exhibits remarkable regioselectivity and compatibility within a wide range of substrates, including alkenes, esters, amines, and aryl halides. This protocol provides an efficient route obtaining a series of alkenyl sulfides from readily available starting materials. Preliminary investigations into the reaction

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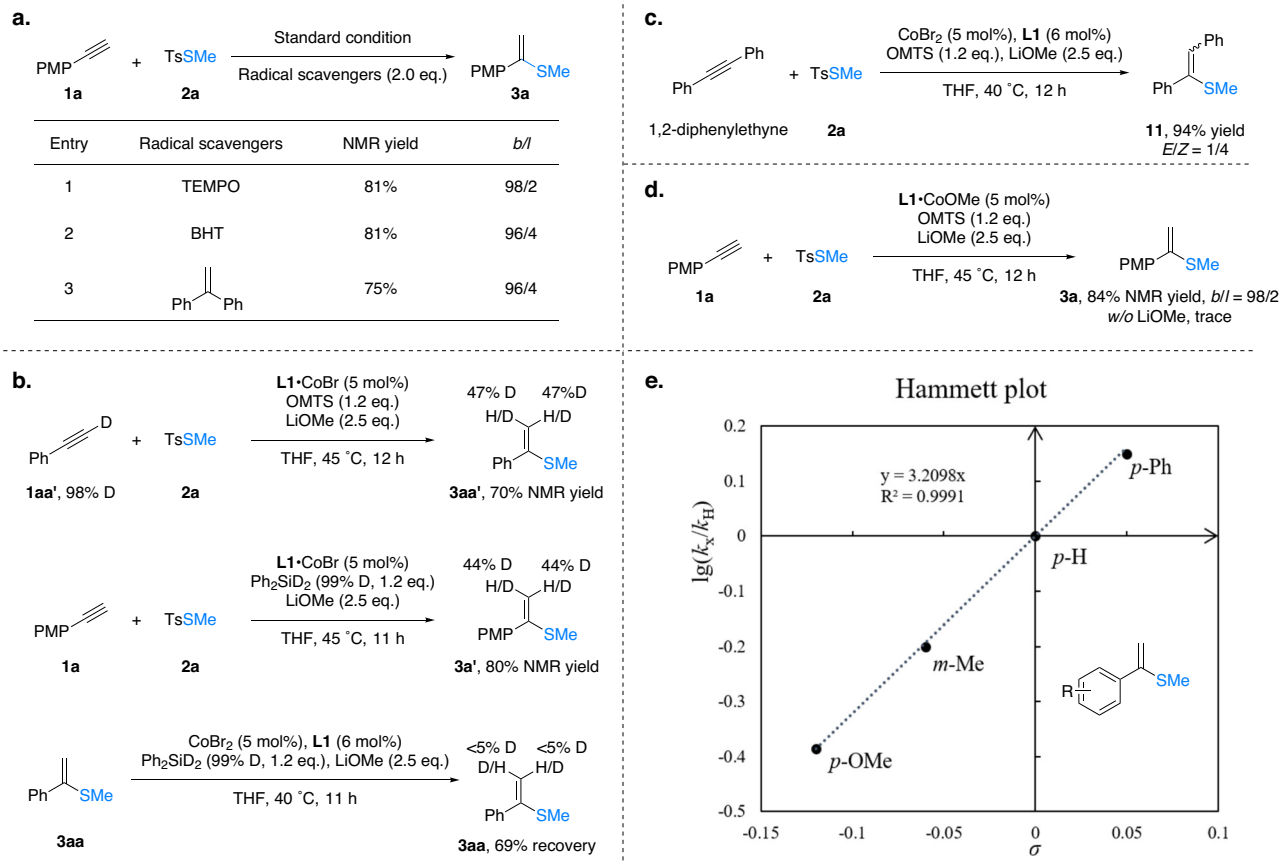

Fig. 5 | Mechanistic studies. a Radical trapping experiments. **b** Deuterium-labeling experiments. **c** Hydromethylthiolation of the internal alkyne. **d** Control experiments. **e** Hammett plot.

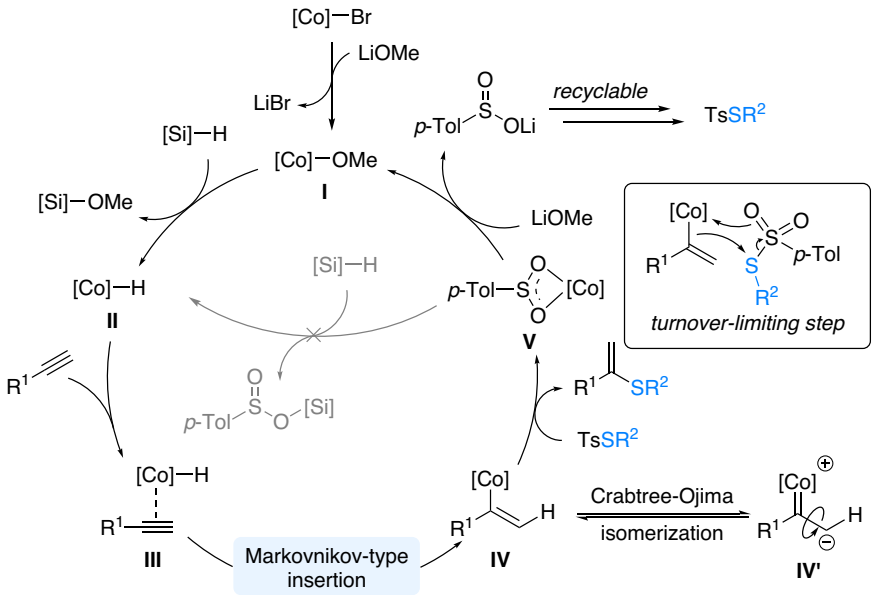

Fig. 6 | Proposed mechanism. Proposed reaction pathway starts from Co–OMe, then alkyne inserts into Co–H, followed by the reaction with the masked sulfurizing reagent.

mechanism provide evidence for alkyne insertion into cobalt hydrides, followed by reaction with the masked sulfurizing reagents. The studies on aerobic oxidation of alkenyl sulfides revealed blind spots in literatures. Further studies on the synthesis and applications of alkenyl sulfides are undergoing.

Methods

General procedure for the synthesis of branched alkenyl sulfides

In a nitrogen-filled glove box, a 10 mL vial equipped with a stir bar was charged with $CoBr_2$ (0.0125 mmol, 5 mol%), **L1** (0.015 mmol, 6 mol%), LiOMe (0.625 mmol, 2.5 eq.), and THF (2.0 mL). The mixture was

stirred for about 20 min to afford a golden solution. Then OMTS (1,1,1,3,5,7,7,7-octamethyltetrasiloxane, 1.2 eq., $\rho = 0.863$ g/mL), alkyne (0.50 mmol, 2.0 eq.), and $TsSR^2$ (0.25 mmol, 1.0 eq.) were added sequentially (dropwise if liquid). The vial was sealed, removed from the glove box, and stirred at 40 °C for 12 h. The reaction mixture was quenched by PE (20 mL), filtered through a short pad of silica, and eluted with ether or PE/EA (5/1). The combined filtrate was concentrated under reduced pressure at 40 °C and flushed with nitrogen gas, then purified by flash column chromatography to give the corresponding product (Caution: the flask must be flushed with nitrogen gas after concentration steps due to the instability of the product under the air).

Data availability

The authors declare that the data Supplementary the findings of this study are available within the paper and its Supplementary Information file. The experimental procedures and characterization of all new compounds are provided in the Supplementary Information. Data supporting the findings of this manuscript are also available from the authors upon request.

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Author contributions

Z.L. proposed this project. J.Y. and Y.T. performed the experiments. Z.L. and J.Y. prepared the manuscript. J.Y. and Y.T. prepared the Supplementary Information.

Competing interests

The authors declare no competing interests.

Additional information

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