A Silicon-Containing Thiol-Specific Bioconjugating Reagent

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ABSTRACT: A new bioconjugation reagent containing silicon has been developed for selective reaction with thiols. The inclusion of silicon significantly improves chemo-selectivity and suppresses retro processes, exceeding the capabilities of traditional reagents. The method is versatile, compatible with a broad range of thiols and unsaturated carbonyl compounds, yielding moderate to high results. These reactions can be conducted under biocompatible conditions, rendering them suitable for protein bioconjugation. The resulting conjugates display good stability in the presence of various biomolecules, suggesting their potential application for synthesizing antibody-drug conjugates. Furthermore, the presence of a silicon moiety within the conjugated products opens up new avenues for drug release and bridging inorganic with other disciplines. This new class of silicon-containing thiol-specific bioconjugation reagents has significant implications for researchers working in bioanalytical science and medicinal chemistry, leading to innovative opportunities for advancing the field of bioconjugation research medicinal chemistry.

Biotherapeutics that utilize a delivery system for targeted therapy have gained significant attention in recent years, with antibody-drug conjugates (ADCs) being a prime example for treating various cancers[1-5]. Cysteine[6,7] is the most commonly used amino acid for conjugation on the antibody due to its scarcity in nature[8,9]. Consequently, many thiol conjugation methods have been developed (**Figure 1A**)[10-15], with the maleimide-thiol click method[16,17] being the most widely used due to its high specificity for thiol groups and its patent-free status. To address the problems associated with retro-Michael[18-20] and ring-opening problems[21,22], our group has developed allenic amide-thiol and *β*-silyl

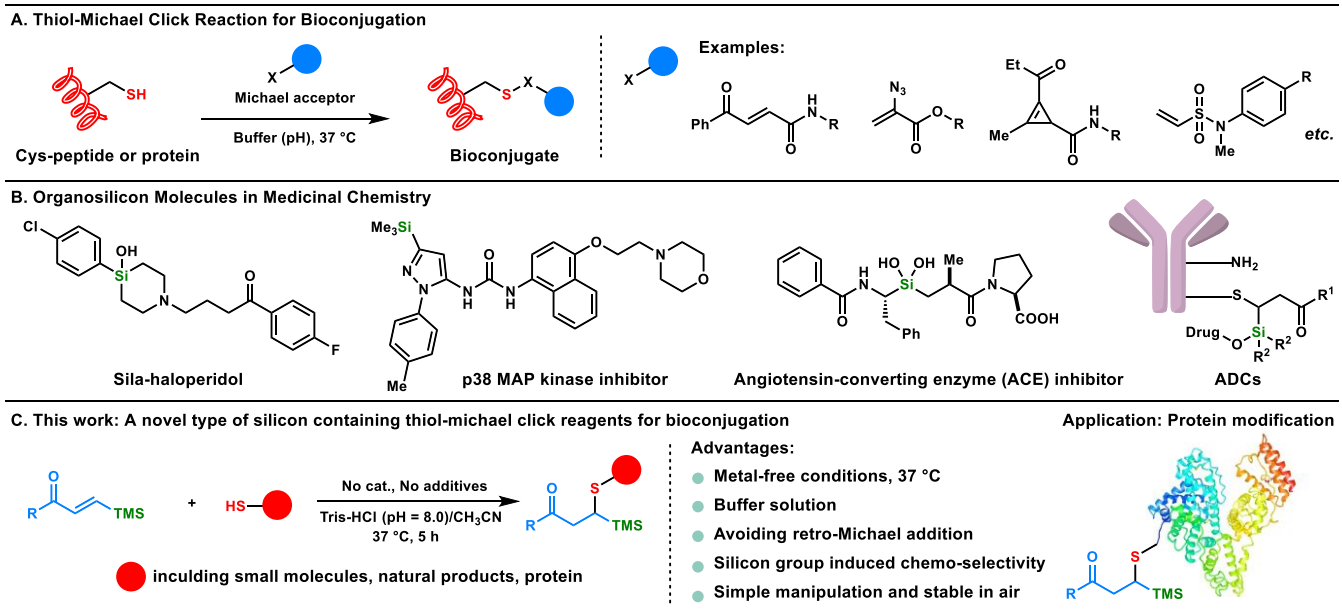
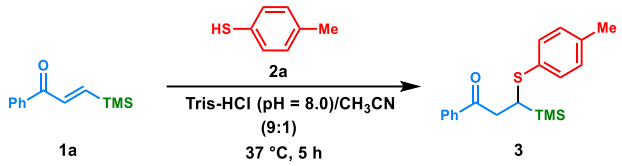


Figure 1. Background and reaction design. (A) Thiol-Michael click reaction for bioconjugation; (B) Organosilicon molecules in medicinal chemistry; (C) *This work*: *β*-silyl enones: a novel type of thiol-specific biocompatible click reagents.

Table 1. Optimization of reaction conditions



entry	solvent	pH value	Yield of **3** (%)
1	H_2O	7	65
2	PBS buffer	6	57[a]
3	PBS buffer	7	64[a]
4	PBS buffer	8	70[a]
5	Tris-HCl buffer	8	75
6	Tris-HCl/DCM	8	73[b]
7	Tris-HCl/EtOH	8	71[b]
8	Tris-HCl/DMSO	8	69[b]
9	Tris-HCl/DMF	8	67[b]
10	Tris-HCl/THF	8	63[b]
11	Tris-HCl/CH_3CN	8	80[b]
12	PBS/CH_3CN	8	70[b]

[a]PBS buffer: Phosphate buffer. [b]Buffer/Organic solvent = 9/1.

alkynone-thiol versions[23,24] that provides stable conjugation products. In our ongoing efforts to create new linkers with added handles such as silicon functionality for biotherapeutics, we explore the reactions of thiol with *β*-silyl unsaturated carbonyl compounds.

The labile silicon-oxygen bond, which can be easily cleaved under acidic or fluoride conditions[25,26], has also been utilized as protecting group for hydroxyl groups, as immolative group for drug release in cancer cells[27,28] and polymer recycling. Representative silicon-containing drugs include Sila-haloperidol, p38 MAP kinase inhibitor and angiotensin-converting enzyme inhibitor **(Figure 1B)**. This paper describes a simple and practical method for thiol-specific conjugation technology using *β*-silyl unsaturated carbonyl compounds as the thiol-specific click reagents **(Figure 1C)**. Although *α,β*-unsaturated compounds have been widely used for 1,4-conjugate addition with various nucleophiles[29], the problems of cross-reactivity with other nucleophiles, retro-Michael addition, and the need to use external bases in organic solvents pose problems for their direct use in bioconjugation of proteins[30-32].

Herein, we report that the introduction of silicon-substituents at the *β*-position enables the 1,4-thiol addition to proceed in a highly chemo-selective manner even in the presence of amino groups. The thiol-conjugated product is stable and no retro-process was observed in the presence of a wide variety of biomolecules, thereby overcoming many limitations of existing methods.

With our continuing interest in green chemistry and the development of a silicon-containing thiol-specific conjugation reagent, we screened the model reaction of 1-phenyl-3-(trimethylsilyl)prop-2-en-1-one **1a** and *p*-toluenethiol **2a** under biocompatible conditions at 37°C. Our results showed that good to excellent yields of the conjugated products could be obtained in water and buffer solutions. We found that the conjugated products could also be obtained in moderate yields at neutral pH, but the use of Tris buffer

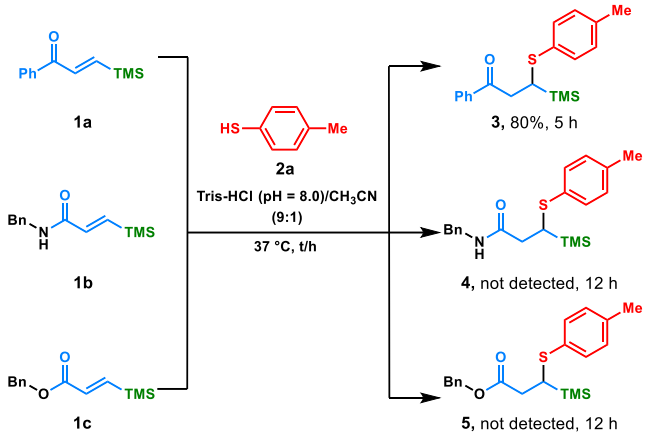


Figure 2. Comparation of ketone motif with ester and amide.

solution at pH 8 gave the best yield. We also experimented by adding different amounts of organic solvents and found that mixing Tris-HCl buffer solution at pH 8 with MeCN at a ratio of 9:1 provided the best yield (**Table 1**). As illustrated in **Figure S4**, the statistical results revealed a significant difference between entry 5 and entry 11 (p = 0.0004, n = 3).

In addition, we compared the reactivity of *α,β*-unsaturated amide **1b** and *α,β*-unsaturated ester **1c** with mercaptan **2a** as the model substrate and found that the desired products (**4, 5**) were not detected, indicating that the ketone moiety is crucial for the thiol-specific click reaction (**Figure 2**).

With optimized conditions, we explored thiol substrate scope in the conjugate addition with TMS-conjugated ketone **1a** (**Figure 3A**). Results indicate good tolerance for phenyl rings and alkyl chains, yielding adducts **3**, **6** to **12** (55-80% yield). Selective reactions with 4-mercaptophenol and 4-aminothiophenol preserved hydroxy and amino groups. Aryl thiols with methyl on *para-*, *meta-*, and *ortho-*positions produced products **3**, **6**, **7**, with yields decreasing in that order. *Para*-position chlorine substitution had higher yields than fluorine and alkyl substitution. Aliphatic chains and heteroarenes provided products **13** to **18** with moderate yields. Reactions with aliphatic chains and benzothiophene substituents yielded lower product yields, even with prolonged reaction time. Gratifying yields (60% and 52%) were obtained for 2-thiophenethiol and 2-pyrimidinethiol, respectively. Product **16** was obtained with a good yield of 65% using 1-hexanethiol.

Next, we explored *β*-silicon-enones (**Figure 3B**). Reactions with TMS alkenones and mercaptan **2a** yielded products **19** to **33** (44-74%). Substituents (**Cl-**, **CF_3-**, **^{n}Bu-**, **Ph-**) and *para*-methyl on the benzene ring produced yields of 72-74%. Methyl in *para-*, *meta-*, and *ortho*-positions of substrate **1** showed increasing product yields (**19-21**). Fused ring (**26**,**27**) or heterocyclic ring (**28-30**) substitutions resulted in moderate yields. Surprisingly, 8-quinoline substitution gave a 73% yield. Aliphatic ketone-derived *β*-TMS enones were compatible, yielding products **31-33** in 44-45%.

Examining the impact of silyl substituents on enones (**Figure 3C**), we found that replacing trimethylsilane with triethylsilane (TES) and tri(isopropyl)silane (TIPS) weakened reactivity, yielding products **34** and **35** in 40% and 35%, respectively, potentially due to increased steric hindrance. Utilizing substrate **1n**, with two *β*-TMS enones groups, yielded product **36** in 71% yield. The hydrosilane

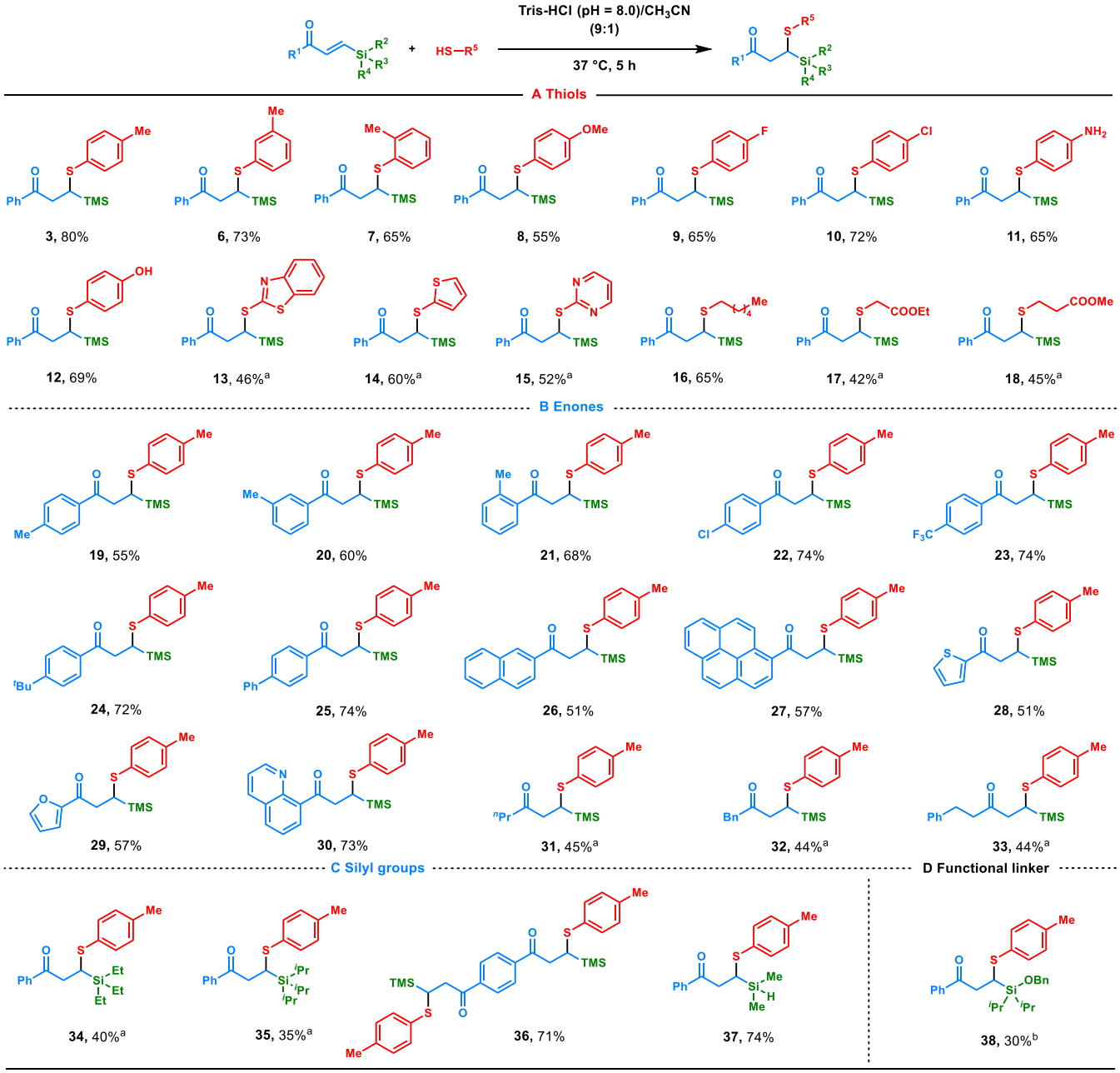


Figure 3. Substrate scope. [a]The reaction time was 12 h. [b]The reaction time was 24 h.

group was compatible, yielding product **37** in a 74% yield. Testing benzyl siloxane under standard conditions initially yielded no target product, but after 24 hours, product **38** was obtained in 30% yield (**Figure 3D**).

To expand our investigation, we explored the derivatization of the mercaptan coupling product **3** (**Figure 4**). We were successful in reducing product **39** with lithium aluminum hydride, while preserving the TMS group. However, our attempts to oxidize the sulfide part of **3** using *m*-CPBA were unsuccessful, resulting in the unexpected product **40**.

To showcase the potential of this methodology in bio-conjugation, we conducted a study to test the chemo-selectivity of the reagent and the stability of the product under various bio-conditions. Firstly, we tested the competition reaction between 2-phenylethyl thiol **2b** and amine **2c**, and observed that only the thiol conjugate was obtained, confirming the thiol-specific reactivity of this TMS-enone reagent. However, in the absence of the TMS group, compound **1d** reacted with both **2b** and **2c**, demonstrating that the addition of a silicon-containing group could decrease electrophilicity of the ketone, providing high thiol-selectivity (**Figure 5A**). Even in the presence of other nucleophilic amino acids, the reaction still proceeded smoothly to furnish only thiol conjugates without observing the reduced yields

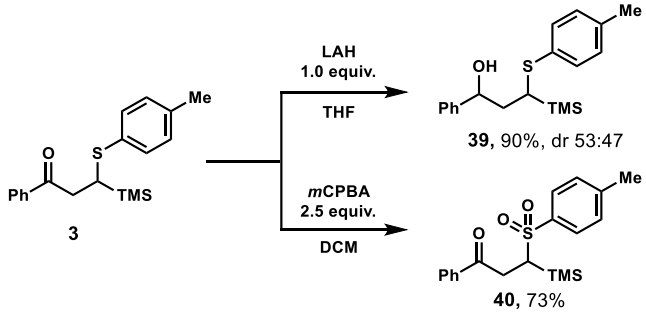


Figure 4. Derivatization of thiol conjugation.

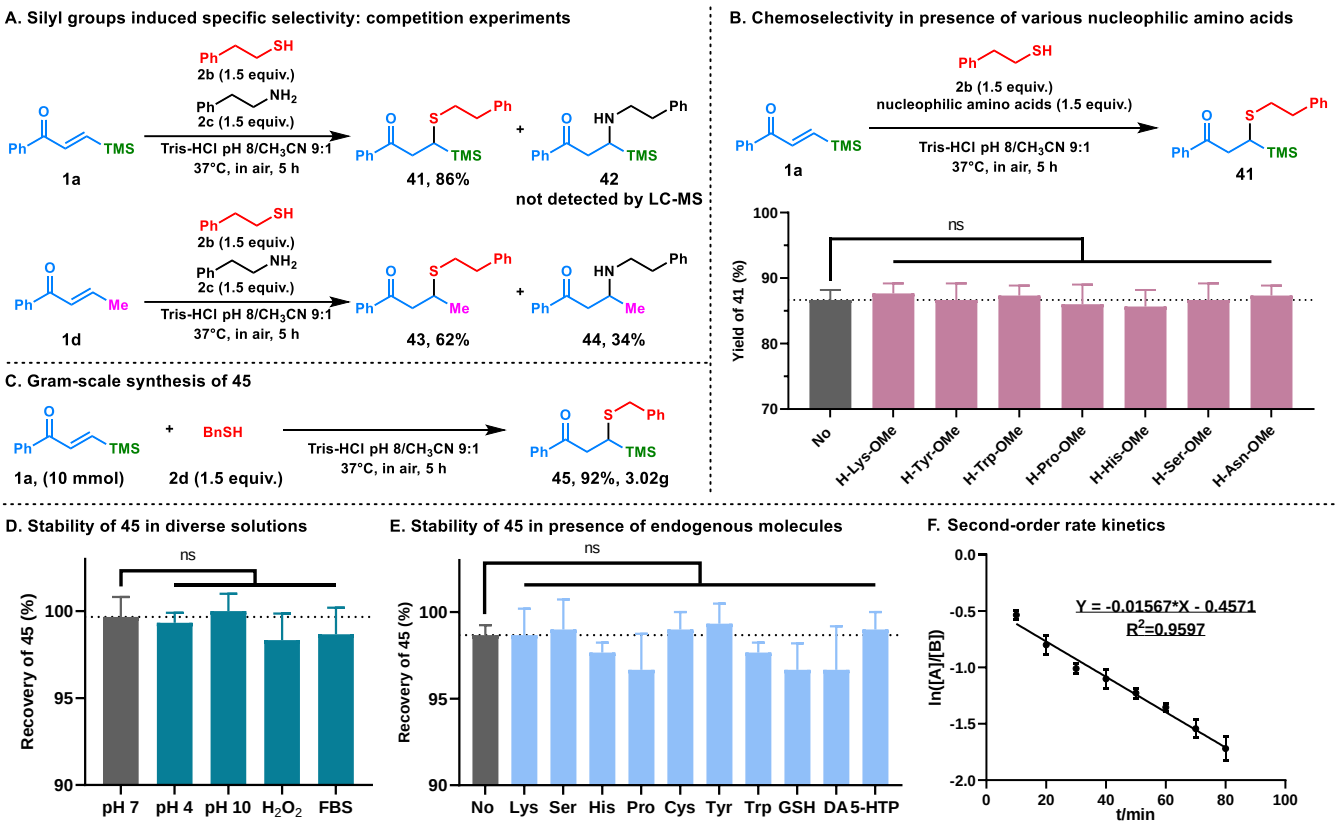


Figure 5. A. Silyl groups induced specific selectivity: competition experiments. **B.** Chemo-selectivity in presence of various nucleophilic amino acids. **C.** Gram-scale synthesis of **45**. **D.** Stability of thiol conjugate **45** under the acidic (pH 4), neutral (pH 7), basic (pH 10), oxidative (50 mM H_2O_2) and fetal bovine serum conditions for 24 h; **E.** Stability of compound **45** in presence of endogenous molecules (1.0 equiv.): 1) Lysine; 2) Serine; 3) Histidine; 4) Proline; 5) Cysteine; 6) Tyrosine; 7) Tryptophan; 8) GSH, Glutathione; 9) DA, Dopamine; 10) 5-HTP, 5-Hydroxytryptophan. **F.** Second-order rate kinetics. Statistical significance in **B**, **D**, and **E**, was calculated *via* one-way ANOVA, ns means no significance, $p > 0.05$. The mean values and SD are presented (n = 3, independent times).

(**Figure 5B**), showing no significance against the standard conditions. To showcase the practical potential, **45** was synthesized in 10 mmol scale under standard conditions in 92% yield (**Figure 5C**). Subsequently, the stability of the silyl thiol-conjugated products was evaluated (**Figures 5D, 5E**). We exposed product **45** in buffer solutions varying pH values from 4 to 10 or in the presence of H_2O_2 and FBS. After stirring for 24 hours, **45** demonstrated outstanding stability without experiencing significant degradation (**Figure 5D**). Furthermore, even in the presence of representative endogenous molecules, **45** maintained robust stability within the 24-hour period, exhibiting no discernible signs of deterioration (**Figure 5E**). Furthermore, we tested the product's stability with thiol molecules such as 4-chlorothiophenol **2e** and glutathione **2f** and found no exchanged product was observed. We were pleased to observe that no retro processes or side reactions occurred over 24 hours (for details, see the Supporting Information, **Figure S16**), indicating that this compound could serve as a linker for antibody-drug conjugates. Overall, these results highlight the potential utility of this TMS-enone reagent and its silyl thiol-conjugated product in bioconjugation applications. Moreover, we investigated the reaction kinetics using UPLC analysis. The second-order rate was shown in **Figure 5F** and the constant was calculated as 0.31 $M^{-1}min^{-1}$ (for details, see the Supporting Information, **Figure S17** and **S18**)

To further assess the feasibility of reactions with various biomolecules and drugs bearing free thiols, we utilized *β*-TMS-enone (**Figure 6**). We first incubated *N*-Boc cysteine methyl ester with **1a** for 12 hours under standard conditions, and successfully functionalized this cysteine derivative to produce the adduct **47**, retaining the silicon moiety. Encouraged by this promising outcome, we also reacted **1a** with a fluorescent fused ring and obtained the corresponding product **46** in a moderate yield of 65%. This product exhibited yellow-green fluorescence under 365 nm UV light. We also successfully modified 1-thio-D-glucose acetates (**48**), though the yield was not high, highlighting the potential of this method in polysaccharide diversification. Furthermore, the anti-hypertensive drug Captopril reacted with β-TMS enone, yielding the desired product **49** in 45% yield. When we used glutathione derivative and mertansine, we also obtained products **50** and **51** in good yields of 69% and 84%, respectively. To verify the specific selectivity of cysteine in peptides containing multiple nucleophilic amino acid side chains with our protocol, TCEP-modified Lanreotide was treated as a substrate for the conjugation with **1a**. Analysis by LC-MS/MS revealed that only cysteines underwent conjugating modification, while other nucleophilic amino acids such as threonine, lysine, tryptophan, tyrosine, and terminal amine remained almost touched (for details, see the Supporting Information, **Figure S22-S24**).

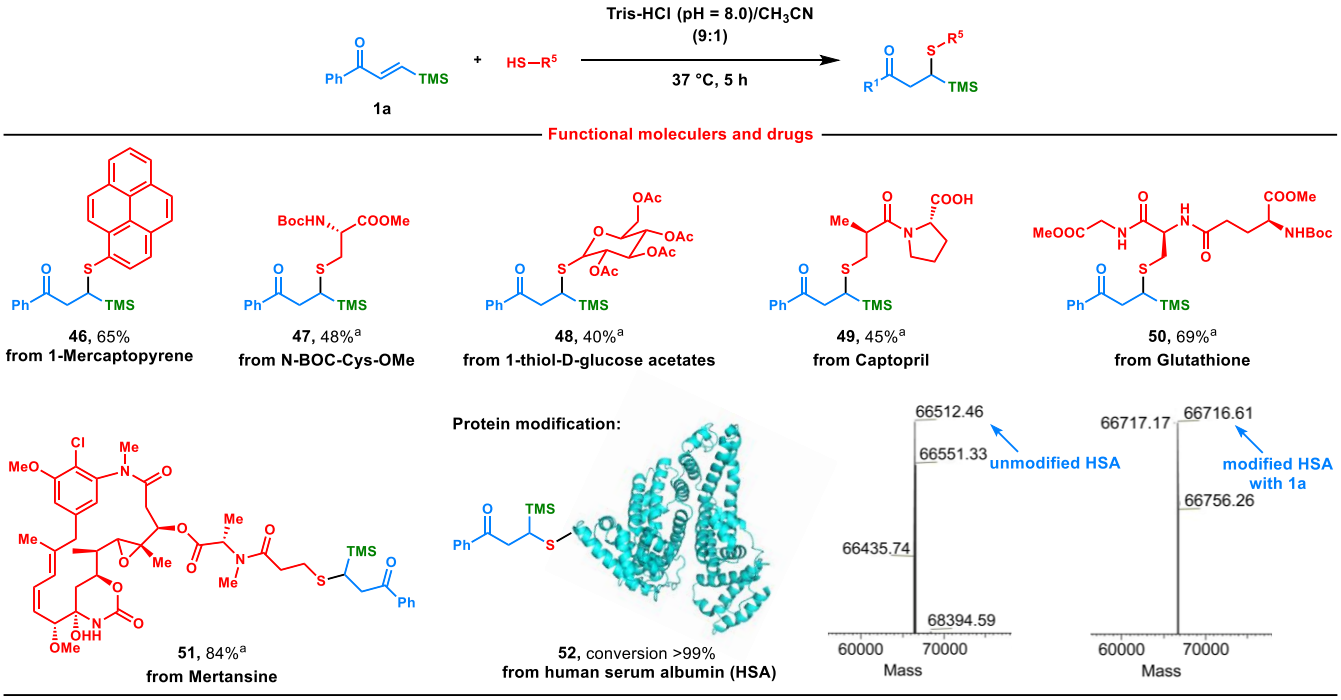


Figure 6. Modification thiol-containing functional molecules and protein with **1a**. [a]The reaction time was 12 h.

Next, we realized the protein modification using Human serum albumin (HSA), which contains one free cysteine residue. Incubating HSA (0.5 mM) with 50 equivalents of *β*-TMS-enone reagent **1a** in Tris-HCl buffer, the thiol-containing conjugates of one-fold modification **52** with over 99% conversion as observed by LC-MS analysis. Furthermore, LC-MS/MS analysis revealed that all relevant peptide segments were also identified (**Figure S29**) and the modification of free cysteine 34 residues in the detected peptides by a molecule (204.09700 Da) corresponding to **1a**, as depicted in **Figure S30** and **S31**. In addition, the circular dichroism (CD) spectra of the modified HSA with **1a** and the original HSA were identical, indicating that our procedure did not alter the three-dimensional structure of the HSA (for details, see the Supporting Information, **Figure S32**). These results demonstrate the potential of this *β*-TMS enones reagent in the bioconjugation of biomolecules and drugs bearing free thiols.

In conclusion, we have discovered that *β*-silyl enones can serve as a novel thiol-specific bioconjugation reagent. The incorporation of silicon functionality has significantly improved thiol chemo-selectivity and suppressed the retro process, surpassing common *α, β*-unsaturated carbonyl Michael acceptors. The reaction proceeds well under biocompatible conditions, making it suitable for protein conjugation. The resulting conjugated products are stable in the presence of various biomolecules, presenting potential applications for the synthesis of antibody-drug conjugates. The silicon moiety within the conjugated products can also be utilized for drug release or to bridge the inorganic and other disciplines.[33-37] We anticipate that this discovery will attract the attention of researchers working in the fields of bioanalytical science and medicinal chemistry and spark new avenues for exploration in bioconjugation research.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at the ACS Publications website.

Experimental procedures, photographs of experimental setup, characterization data, and spectra (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We thank Ms Wei Meng (Nanyang Technological University) for mass analysis of proteins and Dr. Jingsheng Huang (Nanyang Technological University) for statistical analysis. We gratefully acknowledge the financial support from Distinguished University Professor grant (Nanyang Technological University) and the Agency for Science, Technology, and Research (A*STAR) under its MTC Individual Research grant (M21K2c0114) and RIE2025 MTC Programmatic Fund (M22K9b0049) for T.-P.L.

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