CJC Chinese Journal of Chemistry 中国化学 - An International Journal

For submission: https://mc.manuscriptcentral.com/cjoc
For published articles: https://onlinelibrary.wiley.com/journal/16147065

Concise Report

Cite this paper: *Chin. J. Chem.* **2021**, *39*, 1255—1258. **DOI: 10.1002/cjoc.202000607**

A Mild, General, Metal-Free Method for Desulfurization of Thiols and Disulfides Induced by Visible-Light

Wenting Qiu,[a] Shuai Shi,[a] Ruining Li,[a] Xianfeng Lin,[a] Liangming Rao,[b,c] and Zhankui Sun*[,a]

[a] *Shanghai Key Laboratory for Molecular Engineering of Chiral Drugs, School of Pharmacy, Shanghai Jiao Tong University, No. 800 Dongchuan Rd., Shanghai 200240, China*
[b] *Huzhou Research and Industrialization Center for Technology, Chinese Academy of Sciences, 1366 Hongfeng Road, Huzhou, Zhejiang 313000, China*
[c] *Shanghai Institute of Nutrition and Health, Chinese Academy of Sciences, Shanghai 200031, China*

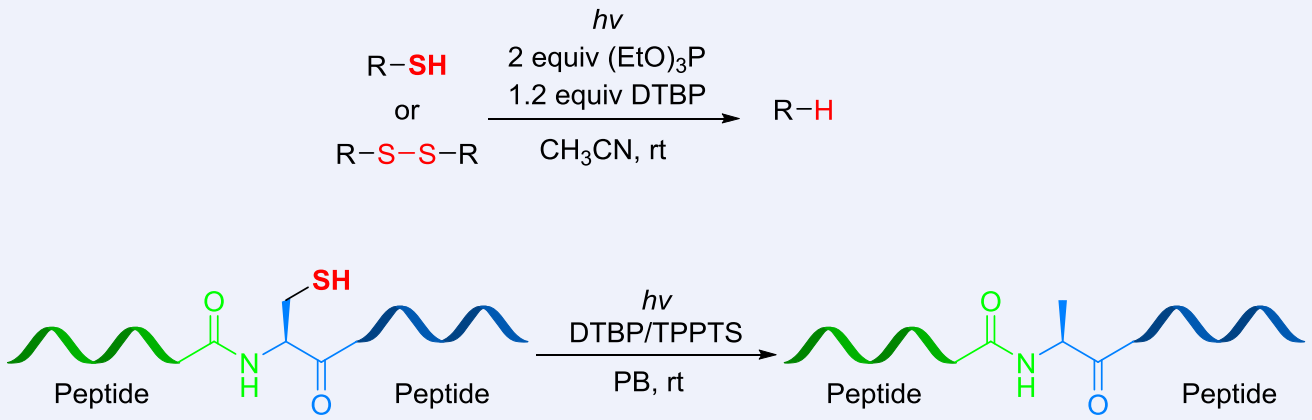
Keywords

Desulfurization | Photochemistry | Radical reactions | Thiol | Visible-light

Main observation and conclusion

A visible-light-induced metal-free desulfurization method for thiols and disulfides has been explored. This radical desulfurization features mild conditions, robustness, and excellent functionality compatibility. It was successfully applied not only to the desulfurization of small molecules, but also to peptides.

Comprehensive Graphic Content



*E-mail: zksun@sjtu.edu.cn

View HTML Article | Supporting Information

Background and Originality Content

Desulfurization reactions are of great importance, not only in organic synthesis,[1] but also in industrial and environmental settings.[2] Desulfurization reactions have a long history. Most reported methods rely heavily on transition metals, for example, Raney nickel,[3] $Fe_3(CO)_{12}$,[4] $Co_2(CO)_8$,[5] $Mo(CO)_6$,[6] *etc*., which suffer from problems such as catalyst instability (unstable in the presence of air or water),[3] poor functional group tolerance,[4-5] high metal loadings,[5-6] *etc*. With the development of native chemical ligation for peptide and protein synthesis by Kent and other groups,[7] several desulfurization methods which convert cysteine into alanine were developed, including the Pd/Al_2O_3 and Raney nickel-mediated methods reported by Dawson (Figure 1b),[3e] the TCEP (tris(2-carboxyethyl)phosphine)/VA-044/*t*-BuSH methods developed by Danishefsky and Wan (Figure 1c),[8] the photocatalytic desulfurization developed by Guo (Figure 1c),[9] and the P-B desulfurization developed by Li (Figure 1d).[10] Recently we reported a site-specific deuteration method induced by visible-light through a desulfurization process.[11] Herein, we disclosed our detailed studies which resulted in a metal-free and highly efficient desulfurization process that enabled the chemoselective desulfurization of small molecules and peptides.

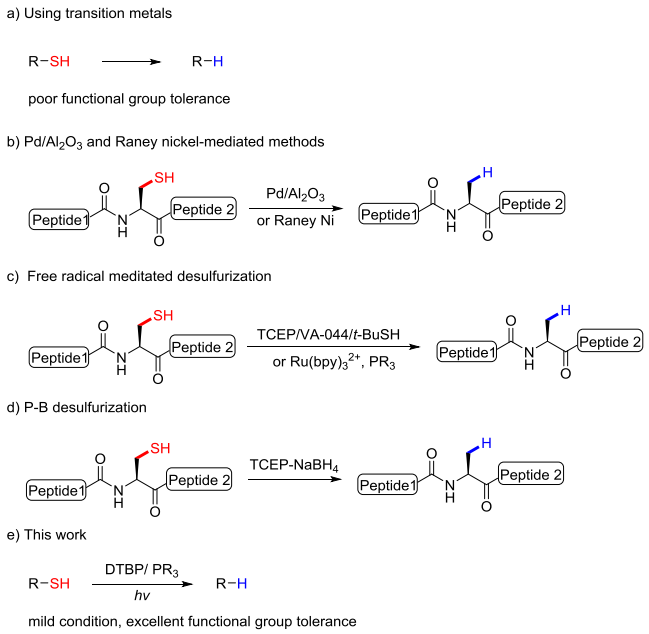
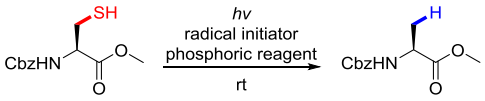


Figure 1 Examples of desulfurization reactions.

Results and Discussion

We began our study by using cysteine **1a** as the model substrate and examined different conditions under visible-light at room temperature. We found that the combination of DTBP (di-*tert*-butyl peroxide) and $P(OEt)_3$ worked smoothly in CH_3CN and gave the product in 96% yield (Table 1, entry 3). The reactions also worked well in different solvents, such as DCM, DMF, toluene, EtOAc, acetone and methanol (see Supporting Information). Besides, PPh_3, HEPT (hexaethyl-phosphoroustriamid) or Ph_2POEt could also provide the desired product with excellent yields (Table 1, entries 5—7). However, replacing DTBP with TBHP (*tert*-butyl hydroperoxide) and DCP (dicumyl peroxide) led to diminished yields (Table 1, entries 8—9). The control experiments suggested that desulfurization hardly took place in the absence of DTBP, $P(OEt)_3$ or visible-light (Table 1, entries 10—12).

Table 1 Optimization of reaction conditions for the desulfurization of small molecules[a]



Entry	Phosphoric reagent	Radical initiator	Yield[b]
1	2.0 equiv $P(OEt)_3$	0.5 equiv DTBP	46%
2	2.0 equiv $P(OEt)_3$	1.0 equiv DTBP	89%
3	2.0 equiv $P(OEt)_3$	1.2 equiv DTBP	96%
4	1.2 equiv $P(OEt)_3$	1.2 equiv DTBP	56%
5	2.0 equiv PPh_3	1.2 equiv DTBP	95%
6	2.0 equiv HEPT	1.2 equiv DTBP	92%
7	2.0 equiv Ph_2POEt	1.2 equiv DTBP	92%
8	2.0 equiv $P(OEt)_3$	1.2 equivTBHP	44%
9	2.0 equiv $P(OEt)_3$	1.2 equiv DCP	82%
10	2.0 equiv $P(OEt)_3$	—	N.D.
11	—	DTBP	N.D.
12[c]	2.0 equiv $P(OEt)_3$	1.2 equiv DTBP	<5%

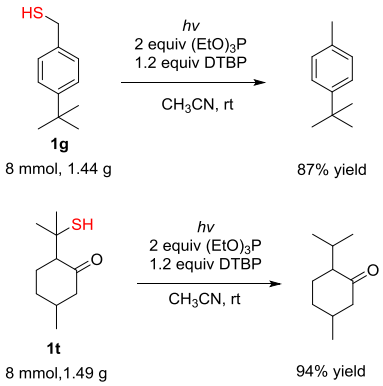
[a] Reactions conditions: **1a** (0.75mmol), phosphoric reagent, radical initiator, 6 mL CH_3CN, 25 °C, 36 W household CFL bulb irradiation on two sides, 6 h. [b] Yields of isolated product. N.D. = not detected. [c] Without light.

We then tested this protocol with different substrates. We found that primary thiols with various functional groups could be tolerated under this condition and excellent yields were achieved, such as carbamate, ester, halogen, ether, hydroxy group, acid group, amide, ketone, *etc*. As for substrate **1l**, the desulfurization and subsequent ring-opening reaction occurred. Secondary thiols also worked well (Table 2, substrates **1n**—**1p**). Sterically hindered tertiary thiols worked smoothly at room temperature and afforded the corresponding products in excellent yields (Table 2, substrates **1q**—**1t**). It should be noted that disulfides also proved to be suitable substrates and delivered the products in good to excellent yields (Table 2, substrates **1u**—**1z**).

This condition even worked for sp^2-hybridized compounds, albeit with lower yields. At elevated temperature, thiols bearing aromatic rings such as benzothiazole, pyridine and quinoline worked successfully with moderate yields, as shown in Table 3.

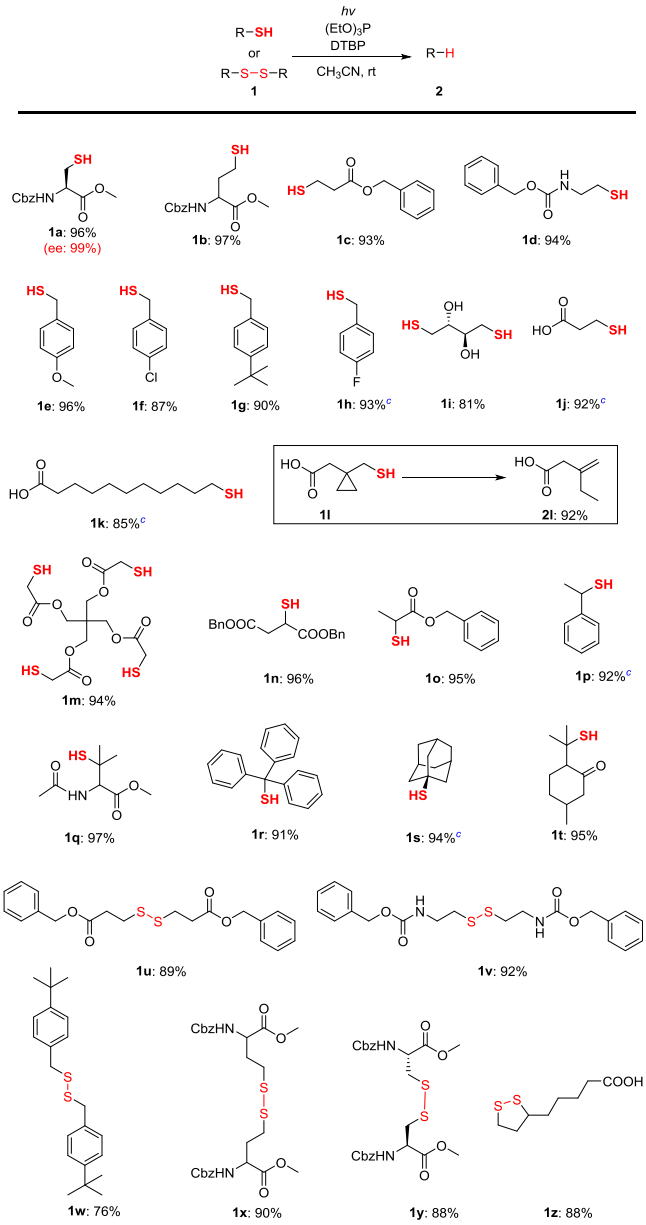
To further demonstrate the feasibility of this protocol, we scaled up the reactions for substrates **1g** and **1t** (Scheme 1). Both products could be obtained in high yields on gram-scale.

Scheme 1 Scale-up reactions of **1g** and **1t** on gram scale



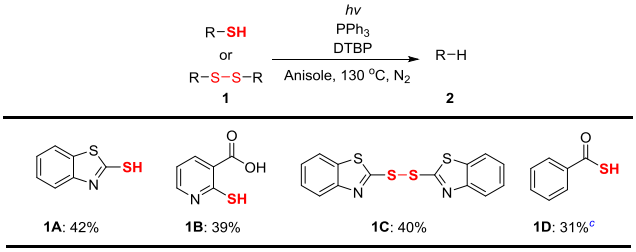
Encouraged by the above-mentioned results, we then turned our attention to the reactions of peptides. We examined glutathione (GSH) as the model substrate with water-soluble phosphine and DTBP under visible-light irradiation in water. When the

Table 2 Substrate scope for the desulfurization of small molecules[a,b]



[a] Reaction conditions: For thiols: substrate (0.75 mmol), DTBP (0.90 mmol), $P(OEt)_3$ (1.50 mmol), CH_3CN (6 mL), 25 °C, 36 W household CFL bulb irradiation on two sides, 6 h. For disulfides: substrate (0.375 mmol), DTBP (0.90 mmol), $P(OEt)_3$ (1.50 mmol). [b] Unless otherwise noted, yields refer to isolated yields. [c] Yields analyzed by ^1H NMR.

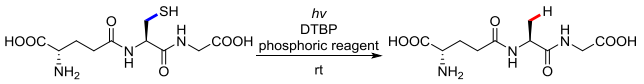
Table 3 Desulfurization of sp^2-hybridized organosulfur compounds[a,b]



[a] Reaction conditions: For thiols: substrate (0.75 mmol), DTBP (0.90 mmol), PPh_3 (1.50 mmol), anisole (6 mL), 130 °C, 36 W household CFL bulb irradiation on two sides, 6 h. [b] Yields refer to isolated yields. [c] Reaction under 50 °C in CH_3CN.

reaction was done at 80 mmol/L concentration, 2 equivalents of DTBP and TPPTS (triphenylphosphine-3,3',3''-trisulfonic acid trisodium salt) were sufficient for the full conversion of glutathione within 6 h (Table 4, entry 1). However, with 1 mmol/L concentration, 30 equivalents of DTBP and TPPTS were needed for the full conversion (Table 4, entry 3). The reaction could also be carried out in phosphate buffer (Table 4, entry 4), with *tert*-butyl mercaptan (TBM) (Table 4, entry 5) and guanidine hydrochloride (Gn·HCl) (Table 4, entry 6). TCEP (tris(2-carboxyethyl)phosphine) could also provide the desired product with excellent yield (Table 4, entry 7).

Table 4 Optimization of reaction conditions for the desulfurization of glutathione[a,b]

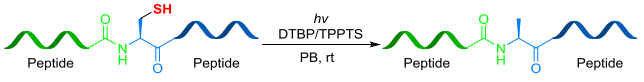


Entry	GSH (mmol/L)	Phosphoric reagent	DTBP	Additive	Solvent	Yield[b]/%
1	80	2 equiv TPPTS	2 equiv	—	H_2O	>95
2	1	2 equiv TPPTS	2 equiv	—	H_2O	<5
3	1	30 equiv TPPTS	30 equiv	—	H_2O	>95
4	1	30 equiv TPPTS	30 equiv	—	PB	>95
5	1	30 equiv TPPTS	30 equiv	30 eq TBM	PB	>95
6	1	30 equiv TPPTS	30 equiv	30 eq TBM	PB, Gn·HCl	>95
7	1	30 equiv TCEP	30 equiv	—	PB	>95
8	1	30 equiv Ph_2POEt	30 equiv	—	PB	N.D.

[a] Reaction conditions: **3a** (mmol/L), phosphoric reagent, DTBP, 25 °C, 36 W household CFL bulb irradiation on two sides, 6 h. [b] Yield by ^1H NMR analysis. PB = phosphate buffer (pH = 7.0, 200 mmol/L), TBM = *tert*-butyl mercaptan, N.D. = not detected.

With the optimized conditions in hand, we next investigated longer peptide substrates with different amino acid residues, and all corresponding desulfurization peptides were obtained in good yields. Peptides with either mono- or multi-cysteine residues worked well. Remarkably, this protocol could also remove the thiol group of cysteine in the presence of phosphorylated serine (Table 5, substrates **3c**, **3h**) and methionine (Table 5, substrate **3g**).

Table 5 Substrate scope for the desulfurization of peptides[a]

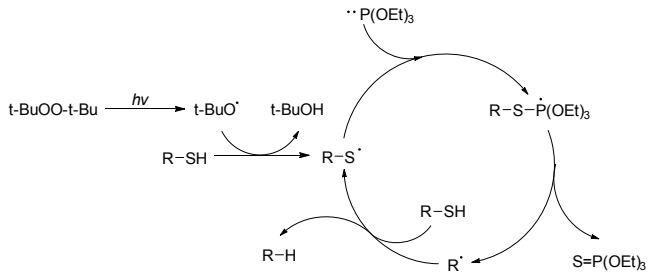


Peptide substrates	Conversion[b]/%
Cys-Gly-Arg-Ala-Ser-Ser-His-Ser-Ser-Gln-Thr-Gln-Gly-Gly-Gly-NH_2 (**3b**)	> 95
Cys-Gly-Arg-Ala-Ser-{pSer}-His-Ser-Ser-Gln-Thr-Gln-Gly-Gly-Gly-NH_2 (**3c**)	> 95
Cys-Glu-Gly-Pro-Glu-Val-Asp-Val-Asn-Leu-Pro-Lys (**3d**)	> 95
Cys-Glu-Leu-Phe-Lys-Phe-Leu-Asp-Gly-Lys-Leu-Leu-Asp-Ile-Asn-Lys-Asp(**3e**)	> 95
Cys-Glu-Leu-Asn-Asp-Pro-Asn-Lys-Ala-Glu-Asp-Pro-Lys-Lys-Phe-Thr (**3f**)	> 95
Ala-Arg-Gly-Asn-Glu-Ser-Ser-Cys-Met-Asp-Thr-Pro-Thr-Glu-Gly-Cys (**3g**)	> 95
Cys-Glu-Leu-Leu-Pro-Asn-{pSer}-Gly-His-Gly-Pro-Asp-Gly-Glu-Val (**3h**)	> 95
Cys-Glu-Leu-Leu-Pro-Asn-Ser-Gly-His-Gly-Pro-Asp-Gly-Glu-Val (**3i**)	79
Glu-Ser-Glu-Lys-Ser-Lys-Ala-Glu-Asn-Arg-Ala-Gln-Cys (**3j**)	> 95

[a] Desulfurization conditions: Cysteinyl peptide (1 mmol/L), TPPTS (30 mmol/L), DTBP (30 mmol/L), TBM (30 mmol/L), PB, 36 W household CFL bulb irradiation on two sides, 25 °C, 6 h. PB = phosphate buffer, 200 mmol/L, pH = 7.0. [b] Conversion was determined by LC-MS.

Based on our understanding, we proposed a possible mechanism which was depicted in Scheme 2.

Scheme 2 Proposed mechanism of the desulfurization reaction



Conclusions

We have developed a general and metal-free desulfurization method induced by visible-light. This method works not only for small molecules, but also for peptides. It features mild conditions, robustness, and excellent functionality compatibility, which makes it a reliable tool for organic chemists and medicinal chemists.

Experimental

General procedure for the desulfurization reactions: To a 25 mL round-bottom flask equipped with a stir bar was added the substrate (0.75 mmol, 1.0 equiv.) and $P(OEt)_3$ (249.2 mg, 1.50 mmol, 2.0 equiv.). CH_3CN was added (6 mL, 8 mol/L concentration) followed by the addition of DTBP (131.6 mg, 0.90 mmol, 1.2 equiv.). The flask was capped and the reaction was stirred and irradiated using two 36 W household CFL bulbs (6 cm away, to keep the reaction at room temperature) at room temperature for 6 h. When the reaction was complete, the solvent was removed under vacuum. The product was obtained by column chromatography on silica with petroleum ether/ethyl acetate mixture as the eluent.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.202000607.

Acknowledgement

We thank Shanghai Jiao Tong University and the National "1000-Youth Talents Plan" for financial support.

References

[1] (a) Magnus, P. D. Recent developments in sulfone chemistry. *Tetrahedron* **1977**, *33*, 2019–2045; (b) Eisch, J.; Hallenbeck, L.; Han, K. Hydrodesulfurization of organosulfur heterocycles by metal hydride-nickel (0) complexes: accelerated single-electron transfer in carbon-sulfur bond cleavage. *J. Am. Chem. Soc.* **1986**, *108*, 7763–7767; (c) Feng, M. H.; Tang, B. Q.; Liang, S. H.; Jiang, X. F. Sulfur Containing Scaffolds in Drugs: Synthesis and Application in Medicinal Chemistry. *Curr. Top. Med. Chem.* **2016**, *16*, 1200–1216; (d) Zhao, J.; Jiang, X. F. The application of sulfur-containing peptides in drug discovery. *Chin. Chem. Lett.* **2018**, *29*, 1079–1087; (e) Wang, N.; Saidhareddy, P.; Jiang, X. F. Construction of sulfur-containing moieties in the total synthesis of natural products. *Nat. Prod. Rep.* **2020**, *37*, 246–275.

[2] (a) Eisch, J. J.; Hallenbeck, L. E.; Lucarelli, M. A. Desulphurization and denitrogenation of SRC liquids by transition metals on solid supports. *Fuel* **1985**, *64*, 440–442; (b) Schreiner, B. Der Claus-Prozess. Reich an Jahren und bedeutender denn je: Herrn Dr.-Ing. Michael Heisel zum 60. Geburtstag gewidmet. *Chem. Unserer Zeit* **2008**, *42*, 378–392; (c) Cook, E.; Peregrine, P. The inventor of the contact process for sulphuric acid. *Nature* **1926**, *117*, 419–421.

[3] (a) Mozingo, R.; Wolf, D. E.; Harris, S. A.; Folkers, K. Hydrogenolysis of sulfur compounds by Raney nickel catalyst. *J. Am. Chem. Soc.* **1943**, *65*, 1013–1016; (b) Snyder, H.; Cannon, G. W. Carbon—Carbon Cleavage in the Hydrogenolysis by Raney Nickel Catalyst of Ethylenedithiol and its Ethers. *J. Am. Chem. Soc.* **1944**, *66*, 155–156; (c) Blicke, F.; Sheets, D. G. Derivatives of Thianaphthene. I[1]. *J. Am. Chem. Soc.* **1948**, *70*, 3768–3770; (d) Hauptmann, H.; Walter, W. F. The Action of Raney Nickel on Organic Sulfur Compounds. *Chem. Rev.* **1962**, *62*, 347–404; (e) Yan, L. Z.; Dawson, P. E. Synthesis of peptides and proteins without cysteine residues by native chemical ligation combined with desulfurization. *J. Am. Chem. Soc.* **2001**, *123*, 526–533.

[4] (a) Alper, H.; Sibtain, F.; Heveling, J. Phase transfer catalyzed desulfurization reactions. *Tetrahedron Lett.* **1983**, *24*, 5329–5332; (b) Alper, H.; Prince, T. L. Äußerst milde Entschwefelung von Thiolen mit Natrium-triethylhydroborat und Übergangsmetallchloriden. *Angew. Chem.* **1980**, *92*, 321–321; (c) Alper, H.; Sibtain, F. Desulfurization of benzylic mercaptans by triiron dodecacarbonyl under acidic and biphasic conditions. *J. Organomet. Chem.* **1985**, *285*, 225–229.

[5] Shim, S. C.; Antebi, S.; Alper, H. Desulfurization of mercaptans to hydrocarbons by carbon monoxide and water in the presence of cobalt carbonyl. *Tetrahedron Lett.* **1985**, *26*, 1935–1938.

[6] Wang, Z.; Kuninobu, Y.; Kanai, M. Molybdenum-Mediated Desulfurization of Thiols and Disulfides. *Synlett* **2014**, *25*, 1869–1872.

[7] (a) Dawson, P. E.; Muir, T. W.; Clark-Lewis, I.; Kent, S. Synthesis of proteins by native chemical ligation. *Science* **1994**, *266*, 776–779; (b) Dawson, P. E.; Kent, S. B. Synthesis of native proteins by chemical ligation. *Annu. Rev. Biochem.* **2000**, *69*, 923–960; (c) Ma, J.; Zeng, J.; Wan, Q. Postligation-Desulfurization: A General Approach for Chemical Protein Synthesis. *Top. Curr. Chem.* **2014**, *363*, 57–101; (d) Jin, K.; Li, X. C. Advances in Native Chemical Ligation-Desulfurization: A Powerful Strategy for Peptide and Protein Synthesis. *Chem.-Eur. J.* **2018**, *24*, 17397–17404; (e) Wang, S. Y.; Thopate, Y. A.; Zhou, Q. Q.; Wang, P. Chemical Protein Synthesis by Native Chemical Ligation and Variations Thereof. *Chin. J. Chem.* **2019**, *37*, 1181–1193; (f) Chow, H. Y.; Zhang, Y.; Matheson, E.; Li, X. C. Ligation Technologies for the Synthesis of Cyclic Peptides. *Chem. Rev.* **2019**, *119*, 9971–10001; (g) Yin, H.; Zheng, M.; Chen, H.; Wang, S.; Zhou, Q.; Zhang, Q.; Wang, P. Stereoselective and Divergent Construction of β-Thiolated/Selenolated Amino Acids via Photoredox-Catalyzed Asymmetric Giese Reaction. *J. Am. Chem. Soc.* **2020**, *142*, 14201–14209.

[8] Wan, Q.; Danishefsky, S. J. Free-radical-based, specific desulfurization of cysteine: a powerful advance in the synthesis of polypeptides and glycopolypeptides. *Angew. Chem. Int. Ed.* **2007**, *46*, 9248–9252.

[9] Gao, X. F.; Du, J. J.; Liu, Z.; Guo, J. Visible-light-induced specific desulfurization of cysteinyl peptide and glycopeptide in aqueous solution. *Org. Lett.* **2016**, *18*, 1166–1169.

[10] Jin, K.; Li, T.; Chow, H. Y.; Liu, H.; Li, X. P–B Desulfurization: An Enabling Method for Protein Chemical Synthesis and Site-Specific Deuteration. *Angew. Chem. Int. Ed.* **2017**, *56*, 14607–14611.

[11] Shi, S.; Li, R.; Rao, L.; Sun, Z. A mild, general, and metal-free method for site specificdeuteration induced by visible light using D_2O as the source of deuterium atoms. *Green Chem.* **2020**, *22*, 669.

Manuscript received: October 29, 2021
Manuscript revised: January 15, 2021
Manuscript accepted: January 17, 2021
Accepted manuscript online: January 21, 2021

