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Visible-Light-Mediated S−H Bond Insertion Reactions of Diazoalkanes with Cysteine Residues in Batch and Flow

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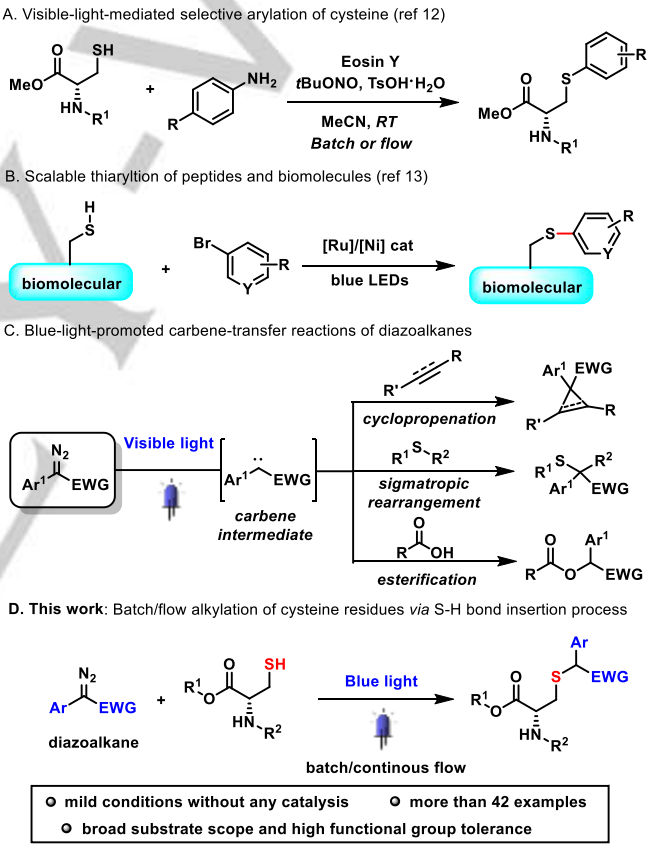
Abstract: We describe the application of S−H bond insertion reactions of aryl diazoacetates with cysteine residues that enabled metal-free, S−H functionalization under visible-light conditions. Moreover, this process could be intensified by a continuous-flow photomicroreactor on the acceleration of the reaction (6.5 min residence time). The batch and flow protocols described were applied to obtain a wide range of functionalized cysteine derivatives and cysteine-containing dipeptides, thus providing a straightforward and general platform for their functionalizations in mild conditions.

Keywords: Visible-Light-Mediated; S−H bond insertion; cysteine residues; continuous-flow

Introduction

The development of chemical methods for achieving selective covalent modifications of α-amino acid derivatives and peptides has become essential for the syntheses of chemical biology, molecular biology and drug candidates.[1] These methods are widely used in various procedures such as protein pull-down, microarray screening and activity-based protein profiling (ABPP).[2] Meanwhile, their applications to therapeutics are exemplified by several marketed pharmaceuticals, including aspirin, penicillin, omeprazole, and neratinib.[3] In contrast to modifications at other common amino acid residues and peptides, modifications at cysteine residues currently constitute one of the most powerful methods in this field, owing to the high nucleophilicity of the cysteine sulfhydryl group and the relatively low frequency (1%–2% in proteins) of cysteine residues in proteins.[4] Several methods, such as disulfide formation,[5] thiol–maleimide reactions,[6] and alkylation with haloalkyl reagents,[7] have been used to selectively modify cysteines. Other strategies use cysteine as a precursor for the formation of



Scheme 1 Visible-light-promoted S−H bond insertion reactions of diazoalkanes with cysteine residues

dehydroalanine (Dha),[8] or as a handle for nucleophilic aromatic substitution allowing access to perfluorinated peptides and proteins.[9] Transition metal catalysis and UV irradiation have been used to some extent as promising ways to achieve modifications of cysteine derivatives and peptides.[10] However, these approaches are consistently limited by their heavy reliance on expensive catalysts or harsh reaction conditions. Hence, the use of photochemical reactions, considered to be an excellent match for biomolecule functionalization, has been explored as a more

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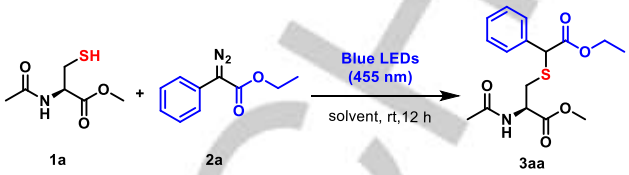
practical pathway towards the selective modification of cysteine due to the milder reaction conditions involved (*e.g.* room temperature and visible light).[11] For example, Noël and co-workers reported a protocol involving visible-light-mediated arylation of cysteine and using corresponding diazonium salts as the aryl source (Scheme 1A).[12] The Molander group developed a method involving a Ni/photoredox catalysis of thioarylation of cysteine-containing peptides (Scheme 1B).[13] Despite these significant achievements, the development of general methods for selective cysteine modification under mild conditions with readily available reagents is still highly desirable.

On the other hand, diazo compounds are used extensively as synthetic building blocks in numerous reactions due to their high reactivity levels and diverse applications.[14] Moreover, the selective visible-light-mediated photolysis of diazoalkanes could provide an appealing and straightforward access to the reactivity of carbenes under photochemical conditions without the need for any additional transition metal catalysts or precautions.[15] The Davies, He and Zhou groups very recently reported an array of appealing examples of using diazo compounds in reactions such as cycloaddition,[16] Doyle–Kirmse rearrangement,[17] esterification[18] and olefination reactions[19] that were mediated by low-energy visible light (Scheme 1C). Based on the above reports, we envisioned that such a protocol involving visible-light-promoted reactions could meet our goals, namely provide a straightforward and milder methodology for C–S functionalizations of cysteine derivatives and their peptides via visible-light photolyses of diazoalkanes, and hence avoid the usual side-reactions that can readily occur under UV irradiation or thermolytic conditions.

Results and discussion

We focused our efforts by choosing *N*-Ac-L-cysteine-OMe (**1a**) and ethyl 2-diazo-2-phenylacetate (**2a**) as model substrates to test the reaction conditions. To our delight, the desired product **3aa** was obtained in 27% isolated yield, and done so by dissolving **1a** (1.0 equiv) and **2a** (2.0 equiv) in solvent (2.0 mL, DCM) at room temperature under irradiation with blue LEDs (455 nm, 50 W) for 2 hours (Table 1, entry 1). However, this product was obtained with both diastereoisomers in a 1:1 mixture. Note that prolonging the reaction time was found to be beneficial to increasing the isolated yields (Table 1, entries 2–5). A relatively good yield of **3aa** (87%) was obtained when the reaction time was extended to 12 hours (Table 1, entry 6). Because of this promising result, we turned our attention to exploring the effect of stoichiometry on this reaction.

Table 1 Optimization of Reaction Conditions[a]



Entry	Ratio**1a:2a**	Reaction time (h)[b]	Solvent	Yield (%)[c]
1	1 : 2	2	DCM	27
2	1 : 2	4	DCM	35
3	1 : 2	6	DCM	48
4	1 : 2	8	DCM	63
5	1 : 2	10	DCM	78
6	1 : 2	12	DCM	87
7	1 : 4	12	DCM	81
8	1 : 2	12	CH_3CN	45
9	1 : 2	12	DMF	39
10	1 : 2	12	DCE	55
11	1 : 2	12	THF	72
12	1 : 2	12	DMSO	44
13	1 : 2	12	DMAC	12
14	1 : 2	12	Water	*Trace*
15	1 : 2	12	PBS	*Trace*
16[d]	1 : 2	12	DCM	*N.R.*
17[e]	1 : 2	12	DCM	48
18[f]	1 : 2	12	DCM	54
19[g]	1 : 2	8	DCM	*Trace*

[a]Reaction conditions: **1a** (0.2 mmol) and **2a** (0.4 mmol) were dissolved in solvent and stirred at room temperature under irradiation with blue LEDs (455 nm, 50 W). [b]Total reaction time including addition time. [c]Isolated yield based on **1a**. [d]Reaction in the dark. [e]Green LEDs instead blue LEDs. [f]White LEDs instead blue LEDs. [g]Irradiated with daylight, 8 h. *N.R.* = no reaction. DCM = dichloromethane; DMF = *N*,*N*-dimethylformamide; DCE = 1,2-dichloroethane; THF = tetrahydrofuran; DMSO = dimethyl sulfoxide; DMAc = *N*,*N*-dimethylacetamide; PBS = Phosphate buffer (pH 7.4).

An excess of the diazo coupling partner showed negative effects for this reaction: a slightly decreased reaction yield was obtained as the ratio of equivalents of **1a** to equivalents **2a** was increased to 1:4 (Table 1, entry 7). Furthermore, the effect of solvent was explored, and various solvents, including CH_3CN, DMF, DCE, THF and DMSO were shown to be compatible with this procedure, albeit showing lower efficiency levels (Table 1, entries 8−12). However, using DMAC instead of DCM as solvent led to a lower

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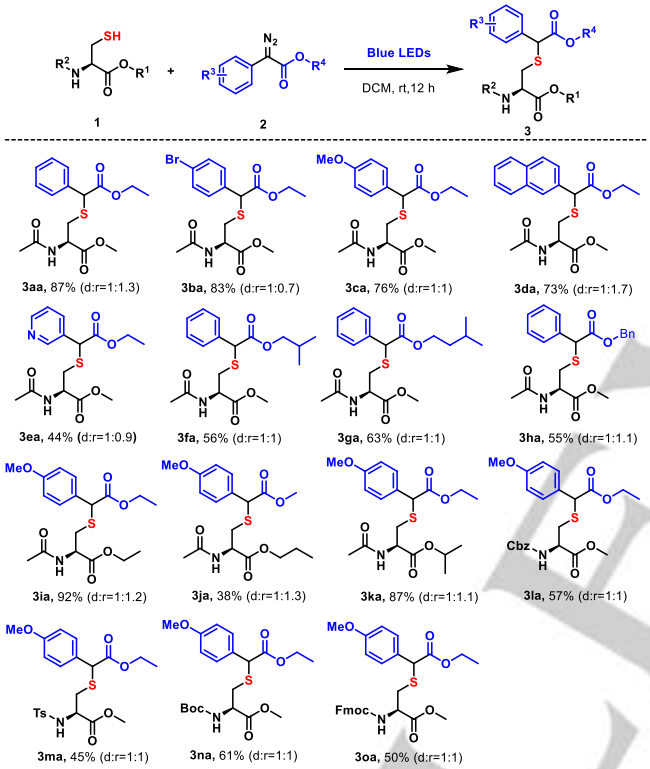
reaction yield (Table 1, entry 13). We also tried water and PBS as reaction solvents, but in each case only a trace amount of the target product was obtained (Table 1, entries 14−15). Blue-light irradiation was found to be crucial to this transformation: removing blue-light irradiation was associated with a dramatic decrease of the efficiency of the reaction (Table 1, entry 16); when green LEDs and white LEDs were used instead of blue LEDs, only 48% and 54% isolated yields were obtained (Table 1, entries 17−18); and while the reaction can proceed under daylight, but only trace amount of target product was observed (Table 1, entry 19).



Scheme 2 S−H bond insertion reactions of aryldiazoacetates **2** (2.0 equiv, 1.0 mmol) with cysteine derivatives **1** (1.0 equiv, 0.5 mmol) at room temperature under irradiation with blue LEDs (455 nm, 50 W). The regioselectivity was determined using NMR analysis (see Supporting Information). Boc = tert-butyloxycarbonyl; Cbz = benzoxycarbonyl; Ts = toluenesufonyl; Fmoc = fluorenylmethoxycarbonyl.

With the optimized reaction conditions in hand, we expanded the scope of this strategy involving, visible-light-mediated S−H bond insertion. First, various substituted phenyl diazoacetates **2** were investigated as substrates to react with the *N*-Ac-L-cysteine-OMe (**1a**) under photochemical conditions and irradiation with blue LEDs gave the corresponding S−H functionalization products in good to excellent yields, regardless of the substitution pattern. It is noteworthy that the electronic character of the aryl group (R^3) did not have much influence on the reaction outcome, and a range of substituents including electron-neutral (H), electron-donating (OMe), and electron-withdrawing (Br) substituents on the aromatic ring para-position were well tolerated, and resulted in the corresponding products with yields ranging from 76% to 87% (**3aa**–**3ca**). In addition to phenyl derivatives, other aryl groups such as naphthalene (**1da**) and pyridine (**1ea**) each proved to be suitable for this S–H insertion reaction, although lower yields were obtained (**3da** and **3ea**). Meanwhile, the reaction also proved to be tolerant to various groups at the R^4 position, including isobutyl, isoamyl and benzyl groups under the optimized reaction conditions (56% yield for **3fa**, 63% yield for **3ga** and 55% yield for **3ha**, respectively). Afterwards, we turned our attention to examining the generality of the R^1 and R^2 groups on the cysteine coupling partner. Seven cysteine derivatives (**1ia** *N*-Ac-L-cysteine-OEt, **1ja** *N*-Ac-L-cysteine-OPro, **1ka** *N*-Ac-L-cysteine-OisoPro, **1la** *N*-Cbz-L-cysteine-OMe, **1ma** *N*-Tosyl-L-cysteine-OMe, **1na** *N*-Boc-L-cysteine-OMe) and **1oa** *N*-Fmoc-L-cysteine-OMe were prepared and subjected to our protocol. Satisfyingly, *N*-Ac-L-cysteine-OEt, *N*-Ac-L-cysteine-OisoPro and *N*-Boc-L-cysteine-OMe afforded the corresponding products **3ia** (92%), **3ka** (87%), and **3na** (61%) in good yields. The other cysteine derivatives, namely *N*-Ac-L-cysteine-OPro, *N*-Cbz-L-cysteine-OMe, *N*-Tosyl-L-cysteine-OMe and *N*-Fmoc-L-cysteine-OMe showcased a lower reactivity, affording the corresponding products in 38%–57% yields.

To further demonstrate the applicability of the visible-light induced S−H bond insertion reactions, we focused on the compatibility of this method with simple cysteine-containing dipeptides. Model studies using *N*-Boc-L-Phe-L-Cys-OMe **1ab** as the trapping reagent were conducted with a series of aryldiazoacetates. As shown in Scheme 3, isobutyl, isoamyl and allyl groups at R^4 position of the aryldiazoacetate substrate each proved to be suitable for this transformation, giving the desired products with 56–65% yields (**3ab**–**3ad**). In subsequent investigations, aryldiazoacetates bearing a variety of substituents including electron-neutral (**3af**, **3ag**, **3al**), electron-rich (**3ah**–**3aj**), and electron-poor (**3ak**) group at different positions of the aromatic ring (R^3) moiety, gave the corresponding products with yields ranging from 31% to 80%. Moreover, the reaction was found to not be limited to *N*-Boc-L-Phe-L-Cys-OMe (**1ab**),

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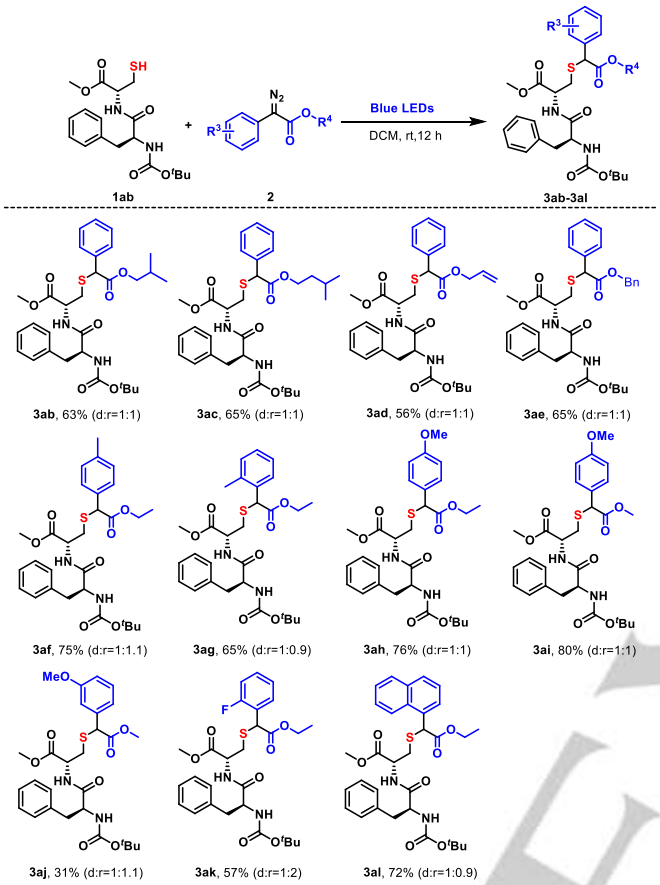
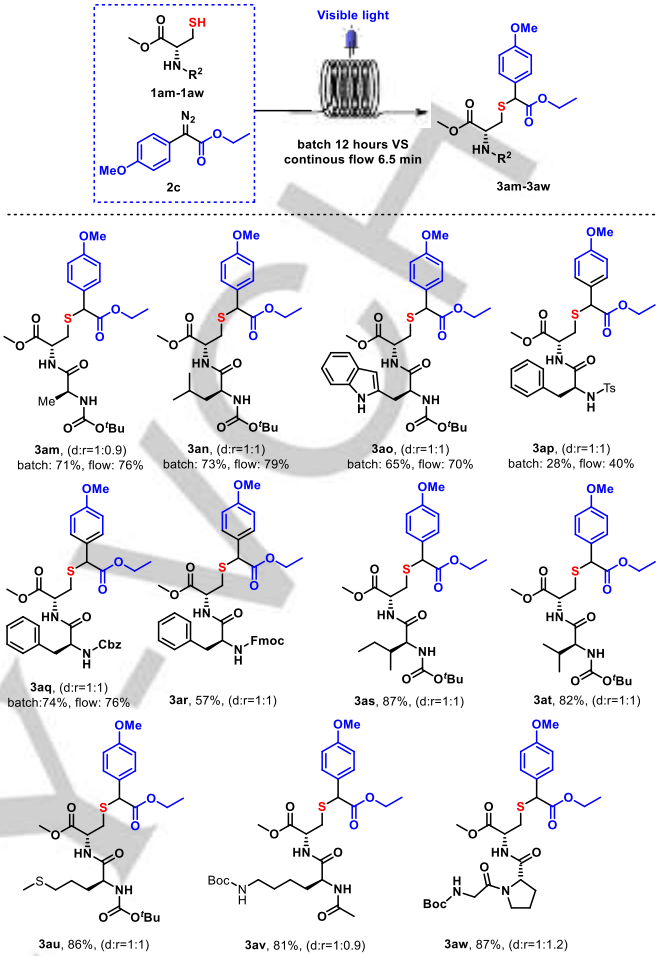
ten cysteine-containing dipeptides with different amine protecting groups were prepared to react with the ethyl 2-diazo-2-(4-methoxyphenyl)-acetate **2c** in sequence (Scheme 4). To our delight, good to excellent yields



Scheme 3 S−H bond insertion reactions of *N*-Boc-L-Phe-L-Cys-OMe **1ab** (1.0 equiv, 0.5 mmol) with aryldiazoacetates **2** (2.0 equiv, 1.0 mmol) at room temperature under irradiation with blue LEDs (455 nm, 50 W). The regioselectivitys was determined form NMR analyses (see Supporting Information).

were obtained for *N*-Boc-L-Ala-L-Cys-OMe (**3am**, 71%), *N*-Boc-L-Leu-L-Cys-OMe (**3an**, 73%), *N*-Boc-L-Trp-L-Cys-OMe (**3ao**, 65%), *N*-Ts-L-Phe-L-Cys-OMe (**3ap**, 28%), *N*-Cbz-L-Phe-L-Cys-OMe (**3aq**, 74%), *N*-Fmoc-L-Phe-L-Cys-OMe (**3ar**, 57%), *N*-Boc-L-Ile-L-Cys-OMe (**3as**, 87%), *N*-Boc-L-Val-L-Cys-OMe (**3at**, 82%), *N*-Boc-L-Met-L-Cys-OMe (**3au**, 86%) and N^1-Ac-N^5-Boc-L-Lys-L-Cys-OMe (**3av**, 81%). These results showcased the compatibility and selectivity of our methodology with cysteine-containing dipeptides. In addition, we also carried out the reaction with the tripeptide *N*-Boc-Gly-Pro-Cys-OMe, and the target product was obtained with a good yield (**3aw**, 82%).

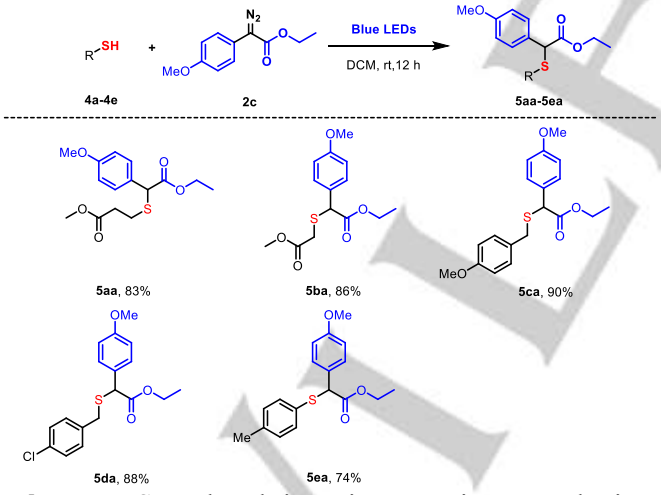


Scheme 4 Reaction conditions in batch: **1am-1aw** (1.0 equiv, 0.5 mmol), **2c** (2.0 equiv, 1.0 mmol), CH_2Cl_2 (2.5 mL), 50 W blue LEDs (λ = 455 nm), room temperature, 12 h. Reaction conditions in flow: **1am-1aq** (1.0 equiv, 0.5 mmol), **2c** (2.0 equiv, 1.0 mmol), CH_2Cl_2 (2.5 mL), 50 W blue LEDs (λ = 455 nm), room temperature, residence time: 6.5 min. Reported yields were those obtained after column chromatography.

In general, continuous-flow chemistry is excellent for conducting photochemical transformations, as it helps overcome the limitations associated with batch photochemistry. The narrow channel of a typical micro-reactor facilitates a uniform irradiation of the entire reaction mixture. Consequently, photochemical reactions can be accelerated to a substantially extent, and lower photocatalyst loadings are often feasible. Furthermore, scale-up of photochemical reactions is facilitated in continuous flow reactors.[20] Encouraged by these experiences and building on our experience with continuous-flow processes,[21] we turned our research attention to extending the protocol involving visible-light-induced S−H bond insertions to continuous-flow conditions.[22] For this purpose, we set up a photochemical continuous-flow microreactor and

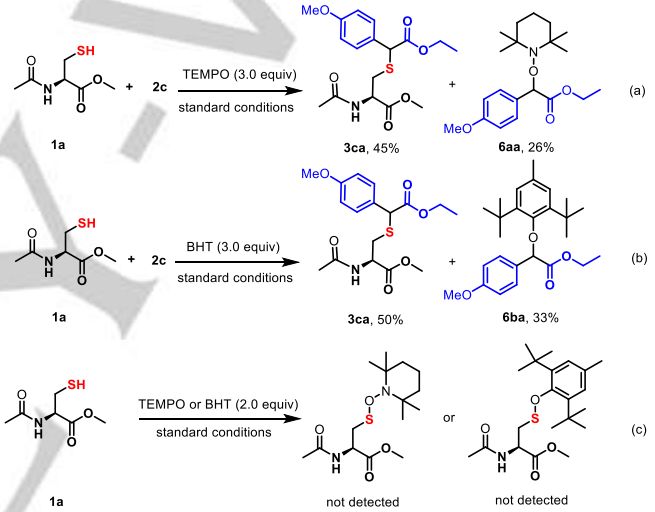
focused on process intensification for this reaction (see Supporting Information Scheme S1 and Figure S1). This photochemical continuous-flow microreactor consisted of perfluoroalkoxyalkane microcapillary tubing (PFA, ID = 500 μm, 5.0 m, 981 μL) wrapped around a reflux condenser, designed to play a role in cooling (see Supporting Information Figure S2). The reactor was subjected to irradiation generated by four blue LEDs (455 nm, 50 W). The two starting material solutions (L-cysteine dipeptides and 2-diazo-2-(4-methoxyphenyl)acetates **2c**) were mixed together and introduced continuously into a tube reactor by means of a syringe pump, which was irradiated by four blue LEDs (455 nm, 50W). In this manner with a residence time of 6.5 min, the desired products **3am-3aq** were obtained with yields of 40%-79%, higher than the 28%-74% of these products obtained under the conventional batch conditions (12 h) and thus demonstrating a much higher efficiency of the irradiation in continuous flow.

Thiols and thiophenol were then investigated (Scheme 5). Common thiols were first examined, and the corresponding products **5aa-5ba** were obtained with good yields (83-86%). Used of benzyl thiols also easily generated the products **5ca** and **5da** in 90% and 88% yields, respectively. Moreover, use of *p*-toluenethiol was also effective, and product **5ea** isolated in 74% yield.



Scheme 5 S−H bond insertion reactions employing thiols and thiophenol **4a-4e** (1.0 equiv, 0.5 mmol) with 2-diazo-2-(4-methoxyphenyl)acetates **2c** (2.0 equiv, 1.0 mmol) at room temperature under irradiation with blue LEDs (455 nm, 50 W).

To further explore the mechanism for these reactions, control experiments were conducted (Scheme 6). *N*-Ac-L-Cysteine **1a** was reacted with **2c** under standard conditions in the presence of the radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or 2,6-*di*-*tert*-butyl-4-methylphenol (BHT), and afforded the corresponding product **3ca** in 45% and 50% yields, respectively. And the radical scavenger adduct products **6aa** and **6ba** were obtained in 26% and 33% yields, respectively. The corresponding products were analyzed by MS and NMR (see Supporting Information description of control experiments), and this analysis indicated a radical mechanism in this system. However, when the substrate **1a** was subjected to reaction with 2.0 equiv of TEMPO, the expected product TEMPO-Cys was not observed (Scheme 6c).



Scheme 6 Control experiments

Conclusions

In summary, we have developed efficient visible-light-mediated S−H bond insertion reactions involving the photolyses of donor–acceptor diazoalkanes with cysteine derivatives or cysteine-containing dipeptides under mild conditions. A series of alkylated cysteine derivatives decorated with a broad range of substituents were achieved in moderate to good yields (37 examples, 28–92%), and common thiols and thiophenol were also tested in satisfactory yields (5 examples, 74-90%). And, various cysteine containing dipeptides were functionalized successfully in batch and in flow (5 examples, 40–79% yield vs 28%–74% yield). We evaluated this protocol in a continuous-flow setup, which allowed a 110-fold increase in productivity over conventional batch S−H bond insertion reactions. The operational simplicity and practicability, as well as the mild reaction conditions using visible light as an energy source, indicate the

protocol to be an attractive way to functionalize amino acids and peptides. Further studies on applying S−H bond insertion reactions for the construction of biologically active compounds are ongoing in our laboratory.

Conflicts of interest

There are no conflicts and declare.

Experimental Section

General information

Unless otherwise stated, all components as well as reagents and solvents were bought from commercial suppliers (Energy Chemical, *J&K* Chemic and TCI) and used without further purification. 50 W blue LEDs were used for light irradiation. Product isolation was performed using silica gel 60 (200-300 mesh).TLC analysis was performed using commercially prepared silica gel plates, and visualization was effected at ultraviolet light (254 nm). ^{1}H (400 MHz), ^{13}C (100 MHz) and ^{19}F (376 MHz) were measured on a 400 MHz Bruker AVANCE spectrometer. Chemical shifts were given in ppm, the coupling constants *J* were given in Hz. Peak multiplicities were designated by the following abbreviations: s = singlet, d = doublet, t = triplet, m = multiplet. ^{1}H NMR spectra were referenced to $CDCl_3$ (7.26 ppm), and ^{13}C NMR spectra were referenced to $CDCl_3$ (77.36 ppm). NMR data was processed using the MestReNova 9.0.1 software package. High resolution mass spectra were obtained on Agligent Technologies 6520 Accurate Series Q-TOF equipped with ESI.

Typical Experimental Procedure for the Synthesis of 3aa: A 25 mL over-dried Schlenk tube was charged with a stir bar, then **1a** (0.5 mmol) was added under argon atmosphere, next **2a** (1.0 mmol) and CH_2Cl_2 (2.5 mL) were added via syringe. The reaction was stirred under 50 W blue LEDs for 12 hours. After completion, the reaction mixture was diluted with CH_2Cl_2 and evaporated under reduced pressure. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate 1/1 v/v) on silica gel to afford the desired product with both diastereoisomers approximately in a 1:1 mixture **3aa** as a white colloid (147.1 mg, 87% yield).

Methyl *N*-acetyl-S-(2-ethoxy-2-oxo-1-phenylethyl)-L-cysteinate (3aa). White colloid (147.1 mg, 87% yield, d:r = 1:1.3). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.48 – 7.39 (m, 2H), 7.38 – 7.28 (m, 3H), 6.37 (d, *J* = 33.7 Hz, 1H), 4.86 – 4.76 (m, 1H), 4.67 – 4.55 (m, 1H), 4.25 – 4.12 (m, 2H), 3.74 (d, J = 16.6 Hz, 3H), 2.96 (s, 2H), 2.01 (d, *J* = 23.1 Hz, 3H), 1.28 – 1.22 (m, 3H). ^{13}C NMR (100 MHz, Chloroform-d) δ 171.1 (d, *J* = 5.7 Hz, 1C) , 170.6 , 169.9 (d, *J* = 5.8 Hz, 1C), 135.6 (d, *J* = 2.8 Hz, 1C) , 128.8 , 128.5 , 128.4, 128.4(2) , 62.0 (d, J = 3.4 Hz, 1C) , 52.7 (d, *J* = 3.7 Hz, 1C) , 52.5 (d, *J* = 15.5 Hz, 1C) , 51.6 (d, *J* = 10.4 Hz, 1C) , 33.7 (d, *J* = 16.5 Hz, 1C) , 23.1 (d, *J* = 3.7 Hz, 1C), 14.0. HRMS (ESI) m/z: calcd for $C_{16}H_{21}NO_5SNa$ $[M+Na]^+$: 362.1033, found: 362.1036.

Methyl *N*-acetyl-*S*-(1-(4-bromophenyl)-2-ethoxy-2-oxoethyl)-L-cysteinate (3ba). White colloid (173.9 mg, 83% yield, d:r = 1:0.7). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.53 – 7.42 (m, 2H), 7.37 – 7.29 (m, 2H), 6.38 – 6.19 (m, 1H), 4.90 – 4.76 (m, 1H), 4.66 – 4.49 (m, 1H), 4.27 – 4.12 (m, 2H), 3.75 (d, *J* = 16.1 Hz, 3H), 3.12 – 2.83 (m, 2H), 2.02 (d, *J* = 19.2 Hz, 3H), 1.28 – 1.23 (m, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 171.0 (d, *J* = 9.8 Hz, 1C), 170.1, 169.9 (d, *J* = 6.0 Hz, 1C) , 134.7 (d, *J* = 3.3 Hz, 1C), 131.9 , 130.2(4), 130.1(6), 122.6 , 62.2 (d, *J* = 5.2 Hz, 1C) , 52.8 (d, *J* = 3.8 Hz, 1C) , 51.9, 51.5 (d, *J* = 11.4 Hz, 1C) , 33.9 (d, *J* = 25.8 Hz, 1C) , 23.1 (d, *J* = 2.4 Hz, 1C) , 14.0. HRMS (ESI) m/z: calcd for $C_{16}H_{20}BrNO_5SNa$ $[M+Na]^+$: 440.0138, found: 440.0141.

Methyl *N*-acetyl-*S*-(2-ethoxy-1-(4-methoxyphenyl)-2-oxoethyl)-L-cysteinate (3ca). White colloid (141.0 mg, 76% yield, d:r = 1:1). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.41 – 7.29 (m, 2H), 6.92 – 6.80 (m, 2H), 6.42 – 6.20 (m, 1H), 4.87 – 4.74 (m, 1H), 4.64 – 4.52 (m, 1H), 4.25 – 4.10 (m, 2H), 3.80 (s, 3H), 3.75 (d, *J* = 13.7 Hz, 3H), 3.05– 2.87 (m, 2H), 2.02 (d, *J* = 19.9 Hz, 3H), 1.28 – 1.22 (m, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 171.1 (d, *J* = 5.3 Hz,1C), 170.8 , 169.9 (d, *J* = 6.3 Hz, 1C) , 159.6 , 129.7, 129.6, 127.4 (d, *J* = 2.5 Hz, 1C) , 114.2 , 61.9 (d, *J* = 3.3 Hz, 1C) , 55.3 , 52.7 (d, *J* = 3.2 Hz, 1C) , 51.9 (d, *J* = 16.8 Hz, 1C) , 51.6 (d, *J* = 10.1 Hz, 1C) , 33.7 (d, *J* = 17.3 Hz, 1C) , 23.1 (d, *J* = 2.8 Hz, 1C) , 14.1. HRMS (ESI) m/z: calcd for $C_{17}H_{23}NO_6SNa$ $[M+Na]^+$: 392.1138, found: 392.1151.

Methyl *N*-acetyl-*S*-(2-ethoxy-1-(naphthalen-2-yl)-2-oxoethyl)-L-cysteinate (3da). White colloid (142.3 mg, 73% yield, d:r = 1:1.7). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.14 (d, *J* = 8.5 Hz, 1H), 7.92 – 7.80 (m, 2H), 7.66 – 7.55 (m, 2H), 7.54 – 7.44 (m, 2H), 6.43 – 6.33 (m, 1H), 5.43 – 5.34 (m, 1H), 4.85 – 4.76 (m, 1H), 4.25 – 4.16 (m, 2H), 3.66 (d, *J* = 6.1 Hz, 3H), 3.17 – 2.94 (m,2H), 1.89 (d, *J* = 21.4 Hz, 3H), 1.22 – 1.17 (m, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 171.1(1) , 171.0(6) , 169.9 , 134.1, 131.1, 130.9, 129.3, 129.1 (d, *J* = 2.7 Hz, 1C), 126.8 , 126.7, 126.1 (d, *J* = 3.5 Hz, 1C), 125.3, 123.3 (d, *J* = 5.8 Hz, 1C) , 62.2, 52.7 (d, *J* = 1.6 Hz, 1C), 51.6 (d, *J* = 13.3 Hz, 1C), 49.6 (d, *J* = 9.4 Hz,1C), 34.0 (d, *J* = 9.9 Hz, 1C) , 22.9 (d, *J* = 5.9 Hz, 1C), 14.0. HRMS (ESI) m/z: calcd for $C_{20}H_{23}NO_5SNa$ $[M+Na]^+$: 412.1189, found: 412.1175.

Methyl *N*-acetyl-*S*-(2-ethoxy-2-oxo-1-(pyridin-3-yl)ethyl)-L-cysteinate (3ea). Yellow colloid (75.1 mg, 44% yield, d:r = 1:0.9) ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.70 – 8.49 (m, 2H), 7.94 – 7.78 (m, 1H), 7.37 – 7.29 (m, 1H), 6.53 – 6.26 (m, 1H), 4.94 – 4.79 (m, 1H), 4.74 – 4.57 (m, 1H), 4.29 – 4.16 (m, 2H), 3.76 (d, *J* = 17.2 Hz, 3H), 3.18 – 2.86 (m, 2H), 2.04 (d, *J* = 13.3 Hz, 3H), 1.30 – 1.24 (m, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 171.0 (d, *J* = 11.6 Hz, 1C), 170.0, 169.9, 149.6(0), 149.5(6), 136.2 (d, *J* = 18.1 Hz, 1C), 123.7, 62.4 (d, *J* = 6.5 Hz, 1C), 52.9 (d, *J* =

3.9 Hz, 1C), 51.5 (d, *J* = 20.5 Hz, 1C), 49.6 (d, *J* = 49.2 Hz, 1C), 34.1 (d, *J* = 19.4 Hz, 1C), 23.1, 14.1. HRMS (ESI) m/z: calcd for $C_{15}H_{20}N_2O_5SNa$ $[M+Na]^+$: 363.0985, found: 363.1005.

Methyl *N*-acetyl-*S*-(2-isobutoxy-2-oxo-1-phenylethyl)-L-cysteinate (3fa). White colloid (102.6 mg, 56% yield, d:r = 1:1). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.50 – 7.39 (m, 2H), 7.39 – 7.28 (m, 3H), 6.37 (d, *J* = 37.3 Hz, 1H), 4.88 – 4.74 (m, 1H), 4.69 – 4.53 (m, 1H), 3.98 – 3.84 (m, 2H), 3.74 (d, *J* = 17.0 Hz, 3H), 3.15 – 2.84 (m, 2H), 2.04 (d, *J* = 25.3 Hz, 3H), 1.93 – 1.85 (m, 1H), 0.86 (d, *J* = 5.0 Hz, 6H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 171.1 (d, *J* = 6.1 Hz, 1C), 170.6, 170.0, 135.7 (d, *J* = 4.3 Hz, 1C), 128.7(9), 128.7(7), 128.5(0), 128.4(6), 128.4, 71.9 (d, *J* = 1.2 Hz, 1C), 52.9 , 52.7 (d, *J* = 3.5 Hz, 1C), 51.6 (d, *J* = 14.3 Hz, 1C), 33.8 (d, *J* = 15.0 Hz, 1C), 27.7, 23.1 (d, *J* = 4.4 Hz, 1C), 18.9. HRMS (ESI) m/z: calcd for $C_{18}H_{25}NO_5SNa$ $[M+Na]^+$: 390.1346, found: 390.1335.

Methyl *N*-acetyl-*S*-(2-(isopentyloxy)-2-oxo-1-phenylethyl)-L-cysteinate (3ga). White colloid (120.4 mg, 63% yield, d:r = 1:1). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.46 – 7.39 (m, 2H), 7.38 – 7.30 (m, 3H), 6.49 – 6.29 (m, 1H), 4.85 – 4.75 (m, 1H), 4.68 – 4.55 (m, 1H), 4.19 – 4.12 (m, 2H), 3.73 (d, *J* = 17.4 Hz, 3H), 3.05 – 2.88 (m, 2H), 2.00 (d, *J* = 24.3 Hz, 3H), 1.64 – 1.54 (m, 1H), 1.53 – 1.46 (m, 2H), 0.90 – 0.84 (m, 6H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 171.1 (d, *J* = 6.5 Hz, 1C), 170.6, 169.9 (d, *J* = 6.4 Hz, 1C), 135.7 (d, *J* = 3.2 Hz, 1C), 128.7(8), 128.7(7), 128.5, 128.4(3), 128.4(0), 64.7 (d, *J* = 3.0 Hz, 1C), 52.7 (d, *J* = 4.1 Hz, 1C), 52.6 (d, *J* = 8.2 Hz, 1C), 51.6 (d, *J* = 14.7 Hz, 1C), 37.1, 33.7 (d, *J* = 17.4 Hz, 1C), 24.97, 23.0 (d, *J* = 3.4 Hz, 1C), 22.4. HRMS (ESI) m/z: calcd for $C_{19}H_{27}NO_5SNa$ $[M+Na]^+$: 404.1502, found: 404.1492.

Methyl *N*-acetyl-*S*-(2-(benzyloxy)-2-oxo-1-phenylethyl)-L-cysteinate (3ha). White colloid (110.3 mg, 55% yield, d:r = 1:1.1). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.46 – 7.38 (m, 2H), 7.36 – 7.23 (m, 8H), 6.35 (d, *J* = 32.8 Hz, 1H), 5.22 – 5.10 (m, 2H), 4.85 – 4.74 (m, 1H), 4.72 – 4.62 (m, 1H), 3.70 (d, *J* = 15.8 Hz, 3H), 3.05 – 2.86 (m, 2H), 1.96 (d, *J* = 17.0 Hz, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 171.0 (d, *J* = 4.6 Hz, 1C), 170.4 (d, *J* = 1.2 Hz, 1C), 169.9 (d, *J* = 6.2 Hz, 1C), 135.4 (d, *J* = 2.4 Hz, 1C), 135.3 (d, *J* = 1.7 Hz, 1C), 128.8(4), 128.8(3), 128.5(9), 128.5(6), 128.5(4), 128.4(9), 128.4 (d, J = 4.3 Hz, 1C), 128.1, 67.5 (d, *J* = 4.2 Hz, 1C), 52.7 (d, *J* = 4.5 Hz, 1C), 52.5 (d, *J* = 11.6 Hz, 1C), 51.6 (d, *J* = 16.2 Hz, 1C), 33.8 (d, *J* = 12.2 Hz, 1C), 23.0 (d, *J* = 2.0 Hz, 1C). HRMS (ESI) m/z: calcd for $C_{21}H_{23}NO_5S$ $[M+Na]^+$: 424.1189, found: 424.1176.

Ethyl *N*-acetyl-*S*-(2-ethoxy-1-(4-methoxyphenyl)-2-oxoethyl)-L-cysteinate (3ia). White colloid (176.8 mg, 92% yield, d:r = 1:1.2). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.43 – 7.31 (m, 2H), 6.93 – 6.82 (m, 2H), 6.58 – 6.44 (m, 1H), 4.87 – 4.72 (m, 1H), 4.68 – 4.55 (m, 1H), 4.26 – 4.12 (m, 4H), 3.82 – 3.78 (m, 3H), 3.07 – 2.81 (m, 2H), 2.06 – 1.97 (m, 3H), 1.32 – 1.22 (m, 6H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 170.8 (d, *J* = 4.4 Hz, 1C), 170.7 (d, *J* = 7.7 Hz, 1C), 170.0 (d, *J* = 5.6 Hz, 1C), 159.6 , 129.7 (d, *J* = 6.1 Hz, 1C), 127.5, 127.4, 114.1, 61.9 (d, *J* = 2.3 Hz, 1C), 61.9, 55.3, 51.8 (d, *J* = 20.2 Hz, 1C), 51.6, 33.7 (d, *J* = 29.0 Hz, 1C), 23.0 (d, *J* = 3.0 Hz, 1C), 14.1, 14.0 (d, *J* = 2.0 Hz, 1C). HRMS (ESI) m/z: calcd for $C_{18}H_{25}NO_5SNa$ $[M+Na]^+$: 406.1295, found: 406.1282.

Propyl *N*-acetyl-*S*-(2-methoxy-1-(4-methoxyphenyl)-2-oxoethyl)-L-cysteinate (3ja). White colloid (72.9 mg, 38% yield, d:r = 1:1.3). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.35 (t, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.53 – 6.37 (m, 1H), 4.87 – 4.74 (m, 1H), 4.69 – 4.58 (m, 1H), 4.17 – 4.04 (m, 2H), 3.79 (s, 3H), 3.75 – 3.68 (m, 3H), 3.04 (s, 2H), 2.02 (d, *J* = 21.7 Hz, 3H), 1.73 – 1.59 (m, 2H), 0.99 – 0.88 (m, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 171.3 (d, *J* = 1.9 Hz, 1C), 170.7 (d, *J* = 5.7 Hz, 1C), 170.0 (d, *J* = 8.1 Hz, 1C), 159.6, 129.7 (d, *J* = 1.1 Hz, 1C), 127.3 (d, *J* = 2.2 Hz, 1C), 114.2, 67.5 (d, *J* = 3.0 Hz, 1C), 55.3, 52.8 (d, *J* = 7.4 Hz, 1C), 51.8, 51.6 (d, *J* = 7.1 Hz, 1C), 33.8 (d, *J* = 26.9 Hz, 1C), 23.1 (d, *J* = 4.1 Hz, 1C), 21.8 (d, *J* = 4.3 Hz, 1C), 10.3. HRMS (ESI) m/z: calcd for $C_{18}H_{25}NO_6SNa$ $[M+Na]^+$: 406.1295, found: 406.1284.

Isopropyl *N*-acetyl-*S*-(2-ethoxy-1-(4-methoxyphenyl)-2-oxoethyl)-L-cysteinate (3ka). White colloid (173.4 mg, 87% yield, d:r = 1:1.1). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.42 – 7.32 (m, 2H), 6.92 – 6.82 (m, 2H), 6.70 – 6.59 (m, 1H), 5.11 – 4.97 (m, 1H), 4.82 – 4.70 (m, 1H), 4.69 – 4.56 (m, 1H), 4.26 – 4.11 (m, 2H), 3.79 (d, *J* = 1.3 Hz, 3H), 3.05 – 2.84 (m, 2H), 2.01 (d, *J* = 19.9 Hz, 3H), 1.29 – 1.20 (m, 9H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 170.8 (d, *J* = 5.1 Hz, 1C), 170.2, 170.1 (d, *J* = 3.6 Hz, 1C), 159.5, 129.7 (d, *J* = 5.7 Hz, 1C), 127.5, 127.4, 114.1, 69.7 (d, *J* = 4.3 Hz, 1C), 61.8 (d, *J* = 7.9 Hz, 1C), 55.2, 51.9 (d, *J* = 10.7 Hz, 1C), 51.6 (d, *J* = 20.2 Hz, 1C), 33.7 (d, *J* = 40.5 Hz, 1C), 22.9 (d, *J* = 3.2 Hz, 1C), 21.7 (d, *J* = 2.0 Hz, 1C), 21.6, 14.0 (d, *J* = 4.1 Hz, 1C). HRMS (ESI) m/z: calcd for $C_{19}H_{27}NO_6SNa$ $[M+Na]^+$: 420.1451, found: 420.1440.

Methyl *N*-((benzyloxy)carbonyl)-*S*-(2-ethoxy-1-(4-methoxyphenyl)-2-oxoethyl)-L-cysteinate (3la). White colloid (176.0 mg, 57% yield, d:r = 1:1). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.46 – 7.20 (m, 7H), 6.83 (d, *J* = 8.0 Hz, 2H), 5.71 (d, *J* = 23.3 Hz, 1H), 5.22 – 5.01 (m, 2H), 4.69 – 4.48 (m, 2H), 4.26 – 4.06 (m, 2H), 3.75 (d, *J* = 2.4 Hz, 3H), 3.71 (d, *J* = 10.0 Hz, 3H), 3.12 – 2.75 (m, 2H), 1.29 – 1.15 (m, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 171.1 (d, *J* = 4.9 Hz, 1C), 170.7 (d, *J* = 8.9 Hz, 1c), 159.6, 155.8, 136.2, 129.7 (d, *J* = 3.9 Hz, 1C), 128.6, 128.5, 128.2, 128.1, 127.4 (d, *J* = 7.4 Hz, 1C), 114.2, 67.1 (d, *J* = 2.7 Hz, 1C), 61.9 (d, *J* = 4.3 Hz, 1C), 55.3, 53.4 (d, *J* = 23.7 Hz, 1C), 52.7, 51.6 (d, *J* = 38.4 Hz, 1C), 33.8 (d, *J* = 33.3 Hz, 1C), 14.1 (d, *J* = 2.1 Hz, 1C). HRMS (ESI) m/z: calcd for $C_{23}H_{27}NO_7SNa$ $[M+Na]^+$: 484.1400, found: 484.1386.

Methyl *S*-(2-ethoxy-1-(4-methoxyphenyl)-2-oxoethyl)-*N*-tosyl-L-cysteinate (3ma). White colloid (108.7 mg, 45% yield, d:r = 1:1). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.78

– 7.65 (m, 2H), 7.38 – 7.27 (m, 4H), 6.86 (d, *J* = 8.7 Hz, 2H), 5.55 – 5.40 (m, 1H), 4.63 (d, *J* = 3.0 Hz, 1H), 4.25 – 4.09 (m, 3H), 3.80 (s, 3H), 3.56 (d, *J* = 2.9 Hz, 3H), 2.97 – 2.75 (m, 2H), 2.42 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 170.6 (d, *J* = 5.8 Hz, 1C), 170.3 (d, *J* = 6.5 Hz, 1C), 159.6, 143.8 (d, *J* = 4.5 Hz, 1C), 136.6 (d, *J* = 9.2 Hz, 1C), 129.8 (d, *J* = 6.9 Hz, 1C), 129.7(3), 129.7(1), 127.4, 127.3, 127.2(1), 114.2(0), 114.1(5), 61.9 (d, *J* = 2.9 Hz, 1C), 55.6, 55.4 (d, *J* = 8.1 Hz, 1C), 52.9, 51.8 (d, *J* = 28.4 Hz, 1C), 34.5 (d, *J* = 15.4 Hz, 1C), 21.6, 14.1. HRMS (ESI) m/z: calcd for $C_{22}H_{27}NO_7S_2Na$ $[M+Na]^+$: 504.1121, found: 504.1102.

Methyl *N*-(tert-butoxycarbonyl)-*S*-(2-ethoxy-1-(4-methoxyphenyl)-2-oxoethyl)-L-cysteinate (3na). White colloid (151.3 mg, 61% yield, d:r = 1:1). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.45 – 7.33 (m, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 5.48 – 5.26 (m, 1H), 4.69 – 4.58 (m, 1H), 4.59 – 4.46 (m, 1H), 4.25 – 4.11 (m, 2H), 3.79 (s, 3H), 3.74 (d, *J* = 10.1 Hz, 3H), 3.07 – 2.78 (m, 2H), 1.45 (d, *J* =5.2 Hz, 9H), 1.30 – 1.21 (m, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 171.4 (d, *J* = 5.4 Hz, 1C), 170.7 (d, *J* = 11.4 Hz, 1C), 159.5, 129.74, 129.70, 127.5 (d, *J* = 8.4 Hz, 1C), 114.1(1), 114.0(9), 80.1 (d, *J* = 4.0 Hz, 1C), 61.8 (d, *J* = 4.4 Hz, 1C), 55.3, 52.9 (d, *J* = 23.1 Hz, 1C), 52.6 (d, *J* = 1.9 Hz, 1C), 51.6 (d, *J* = 34.7 Hz, 1C), 34.0 (d, *J* = 44.4 Hz, 1C), 28.3, 14.1. HRMS (ESI) m/z: calcd for $C_{20}H_{29}NO7_SNa$ $[M+Na]^+$: 450.1557, found: 450.1544.

Methyl *N*-(((9H-fluoren-9-yl)methoxy)carbonyl)-*S*-(2-ethoxy-1-(4-methoxyphenyl)-2-oxoethyl)-L-cysteinate (3oa). White colloid (137.8 mg, 50% yield, d:r = 1:1). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.75 (d, *J* = 7.5 Hz, 2H), 7.61 (q, *J* = 6.9 Hz, 2H), 7.41 – 7.28 (m, 6H), 6.84 (t, *J* = 8.4 Hz, 2H), 5.74 (d, *J* = 15.7 Hz, 1H), 4.62 (d, *J* = 12.2 Hz, 2H), 4.43 – 4.33 (m, 2H), 4.25 – 4.13 (m, 3H), 3.75 (d, *J* = 9.5 Hz, 6H), 3.10 – 2.83 (m, 2H), 1.23 (q, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 171.1, 170.8 (d, *J* = 11.0 Hz, 1C), 159.6 (d, *J* = 2.0 Hz, 1C), 155.8, 143.9 (d, *J* = 1.9 Hz, 1C), 143.8 (d, *J* = 3.7 Hz, 1C), 141.3, 129.8 (d, *J* = 2.3 Hz, 1C), 127.8, 127.1, 125.2, 120.0, 114.2, 67.3 (d, *J* = 9.1 Hz, 1C), 61.9 (d, *J* = 4.7 Hz, 1C), 55.3 (d, *J* = 2.7 Hz, 1C), 53.5 (d, *J* = 18.3 Hz, 1C), 52.8 (d, *J* = 2.1 Hz, 1C), 51.7 (d, *J* = 32.0 Hz, 1C), 33.8 (d, *J* = 19.6 Hz, 1C), 31.6, 22.7, 14.1 (d, *J* = 0.8 Hz, 1C). HRMS (ESI) m/z: calcd for $C_{30}H_{31}NO_7SNa$ $[M+Na]^+$: 572.1713, found: 572.1726.

Methyl *N*-((tert-butoxycarbonyl)-L-phenylalanyl)-*S*-(2-isobutoxy-2-oxo-1-phenylethyl)-L-cysteinate (3ab). White colloid (180.4 mg, 63% yield, d:r = 1:1). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.45 – 7.17 (m, 10H), 6.79 (d, *J* = 36.2 Hz, 1H), 5.16 – 4.89 (m, 1H), 4.83 – 4.70 (m, 1H), 4.70 – 4.56 (s, 1H), 4.40 (s, 1H), 3.99 – 3.83 (m, 2H), 3.70 (d, *J* = 15.2 Hz, 3H), 3.20 – 2.78 (m, 4H), 1.96 – 1.86 (m, 1H), 1.41 (d, *J* = 12.7 Hz, 9H), 0.97 – 0.75 (m, 6H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 171.3 (d, *J* = 10.0 Hz, 1C), 170.7, 170.5 (d, *J* = 8.8 Hz, 1C), 136.5 (d, *J* = 6.4 Hz, 1C), 135.6, 129.4, 128.7 (d, *J* = 1.7 Hz, 1C), 128.6(4), 128.5(8), 128.5, 128.4 (d, *J* = 3.0 Hz, 1C), 126.9, 80.2, 71.9 (d, *J* = 2.0 Hz, 1C), 55.6, 52.9, 52.7 (d, *J* = 3.4 Hz, 1C), 52.4, 51.9, 51.6, 38.3, 33.7, 28.3, 27.7, 18.9. HRMS (ESI) m/z: calcd for $C_{30}H_{40}N_2O_7SNa$ $[M+Na]^+$: 595.2448, found: 595.2438.

Methyl *N*-((tert-butoxycarbonyl)-L-phenylalanyl)-*S*-(2-(isopentyloxy)-2-oxo-1-phenylethyl)-L-cysteinate (3ac). White colloid (190.6 mg, 65% yield, d:r = 1:1). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.45 – 7.38 (m, 2H), 7.36 – 7.16 (m, 8H), 6.93 – 6.83 (m 1H), 5.09 (d, *J* =38.6 Hz, 1H), 4.82 – 4.70 (m, 1H), 4.70 – 4.56(m, 1H), 4.51 –4.34 (m, 1H), 4.21 – 4.12 (m, 2H), 3.70 (d, *J* = 16.0 Hz, 3H), 3.19 – 2.80(m, 4H), 1.62 – 1.55(m, 1H), 1.52 – 1.45 (m, 2H), 1.39 (d, *J* = 2.8 Hz, 9H), 0.90 – 0.82 (m, 6H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 171.3 (d, *J* = 8.9 Hz, 1C), 170.7 (d, *J* = 5.8 Hz, 1C), 170.5 (d, *J* = 10.2 Hz, 1C), 155.4, 136.5 (d, *J* = 5.9 Hz, 1C), 135.6 (d, *J* = 18.4 Hz, 1C), 129.4, 128.8, 128.6(3), 128.5(8), 128.5, 128.4(1), 128.3(8), 126.9, 80.2, 64.7 (d, *J* = 5.4 Hz, 1C), 55.6, 52.7 (d, *J* = 2.9 Hz, 1C), 52.2, 51.7 (d, *J* = 29.0 Hz, 1C), 38.3, 37.0, 33.6 (d, *J* = 9.9 Hz, 1C), 28.3, 25.0, 24.9, 22.4. HRMS (ESI) m/z: calcd for $C_{31}H_{42}N_2O_7SNa$ $[M+Na]^+$: 609.2605, found: 609.2591.

Methyl *S*-(2-(allyloxy)-2-oxo-1-phenylethyl)-*N*-((tert-butoxycarbonyl)-L-phenylalanyl)-L-cysteinate (3ad). White colloid (115.8 mg, 56% yield, d:r = 1:1.1). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.48 – 7.39 (m, 2H), 7.37 – 7.18 (m, 8H), 6.77 (d, *J* = 36.0 Hz, 1H), 5.93 – 5.79 (m, 1H), 5.30 – 5.18 (m, 2H), 5.08 – 4.93 (m, 1H), 4.81 – 4.67 (m, 2H), 4.65 – 4.59 (m, 2H), 4.47 – 4.34 (m, 1H), 3.71 (d, *J* = 14.4 Hz, 3H), 3.16 – 2.83 (m, 4H), 1.39 (s, 9H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 171.3 (d, *J* = 8.8 Hz, 1C), 170.4 (d, *J* = 7.6 Hz, 1C), 170.3 (d, *J* = 5.3 Hz, 1C), 155.3, 136.4 (d, *J* = 5.5 Hz, 1C), 135.4 (d, *J* = 5.4 Hz, 1C), 131.4 (d, *J* = 2.9 Hz, 1C), 129.4, 128.8, 128.7, 128.6, 128.5(2), 128.4(9), 127.0, 118.8, 80.2, 66.4 (d, *J* = 3.6 Hz, 1C), 55.6, 52.7 (d, *J* = 3.0 Hz, 1C), 52.5, 52.1, 51.7 (d, *J* = 21.9 Hz, 1C), 38.3, 33.7 (d, *J* = 6.4 Hz, 1C), 28.3. HRMS (ESI) m/z: calcd for $C_{29}H_{36}N_2O_7SNa$ $[M+Na]^+$: 579.2135, found: 579.2119.

Methyl *S*-(2-(benzyloxy)-2-oxo-1-phenylethyl)-*N*-((tert-butoxycarbonyl)-L-phenylalanyl)-L-cysteinate (3ae). White colloid (197.1 mg, 65% yield, d:r = 1:1). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.45 – 7.14 (m, 16H), 6.76 (d, *J* = 34.9 Hz, 1H), 5.25 – 5.10 (m, 2H), 4.79 – 4.59 (m, 2H), 4.39 (s, 1H), 3.67 (d, *J* = 13.4 Hz, 3H), 3.16 – 2.79 (m, 4H), 1.38 (d, *J* = 2.6 Hz, 9H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 171.2 (d, *J* = 9.2 Hz, 1C), 170.5 (d, *J* = 4.8 Hz, 1C), 170.4 (d, *J* = 6.9 Hz, 1C), 155.3, 136.4 (d, *J* = 4.6 Hz, 1C), 135.4, 135.3, 129.4, 128.8, 128.7, 128.6(3), 128.5(8), 128.5(5), 128.5, 128.4, 128.2 , 126.9, 80.2, 67.6 (d, *J* = 4.1 Hz, 1C), 55.6, 52.7 (d, *J* = 4.1 Hz, 1C), 52.5, 52.1, 51.7 (d, *J* = 29.8 Hz, 1C), 38.2, 33.7 (d, *J* = 7.1 Hz, 1C), 28.3. HRMS (ESI) m/z: calcd for $C_{33}H_{38}N_2O_7SNa$ $[M+Na]^+$: 629.2292, found: 629.2276.

Methyl *N*-((tert-butoxycarbonyl)-L-phenylalanyl)-*S*-(2-ethoxy-2-oxo-1-(p-tolyl)ethyl)-L-cysteinate (3af). White colloid (211.5 mg, 75% yield, d:r = 1:1.1). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.35 – 7.10 (m, 9H), 6.83 (d, *J* =

23.9 Hz, 1H), 5.05 (d, *J* = 34.0 Hz, 1H), 4.83 – 4.69 (m, 1H), 4.66 – 4.53 (m, 1H), 4.49 – 4.35 (m, 1H), 4.27 – 4.06 (m, 2H), 3.70 (d, *J* = 12.2 Hz, 3H), 3.19 – 2.80 (m, 4H), 2.33 (s, 3H), 1.39 (s, 9H), 1.24 (1.28-1.20, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 171.4, 170.8 (d, *J* = 7.9 Hz, 1C), 170.5 (d, *J* = 8.6 Hz, 1C), 155.3, 138.2, 136.6 (d, *J* = 3.6 Hz, 1C), 129.5, 129.4, 128.6, 128.5, 128.4, 126.9, 80.1, 61.9 (d, *J* = 6.4 Hz, 1C), 55.6, 52.7 (d, *J* = 2.7 Hz, 1C), 52.3, 51.8 (d, *J* = 5.8 Hz, 1C), 38.4, 33.6 (d, *J* = 7.1 Hz, 1C), 28.3, 21.1, 14.1. HRMS (ESI) m/z: calcd for $C_{29}H_{38}N_2O_7SNa$ $[M+Na]^+$: 581.2292, found: 581.2280.

Methyl *N*-((tert-butoxycarbonyl)-L-phenylalanyl)-*S*-(2-ethoxy-2-oxo-1-(o-tolyl)ethyl)-L-cysteinate (3ag). White colloid (182.8 mg, 65% yield, d:r = 1:0.9). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.42 (d, *J* = 7.6 Hz, 1H), 7.31 – 7.16 (m, 9H), 6.88 (d, *J* = 14.0 Hz, 1H), 5.03 (s, 1H), 4.91 – 4.82 (m, 1H), 4.79 – 4.71 (m, 1H), 4.24 – 4.15 (m, 2H), 3.71 (d, *J* = 6.5 Hz, 3H), 3.17 – 2.87 (m, 4H), 2.41 (d, *J* = 4.5 Hz, 3H), 1.39 (s, 9H), 1.26 – 1.21 (m, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 171.2, 171.1 (d, *J* = 14.6 Hz, 1C), 170.5, 155.3, 136.5, 136.4 (d, *J* = 14.0 Hz, 1C), 133.7 (d, *J* = 20.2 Hz, 1C), 130.8 (d, *J* = 8.3 Hz, 1C), 129.4, 128.65, 128.62, 128.32, 128.30, 128.2 (d, *J* = 8.3 Hz, 1C), 126.9, 126.5 (d, *J* = 2.2 Hz, 1C), 80.1, 62.1 (d, *J* = 2.0 Hz, 1C), 55.6, 52.7 (d, *J* = 3.0 Hz, 1C), 51.8 (d, *J* = 8.7 Hz, 1C), 49.1 (d, *J* = 27.3 Hz, 1C), 38.4, 33.8 (d, *J* = 36.1 Hz, 1C), 28.3, 19.5 (d, *J* = 0.9 Hz, 1C), 14.1. HRMS (ESI) m/z: calcd for $C_{29}H_{38}N_2O_7SNa$ $[M+Na]^+$: 581.2292, found: 581.2276.

Methyl *N*-((tert-butoxycarbonyl)-L-phenylalanyl)-*S*-(2-ethoxy-1-(4-methoxyphenyl)-2-oxoethyl)-L-cysteinate (3ah). White colloid (218.2 mg, 76% yield, d:r = 1:1). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.42 – 7.28 (m, 3H), 7.25 – 7.16 (m, 4H), 6.92 – 6.80 (m, 3H), 5.17 – 4.96 (m, 1H), 4.82 – 4.70 (m, 1H), 4.67 – 4.53 (m, 1H), 4.42 (s, 1H), 4.24 – 4.12 (m, 2H), 3.79 (d, *J* = 2.3 Hz, 3H), 3.71 (d, *J* = 11.4 Hz, 3H), 3.15-2.81 (m, 4H), 1.39 (d, *J* = 2.9 Hz, 9H), 1.27 – 1.22 m, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 171.4, 170.9 (d, *J* = 10.1 Hz, 1C), 170.5 (d, *J* = 9.0 Hz, 1C), 159.6, 155.3, 136.5 (d, *J* = 4.2 Hz, 1C), 129.8, 129.7, 129.4, 128.6, 126.9, 114.1, 80.1, 61.9 (d, *J* = 6.7 Hz, 1C), 55.3, 52.7 (d, *J* = 2.3 Hz, 1C), 51.9, 51.6, 51.4, 38.3, 33.6 (d, *J* = 12.3 Hz, 1C), 28.2, 14.1. HRMS (ESI) m/z: calcd for $C_{29}H_{38}N_2O_8SNa$ $[M+Na]^+$: 597.2241, found: 597.2225.

Methyl *N*-((tert-butoxycarbonyl)-L-phenylalanyl)-*S*-(2-methoxy-1-(4-methoxyphenyl)-2-oxoethyl)-L-cysteinate (3ai). White colloid (224.0 mg, 80% yield, d:r = 1:1). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.38 – 7.17 (m, 7H), 6.98 – 6.80 (m, 3H), 5.21 – 5.06 (m, 1H), 4.83 – 4.70 (m, 1H), 4.70 – 4.57 (m, 1H), 4.42 (s, 1H), 3.78 (d, *J* = 2.4 Hz, 3H), 3.74 – 3.63 (m, 6H), 3.20 – 2.77 (m, 4H), 1.39 (d, *J* = 3.2 Hz, 9H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 171.4, 171.3, 170.5 (d, *J* = 10.0 Hz, 1C), 159.6, 155.3, 136.5 (d, *J* = 4.5 Hz, 1C), 129.8, 129.7, 129.4, 128.6, 126.9, 114.2, 80.1, 55.3, 52.8 (d, *J* = 8.1 Hz, 1C), 52.7 (d, *J* = 4.3 Hz, 1C), 51.8, 51.7, 51.3, 38.3, 33.7, 33.6, 28.2. HRMS (ESI) m/z: calcd for $C_{28}H_{36}N_2O_8SNa$ $[M+Na]^+$: 583.2085, found: 583.2070.

Methyl *N*-((tert-butoxycarbonyl)-L-phenylalanyl)-*S*-(2-methoxy-1-(3-methoxyphenyl)-2-oxoethyl)-L-cysteinate (3aj). White colloid (88.1 mg, 31% yield, d:r = 1:1.1). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.32 – 7.16 (m, 6H), 7.05 – 6.79 (m, 4H), 5.21 – 5.02 (m, 1H), 4.82 – 4.71 (m, 1H), 4.70 – 4.56 (m, 1H), 4.43 (s, 1H), 3.85 – 3.64 (m, 9H), 3.20 – 2.79 (m, 4H), 1.45 – 1.31 (m, 9H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 171.4 (d, *J* = 9.8 Hz, 1C), 171.1 (d, *J* = 6.2 Hz, 1C), 170.5 (d, *J* = 7.5 Hz, 1C), 159.8 (d, *J* = 2.3 Hz, 1C), 155.4, 136.9 (d, *J* = 14.5 Hz, 1C), 136.5 (d, *J* = 4.5 Hz, 1C), 129.8, 129.3(8), 129.3(7), 128.6, 126.9, 120.9 (d, *J* = 0.98 Hz, 1C), 114.1(2), 114.0(7) (d, *J* = 3.1 Hz, 1C), 113.9, 80.2, 55.6, 55.3, 53.0 (d, *J* = 8.0 Hz, 1C), 52.7 (d, *J* = 4.9 Hz, 1C), 52.5, 52.0, 51.7 (d, *J* = 12.9 Hz, 1C), 38.3, 33.7 (d, *J* = 7.9 Hz, 1C), 28.2. HRMS (ESI) m/z: calcd for $C_{28}H_{30}N_2O_8SNa$ $[M+Na]^+$: 583.2085, found: 583.2070.

Methyl *N*-((tert-butoxycarbonyl)-L-phenylalanyl)-*S*-(2-ethoxy-1-(2-fluorophenyl)-2-oxoethyl)-L-cysteinate (3ak). White colloid (159.3 mg, 57% yield, d:r = 1:2). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.57 – 7.46 (m, 1H), 7.33 – 7.14 (m, 7H), 7.11 – 7.02 (m, 1H), 6.85 (d, *J* = 27.1 Hz, 1H), 5.11 – 4.88 (d, *J* = 7.6 Hz, 2H), 4.77 (s, 1H), 4.40 (s, 1H), 4.26 – 4.10 (m, 2H), 3.72 (d, *J* = 8.9 Hz, 3H), 3.18 – 2.90 (m, 4H), 1.38 (d, *J* = 9.7 Hz, 9H), 1.28-1.20 (m, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 171.2 (d, *J* = 7.0 Hz, 1C), 170.3 (d, *J* = 4.1 Hz, 1C) 170.1, 161.2, 158.8, 155.3, 136.5 (d, *J* = 2.6 Hz, 1C), 130.1 (d, *J* = 3.3 Hz, 1C), 129.8 (d, *J* = 2.5 Hz, 1C), 129.4 (d, *J* = 1.8 Hz, 1C), 128.7, 126.9, 124.6, 123.2(t, *J* = 13.9 Hz, 1C), 115.7 (d, *J* = 4.4 Hz, 1C), 115.5 (d, *J* = 4.5 Hz, 1C), 80.2, 62.2 (d, *J* = 4.7 Hz, 1C), 55.6, 52.7 (d, *J* = 2.0 Hz, 1C), 51.9 (d, *J* = 6.5 Hz, 1C), 44.9 (d, *J* = 23.6 Hz, 1C), 38.3, 34.0 (d, *J* = 33. 9 Hz, 1C), 28.2, 14.0. ^{19}F NMR (376 MHz, Chloroform-*d*) δ 117.06, 117.13. HRMS (ESI) m/z: calcd for $C_{28}H_{35}FN_2O_7SNa$ $[M+Na]^+$: 585.2041, found: 585.2030.

Methyl *N*-((tert-butoxycarbonyl)-L-phenylalanyl)-*S*-(2-ethoxy-1-(naphthalen-1-yl)-2-oxoethyl)-L-cysteinate (3al). White colloid (214.2 mg, 72% yield, d:r = 1:0.9). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.14 (t, *J* = 9.2 Hz, 1H), 7.90 – 7.78 (m, 2H), 7.65 – 7.43 (m, 4H), 7.28 – 7.14 (m, 5H), 7.05 (d, *J* = 24.7 Hz, 1H), 5.41 (d, *J* = 19.0 Hz, 1H), 5.15 – 4.96 (m, 1H), 4.87-4.70 (m, 1H), 4.42 (s, 1H), 4.26 – 4.07 (m, 2H), 3.61 (d, *J* = 9.3 Hz, 3H), 3.19 – 2.83(m, 4H), 1.37 (d, *J* = 5.8 Hz, 9H), 1.24 – 1.10 (m, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 171.4, 171.2, 170.6, 155.3, 136.6, 134.1, 130.9, 129.4, 129.3, 129.0 (d, *J* = 3.9 Hz, 1C), 128.6 (d, *J* = 3.9 Hz, 1C), 126.9, 126.8, 126.7, 126.1 (d, *J* = 5.2 Hz, 1C), 125.3, 123.4, 123.3, 80.1, 62.2, 55.6, 52.7, 51.7 (d, *J* = 12.2 Hz, 1C), 49.8, 49.2, 38.4, 34.0 (d, *J* = 41.3 Hz, 1C), 28.27, 14.0. HRMS (ESI) m/z: calcd for $C_{32}H_{38}N_2O_7SNa$ $[M+Na]^+$: 617.2292, found: 617.2275.

Methyl *N*-((tert-butoxycarbonyl)-L-alanyl)-*S*-(2-ethoxy-1-(4-methoxyphenyl)-2-oxoethyl)-L-cysteinate (3am). White colloid (batch: 176.8 mg, 71% yield, flow: 190.3 mg, 76% yield, d:r = 1:0.9). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.36 (t, *J* = 8.7 Hz, 2H), 7.06 – 6.92 (m, 1H), 6.87 (d, *J* =

7.6 Hz, 2H), 5.19 – 4.96 (m, 1H), 4.87 – 4.73 (m, 1H), 4.71 – 4.55 (m, 1H), 4.29 – 4.10 (m, 3H), 3.80 (s, 3H), 3.74 (d, *J* = 13.1 Hz, 3H), 3.08 – 2.84 (m, 2H), 1.45 (d, *J* = 4.4 Hz, 9H), 1.41 – 1.34 (m, 3H), 1.28 – 1.22 (m, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 172.6 (d, *J* = 6.7 Hz, 1C) , 170.9 (d, *J* = 8.2 Hz, 1C), 170.7 (d, *J* = 10.2 Hz, 1C), 159.6, 155.4, 129.7 (d, *J* = 8.6 Hz, 1C), 127.5, 127.3, 114.1, 80.1, 61.9 (d, *J* = 7.2 Hz, 1C), 55.3, 52.7 (d, *J* = 2.2 Hz, 1C), 52.0, 51.6 (d, *J* = 27.9 Hz, 1C), 51.4, 50.1, 33.6 (d, *J* = 14.1 Hz, 1C), 28.3, 18.3, 14.1 (d, *J* = 1.6 Hz, 1C). HRMS (ESI) m/z: calcd for $C_{23}H_{34}N_2O_8SNa$ $[M+Na]^+$: 521.1928, found: 521.1921.

Methyl *N*-((tert-butoxycarbonyl)-L-leucyl)-*S*-(2-ethoxy-1-(4-methoxyphenyl)-2-oxoethyl)-L-cysteinate (3an). White colloid (batch: 197.2 mg, 73% yield, flow: 212.9 mg, 79% yield, d:r = 1:1). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.41 – 7.31 (m, 2H), 7.09 – 6.95 (m, 1H), 6.91 – 6.83 (m, 2H), 5.02 – 4.85 (m, 1H), 4.83 – 4.74 (m, 1H), 4.69 – 4.57 (m, 1H), 4.26 – 4.12 (m, 3H), 3.80 (d, *J* = 1.2 Hz, 3H), 3.74 (d, *J* = 13.0 Hz, 3H), 3.05 – 2.84 (m, 2H), 1.75 – 1.65 (m, 2H), 1.53 – 1.47 (m, 1H), 1.44 (d, *J* = 5.9 Hz, 9H), 1.28 – 1.22 (m, 3H), 0.99 – 0.92 (m, 6H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 172.6 (d, *J* = 7.0 Hz, 1C), 171.0 (d, *J* = 16.8 Hz, 1C), 170.8 (d, *J* = 10.3 Hz, 1C), 159.6, 155.6, 129.8, 129.7, 127.2, 114.1, 80.1, 61.9 (d, *J* = 6.6 Hz, 1C), 55.3 (d, *J* = 1.3 Hz, 1C), 52.7 (d, *J* = 2.1 Hz, 1C), 52.0, 51.6 (d, *J* = 35.5 Hz, 1C), 51.3, 41.4, 33.6 (d, *J* = 11.7 Hz, 1C), 28.3, 24.7 (d, *J* = 3.3 Hz, 1C), 23.0 (d, *J* = 4.3 Hz, 1C), 21.9, 14.1 (d, *J* = 0.92 Hz, 1C). HRMS (ESI) m/z: calcd for $C_{26}H_{40}N_2O_8SNa$ $[M+Na]^+$: 563.2398, found: 563.2394.

Methyl *N*-((tert-butoxycarbonyl)-L-tryptophyl)-*S*-(2-ethoxy-1-(4-methoxyphenyl)-2-oxoethyl)-L-cysteinate (3ao). White colloid (batch: 199.3 mg, 65% yield, flow: 214.3 mg, 70% yield, d:r = 1:1). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.45 (d, *J* = 14.0 Hz, 1H), 7.65 (d, *J* = 7.4 Hz, 1H), 7.38 – 7.04 (m, 6H), 6.86 – 6.66 (m, 3H), 5.22 (s, 1H), 4.69 (s, 1H), 4.60 – 4.36 (m, 2H), 4.22 – 4.06 (m, 2H), 3.77 (d, *J* = 6.0 Hz, 3H), 3.65 (d, *J* = 12.2 Hz, 3H), 3.42 – 3.13 (m, 2H), 2.96 – 2.74 (m, 2H), 1.41 (s, 9H), 1.26 – 1.18 (m, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 171.8, 171.0 (d, *J* = 1.5 Hz, 1C), 170.5 (d, *J* = 7.5 Hz, 1C), 159.6, 155.5, 136.3, 129.7 (d, *J* = 7.3 Hz, 1C), 127.4 (d, *J* = 18.8 Hz, 1C), 123.7(1), 123.6(9), 122.1 (d, *J* = 3.6 Hz, 1C), 119.6 (d, *J* = 2.8 Hz, 1C), 118.75 , 118.7 (d, *J* = 3.4 Hz, 1C), 114.1, 112.8 (d, *J* = 6.9 Hz, 1C), 111.4, 110.1 (d, *J* = 7.6 Hz, 1C), 80.1, 62.0 (d, *J* = 6.7 Hz, 1C), 55.3, 52.7 (d, *J* = 2.3 Hz, 1C), 51.9, 51.7 (d, *J* = 16.9 Hz, 1C), 51.4, 33.6, 33.5, 28.3, 14.1. HRMS (ESI) m/z: calcd for $C_{31}H_{39}N_3O_8SNa$ $[M+Na]^+$: 636.2350, found: 636.2331.

Methyl *S*-(2-ethoxy-1-(4-methoxyphenyl)-2-oxoethyl)-*N*-(tosyl-L-phenylalanyl)-L-cysteinate (3ap). White colloid (batch: 89.3 mg, 28% yield, flow: 125.8 mg, 40% yield, d:r = 1:1). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.57 – 7.49 (m, 2H), 7.39 – 7.31 (m, 2H), 7.19 –7.08 (m, 6H), 7.02 – 6.95 (m, 2H), 6.87 (d, *J* = 7.9 Hz, 2H), 5.21 (t, *J* = 8.1 Hz, 1H), 4.76 – 4.51 (m, 2H), 4.26 – 4.12 (m, 2H), 4.02 – 3.92 (m, 1H), 3.79 (d, *J* = 3.7 Hz, 3H), 3.72 (d, *J* = 13.3 Hz, 3H), 3.01 – 2.70 (m, 4H), 2.38 (d, *J* = 10.0 Hz, 3H), 1.28 – 1.21 (m, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 171.0 (d, *J* = 9.3 Hz, 1C), 170.3, 170.2 (d, *J* = 2.5 Hz, 1C), 159.6 (d, *J* = 2.7 Hz, 1C) 143.7, 136.0 (d, *J* = 9.3 Hz, 1C) 135.2, 129.8(5), 129.7(7), 129.7, 129.4, 128.8(1), 128.7(9), 127.2 (d, *J* = 2.2 Hz, 1C), 114.2 , 62.0 (d, *J* = 4.2 Hz, 1C), 57.7 (d, *J* = 4.2 Hz, 1C), 55.3, 52.8 (d, *J* = 3.4 Hz, 1C), 52.0 (d, *J* = 4.6 Hz, 1C), 51.6 (d, *J* = 44.1 Hz, 1C), 38.5, 33.6 (d, *J* = 3.1 Hz, 1C), 21.6 (d, *J* = 1.5 Hz, 1C), 14.1 (d, *J* = 0.8 Hz, 1C). HRMS (ESI) m/z: calcd for $C_{31}H_{36}N_2O_8S_2Na$ $[M+Na]^+$: 651.1805, found: 651.1787.

Methyl *N*-(((benzyloxy)carbonyl)-L-phenylalanyl)-*S*-(2-ethoxy-1-(4-methoxyphenyl)-2-oxoethyl)-L-cysteinate (3aq). White colloid (batch: 224.9 mg, 74% yield, flow: 231.1 mg, 76% yield, d:r = 1:1) ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.36 – 7.18 (m, 12H), 6.88 – 6.81 (m, 2H), 6.78 – 6.63 (m, 1H), 5.34 (d, *J* = 36.0 Hz, 1H), 5.12 – 5.04 (m, 2H), 4.80 – 4.68 (m, 1H), 4.65 – 4.41 (m, 2H), 4.24 – 4.10 (m, 2H), 3.78 (d, *J* = 4.0 Hz, 3H), 3.71 (d, *J* = 10.5 Hz, 3H), 3.10 (d, *J* = 6.6 Hz, 4H), 1.27 – 1.19 (m, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 171.0 (d, *J* = 7.8 Hz, 1C), 170.8 (d, *J* = 6.1 Hz, 1C), 170.4 (d, *J* = 7.7 Hz, 1C), 159.6, 155.9, 136.2(2), 136.1(6) (d, *J* = 3.3 Hz, 1C), 132.1, 129.8, 129.7, 129.4, 128.7, 128.5, 128.2(0), 128.1(9), 128.0, 127.1 (d, *J* = 11.8 Hz, 1C), 114.2 (d, *J* = 2.4 Hz, 1C), 67.1, 62.0 (d, *J* = 7.2 Hz, 1C), 56.0 (d, *J* = 4.2 Hz, 1C), 55.3, 52.8 (d, *J* = 2.0 Hz, 1C), 52.0, 51.5, 38.4, 33.6, 14.1 (d, *J* = 1.4 Hz, 1C). HRMS (ESI) m/z: calcd for $C_{32}H_{36}N_2O_8SNa$ $[M+Na]^+$: 631.2085, found: 631.2066.

Methyl *N*-((((9H-fluoren-9-yl)methoxy)carbonyl)-L-phenylalanyl)-*S*-(2-ethoxy-1-(4-methoxyphenyl)-2-oxoethyl)-L-cysteinate (3ar). White solid (198.5 mg, 57% yield, d:r = 1:1. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.74 (d, *J* = 7.2 Hz, 2H), 7.59 – 7.45 (m, 2H), 7.37 (t, *J* = 7.1 Hz, 2H), 7.34 – 7.08 (m, 9H), 6.94 (d, *J* = 26.9 Hz, 1H), 6.81 (d, *J* = 7.7 Hz, 2H), 5.55 (d, *J* = 33.4 Hz, 1H), 4.84 – 4.69 (m, 1H), 4.67 – 4.45 (m, 2H), 4.42 – 4.34 (m, 1H), 4.32 – 4.21 (m, 1H), 4.21 – 4.05 (m, 3H), 3.81 – 3.59 (m, 6H), 3.24 – 2.74 (m, 4H), 1.20 (q, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 171.0, 170.9 (d, *J* = 4.7 Hz, 1C), 170.5 (d, *J* = 8.7 Hz, 1C), 159.6, 155.9, 143.8 (d, *J* = 8.5 Hz, 1C), 141.3,136.3(4), 136.2(8), 129.7 (d, *J* = 9.6 Hz, 1C), 129.5, 128.7, 127.8, 127.1, 127.0, 125.1 (d, *J* = 2.1 Hz, 1C), 120.0, 114.2 (d, *J* = 2.2 Hz, 1C), 67.2, 62.0, 61.9, 56.0, 55.3 (d, *J* = 2.1 Hz, 1C), 52.7 (d, *J* = 1.0 Hz, 1C), 52.0, 51.6 (d, *J* = 31.1 Hz, 1C), 47.1, 38.5, 33.6, 14.1 (d, *J* = 2.3 Hz, 1C). HRMS (ESI) m/z: calcd for $C_{39}H_{40}N_2O_8SNa$ $[M+Na]^+$: 719.2398, found:719.2394.

Methyl *N*-((tert-butoxycarbonyl)-L-alloisoleucyl)-*S*-(2-ethoxy-1-(4-methoxyphenyl)-2-oxoethyl)-L-cysteinate (3as). White colloid (235.0 mg, 87% yield, d:r = 1:1). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.36 (t, *J* = 9.0 Hz, 2H), 6.93 – 6.83 (m, 3H), 5.10 (d, *J* = 18.2 Hz, 1H), 4.88 – 4.75 (m, 1H), 4.71 – 4.59 (m, 1H), 4.26 – 4.14 (m, 2H), 4.10 – 3.99 (m, 1H), 3.80 (d, *J* = 1.6 Hz, 3H), 3.73 (d, *J* = 12.6 Hz,

3H), 3.05 – 2.84 (m, 2H), 1.97 – 1.84 (m, 2H), 1.57-1.49 (m, 1H), 1.44 (d, *J* = 5.2 Hz, 9H), 1.28 – 1.22 (m, 3H), 0.98 – 0.88 (m, 6H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 171.6, 171.0 (d, *J* = 17.5 Hz, 1C), 170.7 (d, *J* = 9.9 Hz, 1C), 159.6, 155.7, 129.7 (d, *J* = 9.3 Hz, 1C), 127.2, 114.1 (d, *J* = 1.3 Hz, 1C), 61.9 (d, *J* = 7.8 Hz, 1C), 59.2, 55.3 (d, *J* = 1.4 Hz, 1C), 52.7 (d, *J* = 2.5 Hz, 1C), 51.8 (d, *J* = 18.0 Hz, 1C), 51.3, 37.5 (d, *J* = 12.3 Hz, 1C), 33.6 (d, *J* = 8.4 Hz, 1C), 28.3, 24.7 (d, *J* = 7.5 Hz, 1C), 15.5, 14.1, 11.6 (d, *J* = 6.0 Hz, 1C). HRMS (ESI) m/z: calcd for $C_{26}H_{40}N_2O_8SNa$ $[M+Na]^+$: 563.2398, found: 563.2409.

Methyl *N*-((tert-butoxycarbonyl)-L-valyl)-*S*-(2-ethoxy-1-(4-methoxyphenyl)-2-oxoethyl)-L-cysteinate (3at). White colloid (216.3 mg, 82% yield, d:r = 1:1). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.35 (t, *J* = 8.5 Hz, 2H), 6.98 – 6.89 (m, 1H), 6.87 (d, *J* = 8.5 Hz, 2H), 5.22 – 5.03 (m, 1H), 4.86 – 4.74 (m, 1H), 4.71 – 4.56 (m, 1H), 4.27 – 4.13 (m, 2H), 4.08 – 3.96 (m, 1H), 3.80 (s, 3H), 3.73 (d, *J* = 12.5 Hz, 3H), 3.09 – 2.81 (m, 2H), 2.22 – 2.10 (m, 1H), 1.45 (d, *J* = 4.7 Hz, 9H), 1.25 (td, *J* = 7.1, 4.3 Hz, 3H), 1.01 – 0.89 (m, 6H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 171.6, 171.0 (d, *J* = 16.0 Hz, 1C), 170.7 (d, *J* = 9.0 Hz, 1C), 159.6, 155.7, 129.7 (d, *J* = 8.7 Hz, 1C), 127.3 (d, *J* = 26.4 Hz, 1C), 114.2 (d, *J* = 2.1 Hz, 1C), 79.9, 61.9 (d, *J* = 7.5 Hz, 1C), 59.6, 55.3 (d, *J* = 1.1 Hz, 1C), 52.7 (d, *J* = 2.2 Hz, 1C), 51.8 (d, *J* = 17.6 Hz, 1C), 51.4, 33.5, 31.0 (d, *J* = 5.3 Hz, 1C) , 28.3, 19.2, 17.6, 14.1. HRMS (ESI) m/z: calcd for $C_{25}H_{38}N_2O_8SNa$ $[M+Na]^+$: 549.241, found: 549.2254.

Methyl *N*-((S)-2-((tert-butoxycarbonyl)amino)-5-(methylthio)pentanoyl)-*S*-(2-ethoxy-1-(-4methoxyphenyl) -2-oxoethyl)-L-cysteinate (3au). White colloid (239.0 mg, 86% yield, d:r = 1:1). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.36 (t, *J* = 9.2 Hz, 2H), 7.26 – 7.11 (m, 1H), 6.87 (d, *J* = 8.3 Hz, 2H), 5.53 – 5.34 (m, 1H), 4.87 – 4.72 (m, 1H), 4.71 – 4.58 (m, 1H), 4.42 – 4.29 (m, 1H), 4.25 – 4.12 (m, 2H), 3.79 (s, 3H), 3.73 (d, *J* = 12.4 Hz, 3H), 3.12 – 2.79 (m, 2H), 2.66 – 2.52 (m, 2H), 2.14 – 1.90 (m, 5H), 1.44 (d, *J* = 5.0 Hz, 9H), 1.25 (td, *J* = 7.1, 4.6 Hz, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 171.6, 170.9 (d, *J* = 12.8 Hz, 1C), 170.6 (d, *J* = 7.8 Hz, 1C), 159.6, 155.4, 129.7 (d, *J* = 8.7 Hz, 1C), 127.2 (d, *J* = 23.4 Hz, 1C), 114.1, 80.0, 61.9 (d, *J* = 7.5 Hz, 1C), 55.2, 53.4, 52.7 (d, *J* = 2.0 Hz, 1C), 51.8 (d, *J* = 8.9 Hz, 1C), 51.4 (d, *J* = 23.7 Hz, 1C), 33.4 (d, *J* = 16.1 Hz, 1C), 31.8 (d, *J* = 3.9 Hz, 1C), 30.0 (d, *J* = 3.7 Hz, 1C), 28.3, 22.6, 15.2 (d, *J* = 2.0 Hz, 1C), 14.0 (d, *J* = 1.0 Hz, 1C). HRMS (ESI) m/z: calcd for $C_{25}H_{38}N_2O_8S_2Na$ $[M+Na]^+$: 581.1962, found: 581.1984.

Ethyl (10*S*,13*R*)-10-acetamido-13-(methoxycarbonyl)-16-(4-methoxyphenyl)-2,2-dimethyl-4,11-dioxo-3-oxa-15-thia-5,12-diazaheptadecan-17-oate (3av). White colloid (241.5 mg, 81% yield, d:r = 1:0.9). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.39 – 7.29 (m, 2H), 6.87 (d, *J* = 7.8 Hz, 2H), 6.75 – 6.47 (m, 2H), 4.86 (s, 1H), 4.74 (d, *J* = 11.2 Hz, 1H), 4.63 (d, *J* = 18.2 Hz, 1H), 4.57 – 4.46 (m, 1H), 4.25 – 4.05 (m, 2H), 3.80 (s, 3H), 3.74 (d, *J* = 11.1 Hz, 3H), 3.20 – 2.77 (m, 4H), 2.00 (d, *J* = 13.0 Hz, 3H), 1.89 – 1.63 (m, 2H), 1.54 – 1.33 (m, 13H), 1.28 – 1.18 (m, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 171.9 (d, *J* = 5.9 Hz, 1C), 171.0 (d, *J* = 5.8 Hz, 1C), 170.7 (d, *J* = 6.5 Hz, 1C), 170.3 (d, *J* = 3.3 Hz, 1C), 159.6, 156.2, 129.7 (d, *J* = 8.9 Hz, 1C), 127.2 (d, *J* = 18.8 Hz, 1C), 114.2 (d, *J* = 2.5 Hz, 1C), 79.0, 62.0 (d, *J* = 8.1 Hz, 1C), 55.3, 52.7 (d, *J* = 2.8 Hz, 1C), 51.9 (d, *J* = 8.2 Hz, 1C), 51.6, 51.4, 39.9, 33.2 (d, *J* = 5.1 Hz, 1C), 32.0, 29.6, 28.4, 23.1, 22.2 (d, *J* = 3.5 Hz, 1C), 14.0 (d, *J* = 1.9 Hz, 1C). HRMS (ESI) m/z: calcd for $C_{28}H_{43}N_3O_9SNa$ $[M+Na]^+$: 620.2612, found: 620.2624.

Methyl *N*-(tert-butoxycarbonyl)glycyl-L-prolyl-*S*-(2-ethoxy-1-(4-methoxyphenyl)-2-oxoethyl)-L-cysteinate (3aw). White colloid (252.3 mg, 87% yield, d:r = 1:1.2). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.55 (d, *J* = 20.1 Hz, 1H), 7.40 – 7.27 (m, 2H), 6.91 – 6.79 (m, 2H), 5.49 (s, 1H), 4.88 – 4.71 (m, 1H), 4.70 – 4.49 (m, 2H), 4.26 –4.11 (m, 2H), 3.80 (s, 3H), 3.73 (d, *J* = 11.2 Hz, 3H), 3.61 – 3.31 (m, 2H), 3.12 – 2.74 (m, 2H), 2.42-2.28 (m, 1H), 2.23 – 1.81 (m, 4H), 1.44 (d, *J* = 4.2 Hz, 9H), 1.29 – 1.20 (m, 3H). ^{13}C NMR (100 MHz, Chloroform-d) δ 171.0 (d, *J* = 2.6 Hz, 1C), 170.9 , 170.8 (d, *J* = 10.5 Hz, 1C) , 168.7 (d, *J* = 11.2 Hz, 1C) , 159.5, 155.8, 129.7 (d, *J* = 3.4 Hz, 1C), 127.5 (d, *J* = 33.3 Hz, 1C), 114.1 (d, *J* = 1.9 Hz, 1C), 79.6, 61.9 (d, *J* = 6.4 Hz, 1C), 60.0, 59.9, 55.3, 52.6 (d, *J* = 1.7 Hz, 1C), 51.8 (d, *J* = 10.5 Hz, 1C), 46.1 (d, *J* = 11.4 Hz, 1C), 43.1, 33.7 (d, *J* = 54.0 Hz, 1C), 28.3 (d, *J* = 1.5 Hz, 1C), 27.5 (d, *J* = 23.2 Hz, 1C), 24.8 (d, *J* = 9.6 Hz, 1C), 14.1 (d, *J* = 3.8 Hz, 1C). HRMS (ESI) m/z: calcd for $C_{27}H_{39}N_3O_9SNa$ $[M+Na]^+$: 604.2299, found: 604.2309.

Methyl 3-((2-ethoxy-1-(4-methoxyphenyl)-2-oxyethyl) thio)propanoate (5aa). White colloid (129.5 mg, 83% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.39 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 4.58 (s, 1H), 4.28 – 4.09 (m, 2H), 3.80 (s, 3H), 3.68 (s, 3H), 2.86 – 2.69 (m, 2H), 2.64 – 2.48 (d, *J* = 7.3 Hz, 2H), 1.25 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 172.1, 170.8, 159.5, 129.7, 127.8, 114.1, 61.7, 55.3, 51.8, 51.7, 34.2, 26.6, 14.1. HRMS (ESI) m/z: calcd for $C_{15}H_{20}O_5SNa$ $[M+Na]^+$: 335.0924, found: 335.0911.

Ethyl 2-((2-methoxy-2-oxoethyl)thio)-2-(4-methoxy phenyl)acetate (5ba). White colloid (128.1 mg, 86% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.38 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 4.80 (s, 1H), 4.26 – 4.10 (m, 2H), 3.80 (s, 3H), 3.71 (s, 3H), 3.27 (d, *J* = 15.1 Hz, 1H), 3.09 (d, *J* = 15.1 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 170.3(8), 170.3(5), 159.6, 129.9, 127.2, 114.2, 61.8, 55.3, 52.4, 51.8, 32.7, 14.1. HRMS (ESI) m/z: calcd for $C_{14}H_{18}O_5SNa$ [M+Na]+: 321.0767, found: 321.0744.

Ethyl 2-((4-methoxybenzyl)thio)-2-(4-methoxyph enyl)acetate (5ca). White colloid (155.7 mg, 90% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.33 (d, *J* = 8.7 Hz, 2H), 7.18 (d, *J* = 8.6 Hz, 2H), 6.84 (t, *J* = 8.0 Hz, 4H), 4.36 (s, 1H), 4.19 – 4.08 (m, 2H), 3.77 (d, *J* = 1.9 Hz, 6H), 3.73 – 3.68 (m, 1H), 3.60 – 3.54 (m, 1H), 1.22 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, Chloroform-*d*) δ 170.9, 159.4, 158.8, 130.2, 129.8, 129.2, 127.9, 114.0, 113.9, 61.6, 55.3, 50.9, 35.6, 14.1. HRMS (ESI) m/z: calcd for $C_{19}H_{22}O_4SNa$ $[M+Na]^+$: 369.1131, found: 369.1114.

Ethyl 2-((4- chlorobenzyl)thio)-2-(4-methoxyphen-yl) acetate (5da). White colloid (154.2 mg, 88% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.32 (d, *J* = 8.7 Hz, 2H), 7.27 (d, *J* = 8.5 Hz, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 4.34 (s, 1H), 4.19 – 4.09 (m, 2H), 3.79 (s, 3H), 3.74 – 3.68 (m, 1H), 3.59 – 3.53 (m, 1H), 1.23 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 170.7, 159.5, 135.9, 132.98, 130.4, 129.8, 128.7, 127.6, 61.7, 55.3, 51.0, 35.5, 14.1. HRMS (ESI) m/z: calcd for $C_{18}H_{19}ClO_3SNa$ $[M+Na]^+$: 373.0636, found: 373.0613.

Ethyl 2-(4-methoxyphenyl)-2-(p-tolylthio)acetate (5ea). White colloid (117.1 mg, 74% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.36 (d, *J* = 8.8 Hz, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 7.07 (d, *J* = 7.9 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 4.80 (s, 1H), 4.17 – 4.04 (m, 2H), 3.80 (s, 3H), 2.31 (s, 3H), 1.16 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 170.7, 159.5, 138.2, 133.3, 130.2, 129.7(4), 129.6(9), 127.8, 114.0, 61.6, 56.1, 55.3, 21.2, 14.0. HRMS (ESI) m/z: calcd for $C_{18}H_{20}O_3SNa$ $[M+Na]^+$: 339.1025, found: 339.1027.

Ethyl 2-(4-methoxyphenyl)-2-((2,2,6,6-tetramethylpiperi din-1-yl)oxy)acetate (**6aa**). Colorless oil (90.7 mg, 26% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.28 (d, *J* = 7.7 Hz, 2H), 6.78 (d, *J* = 7.8 Hz, 2H), 5.04 (s, 1H), 4.14 – 3.96 (m, 2H), 3.71 (s, 3H), 1.81 – 1.24 (m, 6H), 1.24 – 0.86 (m, 12H), 0.65 (s, 3H). HRMS (ESI) m/z: calcd for $C_{18}H_{20}O_3SNa$ $[M+H]^+$: 350.2326, found: 350.2320.

Ethyl 2-(2,6-di-tert-butyl-4-methylphenoxy)-2-(4-methoxyphenyl)acetate (**6ba**). Colorless oil (135.9 mg, 33% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.08 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 2.9 Hz, 1H), 6.67 (d, *J* = 8.8 Hz, 2H), 6.29 (d, *J* = 2.9 Hz, 1H), 4.11 – 3.95 (m, 2H), 3.65 (s, 3H), 3.62 (s, 1H), 1.20 (s, 3H), 1.16 (d, *J* = 7.1 Hz, 3H), 1.13 (s, 9H), 1.03 (s, 9H). HRMS (ESI) m/z: calcd for $C_{18}H_{20}O_3SNa$ $[M+Na]^+$: 435.2506, found: 435.2474.

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Visible-Light-Mediated S−H Bond Insertion Reactions of Diazoalkanes with Cysteine Residues in Batch and Flow

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