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Direct Access to α-Sulfenylated Amides/Esters via Sequential Oxidative Sulfenylation and C-C Bond Cleavage of 3-Oxobutyric Amides/Esters

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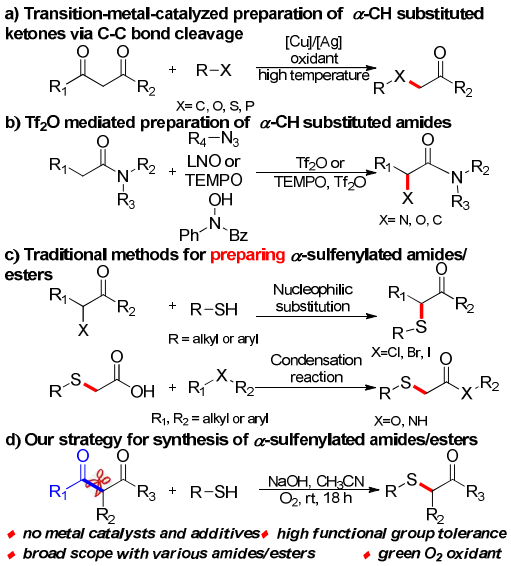
An efficient, environmentally benign and unprecedented synthesis of various α-sulfenylated amides/esters has been developed under oxygen atmosphere. The reaction shows a good functional group tolerance and excellent chemo/regioselectivity, all the desired products were obtained in moderate to excellent yields, even in gram scale. Practically, the related α-thiol Weinreb amide could be readily transferred to a series of prospective compounds, and selenium atom also can be introduced to α-site of the amides in high yields.

Carbonyl is one of the most ubiquitous and fundamentally important chemical groups, which was widely distributed in diverse bioactive natural products[1], pharmaceutical molecules[2] as well as functional materials[3]. Furthermore, as an important precursor, carbonyl serves as a versatile synthetic handle to many other valuable functional groups[4]. For its tremendously broad utilities described above, the functionalization of carbonyl compounds has garnered much attention[5]. Among of them, owing to the lower acidity of α-site of the amides/esters, the α-C–H bond functionalization of amides or esters is still a hotspot and remains a significant challenge[6]. During the last decades, several pioneering studies of α-C–H functionalization of 1,3-dicarbonyl compounds have been described by Lei[7a], Jiao[7b], Bolm[7c] and Peng[7d] via silver/copper-catalyzed selective C–C bond cleavage (Scheme 1a), which are of significant interest to chemists due to their broad applications in organic synthesis[8] and biochemistry[9]. Recently, Maulide and co-workers elegantly introduced nitrogen, oxygen, carbon atom to α-site of the amides using trifluoromethanesulfonic anhydride (Tf_2O) as a strong albeit chemoselective electrophile (Scheme 1b)[10]. To the best of our knowledge, however, with respect to various C–heteroatom



Scheme 1. Methods for synthesis of α-hetero atom substituted amides/esters.

bond formation methods, even though the regioselective α-C–H sulfenylation is extremely special and critical[11], the metal-free access to construction of C–S bonds through selective C–C cleavage of 3-oxobutyric derivatives has not been reported yet[12]. Additionally, traditional methods for synthesis of α-sulfenylated amides/esters generally employed nucleophilic substitution reactions of halogenated carbonyl compounds or condensation reactions of α-sulfenylated carboxylic acids (Scheme 1c)[13]. These methodologies, however, often caused equal equivalence wastes and suffered from multi-step preparation of the coupling precursors. Herein, we report a metal-free protocol to α-sulfenylated amides/esters from commercially available thiols and 3-oxobutyric amides/esters.

Inspired by the retro-Aldol reactions in biochemical pathways[14], our initial study commenced with thiophenol **1a** and *N,N*-dimethyl-3-oxobutanamide **2a** (see the Supporting Information table S1). After judicious evaluation of the reaction parameters, the desired product **3aa** could be obtained in excellent yield (>95%), when NaOH

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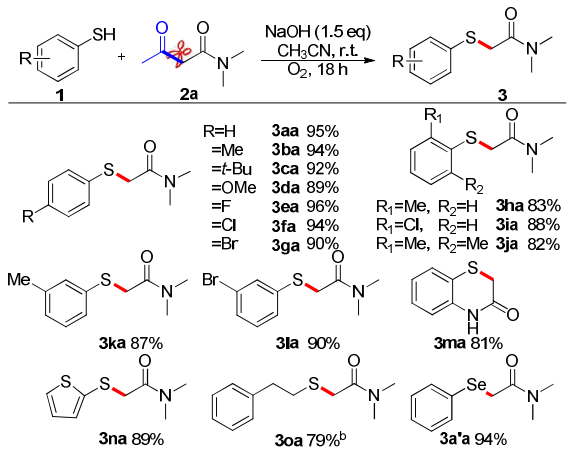
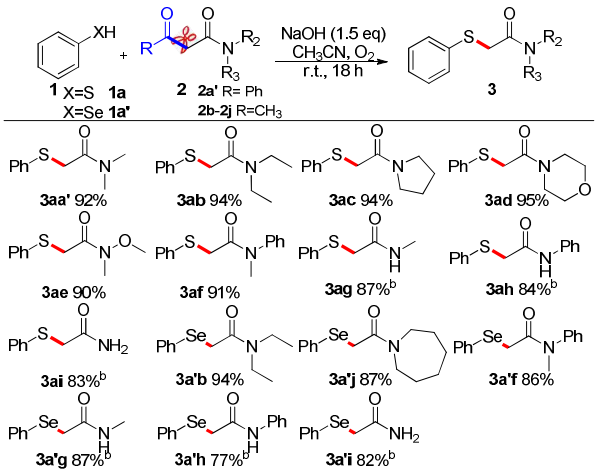


Scheme 2. Scope of thiols to α-sulfenylated amides[a]. [a]Standard conditions. [b]The reaction temperature was 80 °C.

(1.5 equivalence) was used as the base in combination with O_2 as the oxidant in CH_3CN at room temperature over a period of 18 h. A series of control experiments demonstrated that butyronitrile was the best among the screened solvents; several organic bases as well as weaker inorganic bases checked shown worse results. While switching butyronitrile to the more commonly used acetonitrile and lowing the temperature to 80 °C led to a slight increase of the yield. With this in mind, we lowered the reaction temperature in different gradients and a high yield was detected when the reaction was operated at room temperature (62%).To our delight, when the concentration of substrates was increased to 0.2 mmol/mL and the reaction time was prolonged to 18 h, the yield of the desired product was increased dramatically to 83%. Subsequently, nearly a quantitative yield was obtained by increasing the amount of **2a** to 1.2 equivalence. In contrast, when decreasing the amount of NaOH to 1.2 equivalence, the yield was slightly reduced at the same time. Additionally, oxygen was found to be indispensable to the success of this transformation and a reduced yield was got when oxygen was replaced with air (84%).

With the optimized conditions in hand, we first explored the scope of the reaction with respect to aryl thiols **1a-1m** with *N,N*-dimethyl-3-oxobutanamide **2a** (Scheme 2). Aryl thiols bearing electron withdrawing halo groups or electron-donating groups at the *para*- (**1a-1g**), *meta*- (**1k, 1l**), as well as sterically hindered *ortho*-position (**1h-1j**), were able to react with **2a** to afford the corresponding products **3aa–3ma** in excellent yields. Interestingly, when 2-aminobenzenethiol **1m** was used, a successive ammonolysis proceeded and cyclization product **3ma** was formed solely in 81% yield. Moreover, the heteroaromatic thiol **1n** and alkyl thiol **1o** were also suitable in this scenario, as for the transformation for **1o**, which hasn't been realized in the related reports. Unexpectedly, when another benzeneselenol **1a'** was tested, a high yield was observed (**3a'a**, 94%).

Afterwards, various 3-oxo-butanamides were checked further (Scheme 3) (**2a', 2b-2j**). We found that all the alkyl, methoxyl or aryl substitutions on the nitrogen atom of 3-oxo-butanamides were compatible under the standard reaction conditions (**3ab-3af**). Noteworthy, the α-sulfenylated Weinreb amide **3ae** was a readily available synthon that could be transferred into many other useful α-sulfenylated compounds easily. It is noteworthy that the secondary or primary 3-oxo-butanamides are equally applicable in this case (**3ag-3ai**). To the best of our knowledge, this is the first example to realize such kinds of transformation for mono- or none substituted amides. Encouraged by these successful examples, the applicability of benzeneselenol **1a'** was tested in this protocol with diverse 3-oxo-butanamides subsequently. As expected, no matter the acyclic or cyclic alkyl substituents on the N atom of 3-oxo-butanamides were well tolerated (**3a'b**, 94%; **3a'j**, 87%), as well as aryl substituent (**3a'f**, 86%). Logically, the secondary and primary 3-oxo-butanamides were checked at last, and good performances were shown as thiophenol (**3a'g-3a'i,** 77%-87%).



Scheme 3. Scope of 3-oxo-butanamides[a]. [a]Standard conditions. [b]The reaction temperature was 80 °C.

To make the substrates scope broader, as a consequence, a series of 3-oxobutyric derivatives, such as methyl-3-oxobutanoate, 3-oxobutanal, and pentane-2,4-dione etc. were investigated. Unfortunately, no corresponding products were obtained except for 2-alkyl substituted-3-oxobutanoate esters. Keep this in mind, diverse thiols were tested for preparation of α-sulfenylated esters (Scheme 4), which were found owning similar substrates scope as the amides' (**5aa**-**5ma**, 71%-85%). Surprisingly, unlike the amides, the pyridine or benzo[*d*]thiazole substituted thiols could undergo this transformation successfully with good yields (**5na**, 81%; **5oa**, 82%). Subsequently, a sterically hindered ester with an allyl substituent at crowded α-position was checked later, and a moderate yield was observed in this case (**5ab**, 74%), whereas, such transformations were absolutely suppressed for thiols with 3-oxo-butanamides. As for ethyl 2-oxocyclopentanecarboxylate **4c**, an acid product was obtained through the successive ring-opening which was transformed into **5ac** by further esterification.

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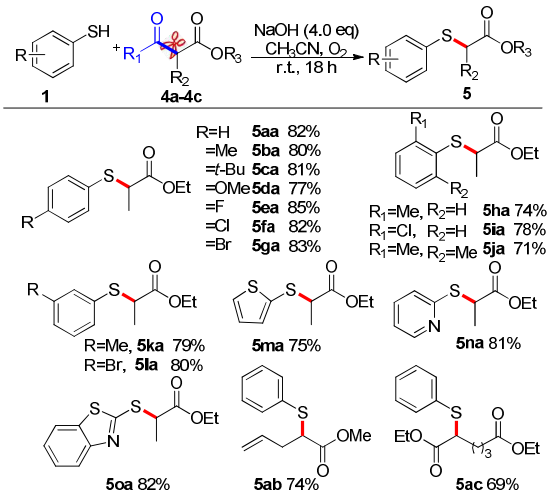
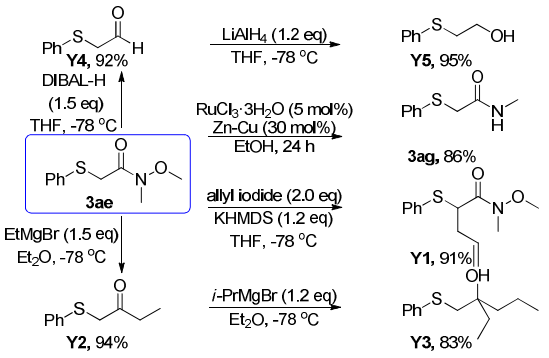


Scheme 4. Scope of thiols and esters[a]. [a]Reaction conditions: considering the hydrolysis, esters **4** was used as 0.5 mmol, NaOH (0.80 mmol), **1** (0.20 mmol), CH_3CN (1.0 mL), O_2 (1 atm), room temperature, 18 h. See Supporting Information table S2.

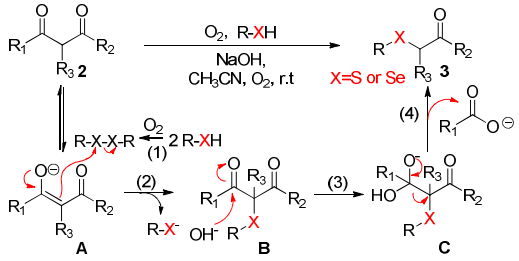
The utility of the present strategy was demonstrated in the transformation of the *α*-sulfenylated Weinreb amide **3ae** (Scheme 5). Treating **3ae** with KHMDS and allyl iodide afforded the *α*-alkylated product **Y1** in 91% yield. In addition, attacked by ethylmagnesium bromide, *α*-sulfenylated ketone **Y2** was obtained in an excellent yield of 94%, which could be further transferred with the same procedure to afford the *α*-sulfenylated tertiary alcohol **Y3**. Meanwhile, after getting *α*-sulfenylated aldehyde **Y4** by reduction reaction with diisobutyl aluminium hydride (DIBAL-H), the valuable *α*-sulfenylated primary alcohol **Y5** was obtained by subsequent reduction reaction.

To gain insight of the detailed mechanism, several controlled experiments were carried out (see the Supporting Information Scheme S2). According to the literatures reported, thiols/benzeneselenol could be oxidized to dimer in air[15], thus we hypothesized which may be the important intermediate. To test this, disulfide **1aa**/diselenide **1a'a'** was directly used as the sulfenylated/selenenylated reagent to the reaction without oxygen, the desired product **3af/3a'f** was truly obtained in 94% and 88% yield (**eq 2**). Furthermore, when the radical inhibitor such as butylated hydroxytoluene (BHT) or 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added to the present reaction conditions, the yield did not decrease, indicating that this transformation did not proceed through a radical pathway (**eq 3**). As we treated **2f** under the standard reaction conditions without thiol/benzeneselenol, no acetyl eliminated product was observed (**eq 4**), using amide **2ff** instead of **2f** to conduct this reaction with strong bases like potassium bis(trimethylsilyl)amide (KHMDS) and potassium tert-butoxide (*t*-BuOK) provided no reaction (**eq 5**). Whereas, when we synthesized **3af'/3a'f'** by the known route[16] and used it in this transformation without thiol/benzeneselenol, the final product **3af/3a'f** was afforded smoothly in 89% and 84% yield (**eq 7**), this result indicated that the elimination of acetoxy proceeded after sulfuration/selenylation. When using **2f'** as substrate, 85%/78% of benzoic acid can be obtained together with 89%/83% yield of the desired product (**eq 8**), which revealed that hydroxyl is a nucleophile reagent for the elimination of acetoxy group.



Scheme 5. Transformation of *α*-sulfenylated Weinreb amide[a].

On the basis of the previous work[7c,17] and the above experimental results, a plausible mechanism for this reaction was proposed in Scheme 6: (1) Thiol/Benzeneselenol was oxidized into dimer under O_2 atmosphere[15]. (2) Enolate **A** attacked the dimer with cleavage the S-S/Se-Se bond to afford intermediate **B** together with generating one molecule of R-SH/R-SeH, which could be oxidized to dimer and participated in the next reaction cycle[7c]. (3) The most electron deficient carbonyl group of intermediate **B** was attacked by the nucleophilic species (OH^-) to afford intermediate **C**. (4) Intermediate **C** decomposed to afford the final product **3**, with the release of one molecule of carboxylic anion simultaneously.



Scheme 6. A proposed mechanism.

In conclusion, inspired by the retro-Aldol reactions in biochemical pathways, we have developed the first example for preparation of *α*-sulfenylated *a*mides/esters under metal-free conditions in good to excellent yields, even in gram scale. In this transformation no additives were needed, which is step concisely and easy to be handled. As a result, various kinds of *α*-sulfenylated amides (tertiary, secondary and primary amides) and esters were prepared with exclusive regioselectivity and high functional group tolerance. Practically, the prepared *α*-sulfenylated Weinreb amide could be transferred into a series of useful compounds by some classic methods, and selenium atom also can be introduced to *α*-site of various amides in high yields. Ongoing studies on the application of this strategy to other systems and late stage modification of pharmaceutical molecules are currently in progress in our laboratory. We believe that the robust nature

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of this protocol renders it highly attractive for both synthetic and medicinal chemistry.

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Conflicts of interest

The authors declare no competing financial interest.

Notes and references

1 a) T. Maxson, J. I. Tietz, G. A. Hudson, X. R. Guo, H.-C. Tai and D. A. Mitchell, *J. Am. Chem. Soc.*, 2016, **138**, 15157; b) Y. Bai, D. C. Davis and M. Dai, *J. Org. Chem.*, 2017, **82**, 2319.

2 a) P. Malátková and V. Wsól, *Drug Metab. Rev.*, 2014, **46**, 96; b) S. Hwang, Y.-M. Lee, G. Aldini and K.-J. Yeum, *Molecules*, 2016, **21**, 280; c) T. Rodrigues, D. Reker, P. Schneider and G. Schneider, *Nat. Chem.*, 2016, **8**, 531.

3 B. Häupler, A. Wild and U. S. Schubert, *Adv. Energy Mater.*, 2015, **5**, 1402034.

4 Selective articles for transformation of carbonyl compounds see: a) T. L. Peppard and S. A. Halsey, *J. Inst. Brew.*, 1981, **87**, 386; b) S. Rozen, M. Brand and D. Zamir, *J. Am. Chem. Soc.*, 1987, **109**, 896; c) D. Habrant, V. Rauhala and A. M. P. Koskinen, *Chem. Soc. Rev.*, 2010, **39**, 2007; d) H. Tamiaki, K. Tsuji, S. Machida, M. Teramura and T. Miyatake, *Tetrahedron Lett.*, 2016, **57**, 788; e) H. Yoneyama, M. Numata, K. Uemura, Y. Usami and S. Harusawa, *J. Org. Chem.*, 2017, **82**, 5538.

5 Selective reviews for functionalization of carbonyl compounds see: a) K. Nakamura and T. Matsuda, *Curr. Org. Chem.*, 2006, **10**, 1217; b) A. Mielgo and C. Palomo, *Chem. - Asian J.*, 2008, **3**, 922; c) S. Chakraborty and H. Guan, *Dalton Trans.*, 2010, **39**, 7427; d) G. Guillena and D. J. Ramon, *Curr. Org. Chem.*, 2011, **15**, 296; e) D. Fernandez Gonzalez, F. Benfatti and J. Waser, *ChemCatChem*, 2012, **4**, 955; f) P. Melchiorre, *Angew. Chem., Int. Ed.*, 2012, **51**, 9748; g) I. Franzoni and C. Mazet, *Org. Biomol. Chem.*, 2014, **12**, 233; h) Z. Huang and G. Dong, *Tetrahedron Lett.*, 2014, **55**, 5869.

6 Selective reports for functionalization of amides or esters see: a) K. H. Shaughnessy, B. C. Hamann and J. F. Hartwig, *J. Org. Chem.*, 1998, **63**, 6546; b) S. Lee and J. F. Hartwig, *J. Org. Chem.*, 2001, **66**, 3402; c) N. A. Beare and J. F. Hartwig, *J. Org. Chem.*, 2002, **67**, 541; d) J. Cossy, A. de Filippis and D. G. Pardo, *Org. Lett.*, 2003, **5**, 3037; e) T. Hama, X. Liu, D. A. Culkin and J. F. Hartwig, *J. Am. Chem. Soc.*, 2003, **125**, 11176; f) X. Liu and J. F. Hartwig, *J. Am. Chem. Soc.*, 2004, **126**, 5182; g) A. M. R. Smith and K. K. Hii, *Chem. Rev.*, 2011, **111**, 1637;. h) P. Biswas, S. Paul and J. Guin, *Angew. Chem., Int. Ed.*, 2016, **55**, 7756; i) K. Tokumasu, R. Yazaki and T. Ohshima, *J. Am. Chem. Soc.*, 2016, **138**, 2664; j) X. Li, F. Lin, K. Huang, J. Wei, X. Li, X. Wang, X. Geng and N. Jiao, *Angew. Chem., Int. Ed.*, 2017, **56**, 12307.

7 a) C. He, S. Guo, L. Huang and A. Lei, *J. Am. Chem. Soc.*, 2010, **132**, 8273; b) C. Zhang, P. Feng and N. Jiao, *J. Am. Chem. Soc.*, 2013, **135**, 15257; c) L.-H. Zou, D. L. Priebbenow, L. Wang, J. Mottweiler and C. Bolm, *Adv. Synth. Catal.*, 2013, **355**, 2558; d) L. Li, W. Huang, L. Chen, J. Dong, X. Ma and Y. Peng, *Angew. Chem., Int. Ed.*, 2017, **56**, 10539.

8 For selective reviews see: a) R. H. Crabtree, *Chem. Rev.*, 1985, **85**, 245; b) C.-H. Jun, *Chem. Soc. Rev.*, 2004, **33**, 610; c) Y. J. Park, J.-W. Park and C.-H. Jun, *Acc. Chem. Res.*, 2008, **41**, 222. d) B. Su, Z.-C. Cao and Z.-J. Shi, *Acc. Chem. Res.*, 2015, **48**, 886. e) H. Liu, C. Dong, Z. Zhang, P. Wu and X. Jiang, *Angew. Chem., Int. Ed.*, 2012, **51**, 12570. Selective articles for transition-metal-catalyzed C-C bond cleavage see: f) R. Zeng and G. Dong, *J. Am. Chem. Soc.*, 2015, **137**, 1408; g) X. Zhou and G. Dong, *J. Am. Chem. Soc.*, 2015, **137**, 13715; h) L. Deng, T. Xu, H. Li and G. Dong, *J. Am. Chem. Soc.*, 2016, **138**, 369; i) M. Murakami and N. Ishida, *J. Am. Chem. Soc.*, 2016, **138**, 13759; j) R. Zeng, P.-h. Chen and G. Dong, *ACS Catal.*, 2016, **6**, 969; k) S. Okumura, F. Sun, N. Ishida and M. Murakami, *J. Am. Chem. Soc.*, 2017, **139**, 12414.

9 R. M. Cicchillo, H. Zhang, J. A. V. Blodgett, J. T. Whitteck, G. Li, S. K. Nair, W. A. van der Donk and W. W. Metcalf, *Nature*, 2009, **459**, 871.

10 a) V. Tona, A. de la Torre, M. Padmanaban, S. Ruider, L. González and N. Maulide, *J. Am. Chem. Soc.*, 2016, **138**, 8348; b) A. de la Torre, D. Kaiser and N. Maulide, *J. Am. Chem. Soc.*, 2017, **139**, 6578; c) D. Kaiser, A. de la Torre, S. Shaaban and N. Maulide, *Angew. Chem., Int. Ed.*, 2017, **56**, 5921; d) S. Shaaban, V. Tona, B. Peng and N. Maulide, *Angew. Chem., Int. Ed.*, 2017, **56**, 10938. A review for carbonyl α-aminations with nitrogen nucleophiles see: e) A. de la Torre, V. Tona and N. Maulide, *Angew. Chem., Int. Ed.*, 2017, **56**, 12416. f) D. Kaiser, C. J. Teskey, P. Adler and N. Maulide, *J. Am. Chem. Soc.*, 2017, **139**, 16040.

11 Reviews for α-sulfenylated carbonyl compounds in organic synthesis: a) B. M. Trost, *Chem. Rev.*, 1978, **78**, 363; b) B. M. Trost, *Acc. Chem. Res.*, 1978, **11**, 453. For transition-metal-catalyzed formation of C-S bond: c) G. Teverovskiy, D. S. Surry and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2011, **50**, 7312; d) L. D. Tran, I. Popov and O. Daugulis, *J. Am. Chem. Soc.*, 2012, **134**, 18237; e) C.-P. Zhang and D. A. Vicic, *J. Am. Chem. Soc.*, 2012, **134**, 183; f) Y. You, Z.-J. Wu, Z.-H. Wang, X.-Y. Xu, X.-M. Zhang and W.-C. Yuan, *J. Org. Chem.*, 2015, **80**, 8470. No metal-catalyzed airticles for construction of C-S bond see: g) C. L. Jarvis, M. T. Richers, M. Breugst, K. N. Houk and D. Seidel, *Org. Lett.*, 2014, **16**, 3556; h) B. V. Varun, K. Gadde and K. R. Prabhu, *Org. Lett.*, 2015, **17**, 2944; i) J.-P. Wan, S. Zhong, L. Xie, X. Cao, Y. Liu and L. Wei, *Org. Lett.*, 2016, **18**, 584.

12 For selective reviews see: a) P. G. Gassman and R. J. Balchunis, *J. Org. Chem.*, 1977, **42**, 3236; b) K. Matsumoto and H. Sugiyama, *J. Organomet. Chem.*, 2004, **689**, 4564. For selected airticles for C-S bond formation see: c) B. Jiang, H. Tian, Z.-G. Huang and M. Xu, *Org. Lett.*, 2008, **10**, 2737; d) J. Feng, M. F. Lv, G. P. Lu and C. Cai, *Org. Biomol. Chem.*, 2015, **13**, 677.

13 For preparation of α-sulfenylated amides or ester using nucleophilic reaction: a) C. B. Reese and H. P. Sanders, *J. Chem. Soc., Perkin Trans. 1.*, 1982, 2719. For preparation of α-sulfenylated amides or ester using condensation reaction: b) F. Tinnis, H. Lundberg and H. Adolfsson, *Adv. Synth. Catal.*, 2012, **354**, 2531; c) R. S. Thombal, A. R. Jadhav and V. H. Jadhav, *RSC Adv.*, 2015, **5**, 12981.

14 T. Eixelsberger, D. Horvat, A. Gutmann, H. Weber and B. Nidetzky, *Angew. Chem., Int. Ed.*, 2017, **56**, 2503.

15 For selective articles aerobic oxygenation thiols to disulfides see: a) J. L. Garcia Ruano, A. Parra, J. Aleman, *Green Chem.*, 2008, **10**, 706; b) A. Corma, T. Rodenas and M. J. Sabater, *Chem. Sci.*, 2012, **3**, 398; c) Y. Liu, H. Wang, C. Wang, J.-P. Wan and C. Wen, *RSC Adv.*, 2013, **3**, 21369; d) M. Li and J. M. Hoover, *Chem. Commun.*, 2016, **52**, 8733.

16 Y.-W. Liu, S. S. Badsara, Y.-C. Liu and C.-F. Lee, *RSC Adv.*, 2015, **5**, 44299.

17 a) H.-H. Wang, T. Shi, W.-W. Gao, Y.-Q. Wang, J.-F. Li, Y. Jiang, Y. S. Hou, C. Chen, X. Peng and Z. Wang, *Chem. - Asian J.*, 2017, **12**, 2675; b) T.-Q. Yu, Y.-S. Hou, Y. Jiang, W.-X. Xu, T. Shi, X. Wu, J.-C. Zhang, D. He and Z. Wang, *Tetrahedron Lett.*, 2017, **58**, 2084.