A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition

GDCh

Chemie

www.angewandte.org

Accepted Article

Title: Electrochemical Oxidative One-Carbon Difunctionalization Towards Multi-Substituted Imino Sulfide Ethers

Authors: Zhipeng Guan, Shuxiang Zhu, Siyuan Wang, Huamin Wang, Siyuan Wang, Xingxing Zhong, Faxiang Bu, Hengjiang Cong, and Aiwen Lei

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.202011329

Link to VoR: https://doi.org/10.1002/anie.202011329

WILEY-VCH

10.1002/anie.202011329

WILEY-VCH

Electrochemical Oxidative One-Carbon Difunctionalization: Towards Multi-Substituted Imino Sulfide Ethers

Zhipeng Guan,[a] Shuxiang Zhu,[a] Siyuan Wang,[a] Huamin Wang,[a] Siyuan Wang,[a] Xingxing Zhong,[a] Faxiang Bu,[a] Hengjiang Cong,[a] Aiwen Lei*[a]

Dedication ((optional))

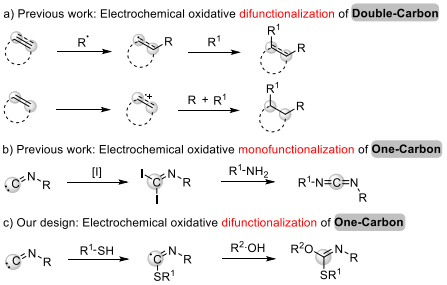
[a] Z. Guan, S. Zhu, S. Wang, H. Wang, S. Wang, X. Zhong, F. Bu, Prof. H. Cong, Prof. A. Lei
College of Chemistry and Molecular Sciences and The Institute for Advanced Studies (IAS), Wuhan University
Wuhan, 430072, Hubei (P. R. China)
E-mail: aiwenlei@whu.edu.cn

Abstract: Ethers (C-O/S) are ubiquitously found in a wide array of functional molecules and natural products. Nonetheless, the synthesis of imino sulfide ethers, containing N(sp^2)=C(sp^2)–O/S fragment, still remains a great challenge due to its sensitivity to acid. Herein, we developed an unprecedented electrochemical oxidative one-carbon difunctionalization of isocyanides, providing a series of novel multi-substituted imino sulfide ethers. Under metal- and external oxidant-free conditions, isocyanides could react smoothly with simple and readily available mercaptans and alcohols. Importantly, the procedure exhibited high stereoselectivities, excellent functional group tolerance, good efficiency in large-scale synthesis as well as further derivatization of products.

Synthetic chemistry plays an extremely important role in the development of human society through the construction of target molecules, which has been widely used from pharmaceutical to materials science.[1] Molecule ethers (C-O/S) are not only ubiquitously found in a wide array of functional molecules and natural products, but also could be extensively considered as valuable building blocks in synthetic chemistry because of the relatively high reactivity of C-O/C-S bond and oxygen/sulfur atoms electronegativity.[2] Over the past several years, a myriad of prevalent and synthetically useful methods have been developed by thermochemistry,[3] photochemistry[4] and electrochemistry[5] respectively, providing a broader array of ethers compounds. Nonetheless, imino ethers, the significant skeletons in a wide array of pharmaceuticals and sugar chemistry, [6] are hitherto far less explored than alkyl ethers, aryl ethers as well as enol ethers owing to its sensitivity to acid.[7] Furthermore, existing method for the synthesis of imino sulfide ethers also needs toxic transition-metal catalysts, strong redox agents or other harsh conditions.[8] Hence, exploiting an efficient and mild strategy to expand the scope, structural diversity, as well as functional group tolerance in the generation of imino sulfide ethers is an appealing and challenging task for chemists.

Organic electrochemistry, utilizing electrons as traceless reagents, is an attractive and sustainable synthetic technology for molecules construction.[9] At the same time, the proton can be reduced to hydrogen at the cathode, which can adress the challenge of the deterioration of acid-sensitive products in the reaction system.[10] Recently, the electrochemical difunctionalization of unsaturated bonds has proven to be a powerful tool, expanding applications of these compounds enormously.[11] In this field, great progress has been achieved via two channels. In 2017, Lin's group reported electrochemical strategy for diazidation and dichlorination of alkenes to synthesize a variety of vicinally 1,2-diazides and dichlorinated compounds respectively.[12] Alternatively, an active intermediate-free radical cation could be obtained through anodic oxidation.[13] For example, Vincent's group and our group achieved the electrochemical dearomative 2,3-difunctionalization of indoles forging C-C, C-O and C-N bonds.[14] Despite numerous advances, these reported reactions involving difunctionalization are limited in utility to between two different atoms of unsaturated bonds. Access to difunctionalization of one-carbon under such conditions still remains room for improvement.[15]

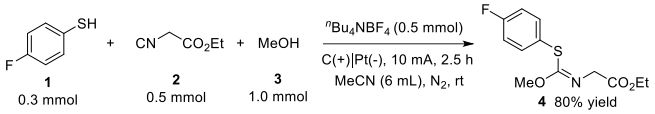
As far as we know, isocyanides, which not only could be inserted into metal-carbon and metal-heteroatom bonds in transition-metal-catalyzed system, but also react with electrophiles, nucleophiles and radicals under suitable conditions, are an important C1 synthons.[16] Recently, the monofunctionalization of isocyanides have been reported to synthesize carbodiimides by electrochemical oxidation (Scheme 1b).[17] In order to realize difunctionalization of isocyanides, we hypothesized that isocyanides could afford imine radical when attacked by radicals. And then, carbocation was generated through an electron transfer from the imine radical, which could be captured further by nucleophiles (Scheme 1c). Herein, we reported an unpresented electrochemical oxidative one-carbon difunctionalization of isocyanides via sequential addition of simple mercaptans and alcohols. A series of multi-substituted imine ethers were facilely obtained under mild condition, with S-C(sp^2)-O bonds forming. In addition, this strategy obviated the need of sacrificial oxidizing reagents and additives, with concomitant valuable hydrogen gas releases.



Scheme 1. Electrochemical oxidative difunctionalization of the unsaturated bonds.

After reaction optimization, utilizing 4-fluorobenzenethiol (**1**, 0.3 mmol), ethyl 2-isocyanoacetate (**2**, 0.5 mmol), methanol (3, 1.0 mmol) as coupling partners, ethyl (E)-2-((((4-fluorophenyl)thio)(methoxy)methylene)amino)acetate **4** could been obtained with 80% isolated yield successfully (Table 1, entry 1). While a lower methanol of 0.6 mmol showed slight decrease in yield, increasing amount of methanol revealed a dramatically lower amount of target compound (entries 2-3). Adding HOAc or NaOAc to the system was found to be detrimental to the reaction process (entries 4-5). The presence of co-solvent, especially DMF, resulted in a sharp drop in yield (entries 6-7). With an alternative cathode material such as graphite rod or nickel plate, lower yields obviously were observed in undivided cell (entries 8-9). As to the electric current, 15 mA showed a similar reactivity, while 5 mA was less effective in promoting the product formation (entries 10-11). The reaction was sensitive to air, and a half yield was only obtained (entry 12). Control experiments indicated that was completely abolished without electricity (entry 13).

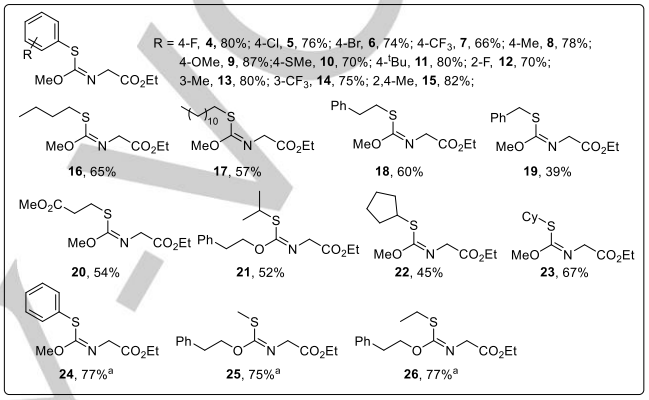
Table 1. Optimization of the Electrochemical Oxidative Difunctionalization



Entry	Variation from standard conditions	Yield/%[a]
1	no	80[b]
2	**3** (0.6 mmol)	71
3	**3** (1 mL)	45
4	HOAc (0.5 mmol)	60
5	NaOAc (0.5 mmol)	63
6	MeCN/DCE = 5 mL/1 mL	60
7	MeCN/DMF = 5 mL/1 mL	18
8	C(+) C(-)	28
9	C(+) Ni(-)	40
10	15 mA, 100 min	75
11	5 mA, 5 h	62
12	under air	50
13	no electric current	0

Standard conditions: **1** (0.3 mmol), **2** (0.5 mmol), **3** (1.0 mmol) $^{n}Bu_4NBF_4$ (0.5 mmol), MeCN (6 mL), C anode, Pt cathode, undivided cell, constant current = 10 mA, room temperature, N_2, 2.5 h. [a] ^{19}FNMR yield, 1-(4-fluorophenyl)ethan-1-one as an internal standard. [b] isolated yield.

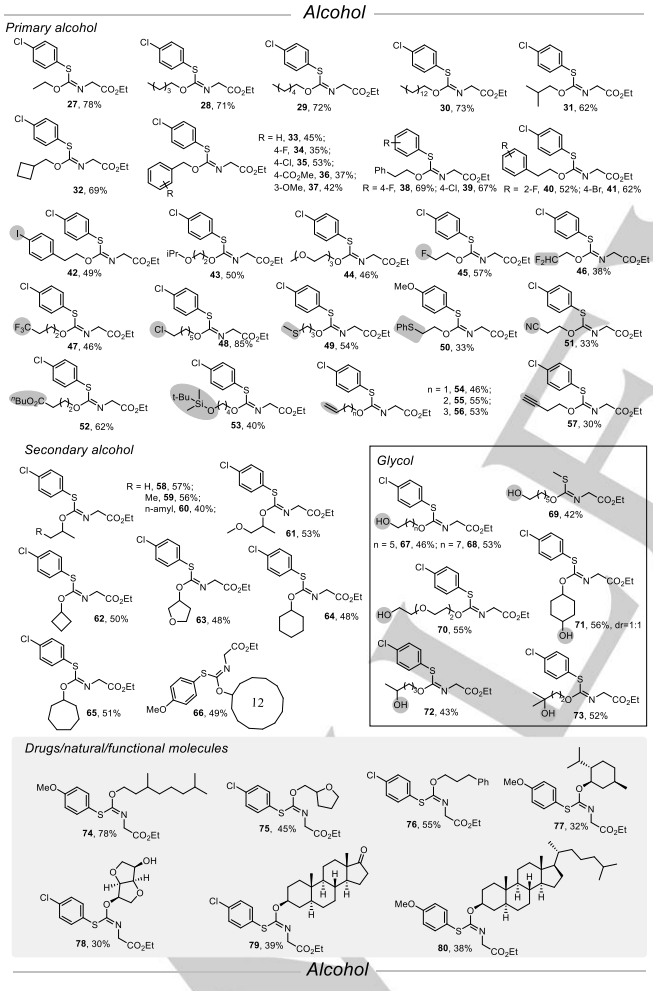
In an effort to explore the scope of difunctionalization of isocyanides, we first sought to examine applicability with respect to mercaptans (Scheme 2). Thiophenols bearing electron-withdrawing groups (F, Cl, Br, CF_3) were also well amenable to this protocol, providing a set of products with 70-87% yields (**4**-**7**). With an electron-donating group on aromatic ring, such as Me, OMe, SMe, and ^{t}Bu, thiophenols could be employed smoothly to afford the corresponding imino sulfide ethers compounds in excellent yields (**8**-**11**). Furthermore, thiophenols containing one group or two groups in different position also showed good reaction efficiency in this transformation (**12**-**15**). Afterwards, we turned our attention to expand the scope from aryl mercaptans to alkyl mercaptans (**16**-**23**). To our delight, the electrochemical protocol was shown to be compatible with a variety of alkyl mercaptans including those bearing dodecyl (**17**), benzyl (**19**), cycloalkyl (**22**,**23**) and ester (**20**). In addition, allow for storage and toxicity of thiophenol, methyl mercaptan, ethyl mercaptan, the satisfactory yields were obtained with the use of corresponding disulfides as substances under slightly modified conditions (**24**-**26**).



Scheme 2. Scope of mercaptans. Standard conditions: thiolating agents (0.3 mmol), ethyl 2-isocyanoacetate (0.5 mmol), alcohol (1.0 mmol) $^{n}Bu_4NBF_4$ (0.5 mmol), MeCN (6 mL), C anode, Pt cathode, undivided cell, constant current = 10 mA, room temperature, N_2, 2.5 h, isolated yield. [a] disulfide (0.15 mmol), constant current = 10 mA, 2 h.

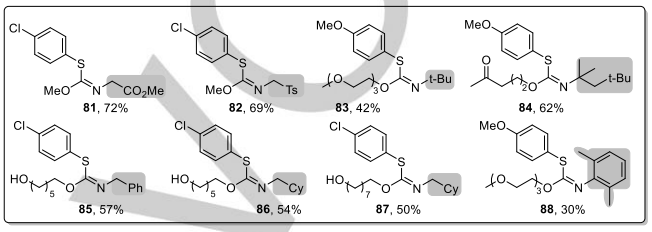
Subsequently, further exploration revealed the difunctionalization of isocyanides was amenable to alcohols (Scheme 3). The reaction efficacy of this protocol showed little dependence on the chain length of primary alcohols (**27**-**30**). Similarly, the reaction proceeded effectively with other fatty alcohols, such as sobutanol (**31**) and cyclobutanemethanol (**32**) in 62% and 69% yields, respectively. The sensitive benzylic C-H bonds of benzylic alcohols (**33**-**37**) and phenethyl alcohols (**38**-**42**) were tolerated in this transformation, providing acceptable yields. Remarkably, subtle C-I bond on benzene ring was also compatible with this strategy (**42**). Alkoxy alcohols were well tolerated, affording the corresponding products in the reaction system (**43**, **44**). Owing to importance of fluorine atom in drug molecules, we tried to introduce fluorine atom into the imino sulfide ethers compounds. To our delight, the targeted molecules, containing monofluoride (**45**), difluoromethyl (**46**) and trifluoromethyl (**47**) were successfully obtained under electrochemical conditions. A substrate bearing a primary chloroalkane was fully tolerated to deliver the desired product in good yield (**48**). A range of functionality vicinal to alcohols such as thiomethyl (**49**), thiomethylene (**50**), cyano (**51**), ester (**52**), carbonyl (**84**) and tert-butyldimethylsilyloxy (**53**), were also tolerated under standard condition. Compared with terminal alkyl alkene and alkyne, thiophenol would preferentially react with isocyanides to obtain a series of imino sulfide ethers along with the additional double or triple bonds intact (**54**-**57**). Extending

the substrate range to contain secondary alcohols enable us to construct C-S and C-O bonds with adjoining tertiary carbon centers. Simple secondary alcohols could be used, representing a practical route to form imino sulfide ethers (**58**-**61**). Additionally, this protocol was not limited to acyclic systems. Cyclic secondary alcohols from four to twelve-membered rings, containing heterocycle alcohol, were also suitable substrates (**62**-**66**). When glycol is used as a substrate, the retention of one hydroxyl group is particularly noteworthy, providing the opportunity for further derivatization (**67**-**71**). Due to steric hindrance effect, primary alcohol could react to form target compound over secondary alcohols (**72**) and tertiary alcohol (**73**). It is particularly noteworthy that three important food additives including tetrahydrogeranol (**74**), tetrahydrofurfuryl alcohol (**75**) and 3-phenyl-1-propanol (**76**) were smoothly converted to the desired products in 45-78% yields. Moreover, natural products and pharmaceuticals such as *L*-menthol (**77**), isosorbide (**78**), androsterone (**79**), dihydrocholesterol (**80**) all underwent functionalization smoothly.



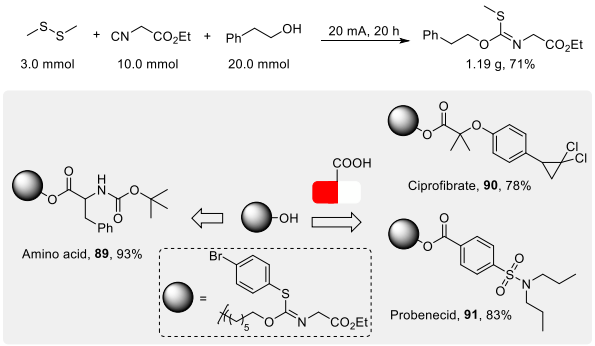
Scheme 3. Scope of alcohol. Standard conditions: thiolating agent (0.3 mmol), isocyanide (0.5 mmol), alcohol (1.0 mmol) $^{n}Bu_4NBF_4$ (0.5 mmol), MeCN (6 mL), C anode, Pt cathode, undivided cell, constant current = 10 mA, room temperature, N_2, 2.5 h, isolated yield. [a] disulfide (0.15 mmol), constant current = 10 mA, 2 h.

Next, the isocyanides coupling partner scope was considered with both mercaptans and alcohols. Methyl isocyanoacetate was tolerated, leading to the formation of imino sulfide ethers in with 72% yield (**81**). Analogously, no obvious negative effect was observed using TOSMIC as a substrate (**82**). Benzyl isocyanide (**85**) and cyclohexyl isocyanides (**86**,**87**) were coupling partners, which could react smoothly with glycols, and one of the hydroxyl groups is retained. Gratifyingly, isocyanides containing steric hindrance, could engage with thiophenols and alcohols to give the corresponding compounds in moderate yields (**83**,**84**). Besides alkyl isocyanides, aryl isocyanide was also a suitable substrate for this strategy (**88**).



Scheme 4. Scope of isocyanides. Standard conditions: thiolating agents (0.3 mmol), isocyanides (0.5 mmol), alcohol (1.0 mmol) $^{n}Bu_4NBF_4$ (0.5 mmol), MeCN (6 mL), C anode, Pt cathode, undivided cell, constant current = 10 mA, room temperature, N_2, 2.5 h, isolated yield.

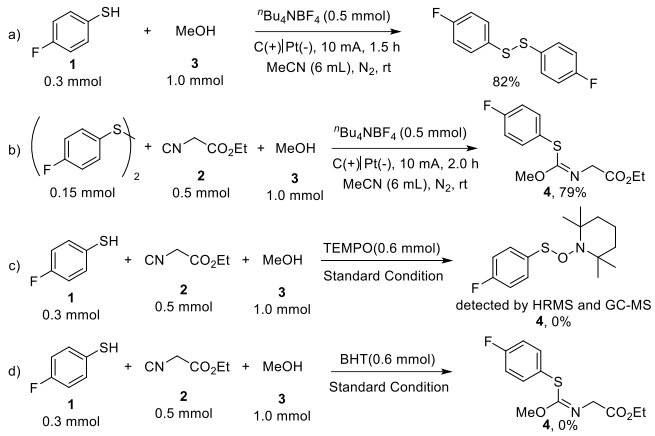
To further demonstrate the potential application of this difunctionalization of isocyanides, a gram scale reaction was performed with similar condition. Using 20 mA constant current, a good yield of the corresponding product was offered. Considering the retention of one hydroxyl group, we introduced pharmaceuticals and amino acid to obtained products, providing an opportunity for new drug discovery.



Scheme 5. Gram scale synthesis and derivatization of product.

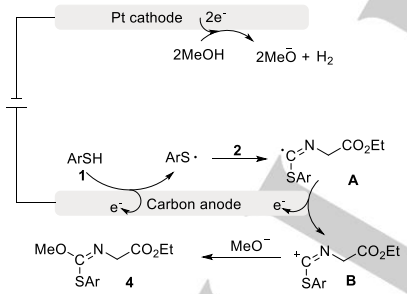
A series of mechanistic studies were carried out to investigate this electrochemical oxidative mechanism. In the absence of isocyanide, 4-fluorobenzenethiol (**1**) underwent dimerization to afford 1,2-bis(4-fluorophenyl)disulfane with 82% isolated yield (Scheme 6a). 1,2-diphenyldisulfane as a substance, 77% yield was also obtained in the difunctionalization reaction (Scheme 6b). Under the standard conditions, when 2.0 equivalent of TEMPO or BHT was added to the reaction, no imine ethers was observed, revealing the existence of a sulfur radical (Scheme 6c and 6d). In order to further explore this reaction mechanism,

electron paramagnetic resonance (EPR) experiments was firstly performed. A S-centred radical was quickly trapped by 5,5-dimethyl-1-pyrroline N-oxide (DMPO) to form arelatively stable radical (g = 2.0065, AN=13.70 G, AH = 11.95 G).



Scheme 6. Control experiments.

On the basis of the aforementioned studies and related literature reports,[16a, 18] we proposed a mechanism for electrochemical oxidative difunctionalization in Scheme 7. Firstly, a sulfur radical could be afforded by a single-electron-transfer (SET) oxidation of the thiophenol at the anode. Subsequently, the sulfur radical adds to the isocyanide (**2**) to generate the imine radical **A**, which is single-electron oxidized quickly to generate carbon cation **B**. And then intermediate **B** is susceptible to MeOH by nucleophilic attack intermolecularly to forge the desired product **4** along with hydrogen evolution.



Scheme 7. Proposed reaction mechanism.

In summary, we have developed a novel electrochemical strategy for the difunctionalization of isocyanides with readily available mercaptans and alcohols, forming S-C(sp^2)-O bonds on one-carbon atom simultaneously. This strategy provides a convenient and powerful synthetic tool for multi-substituted imine ethers with exclusive regioselectivity. Importantly, excellent functional group tolerance, good efficiency in large-scale synthesis as well as further derivatization of products demonstrate the potential application in chemical industry. Ongoing research including further mechanistic details are currently underway.

Acknowledgements ((optional))

This work was supported by the National Natural Science Foundation of China (22031008, 21520102003), the Hubei Province Natural Science Foundation of China (2017CFA010). The Program of Introducing Talents of Discipline to Universities of China (111 Program) is also appreciated.

Dedicated to P.H. Dixneuf for his outstanding (or meaningful) contribution to organometallic chemistry and catalysis.

Keywords: imino sulfide ethers • difunctionalization • electrochemistry • isocyanides • carbon radical

[1] a) F. Strieth-Kalthoff, F. Sandfort, M. H. S. Segler, F. Glorius, *Chem. Soc. Rev.* **2020**, *49*, 6154-6168; b) I. A. Stepek, K. Itami, *ACS Materials Letters* **2020**, *2*, 951-974; c) J. Yamaguchi, K. Amaike, K. Itami, *In Transition Metal-Catalyzed Heterocycle Synthesis via C-H Activation;* X.-F. Wu, Ed.; Wiley-VCH: Weinheim, **2016**; pp 505-550.

[2] a) B.-J. Li, D.-G. Yu, C.-L. Sun, Z.-J. Shi, *Chem. Eur. J.* **2011**, *17*, 1728-1759; b) J. Wu, Y. Zhou, Y. Zhou, C.-W. Chiang, A. Lei, *ACS Catal.* **2017**, *7*, 8320-8323; c) M. Tobisu, N. Chatani, *Acc. Chem. Res.* **2015**, *48*, 1717-1726; d) A. N. Desnoyer, J. A. Love, *Chem. Soc. Rev.* **2017**, *46*, 197-238; e) X. Xiao, J. Zeng, J. Fang, J. Sun, T. Li, Z. Song, L. Cai, Q. Wan, *J. Am. Chem. Soc.* **2020**, *142*, 5498−5503; f) D. Hernández-Guerra, A. Hlavačková, C. Pramthaisong, I. Vespoli, R. Pohl, T. Slanina, U. Jahn, *Angew. Chem.* **2019**, *131*,12570-12575; *Angew. Chem. Int. Ed.* **2019**, *58*, 12440-12445.

[3] a) T. Gensch, F. J. R. Klauck, F. Glorius, *Angew. Chem.* **2016**, *128*, 11457-11461; *Angew. Chem. Int. Ed.* **2016**, *55*, 11287-11291; b) A. W. Williamson, *Q. J. Chem. Soc.* **1852**, *4*, 229-239; c) K. C. K. Swamy, N. N. B. Kumar, E. Balaraman, K. V. P. P. Kumar, *Chem. Rev.* **2009**, *109*, 2551-2651.

[4] a) H. Yi, L. Niu, C. Song, Y. Li, B. Dou, A. K. Singh, A. Lei, *Angew. Chem.* **2017**, 129,1140-1144; *Angew. Chem. Int. Ed.* **2017**, *56*, 1120-1124; b) S. Shibutani, T. Kodo, M. Takeda, K. Nagao, N. Tokunaga, Y. Sasaki, H. Ohmiya, *J. Am. Chem. Soc.* **2020**, *142*, 1211-1216; c) D.-M. Yan, J.-R. Chen, W.-J. Xiao, *Angew. Chem.* **2019**, *131*,384-386; *Angew. Chem. Int. Ed.* **2019**, *58*, 378-380.

[5] a) J. Xiang, M. Shang, Y. Kawamata, H. Lundberg, S. H. Reisberg, M. Chen, P. Mykhailiuk, G. Beutner, M. R. Collins, A. Davies, M. Del Bel, G. M. Gallego, J. E. Spangler, J. Starr, S. Yang, D. G. Blackmond, P. S. Baran, *Nature* **2019**, *573*, 398-402; b) H. Wang, K. Liang, W. Xiong, S. Samanta, W. Li, A. Lei, *Sci. Adv.* **2020**, *6*, eaaz0590; c) N. Sauermann, T. H. Meyer, C. Tian, L. Ackermann, *J. Am. Chem. Soc.* **2017**, *139*, 18452-18455.

[6] a) F. S. Kuan, S. Yei Ho, P. P. Tadbuppa, E. R. T. Tiekink, *CrystEngComm* **2008**, *10*, 548-564; -b) S. C. Ranade, S. Kaeothip, A. V. Demchenko, *Org. Lett.* **2010**, *12*, 5628-5631; c) Y. Murata, S. Asano, R. Kato, Y. Kitamura, M. Matsumura, S. Yasuike, *Catal. Commun.* **2019**, *132*, 105808; d) J-Y. Wu, Jing-Yu, Z-B. Luo, L-X. Dai, X-L. Hou, J. Org. Chem. **2008**, *73*, 9137-9139; e) I. Yavari, M. Ghazanfarpour-Darjani, J. Sulfur Chem. **2014**, *35*, 477-483.

[7] a) G. Zhang, C. Liu, H. Yi, Q. Meng, C. Bian, H. Chen, J.-X. Jian, L.-Z. Wu, A. Lei, *J. Am. Chem. Soc.* **2015**, *137*, 9273-9280; b) M. Tobisu, A. Kitajima, S. Yoshioka, I. Hyodo, M. Oshita, N. Chatani, *J. Am. Chem. Soc.* **2007**, *129*, 11431-11437.

[8] a) K. Peng, M.-Y. Gao, Y.-Y. Yi, J. Guo, Z.-B. Dong, *Eur. J. Org. Chem.* **2020**, 1665-1672; b) A. Samzadeh-Kermani, S. Zamenraz, *Monatsh. Chem.* **2017**, *148*, 1753-1760; c) S. Wu, X. Lei, E. Fan, Z. Sun, *Org. Lett.* **2018**, *20*, 522-525; d) M. Khalaj, *Monatsh. Chem*, **2020**, *151*, 945-952; e) R. Bossio, S. Marcaccini, R. Pepino, *Heterocycles* **1986**, *24*, 2003-2005; f) R. Bossio, S. Marcaccini, R. Pepino, *Heterocycles* **1986**, *24*, 2411-2413; g) R. Bossio, S. Marcaccini, R. Pepino, C. Polo, T.Torroba, *Heterocycles* **1989**, *29*, 1829-1833.

[9] a) M. Yan, Y. Kawamata, P. S. Baran, *Chem. Rev.* **2017**, *117*, 13230-13319; b) P. Xiong, H.-C. Xu, *Acc. Chem. Res.* **2019**, *52*, 3339-3350; c) J.-i. Yoshida, K. Kataoka, R. Horcajada, A. Nagaki, *Chem. Rev.* **2008**, *108*, 2265-2299; d) Y. Jiang, K. Xu, C. Zeng, *Chem. Rev.* **2018**, *118*, 4485-4540; e) A. Jutand, *Chem. Rev.* **2008**, *108*, 2300-2347; f) K.-J. Jiao, Y.-K. Xing, Q.-L. Yang, H. Qiu, T.-S. Mei, *Acc. Chem. Res.* **2020**, *53*, 300-310.

[10] a) H. J. Schäfer, *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 911-934; b) E. Steckhan, *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 683-701; c) Y. Yuan, A. Lei, *Acc. Chem. Res.* **2019**, *52*, 3309-3324; d) S. Tang, Y. Liu, A. Lei, *Chem* **2018**, *4*, 27-45.

[11] a) H. Mei, Z. Yin, J. Liu, H. Sun, J. Han, *Chin. J. Chem.* **2019**, *37,* 292-301; b) P. Wang, X. Gao, P. Huang, A. Lei, *ChemCatChem* **2019**, *12*, 27-40; c) G. M. Martins, B. Shirinfar, T. Hardwick, N. Ahmed, *ChemElectroChem* **2019**, *6*, 1300-1315.

[12] a) N. Fu, G. S. Sauer, A. Saha, A. Loo, S. Lin, *Science* **2017**, *357*, 575-579; b) N. Fu, G. S. Sauer, S. Lin, *J. Am. Chem. Soc.* **2017**, *139*, 15548-15553.

[13] a) Y. Imada, Y. Okada, K. Noguchi, K. Chiba, *Angew. Chem.* **2019**, *131*,131-135; *Angew. Chem. Int. Ed.* **2019**, *58*, 125-129; b) Y. Ma, J. Lv, C. Liu, X. Yao, G. Yan, W. Yu, J. Ye, *Angew. Chem. Int. Ed.* **2019**, *58*, 6756-6760; c) C.-Y. Cai, H.-C. Xu, *Nat. Commun.* **2018**, *9*, 3551; d) H.-C. Xu, K. D. Moeller, *Angew. Chem.* **2010**, *122*, 8176-8179; *Angew. Chem. Int. Ed.* **2010**, *49*, 8004-8007; e) P. Xiong, H. Long, J. Song, Y. Wang, J.-F. Li, H.-C. Xu, *J. Am. Chem. Soc.* **2018**, *140*, 16387-16391; f) H.-C. Xu, K. D. Moeller, *J. Am. Chem. Soc.* **2010**, *132*, 2839-2844.

[14] a) J. Wu, Y. Dou, R. Guillot, C. Kouklovsky, G. Vincent, *J. Am. Chem. Soc.* **2019**, *141*, 2832-2837; b) K. Liu, W. Song, Y. Deng, H. Yang, C. Song, T. Abdelilah, S. Wang, H. Cong, S. Tang, A. Lei, *Nat. Commun.* **2020**, *11*, 3.

[15] a) J. Jeon, H. Ryu, C. Lee, D. Cho, M.-H. Baik, S. Hong, *J. Am. Chem. Soc.* **2019**, *141*, 10048-10059; b) E. Yamamoto, M. J. Hilton, M. Orlandi, V. Saini, F. D. Toste, M. S. Sigman, *J. Am. Chem. Soc.* **2016**, *138*, 15877-15880; c) A. M. Bergmann, S. K. Dorn, K. B. Smith, K. M. Logan, M. K. Brown, *Angew. Chem.* **2019**, *131*, 1733-1737; *Angew. Chem. Int. Ed.* **2019**, *58*, 1719-1723; d) S. Wang, B.-Y. Cheng, M. Srsen, B. König, *J. Am. Chem. Soc.* **2020**, 142, 7524−7531.

[16] a) P. Mampuys, Y. Zhu, T. Vlaar, E. Ruijter, R. V. A. Orru, B. U. W. Maes, *Angew. Chem.* **2014**, *126*, 13063-13068; *Angew. Chem. Int. Ed.* **2014**, *53*, 12849-12854; b) J. W. Collet, T. R. Roose, E. Ruijter, B. U. W. Maes, R. V. A. Orru, *Angew.Chem.* **2020**, *132*, 548-566; *Angew. Chem. Int. Ed.* **2019**, *59,* 540-558; c) G. d. P. Gomes, Y. Loginova, S. Z. Vatsadze, I. V. Alabugin, *J. Am. Chem. Soc.* **2018**, *140*, 14272-14288; d) N. Pan, J. Ling, J.-P. Pulicani, I. Grimaud, M. R. Vitale, *Green Chem.* **2019**. *21*, 6194-6199.

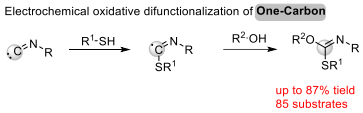
[17] B. K. Malviya, P. K. Jaiswal, V. P. Verma, S. S. Badsara, S. Sharma, *Org. Lett.* **2020**, *22*, 2323-2327.

[18] a) P. Huang, P. Wang, S. Tang, Z. Fu, A. Lei, *Angew. Chem.* **2018**, *130*, 8247-8251; *Angew. Chem. Int. Ed.* **2018**, *57*, 8115-8119; b) T. Ngouansavanh, J. Zhu, *Angew. Chem.* **2007**, *115*, 5877-5880; *Angew. Chem. Int. Ed.* **2007**, *46*, 5775-5778.

10.1002/anie.202011329

Entry for the Table of Contents

Insert text for Table of Contents here. ((The Table of Contents text should give readers a short preview of the main theme of the research and results included in the paper to attract their attention into reading the paper in full. The Table of Contents text **should be different from the abstract** and should be no more than 450 characters including spaces.))



We developed an unprecedented electrochemical oxidative one-carbon difunctionalization of isocyanides, providing a series of novel multi-substituted imino sulfide ethers. Under metal- and external oxidant-free conditions, isocyanides could react smoothly with simple and readily available mercaptans and alcohols.

Institute and/or researcher Twitter usernames: ((optional))