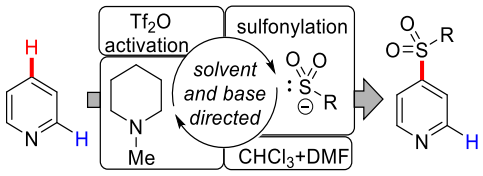
Base-mediated C4-selective C-H-sulfonylation of pyridine.

Marius Friedrich, Georg Manolikakes*

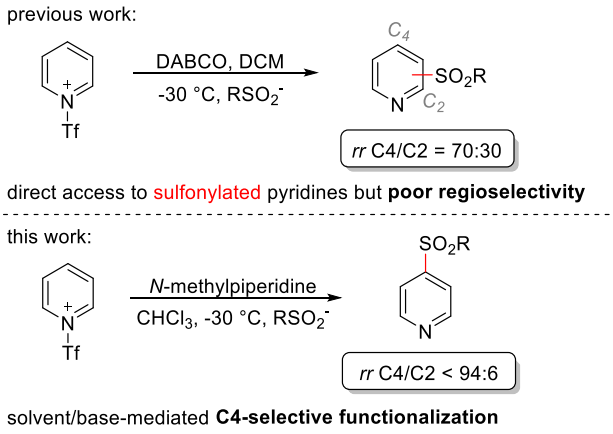
Department of Organic Chemistry
Technical University Kaiserslautern
Erwin-Schrödinger-Str. Geb. 54, D-67663 Kaiserslautern, Germany
E-mail: manolikakes@chemie.uni-kl.de Webpage: https://www.chemie.uni-kl.de/en/manolikakes/



Abstract

The direct regioselective C-H-functionalization of simple, unfunctionalized pyridines is considered a long-standing challenge in heterocyclic chemistry. Herein, we report a novel one-pot protocol for the C4-selective sulfonylation of pyridines via triflic anhydride (Tf_2O) activation, base-mediated addition of a sulfinic acid salt and subsequent elimination/rearomatization. Contrary to previous approaches employing tailored blocking groups, positional selectivity can be controlled by using N-methyl piperidine as simple, readily available external base. This method offers a highly modular and streamlined access to C4-sulfonylated pyridines.

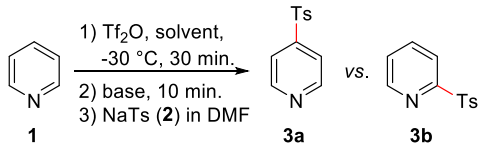
Scheme 1. Para-selective sulfonylation of pyridine



The pyridine ring system is a ubiquitous heterocyclic motif in natural products and active pharmaceutical ingredients.[1] Owing to its relevance, there is a continuous interest in novel and effective methods to prepare this heteroaromatic scaffold. The direct C-H-functionalization of pyridines represents a particular attractive approach for the synthesis or late-stage modification of structural complex pyridine-based heterocyclic structures.[2,3] Recently, we described a novel approach for the direct C-H-sulfonylation of pyridine and related N-heteroaromatics.[4] This process is based on activation of the pyridine ring with triflic anhydride (Tf_2O)[5,6] followed by a 1,4-diazabicyclo[2.2.2]octane (DABCO) mediated addition of a sulfinate salt and rearomatization (Scheme 1a).

Although, it enables a modular synthesis of N-heterocyclic sulfones and sulfonamides, this method sometimes suffers from the poor regioselectivity of the sulfinate addition. As a representative example, the C-H-sulfonylation of the parent pyridine delivers both the C2- and the C4-regiosiomer in a 30:70 ratio (Scheme 1a). An analogous formation of two or more regioisomers has been observed in many similar processes.[2,3,5] Therefore, a general method to address the poor regioselectivity in the C-H-functionalization of activated pyridinium salts would be highly desirable.[7] Herein, we report a novel method for the C4-selective C-H-sulfonlyation of pyridines. Contrary to previous described procedures which exploit tailored C2-blocking groups,[7] we were able to achieve a so far unprecedented base-induced C4-selective C-H-functionalization of pyridine (Scheme 1b).

Table 1. Influence of base and solvent on the regioselective sulfonyation of pyridine



entry	base	solvent	yield in [%][a]	*rr* (C4/C2) in [%][b]
1	DABCO	CH_2Cl_2	87[c]	70:30
2		$CHCl_3$	83	78:22
3	*N*-methyl-piperidine	CH_2Cl_2	73[c]	83:17
4		$CHCl_3$	79[c]	94:6
5	*N*-methyl-pyrrolidine	CH_2Cl_2	61	48:52
6		$CHCl_3$	75	70:30
7	*N*-methyl-morpholine	CH_2Cl_2	<5	nd
8		$CHCl_3$	<5	nd
9	1,2,2,6,6-pentamethyl-piperidine	CH_2Cl_2	9	95:5
10		$CHCl_3$	<5	nd
11	*N*,*N*-dimethyl-piperazine	CH_2Cl_2	43	95:5
12		$CHCl_3$	27	95:5

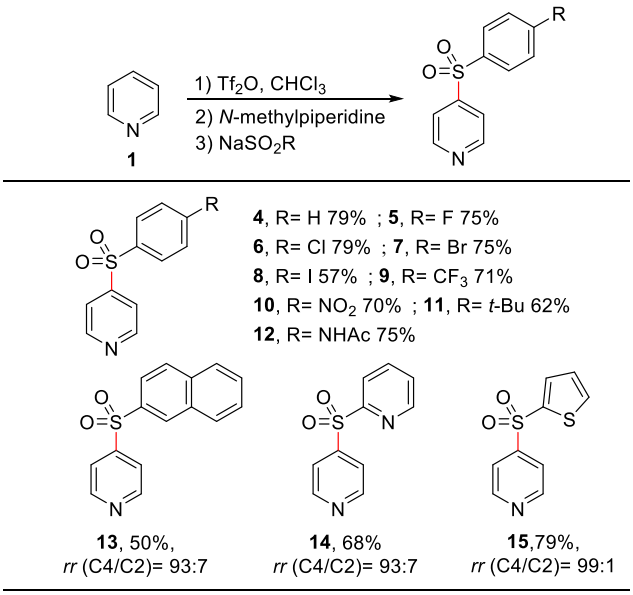
[a]Yield determined by GC with *n*-dodecan as internal standard; [b]regioisomeric ratio *(rr)* determined by ^{1}H NMR of the crude mixture, [c]isolated yield;

During our initial investigations on the C-H-sulfonylation of N-heteroaromatics, we observed some unexpected results in the functionalization of pyridine **1** with sodium para-toluenesuflinate **2** (Table 1). Whereas, the reaction with our previously reported conditions (base: DABCO; solvent: CH_2Cl_2) afforded the sulfonylated pyridine as 70:30 mixture of the C4- and the C2-regiosiomer (3a and 3b) (entry 1), we could observe a significant influence of both base and solvent on the reaction outcome. Replacement of CH_2Cl_2 with $CHCl_3$ led to a slight improvement in terms of regioselectivity (entry 2). Addition of N-methylpiperidine instead of DABCO as base, furnished the sulfonylated pyridine 3 in 73% yield and a C4/C2-selectivity of 83:17 (entry 3). Combining $CHCl_3$ as solvent with N-methylpiperidine as base resulted in a highly regioselective functionalization of pyridine (entry 4). Interestingly, this effect could

not be observed with structurally similar amine bases. N-methylpyrrolidine afforded the desired sulfonylated pyridine with significantly decreased regioselectivity both in CH_2Cl_2 and $CHCl_3$ (entries 5 and 6). Reactions with N-methylmorpholine or pentamethylpiperidine as base mediator resulted in a very low overall yield (< 10%) (entries 7-10). Only the use *N*,*N*-dimethylpyridazine led to an regioselective formation of C4-sulfonylated pyridine in moderate yields (entries 11 and 12).

Using these novel conditions, we investigated the C-H-sulfonylation of pyridine with different sodium sulfinates (Scheme 2). Various aryl sulfinates containing different electron-withdrawing or -donating substituents, such as halogen atoms, a nitro or an amide group could be successfully attached to the heterocyclic ring (**4**-**13**). Good yields and uniformly high regioselectivities were obtained in all cases. To our delight heterocyclic sulfone residues (**14** and **15**) could be attached with a similar efficiency onto pyridine.

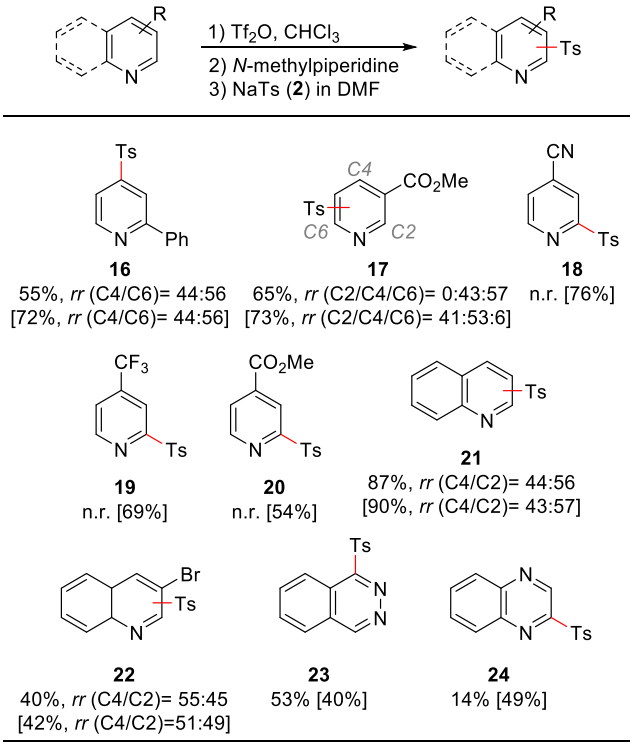
Scheme 2. C4-Selective Sulfonylation of Pyridine[a]



[a]if not specified otherwise a regioisomeric ratio (C4/C2)≥ 95:5 was determined by ^{1}H NMR of the crude mixture.

Next, we (re)investigated the C-H-sulfonylation of substituted pyridines and some other N-heteroaraomatics with a particular focus on the observed differences in regioselectivity (Scheme 3). Therefore, reactions with 2-phenylpyridine and nicotinic acid methyl ester as model substrates for C2- and C3-subsituted pyridines were examined. Interestingly, no changes in regioselectivity were observed for the C-H-sulfonylation of 2-phenyl pyridine using the novel conditions. In contrast, a distinct shift from the C2 to the C6-position occurred in the functionalization of nicotinic acid methyl ester. Strikingly, the C-H-sulfonylation of various 4-subsituted pyridines failed completely with our modified conditions. On the other hand, the N-methylpiperidine-mediated C-H-sulfonylation of quinoline and 3-bromoquinolines proceeded with yields and selectivities in the same range our initial version using DABCO. Direct functionalization of phtalazine and quinoxaline afforded the sulfonylated heterocycles **23** and **24** in 53% and 14% (vs. 40% and 49% with DABCO). These results show a quite distinct effect of the heterocyclic scaffold itself on the outcome of the reaction. However, the choice of base offers a useful handle to steer positioning of the sulfonyl substituent towards a specific position, in particular in the parent pyridine. Therefore, our modified process opens an interesting opportunity to functionalize pyridine at an early stage.[3,7]

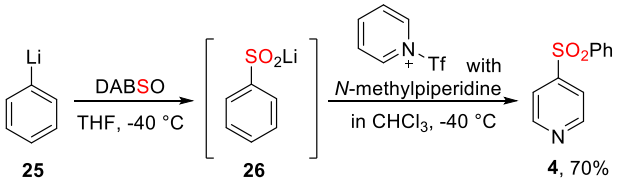
Scheme 3. Sulfonylation of substituted pyridines and other aza-heterocycles[a]



[a]Yield and regioisomeric ratio in brackets refer to the previous method (CH_2Cl_2/DABCO).[4]

Next, we investigated a possible extension of this method to for a modular installation of different sulfonyl residues onto the parent pyridine. At first, we examined the direct incorporation of sulfur dioxide into the final sulfonyl product (Scheme 4).[8] Therefore, a solution of phenyl lithium sulfinate **26** was prepared by the reaction of phenyl lithium **25** with the sulfur dioxide surrogate 1,4-diazabicyclo[2.2.2]octane bis(sulfur dioxide) (DABSO).[9] Direct addition of the obtained crude sulfinate to the activated pyridinium triflate furnished the C4-sulfonylated pyridine **4** in 70% yield and a high regioselectivity.

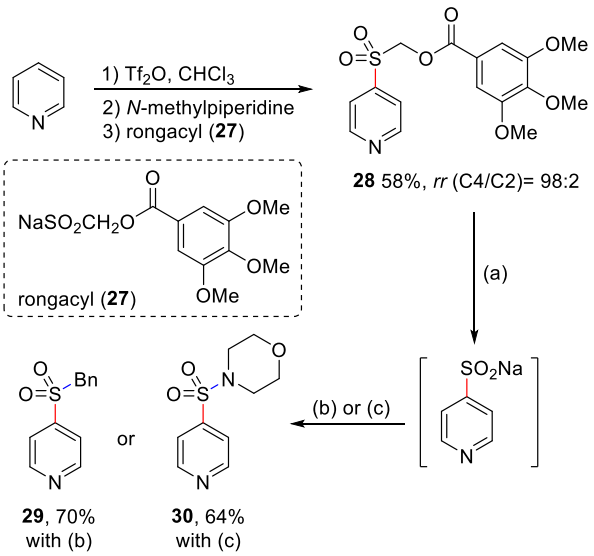
Scheme 4. direct incorporation of SO_2 with DABSO



Regioisomeric ratio (C4/C2) = 94:6 was determined by ^{1}H NMR of the crude mixture.

In parallel, we examined the controlled installation of a masked sulfinate functionality using rongacyl (**27**), a readily available reagent, which offers both high flexibility for further modifications and good tolerance towards our reaction conditions (Scheme 5).[4,10] To our delight, the incorporation of **27** proceeded efficiently and with high C4-selectivity. Using a base-mediated cleavage-electrophilic trapping sequence, the masked sulfinate **28** could be transformed into the sulfone **29** and the sulfonamide **30** in 70% and 64% yield.

Scheme 5. further modification



Reaction conditions (a): aqueous NaOH (1M), TBAB, DMSO, ambient temperature; (b): benzyl bromide, 50 °C; (c) morpholine, NBS in THF, 0 °C

In summary, we have developed a novel, base-mediated highly regioselective C-H-sulfonylation of pyridine. This method gives a fast and efficient access to C4-functionalized pyridines. We could further demonstrate an extension towards the modular construction of various pyridines using either the sulfur dioxide surrogate DABSO or a masked SO_2^{2-} equivalent as key building blocks for the sulfonyl group. To the best of our knowledge, this is the first example for a regioselective functionalization of pyridines via the corresponding activated pyridinium salts controlled simply by an external base. It offers a streamlined access to C4-sulfonylated pyridines in a rapid and inexpensive fashion. Currently, we are examining the mechanism of this intriguing transformation in more detail, with the aim to extend the scope of this method both to other N-heteroaromatics and other types of nucleophiles.[11]

Acknowledgements

Financial support by the Boehringer Ingelheim Foundation (Exploration Grant to G.M.) and the research unit NanoKat at the TU Kaiserslautern is gratefully acknowledged.

Notes

The authors declare no competing financial interest.

Keywords: Sulfones, Sulfinate salts, N-Heteroaromatics, C-H-Functionalization

Author Contributions

Conceptualization: M. Fand G. M.; investigation and methodology: M. F. Funding acquisition: G. M.; supervision: G. M.; writing, original draft: M. F. and G. M.; writing, reviewing & editing: M. F and G. M.

REFERENCES

(1) a) Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of the structural diversity, substitution patterns, and frequency of nitrogen heterocycles among U.S. FDA approved pharmaceuticals. *Journal of medicinal chemistry* **2014**, *57*, 10257–10274. DOI: 10.1021/jm501100b. Published Online: Oct. 7, 2014; b) Ezzat Khan. Pyridine Derivatives as Biologically Active Precursors; Organics and Selected Coordination Complexes. *ChemistrySelect* **2021**, *6*, 3041–3064. DOI: 10.1002/slct.202100332; c) Mohamed, E. A.; Ismail, N. S. M.; Hagras, M.; Refaat, H. Medicinal attributes of pyridine scaffold as anticancer targeting agents. *Futur J Pharm Sci* **2021**, *7*, 1–17. DOI: 10.1186/s43094-020-00165-4;

(2) for selected reviews see: a) Yoshiaki Nakao. Transition-Metal-Catalyzed C-H Functionalization for the Synthesis of SubstitutedPyridines. *Synthesis* **2011**, *2011*, 3209–3219. DOI: 10.1055/s-0030-1260212; b) Brückl, T.; Baxter, R. D.; Ishihara, Y.; Baran, P. S. Innate and guided C-H functionalization logic. *Accounts of chemical research* **2012**, *45*, 826–839. DOI: 10.1021/ar200194b. Published Online: Oct. 21, 2011; c) Murakami, K.; Yamada, S.; Kaneda, T.; Itami, K. C-H Functionalization of Azines. *Chemical reviews* **2017**, *117*, 9302–9332. DOI: 10.1021/acs.chemrev.7b00021. Published Online: Apr. 26, 2017; d) Zhou, F.-Y.; Jiao, L. Recent Developments in Transition-Metal-Free Functionalization and Derivatization Reactions of Pyridines. *Synlett* **2021**, *32*, 159–178. DOI: 10.1055/s-0040-1706552;

(3) for recent examples see: a) Bartels, F.; Weber, M.; Christmann, M. Synthesis of Spongidine A and D and Petrosaspongiolide L Methyl Ester Using Pyridine C-H Functionalization. Organic letters 2020, 22, 552‑555. DOI: 10.1021/acs.orglett.9b04315. Published Online: Dec. 26, 2019; b) Zhu, X.-L.; Huang, Y.; Xu, X.-H.; Qing, F.-L. Silver-Catalyzed C-H Aryloxydifluoromethylation and Arylthiodifluoromethylation of Heteroarenes. Organic letters 2020, 22, 5451‑5455. DOI: 10.1021/acs.orglett.0c01826. Published Online: Jul. 9, 2020; c) Hagui, W.; Soulé, J.-F. Synthesis of 2-Arylpyridines and 2-Arylbipyridines via Photoredox-Induced Meerwein Arylation with in Situ Diazotization of Anilines. J. Org. Chem. 2020, 85, 3655‑3663. DOI: 10.1021/acs.joc.9b03306. Published Online: Feb. 20, 2020; d) Jeon, J.; He, Y.-T.; Shin, S.; Hong, S. Visible-Light-Induced ortho-Selective Migration on Pyridyl Ring: Trifluoromethylative Pyridylation of Unactivated Alkenes. Angewandte Chemie (International ed. in English) 2020, 59, 281‑285. DOI: 10.1002/anie.201912746. Published Online: Nov. 15, 2019; e) Deng, Z.; Zhao, M.; Wang, F.; Tang, P. Selective C-H trifluoromethoxylation of (hetero)arenes as limiting reagent. Nature communications 2020, 11, 2569. DOI: 10.1038/s41467-020-16451-x. Published Online: May. 22, 2020; f) Tan, Z.; He, X.; Xu, K.; Zeng, C. Electrophotocatalytic C-H Functionalization of N-Heteroarenes with Unactivated Alkanes under External Oxidant-Free Conditions. ChemSusChem 2022, 15, e202102360. DOI: 10.1002/cssc.202102360. Published Online: Feb. 15, 2022;

(4) Friedrich, M.; Schulz, L.; Hofman, K.; Zangl, R.; Morgner, N.; Shaaban, S.; Manolikakes, G. Direct C–H-sulfonylation of 6-membered nitrogen-heteroaromatics. *Tetrahedron Chem* **2022**, *1*, 100003. DOI: 10.1016/j.tchem.2021.100003;

(5) for selected examples using triflic anhydride for C-C bond formationa see: (a) Senczyszyn, J.; Brice, H.; Clayden, J. Spirocyclic dihydropyridines by electrophile-induced dearomatizing cyclization of N-alkenyl pyridinecarboxamides. *Org. Lett.* **2013**, *15*, 1922–1925. DOI: 10.1021/ol400571j. Published Online: Apr. 3, 2013; b) Rudler, H.; Parlier, A.; Sandoval-Chavez, C.; Herson, P.; Daran, J.-C. Overall "Pseudocationic" Trifluoromethylation of Dihydropyridines with Triflic Anhydride. *Angew. Chem.* **2008**, *120*, 6949–6952. DOI: 10.1002/ange.200801879; c) Katritzky, A. R.; Zhang, S.; Kurz, T.; Wang, M.; Steel, P. J. Regiospecific synthesis of 4-(2-oxoalkyl)pyridines. *Org. Lett.* **2001**, *3*, 2807–2809. DOI: 10.1021/ol010116f; d) Corey, E. J.; Tian, Y. Selective 4-arylation of pyridines by a nonmetalloorganic process. *Org. Lett.* **2005**, *7*, 5535–5537. DOI: 10.1021/ol052476z; e) Shoji, T.; Inoue, Y.; Ito, S. First synthesis of 1-(indol-2-yl)azulenes by the Vilsmeier–Haack type arylation with triflic anhydride as an activating reagent. *Tetrahedron Letters* **2012**, *53*, 1493–1496. DOI: 10.1016/j.tetlet.2012.01.044; f) Elbert, B. L.; Farley, A. J. M.; Gorman, T. W.; Johnson, T. C.; Genicot, C.; Lallemand, B.; Pasau, P.; Flasz, J.; Castro, J. L.; MacCoss, M.; Paton, R. S.; Schofield, C. J.; Smith, M. D.; Willis, M. C.; Dixon, D. J. C-H Cyanation of 6-Ring N-Containing Heteroaromatics. *Chemistry (Weinheim an der Bergstrasse, Germany)* **2017**, *23*, 14733–14737. DOI: 10.1002/chem.201703931. Published Online: Sep. 22, 2017;

(6) for selected examples using triflic anhydride for C-P bond formation see: a) Levy, J. N.; Alegre-Requena, J. V.; Liu, R.; Paton, R. S.; McNally, A. Selective Halogenation of Pyridines Using Designed Phosphine Reagents. *Journal of the American Chemical Society* **2020**, *142*, 11295–11305. DOI: 10.1021/jacs.0c04674. Published Online: Jun. 10, 2020 and references cited therein; b) Koniarczyk, J. L.; Greenwood, J. W.; Alegre-Requena, J. V.; Paton, R. S.; McNally, A. A Pyridine-Pyridine Cross-Coupling Reaction via Dearomatized Radical Intermediates. *Angewandte Chemie (International ed. in English)* **2019**, *58*, 14882–14886. DOI: 10.1002/anie.201906267. Published Online: Sep. 9, 2019; c) Che, Y.-Y.; Yue, Y.; Lin, L.-Z.; Pei, B.; Deng, X.; Feng, C. Palladium-Catalyzed Electrophilic Functionalization of Pyridine Derivatives through Phosphonium Salts. *Angewandte Chemie (International ed. in English)* **2020**, *59*, 16414–16419. DOI: 10.1002/anie.202006724. Published Online: Jul. 15, 2020;

(7) for some recent examples on the selective C4-alykation of pyridines see: a) Lee, W.; Jung, S.; Kim, M.; Hong, S. Site-Selective Direct C-H Pyridylation of Unactivated Alkanes by Triplet Excited Anthraquinone. *Journal of the American Chemical Society* **2021**, *143*, 3003–3012. DOI: 10.1021/jacs.1c00549. Published Online: Feb. 8, 2021; b) Kim, M.; Shin, S.; Koo, Y.; Jung, S.; Hong, S. Regiodivergent Conversion of Alkenes to Branched or Linear Alkylpyridines. *Organic letters* **2022**, *24*, 708–713. DOI: 10.1021/acs.orglett.1c04156. Published Online: Dec. 29, 2021; c) Moon, Y.; Park, B.; Kim, I.; Kang, G.; Shin, S.; Kang, D.; Baik, M.-H.; Hong, S. Visible light induced alkene aminopyridylation using N-aminopyridinium salts as bifunctional reagents. *Nature communications* **2019**, *10*, 4117. DOI: 10.1038/s41467-019-12216-3. Published Online: Sep. 11, 2019; d) Choi, J.; Laudadio, G.; Godineau, E.; Baran, P. S. Practical and Regioselective Synthesis of C-4-Alkylated Pyridines. *Journal of the*

American Chemical Society **2021**, *143*, 11927–11933. DOI: 10.1021/jacs.1c05278. Published Online: Jul. 28, 2021; e) Obradors, C.; List, B. Azine Activation via Silylium Catalysis. *Journal of the American Chemical Society* **2021**, *143*, 6817–6822. DOI: 10.1021/jacs.1c03257. Published Online: Apr. 28, 2021; f) Jung, S.; Shin, S.; Park, S.; Hong, S. Visible-Light-Driven C4-Selective Alkylation of Pyridinium Derivatives with Alkyl Bromides. *Journal of the American Chemical Society* **2020**, *142*, 11370–11375. DOI: 10.1021/jacs.0c04499. Published Online: Jun. 18, 2020; g) Lee, K.; Lee, S.; Kim, N.; Kim, S.; Hong, S. Visible-Light-Enabled Trifluoromethylative Pyridylation of Alkenes from Pyridines and Triflic Anhydride. *Angewandte Chemie (International ed. in English)* **2020**, *59*, 13379–13384. DOI: 10.1002/anie.202004439. Published Online: Jun. 2, 2020; h) Fricke, P. J.; Dolewski, R. D.; McNally, A. Four-Selective Pyridine Alkylation via Wittig Olefination of Dearomatized Pyridylphosphonium Ylides. *Angewandte Chemie (International ed. in English)* **2021**, *60*, 21283–21288. DOI: 10.1002/anie.202109271. Published Online: Aug. 23, 2021;

(8) a) Deeming, A.; Emmett, E.; Richards-Taylor, C.; Willis, M. Rediscovering the Chemistry of Sulfur Dioxide: New Developments in Synthesis and Catalysis. *Synthesis* **2014**, *46*, 2701–2710. DOI: 10.1055/s-0034-1379042; b) Liang, S.; Hofman, K.; Friedrich, M.; Manolikakes, G. Recent Advances in the Synthesis and Direct Application of Sulfinate Salts. *Eur. J. Org. Chem.* **2020**, *2020*, 4664–4676. DOI: 10.1002/ejoc.202000403;

(9) Woolven, H.; González-Rodríguez, C.; Marco, I.; Thompson, A. L.; Willis, M. C. DABCO-bis(sulfur dioxide), DABSO, as a convenient source of sulfur dioxide for organic synthesis: utility in sulfonamide and sulfamide preparation. *Organic letters* **2011**, *13*, 4876–4878. DOI: 10.1021/ol201957n. Published Online: Aug. 25, 2011;

(10) Shavnya, A.; Hesp, K. D.; Tsai, A. S. A Versatile Reagent and Method for Direct Aliphatic Sulfonylation. *Adv. Synth. Catal.* **2018**, *360*, 1768–1774. DOI: 10.1002/adsc.201800071;