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Construction of Difluoromethylated Tetrazoles via Silver-Catalyzed Regioselective [3 + 2] Cycloadditions of Aryl Diazonium Salts

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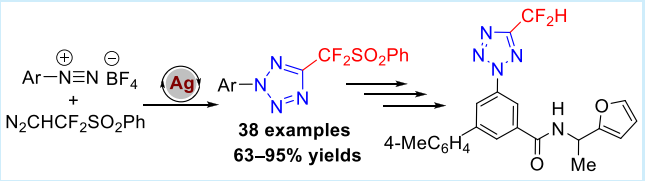
Supporting Information

ABSTRACT: A silver-catalyzed regioselective [3 + 2] cycloaddition reaction of $PhSO_2CF_2CHN_2$ with aryl diazonium salts is described. This protocol enables the straightforward construction of a novel class of difluoromethylated tetrazoles under mild conditions, tolerates a broad spectrum of functionalities, and is applicable to one-pot operation from commercially available aniline derivatives. The synthetic merit of this method is further demonstrated by the facile preparation of versatile difluoromethylated azoles, including a valuable HCF_2-analogue of P2X3 receptor antagonist.



The difluoromethylene (CF_2) unit has emerged as a highly useful moiety in the design and discovery of active pharmaceuticals and agrochemicals.[1] As a consequence, great attention has been paid to the development of various transition-metal-mediated difluoromethylation reactions in the past decade.[2] However, compared with the synthesis of CF_2-arenes, the construction of CF_2-heterocycles often encounters increased challenges.[3] In particular, precedented methods for the preparation of CF_2-tetrazoles have remained extremely rare until now,[4] despite the fact that the tetrazoles represent a remarkable class of commonly found core-azoles in a vast plethora of molecules with medical or biochemical relevance (Figure 1).[5] While the conventional synthetic route to aryl tetrazoles mainly relies on the cycloadditions of azide reagents with nitriles or imidoyl derivatives,[6] unfortunately, this chemistry cannot be easily applied to the synthesis of CF_2-tetrazoles, probably due to the difficult availability of the corresponding CF_2-containing precursors.[7] Recently, our group has first reported that the 1,3-disubstituted tetrazoles could be constructed via a conceptually novel silver-catalyzed regioselective cycloaddition reaction of aryl diazonium salts with trifluorodiazoethane or diazoacetates (Scheme 1a).[8]

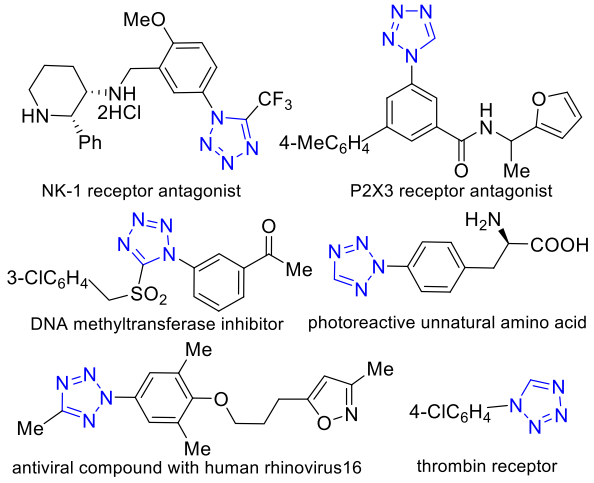
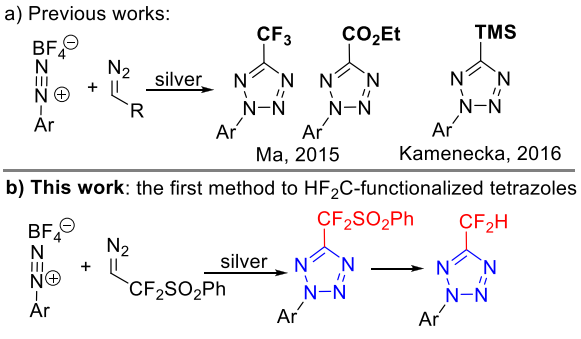


Figure 1. Aryl tetrazoles found applications in medical chemistry and biochemistry.

Scheme 1. State of the Art for the Cycloadditions of Aryl Diazonium Salts with Diazo Compounds



Subsequently, Kamenecka and co-workers demonstrated the feasibility of employing trimethylsilyldiazomethane in such cycloadditions to give the 2-aryl-2*H*-tertrazoles in a similar fashion (Scheme 1a).[9] Encouraged by these results, we envisioned that the difluoromethylated tetrazoles might be obtained by treating a CF_2-diazo reagent with aryl diazonium salts in the presence of an appropriate silver catalyst.[10] Therefore, herein we report the realization of this design by engaging our recently unveiled $PhSO_2CF_2CHN_2$ in the

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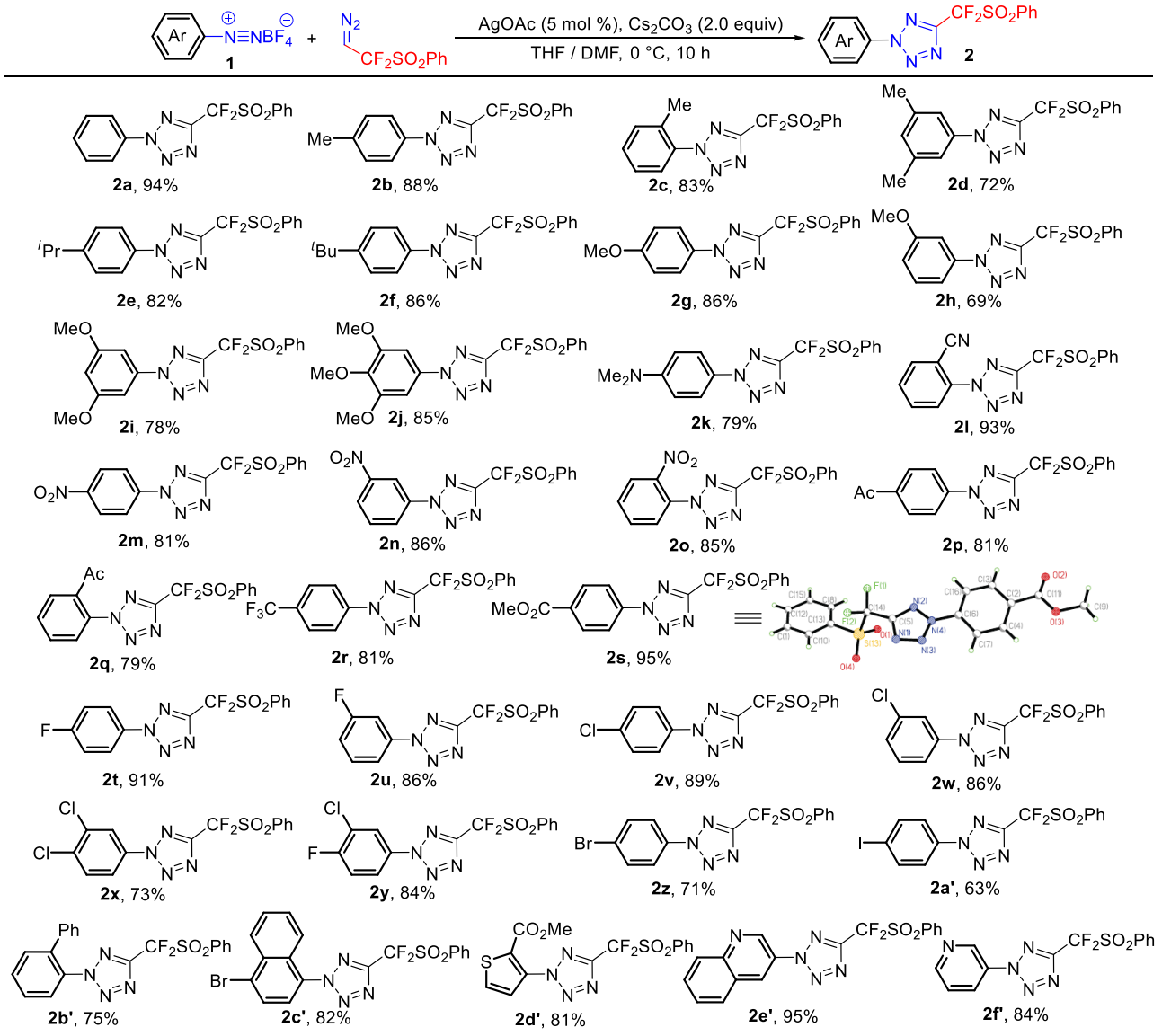
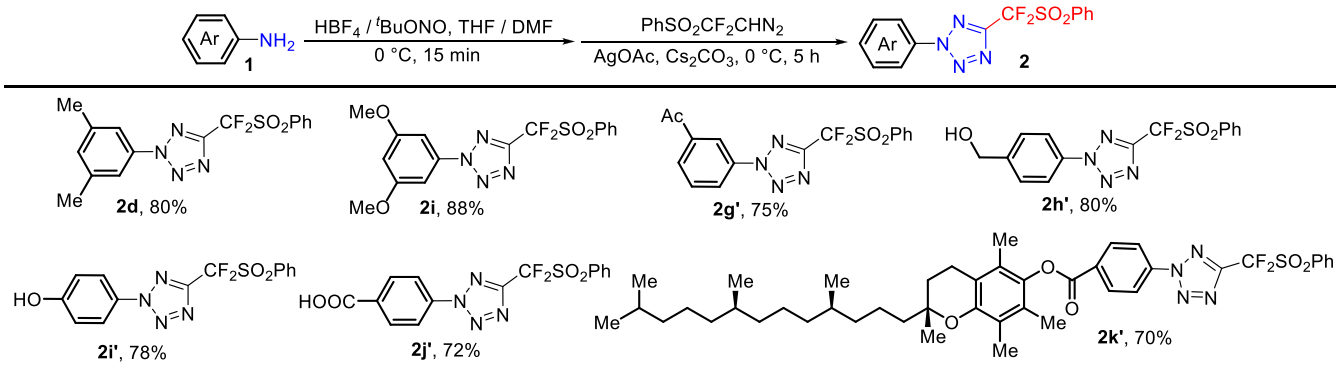
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 2. Substrate Scope of the Cycloaddition Reaction between $PhSO_2CF_2CHN_2$ and Aryl Diazonium Salts 1



Scheme 3. One-Pot Diazotization/Cycloaddition Reaction of Various Aniline Derivatives



cycloaddition process with a broad range of aryl diazonium salts (Scheme 1b).[11] This highly regioselective transformation represents a practical and modular method to access versatile CF_2-functionalized tetrazoles, including a valuable HCF_2-analogue of P2X3 receptor antagonist.[12]

On the basis of our previous study,[13] a systemic screening of various reaction parameters expeditiously identified the optimized conditions as following: in the presence of silver acetate (5 mol %) and cesium carbonate (2 equiv), a [3 + 2] cycloaddition of $PhSO_2CF_2CHN_2$ with phenyl diazonium salt

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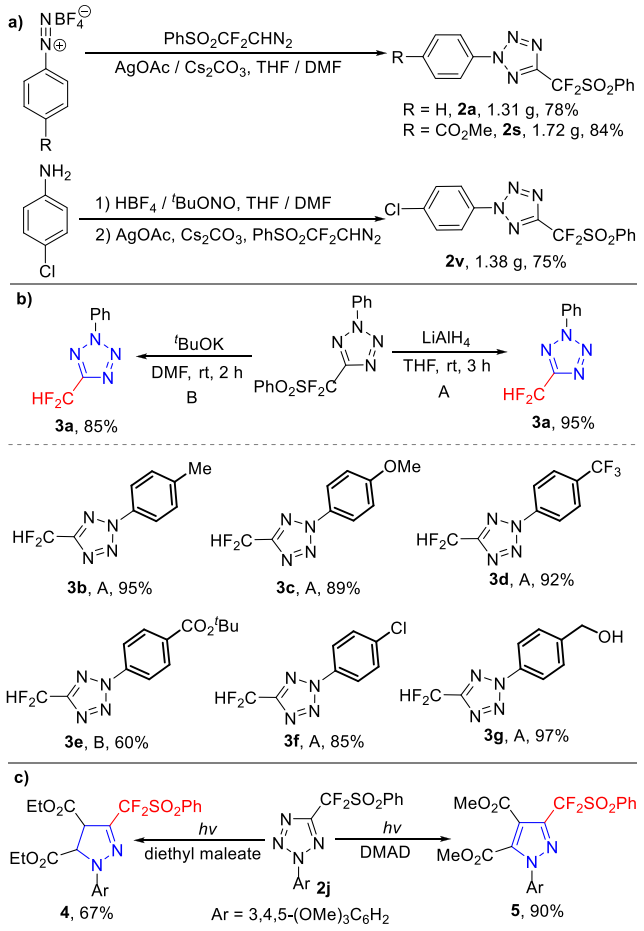
Org. Lett. XXXX, XXX, XXX−XXX

1a proceeded smoothly in a cosolvent of THF/DMF (20/1) at 0 °C, thus giving the desired tetrazole **2a** in 94% yield with exclusive regioselectivity. Subsequently, the remarkably wide substrate scope of this reaction is demonstrated by the evaluation of a large number of aryl diazonium salts (Scheme 2). In general, phenyl substrates bearing substituents with varied electronic or steric properties at different positions on the benzene ring could all participate in the desired transformations uneventfully, thereby delivering the corresponding CF_2-functionalized tetrazoles **2b**–**2b′** in 63–95% yields. In particular, phenyl diazonium salts substituted with a basic amino group or polar nitro group also proved to be feasible reaction partners (products **2k**–**2o**). Notably, the molecular structure of the obtained tetrazoles are assigned by analogue via single-crystal X-ray diffraction analysis of compound **2s**. It should be mentioned that the halogens in the afforded tetrazoles **2v**–**2a′** may offer new possibilities for downstream cross-coupling-type manipulations. Furthermore, diazonium salts possessing other aromatic motifs such as 1-naphthyl, 3-thienyl, 3-quinolyl, and 3-pyridinyl are also well compatible in this reaction and provided the corresponding CF_2-tetrazoles **2c′**–**2f′** in high yields. In all cases, excellent regioselectivities were observed as confirmed by ^{19}F NMR of the crude reaction mixture.

Subsequently, a one-pot sequence directly from aniline derivatives to produce CF_2-tetrazoles was probed. As shown in Scheme 3, by in situ generation of the diazonium salts in almost quantitative yield from corresponding anilines, followed by the successive addition of silver catalyst, base, and the diazo reagent, the desired tetrazole derivatives could be produced in good yields. Substrates with an unprotected hydroxyl or carboxyl group proceeded much more smoothly to give the corresponding cycloadducts **2h′**–**2j′** (72–80% yields) than the preceding two-step protocol (lower than 10% yields). Significantly, this silver-catalyzed one-pot diazotization/cycloaddition sequence is also amenable for the late-stage modification of biologically interesting compounds, as exemplified by the liberation of structurally complex molecular **2k′**, which is derivatized from tocopherol accordingly.[14]

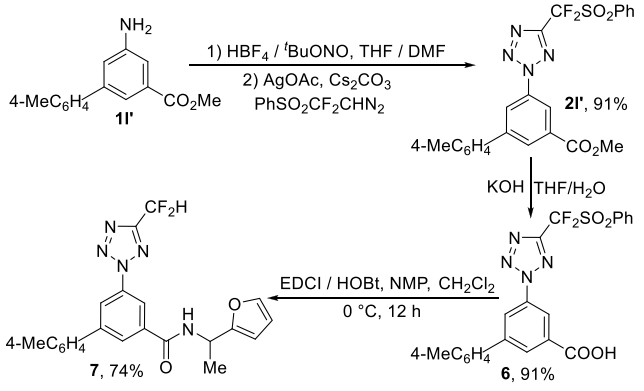
The practicality of this protocol is demonstrated by a gram-scale preparation of **2a** and **2s** in isolated yields of 78% and 84%, respectively (Scheme 4a). Meanwhile, the difluoromethylated tetrazole **2v** could also be obtained in 75% yield through the one-pot diazotization/cycloaddition sequence from 4-chloroaniline directly on a 5.0 mmol scale (Scheme 4a). To further demonstrate the synthetic utility of this method, we also investigated the downstream diversifications of the obtained cycloadducts. The phenyl sulfonyl moiety could be readily cleaved by being treated with $LiAlH_4$ or ^tBuOK at ambient temperature, thus leading to the formation of the corresponding HCF_2-tetrazole **3a** in 95% and 85% yield, respectively (Scheme 4b).[15] The two complementary protocols proved to be applicable to a broad range of substrates and provided HCF_2-tetrazoles **3b**–**3g** in 60–97% yields (Scheme 4b). The tetrazole core has been demonstrated to hold excellent promise as a fluorophore-forming biorthogonal probe in the past few years.[16] As a proof of concept, both diethyl malonate and dimethyl acetylenedicarboxylate (DMAD) were employed as the dipolarophile to undergo the photoinduced 1,3-dipolar cycloaddition reaction with tetrazole **2j**. Pleasingly, CF_2-functionalized pyrazoline **4** and pyrazole **5** were formed in a yield of 67% and 90%, respectively (Scheme 4c). Finally, as tetrazoles have been extensively explored in medical chemistry

Scheme 4. Gram-Scale Experiments and Further Synthetic Transformations



owing to their enhanced metabolic stability and bioisosterism to carboxylic acid and amide moieties,[5] we also proceeded to pursue the construction of the difluoromethylated analogue of a P2X3 receptor antagonist.[12] As outlined in Scheme 5, the tetrazole **2l′** was obtained in 91% yield by a one-pot diazotization/cycloaddition reaction from easily accessible aniline **1l′**. The target HF_2C-functionalized aryltetrazole **7** was then provided in a total yield of 67% after hydrolysis,

Scheme 5. Synthesis of Difluoromethylated P2X3 Receptor Antagonist Analogue



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Org. Lett. XXXX, XXX, XXX–XXX

amidation, and simultaneous desulfonation under operationally simple conditions.[17]

In conclusion, we have successfully developed a silver-catalyzed regioselective [3 + 2] cycloaddition reaction of $PhSO_2CF_2CHN_2$ with aryl diazonium salts to give the novel difluoromethylated tetrazoles. This protocol exhibits high functional group compatibility, mild reaction conditions, good scalability, and feasible one-pot operation from commercially available aniline derivatives. A variety of structurally diverse CF_2-functionalized tetrazoles, pyrazoline, pyrazole, and a valuable HCF_2 analogue of P2X3 receptor antagonist, were constructed via further synthetic transformations. Future investigations including mechanistic elucidation and other relevant applications are underway in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01697.

Experimental details and spectral data of all the new compounds (PDF)

Accession Codes

CCDC 1915044 and 1915069 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (b) Kirk, K. L. *Org. Process Res. Dev.* **2008**, *12*, 305. (c) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. *J. Med. Chem.* **2015**, *58*, 8315. (d) Zafrani, Y.; Yeffet, D.; Sod-Moriah, G.; Berliner, A.; Amir, D.; Marciano, D.; Gershonov, E.; Saphier, S. *J. Med. Chem.* **2017**, *60*, 797. (e) Sessler, C. D.; Rahm, M.; Becker, S.; Goldberg, J. M.; Wang, F.; Lippard, S. J. *J. Am. Chem. Soc.* **2017**, *139*, 9325.

(2) For selected reviews, see: (a) Hu, J.; Zhang, W.; Wang, F. *Chem. Commun.* **2009**, 7465. (b) Chen, B.; Vicic, D. *Top. Organomet. Chem.* **2014**, *52*, 113. (c) Lu, Y.; Liu, C.; Chen, Q.-Y. *Curr. Org. Chem.* **2015**, *19*, 1638. (d) Belhomme, M.-C.; Besset, T.; Poisson, T.; Pannecoucke, X. *Chem. - Eur. J.* **2015**, *21*, 12836. (e) Xu, P.; Guo, S.; Wang, L.; Tang, P. *Synlett* **2014**, *26*, 36. (f) Ni, C.; Hu, M.; Hu, J. *Chem. Rev.* **2015**, *115*, 765. (g) Rong, J.; Ni, C.; Hu, J. *Asian J. Org. Chem.* **2017**, *6*, 139. (h) Yerien, D. E.; Barata-Vallejo, S.; Postigo, A. *Chem. - Eur. J.* **2017**, *23*, 14676. (i) Feng, Z.; Xiao, Y.-L.; Zhang, X. *Acc. Chem. Res.* **2018**, *51*, 2264. (j) Lemos, A.; Lemaire, C.; Luxen, A. *Adv. Synth. Catal.* **2019**, *361*, 1500.

(3) For selected examples, see: (a) Fujiwara, Y.; Dixon, J. A.; Rodriguez, R. A.; Baxter, R. D.; Dixon, D. D.; Collins, M. R.; Blackmond, D. G.; Baran, P. S. *J. Am. Chem. Soc.* **2012**, *134*, 1494. (b) Mykhailiuk, P. K. *Angew. Chem., Int. Ed.* **2015**, *54*, 6558. (c) Okusu, S.; Tokunaga, E.; Shibata, N. *Org. Lett.* **2015**, *17*, 3802. (d) Zhu, S.-Q.; Liu, Y.-L.; Li, H.; Xu, X.-H.; Qing, F.-L. *J. Am. Chem. Soc.* **2018**, *140*, 11613. (e) Xu, C.; Guo, W.-H.; He, X.; Guo, Y.-L.; Zhang, X.-Y.; Zhang, X. *Nat. Commun.* **2018**, *9*, 1170.

(4) Fore relevant reviews, see: (a) Petrov, V. A. *Fluorinated Heterocyclic Compounds: Synthesis, Chemistry, and Applications*; John Wiley & Sons: Hoboken, NJ, 2009. (b) Ostrovskii, V. A.; Trifonov, R. E. Fluorinated Triazoles and Tetrazoles. In *Fluorine in Heterocyclic Chemistry Vol. 1:5-Membered Heterocycles and Macrocycles*; Nenajdenko, V., Ed.; Springer International Publishing: Switzerland, 2014. (c) Zhang, F.-G.; Peng, X.; Ma, J.-A. *Youji Huaxue* **2019**, *39*, 109. For the only reported example to prepare ArF_2C-tetrazoles, see: (d) Kotoris, C. C.; Chen, M.-J.; Taylor, S. D. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3275.

(5) (a) Herr, R. *Bioorg. Med. Chem.* **2002**, *10*, 3379. (b) Gaponik, P. N.; Voitekhovich, S. V.; Ivashkevich, O. A. *Russ. Chem. Rev.* **2006**, *75*, 507. (c) Myznikov, L. V.; Hrabalek, A.; Koldobskii, G. I. *Chem. Heterocycl. Compd.* **2007**, *43*, 1. (d) Ostrovskii, V. A.; Trifonov, R. E.; Popova, E. A. *Russ. Chem. Bull.* **2012**, *61*, 768. (e) Neochoritis, C. G.; Zhao, T.; Dömling, A. *Chem. Rev.* **2019**, *119*, 1970.

(6) Roh, J.; Vávrová, K.; Hrabálek, A. *Eur. J. Org. Chem.* **2012**, *2012*, 6101.

(7) (a) Norris, W. P. *J. Org. Chem.* **1962**, *27*, 3248. (b) Uneyama, K. *J. Fluorine Chem.* **1999**, *97*, 11. (c) Xiao, J.; Zhang, X.; Wang, D.; Yuan, C. *J. Fluorine Chem.* **1999**, *99*, 83. (d) Armour, D. R.; Chung, K. M. L.; Congreve, M.; Evans, B.; Guntrip, S.; Hubbard, T.; Kay, C.; Middlemiss, D.; Mordaunt, J. E.; Pegg, N. A.; Vinader, M. V.; Ward, P.; Watson, S. P. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1015.

(8) Chen, Z.; Fan, S.-Q.; Zheng, Y.; Ma, J.-A. *Chem. Commun.* **2015**, *51*, 16545.

(9) Patouret, R.; Kamenecka, T. M. *Tetrahedron Lett.* **2016**, *57*, 1597.

(10) For a recent review on HF_2CCHN_2, see: Mykhailiuk, P. K.; Koenigs, R. M. *Chem. - Eur. J.* **2019**, *25*, 6053. HF_2CCHN_2 was also employed to react with phenyl diazonium salt **1a** under otherwise identical reaction conditions, but no desired product **3a** was observed.

(11) (a) Zeng, J.-L.; Chen, Z.; Zhang, F.-G.; Ma, J.-A. *Org. Lett.* **2018**, *20*, 4562. (b) Ma, J.-A.; Zeng, J.-L.; Zhang, F.-G. China Patent CN 108383761A, 2018.

(12) (a) Ford, A. P. *Purinergic Signalling* **2012**, *8*, S3. (b) Dillon, M. P.; Hawley, R. C.; Chen, L.; Feng, L.; Yang, M. U.S. Pat. Appl. Publ. US 20150191487 A1, 2015.

(13) See the Supporting Information for detailed screening results.

(14) Tolstyakov, V. V.; Tolstobrova, E. S.; Zarubina, O. S.; Popova, E. A.; Protas, A. V.; Chuprun, S. S.; Trifonov, R. E. *Russ. J. Org. Chem.* **2016**, *52*, 1681.

(15) (a) Alonso, D. A.; Ajera, C. *Org. React.* **2009**, *72*, 367. (b) Akgun, E.; Mahmood, K.; Mathis, C. A. *J. Chem. Soc., Chem. Commun.* **1994**, 761.

(16) Lim, R. K. V.; Lin, Q. *Acc. Chem. Res.* **2011**, *44*, 828. (b) Tian, Y.; Lin, Q. *Chimia* **2018**, *72*, 758.

(17) As shown in Scheme 4b, an appropriate base can facilitate the cleavage of $PhSO_2$-group. We assumed that the observed simultaneous desulfonation in this particular case is attributed to the basic property of the amidating reagents or corresponding intermediates.

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Org. Lett. XXXX, XXX, XXX−XXX