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# Stereoselective Synthesis of β-Lactam-triflones under Catalyst-Free Conditions

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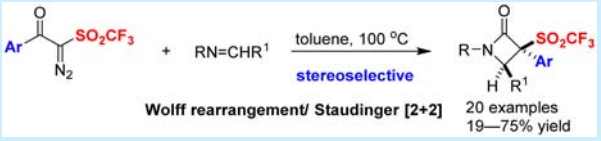
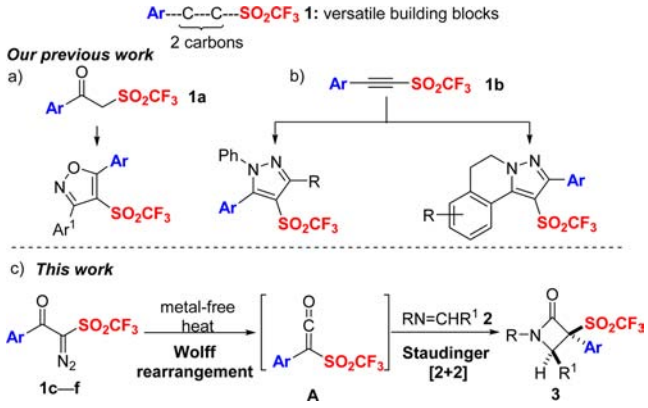
Supporting Information

**ABSTRACT:** The first example of the synthesis of β-lactam-triflones is described. Treatment of 2-diazo-1-aryl-2-(trifluoromethylsulfonyl)ethanones **1c—f** with imines **2** under catalyst-free heating conditions provides pharmaceutically attractive multisubstituted β-lactam-triflones **3** in good to high yields with regio- and diastereoselectivities. A successive Wolff rearrangement and Staudinger [2 + 2] cycloaddition reaction are key elements for the success of this transformation.




The development of novel and efficient methods for the synthesis of organofluorine compounds is of great importance in the fields of material sciences, agrochemicals, and pharmaceuticals.[1] Trifluoromethylated ($CF_3$) compounds are frequently encountered in these areas of study due to the unique properties induced by the high lipophilicity and strong electron-withdrawing effect of the $CF_3$ group.[2] Recently, interest in $CF_3$-heteroatom variants has expanded, exemplified by the X–$CF_3$ group, such as O–$CF_3$ (trifluoromethoxy) and S–$CF_3$ (trifluoromethylthio), etc.[3] Among the potential X–$CF_3$ groups, we have become interested in triflones. Triflones are compounds with a trifluoromethanesulfonyl (trifly, $SO_2CF_3$) group in their structures.[4] The triflyl group is the strongest electron-withdrawing group ($\sigma_m$ = 0.79, $\sigma_p$ = 0.93), but its lipophilicity is somewhat milder ($\pi$ = 0.55) than that of the trifluoromethyl group ($CF_3$, $\pi$ = 0.88, $\sigma_m$ = 0.43, $\sigma_p$ = 0.54).[5] The uniqueness of the triflyl group has prompted chemists to develop novel methodologies for the synthesis of triflones and to use this functional group for the structural design of bioactive compounds,[6] catalysts,[7] and functional materials.[8] In the past few decades, numerous methodologies have been developed for the introduction of a triflyl group into molecules,[3e] including oxidation of corresponding trifluoromethylthio compounds or trifluoromethylsulfoxides,[9] direct triflylation reagents,[10] transformation from $SO_2CF_3$-containing building blocks,[11] and intramolecular rearrangement.[12] Although tremendous progress has been made in the synthesis of triflones, the vast majority of these methodologies has focused on the synthesis of aryl triflones. Thus, the synthesis of triflones with heterocyclic frameworks still remains challenging. In this context, our group reported an efficient synthesis of heteroaryl triflones using $SO_2CF_3$-containing aryl-2-carbon building blocks, Ar–C–C–$SO_2CF_3$ **1**. Thus, a synthesis of 4-triflyl isoxazoles from α-triflyl aryl ketones **1a** was achieved with imidoyl chlorides (Scheme 1a),[13] and a synthesis of pyrazole triflones and pyrazolo[5,1-*a*]isoquinoline triflones via cycloaddition of aryl triflyl alkynes **1b** with the corresponding hydrazonoyl chlorides or C,N-cyclic azomethine imines (Scheme 1b).[14]

**Scheme 1. Synthesis of Heterocyclic Triflones from Ar–C–C–$SO_2CF_3$ Building Blocks 1**




As an extension to our research on heterocyclic triflones, we became focused on β-lactam triflones. β-Lactams are a biologically important class of heterocyclic compound,[15] and a large number of derivatives have been registered in the SciFinder database.[16] However, there is no report of β-lactams having a triflyl group at their carbon(s) in the ring.[17] We herein report a highly stereoselective synthesis of 3,3-aryltriflyl multisubstituted β-lactams **3** via a Staudinger [2 + 2] cycloaddition of imines **2** with aryl trifly ketenes **A** generated in situ from 2-diazo-1-aryl-2-(trifluoromethylsulfonyl)ethanones **1c—f**[18] by a Wolff rearrangement in satisfactory to good yields and with a broad scope (Scheme 1c). The method shows wide substrate generality, and a variety of β-lactam triflones **3** can be obtained under catalyst-free conditions. The reaction mechanism and stereochemistry of the successive Wolff rearrangement/Staudinger cycloaddition are also discussed.

To generate a carbenoid intermediate,[19] we initiated our investigation with the reaction of 2-diazo-1-phenyl-2-(trifluoro-

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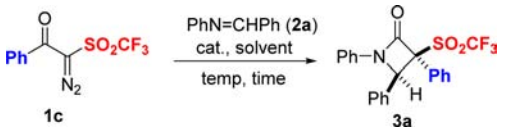
methylsulfonyl)ethanones **1c** and imine **2a** under catalysis of $CuF_2$ in DMF (Table 1, entry 1). However, no desired product **3a** was obtained. We next attempted the reaction of THF in the presence of a catalytic amount of $CuF_2$ or $Ag_2O$ under reflux for 12 h. No product **3a** or trace amount was detected (entries 2—4, 6). Gratifyingly, the desired $\beta$-lactam **3a** was detected in 35% yield in toluene (entry 5). This result encouraged us to further attempt the reaction optimization. After screening several catalysts, we found that no catalyst afforded the best result (i.e., 38%) while metal catalysts gave lower yields (entries 5—7). A higher reaction temperature did not improve yield, and toluene was found to be the best solvent for this transformation (entries 7—11). The yield was increased to 50% when the reaction was conducted in two steps in one pot. First, diazo-triflone **1c** was heated in toluene at 100 °C for 1 h, and then imine **2a** in toluene was added dropwise (entry 12). The yield increased as diazo-triflone **1c** was increased to 1.5—2.0 equiv, whereupon the desired $\beta$-lactam **3a** was detected in 85% yield (entries 13 and 14). Heating was crucial for this transformation, and the reaction did not proceed under UV light (entry 15).

**Table 1. Optimization of Reaction Conditions for Successive Wolff Rearrangement/Staudinger Cycloaddition to 3a**[a]



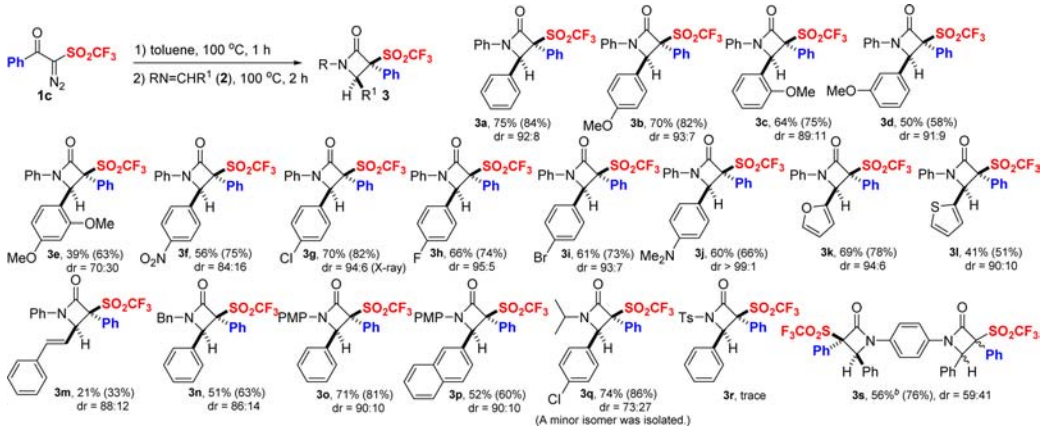

| entry | solvent | cat. (mol %) | temp (°C) | time (h) | yield (%)[b] |
|---|---|---|---|---|---|
| 1 | DMF | $CuF_2$ (20) | 50 | 12 | 0 |
| 2 | THF | $CuF_2$ (20) | 70 | 12 | 0 |
| 3 | THF | $Ag_2O$ (20) | 70 | 12 | 0 |
| 4 | toluene | $CuF_2$ (20) | 100 | 5 | 2 |
| 5 | toluene | $Ag_2O$ (20) | 100 | 2 | 35 |
| 6 | toluene | $Rh_2(AcO)_4$ (5) | 100 | 2 | 3 |
| 7[c] | toluene | | 100 | 2 | 38 |
| 8 | toluene | | 120 | 2 | 35 |
| 9 | *p*-xylene | | 100 | 2 | 35 |
| 10 | DCE | | 100 | 8 | 30 |
| 11 | dioxane | | 110 | 2 | 32 |
| 12[d] | toluene | | 100 | 3 | 50 |
| 13[d,e] | toluene | | 100 | 3 | 66 |
| 14[d,f] | toluene | | 100 | 3 | 85 |
| 15[g] | THF | | 25 | 10 | 0 |

[a]Reaction conditions: Imine **2a** (0.1 mmol), diazo-triflone **1c** (0.1 mmol), cat., solvent (1.0 mL), heat. [b]Yields were determined by $^{19}F$ NMR spectroscopy with trifluoromethylbenzene as an internal standard. A small amount of minor isomer was detected. [c]Isolated yield. [d]Diazo-triflone **1c** (0.1 mmol), solvent (3.0 mL), 100 °C, heating for 1 h, then imine **2a** (0.1 mmol) in 0.5 mL of toluene was added and stirred at 100 °C for additional 2 h. [e]0.15 mmol diazo-triflone **1c** was used. [f]0.2 mmol diazo-triflone **1c** was used. [g]Under UV.

With these optimized conditions in hand, the scope of this cyclization reaction was then investigated with **1c** and a variety of imines **2** (Scheme 2). All the imines **2a—q**, with $R^1$ bearing either electron-donating or -withdrawing substituents and halogen in different positions on the benzene ring, were smoothly converted to the corresponding multisubstituted $\beta$-lactam-triflones **3a—q** in good to high yields independent of the electronic character and the steric hindrance of the aryl moieties in the imines. The substituted position in the phenyl group of $R^1$ might influence the cyclization to the $\beta$-lactam ring due to an electronic effect and steric hindrance (**3b—d**). Interestingly, imine **2m**, which was transformed into the corresponding $\beta$-lactam-triflone **3m** in 21% yield, contains a double bond for further transformation. All *N*-alkyl and *N*-aryl substituted aryl imines **2n—r** could be transformed to the corresponding $\beta$-lactams **3n—r** in good yields except for **2r**. To our surprise, bis-imine **2s** afforded bis-$\beta$-lactam-triflone **3s** in 56% yield. The diastereoselectivity is generally high in all cases, except the case of **3e**, **3q**, and **3s**. To our knowledge, this is the first example of the synthesis of $\beta$-lactam-triflones.[15−17]

After the success of different imines **2** with diazo-triflone **1c**, we further attempted the reaction using different diazo-triflones **1d—f** with imine **2o**. The results in Scheme 3 show that the electron-rich aryl group in diazo-triflone **1d** (X = OMe, $\sigma_p$ = −0.28)[5c] allowed $\beta$-lactam-triflones **3do** to be obtained in 62% yield, while the electron-deficient diazo-triflone **1e** (X = Cl, $\sigma_p$ = 0.22)[5c] afforded **3eo** in low yield (19%). The trifluoromethyl

**Scheme 2. Scope and Limitations of the Reaction of Diazo-triflone 1c with Imines 2**[a]




[a]Reaction conditions: diazo-triflone **1c** (0.4 mmol), toluene (6.0 mL), 100 °C for 1 h, then imines **2** (0.2 mmol) in 1.0 mL toluene was added and stirred at 100 °C for another 2 h. All yields refer to isolated yields of major isomer, except for **3q** and **3s** as a mixture of isomers. $^{19}F$ NMR yields (a mixture of isomers) are shown in parentheses. The dr indicates a ratio of isomers determined by crude $^{19}F$ NMR. [b]**3s** was conducted with **1c** (0.6 mmol), toluene (6.0 mL), 100 °C for 1 h, then imine **2s** (0.15 mmol) in 1.5 mL of toluene was added slowly in 5 min, and stirred at 100 °C for another 5 h; the dr ratio was determined by $^1H$ NMR.



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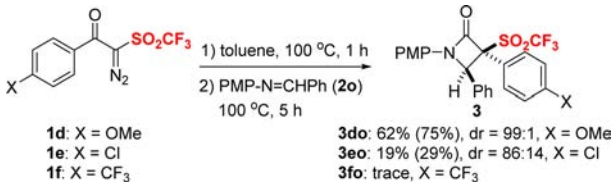
**Scheme 3. Reaction of Diazo-triflones 1d–f with Imine 2o**[a]




[a]Reaction conditions: diazo-triflones **1** (0.4 mmol), toluene (6.0 mL), 100 °C for 1 h, then imine **2o** (0.2 mmol) in 1.0 mL of toluene was added and stirred at 100 °C for another 5 h. All yields refer to isolated yields of major isomer; values in the parentheses refer to $^{19}$F NMR yield; the dr ratio was determined by crude $^{19}$F NMR.

analogue **1f** was unreactive under the same reaction conditions (X = $CF_3$, $\sigma_p$ = 0.54).[5c] The reactivity of **1d—f** decreased as the electron-withdrawing effects of the aryl functional groups increased ($\sigma_p$: $CF_3$ > Cl > OMe) due to the lower migration abilities of the electron-deficient aryl groups providing ketene intermediates under the Wolff aryl rearrangement. Information gleaned from $^1$H NMR, $^{13}$C NMR, $^{19}$F NMR, IR, and mass spectra led to the formulation of *β*-lactam-triflones **3**. Finally, the stereochemistry of **3** was confirmed unambiguously by the single crystal X-ray structure analysis of *β*-lactam-triflone **3g** (Figure 1,

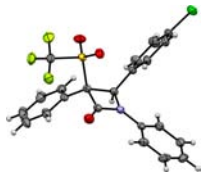


**Figure 1.** X-ray crystallographic structure of *β*-lactam **3g** shows (3*S**,4*R**) conformation (CCDC 1412034).

CCDC1412034). While the isolation of minor diastereomers was not easy due to the high selectivities, a minor isomer of **3q** was isolated to confirm its structure. The existences of other minor isomers were tentatively assigned by analogy based on the $^{19}$F NMR.

The proposed transition state for the highly stereoselective construction of a *β*-lactam ring is shown in Figure 2. According to a report by Xu and co-workers,[20] the *cis*/*trans* stereoselectivity is generated as a result of the competition between direct ring closure ($k_1$, $k_3$) and isomerization of the imine moiety ($k_2$) in

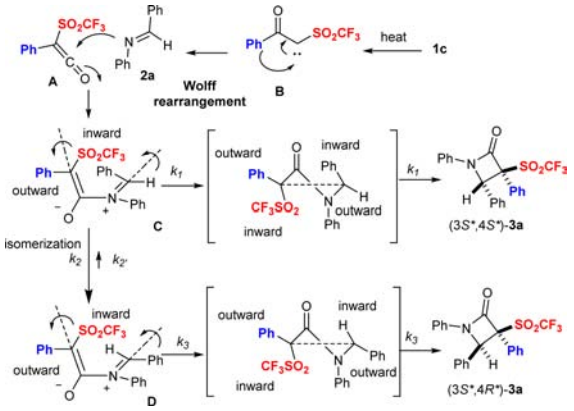



**Figure 2.** Proposed transition-state models for the stereoselective [2 + 2] cycloaddition of ketene-triflone **A** with imine **2a**.

zwitterionic intermediates. The ketene-triflone **A**[21] generated from **1c** via carbene **B** by a Wolff rearrangement intermediate reacts with imine **2a** to give a zwitterionic intermediate **C** where the donor, a phenyl group, faces outward, while the acceptor, a triflyl group, prefers to reside inside because of a torquoelectronic effect.[22] The strong electron-withdrawing effect of the triflyl group decreases the nucleophilicity of the enolate in **C**, which significantly slows the direct ring closure (decrease in $k_1$) to (3*S**,4*S**)-**3a**. On the other hand, the imine moiety in **C** is isomerized to provide another zwitterionic intermediate **D** for steric reasons. An electrocyclic conrotatory ring closure in the Staudinger [2 + 2] cycloaddition reaction would give (3*S**,4*R**)-*β*-lactam-triflone **3a**.[20b] The possibility of an intramolecular nucleophilic addition of the enolate to the imine moiety in **D** to form (3*S**,4*R**)-**3a**, instead of the electrocyclic conrotatory mechanism, cannot be denied.[20b]

It should be noted that a nonfluorinated, $CH_3SO_2$ analogue of **1c**, i.e., 2-diazo-1-phenyl-2-(methanesulfonyl)ethanone,[23] did not give a corresponding *β*-lactam under the same reaction conditions. Besides, to our knowledge, there is no example of direct formation of 3-methanesulfonyl-*β*-lactams in the [2 + 2] ring closure in the Staudinger ketene–imine cycloaddition reaction.[24] Therefore; the trifluoromethyl group should play an important role in the activation of this [2 + 2] ring-closing reaction.

In summary, we disclose here a highly stereoselective synthesis of 3,3-aryltriflyl multisubstituted *β*-lactams from the reaction of diazo-triflones with imines. The protocol is the first report about the introduction of a triflyl group into the 3-position of a *β*-lactam. The electronic effect and steric hindrance of $R^2$ in the imines, and the electronic effect of the aryl group in the diazo-triflones, influence the final [2 + 2] ring closure in the Staudinger ketene–imine cycloaddition reaction. The triflyl- and aryl-substituted groups in ketenes direct the stereoselectivity of the final *β*-lactams. Further applications and demonstration of the utility of diazo-triflones reagent **1c** are under investigation.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02827.

General procedures; NMR spectra (PDF)

Crystallographic data (CIF)

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### Notes

The authors declare no competing financial interest.

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## REFERENCES


(1) (a) Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*; Wiley-VCH: Weinheim, Germany, 2004. (b) Hiyama, T. *Organofluorine Compounds: Chemistry and Properties*; Springer: Berlin, 2000. (c) Uneyama, K. *Organofluorine Chemistry*; Blackwell: Oxford, U.K., 2006. (d) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308. (e) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432.

(2) For selected reviews, see: (a) Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 8214. (b) Charpentier, J.; Früh, N.; Togni, A. *Chem. Rev.* **2015**, *115*, 650. (c) Liu, X.; Xu, C.; Wang, M.; Liu, Q. *Chem. Rev.* **2015**, *115*, 683. (d) Ni, C.; Hu, M.; Hu, J. *Chem. Rev.* **2015**, *115*, 765. (e) Zhu, W.; Wang, J.; Wang, S.; Gu, Z.; Acena, J. L.; Izawa, K.; Liu, H.; Soloshonok, V. A. *J. Fluorine Chem.* **2014**, *167*, 37.

(3) For selected reviews, see: (a) Boiko, V. N. *Beilstein J. Org. Chem.* **2010**, *6*, 880. (b) Landelle, G.; Panossian, A.; Pazenok, S.; Vors, J.-P.; Leroux, F. R. *Beilstein J. Org. Chem.* **2013**, *9*, 2476. (c) Thili, A.; Billard, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 6818. (d) Toulgoat, F.; Alazet, S.; Billard, T. *Eur. J. Org. Chem.* **2014**, *2014*, 2415. (e) Xu, X.-H.; Matsuzaki, K.; Shibata, N. *Chem. Rev.* **2015**, *115*, 731.

(4) (a) Sheppard, W. *J. Am. Chem. Soc.* **1963**, *85*, 1314. (b) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165. (c) Goumont, R.; Kizilian, E.; Buncel, E.; Terrier, F. *Org. Biomol. Chem.* **2003**, *1*, 1741. (d) Terrier, F.; Magnier, E.; Kizilian, E.; Wakselman, C.; Buncel, E. *J. Am. Chem. Soc.* **2005**, *127*, 5563.

(5) (a) Bégué, J. P.; Bonnet-Delpon, D. C. *Bioorganic and medicinal chemistry of fluorine*; Wiley: Hoboken, NJ, 2008. (b) Hansch, C.; Muir, R. M.; Fujita, T.; Maloney, P. P.; Geiger, F.; Streich, M. *J. Am. Chem. Soc.* **1963**, *85*, 2817. (c) Papp, T.; Kollár, L.; Kégl, T. *Chem. Phys. Lett.* **2013**, *588*, 51.

(6) For selected examples, see: (a) Wu, P.; Hilgraf, R.; Fokin, V. V. *Adv. Synth. Catal.* **2006**, *348*, 1079. (b) Park, C.-M.; Bruncko, M.; Adickes, J.; Bauch, J.; Ding, H.; Kunzer, A.; Marsh, K. C.; Nimmer, P.; Shoemaker, A. R.; Song, X.; Tahir, S. K.; Tse, C.; Wang, X.; Wendt, M. D.; Yang, X.; Zhang, H.; Fesik, S. W.; Rosenberg, S. H.; Elmore, S. W. *J. Med. Chem.* **2008**, *51*, 6902. (c) Yanai, H.; Ogura, H.; Fukaya, H.; Kotani, A.; Kusu, F.; Taguchi, T. *Chem. - Eur. J.* **2011**, *17*, 11747. (d) Yanai, H.; Yoshino, T.; Fujita, M.; Fukaya, H.; Kotani, A.; Kusu, F.; Taguchi, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 1560.

(7) For selected examples, see: (a) Kargbo, R.; Takahashi, Y.; Bhor, S.; Cook, G. R.; Lloyd-Jones, G. C.; Shepperson, I. R. *J. Am. Chem. Soc.* **2007**, *129*, 3846. (b) Barta, K.; Francio, G.; Leitner, W.; Lloyd-Jones, G. C.; Shepperson, I. R. *Adv. Synth. Catal.* **2008**, *350*, 2013. (c) Masui, M.; Ando, A.; Shioiri, T. *Tetrahedron Lett.* **1988**, *29*, 2835. (d) Mouhtady, O.; Gaspard-Iloughmane, H.; Laporterie, A.; Roux, C. L. *Tetrahedron Lett.* **2006**, *47*, 4125.

(8) For selected examples, see: (a) Koshar, R. J.; Mitsch, R. A. *J. Org. Chem.* **1973**, *38*, 3358. (b) Hendrickson, J. B.; Bair, K. W. *J. Org. Chem.* **1977**, *42*, 3875. (c) Creary, X. *J. Org. Chem.* **1980**, *45*, 2727. (d) Hendrickson, J. B.; Judelson, D. A.; Chancellor, T. *Synthesis* **1984**, *1984*, 320. (e) Magar, S. S.; Fuchs, P. L. *Tetrahedron Lett.* **1992**, *33*, 745. (f) Mahadevan, A.; Fuchs, P. L. *Tetrahedron Lett.* **1994**, *35*, 6025. (g) Sevenard, D. V.; Kolomeitsev, A. A.; Hoge, B.; Lork, E.; Röschenthaler, G.-V. *J. Am. Chem. Soc.* **2003**, *125*, 12366. (h) Hellmann, G.; Hack, A.; Thiemermann, E.; Luche, O.; Raabe, G.; Gais, H.-J. *Chem. - Eur. J.* **2013**, *19*, 3869.

(9) For selected references, see: (a) Harris, J. F., Jr. *J. Am. Chem. Soc.* **1962**, *84*, 3148. (b) Yagupolskii, L. M.; Kondratenko, N. V.; Sambur, V. P. *Synthesis* **1975**, *1975*, 721. (c) Kosack, S.; Himbert, G. *Chem. Ber.* **1987**, *120*, 71. (d) Tordeux, M.; Francese, C.; Walkselman, C. *J. Fluorine Chem.* **1989**, *43*, 27. (e) Kirsch, P.; Lenges, M.; Kühne, D.; Wanczek, K.-P. *Eur. J. Org. Chem.* **2005**, *2005*, 797. (f) Langlois, B. R.; Billard, T.; Mulatier, J.-C.; Yezeguelian, C. *J. Fluorine Chem.* **2007**, *128*, 851.

(10) For selected references, see: (a) Koshar, R. J.; Mitsch, R. A. *J. Org. Chem.* **1973**, *38*, 3358. (b) Hendrickson, J. B.; Judelson, D. A.; Chancellor, T. *Synthesis* **1984**, *1984*, 320. (c) Billard, T.; Langlois, B. R. *Tetrahedron* **1999**, *55*, 8065. (d) Petrov, V. A.; Krespan, C. G.; Marshall, W. *J. Fluorine Chem.* **2005**, *126*, 1332. (e) Xu, X.-H.; Liu, G.-K.; Azuma, A.; Tokunaga, E.; Shibata, N. *Org. Lett.* **2011**, *13*, 4854. (f) Zhang, K.; Xu, X.-H.; Qing, F.-L. *J. Org. Chem.* **2015**, *80*, 7658.

(11) For selected references, see: (a) Glass, R. S.; Smith, D. L. *J. Org. Chem.* **1974**, *39*, 3712. (b) Isobe, H.; Sato, S.; Tanaka, T.; Tokuyama, H.; Nakamura, E. *Org. Lett.* **2004**, *6*, 3569. (c) Wang, X.-J.; Liu, J.-T. *Chin. J. Chem.* **2007**, *25*, 649. (d) Shikanai, D.; Murase, H.; Hata, T.; Urabe, H. *J. Am. Chem. Soc.* **2009**, *131*, 3166.

(12) For selected references, see: (a) Hendrickson, J. B.; Skipper, P. L. *Tetrahedron* **1976**, *32*, 1627. (b) Crevatín, L. K.; Bonesi, S. M.; Erra-Balsells, R. *Helv. Chim. Acta* **2006**, *89*, 1147. (c) Xu, X.-H.; Wang, X.; Liu, G.-K.; Tokunaga, E.; Shibata, N. *Org. Lett.* **2012**, *14*, 2544. (d) Xu, X.-H.; Taniguchi, M.; Azuma, A.; Liu, G.-K.; Tokunaga, E.; Shibata, N. *Org. Lett.* **2013**, *15*, 686. (e) Xu, X.-H.; Taniguchi, M.; Wang, X.; Tokunaga, E.; Ozawa, T.; Masuda, H.; Shibata, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 12628.

(13) Kawai, H.; Sugita, Y.; Tokunaga, E.; Shibata, N. *Eur. J. Org. Chem.* **2012**, *2012*, 1295.

(14) Kawai, H.; Yuan, Z.; Tokunaga, E.; Shibata, N. *Org. Lett.* **2012**, *14*, 5330.

(15) (a) Morin, R. B.; Gorman, M. *Chemistry and Biology of β-Lactam Antibiotics*; Academic: New York, NY, 1982; Vols. *1*−*3*. (b) Georg, G. I. *The Organic Chemistry of β-Lactams*; Chemie: New York, NY, 1993. (c) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Eur. J. Org. Chem.* **1999**, *1999*, 3223. (d) Singh, G. S. *Tetrahedron* **2003**, *59*, 7631. (e) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Curr. Med. Chem.* **2004**, *11*, 1837. (f) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Rev.* **2007**, *107*, 4437. (g) Cossío, F. P.; Arrieta, A.; Sierra, M. A. *Acc. Chem. Res.* **2008**, *41*, 925. (h) Brandi, A.; Cicchi, S.; Cordero, F. M. *Chem. Rev.* **2008**, *108*, 3988. (i) Fu, N. Y.; Tidwell, T. T. *Tetrahedron* **2008**, *64*, 10465. (j) Xu, J. X. *ARKIVOC* **2009**, *9*, 21. (k) Aranda, M. T.; Perez-Faginas, P.; Gonzalez-Muniz, R. *Curr. Org. Synth.* **2009**, *6*, 325.

(16) Substructure searching of β-lactam ring indicates that more than 300 000 compounds have been registered (September, 2015).

(17) One β-lactam compound having $SO_2CF_3$ directly on the 3-carbon of the β-lactam ring is reported ($C_3$-$SO_2CF_3$); however, it should be the *O*-$SO_2CF_3$ compound; see Buynak, J. D.; Borate, H. B.; Lamb, G.; Isom, H.; Husting, C.; Khasnis, D. *J. Chem. Soc., Chem. Commun.* **1990**, 294.

(18) (a) Pang, W.; Zhu, S.; Xing, C.; Luo, N.; Jiang, H.; Zhu, S. *J. Fluorine Chem.* **2008**, *129*, 343. (b) The preparation of diazo triflone **1c** was reported (ref 18a), but we prepared **1c—f** by an alternative protocol using $CF_3SO_2N_3$. See Supporting Information for details.

(19) (a) Yang, Y.-D.; Azuma, A.; Tokunaga, E.; Yamasaki, M.; Shiro, M.; Shibata, N. *J. Am. Chem. Soc.* **2013**, *135*, 8782. (b) Huang, Z.; Yang, Y.-D.; Tokunaga, E.; Shibata, N. *Org. Lett.* **2015**, *17*, 1094. (c) Arimori, S.; Takada, M.; Shibata, N. *Org. Lett.* **2015**, *17*, 1063. (d) Huang, Z.; Yang, Y.-D.; Tokunaga, E.; Shibata, N. *Asian J. Org. Chem.* **2015**, *4*, 525.

(20) (a) Jiao, L.; Zhang, Q. F.; Liang, Y.; Zhang, S. W.; Xu, J. X. *J. Org. Chem.* **2006**, *71*, 815. (b) Jiao, L.; Liang, Y.; Xu, J. X. *J. Am. Chem. Soc.* **2006**, *128*, 6060.

(21) The IR spectroscopy of **1c** under thermal, solvent-free conditions for 30 min showed a production of ketene triflone **A** at 2150 $cm^{-1}$, while the original **1c** indicated a peak at 2131 $cm^{-1}$. The $^{19}F$ NMR peak of **1c** was also shifted from −77.401 to −77.671 ppm (internal standard, $C_6F_6$, −162.200 ppm) after heating. See Supporting Information for details.

(22) (a) Lopez, R.; Sordo, T. L.; Sordo, J. A.; González, J. *J. Org. Chem.* **1993**, *58*, 7036. (b) Dumas, S.; Hegedus, L. S. *J. Org. Chem.* **1994**, *59*, 4967. (c) Venturini, A.; González, J. *J. Org. Chem.* **2002**, *67*, 9089. (d) Macías, A.; Alonso, E.; del Pozo, C.; Venturini, A.; González, J. *J. Org. Chem.* **2004**, *69*, 7004.

(23) Jiang, Y.; Loh, T.-P. *Chem. Sci.* **2014**, *5*, 4939.

(24) (a) Zarei, M.; Mohamadzadeh, M. *Tetrahedron* **2011**, *67*, 5832. (b) Xu, J. *Tetrahedron* **2012**, *68*, 10696.




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