CHEMISTRY & SUSTAINABILITY

CHEMSUSCHEM

ENERGY & MATERIALS

Accepted Article

Title: Dual Roles of tert-Butyl Nitrite in the Transition Metal- and External Oxidant-Free Trifluoromethyloximation of Alkenes

Authors: Ya Wu, Yanli Zhang, Zhen Yang, Jingchao Jiao, Xiaoke Zheng, Weisheng Feng, Mengsha Zhang, Hao Cheng, and Lin Tang

To be cited as: *ChemSusChem* 10.1002/cssc.201901856

Link to VoR: http://dx.doi.org/10.1002/cssc.201901856

A Journal of

ChemPubSoc Europe

WILEY-VCH

www.chemsuschem.org

Dual Roles of *tert*-Butyl Nitrite in the Transition Metal- and External Oxidant-Free Trifluoromethyloximation of Alkenes

Ya Wu,[a] Yanli Zhang,[a] Zhen Yang,[b] Jingchao Jiao,[b] Xiaoke Zheng,[a] Weisheng Feng,[a] Mengsha Zhang,[a] Hao Cheng,[b] and Lin Tang*[b]

Abstract: By employing *tert*-butyl nitrite as both nitrogen source and oxidant, the first example of alkene trifluoromethyloximation is reported. The developed difunctionalization reaction provides practical and efficient synthesis of a wide range of α-CF_3 ketoximes in moderate yields with excellent regioselectivity. This protocol features the use of inexpensive CF_3SO_2Na as a CF_3 reagent, no involvement of transition metal and external oxidant, and room temperature conditions. Moreover, a scale-up reaction, further transformation of the products to various valuable CF_3-containing compounds, and removal of trifluoromethyl are readily achieved.

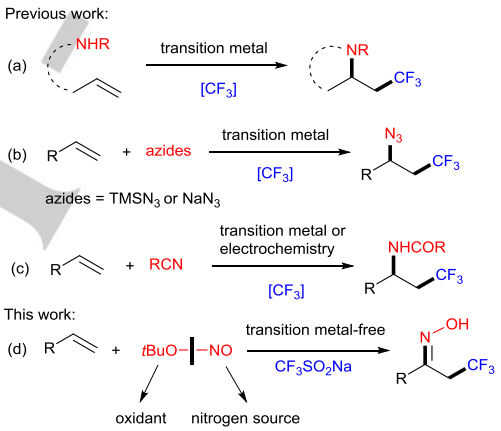
The trifluoromethyl incorporation into organic molecules dramatically leads to a unique influence on chemical and biological properties such as metabolic stability, bioavailability and membrane permeability.[1] During the past decade, great endeavors have been spurred in the development of a variety of synthetic approaches for the introduction of the trifluoromethyl into alkenes.[2] In particular, trifluoromethyl-containing alkene difunctionalization, mainly relying on carbotrifluoromethylation,[3] oxytrifluoromethylation,[4] halotrifluoromethylation,[5] and aminotrifluoromethylation,[6,7,8] reveals the most straightforward and practical synthetic strategy for the simultaneous introduction of trifluoromethyl and a second vicinal functionality. The aforementioned aminotrifluoromethylation of alkenes was successfully achieved under the catalysis of transition metals or electrochemical oxidation , however, the reported nitrogen sources (nucleophiles) were restricted to amines (protected amines) (Scheme 1a),[6] azides (Scheme 1b)[6a,7] and nitrile (Scheme 1c).[8] To date, aminotrifluoromethylation of alkenes with other types of nitrogen sources is still undiscovered. Given the significance of these studies, it is highly desirable to exploit a new and efficient approach to extend the scope of aminotrifluoromethylation of alkenes.

On the other hand, oximes are versatile structural motifs because of their extensive applications as synthons in the preparation of nitriles,[9] amides,[10] amines,[11] carbonyl compounds,[12] *N*-containing heterocycles[13] and other alternative compounds.[14] In this regard, the direct incorporation of oxime and trifluoromethyl into organic molecules in a step-economical manner demonstrates an ideal and valuable protocol.

[a] Dr. Y. Wu, Dr. Y. Zhang, X. Zheng, Dr. W. Feng, M. Zhang
School of Pharmacy & Collaborative Innovation Center for Respiratory disease Diagnosis and Treatment & Chinese Medicine Development of Henan Province
Henan University of Chinese Medicine
Zhengzhou 450046 (P. R. China)
[b] Dr. Z. Yang, J. Jiao, H. Cheng, Prof. Dr. L. Tang
College of Chemistry and Chemical Engineering
Xinyang Normal University
Xinyang 464000 (P. R. China)
E-mail: lintang@xynu.edu.cn

Supporting information for this article is given via a link at the end of the document.

Encouraged by the recent remarkable achievement of the C-N bond formation reactions with *tert*-butyl nitrite as a nitrogen source[15] and our interest in the exploration of metal-free radical reactions,[16] we envisioned that the *tert*-butyl nitrite-mediated radical aminotrifluoromethylation of alkenes with readily available and inexpensive CF_3SO_2Na might afford α-CF_3 ketoximes. Although it was challenging to explore a new method of transition metal- and external oxidant-free aminotrifluoromethylation of alkenes, the proposed protocol was successfully achieved by employing *tert*-butyl nitrite as both the nitrogen source and the oxidant because the redox of $^{\cdot}CF_3$ and *tert*-butyl nitrite could efficiently take place without a transition metal catalyst via a free-radical pathway (Scheme 1d).

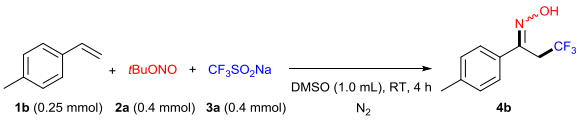


Scheme 1. Aminotrifluoromethylation of alkenes.

The initial reaction conditions for *tert*-butyl nitrite-mediated trifluoromethyloximation of alkenes were selected with 1-methyl-4-vinylbenzene (**1b**, 0.25 mmol) as the model substrate in the presence of *tert*-butyl nitrite (**2a**, 1.6 equiv) and CF_3SO_2Na (**3a**, 1.6 equiv) at room temperature for 4 h (Table 1). The reaction was able to proceed smoothly in the solvent of DMSO, affording the desired α-CF_3 ketoxime **4b** in 66% yield with an excellent stereoselectivity (Entry 1). Relatively low yields (29-48%) were offered when acetonitrile, tetrahydrofuran and $ClCH_2CH_2Cl$ were involved (Entries 2-4). Interestingly, the trifluoromethyloximation reaction could hardly take place in the presence of water because of the construction of 2-nitro-1-(p-tolyl)ethan-1-one oxime via the nitration and oximation of **1b** (Entry 5). Further experiments reveal that the transition metal catalysts of CuBr, $FeSO_4$ and $AgNO_3$ could not accelerate the radical fragmentation in this reaction (Entries 6-8). Moreover, higher temperature suppressed the formation of **4b** (Entries 9 and 10). The results obtained in Entries 11 and 12 indicate that decreasing the amount of **2a** or **3a** had a negative influence on this difunctionalization reaction. Additionally, the reaction was not affected by the prolonged time (16 h) as shown in Entry 13.

Therefore, the reaction conditions in Entry 1 were chosen as the optimal for the next investigation.

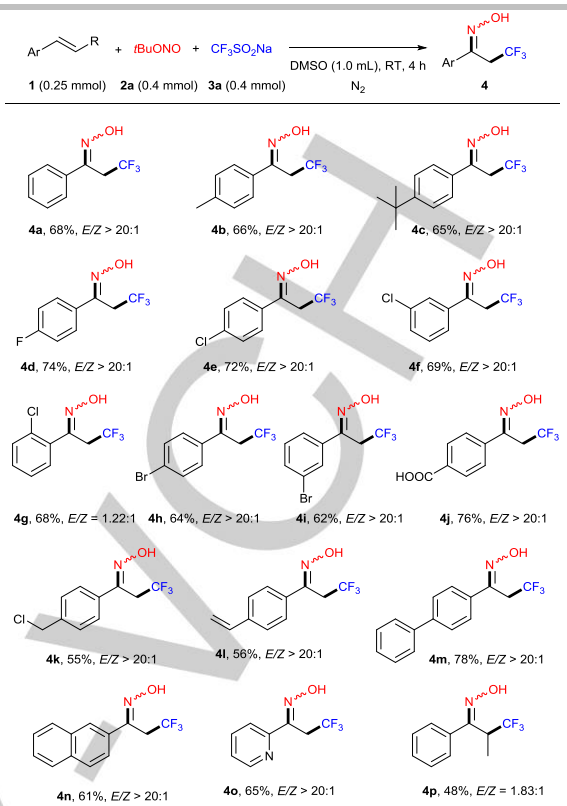
Table 1. Optimization of reaction conditions.



Entry	Variation from the conditions	Yield [%][a]
1	***none***	***66 (E/Z > 20:1)***
2	MeCN instead	48 (*E*/*Z* > 20:1)
3	THF instead	29 (*E*/*Z* > 20:1)
4	$ClCH_2CH_2Cl$ instead	39 (*E*/*Z* > 20:1)
5	DMSO:H_2O (1:1) instead	trace
6	addition of 5 mol% CuBr	62 (*E*/*Z* > 20:1)
7	addition of 5 mol% $FeSO_4$	65 (*E*/*Z* > 20:1)
8	addition of 5 mol% $AgNO_3$	49 (*E*/*Z* > 20:1)
9	50 °C	62 (*E*/*Z* > 20:1)
10	80 °C	54 (*E*/*Z* > 20:1)
11	**1b**/**2a**/**3a** = 1:1.6:1	58 (*E*/*Z* > 20:1)
12	**1b**/**2a**/**3a** = 1:1:1.6	52 (*E*/*Z* > 20:1)
13	16 h	67 (*E*/*Z* > 20:1)

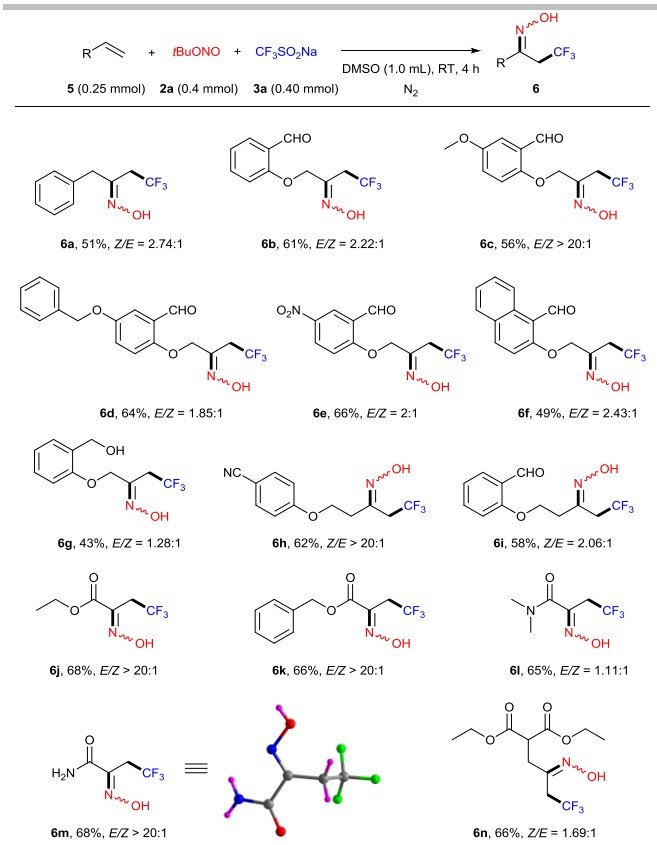
[a] Isolated yield; the mixed isomers were measured according to ^{1}H NMR.

After confirmation of the optimized conditions, expanding the scope of styrenes was carried out in the trifluoromethyloximation reaction (Scheme 2). When the electron-donating groups of methyl and *tert*-butyl (**4b** and **4c**) and weakly electron-drawing groups of halogen (**4d**-**4i**) appeared on the benzene ring, the corresponding styrenes could afford the desired products in good yields of 62-74%. The results obtained above show that the substituent's steric hindrance had little impact on the yields (**4e**, **4f** vs **4g**). However, low stereoselectivity of the *ortho*-substituted product **4g** was obtained because of the steric hindrance. Interestingly, the substrates bearing versatile groups of carboxyl, chloromethyl and vinyl yielded the target products **4j**-**4l** in moderate to good yields. Moreover, biphenyl and naphthalene were commendably tolerated to provide **4m** and **4n** in 78 and 61% yield, respectively. The *N*-heterocycle product **4o** was obtained with excellent stereoselectivity. When R was methyl, **1p** could also serve as an efficient substrate, leading to **4p** in an acceptable yield, even though low stereoselectivity (*E*/*Z* = 1.83:1) was observed.



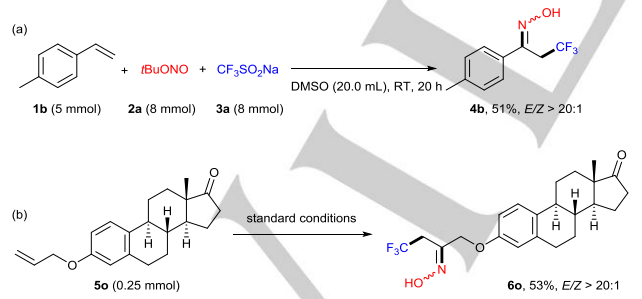
Scheme 2. Isolated yield; the mixed isomers were measured according to ^{1}H NMR.

Furthermore, a series of aliphatic alkenes were successfully converted to the α-CF_3 ketoximes under the standard conditions (Scheme 3). Allylbenzene **5a** readily afforded the corresponding product **6a** in 51% yield with mixed isomers (*Z*/*E* = 2.74:1). Different allyl salicylaldehydes could be well compatible, affording the desired **6b**-**6f** in a regioselective manner regardless of the electronic effect of the substituents, however, low stereoselectivity was observed except **6c**. The reason for the stereoselective difference of **6c** with other products is unclear up to now. Relatively low yield of **6g** was obtanied when hydroxymethyl appeared on the benzene ring, which was attributed to the construction of the byproduct **6b**. The results obtained in **6h** and **6i** indicate that the steric hindrance immensely restrained the stereoselectivity. Moreover, reactions involving acrylic esters, acrylic amides and malonic ester smoothly proceeded to supply the desired products **6j**-**6n** in good yields. Similarly, low stereoselectivity was obtained due to the steric hindrance (**6l** vs **6m**). The single-crystal X-ray diffraction analysis unambiguously established the *E* isomer of **6m**.[17]



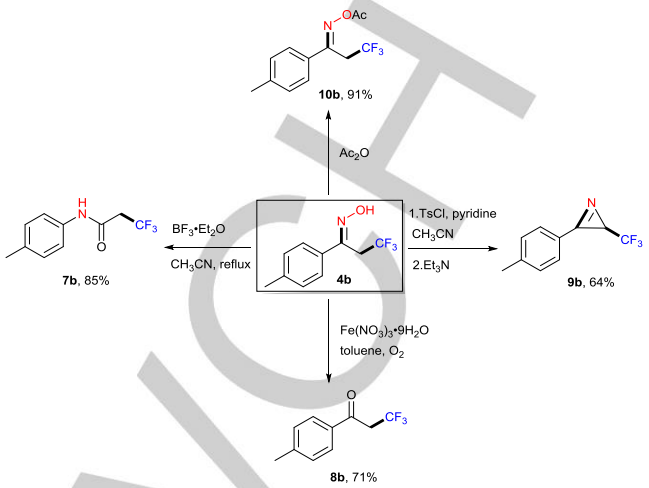
Scheme 3. Isolated yield; the mixed isomers were measured according to ^{1}H NMR.

In order to further assess the synthetic generality of this green and efficient trifluoromethyloximation, a scale-up experiment with 5 mmol of **1b** as the substrate was carried out, which leaded to **4b** in 51% yield (Scheme 4a). Pleasingly, the bioactive molecule of estrone derivative **5o** was well tolerated to afford the desired α-CF_3 ketoxime **6o** in 53% yield with a single *E* isomer (Scheme 4b), revealing potential applications in pharmaceutical synthesis.



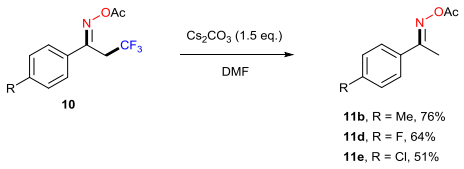
Scheme 4. Examination of the synthetic utility.

Further transformations of the resulting α-CF_3 ketoxime **4b** were successfully achieved to offer many valuable building blocks as depicted in Scheme 5. **7b** were easily formed via the Beckman rearrangement in the presence of $BF_3{\cdot}Et_2O$. The deoximation of **4b** was smoothly performed to give α-CF_3 ketone **8b** in 71% yield. Moreover, the 2*H*-azirine, one of the most important skeletal units for the preparation of heterocyclic compounds, was readily obtained through dehydration of **4b**. The versatile *O*-acetyl oxime **10b** could also be efficiently constructed by treating **4b** with acetic anhydride.



Scheme 5. Transformations of the α-CF_3 ketoxime **4b**.

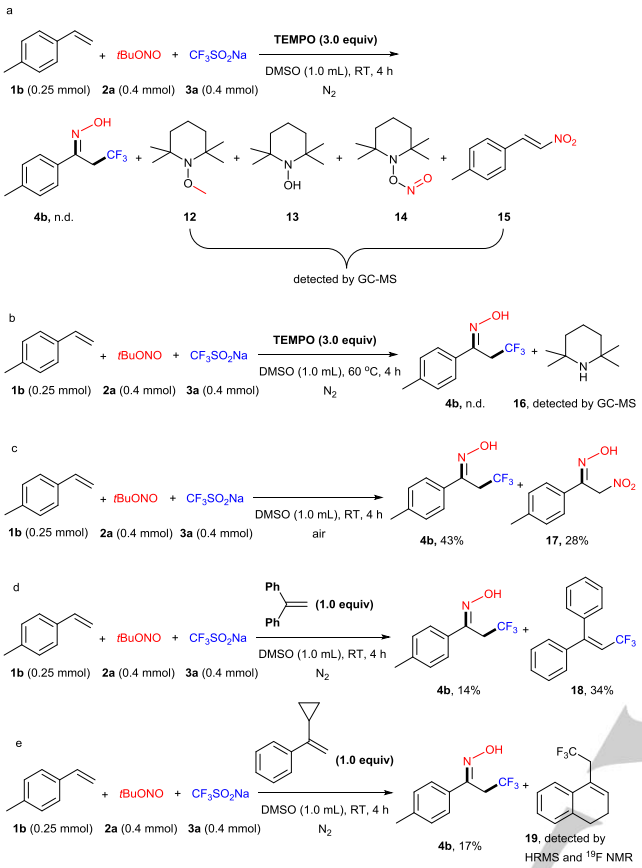
Additionally, the exchange of a hydrogen atom for a fluorine-containing group is regarded as an essential strategy for adjusting the physiochemical and metabolic properties of candidate drugs.[18] In this context, the cesium carbonate-promoted detrifluoromethylation of **10** was conducted in DMF, affording the corresponding *O*-acetyl ketoximes **11b**, **11d** and **11e** in satisfactory yields (Scheme 6).



Scheme 6. Removal of trifluoromethyl.

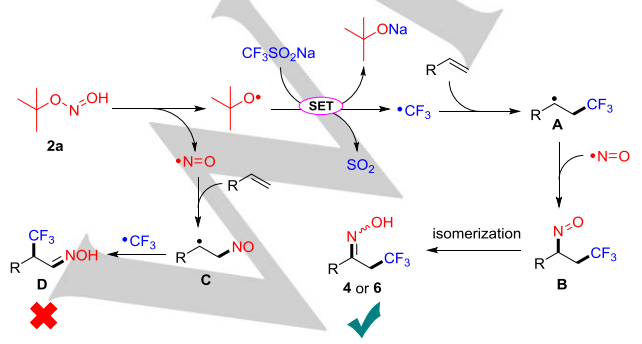
Several control experiments in Scheme 7 were conducted to gain a mechanistic insight into the alkene trifluoromethyloximation. With the addition of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) under the standard conditions, the formation of **4b** was absolutely suppressed, however, the compounds **12**, **13**, **14** and **15** were detected by GC-MS (Scheme 7a). Additionally, **16** was also detected when the reaction temperature was increased to 60 ^oC (Scheme 7b). The results obtained in Scheme 7a and 7b suggest that a single electron transfer process was involved in the trifluoromethyloximation reaction through free-radicals of *t*-BuO· and ·NO.[19] Upon conducting the reaction under air atmosphere, the yield of **4b** was decreased to 43% and **17** was obtained in 28% yield via nitro-oximation of **1b**, which again implies the existence of ·NO that could be easily transformed to $\cdot NO_2$ in the presence of air (Scheme 7c). When a radical scavenger 1,1-diphenyethylene was added to the reaction, the alkene trifluoromethyloximation was suppressed, and the radical $\cdot CF_3$ could be trapped to offer the product **18** in 34% yield (Scheme 7d). Furthermore, with the addition of a radical

clock 1-phenylvinylcyclopropane to the reaction, a ring expansion product **19** was detected by HRMS and ^{19}F NMR, which indicates the existence of the radical ·CF_3 (Scheme 7e).



Scheme 7. Preliminary mechanistic experiments.

Based on the results described above, we proposed a plausible mechanism for the trifluoromethyloximation reaction (Scheme 8). Firstly, *tert*-butyl nitrite decomposes into radicals *t*BuO· and ·NO. *t*BuO· then oxidizes CF_3SO_2Na to ·CF_3 via a SET (single electron transfer) process, along with the generation of SO_2 and *t*BuONa. The addition of ·CF_3 to alkenes provides the radical **A** that seizes ·NO to afford the intermediate **B**. Lastly, the final products **4** or **6** are constructed through the tautomerization of **B**. Nevertheless, the formation of products **D** is totally suppressed, which represents an excellent regioselectivity.



Scheme 8. Proposed reaction mechanism.

In summary, we have disclosed a convenient and precise trifluoromethyloximation of alkenes for the first time. The challenging conversion of unactivated and activated alkenes into various α-CF_3 ketoximes is achieved with excellent regioselectivity, as well as excellent stereoselectivity for most of styrenes, and good functional group tolerance under transition metal- and external oxidant-free conditions. By use of bifunctional *tert*-butyl nitrite as both nitrogen source and oxidant, these transformations can proceed smoothly via a free-radical process with readily available and stable alkenes as the substrates, inexpensive CF_3SO_2Na as the CF_3 reagent, and DMSO as the green solvent under mild conditions. A gram-scale reaction is successfully achieved to further demonstrate the synthetic generality of the developed protocol. More interestingly, the obtained α-CF_3 ketoximes can be efficiently converted to structurally important CF_3-containing target molecules, and CF_3 group can be readily removed in the presence of Cs_2CO_3.

Experimental Section

General reaction procedures for the synthesis of 4 and 6

To a 10 mL schlenk tube was added CF_3SO_2Na (0.40 mmol), and the tube was vacuumized and back-filled with nitrogen (this process was repeated for three times). Alkenes **1** or **5** (0.25 mmol), dry DMSO (1.0 mL) and *tert*-butyl nitrite (0.40 mmol) were added to the tube via syring, respectively. The resulting mixture was stirred at room temperature for 4 h. When the reaction was finished, appropriate ethyl acetate was added to the mixture and DMSO was extracted by saturated NaCl solution. The obtained organic phase was evaporated to remove the solvent and the resulting residue was further purified by flash column chromatography using petroleum ether/ethyl acetate to afford the products **4** or **6**.

Acknowledgements

This work was supported by no. 21602190 and 21402044 from the National Natural Science Foundation of China, no. 172102210456 from the Foundation of Department of Science and Technology of Henan Province, no. 17A150049 and 18A150049 from the Henan Key Scientific Research Project, and the Nanhu Scholars Program for Young Scholars of XYNU.

Keywords: alkenes • trifluoromethylation • free-radical • *tert*-butyl nitrite • metal-free

[1] a) R. E. Banks, B. E. Smart, J. C. Tatlow, *Organofluorine Chemistry: Principles and Commercial Applications*; Plenum: New York, **1994**; b) O. A. Tomashenko, V. V. Grushin, *Chem. Rev*. **2011**, *111*, 4475; c) N. A. Meanwell, *J. Med. Chem*. **2011**, *54*, 2529; d) Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Aceña, V. A. Soloshonok, K. Izawa, H. Liu, *Chem. Rev*. **2016**, *116*, 422.

[2] For selected examples, see: a) H. Egami, R. Shimizu, Y. Usui, M. Sodeoka, *J. Fluorine Chem*. **2014**, *167*, 172; b) Q.-Y. Lin, X.-H. Xu, F.-L. Qing, *J. Org. Chem*. **2014**, *79*, 10434; c) C. Feng, T.-P. Loh, *Angew. Chem., Int. Ed*. **2013**, *52*, 12414; d) R. Tomita, Y. Yasu, T. Koike, M. Akita, *Beilstein J. Org. Chem*. **2014**, *10*, 1099; e) H. Egami, Y. Usui, S. Kawamura, S. Nagashima, M. Sodeoka, *Chem.-Asian J*. **2015**, *10*, 2190; f) X. Zhang, P. Huang, Y. Li, C. Duan, *Org. Biomol. Chem*. **2015**, *13*, 10917; g) Z. Feng, Q.-Q. Min, H.-Y. Zhao, J.-W. Gu, X. Zhang, *Angew. Chem., Int. Ed*. **2015**, *54*, 1270; h) L.-H. Wu, K. Zhao, T.-P. Loh, *Org. Chem. Front*. **2017**, *4*, 1872; i) N. J. W. Straathof, S. E. Cramer, V. Hessel, T. Noël, *Angew. Chem., Int. Ed*. **2016**, *55*, 15549; j) K.-F.

Zhang, K.-J. Bian, J. Sheng, Y. Li, X.-S. Wang, *Angew. Chem., Int. Ed*. **2019**, *58*, 5069.

[3] For selected examples, see: a) W. Kong, M. Casimiro, E. Merino, C. Nevado, *J. Am. Chem. Soc*. **2013**, *135*, 14480; b) H. Egami, R. Shimizu, S. Kawamura, M. Sodeoka, *Angew. Chem., Int. Ed*. **2013**, *52*, 4000; c) F. Wang, D. Wang, X. Mu, P. Chen, G. Liu, *J. Am. Chem. Soc*. **2014**, *136*, 10202; d) L.-Z. Yu, Q. Xu, X.-Y. Tang, M. Shi, *ACS Catal*. **2016**, *6*, 526; e) Z.-L. Li, X.-H. Li, N. Wang, N.-Y. Yang, X.-Y. Liu, *Angew. Chem., Int. Ed*. **2016**, *55*, 15100; f) S. Zhou, T. Song, H. Chen, Z. Liu, H. Shen, C. Li, *Org. Lett*. **2017**, *19*, 698; g) X. Tang, A. Studer, *Chem. Sci*. **2017**, *8*, 6888; h) Z. Wu, D. Wang, Y. Liu, L. Huan, C. Zhu, *J. Am. Chem. Soc*. **2017**, *139*, 1388; i) H. Jiang, Y. He, Y. Cheng, S. Yu, *Org. Lett*. **2017**, *19*, 1240; j) X.-J. Shang, D. Liu, Z.-Q. Liu, *Org. Chem. Front*. **2018**, *5*, 2856; k) Q. Ye, M. Jiang, Q.-H. Deng, J.-T. Liu, *Adv. Synth. Catal*. **2018**, *360*, 1402; l) W. Jin, M. Wu, Z. Xiong, G. Zhu, *Chem. Commun*. **2018**, *54*, 7924.

[4] For selected examples, see: a) R. Tomita, Y. Yasu, T. Koike, M. Akita, *Angew. Chem., Int. Ed*. **2014**, *53*, 7144; b) Q. Lu, C. Liu, Z. Huang, Y. Ma, J. Zhang, A. Lei, *Chem. Commun*. **2014**, *50*, 14101; c) Q.-H. Deng, J.-R. Chen, Q. Wei, Q.-Q. Zhao, L.-Q. Lu, W.-J. Xiao, *Chem. Commun*. **2015**, *51*, 3537; d) J.-H. Ye, L. Song, W.-J. Zhou, T. Ju, Z.-B. Yin, S.-S. Yan, Z. Zhang, J. Li, D.-G. Yu, *Angew. Chem., Int. Ed*. **2016**, ***55***, 10022; e) M. Daniel, G. Dagousset, P. Diter, P.-A. Klein, B. Tuccio, A.-M. Goncalves, G. Masson, E. Magnier, *Angew. Chem., Int. Ed*. **2017**, *56*, 3997; f) J.-S. Lin, F.-L. Wang, X.-Y. Dong, W.-W. He, Y. Yuan, S. Chen, X.-Y. Liu, *Nat. Commun*. **2017**, *8*, 14841; g) Y.-b. Wu, G.-p. Lu, T. Yuan, Z.-b. Xu, L. Wan, C. Cai, *Chem. Commun*. **2016**, *52*, 13668; h) T. Kawamoto, R. Sasaki, A. Kamimura, *Angew. Chem., Int. Ed*. **2017**, *56*, 1342; i) S. Zhang, L. Li, J. Zhang, J. Zhang, M. Xue, K. Xu, *Chem. Sci*. **2019**, *10*, 3181.

[5] For selected examples, see: a) C.-J. Wallentin, J. D. Nguyen, P. Finkbeiner, C. R. J. Stephenson, *J. Am. Chem. Soc*. **2012**, *134*, 8875; b) Z. Hang, Z. Li, Z.-Q. Liu, *Org. Lett*. **2014**, *16*, 3648; c) T. Xu, C. W. Cheung, X. Hu, *Angew. Chem., Int. Ed*. **2014**, *53*, 4910; d) S. H. Oh, Y. R. Malpani, N. Ha, Y.-S. Jung, S. B. Han, *Org. Lett*. **2014**, *16*, 1310; e) W. An, N. Ha, H. M. Lee, Y. R. Malpani, D.-H. Lee, Y.-S. Jung, S. B. Han, *Adv. Synth. Catal.* **2015**, *357*, 3949; f) X.-J. Tang, W. R. Dolbier, *Angew. Chem., Int. Ed.* **2015**, *54*, 4246; g) J. Fang, Z.-K. Wang, S.-W. Wu, W.-G. Shen, G.-Z. Ao, F. Liu, *Chem. Commun*. **2017**, *53*, 7638; h) Z.-Q. Liu, D. Liu, *J. Org. Chem.* **2017**, *82*, 1649.

[6] For selected examples of alkene aminotrifluoromethylation with amines (protected amines) as nitrogen sources, see: (a) G. Dagousset, A. Carboni, E. Magnier, G. Masson, *Org. Lett*. **2014**, *16*, 4340. (b) S. Kawamura, H. Egami, M. Sodeoka, *J. Am. Chem. Soc*. **2015**, *137*, 4865. (c) J.-S. Lin, X.-Y. Dong, T.-T. Li, N.-C. Jiang, B. Tan, X.-Y. Liu, *J. Am. Chem. Soc*. **2016**, *138*, 9357. (d) K. Shen, Q. Wang, *Org. Chem. Front*. **2016**, *3*, 222. (e) B. Chang, Y. Su, D. Huang, K.-H. Wang, W. Zhang, Y. Shi, X. Zhang, Y. Hu, *J. Org. Chem*. **2018**, *83*, 4365. (f) N. Noto, T. Koike, M. Akita, *Chem. Sci*. **2017**, *8*, 6375.

[7] For selected examples of alkene aminotrifluoromethylation with azides as nitrogen sources, see: a) F. Wang, X. Qi, Z. Liang, P. Chen, G. Liu, *Angew. Chem., Int. Ed*. **2014**, *53*, 1881; b) H. Liu, Q. Guo, C. Chen, M. Wang, Z. Xu, *Org. Chem. Front*. **2018**, *5*, 1522; c) L.-Z. Yu, Y. Wei, M. Shi, *Chem. Commun*. **2016**, *52*, 13163; d) X. Geng, F. Lin, X. Wang, N. Jiao, *Org. Lett*. **2017**, *19*, 4738; e) Y. Zhang, X. Han, J. Zhao, Z. Qian, T. Li, Y. Tang, H.-Y. Zhang, *Adv. Synth. Catal*. **2018**, *360*, 2659; f) Q. Meng, F. Chen, W. Yu, B. Han, *Org. Lett*. **2017**, *19*, 5186; g) C.-L. Zhu, C. Wang, Q.-X. Qin, S. Yruegas, C. D. Martin, H. Xu, *ACS Catal*. **2018**, *8*, 5032.

[8] a) Y. Yasu, T. KoiKe, M. Akita, *Org. Lett.* **2013**, *15*, 2136; b) L. Zhang, G. Zhang, P. Wang, Y. Li, A. Lei, *Org. Lett.*, **2018**, *20*, 7396.

[9] For selected examples, see: a) X. Zhang, J. Sun, Y. Ding, L. Yu, *Org. Lett*. **2015**, *17*, 5840; b) J.-F. Paquin, M. Keita, M. Vandamme, *Synthesis* **2015**, *47*, 3758; c) K. Hyodo, S. Kitagawa, M. Yamazaki, K. Uchida, *Chem.-Asian J*. **2016**, *11*, 1348; d) Y.-J. Zhuang, J. Liu, Y.-B. Kang, *Tetrahedron Lett*. **2016**, *57*, 5700; e) A. Rapeyko, M. J. Climent, A. Corma, P. Concepción, S. Iborra, *ACS Catal*. **2016**, *6,* 4564; f) D. Sun, E. Kitamura, Y. Yamada, S. Sato, *Green Chem*. **2016**, *18*, 3389; g) A. Leggio, E. L. Belsito, S. Gallo, A. Liguori, *Tetrahedron Lett*. **2017**, *58*, 1512.

[10] For selected reviews, see: a) R. R. Kumar, K. A. Vanithan, M. Balasubramanian, *in Name Reactions for Homologation: Part 2,* ed. Li, J. J. John Wiley & Sons, Hoboken, **2009**, 274-292; b) N. Kaur, P. Sharma, D. Kishore, *J. Chem. Pharm. Res*. **2012**, *4*, 1938; c) P. Crochet, V. Cadierno, *Chem. Commun*. **2015**, *51*, 2495, and references cited therein.

[11] a) Y. Chu, Z. Shan, D. Liu, N. Sun, *J. Org. Chem*. **2006**, *71*, 3998; b) K. Huang, F. G. Merced, M. Ortiz-Marciales, H. J. Melendez, W. Correa, M. De Jesus, *J. Org. Chem*. **2008**, *73*, 4017; c) M. M. Pakulski, S. K. Mahato, M. J. Bosiak, M. P. Krzeminski, M. Zaidlewicz, *Tetrahedron: Asymmetry* **2012**, *23*, 716; d) W. P. Hong, A. V. Iosub, S. S. Stahl, *J. Am. Chem. Soc*. **2013**, *135*, 13664.

[12] For selected reviews and examples, see: a) A. Corsaro, M. A. Chiacchio, V. Pistarà, *Curr. Org. Chem*. **2009**, *13*, 482; b) X.-T. Zhou, Q.-L. Yuan, H.-B. Ji, *Tetrahedron Lett*. **2010**, *51*, 613; c) M. H. Lin, H. J. Liu, C. Y. Chang, W. C. Lin, T. H. Chuang, *Molecules* **2012**, *17*, 2464; d) G. Zhang, X. Wen, Y. Wang, X. Han, Y. Luan, L. Zheng, C. Ding, X. Cao, *RSC Adv*. **2013**, *3*, 22918.

[13] For selected examples, see: a) H. Huang, J. Cai, G.-J. Deng, *Org. Biomol. Chem*. **2016**, *14*, 1519; b) W. Hu, J. Li, Y. Xu, J. Li, W. Wu, H. Liu, H. Jiang, *Org. Lett.* **2017**, *19*, 678; c) T.-X. Liu, S. Hua, N. Ma, P. Zhang, J. Bi, Z. Zhang, G. Zhang, *Adv. Synth. Catal*. **2018**, *360*, 142; d) D. Bai, X. Wang, G. Zheng, X. Li, *Angew. Chem., Int. Ed*. **2018**, *57*, 6633; e) Y. Yi, M.-N. Zhao, Z.-H. Ren, Y.-Y. Wang, Z.-H. Guan, *Green Chem*. **2017**, *19*, 1023; f) H. Kim, S. Chang, *Angew. Chem., Int. Ed.* **2017**, *56*, 3344; g) G. Zhao, C. He, P. Yin, G. H. Imler, D. A. Parrish, J. M. Shreeve, *J. Am. Chem. Soc*. **2018**, *140*, 3560.

[14] For selected reviews, see: a) K. Narasaka, M. Kitamura, *Eur. J. Org. Chem.* **2005**, *2005*, 4505; b) A. A. Tabolin, S. L. Ioffe, *Chem. Rev*. **2014**, *114*, 5426; c) H. Huang, X. Ji, W. Wu, H. Jiang, *Chem. Soc. Rev*. **2015**, *44*, 1155; d) D. S. Bolotin, N. A. Bokach, M. Y. Demakova, V. Y. Kukushkin, *Chem. Rev*. **2017**, *117*, 13039; e) D. K. Kölmel, E. T. Kool, *Chem. Rev*. **2017**, *117*, 10358, and references cited therein.

[15] For selected examples, see: a) U. Dutta, D. W. Lupton, D. Maiti, *Org. Lett*. **2016**, *18*, 860; b) Y. Lin, W. Kong, Q. Song, *Org. Lett*. **2016**, *18*, 3702; c) Y. Zhou, Z. Tang, Q. Song, *Chem. Commun*. **2017**, *53*, 8972; d) S. Mondal, S. Samanta, A. Hajra, *Adv. Synth. Catal*. **2018**, *360*, 1026; e) J. Pan, X. Li, F. Lin, J. Liu, N. Jiao, *Chem* **2018**, *4,* 1427; f) J. Luo, W.-T. Wei, *Adv. Synth. Catal*. **2018**, *360*, 2076; g) X. He, X. Yue, L. Zhang, S. Wu, M. Hu, J.-H. Li, *Chem. Commun*. **2019**, *55*, 3517; h) B. Wang, Z. Yan, L. Liu, J. Wang, Z. Zha, Z. Wang, *Green Chem*. **2019**, *21*, 205; i) Y. He, Z. Zheng, Y. Liu, J. Qiao, X. Zhang, X. Fan, *Org. Lett*. **2019**, *21*, 1676; j) Y. Chen, Y. Ma, L. Li, H. Jiang, Z. Li, *Org. Lett*. **2019**, *21*, 1480.

[16] (a) L. Tang, Y. Yang, L. Wen, X. Yang, Z. Wang, *Green Chem*. **2016**, *18,* 1224; b) L. Tang, Z. Yang, T. Sun, D. Zhang, X. Ma, W. Rao, Y. Zhou, *Adv. Synth. Catal*. **2018**, *360*, 3055; c) L. Tang, Z. Yang, X. Chang, G. Zou, Y. Zhou, W. Rao, X. Ma, G. Zhao, *Tetrahedron Lett*. **2018**, *59*, 4272; d) L. Tang, Z. Yang, X. Chang, J. Jiao, X. Ma, W. Rao, Q. Zhou, L. Zheng, *Org. Lett*. **2018**, *20*, 6520; e) L. Li, Y.-N. Ma, M. Tang, J, Guo, Z. Yang, Y. Yan, X. Ma, L. Tang, *Adv. Synth. Catal*. **2019**, DOI: 10.1002/adsc.201900521; f) L. Tang, Z. Yang, J. Jiao, Y. Cui, G.-D. Zou, Q. Zhou, Y.-Q. Zhou, W.-H. Rao, X. Ma, *J. Org. Chem*. **2019**, DOI: 10.1021/acs.joc.9b01808.

[17] The CCDC number of **6m** is 1912730 and the supplementary crystallographic data for this manuscript can be gained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

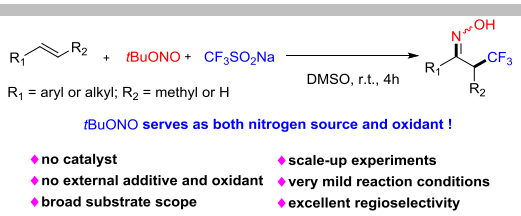
[18] For selected examples and reviews, see: a) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev*. **2014**, *114*, 2432; b) N. A. Meanwell, *J. Med. Chem*. **2018**, *61*, 5822; c) J. J. Gair, R. L. Grey, S. Giroux, M. A. Brodney, *Org. Lett*. **2019**, *21*, 2482, and references cited therein.

[19] See the supporting information for the possible reaction routes for the formation of compounds **12**, **13**, **14**, **15** and **16**.

10.1002/cssc.201901856

WILEY-VCH

By use of bifunctional *tert*-butyl nitrite as both nitrogen source and oxidant, the trifluoromethyloximation of alkenes proceeds smoothly via a free-radical process with readily available and stable alkenes as the substrates, inexpensive CF_3SO_2Na as the CF_3 reagent, and DMSO as the green solvent under mild conditions. Moreover, a scale-up reaction, further transformation of the products to various valuable CF_3-containing compounds, and removal of trifluoromethyl are readily achieved.



*Y. Wu, Y. Zhang, Z. Yang, J. Jiao, X. Zheng, W. Feng, M. Zhang, H. Cheng, and L. Tang**

Page No. – Page No.

Dual Roles of *tert*-Butyl Nitrite in the Transition Metal- and External Oxidant-Free Trifluoromethyloximation of Alkenes