

A Convenient Formal [4 + 2] Heterocyclization Route to Bis(triflyl)tetrahydroquinolines

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Abstract: We report the sustainable and efficient synthesis of a new type of quinoline derivatives bearing one or two SO₂CF₃ groups. The protocol is metal-, catalyst- and irradiation-free, involves the use of readily available and stable precursors, and avoids the formation of side products. Also, the mild conditions of the process allow the tolerance of a wide range of functional groups.

The tetrahydroquinoline (THQ) heterocyclic scaffolds is widely found in a large number of natural products, such as angustureine, benzastatin D, and pharmaceutically active drugs (Scheme 1, top).^[1] As a result, the development of efficient synthetic strategies to this privileged nitrogen heterocycle has experienced notable interest.^[1] Main synthetic approaches are Povarov reaction (Scheme 1a), partial reduction of quinolines (Scheme 1b), and transition-metal catalyzed cyclizations (Scheme 1c). Despite the power of the above methods, they normally use harsh reaction conditions, some of them utilize expensive transition metals, and cause environmental pollution. The widespread occurrence of sulfones in pharmaceuticals, agrochemicals, and advanced materials, coupled to its synthetic power makes the sulfone motif as a very attractive functional group.^[2] Among sulfones, the SO₂CF₃ (Tf, triflyl) group is of particular attractiveness because its presence in an organic molecule improves the bioavailability.^[3] We describe herein a novel and sustainable approach towards a class of unprecedented THQs containing a Tf₂C unit, based on a formal [4 + 2]

heterocyclization from 1-(2-aminophenyl)prop-2-en-1-ol precursors (Scheme 1d). Low energy consumption, the absence of any metal or catalyst, use of equimolar reactants, efficiency, simple work-up, and the use of a safe solvent are the main features of our synthetic protocol to meet some of the principles of green chemistry.^[4]

Yanai has reported that betaine **1** having both a 2-fluoropyridinium cation as well as a stabilized carbanion moiety quickly equilibrated in acetonitrile to form mixtures of the betaine along with (CF₃SO₂)₂C=CH₂ and volatile 2-fluoropyridine, which permits it to be employed as shelf-stable, eco-

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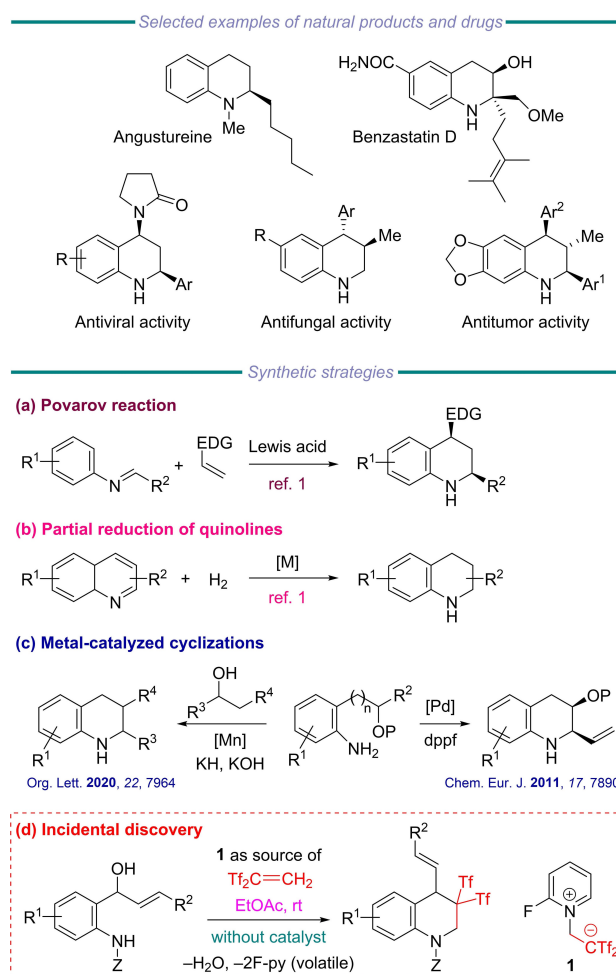
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Supporting information for this article is available on the WWW under <https://doi.org/10.1002/chem.202102254>

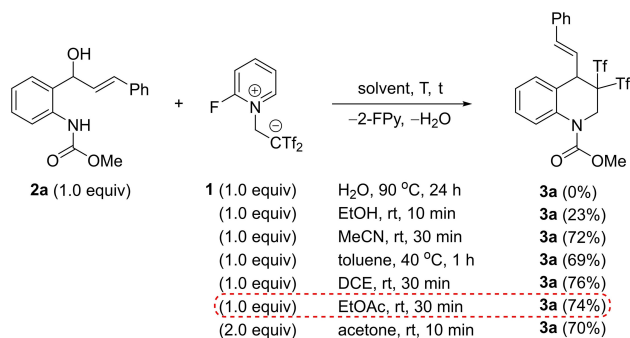
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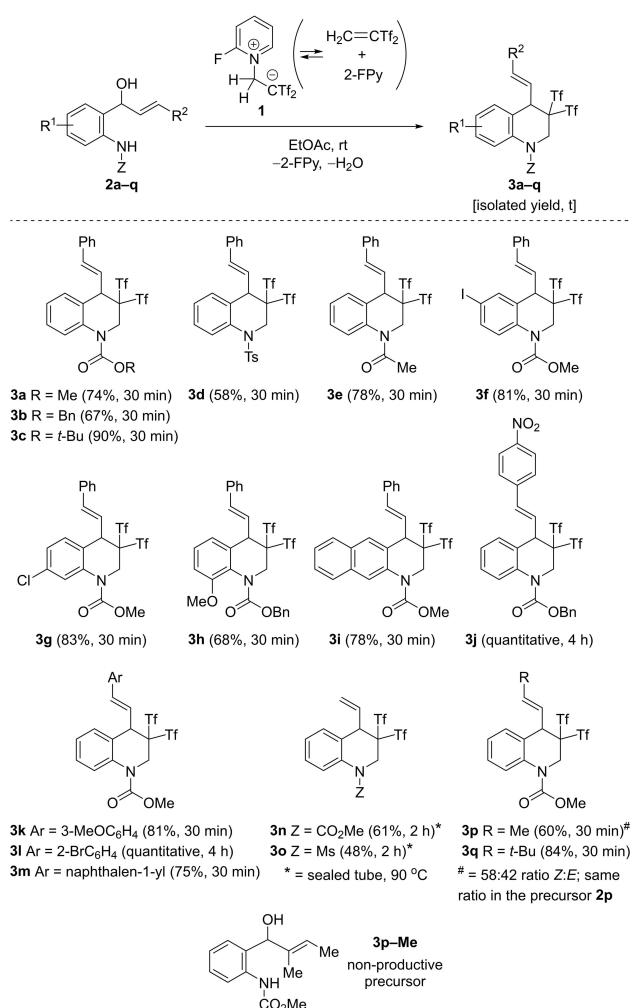
Scheme 1. Selected examples of alkaloids and drugs containing the THQ motif (top) and synthetic approaches (bottom).

friendly^[5] and easy-to-handle source of $(\text{CF}_3\text{SO}_2)_2\text{C}=\text{CH}_2$.^[6] We have recently taken advantage of this ability of **1**, revealing the usefulness of 1-arylbuta-2,3-dien-1-ols as building blocks in the stereocontrolled preparation of bis(triflyl)ated α,β -enones and indolines.^[7] In continuation of this effort, when we used precursor **2a** possessing an 1-(2-aminophenyl)-3-phenylprop-2-en-1-ol moiety, a new product, bis(triflyl)ated tetrahydroquinoline **3a** was isolated (Scheme 2). Captivated by the unanticipated discovery, we aspired to comprehensively study this transformation. The effect of solvents (water, ethanol, acetone, ethyl acetate, acetonitrile, toluene, and DCE) was evaluated. The reaction gave rise to the desired product **3a** in more of the tested solvents, but did not proceed in hot water and evolved poorly in ethanol (Scheme 2). Ethyl acetate was selected as the solvent of choice taking into account environmental, health and safety criteria.^[8] We suspect that the assembly of $\text{Tf}_2\text{C}=\text{CH}_2$ as 2- π partner could be realized through the union with and in situ generated aza-*ortho*-quinone methide^[9] via a cascade reaction. Moreover, conducting the reaction in the presence of radical scavenger 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) did not trim the yield, thus discarding the implication of radical intermediates.

With the optimized condition on hand, the scope for the THQ formation reaction was investigated. A good tolerance to the protective group at the anilide moiety was observed. For the 1-(2-aminophenyl)prop-2-en-1-ol precursor, the electronic properties of the anilide ring in **2a–q** did not importantly influenced the performance of the annulation sequence and good yields of bicycles **3a–q** were achieved (Scheme 3). Interestingly, placement of either aliphatic or aromatic (both electron-rich and electron-poor) scaffolds in the starting prop-2-en-1-ol moiety was well tolerated, and the desired benzo-fused THQs **3** were obtained in good yields. Besides, the C-halogen functionality is compatible with this transformation, and may supply a reactive platform for further functionalization of the THQ core through cross-coupling protocols. Compounds **3** are potentially valuable as its scaffold incorporates a THQ core, a bis(triflyl) functionality and an alkene moiety. However, when the protocol was applied to 2,3-disubstituted alkenol **3p–Me**, a complicated mixture was formed and the assembly of the desired azacycle could not be attained (Scheme 3).



Scheme 2. Impact of the solvent and temperature on the preparation of bis(triflyl)ated tetrahydroquinoline **3a**.

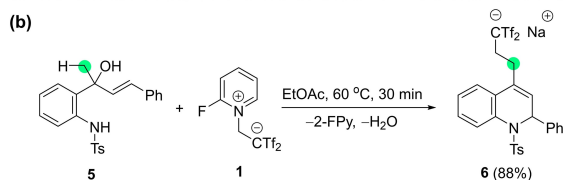
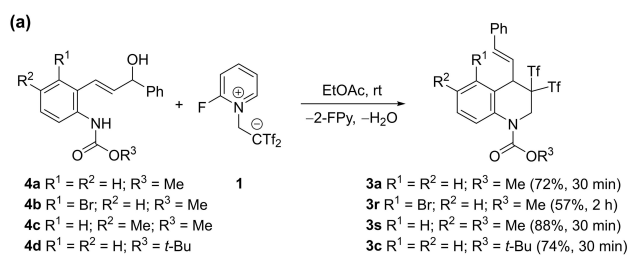


Scheme 3. Controlled synthesis of bis(triflyl)ated tetrahydroquinolines **3a–q**.

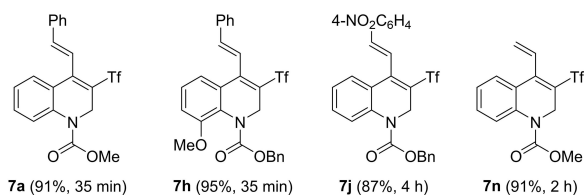
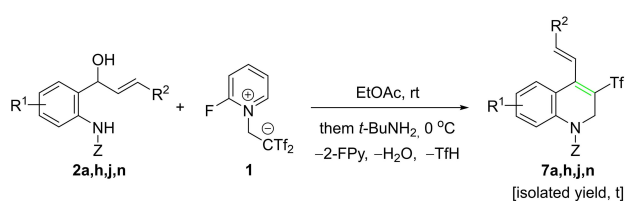
Allylic alcohols **4a–c** showed the same above reactivity when they were used instead of isomeric **2** as starting materials for the formation of THQs **3** (Scheme 4a). However, the use of tertiary allylic alcohol **5** resulted in a dramatic influence in the reactivity and bis(triflyl)ethylated DHQ **6** was formed as exclusive product (Scheme 4b).

The reaction between aminophenyl-tethered alkenol **2a** and betaine **1** was investigated without isolation of bis(triflyl)ated tetrahydroquinoline **3a** through the further addition of a base. Thus, bis(triflyl)ated adduct **3a** suffered in situ a loss of TfH to provide 3-[(trifluoromethyl)sulfonyl]-1,2-dihydroquinoline **7a** in a 91% overall yield. It should be noted that the hydrodetriflylation step proceeded with total selectivity giving rise exclusively to the 1,3-diene moiety. Several 1,2-dihydroquinoline-based triflones **7** were synthesized running the reaction in this manner. This one-pot protocol allowed us the preparation of 1,2-dihydroquinoline-based triflones **7a,h,j,n** in excellent yields starting from alkenols **2** and betaine **1** (Scheme 5).

Next, we explore the substrate scope of the intermolecular annulation by the reaction of betaine **1** with (2-aminophenyl)

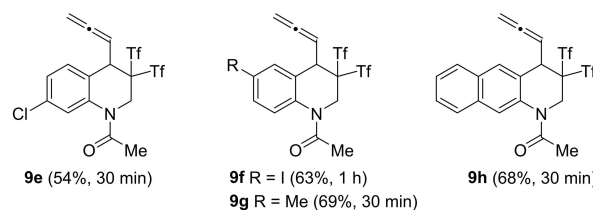
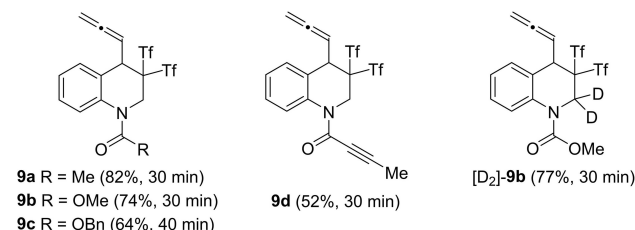
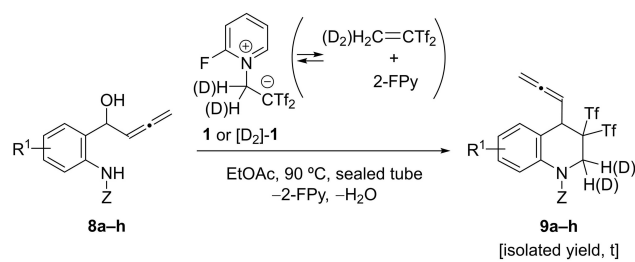


Scheme 4. Synthesis of bis(triflyl)-decorated unsaturated quinolines **3a, c, r, s** and **6**.



Scheme 5. Controlled synthesis of triflylated 1,2-dihydroquinolines **3a–q**.

methanols in which the alkene has been replaced by hydrocarbons with different degree of unsaturation. Functionalized anilides with alkynol instead alkenol substituents gave complex mixtures of products, likely due to off-target reactions between the alkyne and $\text{Tf}_2\text{C}=\text{CH}_2$.^[10] Notably, as shown in Scheme 6, the reaction progressed in hot ethyl acetate with a variety of 1-(2-aminophenyl)buta-2,3-dien-1-ol precursors **8a–j**, bearing substituents of distinct electronic nature in different positions at the benzene ring, affording the required bis(triflyl)ated THQs **9a–j** in good yields. Besides, the reaction proceeded well when different amide-like functionalities were incorporated in the nitrogen atom. Considering the relevance of organic compounds bearing C–D bonds,^[11] the reaction between precursor **8b** and deuterated Yanai's reagent [D₂]-**1** was explored. Noteworthy, bis(triflyl)ated THQ [D₂]-**9b** was smoothly obtained in 77% yield (Scheme 6). Due to the widespread use of allenols as versatile building blocks for the synthesis of functionalized organic compounds of chemical and pharmacological rele-

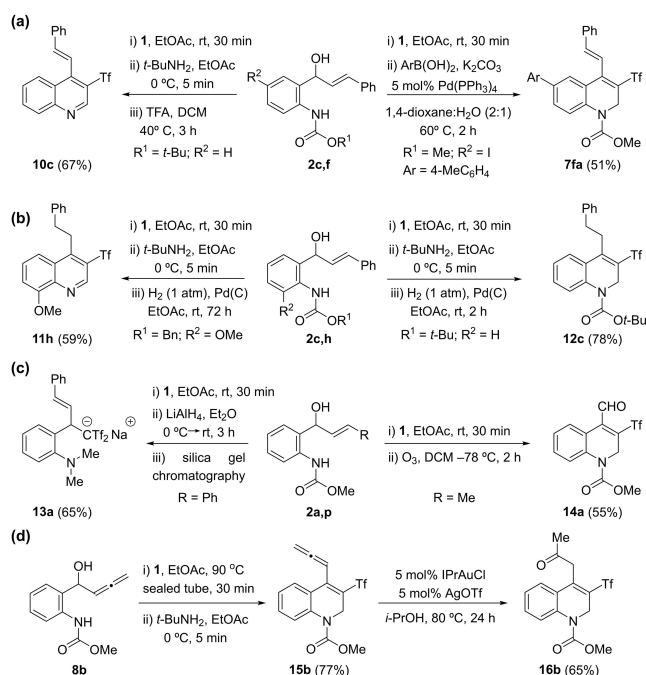


Scheme 6. Controlled synthesis of bis(triflyl)ated tetrahydroquinolines **9a–h**.

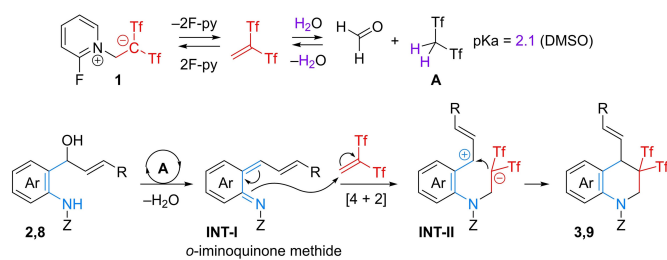
vance, the presence of an allene moiety is relevant as it may enable further functionalization.

To demonstrate the synthetic utility of our protocol, follow-up transformations were performed. For instance, we easily transformed bis(triflyl)ated THQ **3c** into (*E*)-4-styryl-3-(triflyl)quinoline **10c** by sequential basic and acidic treatment (Scheme 7a, left). Besides, bis(triflyl)ated THQ **3f** underwent Suzuki-Miyaura coupling in aqueous medium with concomitant TfH release to provide triflylated dihydroquinoline (DHQ) **7fa** (Scheme 7a, right). Base-promoted loss of TfH in bis(triflyl)ated THQs **3c** and **3h** followed by hydrogenation yielded 4-phenethyl-3-(triflyl)quinoline **11h** (Scheme 7b, left) and 4-phenethyl-3-(triflyl)-1,2-dihydroquinoline **12c** (Scheme 7b, right), respectively. Furthermore, selective ring opening of bis(triflyl)ated THQ **3a** to yield **13a** occurred under reductive conditions (Scheme 7c, left), while formation of Tf-decorated enal **14a** proceeded smoothly upon treatment of **3a** with ozone (Scheme 7c, right). Detriflylation of allenyl-THQ **9b** was achieved under basic conditions furnishing the stable trienyl DHQ **15b**, which suffered further hydration under Au-catalysis giving rise to ketone **16b** (Scheme 7d). Noteworthy, all the transformations depicted in Scheme 7 were performed in one-pot from the appropriate precursors **2** or **8** without isolation of bis(triflyl)ated THQs **3** or **9**.^[12]

A possible pathway for the formation of bis(triflyl)ated tetrahydroquinolines **3** and **9** from (2-aminophenyl)-tethered alkenols/allenols **2** and **8** is depicted in Scheme 8. First, the *ortho*-quinone methide **INT-I** should be generated from **2** and **8** through dehydration catalyzed by bis((trifluoromethyl)sulfonyl)methane **A**, which may be formed in situ from betaine **1** in



Scheme 7. Product elaborations that showcase utility of our protocol.



Scheme 8. Rationalization for the generation of bis(triflyl)ated tetrahydroquinolines 3 and 9.

presence of water.^[13] Afterwards, the formation of a zwitterionic intermediate INT-II should take place through nucleophilic attack of the nitrogen atom of species INT-I onto the methylenic carbon atom of in situ generated $\text{Tf}_2\text{C}=\text{CH}_2$. Ring closure with concurrent formation of THQs 3 and 9 would finally occur by intramolecular attack of the bis(triflyl) carbanion towards the allyl carbocation.

To summarize, the easily prepared and bench stable 2-fluoropyridinium-based zwitterionic reagent 1 is competent for the user-friendly preparation of tetrahydroquinolines bearing one or two SO_2CF_3 groups. This sustainable approach is carried out in ethyl acetate under ambient conditions, does not require the use of metals, additives or irradiation, and is applicable to various types of unsaturated alcohols.

Acknowledgements

This work was supported in part by AEI (MICIU) and FEDER (Project PGC2018-095025-B-I00). C. L.-M. thanks MICIU and UCM for a postdoctoral contract.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: alkenes · allenes · fluorine · metal-free reactions · synthetic methods

- [1] For seminal reviews, see: a) V. Sridharan, P. Suryavanshi, J. C. Menéndez, *Chem. Rev.* **2011**, *111*, 7157; b) I. Muthukrishnan, V. Sridharan, J. C. Menéndez, *Chem. Rev.* **2019**, *119*, 5057. For selected contributions, see: c) B. M. Trost, B. M. O'Boyle, W. Torres, M. K. Ameriks, *Chem. Eur. J.* **2011**, *17*, 7890; d) N. Hofmann, L. Homberg, K. C. Hultzs, *Org. Lett.* **2020**, *22*, 7964; e) Z. Tan, B. Xiong, J. Yang, C. Ci, H. Jiang, M. Zhang, *J. Catal.* **2020**, *392*, 135; f) S. Chen, L. Yang, Y. Shang, J. Mao, P. J. Walsh, *Org. Lett.* **2021**, *23*, 1594.
- [2] For reviews, see: a) A. El-Awa, M. N. Noshi, X. M. du Jourdin, P. L. Fuchs, *Chem. Rev.* **2009**, *109*, 2315; M. Feng, B. Tang, S. H. Liang, X. Jiang, *Curr. Top. Med. Chem.* **2016**, *16*, 1200; b) B. M. Trost, C. A. Kalnals, *Chem. Eur. J.* **2019**, *25*, 11193; c) S. Ye, M. Yang, J. Wu, *Chem. Commun.* **2020**, *56*, 4145 and references therein.
- [3] a) X.-H. Xu, K. Matsuzaki, N. Shibata, *Chem. Rev.* **2015**, *115*, 731; b) J. Ni, Y. Jiang, Z. An, J. Lan, R. Yan, *Chem. Commun.* **2019**, *55*, 7343 and references therein; c) V. Krishnamurti, C. Barrett, G. K. S. Prakash, D. Cahard, J.-A. Ma, *Synthesis and Applications of Fluorinated Sulfoxides (RSORF) and Sulfones (RSO₂RF) Emerging Fluorinated Motifs. Synthesis, Properties, and Applications* Wiley-VCH Verlag, Weinheim, **2020**, Vol. II, p. 477–550.
- [4] a) M. Poliakov, J. M. Fitzpatrick, T. R. Farren, P. T. Anastas, *Science* **2002**, *297*, 807; b) B. H. Lipshutz, S. Ghoral, *Green Chem.* **2014**, *16*, 3660; c) D. Prat, A. Wells, J. Hayler, H. Sneddon, C. R. McElroy, S. Abou-Shehadad, P. J. Dunn, *Green Chem.* **2016**, *18*, 288; d) B. H. Lipshutz, F. Gallou, S. Handa, *ACS Sustainable Chem. Eng.* **2016**, *4*, 5838; e) S. Sharma, J. Das, W. M. Braje, A. K. Dash, S. Handa, *ChemSusChem* **2020**, *13*, 2859.
- [5] A recent study reported the low ecotoxicity of zwitterionic compounds structurally related to betaine 1: F. Jesus, H. Passos, A. M. Ferreira, K. Kuroda, J. L. Pereira, F. J. M. Gonçalves, J. A. P. Coutinho, S. P. M. Ventura, *Green Chem.* **2021**, *23*, 3683.
- [6] a) H. Yanai, Y. Takahashi, H. Fukaya, Y. Dobashi, T. Matsumoto, *Chem. Commun.* **2013**, *49*, 10091; b) H. Yanai, R. Takahashi, Y. Takahashi, A. Kotani, H. Hakamata, T. Matsumoto, *Chem. Eur. J.* **2017**, *23*, 8203; c) H. Yanai, T. Yoshino, M. Fujita, H. Fukaya, A. Kotani, F. Kusu, T. Taguchi, *Angew. Chem. Int. Ed.* **2013**, *52*, 1560; *Angew. Chem.* **2013**, *125*, 1600; d) H. Yanai, H. Ogura, H. Fukaya, A. Kotani, F. Kusu, T. Taguchi, *Chem. Eur. J.* **2011**, *17*, 11747; e) H. Yanai, M. Fujita, T. Taguchi, *Chem. Commun.* **2011**, *47*, 7245.
- [7] a) C. Lázaro-Milla, J. Macicior, H. Yanai, P. Almendros, *Chem. Eur. J.* **2020**, *26*, 8983; b) C. Lázaro-Milla, H. Yanai, P. Almendros, *Org. Lett.* **2021**, *23*, 2921.
- [8] a) A. J. Doolin, R. G. Charles, C. S. P. De Castro, R. Garcia Rodriguez, E. V. Péan, R. Patidar, T. Dunlop, C. Charbonneau, T. Watson, M. L. Davies, *Green Chem.* **2021**, *23*, 2471; b) D. Zhu, H. Peng, Y. Sun, Z. Wu, Y. Wang, B. Luo, T. Yu, Y. Hu, P. Huang, S. Wen, *Green Chem.* **2021**, *23*, 1972; c) F. Gao, F. Ferlin, R. Bai, M. Li, L. Vaccaro, Y. Gu, *Green Chem.* **2021**, *23*, 3588; d) Q.-W. Gui, B.-B. Wang, S. Zhu, F.-L. Li, M.-X. Zhu, M. Yi, J.-L. Yu, Z.-L. Wub, W.-M. He, *Green Chem.* **2021**, *23*, 4430.
- [9] Aza-ortho-quinone methides are highly reactive intermediates, which can be formed from conveniently functionalized precursors under suitable oxidative, acidic, basic and irradiation driven conditions. For a review see: a) B. Yang, S. Gao, *Chem. Soc. Rev.* **2018**, *47*, 7926. For selected references: b) Y.-Y. Liu, X.-Y. Yu, J.-R. Chen, M.-M. Qiao, X. Qi, D.-Q. Shi, W.-J. Xiao, *Angew. Chem. Int. Ed.* **2017**, *56*, 9527; *Angew. Chem.* **2017**, *129*, 19655; c) D.-Q. Ji, C. Wang, J.-T. Sun, *Org. Lett.* **2018**, *20*, 3710; d) Y. Zheng, L. Tu, N. Li, R. Huang, T. Feng, H. Sun, Z. Li, J. Liu, *Adv. Synth.*

- Catal.* **2019**, *361*, 44; e) D. Liang, L. Rao, C. Xiao, J.-R. Chen, *Org. Lett.* **2019**, *21*, 8783; f) F. Zhou, Y. Cheng, X.-P. Liu, J.-R. Chen, W.-J. Xiao, *Chem. Commun.* **2019**, *55*, 3117; g) M. M. D. Pramanik, F. Yuan, D.-M. Yan, W.-J. Xiao, J.-R. Chen, *Org. Lett.* **2020**, *22*, 2639; h) D. Liang, L.-P. Tan, W.-J. Xiao, J.-R. Chen, *Chem. Commun.* **2020**, *56*, 3777; i) T.-B. Hua, F. Chao, L. Wang, C.-Y. Yan, C. Xiao, Q.-Q. Yang, W.-J. Xiao, *Adv. Synth. Catal.* **2020**, *362*, 2615; j) L. Chen, X.-Y. Liu, J. Zhang, L. Duan, Z. Wen, H.-L. Ni, *Adv. Synth. Catal.* **2021**, *363*, 3006.
- [10] We have reported that the [2+2] cyclization of alkynes with $\text{Tf}_2\text{C}=\text{CH}_2$ formed bis(triflyl)cyclobutenes: B. Alcaide, P. Almendros, I. Fernández, C. Lázaro-Milla, *Chem. Commun.* **2015**, *51*, 3395.
- [11] a) J. Atzrodt, V. Derau, W. J. Kerr, M. Reid, *Angew. Chem. Int. Ed.* **2018**, *57*, 1758; *Angew. Chem.* **2018**, *130*, 1774; b) A. L. Garreau, H. Zhou, M. C. Young, *Org. Lett.* **2019**, *21*, 7044; c) P. Eisele, F. Ullwer, S. Scholz, B. Plietker, *Chem. Eur. J.* **2019**, *25*, 16550; d) X. Han, J. Hu, C. Chen, Y. Yuan, Z. Shi, *Chem. Commun.* **2019**, *55*, 6922; e) X. Zhang, Q. Chen, R. Song, J. Xu, W. Tian, S. Li, Z. Jin, Y. R. Chi, *ACS Catal.* **2020**, *10*, 5475; f) Zo. P. Vang, S. J. Hintzsche, J. R. Clark, *Chem. Eur. J.* **2021**, *27*, 9988.
- [12] Please, see Supporting Information (pictures of TLC plates) for the extremely clean reaction crudes.
- [13] The formation of intermediate aza-ortho-quinone methide INT-I from alkenols **2** and **8** may be catalyzed by bis(trifluoromethyl)sulfonyl methane **A**, which arises from betaine **1** in presence of water, and should be ascribed to its acidic nature. For the use of Tf_2CH -based carbon acid **1** as acid catalysis in Mukaiyama aldol reaction by Yanai et al., see Ref. [6b].

Manuscript received: June 23, 2021

Version of record online: August 10, 2021