Check for updates

TBAF-promoted carbanion-mediated sulfonamide cyclization of CF₃-substituted *N*-allenamides: an access to fluorinated γ-sultams†

Clément Gommenginger, [ID] [a] Yongxiang Zheng,[a] Daniele Maccarone, [ID] [b] Ilaria Ciofini[b] and Laurence Miesch [ID] *[a]

Upon treatment with TBAF, CF₃-substituted *N*-allenamides were transformed into γ-sultams. Cyclic sulfonamides bearing an ene-*gem*-difluorinated tether could be obtained by addition of acetic acid to the ammonium salt whereas TBAF alone provided the corresponding trifluorinated ethyl sultams. A combined experimental and computationnal mechanistic study suggested that this transformation involves a 5-*endo-dig* cyclization on the ene-ynamide generated *in situ*.

Introduction

Since the discovery of sulfonamide antibacterials,[1] sulfonamides have played a key role in medicinal chemistry. The cyclic counterparts of sulfonamide compounds (sultams) display enhanced biological activities compared to their acyclic congeners.[2] Although not found in nature, these amide surrogates are considered privileged motifs that have found diverse applications in drug discovery such as in sultiame, an anticonvulsant agent,[3] S-2474, a non-steroidal anti-inflammatory drug,[4] taurolidine, which exhibits antimicrobial and anticancer activities,[5] a naphthyridine derivative that is an HIV-1 inhibitor,[6] and an antidiabetes agent developed by Boehringer Ingelheim (Fig. 1).[7]

In view of this important structural motif, numerous methods for their synthesis have been developed. The carbanion-mediated sulfonate (or sulfonamide) cyclization constitutes a well-known approach to these important scaffolds (Scheme 1A).[8]

In this process, the carbanion resulting from deprotonation of the proton located at the α-position of the SO₂ group reacts with a suitable electrophile to form various cyclic sulfonamides. Intramolecular Diels–Alder cycloadditions of vinylsulfonamides have proven to be essential to construct specific sultams (Scheme 1B).[9] Although effective, these protocols require strong bases and harsh reaction conditions often detrimental to sensitive functional groups. Transition-metal catalyzed-processes,[10] including intramolecular Heck reactions of α-bromovinylsulfonamides,[11] rhodium-catalyzed intramolecular aziridination of unsaturated sulfonamides,[12] as well as ring-closing metathesis,[10,13] have emerged as powerful methods to prepare cyclic sulfonamides (Scheme 1C). Recently, Mykhailiuk reported a photochemical cyclization providing access to a new class of bicyclic sultams (Scheme 1D).[14] Related to this present work, it is important to mention Cui's contribution, who observed an unusual reorganization divergence on *N*-sulfonyl ynamides upon basic treatment *via* a 4-*exo-dig* cyclization and subsequent 1,3 sulfonyl-migration (Scheme 1E).[15] Because organofluorine compounds play a critical role in life science and agrochemistry, the judicious introduction of fluorine atoms into organic molecules has become an increasingly dominant research area.[16] In particular, the *gem*-difluoro-ene group, a mimic of carbonyl compounds,[17] and the CF₃ moiety are attractive
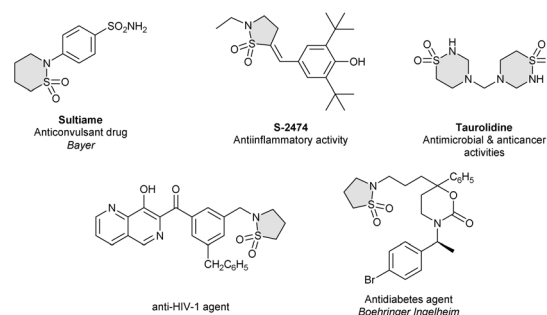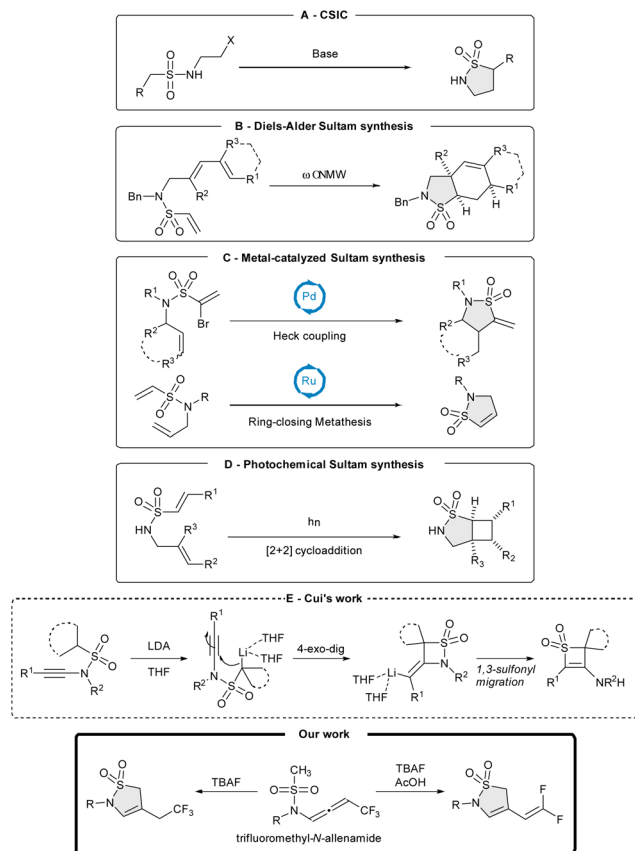
[a]Equipe Synthèse Organique et Phytochimie, Institut de Chimie, CNRS-UdS, UMR 7177, 4 rue Blaise Pascal, CS 90032, 67081 Strasbourg, France. E-mail: lmiesch@unistra.fr

[b]Chimie ParisTech, PSL University, CNRS, Institute of Chemistry for Life and Health Sciences, Chemical Theory and Modelling Group, F-75005 Paris, France

Fig. 1 Biologically active sultams.

This journal is © the Partner Organisations 2023

Org. Chem. Front., 2023, **10**, 4055–4060 | **4055**

Scheme 1 Synthetic routes to γ-sultams.

targets because of their impact on the development of marketed drugs.[18]

In view of our previous results on CF$_3$-substituted *N*-allenamides, we anticipated that deprotonation at the α-position of the sulfonyl moiety of *N*-sulfonyl-allenamides might initiate an anionic 5-*endo-dig* cyclization to produce cyclic sulfonamides.

We report herein a tetra-*n*-butylammonium fluoride (TBAF)-promoted cyclization of CF$_3$-substituted *N*-sulfonyl-allenamides for the preparation of trifluoethyl-substituted and difluoro-ene sultams (Scheme 1). Trifluoromethylated *N*-allenamides were obtained by treatment of terminal ynamides with trifluoromethylated diazomethane according to our previously developed strategy.[19]

Results and discussion

In consideration of the work of Cui *et al.*,[15] who noticed that the deprotonation of the α-position if the sulfonyl moiety of *N*-sulfonyl ynamides initiated a 4-*exo-dig* cyclization, we performed our first experiment by treatment of trifluoromethylated *N*-allenamide **1a** with lithium diisopropylamide (LDA) in THF. In this case, only the corresponding ene-ynamide **6** was observed along with some stating material (Table 1, entry 1).[20] By employing weaker bases such as Cs$_2$CO$_3$, the starting

Table 1 Optimization

Entry[a]	Base ([equiv.])	Acid ([equiv.])	Yield[b] [%]		
			2a	**3a**	**1a**
1[c]	LDA (1.2)	—	—	—	30
2	Cs$_2$CO$_3$ (1.2)	—	—	—	100
3[d]	TBAF (1)	—	14	41	27
4	TBAF (5)	—	—	57	—
5	TBAF (5)	BF$_3$·OEt$_2$ (3)	55	13	—
6	TBAF (5)	TMSOTf (1.2)	43	7	37
7	TBAF (5)	FeCl$_3$ (5)	35	26	—
8	TBAF (5)	TfOH (4.5)	45	11	—
9	TBAF (5)	TFA (2.5)	36	26	—
10	TBAF (5)	AcOH (5)	69	*Traces*	—
11[e]	—	TFA (5)	—	—	—
12[e]	—	TfOH (5)	—	—	—
13	—	AcOH (5)	—	—	>98
14[f]	—	HF (cat.)	—	—	—

[a] Reaction conditions: to a solution of **1a** (0.25 mmol) in THF (2 mL), was added a solution of TBAF (1 M in THF, 1.25 mmol) at 23 °C, and the mixture was stirred for 18 h. [b] Isolated yields. [c] The mixture was stirred from −78 °C to 0 °C for 1 day. The corresponding ene-ynamide **6** was observed in mixture with **1a**. [d] The mixture was stirred for 1 h instead 18 h. [e] Only degradation of starting material was observed. [f] 94% of mesylsulfonamide was isolated.
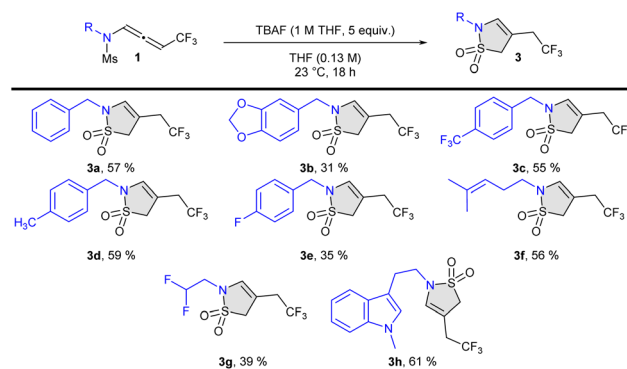
material was totally recovered (Table 1, entry 2). Taking into consideration these results, we wondered whether tetraalkyl ammonium fluoride salts would provide an efficient solution to this problem. When TBAF was employed as a base, we noticed that a mixture of two cyclic unsaturated sulfonamides, a CF$_3$-substituted and an ene-difluorinated sultam, **3a** and **2a**, respectively, were isolated along with some starting material **1a** (Table 1, entry 3). By increasing the amount of TBAF, this transformation was exclusively directed toward the formation of CF$_3$-substituated sultam **3a** (Table 1, entry 4). To guide the reaction solely toward the difluorinated ene product **2a**, our objective was to quench the released fluoride ion with an acid to avoid the re-introduction of the fluoride ion on the difluorinated ene moiety.[20] First trials were carried out with a Lewis acid. Whether with BF$_3$·Et$_2$O, TMSOTf, or FeCl$_3$ (Table 1, entries 5–7), the outcome of this transformation led to a mixture of compounds **2a** and **3a**, albeit the selectivity is poorer with the latter. We then turned our attention to the utilization of a Brønsted acid. Triflic acid (TfOH) and trifluoroacetic acid (TFA) led to a mixture of sultams **2a** and **3a**, whereas acetic acid provided the desired difluorinated ene-sultam **2a** with 69% yield along with traces of the trifluorinated derivative **3a** (Table 1, entries 8–10). Controlled experiments with Brønsted acids such as TFA and TfOH alone led to degradation of the starting material (Table 1, entries 11 and 12), whereas with acetic acid the starting material was totally recovered (Table 1, entry 13). When CF$_3$-substituted *N*-allenamide **1a** was subjected to hydrofluoric acid (HF), the corresponding mesylsulfonamide was exclusively isolated (Table 1, entry 14).

4056 | *Org. Chem. Front.*, 2023, **10**, 4055–4060

This journal is © the Partner Organisations 2023

Under the optimized conditions, the reaction scope of this 5-*endo-dig* cyclization was examined. First, we investigated the chemical space of the unsaturated ene-difluorinated sultams. Linear alkyls (**2b**) and cyclic alkyls (**2c–e**) were tolerated for this transformation. Aryl substituents (**2a–j**) were accommodated as well. Pleasingly, functionalized sidechains suitable for late-stage transformations could be installed on the sultam ring through this transformation. In particular, unsaturated side-chains (**2k–2l**), protected aldehydes (**2m**), di- and tri-fluorinated sidechains (**2n–o**), and ferrocenyl derivatives (**2p**)[21] were successfully adapted (Scheme 2). X-Ray analysis of **2p** confirmed the structure of the difluoro-ene sultam (CCDC 2259326† contains the supplementary crystallographic data for the structure).[22]

We then focused on access of the unsaturated sultams to products bearing a CF_3-tether. Aryl derivatives (**3a–e**), unsaturated sidechains (**3f**), di-fluorinated sidechains (**3g**), as well as tryptamine derivatives (**3h**) could be adapted, albeit with lower yields because of instability of the targeted compounds (Scheme 3).

To gain greater insight into the reaction mechanism, a series of control experiments were performed. When the difluorinated substrate **1a** was exposed to the same reaction conditions, *i.e.*, TBAF/AcOH, the corresponding sultam was not observed; the monofluorinated ene-ynamide **5** was exclusively obtained in 88% yield as a 3 : 1 mixture of *E*- and *Z*-compounds. We have recently demonstrated that *gem*-difluorinated ene-ynamides **6** could be obtained directly through base-induced treatment of trifluoromethylated *N*-allenamides.[20] Additionally, when the difluorinated ene-ynamide **6** was treated under the same conditions (*i.e.*, a
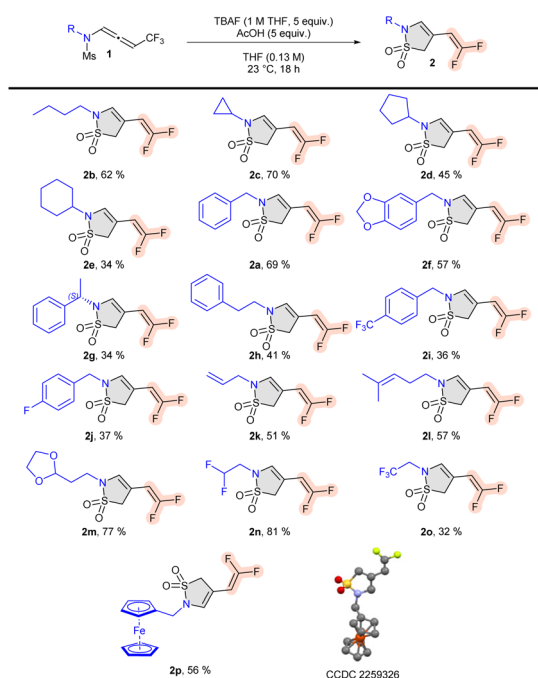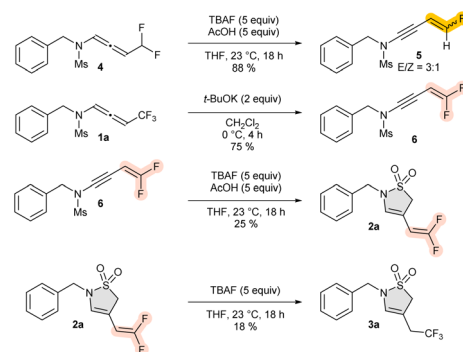
mixture of TBAF and AcOH) the corresponding ene-difluorinated sultam **2a** was obtained, providing evidence that the ene-ynamide species **6** is an intermediate of the transformation. It is also possible to achieve the synthesis of CF_3-substituted sultam **3a** directly from the ene-difluorinated sultam **2a**, which reinforces the theory that the fluoride ion must be quenched to access to sultams bearing an ene-difluorinated tether (Scheme 4).[23]

Based on the aforementioned experimental results, calculations based on Density Functional Theory (DFT) were performed to provide support for a plausible reaction mechanism. A simplified reaction scheme is depicted in Scheme 5, while the full computed reaction profile is reported in Scheme 6. Thanks to the presence of fluoride ions in the reaction medium, the *N*-allenamide **1-A** is deprotonated α to the nitrogen, thus allowing a subsequent δ-elimination of a fluoride ion, providing difluorinated ene-ynamide **2-A**. This is consistent with the formation of compound **5** (Scheme 4). Ylide **3-A** is generated *in situ* through an HF-catalyzed process.[24] 5-*endo-dig* addition of ylide **3-A** on the ynamide part of the molecule provides γ-sultam with a *gem*-difluorinated ene-tether **4-A**. Further addition of the fluoride ion on compound **4-A** led finally to the trifluorinated adduct **6-A** *via* compound **5-A** (Scheme 5).

The full computed energy profile reported in Scheme 6 is more complex because of the formation of a larger number of reaction intermediates (refer to ESI† for Computational

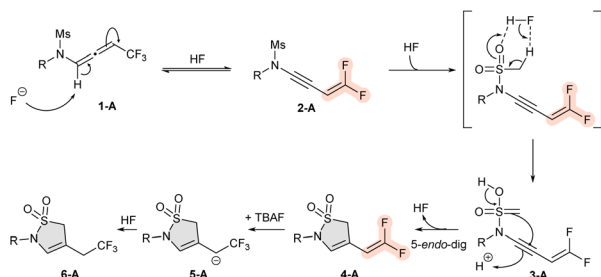**Scheme 3** Scope of the synthesis trifluorinated γ-sultams.

Scheme 2 Scope of the synthesis *gem*-difluorinated γ-sultams.

Scheme 4 Mechanistic insights.

This journal is © the Partner Organisations 2023

Org. Chem. Front., 2023, **10**, 4055–4060 | **4057**

Scheme 5 Schematic representation of the proposed mechanism.

details). Nonetheless, it reveals that the energetically demanding step is the deprotonation, with an energetic barrier of about 29 kcal mol⁻¹. Once the deprotonation has taken place, the reaction proceeds toward the thermodynamically more stable products with barriers all below 20 kcal mol⁻¹. It is also important to stress the role played by the F⁻/HF pair in stabilizing the different reaction intermediates and transition states (TS). Analysis of the evolution of the carbon–carbon bonds (reported in the ESI†) along the molecular skeleton indicates that starting from the allene **1-A** (showing two C–C double bonds of 1.306 Å for the allene and single bond of 1.488 Å), a triple- (1.208 Å) single- (1.409 Å) and double bond (1.330 Å) are formed in intermediates **2-A** and **3-A** before the formation of the cyclic product.

From intermediate **3-A**, cyclization to yield a four-membered ring was also tested (see ESI†). Nonetheless, the associ-
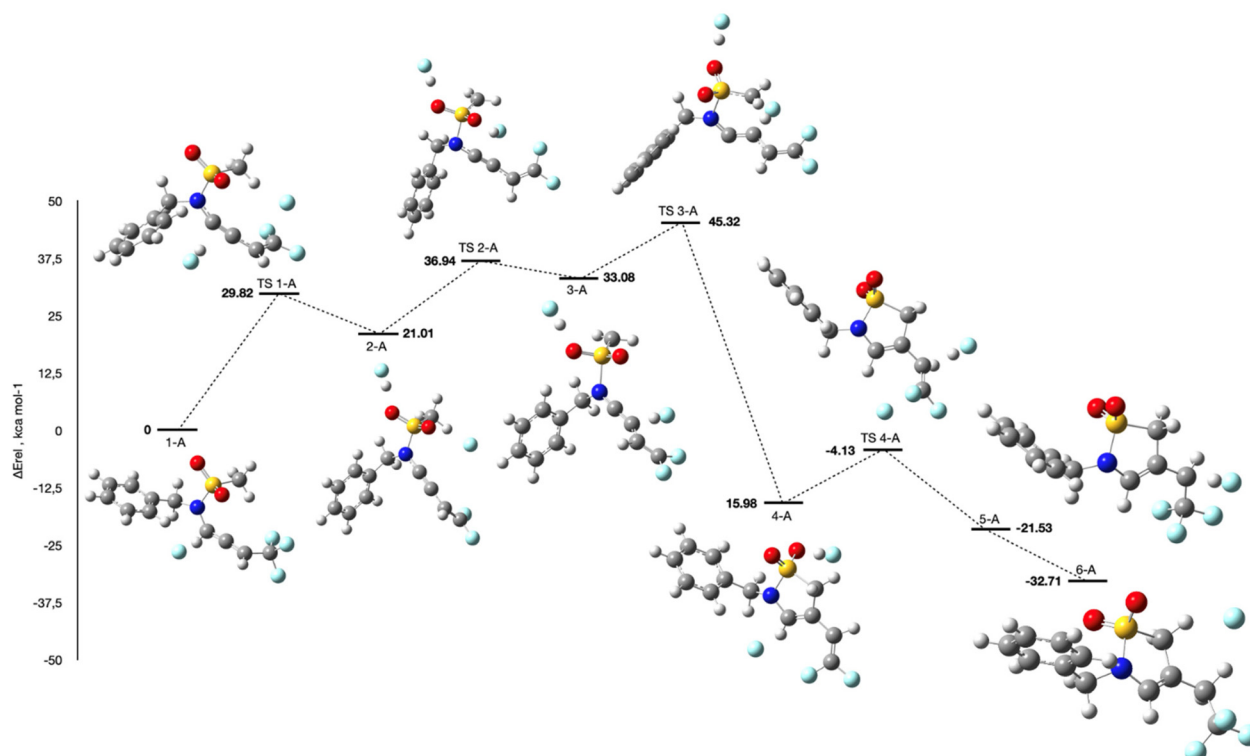
ated TS is higher in energy with respect to the corresponding one leading to the formation of the experimentally observed sultam, and the four-membered ring product is less stable than compound **4-A** by about 12 kcal mol⁻¹. Calculations performed on the analogous difluorinated substrate (see ESI†) show that while the reaction barrier associated with the deprotonation of the proton α to the nitrogen is relatively similar, the transition state for the cyclization step is actually much higher (roughly 40 kcal mol⁻¹), thus impeding the formation of the corresponding sultam as experimentally observed.

Conclusions

In conclusion, we have developed a mild and efficient access to trifluorinated- and ene-*gem*-difluorinated γ-sultams from CF₃-substituted *N*-allenamides. Addition of TBAF allowed the formation of CF₃-substituted sultams, whereas addition of acetic acid to the ammonium salt led to the formation of cyclic sulfonamides bearing a difluorinated ene moiety. The developed strategy shows broad functional group tolerance and a good substrate scope. Furthermore, DFT calculations corroborated a transformation proceeding by a 5-*endo*-dig cyclization on the ene-ynamide formed *in situ*.

Conflicts of interest

There are no conflicts to declare.

Scheme 6 Computed reaction pathway (relatives energies in kcal mol⁻¹).

4058 | *Org. Chem. Front.*, 2023, **10**, 4055–4060

This journal is © the Partner Organisations 2023

Author contributions

L. M., C. G., and Y. Z. conceived and designed the experiments. L. M. directed the project. C. G. performed the experiments. I. C. and D. M. performed the DFT calculations. L. M. and I. C. wrote the paper. L. M., I. C., Y. Z., C. G., and D. M. discussed the results and commented on the manuscript.

Acknowledgements

References

1 J. E. Lesch, *The First Miracle Drugs: How the Sulfa Drugs Transformed Medicine*, Oxford University Press, Oxford, 2007.

2 S. Debnath and S. Mondal, Sultams: Recent Syntheses and Applications, *Eur. J. Org. Chem.*, 2018, 933–956.

3 K. M. Gorman and A. Shahwan, Sultiame revisited: treatment of refractory absence seizures, *Epileptic Disord.*, 2016, **18**, 329–330.

4 M. Inagaki, T. Tsuri, H. Jyoyama, T. Ono, K. Yamada, M. Kobayashi, Y. Hori, A. Arimura, K. Yasui, K. Ohno, S. Kakudo, K. Koizumi, R. Suzuki, M. Kato, S. Kawai and S. Matsumoto, Novel Antiarthritic Agents with 1,2-Isothiazolidine-1,1-dioxide (γ-Sultam) Skeleton: Cytokine Suppressive Dual Inhibitors of Cyclooxygenase-2 and 5-Lipoxygenase, *J. Med. Chem.*, 2000, **43**, 2040–2048.

5 (*a*) P. M. Neary, P. Hallihan, J. H. Wang, R. W. Pfirrmann, D. J. Bouchier-Hayes and H. P. Redmond, The Evolving Role of Taurolidine in Cancer Therapy, *Ann. Surg. Oncol.*, 2010, **17**, 1135–1143; (*b*) Y. Liu, A.-Q. Zhang, L. Cao, H.-T. Xia and J.-J. Ma, Taurolidine Lock Solutions for the Prevention of Catheter-Related Bloodstream Infections: A Systematic Review and Meta-Analysis of Randomized Controlled Trials, *PLoS One*, 2013, **8**, e79417.

6 L. Zhuang, J. S. Wai, M. W. Embrey, T. E. Fisher, M. S. Egbertson, L. S. Payne, J. P. Guare, J. P. Vacca, D. J. Hazuda, P. J. Felock, A. L. Wolfe, K. A. Stillmock, M. V. Witmer, G. Moyer, W. A. Schleif, L. J. Gabryelski, Y. M. Leonard, J. J. Lynch, S. R. Michelson and S. D. Young, Design and Synthesis of 8-Hydroxy-[1,6]Naphthyridines as Novel Inhibitors of HIV-1 Integrase in Vitro and in Infected Cells, *J. Med. Chem.*, 2003, **46**, 453–456.

7 D. A. Claremon, L. Zhuang, K. Leftheris, C. M. Tice, Y. Ye, S. B. Singh and F. Himmelsbach, Cyclic inhibitors of 11BETA-hydroxysteroid dehydrogenase 1, US 8592410B2, 2013.

8 (*a*) D. Postel, A. N. Van Nhien and J. L. Marco, Chemistry of Sulfonate- and Sulfonamide-Stabilized Carbanions – The

CSIC Reactions, *Eur. J. Org. Chem.*, 2003, 3713–3726; (*b*) A. V. Dobrydnev and J. Marco-Contelles, Updating the CSIC Reaction (2003–2020), *Eur. J. Org. Chem.*, 2021, 1229–1248.

9 (*a*) P. Metz, D. Seng, R. Fröhlich and B. Wibbeling, Intramolecular Diels-Alder Reactions of Vinylsulfonamides, *Synlett*, 1996, 741–742; (*b*) A. D. Brosius, L. E. Overman and L. Schwink, Total Synthesis of (+)-Aloperine. Use of a Nitrogen-Bound Silicon Tether in an Intramolecular Diels–Alder Reaction, *J. Am. Chem. Soc.*, 1999, **121**, 700–709.

10 A. Zhou, D. Rayabarapu and P. R. Hanson, "Click, Click, Cyclize": A DOS Approach to Sultams Utilizing Vinyl Sulfonamide Linchpins, *Org. Lett.*, 2009, **11**, 531–534.

11 S. Merten, R. Fröhlich, O. Kataeva and P. Metz, Synthesis of Sultams by Intramolecular Heck Reaction, *Adv. Synth. Catal.*, 2005, **347**, 754–758.

12 J.-L. Liang, S.-X. Yuan, P. W. H. Chan and C.-M. Che, Rhodium(II,II) Dimer as an Efficient Catalyst for Aziridination of Sulfonamides and Amidation of Steroids, *Org. Lett.*, 2002, **4**, 4507–4510.

13 (*a*) S. Hanessian, H. Sailes and E. Therrien, Synthesis of functionally diverse bicyclic sulfonamides as constrained proline analogues and application to the design of potential thrombin inhibitors, *Tetrahedron*, 2003, **59**, 7047–7056; (*b*) S. Mondal and S. Debnath, Synthesis of Sultams by Ring-Closing Metathesis, *Synthesis*, 2014, 368–374.

14 D. Dibchak, V. Shcherbacova, A. V. Denisenko and P. K. Mykhailiuk, Convenient Access to Conformationally Rigid Sultams, *Org. Lett.*, 2019, **21**, 8909–8914.

15 L. Zeng, Y. Lin, J. Li, H. Sajiki, H. Xie and S. Cui, Skeletal reorganization divergence of *N*-sulfonyl ynamides, *Nat. Commun.*, 2020, **11**, 5639–5649.

16 (*a*) J.-P. Bégué and D. Bonnet-Delpon, *Bioorganic and Medicinal Chemistry of Fluorine*, Wiley, Hoboken, NJ, 2008; (*b*) W. K. Hagmann, The Many Roles for Fluorine in Medicinal Chemistry, *J. Med. Chem.*, 2008, **51**, 4359–4369; (*c*) P. Kirsch, *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*, Wiley-VCH, Weinheim, Germany, 2nd edn, 2013.

17 N. A. Meanwell, Synopsis of Some Recent Tactical Application of Bioisosteres in Drug Design, *J. Med. Chem.*, 2011, **54**, 2529–2591.

18 (*a*) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok and H. Liu, Fluorine in Pharmaceutical Industry: Fluorine-Containing Drugs Introduced to the Market in the Last Decade (2001–2011), *Chem. Rev.*, 2014, **114**, 2432–2506; (*b*) H. Mei, J. Han, S. Fustero, M. Medio-Simon, D. M. Sedgwick, C. Santi, R. Ruzziconi and V. A. Soloshonok, Fluorine-Containing Drugs Approved by the FDA in 2018, *Chem. – Eur. J.*, 2019, **25**, 11797–11819.

19 Y. Zheng, B. Moegle, S. Ghosh, A. Perfetto, D. Luise, I. Ciofini and L. Miesch, Copper-Catalyzed Synthesis of Terminal *vs.* Fluorine-Substituted *N*-Allenamides *via* Addition of Diazo Compounds to Terminal Ynamides, *Chem. – Eur. J.*, 2022, **28**, e202103598.

This journal is © the Partner Organisations 2023

Org. Chem. Front., 2023, **10**, 4055–4060 | **4059**

20 M. Hourtoule and L. Miesch, Regio- and Stereoselective Addition to *gem*-Difluorinated Ene–Ynamides: Access to Stereodefined Fluorinated Dienes, *Org. Lett.*, 2022, **24**, 3896–3900.

21 C. Mahe, O. Blacque, G. Gasser, V. Gandon and K. Cariou, *N*-Metallocenyl Ynamides: Preparation, Reactivity, and Synthesis of *ansa*[3]-Ferrocenylamides, *Org. Lett.*, 2023, **25**, 624–629.

22 CCDC 2259326 (**2p**) contains the supplementary crystallographic data for this paper.†

23 Y. Qiao, T. Si, M.-H. Yang and R. A. Altman, Metal-Free Trifluoromethylation of Aromatic and Heteroaromatic Aldehydes and Ketones, *J. Org. Chem.*, 2014, **79**, 7122–7131.

24 A. J. Mota, A. Klein, F. Wendling, A. Dedieu and M. Miesch, Controlled Synthesis of α-Allenic Ester and Spiro Ketone Derivatives from Tailored α-Substituted Cycloalkanones Through Cascade Reactions: Exploring the Possible Reaction Pathways by Means of Semiempirical MO Calculations, *Eur. J. Org. Chem.*, 2005, 4346–4358.

4060 | *Org. Chem. Front.*, 2023, **10**, 4055–4060

This journal is © the Partner Organisations 2023