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DABCO-promoted highly diastereo- and regioselective construction of C-3 functionalized spirooxindoles via [3 + 2] cycloaddition of 2-aryl/heteroarylidene-1*H*-indene-1,3(2*H*)-diones with *N*-2,2,2-trifluoroethylisatin ketimines at ambient conditions[†]

Madavi S. Prasad, ^a Sankar Bharani, ^a Syed Mastan Sharief, ^a Mudavath Ravi, ^a Murugesan Sivaprakash, ^a Biplob Borah ^b and L. Raju Chowhan ^{*b}

The application of 2-aryl/heteroarylidene-1*H*-indene-1,3(2*H*)-dione as an activated olefin source in the DABCO-catalyzed [3 + 2] cycloaddition with *N*-2,2,2-trifluoroethylisatin ketimines has been disclosed. This highly efficient 1,3-dipolar cycloaddition reaction offered a variety of trifluoro methyl group bearing spiro-pyrrolidine linked oxindoles with four consecutive stereocentres in good to excellent yield and excellent diastereoselectivity. The synthetic practicality of the protocol was established by demonstrating the enantioselective construction of spiro-pyrrolidine-oxindoles with two vicinal spiro-quaternary chiral centres in good yield excellent enantioselectivity (>90% ee) by using ultralow loading of quinine as the catalyst at room temperature.

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Introduction

Spirocyclic compounds, especially spirooxindoles, which are categorized by a tetrahedral sp^3 -hybridized carbon atom at the C-3 position of an orthogonally structured bicyclic structure, have recently drawn tremendous interest in the research and development area of pharmaceuticals, organic, and medicinal chemistry.¹ These structural scaffolds are well-featured in a wide variety of natural alkaloids, and synthetic drug candidates.² Because of the occurrences of their sp^3 -hybridized quaternary stereocenters at the 3-position, spirooxindoles have often offered excellent lipophilicity, stereochemical geometry, and increased binding potential with many receptors as compared to planar aromatic rings.³ Representative examples of some potential pharmacologically active natural alkaloids and synthetic drug candidates bearing spiro-pyrrolidine oxindoles as the core structure are represented in Fig. 1.⁴

On the other hand, the incorporation of fluorine either as a single molecule or as a substituted molecule into organic

compounds either alters or enhances the properties of the parent material, and the resulting compounds may generally display promising metabolic stability, binding potential, stereochemical integrity, or even unprecedented properties.⁵ Particularly, the installation of the CF_3 group adjacent to the nitrogen atom located at the α -position affects the binding potential of the drug receptor by reducing the alkalinity of the amide group.^{6–10}

Recognizing the broad chemical landscape, the significant potential of spiro-pyrrolidine oxindoles, the immense importance of fluorine-containing molecules, and the development of

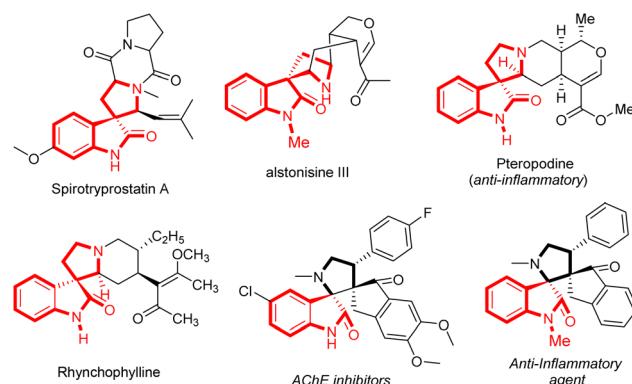


Fig. 1 Representative examples of bioactive spiro-pyrrolidine oxindole scaffolds.

^aAsymmetric Synthesis and Catalysis Laboratory, Department of Chemistry, Central University of Tamil Nadu (CUTN), Tiruvarur-610 005, India

^bSchool of Applied Material Sciences, Centre for Applied Chemistry, Central University of Gujarat, Sector-30, Gandhinagar-382030, Gujarat, India. E-mail: rchowhan@cug.ac.in

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an elegant synthetic strategy for the expeditious stereodivergent construction of spirooxindoles embedded with the fluorine-containing group as the key moiety is highly desired.

For the construction of carbon–carbon, carbon–heteroatom bonds, as well as spirocyclic compounds, the 1,3-dipolar cycloaddition reaction has been demonstrated as one of the most fundamental approaches in organic chemistry.¹¹ Intriguingly, many 1,3-dipoles, including azomethine ylides,¹² nitrones,¹³ carbonyl ylides,¹⁴ and others, have been extensively discovered and explored in cycloaddition reactions throughout the past few decades. Among them, recently, *N*-2,2,2-trifluoroethylisatin ketimines which are easily accessible and highly reactive azomethine ylide precursors¹⁵ have been successfully employed in many 1,3-dipolar cycloadditions with various activated olefins and has been demonstrated as one of the efficient approaches for the stereoselective construction of spiro-pyrrolidine oxindoles. In 2015, Wang *et al.*, introduced *N*-2,2,2-trifluoroethylisatin ketimines as a new type of 1,3-dipoles which was demonstrated for the assembly of spiro[pyrrolidin-3,2'-oxindole] by a secondary amine catalyzed enantioselective [3 + 2] cycloaddition with enals (Scheme 1a).¹⁵ In 2020, Zhou *et al.*, disclosed the utilization of 4-oxo-4H-chromene-3-carboxylic acid as the dipolarophiles in the 1,3-dipolar cycloaddition with *N*-2,2,2-trifluoroethylisatin ketimines for the assembly of various chromone fused spiro-pyrrolidine oxindoles (Scheme

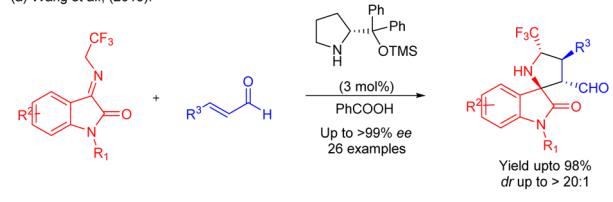
1b).¹⁶ The exploitation of chalcone types of compounds for the [3 + 2] cycloaddition with *N*-2,2,2-trifluoroethylisatin ketimines was developed by Wang *et al.*, which also leads to the formation of spirooxindoles in good yields with excellent diastereoselectivity (Scheme 1c).¹⁷ However, the expeditious construction of spiro-pyrrolidine oxindoles from 2-aryl/heteroarylidene-1*H*-indene-1,3(2*H*)-dione as the dipolarophiles was not reported so far. Here, we have demonstrated the DABCO-catalyzed highly efficient and diastereoselective [3 + 2] cycloaddition of *N*-2,2,2-trifluoroethylisatin ketimines with 2-arylidene-1*H*-indene-1,3(2*H*)-dione as the dipolarophiles for the facile construction of diverse spiro-pyrrolidine oxindoles fused with indeno moiety for the first time (Scheme 1d).

Results and discussion

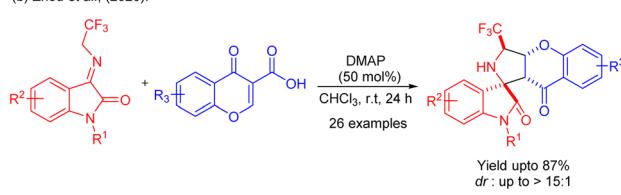
Our initial investigation for optimizing the reaction conditions starts with the execution of the reaction of *N*-2,2,2-trifluoroethylisatin ketimines **1a** and 2-benzylidene-1*H*-indene-1,3(2*H*)-dione **2a** as the model substrate and the reaction was carried out in presence of different catalytic systems as well as solvent systems at room temperature (Table 1). Using 5 mol% of triethylamine **3a** as the basic catalyst, the reaction afforded the corresponding spiro-pyrrolidine oxindole **4a** in 37% yield with 8 : 1 dr after 1 hour (Table 1, entry 1). Then we examined the

Previous Work:

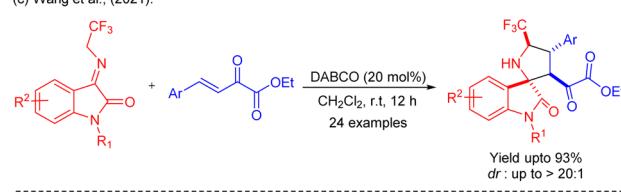
(a) Wang *et al.*, (2015):



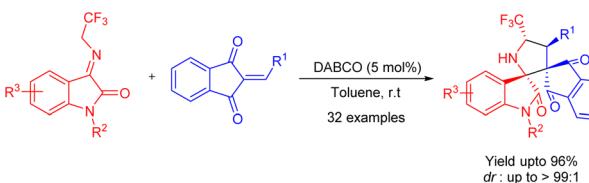
(b) Zhou *et al.*, (2020):



(c) Wang *et al.*, (2021):

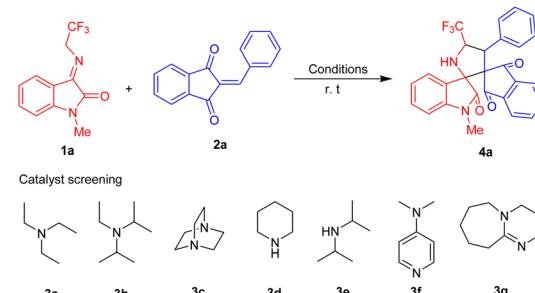


(d) This Work:



Scheme 1 Previous strategy for the construction of spirooxindoles via 1,3-dipolar cycloaddition reactions and the current approach.

Table 1 Optimization of [3 + 2] annulation reaction^a



Entry	Catalyst	Solvent	Time (h)	Yield ^b (%)	dr ^c
1	3a	Chloroform	1	37	8 : 1
2	3b	Chloroform	2	23	4 : 1
3	3c	Chloroform	38	60	>20 : 1
4	3d	Chloroform	6	52	6 : 1
5	3e	Chloroform	4	45	6 : 1
6	3f	Chloroform	10	10	4 : 1
7	3g	Chloroform	3	36	6 : 1
8	3c	Toluene	5	64	>99 : 1
9	3c	Dioxane	43	51	>99 : 1
10	3c	Hexane	13	56	>20 : 1
11	3c	Acetonitrile	26	15	>20 : 1
12 ^{d,e}	3c	Toluene	5	91	>99 : 1

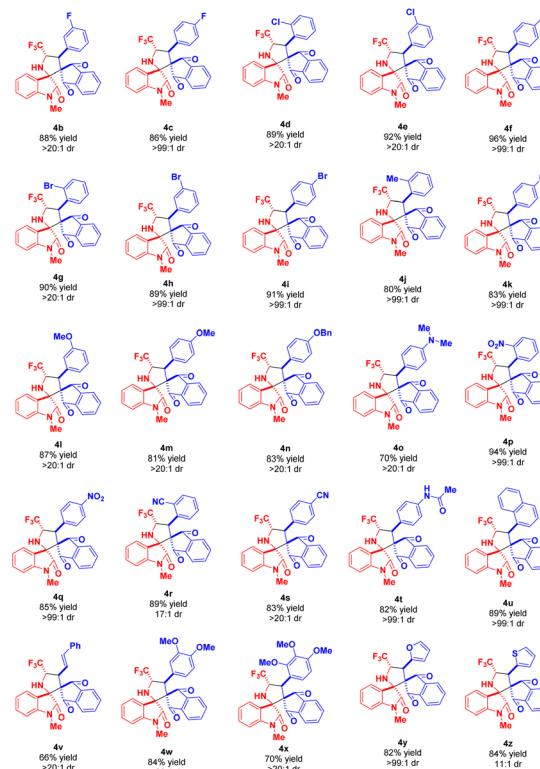
^a Unless otherwise mentioned, all the reactions were performed using **1a** (0.11 mmol), **2a** (0.1 mmol), and catalyst **3a–g** (0.005 mmol), in 0.2 M solvent at room temperature. ^b Yield refers to the column purified product. ^c dr was determined for crude product **4a** by ¹H NMR analysis. ^d Yield refers to the centrifuge-purified product. ^e dr was determined for purified product **4a** by ¹H NMR analysis.



efficiency of various amine catalysts such as *N*-ethyl-*N*-isopropylpropan-2-amine **3b** (Table 1, entry 2), DABCO **3c** (Table 1, entry 3), piperidine **3d** (Table 1, entry 4), diisopropylamine **3e** (Table 1, entry 5), *N,N*-dimethylpyridin-4-amine **3f** (Table 1, entry 6), and catalyst **3g** (Table 1, entry 7) in chloroform as the solvent system for the model reaction at room temperature. A quick survey of the results disclosed in the Table 1 revealed that the reaction conducted in presence of catalysts **3b**, **3d**, **3e**, **3f**, and **3g** leads to a lower yield of product **4a** and necessitates longer reaction time. However, surprisingly it was noticed that using DABCO as the catalyst which also required 38 hours to complete conversion of the product **4a**, excellent diastereoselectivity ($>20 : 1$ dr) was achieved (Table 1, entry 3). Inspired by this result, then we carried out the reaction by changing the solvent system from chloroform to dioxane, hexane, acetonitrile, and toluene for optimizing the appropriate solvent for the model reaction. With 5 mol% of DABCO as the catalyst and dioxane as the solvent, an increase in the diastereoselectivity was observed albeit with a low yield of the product even after 43 hours (Table 1, entry 9). The screening of hexane and acetonitrile also furnished the product with a very low yield (Table 1, entry 10–11). To our delight, the reaction in presence of toluene pleasingly afforded the desired product **4a** in 91% yield with $>99 : 1$ dr after 5 hours (Table 1, entry 12). On the other hand, increasing or decreasing the catalyst loading had no auspicious effects on the rate of the reaction. Consequently, the utilization of 5 mol% of DABCO as the catalyst and toluene as the solvent was recognized as the best optimum condition for this cycloaddition addition reaction.

After ascertaining the standard reaction condition, the feasibility of the protocol was investigated by executing the reaction with different *N*-2,2,2-trifluoroethylisatin ketimines and 2-aryl/heteroarylidene-1*H*-indene-1,3(2*H*)-dione. At first, the efficiency of various 1*H*-indene-1,3(2*H*)-dione ring bearing diverse electron-withdrawing group at the different positions of R¹ were well tolerated under the standard reaction condition and deliver the products **4b**–**4i** in good to excellent yield with excellent diastereoselectivity up to $>99 : 1$ (Table 2, entry **4b**–**4i**). The best yield of the product was obtained for 4-

Table 2 Reaction scope of indane-1,3-dione enophile **2b**–**2z** with ketimine **1a**^{a,b,c,d}



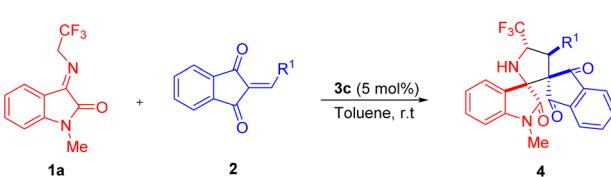
^a Unless otherwise mentioned, all the reactions were performed using **1** (0.11 mmol), **2** (0.1 mmol), and catalyst **3c** (0.005 mmol), in 0.2 M of toluene at room temperature. ^b Yield refers to the purified product.

^c dr was determined for purified product **4** by ¹H NMR analysis.

^d Yield refers to the column purified product (**4o**, **4t**).

chloro substituted 1*H*-indene-1,3(2*H*)-diones (Table 2, entry **4f**). Similarly, the reaction was also amenable with broad electron-donating substituents in the different positions of the reaction of 1*H*-indene-1,3(2*H*)-dione (Table 2, entry **4j**–**4o**). On the other hand, strong electron-withdrawing groups such as nitro- and cyano substituted 1*H*-indene-1,3(2*H*)-dione successfully proceeded for this reaction and delivered the products in almost quantitative yield with good to excellent diastereoselectivity (Table 2, entry **4q**–**4t**). Not only with aryl substitution but heteroaryl substituted 1*H*-indene-1,3(2*H*)-dione have also been well documented for the present reaction (Table 2, entry **4y** and **4z**). With furyl substituted 1*H*-indene-1,3(2*H*)-dione, up to $>99 : 1$ dr was observed, while thiaryl substitution afforded a moderate dr up to 11 : 1.

Enlightened by these successful achievements, and to further broaden the scope of this reaction, we carried out the reaction of various *N*-substituted *N*-2,2,2-trifluoroethylisatin ketimines with 2-benzylidene-1*H*-indene-1,3(2*H*)-dione **2a** in presence of 5 mol% of DABCO (**3c**) in toluene at room temperature. *N*-Substituted ketimines **1b** and **1c** having methyl and methoxy group at the C-5 position of the aryl ring efficiently participated in the reaction to provide the respective products **4a'** and **4b'** in 89% and 94% yield with $>20 : 1$ and $>99 : 1$ dr

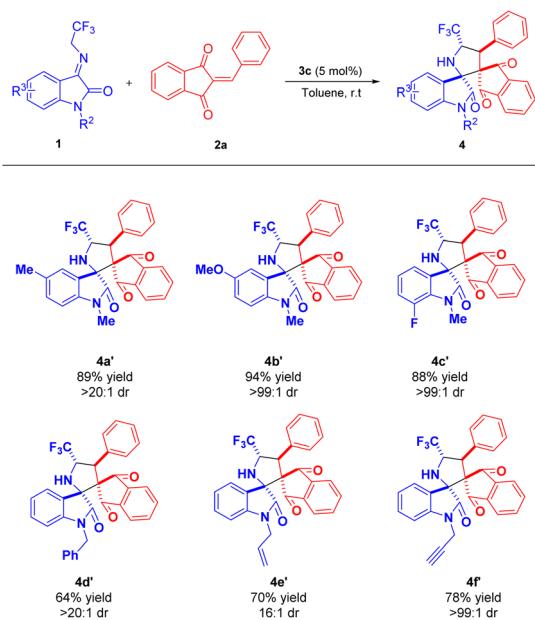


R¹ = 3-FC₆H₄, 4-FC₆H₄, 2-ClC₆H₄, 3-ClC₆H₄, 4-ClC₆H₄, 2-BrC₆H₄, 3-BrC₆H₄, 4-BrC₆H₄, 2-MeC₆H₄, 4-MeC₆H₄, 3-OMeC₆H₄, 4-OMeC₆H₄, 4-OBnC₆H₄, 4-N-(CH₂)₂C₆H₄, 2-NO₂C₆H₄, 4-NO₂C₆H₄, 2-CNC₆H₄, 4-CNC₆H₄, 4-NHCO-CH₃C₆H₄, 1-Naphthyl, -CH=CH-Ph, 3,4-(OMe)₂C₆H₃, 2,3,4-(OMe)₃C₆H₂, furyl, Thiaryl

Scheme 2 Synthesis of spiro-pyrrolidine oxindoles under the standard conditions.



Table 3 Reaction scope of ketimine **1b–1g** with indane-1,3-dione enophile **2aa**^{a,b,c}



^a Unless otherwise mentioned, all the reactions were performed using **1** (0.11 mmol), **2** (0.1 mmol) and catalyst **3c** (0.005 mmol), in 0.2 M of toluene at room temperature. ^b Yield refers to the purified product. ^c dr was determined for purified product **4** by ¹H NMR analysis.

respectively, Table 3. The presence of a fluoro group on the C-7 position of the aryl ring of *N*-methyl substituted ketimines, is also very suitable for this reaction, delivering the product **4c'** in 88% yield with >99:1 dr. On the other hand, changing the methyl substitution on the nitrogen atom of ketimines by benzyl, allyl, and propargyl had no detrimental effect on the yield of the products. While *N*-benzyl and *N*-propargyl substituted ketimines **1e** and **1g** afforded the products **4d'** and **4f'** in 64% and 78% yields with >20:1 and >99:1 dr respectively, the *N*-allyl substituted ketimines leads to a good yield of the product **4e'** but 16:1 diastereomeric ratio. All the synthesized compounds are new and characterized by using ¹H NMR, ¹³C NMR, ¹⁹F NMR, HRMS, and FT-TR spectroscopic analysis (see

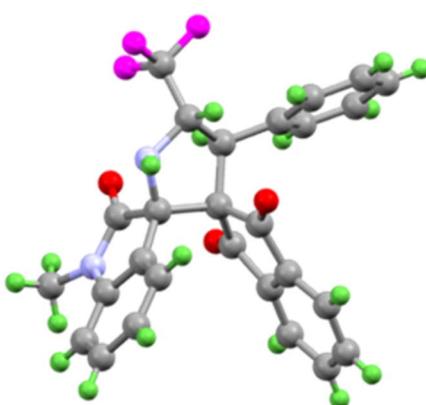
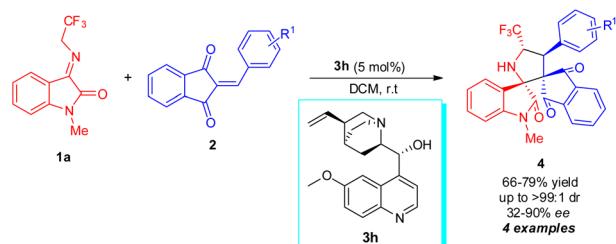
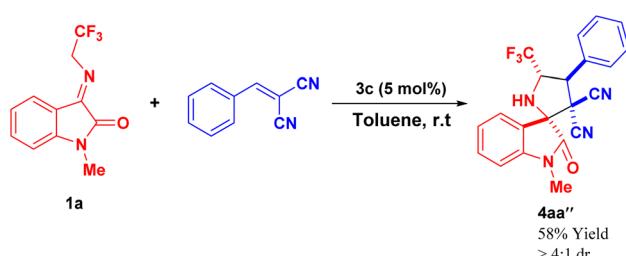


Fig. 2 XRD structure of compound **4a** (CCDC 1880719†).



Scheme 3 Preliminary investigation on the catalytic asymmetric reaction.



Scheme 4 Application of arylidene malononitrile as the olefinic source.

ESI†). The structure of compound **4a** is further confirmed by single-crystal X-ray analysis, Fig. 2.

To further established the synthetic potentiality of the present protocol, an enantioselective [3 + 2] cycloaddition of *N*-2,2,2-trifluoroethylisatin ketimine **1a** with 2-benzylidene-1*H*-indene-1,3(2*H*)-dione **2a** was performed. With the help of 5 mol% of quinine **3h** as the organocatalyst, the reaction provided the corresponding spiro-pyrrolidine product **4a** bearing four contiguous stereogenic centres with two vicinal spiro-all carbon quaternary stereogenic centres in good yield (66% yield), excellent enantioselectivity (87% ee). Inspired by this result, we then synthesized a total of four examples of an asymmetric version of the spirooxindole products. The final product **4** was isolated by using flash chromatography (Scheme 3). Furthermore, to validate the synthetic potentiality of the present strategy, we conducted a reaction between arylidene malononitrile and **1a** under identical conditions. To our delight, the corresponding product **4aa''** was accomplished in 58% yield (Scheme 4).

Conclusions

In conclusion, we have demonstrated the exploitation of 2-aryl/heteroarylidene-1*H*-indene-1,3(2*H*)-dione as the new olefin



source for the expeditious construction of trifluoro methyl containing spiro-pyrrolidine oxindoles fused with indeno moiety *via* a DABCO-catalyzed [3 + 2] cycloaddition with readily accessible *N*-2,2,2-trifluoroethylisatin ketimines at ambient temperature. The mild reaction conditions, ultra-low loading of catalyst, energy efficiency, eco-compatible, and diverse functionality are some of the key features of this approach. The synthetic applicability of the present approach was highlighted by the enantioenriched construction of spiro-pyrrolidine oxindole with four stereogenic centres out of which two vicinal spiro-quaternary centers were formed. The developments of further synthetic strategies for improving the enantioselectivity of the synthesized products, indeno fused spiro-pyrrolidine oxindoles may would find the future scopes of applications.

Author contributions

MSP: conceptualization-equal, data curation-equal, formal analysis-equal, investigation-equal, writing – original draft-equal, supervision-equal. SB, SMS, MR and MS: investigation and original draft. BB: writing – investigation and original draft. RC: supervision-equal.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

- (a) A. J. Boddy and J. A. Bull, *Org. Chem. Front.*, 2021, **8**, 1026–1084; (b) B. Borah, J. Bora, P. Ramesh and L. R Chowhan, *RSC Adv.*, 2022, **12**, 12843–12857; (c) M. Ganesh and S. Suraj, *Org. Biomol. Chem.*, 2022, **20**, 5651–5693; (d) W. H. Zhang, S. Chen, X. L. Liu, X. W. Liu and Y. Zhou, *Bioorg. Med. Chem. Lett.*, 2020, **30**, 127410; (e) M. Zhang, J. X. Wang, S. Q. Chang, X. L. Liu, X. Zuo and Y. Zhou, *Chin. Chem. Lett.*, 2020, **31**, 381–385.
- (a) B. Borah and L. R. Chowhan, *Tetrahedron Lett.*, 2022, **104**, 154014; (b) V. A. D'yakonov, O. G. A. Trapeznikova, A. de Meijere and U. M. Dzhemilev, *Chem. Rev.*, 2014, **114**, 5775–5814; (c) L. M. Zhou, R. Y. Qu and G. F. Yang, *Expert Opin. Drug Discovery*, 2020, **15**, 603–625; (d) K. Zhang, H. Han, L. Wang, Z. Zhang, Q. Wang, W. Zhang and Z. Bu, *Chem. Commun.*, 2019, **55**, 13681–13684; (e) Y. Zhu, J. Zhou, S. Jin, H. Dong, J. Guo, X. Bai and Z. Bu, *Chem. Commun.*, 2017, **53**, 11201–11204.
- (a) M. Aldeghi, S. Malhotra, D. L. Selwood and A. W. E. Chan, *Chem. Biol. Drug Des.*, 2014, **83**, 450–461; (b) F. Lovering, J. Bilkker and C. Humblet, *J. Med. Chem.*, 2009, **52**, 6752–6756; (c) J. Guo, X. Bai, Q. Wang and Z. Bu, *J. Org. Chem.*, 2018, **83**, 3679–3687; (d) M. Li, W. L. Yang, L. R. Wen and F. Q. Li, *Eur. J. Chem.*, 2008, **16**, 2751–2758; (e) N. V. Lakshmi, P. Thirumurugan and P. T. Perumal, *Tetrahedron Lett.*, 2010, **51**, 1064–1068; (f) M. Rajeswari, J. Sindhu, H. Singh and J. M. Khurana, *RSC Adv.*, 2015, **5**, 39686–39691.
- (a) T. Peng, T. Liu, J. Zhao, J. Dong, Y. Zhao, Y. Yang, X. Yan, W. Xu and X. Shen, *J. Org. Chem.*, 2022, DOI: [10.1021/acs.joc.2c02391](https://doi.org/10.1021/acs.joc.2c02391); (b) R. C. Elderfield and R. E. Gilman, *Phytochem.*, 1972, **11**, 339–343; (c) K. C. Chan, F. Morsingh and G. B. Yeoh, *J. Chem. Soc. C*, 1966, 2245–2249; (d) R. G. Geetha and S. Ramachandran, *Pharmaceutics*, 2021, **13**, 1170; (e) M. Asad, M. N. Arshad, A. M. Asiri, S. A. Khan, M. Rehan and M. Oves, *Polycyclic Aromat. Compd.*, 2022, **42**, 5385–5397; (f) A. S. Girgis, *Eur. J. Med. Chem.*, 2009, **44**, 91–100.
- S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320–330.
- Q. Sun, X. Li, J. Su, L. Zhao, M. Ma, Y. Zhu and R. Wang, *Adv. Synth. Catal.*, 2015, **357**, 3187–3196.
- J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. Del Pozo, A. E. Sorochinsky, S. Fustero and H. Liu, *Chem. Rev.*, 2014, **114**, 2432–2506.
- W. R. Dolbier Jr, *J. Fluorine Chem.*, 2005, **126**, 157–163.
- K. Muller, C. Faeh and F. Diederich, *Science*, 2007, **317**, 1881–1886.
- T. Furuya, A. S. Kamlet and T. Ritter, *Nature*, 2011, **473**, 470–477.
- (a) T. Hashimoto and K. Maruoka, *Chem. Rev.*, 2015, **115**, 5366–5412; (b) M. Kissane and A. R. Maguire, *Chem. Soc. Rev.*, 2010, **39**, 845–883; (c) M. S. Reddy, N. S. Kumar and L. R. Chowhan, *RSC Adv.*, 2018, **8**, 35587–35593; (d) M. S. Reddy, L. R. Chowhan, N. S. Kumar, P. Ramesh and S. B. Mukkamala, *Tetrahedron Lett.*, 2018, **59**, 1366–1371; (e) V. Singh, S. R. Lakshmi and L. R. Chowhan, *Front. Chem.*, 2022, 1095; (f) P. Roy, S. R. Anjum and D. B. Ramachary, *Org. Lett.*, 2020, **22**, 2897–2901.
- (a) I. Coldham and R. Hufton, *Chem. Rev.*, 2005, **105**, 2765–2810; (b) G. Pandey, P. Banerjee and S. R. Gadre, *Chem. Rev.*, 2006, **106**, 4484–4517; (c) G. Surendra Reddy, A. Suresh Kumar and D. B. Ramachary, *Org. Biomol. Chem.*, 2020, **18**, 4470–4478.
- W. S. Jen, J. J. Wiener and D. W. MacMillan, *J. Am. Chem. Soc.*, 2000, **122**, 9874–9875.
- H. Suga, D. Ishimoto, S. Higuchi, M. Ohtsuka, T. Arikawa, T. Tsuchida and T. Baba, *Org. Lett.*, 2007, **9**, 4359–4362.
- M. Ma, Y. Zhu, Q. Sun, X. Li, J. Su, L. Zhao and R. Wang, *Chem. Commun.*, 2015, **51**, 8789–8792.
- X. W. Liu, J. Yue, Z. Li, D. Wu, M. Y. Tian, Q. L. Wang and Y. Zhou, *Tetrahedron*, 2020, **76**, 131678.
- Y. Xiong, X.-X. Han, Y. Lu, H.-J. Wang, M. Zhang and X.-W. Liu, *Tetrahedron*, 2021, **87**, 132112.

