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Dearomative spirocyclization of ynamides†

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Spiro N-heterocycles, particularly aza-spiro piperidines, have shown significant promise in pharmaceutical applications due to their ability to enhance physicochemical properties. Despite their potential, the preparation of these complex structures poses significant challenges. To address this, we propose a one-pot dearomative spirocyclization reaction of ynamides. This method involves a copper-catalyzed carbomagnesiation reaction, achieving chemo-, regio-, and stereoselective formation of vinyl metal intermediates. Upon the addition of a Lewis acid, these intermediates undergo a regioselective nucleophilic dearomatization event, facilitating the synthesis of diverse aza-spiro dihydropyridine scaffolds with multiple functional handles. Various Grignard reagents, diverse ynamides, and acylating reagents have been explored. A subsequent hydrogenation reaction provides access to both partially and fully reduced spirocyclic frameworks, broadening the scope of spirocyclic structures with potential medicinal applications.

Introduction

The majority of pharmaceuticals and natural products contain saturated and unsaturated five- and six-membered N-heterocycles,[1] with a tendency towards increased saturation for improved physicochemical properties.[2] However, during lead optimization, unconventional structures have been discovered to finely tune physicochemical properties such as basicity, lipophilicity, and solubility.[1b–d] Among these structures are spiro N-heterocycles, particularly spiro piperidines stand out for their ability to introduce conformational restrictions, potentially modulating binding potency and specificity (Fig. 1A).[3,4] Consequently, their integration into lead structures has proven rewarding, particularly in antidiabetic,[5] anticancer,[6] and anti-Alzheimer pharmacological applications,[7] with some successfully developed as commercial drugs (Fig. 1A).[3] Nonetheless, the primary challenge lies in their preparation,[8,9] which often entails a higher number of synthetic steps and/or unconventional reaction procedures,[10] thus hindering further advancement of pharmacological applications. This challenge becomes even more evident in the preparation of diaza-spiro heterocyclic scaffolds.

To address this issue, several protocols involving dearomatization reactions[11] of pyridines towards the formation of aza-spiro piperidines have been developed. For instance, the addition of trifluoromethanesulfonic anhydride to *N*-arylisonicotinamides triggers an intramolecular nucleophilic attack of the aryl ring on the pyridinium salt, delivering diaza-spiro

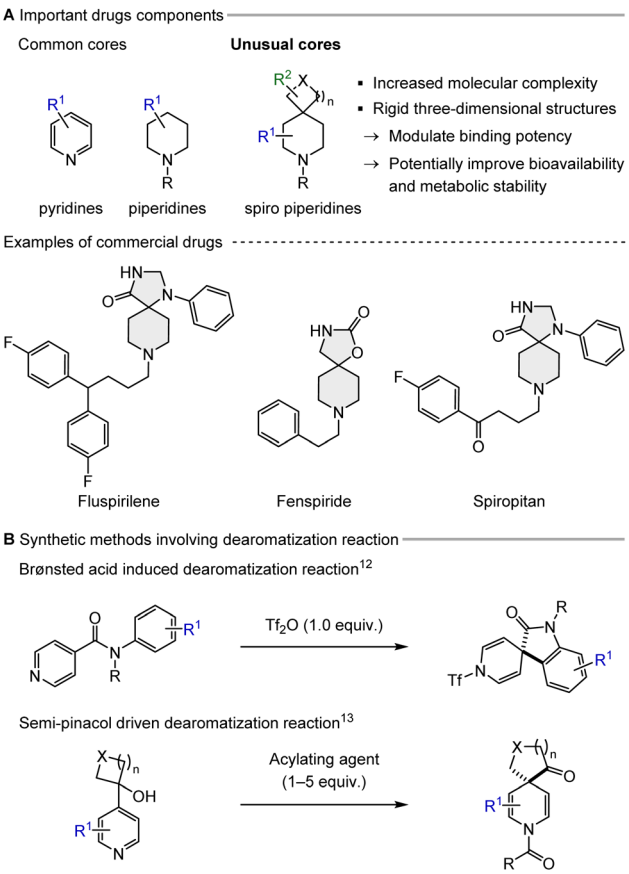

Fig. 1 (A) Pyridines and piperidines are common cores in commercial drugs. Spiro piperidines (and dihydropyridines) are gaining more attention owing to their interesting pharmacokinetic properties. However, strategies to construct diverse structures are heavily underdeveloped. (B) Previous work on the formation of aza-spiro dihydropyridines involving dearomatization reaction.

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heterocycles in moderate to good yields, albeit with a poor regioisomeric ratio (Fig. 1B).[12] Moreover, the semi-pinacol rearrangement of 4-(hydroxycyclobutyl)-pyridines elegantly facilitates the synthesis of spirocyclic piperidine derivatives (Figure 1B),[13] although this approach has been less explored for the preparation of aza-spiro piperidines.

Additional elegant approaches towards the formation of aza-spiro piperidines involve the dearomatization of indole derivatives, delivering diverse six membered spiroindolenines with excellent stereoselectivity.[14,15] Notably, the enantioselective formation of diaza-spirocycles has been achieved,[16] albeit limited to spirocyclic 2*H*-pyrroles.

In light of the above, and considering our continuous efforts in constructing complex N-heterocycles through dearomative functionalization reactions,[17] we sought to explore systematically the chemical space of aza-spiropiperidyl compounds. Envisioning the formation of diaza-spirocyclic **3** through a regioselective intramolecular nucleophilic dearomatization reaction of alkylmetal species **2′** seemed logical. However, fine-tuning the nature of the metalated nucleophile is essential to control the regioselective outcome (Fig. 2), especially in the presence of longer linkers.[18] The synthesis of the latter species could be achieved *via* a carbometalation reaction of a pyridine derivative bearing a C–C triple bond **1**. However, challenges related to the chemoselectivity of the carbo-addition reaction, as well as regio- and stereoselectivity of the carbometalation, need to be addressed. Note that this envisioned strategy allows the easy exploration of versatile substitution on both rings. Furthermore, it allows the preparation of different ring sizes of aza-spiropiperidyl scaffolds (Fig. 2).

Herein, we present a protocol for the carbometalation–dearomatization reaction of ynamides, offering a convenient, chemo-, regio- and stereoselective route to diverse aza-spiropiperidine scaffolds (Fig. 3). The resulting architectures could offer versatility for diverse modifications, allowing for the synthesis of medicinally relevant spiro heterocyclic scaffolds through multidirectional elaboration.

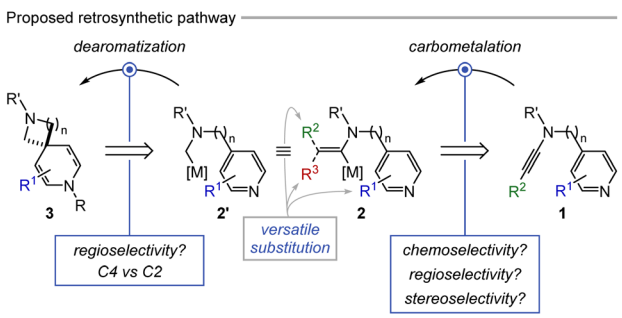


Fig. 2 Proposed approach for the synthesis of aliphatic spiro N-heterocycles.

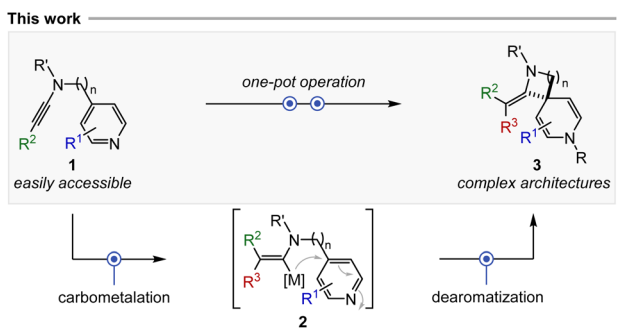
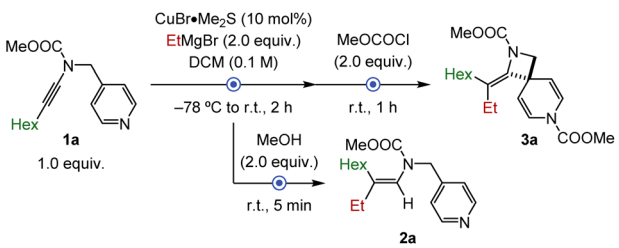


Fig. 3 This work: the dearomative spirocyclization of easily accessible ynamides delivers highly decorated spiro dihydropyridine derivatives.

Results and discussion

Our journey began with the synthesis of ynamides **1**,[19] easily obtained by a C–N coupling reaction between bromoalkynes and aminopyridine derivatives.[16,20] Subsequently we subjected the latter to a carbometalation reaction. Inspired by literature reports on carbocupration of ynamides[21,22] and following extensive optimization studies,[23] we identified the optimal reaction conditions as summarized in Table 1. Notably, the copper-catalyzed carbomagnesiation of ynamide **1a** (R^1 = H, R^2 = Hex, R′ = COOMe) with EtMgBr in dichloromethane (DCM) enabled the clean formation of vinyl metal pyridin-4-ylmethanamine as a single regio- and stereoisomer. The stereochemistry of the intermediate was confirmed by NMR spectroscopy of the corresponding protonated product **2a** (entry 1). Excellent selectivity values are attributed to the chelation of the metaled species with the electron-withdrawing group (R′ = COOMe).[21]

Table 1 Optimization studies[a]



Entry	Deviation from standard conditions	Yield[b]
1	None	79% (75%)[c] (**2a**)
2	None	72% (68%)[c] (**3a**)
3	Toluene instead of DCM	48% (**2a**)
4	THF instead of DCM	43% (**2a**)
5	CuI instead of CuBr·Me_2S	30% (**2a**)
6	CuBr instead of CuBr·Me_2S	33% (**2a**)
7	CuBr·Me_2S (2.0 equiv.)	60% (**2a**)
8[d]	TMEDA as additive	48% (**3a**)
9[d]	DMPU as additive	60% (**3a**)
10	2nd step at −78 °C	26% (**3a**)
11	2nd step at 0 °C	65% (**3a**)

[a] Reactions were performed under N_2 with 0.2 mmol of **1a**. [b] Yields were determined using ^{1}H NMR spectroscopy with CH_2Br_2 as the internal standard. [c] Isolated yield. [d] The additive was added in the second step prior to the addition of the Lewis acid. See ESI, for more details on optimization studies. Me, methyl; Et, ethyl; Hex, hexyl; TMEDA, tetramethylethylenediamine; DMPU, *N*,*N*′-dimethylpropyleneurea.

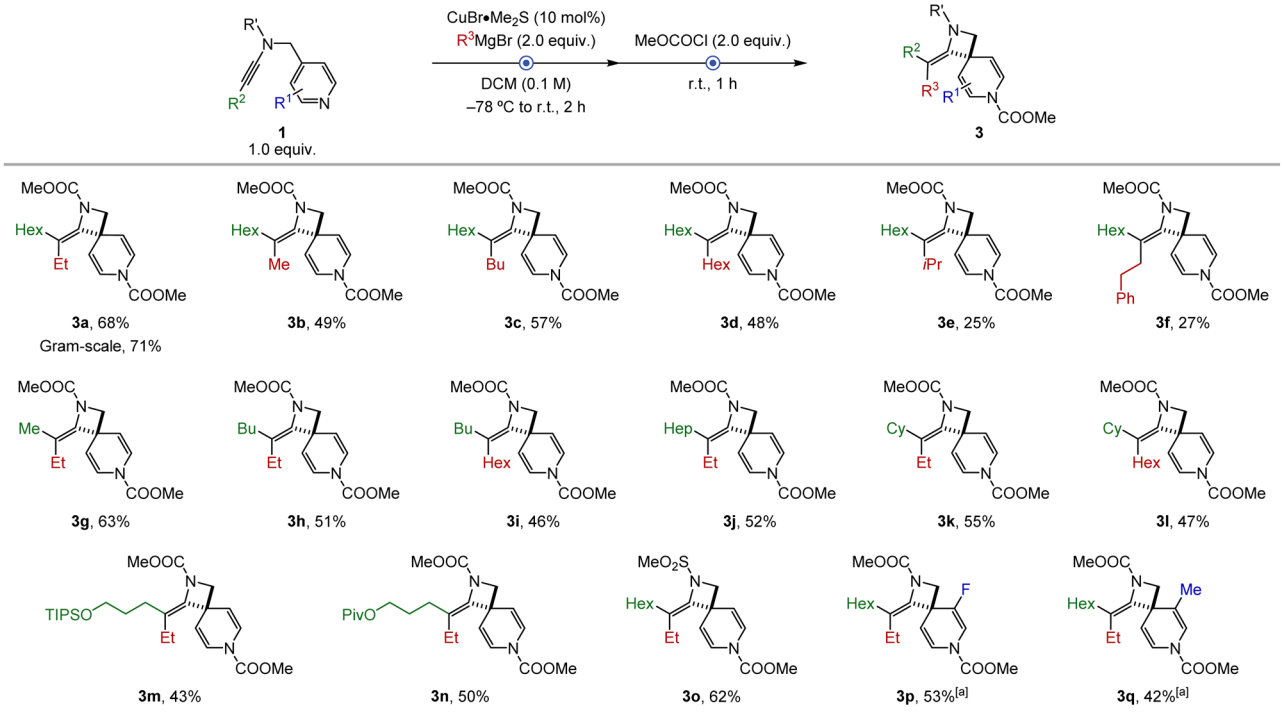
Additional control experiments provided insights into critical factors impacting the efficiency of this transformation. Interestingly, the choice of reaction solvent turned to be a crucial factor. Replacing DCM with standard carbomagnesiation solvents such as diethyl ether, THF and toluene resulted in decreased yields of the intermediate (entries 3 and 4). Furthermore, the presence of a catalytic amount of copper bromide dimethyl sulfide complex proved essential (entries 5–7).

Having achieved a highly regio- and stereoselective carbometalation reaction, the spirocyclization reaction was triggered through the addition of methyl chloroformate at room temperature (Table 1). The regioselectivity of the nucleophilic attack was ensured by the soft nature of the vinyl metal species.[18] Subsequent efforts to enhance the efficiency of the second step led to the isolation of the final product **3a** in a good overall yield (entry 2). The addition of metal scavengers such as TMEDA or DMPU to the reaction mixture decreased the overall yield (entries 8 and 9). Notably, conducting the second step under lower temperatures influenced the performance of this transformation (entries 10 and 11).

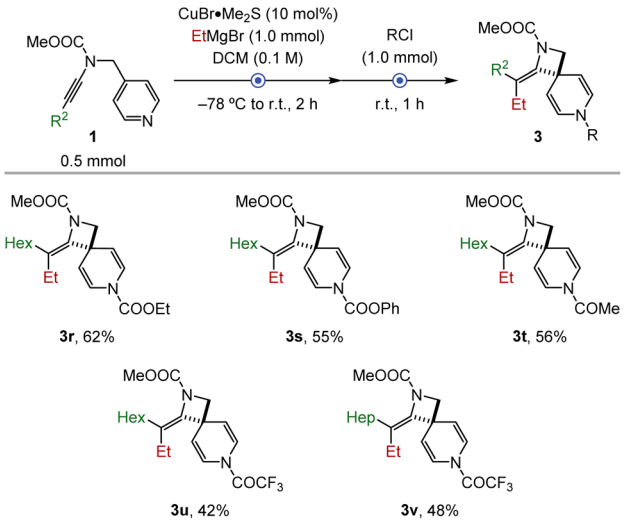
After identifying the optimal reaction conditions, we initiated scoping studies for the dearomative spirocyclization reaction (Scheme 1). Generally, the products were obtained as single isomers with moderate to high overall yields. Additionally, purification through standard column chromatography proved sufficient for obtaining pure compounds.

We began our investigation with ynamide **1a** (R^2 = Hex). Initially, we examined the addition of primary alkyl Grignard reagents, including methyl (Me), ethyl (Et), butyl (Bu), and hexyl (Hex) magnesium bromides. Pleasingly, the corresponding spiro heterocycles **3a–3d** were obtained in moderate to good overall yields. This reaction was also successfully carried out on a gram scale, delivering 0.94 g of **3a** as a single isomer with a good overall yield. The addition of secondary Grignard reagent, such iPrMgBr, resulted in the final product **3e** with a reduced yield, primarily due to less efficient carbometalation reaction caused by steric hindrance. Similar behaviour was observed when phenethylmagnesium bromide was used, resulting in **3f** being obtained in low yield. In contrast, the addition of aryl Grignard reagents delivered only the carbometalated products as single isomers.[24] Further optimization studies aimed at facilitating the dearomatization reaction were ultimately unsuccessful.

Next, we sought to explore the influence of diverse ynamides on the reaction outcome (Scheme 1). Replacing the alkyl group R^2 present on the alkyne with Me, Bu, heptyl (Hep) and cyclohexyl (Cy) provided the corresponding adducts **3g–3l** in satisfactory yields. Interestingly, by exchanging R^2 and R^3 present on the alkyne and the Grignard reagent, respectively, and performing the carbometalation-spirocyclization reaction, the opposite isomer **3i** was obtained in 46% yield, still as a single isomer. This demonstrates that both isomers of diazaspiro[3.5]nonadiene **3** can be readily accessed through this one-pot operation. Ynamides bearing triisopropylsilyl (TIPS)- and pivaloyl (Piv)-protected alcohols were well-tolerated under the reaction conditions, furnishing functionalized spiro heterocycles **3m–3n** in moderate yields. Further investigation showed that replacing the carbamate with methanesulfonamide



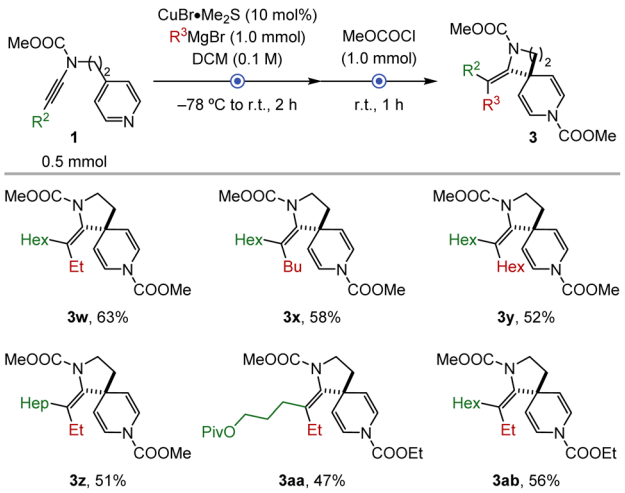
Scheme 1 Scope of the dearomative spirocyclization reaction. Reactions were carried out on a 0.5 mmol scale. Yields were determined after column chromatography. For detailed experimental procedures, see ESI.† [a]Reaction was performed on a 0.2 mmol scale. Me, methyl; Et, ethyl; iPr, iso-propyl; Bu, butyl; Hex, hexyl; Hep, heptyl; Ph, phenyl; TIPS, triisopropylsilyl; Piv, pivaloyl.



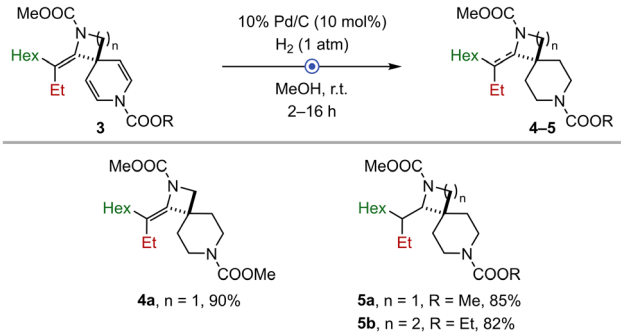
Scheme 2 Scope of the Lewis acids. Reactions were carried out on a 0.5 mmol scale. Yields were determined after column chromatography. For detailed experimental procedures, see ESI.†

afforded the final product **3o** with a good overall yield. To further demonstrate the utility of this methodology in the preparation of high complex spiropiperidines, substituted pyridines were incorporated, allowing for the formation of the desired products **3p–3q** in good overall yields and thus providing new molecular structures that cannot be accessed using standard methods.

To provide a comprehensive scope, we also tested the effect of various Lewis acids on the dearomatization reaction (Scheme 2). Generally, alkyl chloroformates delivered the final products (**3r**) with higher efficiency compared to aryl chloroformates (**3s**), acyl chlorides (**3t**) or trifluoroacetic anhydride (**3u** and **3v**). However, leveraging this approach allows the formation of diazaspiro[3.5]nonadiene **3** with orthogonally *N*-protected groups. Regrettably, attempts to trigger the



Scheme 3 Scope of 2,8-diazaspiro[4.5]decadiene derivatives. Reactions were carried out on a 0.5 mmol scale. Yields were determined after column chromatography. For detailed experimental procedures, see ESI.†



Scheme 4 Partial and full hydrogenation of spiro dihydropyridine derivatives. Yields were determined after column chromatography. For detailed experimental procedures, see ESI.†

dearomatization reaction with other Lewis acids, such as fluorenylmethoxycarbonyl chloride, were unsuccessful.

Motivated by these results, we then wondered whether the formation of diazaspiro[4.5]decadiene is feasible following the developed transformation. Suitable starting materials were obtained by adopting the previously mentioned protocol for the C–N coupling reaction.[16,20] The resulting ynamides were then subjected to the carbometalation-spirocyclization sequence. To our delight, the addition of EtMgBr to ynamide **1a** (R^2 = Hex) furnished the desired compound **3w** in a good overall yield and as a single isomer (Scheme 3). Several products were also obtained independent of the nature of the Grignard reagents (**3x** and **3y**), the employed ynamides (**3z** and **3aa**), or the acylating reagents (**3ab**).

Finally, we demonstrated that the reduction of olefin moieties in dihydropyridine spirocycles **3** can be precisely controlled. Specifically, under partial reduction conditions, piperidine spirocycle **4a** was selectively obtained, with remaining alkene functionality suitable for further functionalization. In contrast, extended reaction times facilitated complete hydrogenation, delivering fully saturated piperidine spirocyclic scaffolds **5a** and **5b** in high yields (Scheme 4). This controllable reduction pathway provides access to both partially and fully reduced spirocyclic frameworks, broadening the utility of the proposed dearomative spirocyclization reaction (Scheme 4).

Conclusions

In conclusion, the stereoselective formation of spiropiperidine derivatives can be efficiently achieved through a dearomative spirocyclization reaction. This approach utilizes a chemo-, regio-, and stereoselective carbometalation event followed by a regioselective dearomatization reaction. Notably, this methodology enables the synthesis of diverse diazaspiro heterocycles with varying ring sizes and functional groups, making it a valuable tool in synthetic and medicinal chemistry.

Author contributions

Z. N. conceived the project. M. A. designed and conducted the experiments, with assistance from N. E. The manuscript was written with contributions from all authors.

Conflicts of interest

There are no conflicts to declare.

Data availability

Data for this article, including experimental procedures, and characterization data of all the substrates and products, are available in the ESI of the manuscript.

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Notes and references

1 (*a*) D. O'Hagan, *Nat. Prod. Rep.*, 2000, **17**, 435; (*b*) E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 10257; (*c*) R. D. Taylor, M. MacCoss and A. D. G. Lawson, *J. Med. Chem.*, 2014, **57**, 5845; (*d*) P. Bhutani, G. Joshi, N. Raja, N. Bachhav, P. K. Rajanna, H. Bhutani, A. T. Paul and R. Kumar, *J. Med. Chem.*, 2021, **64**, 2339.

2 (*a*) D. C. Blakemore, L. Castro, I. Churcher, D. C. Rees, A. W. Thomas, D. M. Wilson and A. Wood, *Nat. Chem.*, 2018, **10**, 383; (*b*) K. R. Campos, P. J. Coleman, J. C. Alvarez, S. D. Dreher, R. M. Garbaccio, N. K. Terrett, R. D. Tillyer, M. D. Truppo and E. R. Parmee, *Science*, 2019, **363**, eaat0805; (*c*) M. A. Hardy, B. A. Wright, J. Logan Bachman, T. B. Boit, H. M. S. Haley, R. R. Knapp, R. F. Lusi, T. Okada, V. Tona, N. K. Garg and R. Sarpong, *ACS Cent. Sci.*, 2020, **6**, 1017.

3 (*a*) Y. Zheng, C. M. Tice and S. B. Singh, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 3673; (*b*) K. Hiesinger, D. Dar'in, E. Proschak and M. Krasavin, *J. Med. Chem.*, 2021, **64**, 150.

4 (*a*) C. M. Marson, *Chem. Soc. Rev.*, 2011, **40**, 5514; (*b*) K. Acosta-Quiroga, C. Rojas-Peña, L. S. Nerio, M. Gutiérrez and E. Polo-Cuadrado, *RSC Adv.*, 2021, **11**, 21926.

5 (*a*) C. M. Tice, W. Zhao, Z. Xu, S. T. Cacatian, R. D. Simpson, Y.-J. Ye, S. B. Singh, B. M. McKeever, P. Lindblom, J. Guo, P. M. Krosky, B. A. Kruk, J. Berbaum, R. K. Harrison, J. J. Johnson, Y. Bukhtiyarov, R. Panemangalore, B. B. Scott, Y. Zhao, J. G. Bruno, L. Zhuang, G. M. McGeehan, W. He and D. A. Claremon, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 881; (*b*) Y. Ohtake, T. Sato, T. Kobayashi, M. Nishimoto, N. Taka, K. Takano, K. Yamamoto, M. Ohmori, M. Yamaguchi, K. Takami, S.-Y. Yeu, K.-H. Ahn, H. Matsuoka, K. Morikawa, M. Suzuki, H. Hagita, K. Ozawa, K. Yamaguchi, M. Kato and S. Ikeda, *J. Med. Chem.*, 2012, **55**, 7828; (*c*) Y. Wang, J. Liu, P. J. Dransfield, L. Zhu, Z. Wang, X. Du, X. Jiao, Y. Su, A.-R. Li, S. P. Brown, A. Kasparian, M. Vimolratana, M. Yu, V. Pattaropong, J. B. Houze, G. Swaminath, T. Tran, K. Nguyen, Q. Guo, J. Zhang, R. Zhuang, F. Li, L. Miao, M. D. Bartberger, T. L. Correll, D. Chow, S. Wong, J. Luo, D. C.-H. Lin and J. C. Medina, *ACS Med. Chem. Lett.*, 2013, **4**, 551; (*d*) J. S. Scott, F. W. Goldberg and A. V. Turnbull, *J. Med. Chem.*, 2014, **57**, 4466.

6 (*a*) Y. Zhao, S. Yu, W. Sun, L. Liu, J. Lu, D. McEachern, S. Shargary, D. Bernard, X. Li, T. Zhao, P. Zou, D. Sun and S. Wang, *J. Med. Chem.*, 2013, **56**, 5553; (*b*) A. Bertamino, M. Soprano, S. Musella, M. R. Rusciano, M. Sala, E. Vernieri, V. Di Sarno, A. Limatola, A. Carotenuto, S. Cosconati, P. Grieco, E. Novellino, M. Illario, P. Campiglia and I. Gomez-Monterrey, *J. Med. Chem.*, 2013, **56**, 5407.

7 (*a*) T. A. Dineen, M. M. Weiss, T. Williamson, P. Acton, S. Babu-Khan, M. D. Bartberger, J. Brown, K. Chen, Y. Cheng, M. Citron, M. D. Croghan, R. T. Dunn, J. Esmay, R. F. Graceffa, S. S. Harried, D. Hickman, S. A. Hitchcock, D. B. Horne, H. Huang, R. Imbeah-Ampiah, T. Judd, M. R. Kaller, C. R. Kreiman, D. S. La, V. Li, P. Lopez, S. Louie, H. Monenschein, T. T. Nguyen, L. D. Pennington, T. S. Miguel, E. A. Sickmier, H. M. Vargas, R. C. Wahl, P. H. Wen, D. A. Whittington, S. Wood, Q. Xue, B. H. Yang, V. F. Patel and W. Zhong, *J. Med. Chem.*, 2012, **55**, 9025; (*b*) M. M. Weiss, T. Williamson, S. Babu-Khan, M. D. Bartberger, J. Brown, K. Chen, Y. Cheng, M. Citron, M. D. Croghan, T. A. Dineen, J. Esmay, R. F. Graceffa, S. S. Harried, D. Hickman, S. A. Hitchcock, D. B. Horne, H. Huang, R. Imbeah-Ampiah, T. Judd, M. R. Kaller, C. R. Kreiman, D. S. La, V. Li, P. Lopez, S. Louie, H. Monenschein, T. T. Nguyen, L. D. Pennington, C. Rattan, T. S. Miguel, E. A. Sickmier, R. C. Wahl, P. H. Wen, S. Wood, Q. Xue, B. H. Yang, V. F. Patel and W. Zhong, *J. Med. Chem.*, 2012, **55**, 9009; (*c*) J. Yuan, S. Venkatraman, Y. Zheng, B. M. McKeever, L. W. Dillard and S. B. Singh, *J. Med. Chem.*, 2013, **56**, 4156.

8 S. Kotha, N. R. Panguluri and R. Ali, *Eur. J. Org Chem.*, 2017, **2017**, 5316.

9 For selected examples on the preparation of piperidine spirocycles that includes cyclization reactions, see: (*a*) H. Habashita, M. Kokubo, S.-I. Hamano, N. Hamanaka, M. Toda, S. Shibayama, H. Tada, K. Sagawa, D. Fukushima, K. Maeda and H. Mitsuya, *J. Med. Chem.*, 2006, **49**, 4140; (*b*) I. D. Jenkins, F. Lacrampe, J. Ripper, L. Alcaraz, P. Van Le, G. Nikolakopoulos, P. De Almeida Leone, R. H. White and R. J. Quinn, *J. Org. Chem.*, 2009, **74**, 1304; (*c*) D. G. Brown, P. R. Bernstein, A. Griffin, S. Wesolowski, D. Labrecque, M. C. Tremblay, M. Sylvester, R. Mauger, P. D. Edwards, S. R. Throner, J. J. Folmer, J. Cacciola, C. Scott, L. A. Lazor, M. Pourashraf, V. Santhakumar, W. M. Potts, S. Sydserff, P. Giguère, C. Lévesque, M. Dasser and T. Groblewski, *J. Med. Chem.*, 2014, **57**, 733; (*d*) T. A. King, H. L. Stewart, K. T. Mortensen, A. J. P. North, H. F. Sore and D. R. Spring, *Eur. J. Org Chem.*, 2019, **2019**, 5219.

10 (*a*) P. S. Baran, T. J. Maimone and J. M. Richter, *Nature*, 2007, **446**, 404; (*b*) I. S. Young and P. S. Baran, *Nat. Chem.*, 2009, **1**, 193; (*c*) P. A. Wender and B. L. Miller, *Nature*, 2009, **460**, 197; (*d*) K. E. Kim, A. N. Kim, C. J. McCormick and B. M. Stoltz, *J. Am. Chem. Soc.*, 2021, **143**, 16890.

11 For comprehensive reviews, see: (*a*) S. P. Roche and J. A. Porco Jr, *Angew. Chem., Int. Ed.*, 2011, **50**, 4068; (*b*) Q. Ding, X. Zhou and R. Fan, *Org. Biomol. Chem.*, 2014, **12**, 4807; (*c*) W.-T. Wu, L. Zhang and S.-L. You, *Chem. Soc. Rev.*, 2016, **45**, 1570; (*d*) W. C. Wertjes, E. H. Southgate and D. Sarlah, *Chem. Soc. Rev.*, 2018, **47**, 7996; (*e*) C. J. Huck and D. Sarlah, *Chem*, 2020, **6**, 1589.
12 G. Arnott, H. Brice, J. Clayden and E. Blaney, *Org. Lett.*, 2008, **10**, 3089.
13 J. C. Abell, C. P. Bold, L. Vicens, T. Jentsch, N. Velasco, J. L. Tyler, R. N. Straker, A. Noble and V. K. Aggarwal, *Org. Lett.*, 2023, **25**, 400.
14 For selected studies: (*a*) Q.-F. Wu, H. He, W.-B. Liu and S.-L. You, *J. Am. Chem. Soc.*, 2010, **132**, 11418; (*b*) X. Zhang, W.-B. Liu, Q.-F. Wu and S.-L. You, *Org. Lett.*, 2013, **15**, 3746; (*c*) T. D. Montgomery, A. E. Nibbs, Y. Zhu and V. H. Rawal, *Org. Lett.*, 2014, **16**, 3480; (*d*) Y. Wang, C. Zheng and S.-L. You, *Angew. Chem., Int. Ed.*, 2017, **56**, 15093; (*e*) W.-T. Wu, L. Ding, L. Zhang and S.-L. You, *Org. Lett.*, 2020, **22**, 1233; (*f*) G. Liang, Y. Ji, H. Liu, Y. Pang, B. Zhou, M. Cheng, Y. Liu, B. Lin and Y. Liu, *Adv. Synth. Catal.*, 2020, **362**, 192; (*g*) A. Becker, C. P. Grugel and B. Breit, *Org. Lett.*, 2021, **23**, 3788; (*h*) S. Ta, S. Ding, D. Li, L. Li, H. Zhao, M. Chai and J. Wang, *Chem. Commun.*, 2021, **57**, 10576; (*i*) Y. Zhu, S. Yang, E. Pu, L. Li, S. Ye, L. Wei, G. Ma, Y. Zhang, H. Zhang and J. Chen, *Org. Lett.*, 2023, **25**, 3533.
15 For recent reviews on the dearomatization of indoles, see: (*a*) C. Zheng and S.-L. You, *ACS Cent. Sci.*, 2021, **7**, 432; (*b*) F. Buttard and X. Guinchard, *ACS Catal.*, 2023, **13**, 9442.
16 Y.-Q. Zhang, Y.-B. Chen, J.-R. Liu, S.-Q. Wu, X.-Y. Fan, Z.-X. Zhang, X. Hong and L.-W. Ye, *Nat. Chem.*, 2021, **13**, 1093.
17 (*a*) M. Hu, D. Ding, W. Desnoo, D. J. Tantillo and Z. Nairoukh, *Angew. Chem., Int. Ed.*, 2023, **62**, e202315108; (*b*) R. Mondal, M. Agbaria, O. Cohen and Z. Nairoukh, *Chem. - Eur. J.*, 2024, **30**, e202303588.
18 J. A. Bull, J. J. Mousseau, G. Pelletier and A. B. Charette, *Chem. Rev.*, 2012, **112**, 2642.
19 (*a*) K. A. DeKorver, H. Li, A. G. Lohse, R. Hayashi, Z. Lu, Y. Zhang and R. P. Hsung, *Chem. Rev.*, 2010, **110**, 5064; (*b*) G. Evano, A. Coste and K. Jouvin, *Angew. Chem., Int. Ed.*, 2010, **49**, 2840; (*c*) F.-L. Hong and L.-W. Ye, *Acc. Chem. Res.*, 2020, **53**, 2003; (*d*) C. C. Lynch, A. Sripada and C. Wolf, *Chem. Soc. Rev.*, 2020, **49**, 8543; (*e*) Y. -Bo Chen, P.-C. Qian and L.-W. Ye, *Chem. Soc. Rev.*, 2020, **49**, 8897; (*f*) S. Dutta, R. K. Mallick and A. K. Sahoo, *Angew. Chem., Int. Ed.*, 2023, **62**, e202300816.
20 (*a*) Y. Zhang, R. P. Hsung, M. R. Tracey, K. C. M. Kurtz and E. L. Vera, *Org. Lett.*, 2024, **6**, 1151; (*b*) P.-Y. Yao, Y. Zhang, R. P. Hsung and K. Zhao, *Org. Lett.*, 2008, **10**, 4275; (*c*) J. P. Das, H. Chechik and I. Marek, *Nat. Chem.*, 2009, **1**, 128.
21 For selected reviews, see: (*a*) A. Basheer and I. Marek, *Beilstein J. Org. Chem.*, 2010, **6**, 77; (*b*) Y. Minko, M. Pasco, H. Chechik and I. Marek, *Beilstein J. Org. Chem.*, 2013, **9**, 526; (*c*) I. Marek, Y. Minko, M. Pasco, T. Mejuch, N. Gilboa, H. Chechik and J. P. Das, *J. Am. Chem. Soc.*, 2014, **136**, 2682; (*d*) D. S. Mueller and I. Marek, *Chem. Soc. Rev.*, 2016, **45**, 4552.
22 For selected recent studies, see: (*a*) Y. Minko, M. Pasco, L. Lercher, M. Botoshansky and I. Marek, *Nature*, 2012, **490**, 522; (*b*) R. Vabre, B. Island, C. J. Diehl, P. R. Schreiner and I. Marek, *Angew. Chem., Int. Ed.*, 2015, **54**, 9996; (*c*) Z. Nairoukh and I. Marek, *Angew. Chem., Int. Ed.*, 2015, **54**, 14393; (*d*) P. Starkov, J. T. Moore, D. C. Duquette, B. M. Stoltz and I. Marek, *J. Am. Chem. Soc.*, 2017, **139**, 9615.
23 See the ESI† for full optimization results.
24 See the ESI† for more details.