RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2025, **15**, 20810

Stereocontrolled four-carbon homologation of vicinally functionalized allylic pyrrolidines to highly customized azonines bearing remote benzylic stereocenters†

Timothy K. Beng,* Ailan Johnsen, Alan Gitonga and Jasleen Kaur

Polysubstituted pyrrolidines and azonanes bearing at least two (vicinal) stereocenters constitute the core of several pharmaceuticals or advanced intermediates that directly lead to marketed drugs. Here, we leverage our recently developed 1,3-azadiene-succinic anhydride annulation protocol to produce vicinally functionalized allylic pyrrolidine methanols and explore their amenability to four-carbon homologation. The success of the aza-Cope rearrangement hinges on the use of hexafluoroisopropanol (HFIP) as the reaction medium. The method provides rapid, modular, and efficient access to highly customized azonines. The ring expansion reaction of these sterically-imposing and vicinally functionalized α-styrenyl pyrrolidine methanols proceeds with complete control of the *E*/*Z* geometries of the enamine and alkene C=C double bonds resident in the 9-membered ring. Additionally, the approach furnishes sp^3-rich nine-membered nitrogen heterocycles bearing at least two tetrahedral stereocenters, including a remote benzylic stereocenter.

Received 18th May 2025
Accepted 12th June 2025

DOI: 10.1039/d5ra03502c

rsc.li/rsc-advances

Introduction

The pyrrolidine motif is a privileged scaffold from the medicinal chemistry standpoint. For instance, it ranks first among the top five most common five-membered non-aromatic nitrogen heterocycles and is prevalent in 37 drugs that have been approved by the United States (US) Food and Drug Administration (FDA).[1] Moreover, it constitutes the core of numerous chiral ligands and organocatalysts, and has also served as a key intermediate for the synthesis of a broad range of alkaloids.[2] In particular, polysubstituted allylic pyrrolidines and allylic 2-oxopyrrolidines, which harbor at least two contiguous stereocenters, make up the core of advanced intermediates that directly lead to marketed drugs (Fig. 1, see **A1** and **A2**).

Several applications in the fields of medicinal chemistry, natural product synthesis, materials science, supramolecular chemistry, catalysis, and nanotechnology rely on the synthesis of functionalized medium-sized *N*-heterocycles (*i.e.*, 8- to 11-membered azaheterocycles).[3] Specifically, functionalized azonanes are part of the core structure of several biologically active molecules, including cleavamine, daphhimalenine A, and rhazilinam (Fig. 1).[4]

Despite the literature being inundated with well-defined biological properties associated with small-sized nitrogen heterocycles such as pyrrolidines and piperidines, compounds containing the 9-membered ring homologues are still underrepresented in the current pharmacopoeia. However, medium-sized nitrogen heterocycles such as azonanes are more flexible compared to their small-sized congeners. They show the propensity to more readily adopt a greater number of

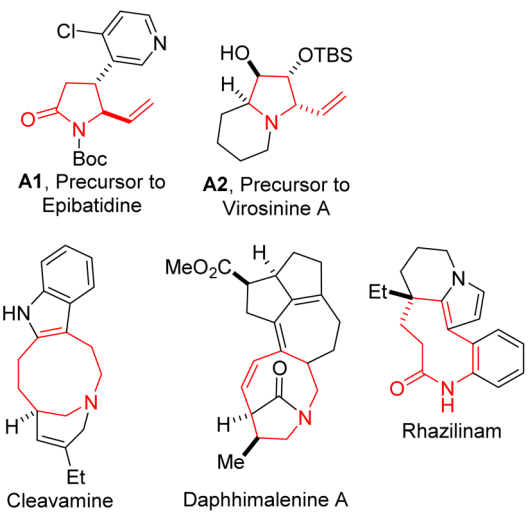


Fig. 1 Examples of bioactive allylic pyrrolidines and azonanes bearing tetrahedral stereocenters.

Department of Chemistry, Central Washington University, Ellensburg, WA 98926, USA. E-mail: Timothy.beng@cwu.edu

† Electronic supplementary information (ESI) available: Experimental procedures and spectroscopic data. See DOI: https://doi.org/10.1039/d5ra03502c

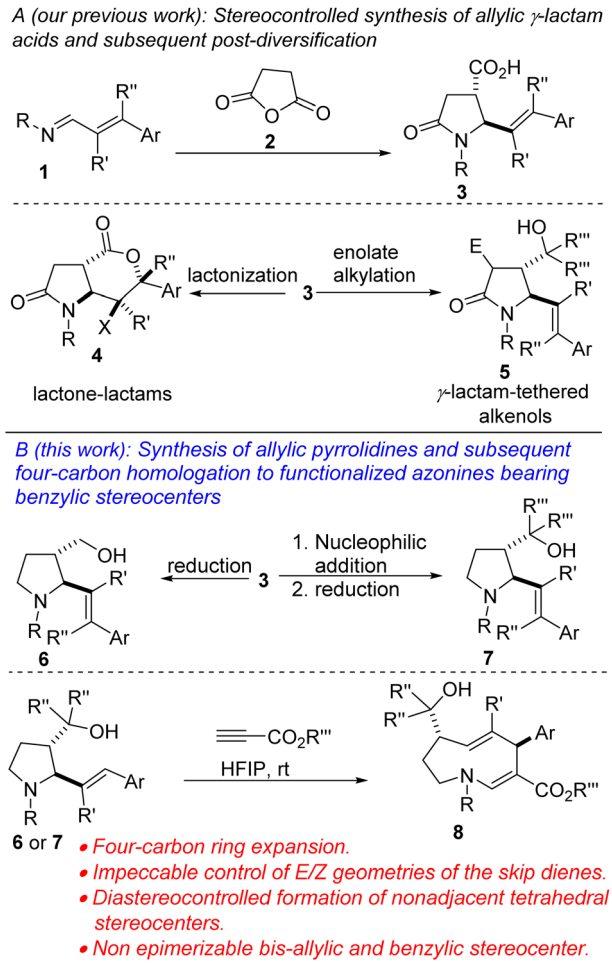
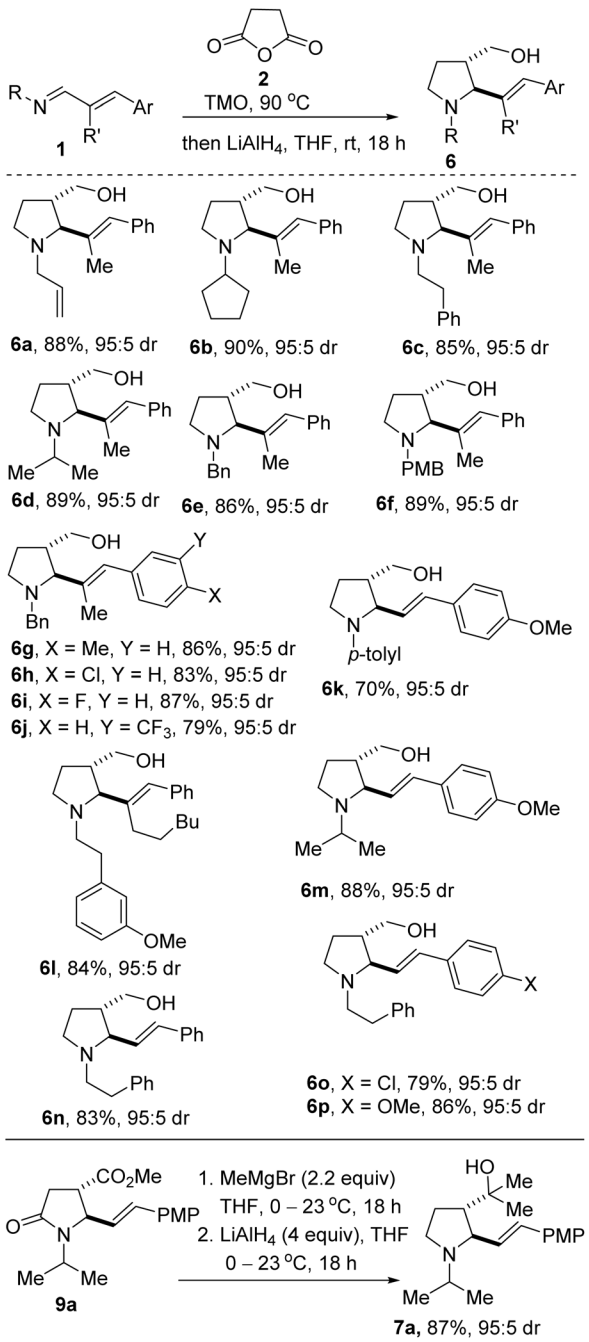


Fig. 2 (A) Prior synthesis of allylic 2-pyrrolidinones using the 1,3-azadiene-succinic anhydride annulation, (B) proposed plan for the synthesis of highly customized 9-membered azaheterocycles by four-carbon ring expansion of allylic pyrrolidine methanols.

conformations, which in turn increases the probability of finding the ideal active site for a biological target.[5] This conformational functionality makes azonanes and other medium-sized azaheterocycles highly sought after in drug discovery programs against less 'druggable' targets such as protein–protein interactions.[6] The relative scarcity of medium-sized nitrogen heterocycles can mainly be attributed to the challenges associated with the efficient and modular construction of these motifs. These challenges include fragility (the ring/bond angle (Bayer) strain for a 9-membered ring is approximately 12.6 kcal mol^{-1}), transannular strain, destabilizing torsional (Pitzer) strain, and the unfavorable loss of entropy.[7] The combination of these destabilizing factors make medium-sized nitrogen-containing rings exponentially difficult to access using conventional methods (*e.g.*, ring-closing metathesis, lactamization, cycloaddition, and homologations).[8] In order for more beneficial applications of medium-sized N-heterocycles such as azonanes to be discovered, we reasoned that a streamlined approach to construct them in a stereocontrolled and atom-economical manner, and with as many functional handles (vector points) as possible, represents an important research objective.

It is well appreciated that a simple cyclic tertiary amine containing *N*-alkenyl and α-amino vinyl substituents can undergo a 3-aza-Cope rearrangement with electron-deficient terminal and internal alkynes to afford a ring-expanded product.[9] The reaction generally takes advantage of the dipolar nature of the resulting zwitterionic conjugate amination intermediate, which then undergoes relatively fast [3,3] sigmatropic rearrangement to furnish the four-carbon homologation



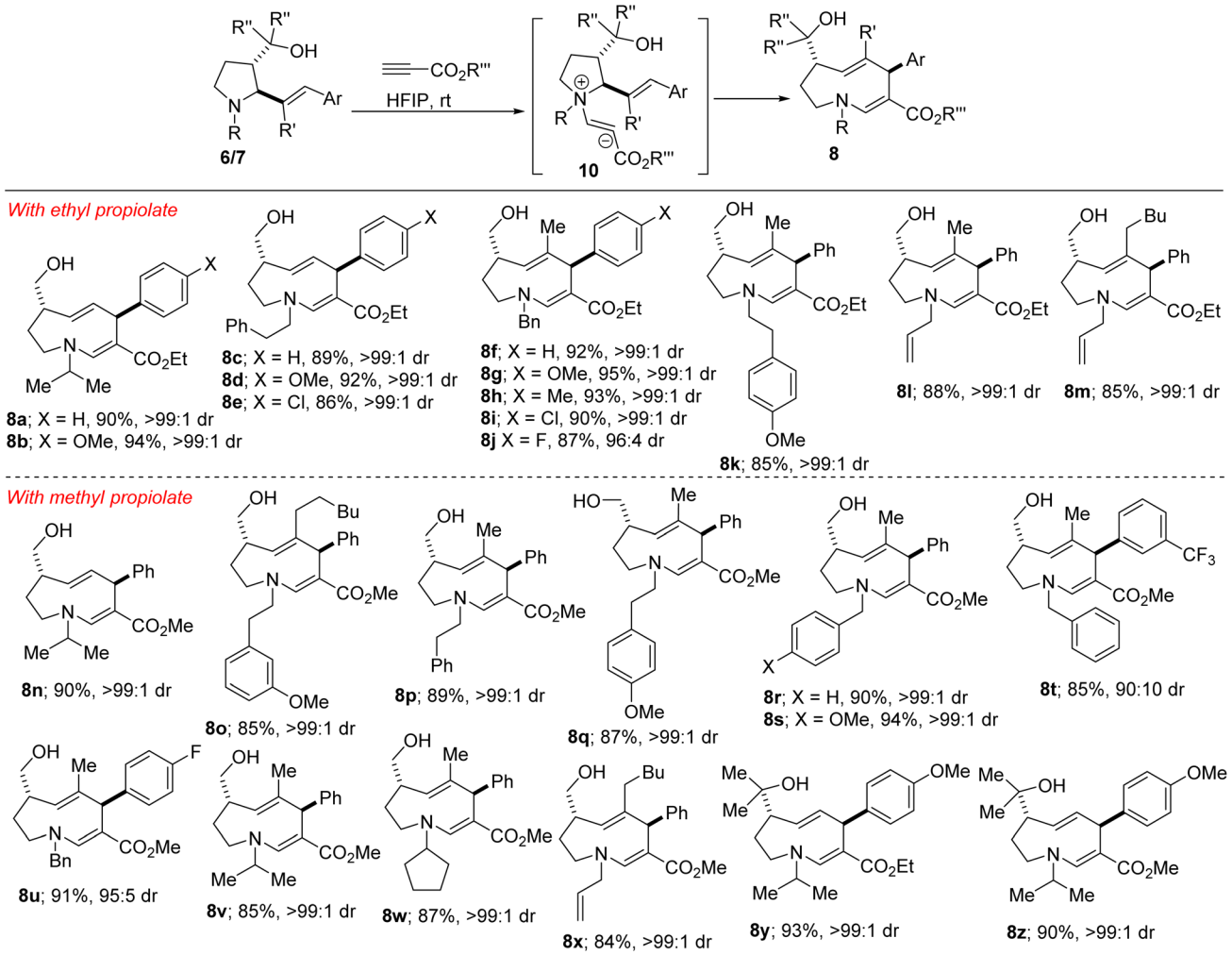
Scheme 1 Synthesis of vicinally functionalized allylic primary pyrrolidinols.

product. Despite the rich history of this aza-Cope rearrangement reaction, sterically imposing α-styrenyl tertiary pyrrolidine methanols and vicinally functionalized allylic tertiary pyrrolidines are yet to be interrogated in this homologation protocol.

Recently, we reported that a formal cycloaddition reaction between 1,3-azadienes of type **1** and succinic anhydride (**2**), affords allylic 2-pyrrolidinones bearing contiguous stereocenters (Fig. 2A, see **3**).[10] The transformation proved to be readily scalable, thus, providing a unified platform that expediates access to advanced sp^3 architectures through catalytic halolactonization (see **4**) or enolate alkylation (see **5**). We next sought to convert **3** to vicinally difunctionalized allylic pyrrolidines such as **6**/**7** and interrogate the latter in a four-carbon ring expansion protocol, in view of preparing highly customized azonines of type **8** (Fig. 2B). The successful implementation of our ideals would lead to the construction of medium-sized endocyclic dienamines with complete control of the *E*/*Z* geometries of the enamine and alkene C=C double bonds resident in the ring. Additionally, this approach would furnish sp^3-rich nine-membered nitrogen heterocycles bearing at least two tetrahedral sterocenters, including a remote benzylic stereocenter. Efforts toward a succinct manifestation of this 'scaffold hopping' concept, which skeletally remodels sterically imposing and vicinally functionalized allylic pyrrolidine methanols to functionalized azonines are described herein. The method takes advantage of the highly polar nature of the initially formed aza-Michael intermediate in the reaction of allylic cyclic amines and electron-deficient alkynes and employs HFIP as the reaction medium.

Results and discussion

We initiated studies toward the skeletal remodelling of vicinally functionalized allylic pyrrolidines to functionalized azonines by attempting to synthesize the starting materials (*i.e.*, **6** and **7**). In the event, we found that the annulation of **1** with **2** using our



Performed on 1.0 mmol scale using 5 mL HFIP. Isolated yields are reported in all cases. Reaction times ranged from 48 to 72 h. Diastereomeric ratios were determined by GC-MS and ^{1}H NMR analyses of the crude product. Relative configurations were established through coupling constants, 1D-, and 2D-NOE analyses.

Scheme 2 Diastereoselective four-carbon homologation of alkenol-tethered pyrrolidines to highly customized azonines.

previously reported conditions[10] followed by lithium aluminum hydride-assisted reduction of the allylic lactam acid proceeds cleanly to furnish the vicinally functionalized allylic primary pyrrolidinols **6** (Scheme 1). Tertiary pyrrolidinol **7a** was prepared by chemoselective addition of methylmagnesium bromide **9a** and subsequent reduction.

With an assorted wardrobe of vicinally functionalized allylic pyrrolidinols in hand, we next sought efficient conditions for the four-carbon ring expansion to sp^3-rich azonines bearing benzylic stereocenters. The unique chemical and physical properties that fluoroalkyl alcohols have in comparison with their non-fluorinated analogues (*e.g.*, high hydrogen bond donor ability, low nucleophilicity values, high polarity and ionizing power, and slightly acidic character), make them reaction media for reactions involving ionic processes.[11] Recognizing the highly polar nature of the initially formed aza-Michael intermediate in the reaction of allylic cyclic amines and electron-deficient alkynes (see **10**, Scheme 2), we surmised that HFIP would be an ideal solvent for the envisioned aza-Cope rearrangement of sterically encumbered α-styrenyl pyrrolidine methanols. Thus, a mixture of allylic pyrrolidinol **6m** (1 mmol) in HFIP (5 mL, 0.05 M) and ethyl propiolate (2 equiv.) was stirred at room temperature. After 48 h (based on GC-MS, TLC, and NMR analyses), a single diastereomer of azonine **8a** was obtained in high yield after purification (Scheme 1). Other solvents such as dichloromethane (DCM), 1,2-dichloroethane (DCE), ethanol, methanol, trifluoroethanol, and isopropyl alcohol were evaluated but they did not perform as well as HFIP. Encouraged by this outcome, several allylic primary pyrrolidinols were interrogated under the same reaction conditions. In the event, some of the structurally diverse 9-membered azaheterocycles depicted in Scheme 1 were obtained (see **8a–l**). Differentially *N*-substituted cyclic amines tend to display diverse reactivity and biological activity profiles.[12] The strategic construction of azonines harboring the *N*-phenethyl group (see **8c–e**) is noteworthy given that the latter is often employed as a precursor to the indolizidine/quinolizidine/tetrahydroisoquinoline scaffolds.[13] Azonines bearing electron-rich and electron-deficient aryl groups at the benzylic stereocenters have been assembled. The transformation displays excellent chemoselectivity given that allylic pyrrolidines bearing an *N*-allyl substituent reacts with ethyl propiolate to afford ring expanded products **8l**/**m**, without complications arising from homologation at the kinetically more accessible allyl group. This came as a surprise to us since there are several reports describing the 3-aza-Cope rearrangement of *N*-allyl amines with electron-deficient terminal and internal alkynes.[9a,g] These studies have revealed that allylic pyrrolidines bearing halogenated arenes are well tolerated (see **8e**/**i**/**j**), which bodes well for late-stage diversification since the halogen group may be utilized as a requisite group for cross-coupling purposes. It is noteworthy that *N*-benzyl substituents performed remarkably well in the four-carbon ring expansion protocol given that the benzyl group is easily removable under diverse reaction conditions.[14] These skip dienes are formed in impeccable *E*/*Z* stereoselectivities at each of the alkene termini. This includes the formation of trisubstituted alkenes (see **8f–m** and **8o–x**), which are traditionally difficult to prepare in a stereoselective manner. The reaction also proceeds with complete stereochemical control at the benzylic stereocenter. Similar results are obtained when the α-styrenyl pyrrolidine methanols are subjected to the homologation protocol using methyl propiolate in place of ethyl propiolate (see **8n–x**). However, a current limitation of these studies is that we are yet to find suitable reaction conditions for the successful deployment of internal alkynes such as dimethyl acetylenedicarboxylate (DMAD). These studies have revealed that tertiary pyrrolidinol **7a** reacts efficiently with ethyl propiolate and methyl propiolate (see **8y**/**z**).

Conclusions

In summary, we have leveraged the synthetic versatility of allylic pyrrolidine methanols to develop a scaffold hopping strategy that skeletally remodels vicinally functionalized allylic pyrrolidines to highly decorated azonines bearing benzylic stereocenters. The success of the protocol hinges on the use of a polar solvent (*i.e.*, HFIP) as the reaction medium, which served to enhance the interaction with the highly charged zwitterionic intermediate during the subsequent [3,3] sigmatropic rearrangement that furnishes the four-carbon homologation product. These studies represent a significant advance over existing strategies in that sterically imposing α-styrenyl tertiary pyrrolidines and vicinally functionalized allylic tertiary pyrrolidines can now be ring-expanded efficiently. The resulting aza-heterocyclic skip dienes are formed in impeccable *E*/*Z* stereoselectivities at each of the alkene termini, which is noteworthy given that unsymmetrical trisubstituted alkenes are typically difficult to prepare in a stereoselective manner. The stereochemical fidelity of the tetrahedral benzylic stereocenter formed during the homologation reaction is quite impressive. We anticipate that the scalable as well as operationally simple natures of this protocol would endear it to the organic and medicinal chemistry communities.

Data availability

The data supporting this article have been included as part of the ESI.†

Author contributions

T. K. B. – conceptualization, project administration, supervision, investigation, data curation, methodology, writing – original draft, internal funding acquisition; A. J., A. G., and J. K. – investigation, data curation, methodology.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

T. K. B. is grateful to Central Washington University (CWU) for financial support and for the continued maintenance of major

research instrumentation. The Office of University Research (OUR) at CWU is acknowledged for research fellowships awarded to A. J., A. G., and J. K. The School of Graduate Studies and Research at CWU is thanked for partial support of this project through a Faculty Research Award.

Notes and references

1 (*a*) E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 10257–10274; (*b*) R. D. Taylor, M. MacCoss and A. D. G. Lawson, *J. Med. Chem.*, 2014, **57**, 5845–5859; (*c*) F. Makolo, A. Viljoen and C. G. L. Veale, *Phytochem*, 2019, **166**, 112061.

2 (*a*) S. Mukherjee, J. W. Yang, S. Hoffmann and B. List, *Chem. Rev.*, 2007, **107**, 5471–5569; (*b*) A. G. Doyle and E. N. Jacobsen, *Chem. Rev.*, 2007, **107**, 5713–5743; (*c*) G. Li Petri, M. V. Raimondi, V. Spano, R. Holl, P. Barraja and A. Montalbano, *Top. Curr. Chem.*, 2021, **379**, 34.

3 (*a*) R. H. Kohli, C. T. Walsh and M. D. Burkart, *Nature*, 2002, **418**, 658; (*b*) E. M. Driggers, S. P. Hale, J. Lee and N. K. Terrett, *Nat. Rev. Drug Discovery*, 2008, **7**, 608; (*c*) E. Marsault and M. L. Peterson, *J. Med. Chem.*, 2011, **54**, 1961; (*d*) J. Xie and N. Bogliotti, *Chem. Rev.*, 2014, **114**, 7678; (*e*) A. K. Yudin, *Chem. Sci.*, 2015, **6**, 30; (*f*) S. Dawn, M. B. Dewal, D. Sobransingh, M. C. Paderes, A. C. Wibowo, M. D. Smith, J. A. Krause, P. J. Pellechia and L. S. Shimizu, *J. Am. Chem. Soc.*, 2011, **133**, 7032; (*g*) Y. Demizu, N. Yamagata, S. Nagoya, Y. Sato, M. Doi, M. Tanaka, K. Nagasawa, H. Okuda and M. Kurihara, *Tetrahedron*, 2011, **67**, 6155; (*h*) K. Sato, Y. Itoh and T. Aida, *J. Am. Chem. Soc.*, 2011, **133**, 13767; (*i*) N. H. Evans and P. D. Beer, *Chem. Soc. Rev.*, 2014, **43**, 4658; (*j*) M. Xue, Y. Yang, X. Chi, X. Yan and F. Huang, *Chem. Rev.*, 2015, **115**, 7398; (*k*) M. Iyoda, J. Yamakawa and M. J. Rahman, *Angew. Chem., Int. Ed.*, 2011, **50**, 10522; (*l*) M. Yu, C. Wang, A. F. Kyle, P. Jakubec, D. J. Dixon, R. R. Schrock and A. H. Hoveyda, *Nature*, 2011, **479**, 88; (*m*) W. P. Unsworth, K. A. Gallagher, M. Jean, J. P. Schmidt, L. J. Diorazio and R. J. K. Taylor, *Org. Lett.*, 2013, **15**, 62; (*n*) T. O. Ronson, R. J. K. Taylor and I. J. S. Fairlamb, *Tetrahedron*, 2015, **71**, 89; (*o*) S. M. Rummelt, J. Preindl, H. Sommer and A. Furstner, *Angew. Chem., Int. Ed.*, 2015, **54**, 6241.

4 (*a*) L. G. Baud, M. A. Manning, H. L. Arkless, T. C. Stephens and W. P. Unsworth, *Chem. – Eur. J.*, 2017, **23**, 2225; (*b*) U. Nubbemeyer, *Stereoselective Heterocyclic Synthesis III; Topics in Current Chemistry*, Springer, Berlin, 2001, vol. 216, p. 125.

5 L. A. Marcaurelle, E. Comer, S. Dandapani, J. R. Duvall, B. Gerard, S. Kesavan, M. D. Lee, H. Liu, J. T. Lowe, J.-C. Marie, C. A. Mulrooney, B. A. Pandya, A. Rowley, T. D. Ryba, B.-C. Suh, J. Wei, D. W. Young, L. B. Akella, N. T. Ross, Y. L. Zhang, D. M. Fass, S. A. Reis, W.-N. Zhao, S. J. Haggarty, M. Palmer and M. A. Foley, *J. Am. Chem. Soc.*, 2010, **132**, 16962.

6 J. Kim, J. Jung, J. Koo, W. Cho, W. S. Lee, C. Kim, W. Park and S. B. Park, *Nat. Commun.*, 2016, **7**, 13196.

7 G. Illuminati and L. Mandolini, *Acc. Chem. Res.*, 1981, **14**, 95.

8 (*a*) N. Brown, G. Gao, M. Minatoya, B. Xie, D. VanderVeide, G. H. Lushington, J. P. H. Perchellet, E. M. Perchellet, K. R. Crow and K. R. Buszek, *J. Comb. Chem.*, 2008, **10**, 628–631; (*b*) I. Shiina, *Chem. Rev.*, 2007, **107**, 239; (*c*) L. Huang, L. X. Dai and S. L. You, *J. Am. Chem. Soc.*, 2016, **138**, 5793; (*d*) J. E. Hall, J. V. Matlock, J. W. Ward and J. Clayden, *Angew. Chem., Int. Ed.*, 2016, **55**, 11153; (*e*) M. A. Casadei, C. Galli and L. Mandolini, *J. Am. Chem. Soc.*, 1984, **106**, 1051; (*f*) K. C. Majumdar, *RSC Adv.*, 2011, **1**, 1152; (*g*) A. Sharma, P. Appukkuttan and E. Van der Eycken, *Chem. Commun.*, 2012, **48**, 1623; (*h*) J. Fastrez, *J. Phys. Chem.*, 1989, **93**, 2635; (*i*) J. C. Collins and K. James, *MedChemComm*, 2012, **3**, 1489; (*j*) H. Kurouchi and T. Ohwada, *J. Org. Chem.*, 2020, **85**, 876; (*k*) T. P. Majhi, B. Achari and P. Chattopadhyay, *Heterocycles*, 2007, **71**, 1011; (*l*) F. Kopp, C. F. Stratton, L. B. Akella and D. S. Tan, *Nat. Chem. Biol.*, 2012, **8**, 358; (*m*) R. A. Bauer, T. A. Wenderski and D. S. Tan, *Nat. Chem. Biol.*, 2013, **9**, 21; (*n*) C. Zhao, Z. Ye, Z.-X. Ma, S. A. Wildman, S. A. Blaszczyk, L. Hu, I. A. Guizei and W. Tang, *Nat. Commun.*, 2019, **10**, 4015; (*o*) G. A. Molander, *Acc. Chem. Res.*, 1998, **31**, 603; (*p*) W. P. Unsworth and J. R. Donald, *Chem.–Eur. J.*, 2017, **23**, 8780; (*q*) T. C. Stephens and W. P. Unsworth, *Synlett*, 2020, **31**, 133.

9 (*a*) E. Vedejs and M. Gingras, *J. Am. Chem. Soc.*, 1994, **116**, 579–588; (*b*) E. W. Baxter, D. Labaree, H. L. Ammon and P. S. Mariano, *J. Am. Chem. Soc.*, 1990, **112**, 7682–7692; (*c*) A. L. Schwan and J. Warkentin, *Can. J. Chem.*, 1988, **66**, 1686–1694; (*d*) A. Hassner, R. D'Costa, A. T. McPhail and W. Butler, *Tetrahedron Lett.*, 1981, **22**, 3691–3694; (*e*) T. G. Back, *Tetrahedron*, 2001, **57**, 5263–5301; (*f*) T. G. Back and K. Nakajima, *J. Org. Chem.*, 1998, **63**, 6566–6571; , 2000, **65**, 4543–4552; (*g*) T. G. Back, M. D. Hamilton, V. J. J. Lim and M. Parvez, *J. Org. Chem.*, 2005, **70**, 967–972; (*h*) T. G. Back, M. Parvez and J. E. Wulff, *J. Org. Chem.*, 2003, **68**, 2223–2233; (*i*) H. Zhai, M. Parvez and T. G. Back, *J. Org. Chem.*, 2007, **72**, 3853–3858; (*j*) M. H. Weston, K. Nakajima, M. Parvez and T. G. Back, *Chem. Commun.*, 2006, 3903–3905; (*k*) M. H. Weston, K. Nakajima and T. G. Back, *J. Org. Chem.*, 2008, **73**, 4630–4637.

10 I. S. Anosike and T. K. Beng, *RSC Adv.*, 2024, **14**, 18501–18507.

11 (*a*) I. Colomer, A. E. R. Chamberlain, M. B. Haughey and T. J. Donohoe, *Nat. Rev. Chem.*, 2017, **1**, 88; (*b*) J. Wencel-Delord and F. Colobert, *Org. Chem. Front.*, 2016, **3**, 394–400; (*c*) T. Sugiishi, M. Matsugi, H. Hamamoto and H. Amii, *RSC Adv.*, 2015, **5**, 17269–17282; (*d*) S. Khaksar and J. Fluor, *Chem*, 2015, **172**, 51–61; (*e*) I. A. Shuklov, N. V. Dubrovina and A. Börner, *Synthesis*, 2007, **19**, 2925–2943.

12 T. K. Beng and R. E. Gawley, *J. Am. Chem. Soc.*, 2010, **132**, 12216.

13 A. Calcaterra, L. Mangiardi, G. D. Monache, D. Quaglio, S. Balducci, S. Berardozzi, A. Iazzetti, R. Franzini, B. Botta and F. Ghirga, *Molecules*, 2020, **25**, 414.

14 T. W. Greene, *Protective Groups in Organic Synthesis*, Wiley Interscience, New York, 1981.