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Access to pyrrolines and fused diaziridines by selective radical addition to homoallylic diazirines†‡

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Pyrroline derivatives are common in bioactive natural products and therapeutic agents. We report here a synthesis of pyrrolines and fused diaziridines by divergent radical cyclization of homoallylic diazirines, which can serve as an internal radical trap and a nitrogen source. This reaction proceeds by selective radical addition to C=C or N=N bonds followed by intramolecular cyclization. Frontier molecular orbital analysis provides a deep insight into the origin of the selectivity. The reaction demonstrates a new cyclization mode, broad functional group compatibility and high product diversity, and reveals a much broader chemical space for diazirine studies.

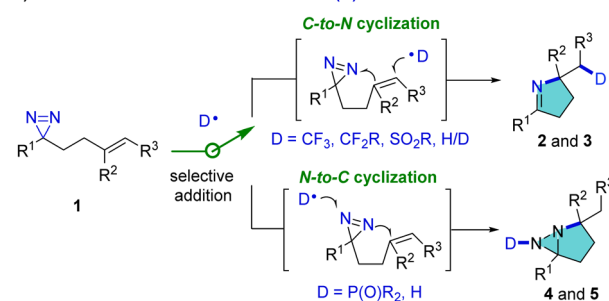
Pyrroline and pyrrolidine structural motifs are widely encountered in bioactive natural products in plants, insects such as myrmicine ants and animals, including poison frogs.^{1,2} Consequently, new strategies to access pyrrolines and analogues address a long-standing interest of chemists. Notwithstanding the interest in transition-metal catalyzed synthesis of pyrroline derivatives over the past few decades,³ radical approaches have also received remarkable attention owing to their innately attractive features which include mild reaction conditions and good tolerance of susceptible functional groups.⁴ The conventional radical approaches proceed through the generation of an iminyl radical by homolysis or single-electron transfer (SET) in labile precursors and the subsequent intramolecular N → C cyclization of the iminyl radical with C=C bonds. External radical acceptors are sought which can terminate the cascade reaction and furnish pyrroline products (Fig. 1a).⁵ We have conceived a reverse route which can access pyrrolines by C → N cyclization using external radical donors rather than acceptors (Fig. 1b). This process is intended to enrich product diversity and lead to distinct pyrrolines, such as CF₃-substituted pyrrolines, which are difficult to produce by conventional methods. This is because there are no SOMOphiles that lead to the introduction of, for example, CF₃ groups.

Diazirines, which consist of one carbon and two nitrogen atoms in an unsaturated three-membered ring, are often exploited in chemical biology as carbene precursors.⁶ They have been reported only rarely in radical reactions. The use of

a) Conventional radical approaches: with external radical acceptor (A)



b) This work: with external radical donor (D)



c) LUMO and HOMO analysis of diazirine substrate

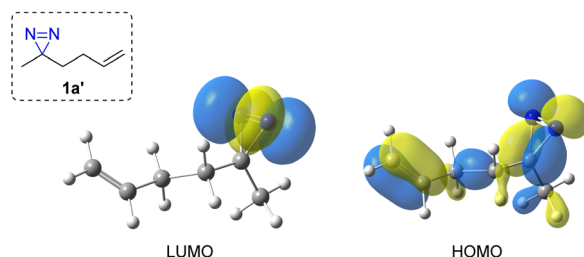


Fig. 1 Radical synthetic approaches of pyrroline derivatives.

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smoothly, leading to an aza-spiro product (**2u**) with exclusive diastereoselectivity (*dr* > 20 : 1). Aryl-substituted diazirines (**2v**) are also suitable substrates for the reaction. In addition to pyrrolines, tetrahydropyridine as a six-membered analogue could also be produced under the same conditions (**2w**, **2x** and **2y**), enriching the product library. Construction of other six-membered N-containing heterocycles could also be anticipated by placing various heteroatoms on the aliphatic chain. Attempts to construct seven- or eight-membered or even larger N-containing heterocycles by extending the aliphatic chain were unsuccessful. Remarkably, it was found however that this protocol can be applied to the dearomative 2,3-difunctionalization of indoles, providing spiro-indoline products (**2z–2ab**) with excellent stereo-selectivity. These three-dimensional indolines are widely distributed in various bioactive molecules.¹¹

Using electrophilic radicals other than the CF₃ radical further enriched the diversity of products from the reaction. As shown in Fig. 3, a portfolio of external radicals, such as di- or perfluoroalkyl radicals, electron-deficient alkyl radicals and

sulfonyl radicals proved to be amenable to photoredox catalytic conditions, leading to the corresponding pyrrolines (**3a–3m**) in acceptable yields. The formation of **3e** and **3f** from the enyne-substituted diazirine precursors, is noteworthy, as the nascent propargyl radical was retained and engaged in the cyclization without conversion to the tautomeric allenyl radical.¹² A set of (hetero)aryl, alkyl and styryl substituted sulfonyl radicals were added readily to the substrates, but the strong electron-deficient radicals delivered a lower yield (**3k**). A sulfonyl radical could also be generated under thermal conditions using copper(II) acetate as the oxidant and sodium *p*-toluenesulfonate as the radical source (**3g**). Combining this process with a metal-hydride hydrogen atom transfer (MHAT) led to the products containing incorporated hydrogen or deuterium (**3n**, **3o**) in good yields, demonstrating the breadth of the method.

It was found that the addition of P-centered radicals to diazirine (**1**) proceeded through a distinct pathway and resulted in fused diaziridine products (Fig. 4). Diarylphosphinoyl radicals were generated from diarylphosphine oxides in the presence of silver nitrate as a catalyst, and were selectively added to the N=N rather than the C=C bond. The N → C cyclization generated an alkyl radical reaction which was terminated by HAT from diarylphosphine oxide. Meanwhile, the diarylphosphinoyl radical was regenerated, perpetuating the radical chain process. Compared to the diazirines (**4a**, **4b**) which bear a 1,2-dialkyl alkene, the diazirine bearing a trisubstituted alkene delivered a lower yield (**4c**), probably because of the weak H-atom transfer (HAT) ability of the tertiary alkyl radical and the steric congestion that impeded the



Fig. 3 Investigation of external radicals. Condition A: **1** (0.2 mmol), (fluoro)alkyl bromide (0.4 mmol), *fac*-Ir(ppy)₃ (0.004 mmol), Hantzsch ester (0.4 mmol) and 2,6-lutidine (0.4 mmol) in dry MeCN (2.0 mL) under Ar irradiated with 5 W × 2 blue LEDs at rt for 12 h. Condition B: **1** (0.2 mmol), sulfonyl chloride (0.4 mmol), *fac*-Ir(ppy)₃ (0.004 mmol), DIPEA (0.4 mmol) and K₂HPO₄ (0.4 mmol) in MeCN/H₂O (2.0 mL/0.2 mL) under Ar irradiated with 5 W × 2 blue LEDs at rt for 12 h. Condition C: **1** (0.2 mmol), PhSiH₃ or PhSiD₃ (0.4 mmol), Fe(acac)₃ (0.06 mmol) and EtOH (0.4 mmol) in THF (2.0 mL) under air at 60 °C. Yields of isolated products are given. ^aPerfluoroalkyl iodide was used. ^bWith sodium *p*-toluenesulfonate (0.3 mmol) and Cu(OAc)₂ (0.2 mmol) in MeCN (2.0 mL) at 60 °C for 13 h.



Fig. 4 Synthesis of fused diaziridines by P-radical addition. Reaction conditions: **1** (0.2 mmol), diarylphosphine oxide **6** (0.4 mmol) and AgNO₃ (0.02 mmol) in EA (2.0 mL) under Ar at 30 °C. Yields of isolated products are given. For **4a–4i**, *dr* > 20 : 1. ^aAt 40 °C.



HAT. The engagement of the highly reactive primary alkyl radicals from HAT was less controllable, and also led to a decreased yield (**4d**). Skeletal complex polycyclic diaziridines (**4e**, **4f**) are otherwise difficult to prepare, but were furnished in useful yields by this method. A quaternary carbon center can be readily constructed in this reaction.

The reductive cyclization of **1** was accomplished to generate a new type of fused diaziridine (**5**) under photochemical conditions using a Hantzsch ester (HE) as a reducing agent (Fig. 5). These fused diaziridines might serve as versatile precursors for various N-heterocycles according to published approaches.¹³ The reaction leading to fused diaziridines was initiated by the reductive quenching of excited *fac*-Ir(ppy)₃ with the Hantzsch ester to form an Ir(II) species. Its strong reduction potential ($E_{1/2}^{\text{III/II}} = -2.19$ V vs. SCE) enables single-electron reduction of the N=N bond of diazirine ($E_{1/2}^{\text{RE}} = -2.06$ V vs. SCE) to an N-centered radical anion (for details, see the ESI†), and this is followed by a sequence of intramolecular cyclization, HAT and protonation. It should be noted that excited *fac*-Ir(ppy)₃ ($E_{1/2}^{\text{III*}/\text{IV}} = -1.73$ V vs. SCE) is not sufficient to reduce diazirines to trigger the reaction.

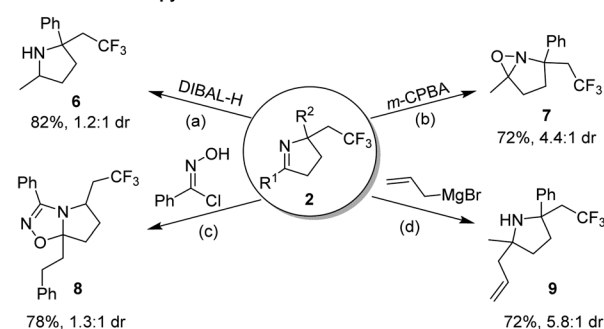
A scaled-up preparation of pyrroline (**2m**) from 2 mmol of **1m** was achieved with 82% isolated yield, illustrating the practicality of the protocol. The products could be further converted to other valuable molecules (Fig. 6). For example, in the presence of diisobutyl aluminum-hydride (DIBAL-H), **2m** was readily reduced to a pyrrolidine (**6**). The treatment of **2m** with *m*-CPBA gave rise to a fused oxaziridine (**7**). The [3 + 2] cycloaddition of **2a** with *N*-hydroxybenzimidoyl chloride generated the biologically relevant, CF₃-substituted 1,2,4-oxadiazoline (**8**).¹⁴ Addition of an allyl Grignard reagent to the C=N bond of **2m** in the presence of BF₃·Et₂O afforded 2,2,5,5-tetrasubstituted pyrroline (**9**). Simple treatment of **5a** with acetyl chloride resulted in *N*-acetyl-tetrahydropyridazine (**10**) by a ring-opening process.

Based on the above experimental and computational results, a plausible mechanism is depicted in Fig. 7. For electrophilic radicals such as the fluoroalkyl and sulfonyl radicals, the selective addition to the C=C bond of **1**, followed by intramolecular trapping of a radical (**a**) by the N=N bond gives rise to an N-centered radical (**b**), which can form a dimer (**c**). Intermediate **c** is unstable, and simultaneously undergoes N₂ extrusion to afford two molecules of the pyrroline product.^{7,15}



Fig. 5 Reductive cyclization generating fused diaziridines. Reaction conditions: **1** (0.2 mmol), *fac*-Ir(ppy)₃ (0.004 mmol) and Hantzsch ester (0.4 mmol) in dry DCM (4.0 mL) under Ar irradiated with 5 W × 2 blue LEDs at rt for 4 h. Yields of isolated products are given. For **5a**–**5c**, dr > 20 : 1.

Transformation of pyrroline



Transformation of fused diaziridine



Fig. 6 Product transformations. Reaction conditions: (a) **2m** (0.2 mmol), DIBAL-H (0.6 mmol) in DCM (2.0 mL) at -78 °C for 4 h; (b) **2m** (0.2 mmol), *m*-CPBA (0.3 mmol) and Na₂HPO₄ (0.3 mmol) in DCM at rt for 2 h; (c) **2a** (0.1 mmol), *N*-hydroxybenzimidoyl chloride (0.15 mmol) and Et₃N (0.2 mmol) in DCM (2.0 mL) at rt for 3 h; (d) **2m** (0.2 mmol), Et₂O·BF₃ (0.6 mmol) and allyl magnesium bromide (0.6 mmol) in THF (5.0 mL) at -78 °C for 4 h; (e) **5a** (0.2 mmol), AcCl (0.6 mmol) and Et₃N (0.6 mmol) in DCM (2.0 mL) for 3 h at rt.

The formation of radical **b** was confirmed by the detection by HRMS of the fused diaziridine (**d**) which is gained from competitive HAT. In contrast, the relatively nucleophilic phosphinoyl radical prefers addition to the N=N bond of **1**, resulting in radical **e**. The subsequent intramolecular cyclization to the C=C bond and HAT affords the fused diaziridine products. The formation of intermediate **e** was confirmed by the isolation of byproduct **g** derived from HAT.

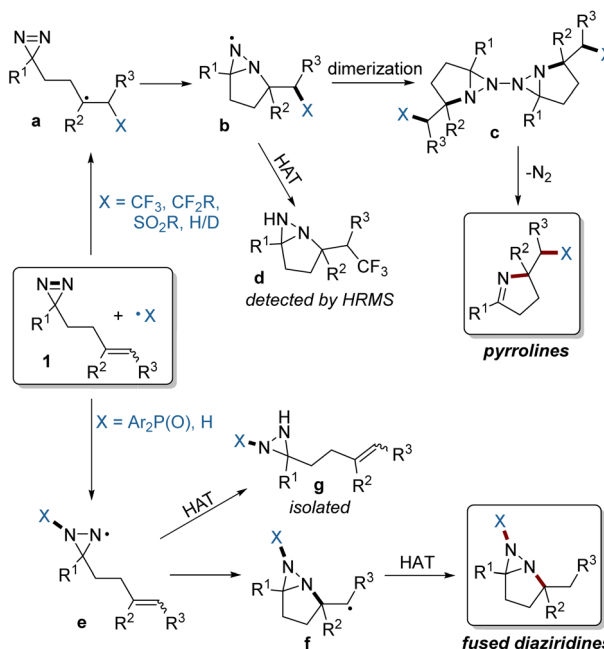


Fig. 7 Proposed reaction mechanism.



Conclusions

In summary, a novel radical-mediated divergent synthesis of pyrrolines and fused diaziridines from rationally designed alkene-substituted diazirines is described. The key to the success of the reaction is the selective addition of an external radical to the C=C or N=N bond, which is controlled by the inherent electronic characteristics of the external radical. FMO analysis sheds light on the underlying reason for the chemoselectivity. The protocol features good functional group tolerance and high product diversity, and creates a much broader chemical space for diazine studies.

Data availability

All relevant experimental and computational data and characterization details are provided in the ESI.†

Author contributions

C. Z. conceived the idea and designed the experiments, Z. M. performed most of the experiments, X. W. performed the DFT calculations, H. L. synthesized some of the starting materials, Z. C. helped with analysis of the data, and C. Z. supervised the research and co-wrote the manuscript.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

- (a) J. W. Daly, H. M. Garraffo and T. F. Spande, in *Alkaloids Chem. Biol. Perspect.*, ed. S. W. Pelletier, Elsevier, Oxford, 1999, pp. 1–161; (b) T. Aniszewski, in *Alkaloids – Secrets Life*, Elsevier, 2007, pp. 61–139; (c) T. H. Jones, V. E. Zottig, H. G. Robertson and R. R. Snelling, *J. Chem. Ecol.*, 2003, **29**, 2721–2727; (d) T. H. Jones, A. N. Andersen and J. C. Kenny, *Chem. Biodiversity*, 2009, **6**, 1034–1041; (e) J. Chen, C. L. Cantrell, D. Oi and M. J. Grodowitz, *Toxicon*, 2016, **122**, 127–132.
- (a) R. D. Taylor, M. MacCoss and A. D. G. Lawson, *J. Med. Chem.*, 2014, **57**, 5845–5859; (b) E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 10257–10274; (c) A. Kondo, N. Morita, T. Ishikawa, M. Yoshida, A. Moriyama and I. Wanajo, *US Pat.*, US10995084B2, 2018; (d) A. Kondo, N. Morita, T. Ishikawa, M. Yoshida, A. Moriyama and I. Wanajo, EP3459941A1, 2019; (e) A. Kondo, N. Morita, T. Ishikawa, M. Yoshida, A. Moriyama and I. Wanajo, *US Pat.*, US2020/0299273A1, 2020; (f) E. Martinborough, Y. Shen, A. van Oeveren, Y. O. Long, T. L. S. Lau, K. B. Marschke, W. Y. Chang, F. J. López, E. G. Vajda, P. J. Rix, O. H. Viveros, A. Negro-Vilar and L. Zhi, *J. Med. Chem.*, 2007, **50**, 5049–5052; (g) H. Ü. Kaniskan, M. S. Eram, K. Zhao, M. M. Szweczyk, X. Yang, K. Schmidt, X. Luo, S. Xiao, M. Dai, F. He, I. Zang, Y. Lin, F. Li, E. Dobrovetsky, D. Smil, S. J. Min, J. Lin-Jones, M. Schapira, P. Atadja, E. Li, D. Barsyte-Lovejoy, C. H. Arrowsmith, P. J. Brown, F. Liu, Z. Yu, M. Vedadi and J. Jin, *J. Med. Chem.*, 2018, **61**, 1204–1217.
- For selected examples, see: (a) A. Faulkner, J. S. Scott and J. F. Bower, *Chem. Commun.*, 2013, **49**, 1521–1523; (b) A. Faulkner, N. J. Race, J. S. Scott and J. F. Bower, *Chem. Sci.*, 2014, **5**, 2416–2421; (c) A. Faulkner, J. S. Scott and J. F. Bower, *J. Am. Chem. Soc.*, 2015, **137**, 7224–7230; (d) C. Chen, L. Hou, M. Cheng, J. Su and X. Tong, *Angew. Chem., Int. Ed.*, 2015, **54**, 3092–3096; (e) N. J. Race, A. Faulkner, G. Fumagalli, T. Yamauchi, J. S. Scott, M. R. Landergren, H. A. Sparkes and J. F. Bower, *Chem. Sci.*, 2017, **8**, 1981–1985; (f) H.-B. Yang, S. R. Pathipati and N. Selander, *ACS Catal.*, 2017, **7**, 8441–8445; (g) L. Wang and C. Wang, *J. Org. Chem.*, 2019, **84**, 6547–6556; (h) Y. Zhang, H.-J. Ai and X.-F. Wu, *Org. Chem. Front.*, 2020, **7**, 2986–2990; (i) X. Zhang, D. Qi, C. Jiao, Z. Zhang, X. Liu and G. Zhang, *Org. Chem. Front.*, 2021, **8**, 6522–6529.
- For selected reviews, see: (a) M. M. Jackman, Y. Cai and S. L. Castle, *Synthesis*, 2017, **49**, 1785–1795; (b) J. Fu, G. Zanon, E. A. Anderson and X. Bi, *Chem. Soc. Rev.*, 2017, **46**, 7208–7228; (c) P. Xiong and H.-C. Xu, *Acc. Chem. Res.*, 2019, **52**, 12–22; (d) X.-Y. Yu, Q.-Q. Zhao, J. Chen, W.-J. Xiao and J.-R. Chen, *Acc. Chem. Res.*, 2020, **53**, 1066–1083; (e) J. Boivin, E. Fouquet and S. Z. Zard, *Tetrahedron Lett.*, 1991, **32**, 4299–4302; (f) X. Sun and S. Yu, *Chem. Commun.*, 2016, **52**, 10898–10901; (g) X.-Y. Yu, J.-R. Chen, P.-Z. Wang, M.-N. Yang, D. Liang and W.-J. Xiao, *Angew. Chem., Int. Ed.*, 2018, **57**, 738–743; (h) E. M. Dauncey, S. U. Dighe, J. J. Douglas and D. A. Leonori, *Chem. Sci.*, 2019, **10**, 7728–7733; (i) J. Singh, G. A. Nickel, Y. Cai, D. D. Jones, T. J. Nelson, J. E. Small and S. L. Castle, *Org. Lett.*, 2021, **23**, 3970–3974.
- (a) J. Davies, S. G. Booth, S. Essafi, R. A. W. Dryfe and D. Leonori, *Angew. Chem., Int. Ed.*, 2015, **54**, 14017–14021; (b) J. Davies, N. S. Sheikh and D. Leonori, *Angew. Chem., Int. Ed.*, 2017, **56**, 13361–13365; (c) H. Jiang and A. Studer, *Angew. Chem., Int. Ed.*, 2017, **56**, 12273–12276; (d) S.-H. Cai, J.-H. Xie, S. Song, L. Ye, C. Feng and T.-P. Loh, *ACS Catal.*, 2016, **6**, 5571–5574; (e) S.-H. Cai, D.-X. Wang, L. Ye, Z.-Y. Liu, C. Feng and T.-P. Loh, *Adv. Synth. Catal.*, 2018, **360**, 1262–1266; (f) X. Shen, C. Huang, X.-A. Yuan and S. Yu, *Angew. Chem., Int. Ed.*, 2021, **60**, 9672–9679.
- (a) R. A. Moss, *Acc. Chem. Res.*, 2006, **39**, 267–272; (b) J. Das, *Chem. Rev.*, 2011, **111**, 4405–4417.



- 7 D. H. R. Barton, J. C. Jaszberenyi, E. A. Theodorakis and J. H. Reibenspies, *J. Am. Chem. Soc.*, 1993, **115**, 8050–8059.
- 8 (a) P. P. Chandrachud, L. Wojtas and J. M. Lopchuk, *J. Am. Chem. Soc.*, 2020, **142**, 21743–21750; (b) V. Maharaj, P. P. Chandrachud, W. Che, L. Wojtas and J. M. Lopchuk, *Org. Lett.*, 2021, **23**, 8838–8842.
- 9 X. Shu, R. Xu and S. Liao, *Sci. China: Chem.*, 2021, **64**, 1756–1762.
- 10 (a) M. Lebœuf, A. Ranaivo, A. Cavé and H. Moskowicz, *J. Nat. Prod.*, 1989, **52**, 516–521; (b) S. Kim, Y. M. Lee, J. Lee, T. Lee, Y. Fu, Y. Song, J. Cho and D. Kim, *J. Org. Chem.*, 2007, **72**, 4886–4891.
- 11 (a) Y. J. Zheng, C. M. Tice and S. B. Singh, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 3673–3682; (b) N. Ye, H. Y. Chen, E. A. Wold, P. Y. Shi and J. Zhou, *ACS Infect. Dis.*, 2016, **2**, 382–392; (c) Y. T. Yang, J. F. Zhu, G. C. Liao, H. J. Xu and B. Yu, *Curr. Med. Chem.*, 2018, **25**, 2233–2244.
- 12 (a) F. Wang, D. Wang, Y. Zhou, L. Liang, R. Lu, P. Chen, Z. Lin and G. Liu, *Angew. Chem., Int. Ed.*, 2018, **57**, 7140–7145; (b) K.-F. Zhang, K.-J. Bian, C. Li, J. Sheng, Y. Li and X.-S. Wang, *Angew. Chem., Int. Ed.*, 2019, **58**, 5069–5074; (c) X. Zhu, W. Deng, M.-F. Chiou, C. Ye, W. Jian, Y. Zeng, Y. Jiao, L. Ge, Y. Li, X. Zhang and H. Bao, *J. Am. Chem. Soc.*, 2019, **141**, 548–559.
- 13 (a) Y. B. Koptelov, *Russ. J. Org. Chem.*, 2006, **42**, 1510–1515; (b) J. M. Allen and T. H. Lambert, *Tetrahedron*, 2014, **70**, 4111–4117; (c) A. O. Chagarovskiy, V. S. Vasin, V. V. Kuznetsov, O. A. Ivanova, V. B. Rybakov, A. N. Shumsky, N. N. Makhova and I. V. Trushkov, *Angew. Chem., Int. Ed.*, 2018, **57**, 10338–10342; (d) H. Zheng and M. P. Doyle, *Angew. Chem., Int. Ed.*, 2019, **58**, 12502–12506; (e) H. Hu, J. Xu, F. Wang, S. Dong, X. Liu and X. Feng, *Org. Lett.*, 2020, **22**, 93–97; (f) T. Sarkar, K. Talukdar, S. Roy and T. Punniyamurthy, *Chem. Commun.*, 2020, **56**, 3381–3384; (g) A. A. Penney, M. M. Efremova, A. P. Molchanov, M. A. Kryukova, A. Y. Kudinov, A. S. Bunev, V. M. Keresten and M. A. Kuznetsov, *ChemistrySelect*, 2022, **7**, e202202627.
- 14 G. Dannhardt, K. K. Mayer and I. Sommer, *Sci. Pharm.*, 1984, **52**, 280–290.
- 15 (a) D. M. Gale, W. J. Middleton and C. G. Krespan, *J. Am. Chem. Soc.*, 1966, **88**, 3617–3623; (b) D. H. R. Barton, N. Ozbalik and B. Vacher, *Tetrahedron*, 1988, **44**, 7385–7392.

