



Cite this: *RSC Adv.*, 2022, **12**, 17617

Stereocontrolled access to δ -lactone-fused- γ -lactams bearing angular benzylic quaternary stereocenters[†]

Timothy K. Beng, * Morgan J. Rodriguez and Claire Borg

C-fused γ -lactam-lactones are resident in several bioactive molecules, including anticancer agents such as omuralide. In this embodiment, we report mild conditions for the catalytic halolactonization of lactam-tethered 5-aryl-4(*E*)-pentenoic acids. The use of dichloromethane as the solvent and $\text{Ph}_3\text{P}=\text{S}$ as the catalyst led to predominant 6-*endo*-*trig* cyclization and furnished the *trans*-fused- γ -lactam- δ -lactones. The transformation is modular, regioselective, chemoselective, and diastereoselective. The γ -lactam- δ -lactones bear angular quaternary benzylic stereocenters, which is noteworthy since the presence of a quaternary carbon in bioactive small molecules often promotes an element of conformational restriction that imparts potency, selectivity, and metabolic stability. The generated halogen and lactone motifs are important functional handles for late-stage diversification.

Received 4th April 2022
Accepted 7th June 2022

DOI: 10.1070/d2ra02167

rsc.li/rsc-advances

There are high incentives for the construction of architecturally complex sp^3 -enriched azaheterocyclic scaffolds. Specifically, the lactam topology is omnipresent in medicinal chemistry and drug discovery programs.¹ In addition to their well-studied antibiotic activity,² several functionalized lactams act as opioid receptor agonists,³ HIV-1 integrase inhibitors,⁴ anti-cancer,⁵ antidepressant,⁶ and anti-inflammatory agents.⁷ Meanwhile, lactones are ubiquitous architectures in a variety of natural products and pharmaceuticals.⁸ Lactones are also frequently used as versatile building blocks for accessing other oxygen-containing heterocycles and carboxylic acid derivatives.⁹ Importantly, sp^3 -rich fused γ -lactam-lactones are resident in bioactive molecules such as neooxazolomycin, UCS 1025 A, and omuralide (Fig. 1). Lovering has articulated that both molecular complexity (as measured by Fsp^3 , where Fsp^3 refers to the ratio of sp^3 hybridized carbons to the total number of carbons) and the presence of carbon stereocenters correlate with success as compounds transition from discovery, through clinical testing, to drugs.¹⁰ Medicinal chemists are therefore becoming increasingly keen on escaping flatland in view of exploring 3D-structural space, which makes these sp^3 -rich fused lactam-lactones valued targets for pharmaceutical companies. Some elegant strategies have fittingly emerged for the construction of fused lactam-lactones, including those developed by Wee¹¹ (using C-H insertion) and Burton¹² (*via* oxidative radical cyclization).

Our interest in the synthesis and post-diversification of 1,3-azadiene-cyclic anhydride annulation products¹³ prompted us to explore a lactamization/lactonization sequence as a method to rapidly construct sp³-rich fused γ -lactam- δ -lactones bearing quaternary and contiguous stereocenters. Toward this end, we sought to interrogate lactam-bearing alkenoic acids of type 3 in a catalytic halolactonization protocol (Fig. 2). Molecules containing all-carbon quaternary stereocenters have the propensity

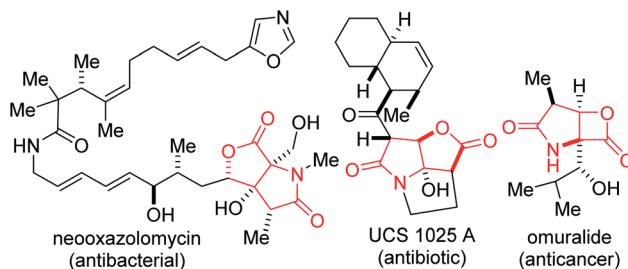


Fig. 1 Examples of C-fused bioactive γ -lactam-lactones.

Catalytic, regioselective, and stereocontrolled halolactonization of **3**

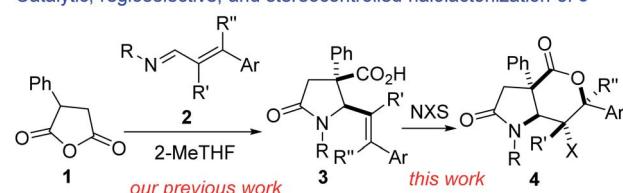


Fig. 2 Proposed plan for the synthesis of fused γ -lactam-fused- δ -lactones.

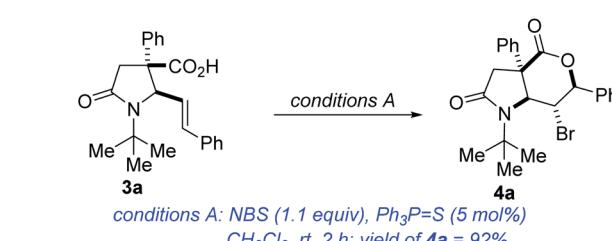
to mitigate a spectrum of structural diversity issues in medicinal chemistry mainly because the presence of a quaternary carbon in bioactive small molecules promotes an element of conformational restriction that imparts potency, selectivity, and metabolic stability.¹⁴ Indeed, of the top 120 chiral small-molecule pharmaceuticals by retail sales in the United States in 2018, 13% contained a quaternary stereocenter.¹⁵

Among the reported methods for the construction of common-ring lactones,¹⁶ halogen-initiated cyclization of unsaturated carboxylic acids is an attractive approach for the stereoselective synthesis of halogenated lactones.^{17,18} The transformation is very versatile given that the generated halogen and lactone motifs are important functional handles for late-stage diversification. In these studies, we show that lactam-tethered alkenoic acids of type 3 undergo efficient catalytic halolactonization to furnish fused γ -lactam- δ -lactones of type 4.

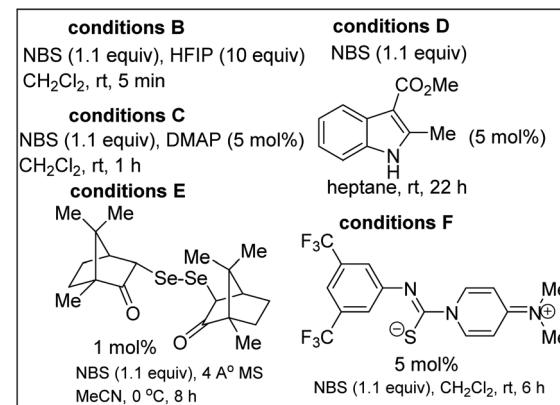
We initiated studies toward the construction of fused γ -lactam-lactones by benchmarking our optimization efforts for bromolactonization of alkenoic acid 3a with the reaction conditions described in Table 1. Dichloromethane emerged as the preferred reaction medium (entries 1–4). Other sources of bromine that were surveyed were less efficient than *N*-bromo-succinimide (entries 5 and 6). $\text{Ph}_3\text{P}=\text{S}$ emerged as the most effective catalyst (entries 7–12). Other reaction conditions known to promote bromolactonization of simple alkenoic acids were also surveyed (entries 13–17). Under the optimized conditions, lactam-lactone 4a was obtained in good yield, high *anti*-stereoselectivity, and in impeccable 6-*endo* selectivity. A widely accepted mechanism for this electrophilic halolactonization is that an electrophilic halogen is first transferred from a halogen source to the olefin to form a halonium ion, followed by an intramolecular attack by the carboxylate group. The observed *anti* addition in a Markovnikov sense is the expected outcome for such 5-aryl-4(*E*)-pentenoic acids, characterized by an unsymmetrical build-up of positive charge next to the aryl group in the transition state.¹⁹ Previous *ab initio* simulations revealed some *syn*-directing noncovalent interactions such as hydrogen bonding between the nucleophile and the halogen source, which control the formation of the *syn*-product.²⁰ The disruption of these *syn*-directing interactions by a basic additive or a protic solvent, results in a strongly increased diastereoselectivity toward the *anti*-product. Thus, we surmise that $\text{Ph}_3\text{P}=\text{S}$ enhances the *anti*-diastereoselectivity. This is further supported by observations that in the absence of $\text{Ph}_3\text{P}=\text{S}$ (entry 7), 4a was obtained in 83 : 17 (*anti* : *syn*) ratio.

The scope of the transformation with respect to the nature of the styrenyl group and the substituent on nitrogen (alkyl, aryl, allyl, and benzyl) has been explored. Gratifyingly, several γ -lactam-tethered alkenoic acids undergo 6-*endo* bromolactonization, giving rise to the 5,6-bicycles depicted in Scheme 1 (see 4a–s). Electron-deficient styrenoic acids are more competent than their electron-rich congeners, owing to their ability to further stabilize the benzylic positive charge (4b vs. 4c). The *N*-substituent has a profound effect on the diastereoselectivity as exemplified by the switch from a *tert*-butyl group to a less bulky but electronically similar isopropyl substituent (4a vs. 4g).

Table 1 Optimization of the bromolactonization of lactam acid 3a



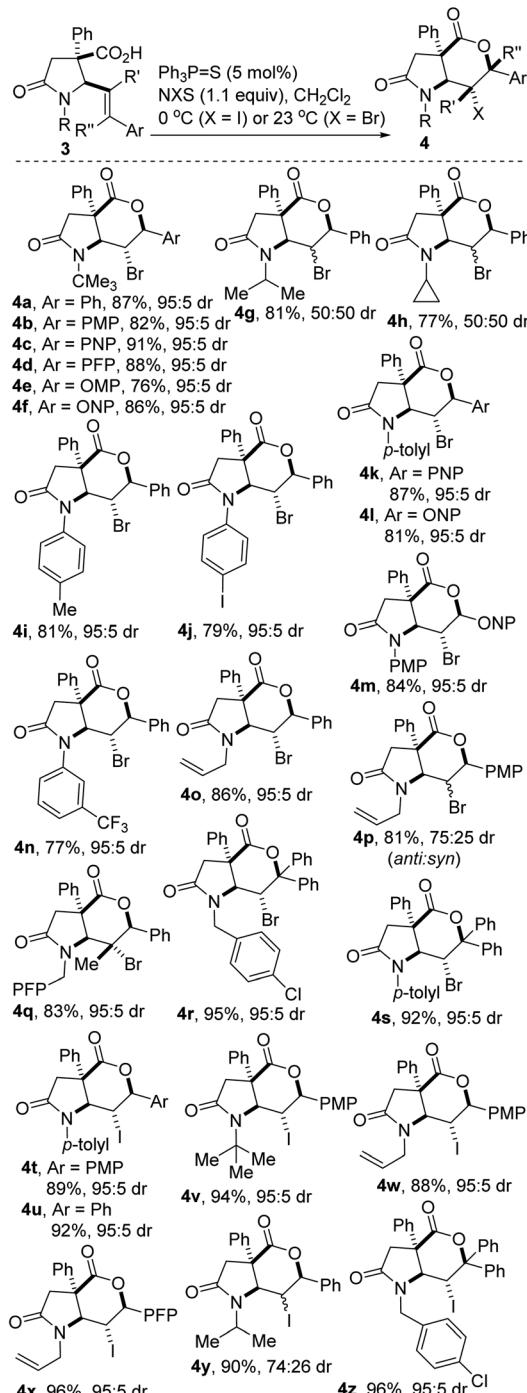
Entry	Deviation from conditions A	% yield of 4a (isolated)
1	1,2-Dichloroethane as solvent	75
2	<i>N,N</i> -Dimethylformamide as solvent	0 ^a
3	Acetonitrile as solvent	79
4	Methanol as solvent	83
5	Br_2 in place of NBS	0
6	DBH in place of NBS	68
7	$\text{Ph}_3\text{P}=\text{S}$ omitted	22
8	$\text{Ph}_3\text{P}=\text{O}$ in place of $\text{Ph}_3\text{P}=\text{S}$	73
9	$\text{Ph}_3\text{P}=\text{Se}$ in place of $\text{Ph}_3\text{P}=\text{S}$	82
10	$(\text{PhSe})_2$ in place of $\text{Ph}_3\text{P}=\text{S}$	68
11	$\text{Cy}_3\text{P}=\text{S}$ in place of $\text{Ph}_3\text{P}=\text{S}$	77
12	$n\text{-Bu}_3\text{P}=\text{S}$ in place of $\text{Ph}_3\text{P}=\text{S}$	73
13	Conditions B in place of conditions A	80
14	Conditions C in place of conditions A	79
15	Conditions D in place of conditions A	52
16	Conditions E in place of conditions A	80
17	Conditions F in place of conditions A	76



^a The 5-exo cyclization product was formed predominantly in 69% yield.

Encouragingly, several *N*-arylated γ -lactam-tethered alkenoic acids underwent productive 6-*endo*-cyclization (see 4i–n), which is noteworthy since *N*-aryl γ -lactams are embedded in several pharmacologically pertinent targets. As a testament to the remarkable chemoselectivity of the transformation, lactam-tethered alkenoic acids bearing an *N*-allyl substituent react with NBS to afford bicycles 4o/p, without complications arising from bromolactonization of the kinetically more accessible allyl group. We attribute this chemoselective bromolactonization to conformational constraints and to the more activated nature of the styrenyl double bond. The use of trisubstituted alkenoic acids has facilitated the stereocontrolled construction of





Performed on 1.0 mmol scale using 5 mL DCM.

Isolated yields reported. Reaction times ranged from 1 to 6 h.

PMP = *para*-methoxyphenyl; OMP = *ortho*-methoxyphenyl.

PNP = *para*-nitrophenyl; ONP = *ortho*-nitrophenyl.

PFP = *para*-fluorophenyl;

Diastereomeric ratios were determined by GC-MS and ¹H NMR analysis of the crude products.

Scheme 1 Regioselective 6-endo-cyclization of γ -lactam-tethered alkenoic acids by catalytic halolactonization.

lactam-lactones bearing two tetrasubstituted stereocenters (see 4q-s). This is noteworthy since halolactonization reactions of trisubstituted alkenes are not often stereospecific.¹⁹ The

successful and efficient synthesis of 4r/s suggests that the electronic benefit of the two phenyl groups far outweighs the presumed steric encumbrance.

Idolactonization with *N*-iodosuccinimide (NIS) also proceeded regio- and diastereoselectively (see 4t-z). In these cases, the iodolactonization was performed at 0 °C, owing to the enhanced reactivity of NIS. The results indicate that the *anti*:*syn* ratio is further enhanced when NIS is used in place of NBS (4g vs. 4y or 4p vs. 4w).

In summary, the site-selective, diastereoselective, and scalable synthesis of halogenated fused γ -lactam- δ -lactones has been accomplished, through the deployment of γ -lactam-tethered alkenoic acids²¹ in a catalytic halolactonization protocol. The expected 6-*endo* cyclization of these lactam-tethered 5-aryl-4(*E*)-pentenoic acids predominates in dichloromethane. These *sp*³-rich fused γ -lactam- δ -lactones bear medicinally relevant quaternary and contiguous stereocenters. We anticipate that this practical, cost-effective, and catalytic strategy would undeniably expand the 3D-structural space for the discovery of new γ , δ -lactam-lactones with medicinal value. Post-modification of these versatile N,O-heterocycles is underway. Additionally, efforts to render the transformation enantioselective will be reported in due course following completion of the studies.

Author contributions

M. J. R. – investigation, data curation, validation; C. B. – investigation, methodology; T. K. B. – conceptualization, project administration, supervision, writing – original draft, internal funding acquisition.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

We are grateful to Central Washington University for financial support through startup funds. The school of graduate studies is thanked for research fellowships to T. K. B. and M. J. R. We also thank the Office of Undergraduate Studies and Provost Den Beste for research fellowships to C. B.

Notes and references

- (a) L. I. Llarrull, S. A. Testero, J. F. Fisher and S. Mabashery, *Curr. Opin. Microbiol.*, 2010, **13**, 551–557; (b) J. Caruano, G. G. Muccioli and R. Robiette, *Org. Biomol. Chem.*, 2016, **14**, 10134–10156; (c) A. Lepikhina, O. Bakulina, D. Darin and M. Krasavin, *RSC Adv.*, 2016, **6**, 83808–83813; (d) P. Gross and J. A. Zapp, *CRC Crit. Rev. Toxicol.*, 1984, **13**, 205–216; (e) F. J. R. Rombouts, G. Tresadern, O. Delgado, C. Martinez Lamenca, M. Van Gool, A. Garcia-Molina, S. A. Alonso de Diego, D. Oehlrich, H. Prokopeva, J. M. Alonso, N. Austin, H. Borghys, S. Van Brandt, M. Surkyn, M. De Cleyn, A. Vos, R. Alexander,



G. Macdonald, D. Moelchers, H. Gijsen and A. A. Trabanco, *J. Med. Chem.*, 2015, **58**, 8216.

2 (a) M. Shahid, F. Sobia, A. Singh, A. Malik, H. M. Khan, D. Jonas and P. M. Hawkey, *Crit. Rev. Microbiol.*, 2009, **35**, 81–108; (b) K.-F. Kong, L. Schneper and K. Mathee, *APMIS*, 2010, **118**, 1–36; (c) G. Kapoor, S. Saigal and A. Elongavan, *J. Anaesthesiol. Clin. Pharmacol.*, 2017, **33**, 300–305.

3 (a) R. D. Marco, A. Bedini, S. Spampinato, L. Comellini, J. Zhao, R. Artali and L. Gentilucci, *J. Med. Chem.*, 2018, **61**, 5751–5757; (b) S. M. Rawls, W. Robinson, S. Patel and A. Baron, *Neuropharmacology*, 2008, **55**, 865.

4 E. J. Velthuisen, B. A. Johns, D. P. Temelkoff, K. W. Brown and S. C. Danehower, *Eur. J. Med. Chem.*, 2016, **117**, 99–112.

5 (a) M. Baiula, P. Galletti, G. Martelli, R. Soldati, L. Belvisi, M. Civera, S. D. Dattoli, S. M. Spampinato and D. Giacomini, *J. Med. Chem.*, 2016, **59**, 9721–9742; (b) D. Kuhn, C. Coates, K. Daniel, D. Chen, M. Bhuiyan, A. Kazi, E. Turos and Q. P. Dou, *Front. Biosci.*, 2004, **9**, 2605–2617; (c) B. Xing, J. Rao and R. Liu, *Mini-Rev. Med. Chem.*, 2008, **8**, 455–471.

6 (a) D. J. Greenblatt and R. I. Shader, *N. Engl. J. Med.*, 1978, **299**, 1342–1344; (b) I. A. Volchegorskii and E. A. Trenina, *Bull. Exp. Biol. Med.*, 2006, **142**, 73–75; (c) K. Gillard, H. B. Miller and M. S. Blackledge, *Chem. Biol. Drug Des.*, 2018, **92**, 1822–1829.

7 (a) C. Saturnino, B. Fusco, P. Saturnino, G. D. E. Martino, F. Rocco and J.-C. Lancelot, *Biol. Pharm. Bull.*, 2000, **23**, 654–656; (b) J. Wei, X. Pan, Z. Pei, W. Wang, W. Qiu, Z. Shi and G. Xiao, *J. Trauma Acute Care Surg.*, 2012, **73**, 654–660.

8 (a) R. M. Trend, Y. K. Ramtohul, E. M. Ferreira and B. Stoltz, *Angew. Chem., Int. Ed.*, 2003, **42**, 2892; (b) X.-F. Cheng, Y. Li, Y.-M. Su, F. Yin, J.-Y. Wang, J. Sheng, H. U. Vora, X.-S. Wang and J.-Q. Yu, *J. Am. Chem. Soc.*, 2013, **135**, 1236; (c) W. Yang, S. Wang, Q. Zhang, Q. Liu and X.-X. Xu, *Chem. Commun.*, 2015, **51**, 661; (d) X.-M. Xie and S. S. Stahl, *J. Am. Chem. Soc.*, 2015, **137**, 3767; (e) H. Shigehisa, M. Hayashi, H. Ohkawa, T. Suzuki, H. Okayasu, M. Mukai, A. Yamazaki, R. Kawai, H. Kikuchi, Y. Satoh, A. Fukuyama and K. Hiroya, *J. Am. Chem. Soc.*, 2016, **138**, 10597; (f) Y.-J. Zhang, T. Abe, T. Tanaka, C.-R. Yang and I. Kouno, *J. Nat. Prod.*, 2001, **64**, 1527; (g) J. J. Beck and S.-C. Chou, *J. Nat. Prod.*, 2007, **70**, 891; (h) Y. Wache, M. Aguedo, J. M. Nicaud and J. M. Belin, *Appl. Microbiol. Biotechnol.*, 2003, **61**, 393; (i) A. Parenty, X. Moreau and J. M. Campagne, *Chem. Rev.*, 2006, **106**, 911; (j) M. I. Konaklieva and B. J. Plotkin, *Mini-Rev. Med. Chem.*, 2005, **5**, 73; (k) I. Collins, *J. Chem. Soc., Perkin Trans. 1*, 1998, **1**, 1869–1888.

9 (a) S. Rashid, B. A. Bhat and G. Mehta, *Org. Lett.*, 2015, **17**, 3604–3607; (b) J. Cao and P. Perlmutter, *Org. Lett.*, 2013, **15**, 4327–4329.

10 F. Lovering, J. Bikker and C. Humblet, *J. Med. Chem.*, 2009, **52**, 6752–6756.

11 A. G. H. Wee, G.-J. Fan and H. M. Bayirinoba, *J. Org. Chem.*, 2009, **74**, 8261–8271.

12 A. W. J. Logan, S. J. Sprague, R. W. Foster, L. B. Marx, V. Garzya, M. S. Hallside, A. L. Thompson and J. W. Burton, *Org. Lett.*, 2014, **16**, 4078–4081.

13 (a) H. Braunstein, S. Langevin, M. Khim, J. Adamson, K. Hovenkotter, L. Kotlarz, B. Mansker and T. K. Beng, *Org. Biomol. Chem.*, 2016, **14**, 8864–8872; (b) T. K. Beng and A. Moreno, *New J. Chem.*, 2020, **44**, 4257–4261; (c) T. K. Beng, M. Bauder, M. J. Rodriguez and A. Moreno, *New J. Chem.*, 2018, **42**, 16451–16455; (d) K. Hovenkotter, H. Braunstein, S. Langevin and T. K. Beng, *Org. Biomol. Chem.*, 2017, **15**, 1217–1221; (e) T. K. Beng and A. Moreno, *RSC Adv.*, 2020, **10**, 8805–8809.

14 (a) L. D. Julian and J. F. Hartwig, *J. Am. Chem. Soc.*, 2010, **132**, 13813–13822; (b) H. Shigehisa, N. Koseki, N. Shimizu, M. Fujisawa, M. Niitsu and K. Hiroya, *J. Am. Chem. Soc.*, 2014, **136**, 13534–13537; (c) Z. Fang, Y. Song, P. Zhan, Q. Zhang and X. Liu, *Future Med. Chem.*, 2014, **6**, 885–901; (d) P. A. Clemons, J. A. Wilson, V. Dancik, S. Muller, H. A. Carrinski, B. K. Wagner, A. N. Koehler and S. L. Schreiber, *Proc. Natl. Acad. Sci.*, 2011, **108**, 6817–6822; (e) Y. Liu, S. J. Han, W. B. Liu and B. M. Stoltz, *Acc. Chem. Res.*, 2015, **48**, 740–751.

15 N. A. McGrath, M. Brichacek and J. T. Njardarson, *J. Chem. Educ.*, 2010, **87**, 1348–1349.

16 M. Maier, in *Science of Synthesis*, ed. E. M. Carreira and J. S. Panek, Thieme, Stuttgart, 2010, vol. 20, pp. 1421–1551.

17 (a) A. N. French, S. Bissmire and T. Wirth, *Chem. Soc. Rev.*, 2004, **33**, 354; (b) H. Fujioka and K. Murai, *Heterocycles*, 2013, **87**, 763; (c) Y. Cheng, W. Yu and Y.-Y. Yeung, *Org. Biomol. Chem.*, 2014, **12**, 2333.

18 (a) M. Okada, K. Kaneko, M. Yamanaka and S. Shirakawa, *Org. Biomol. Chem.*, 2019, **17**, 3747–3751; (b) R. Kristianslund, J. E. Tungen and T. V. Hansen, *Org. Biomol. Chem.*, 2019, **17**, 3079–3092; (c) T. Chen, T. J. Y. Foo and Y.-Y. Yeung, *ACS Catal.*, 2015, **5**, 4751–4755; (d) J. Wong and Y.-Y. Yeung, *RSC Adv.*, 2021, **11**, 13564–13570; (e) K. Moriyama, M. Kuramochi, S. Tsuzuki, K. Fujii and T. Morita, *Org. Lett.*, 2021, **23**, 268–273; (f) J. E. Tungen, R. Kristianslund, A. Vik and T. V. Hansen, *J. Org. Chem.*, 2019, **84**, 11373–11381; (g) Y. A. Cheng, T. Chen, C. K. Tan, J. J. Heng and Y.-Y. Yeung, *J. Am. Chem. Soc.*, 2012, **134**, 16492–16495.

19 (a) F. Freeman, *Chem. Rev.*, 1975, **75**, 439–490; (b) K. Murai, A. Nakamura, T. Matsushita, M. Shimura and H. Fujioka, *Chem.-Eur. J.*, 2012, **18**, 8448–8453.

20 R. Van Lommel, J. Bock, C. G. Daniliuc, U. Hennecke and F. De Proft, *Chem. Sci.*, 2021, **12**, 7746–7757.

21 T. K. Beng, J. Fessenden, K. Quigley, J. Eichwald and J. Zesiger, *New J. Chem.*, 2022.

