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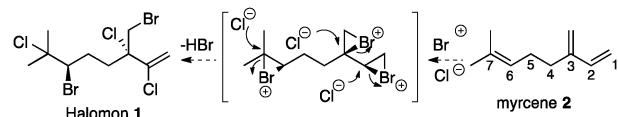
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A novel dihydroxylation–dibromination–dihydroxylation sequence employing *in situ* protection of diols as boronate esters during the dihydroxylation reactions provides the first enantiomerically pure hexafunctionalised myrcene derivative. This concise four-step asymmetric sequence provides an advanced intermediate for the targeted synthesis of halomon *via* stereospecific transformations, where both stereogenic centres of the natural product have been set.

Halomon **1** is an acyclic pentahalogenated terpene isolated in pure form as a major component of the organic extracts of red algae *Portieria hornemannii* and characterised by X-ray crystallography by Boyd in 1992.¹ Halomon's biological profile – initially found to display highly differential cytotoxicity against a diverse panel of human tumor cell lines,¹ and also shown more recently to be an inhibitor of DNA methyl transferase 1² – has attracted much interest,³ but there is a lack of a reliable natural source from the algae due to site-to-site and temporal variations in terpene content.⁴ Synthetic efforts have resulted in the successful synthesis of halomon, but only in racemic form and as a mixture of stereoisomers, thereby requiring subsequent separation.^{5,6} There is therefore a clear need for an asymmetric and stereoselective strategy to access halomon and its related congeners^{4,7} for further biological evaluation. However, the introduction of each of the five halogens *via* site-selective functionalisations, including asymmetric fashioning of the two halogen-bearing stereocentres and installation of the vinyl chloride offers significant synthetic challenge.

Halomon **1** and its related congeners are considered to arise biogenetically *via* enzyme mediated Markovnikov addition of BrCl to the Δ^1 , Δ^6 and/or C-3 methylene double bonds of myrcene **2**



Scheme 1 Halomon **1** and its proposed biogenesis from myrcene **2**.

followed by elimination of HBr and/or HCl (Scheme 1, halomon only).^{8–10} With halomon **1** being isolated as a single enantiomer compound this implicates the intermediacy of enantiopure bromonium ions as promoted by bromoperoxidase in the algae.¹¹ However, despite the recent rapid advance in asymmetric olefin halogenation methods,¹² a general method for direct enantioselective bromonium ion formation on one face of an isolated alkene followed by intermolecular regioselective and stereospecific capture with a nucleophile does not yet exist,¹³ thus precluding attempted asymmetric synthesis of halomon **1** from myrcene **2** in this fashion.

On the other hand, we¹⁴ and Denmark¹⁵ have shown that enantiomerically pure bromonium ions can be generated from enantiopure bromohydrins and/or their *O*-derivatives. In particular, we have shown that either regiosomer of single enantiomer 1,2-bromotosylates of terminal aliphatic alkenes can generate single enantiomer bromonium ions that can be trapped with chloride anion to give enantiopure 1,2-chlorobromides.^{14a} We have also shown that Sharpless dihydroxylation¹⁶ of a trisubstituted olefin provides access to single enantiomer bromohydrins *via* stereospecific epoxide formation¹⁷ and bromide ring-opening,¹⁸ where suitable subsequent activation leads to single enantiomer bromonium ions.^{14b,c} With these considerations in mind, we have therefore targeted dibromotetrol (*3R,6S,7S*)-3 as an advanced intermediate for the synthesis of enantiopure halomon starting from myrcene **2** (Scheme 2). Here the diol of the original Δ^6 trisubstituted alkene could potentially be advanced as previously demonstrated to an enantiopure bromonium ion and trapped with chloride anion. Likewise, the bisbromohydrin tetrad of the original Δ^1 and C-3 \ddagger methylene olefins of myrcene **2** could serve for the formation of two enantiomerically pure bromonium ions each to be trapped in a

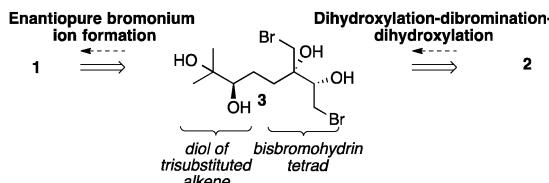
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† Electronic supplementary information (ESI) available: Experimental procedures, characterising data and copies of ^1H and ^{13}C NMR spectra for compounds 5–7, 9–10, 12/13 mix, (*3R,6S,7S*)-3 and (*3R,6R,7R*)-3; X-ray crystallographic details for **6** and (*3R,6S,7S*)-3. CCDC 1017807 and 1017806. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4cc06234e





Scheme 2 Retrosynthesis of halomon **1** to myrcene **2** via hexafunctionalised (3*R*,6*S*,7*S*)-dibromotetrol **3**.

Markovnikov fashion with chloride anion. Herein, we report the successful asymmetric synthesis of dibromotetrol (3*R*,6*S*,7*S*)-3 from myrcene **2** via a novel dihydroxylation–dibromination–dihydroxylation sequence employing *in situ* protection of diols as boronate esters during the dihydroxylation reactions. Critically, a citric acid buffered Upjohn reaction allows post-dibromination dihydroxylation to be effected successfully where other conditions compromise the diol dibromide products. Moreover the employment of a boronate ester as a protecting group allows quantitative and *E*-selective 1,4-dibromination of a diene that is otherwise impossible in the presence of a diol. To the best of our knowledge this represents the first synthesis of an enantiomerically pure hexafunctionalised myrcene derivative, and provides an advanced intermediate for the targeted synthesis of halomon **1** via subsequent stereospecific transformations.

Our studies commenced by using isoprene **4** as a model for the eastern portion of halomon, with a view to dihydroxylating known dibromide **5** into dibromodiol **6** (Table 1). However, we were aware that there have been no reports of a dihydroxylation of any kind on a 2-alkyl-1,4-dibromo-but-2-ene such as dibromide **5**. Thus, isoprene was dibrominated according to the method of Alexakis¹⁹ giving the 1,4-dibromide **5** as a 94:6 *E*:*Z* mixture[§] and dihydroxylation conditions were investigated (Table 1).

Attempted Sharpless asymmetric dihydroxylation (entry 1) of dibromide **5** with AD-mix- β and added methanesulphonamide¹⁶

Table 1 Synthesis of dibromide **5** and attempted dihydroxylation to dibromodiol **6**

Entry	Conditions	Yield 6 ^a
1	AD-mix β + MeSO ₂ NH ₂ ^b	0 ^c
2	AD-mix β + MeSO ₂ NH ₂ ^b + NaHCO ₃	0 ^c
3	AD-mix β + MeSO ₂ NH ₂ ^b + NaHCO ₃ ^d	0 ^c
4	AD-mix β + MeSO ₂ NH ₂ ^b + PhB(OH) ₂ ^e	0 ^f
5	K ₂ OsO ₂ (OH) ₄ , NMO ^g	0 ^c
6	K ₂ OsO ₂ (OH) ₄ , NMO, PhB(OH) ₂ ^h	0 ⁱ
7	K ₂ OsO ₂ (OH) ₄ , NMO, citric acid ^j	77

^a Isolated yield after chromatography. ^b Dihydroxylations were performed with 0.5 mol% K₂OsO₂(OH)₄, 1 mol% (DHQD)₂PHAL, K₃Fe(CN)₆ (3 equiv.), K₂CO₃ (3 equiv.) and MeSO₂NH₂ in ¹BuOH–H₂O. ^c Characteristic signals for epoxides could be seen in the ¹H NMR of the crude reaction mixtures. ^d An additional 1.5 mol% of K₂OsO₂(OH)₄ and 3 mol% (DHQD)₂PHAL were added, and a 3:2 ratio of K₂CO₃:NaHCO₃ was employed.

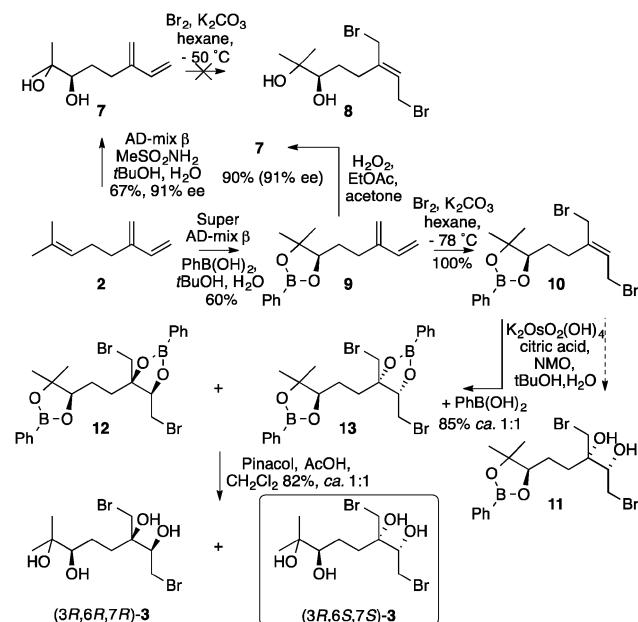
^e An additional 1 mol% of K₂OsO₂(OH)₄ and 3 mol% (DHQD)₂PHAL were added. ^f The expected boronate ester was not observed. ^g Acetone:water (8:1) as solvent. ^h CH₂Cl₂ as solvent. ⁱ No reaction of **5** was observed. ^j ¹BuOH:H₂O (1:1) as solvent.

failed, however, where the substrate was consumed but no diol **6** was detected, and characteristic signals for epoxides could be observed in the ¹H NMR spectrum of the crude material.^{||} The limited literature precedent for osmium catalysed asymmetric dihydroxylation of allylic bromides suggests that NaHCO₃-buffered AD-mix can suppress the unwanted pathways of hydrolysis of the starting material and base mediated ring-closure of the bromohydrin product to an epoxide.²⁰ However, attempts to apply these conditions to the conversion of dibromide **5** into diol **6** also failed (entry 2). The use of other reported protocols for allylic bromides (entry 3)²¹ or attempted *in situ* capture of the diol as a boronate ester by addition of phenylboronic acid (entry 4)²² also failed. The observation of characteristic epoxide signals in each of the crude reaction mixtures led us to conclude that the inherently basic nature of the reaction medium was the central problem. Attempted non-asymmetric dihydroxylations under relatively neutral Upjohn conditions (entry 5)²³ or using Narasaka's anhydrous modification of the Upjohn procedure (entry 6)²⁴ also failed. Gratifyingly, the application of an osmium catalysed dihydroxylation under acidic conditions – a modified Upjohn reaction with NMO as the re-oxidant with added citric acid²⁵ – allowed the smooth conversion of dibromide **5** into (\pm)-dibromodiol **6** in good isolated yield (entry 7),^{**††} and its structure was confirmed by X-ray crystallography.[¶]

Having demonstrated an effective dibromination–dihydroxylation on isoprene, attention turned to myrcene **2** where we wished to effect a dihydroxylation–dibromination–dihydroxylation sequence (*cf.* Scheme 2). A regioselective Sharpless dihydroxylation for the trisubstituted olefin of myrcene has been reported,²⁶ but information on the sense of induction or enantiomeric excess was not provided. In the event, asymmetric dihydroxylation¹⁶ of myrcene **2** gave diol (3*R*)-²⁷ as expected^{‡‡} in 91% ee^{§§} (Scheme 3). Attempted dibromination of diene diol **7** to give dibromide **8** failed – as expected – due to presumed competing intramolecular bromoetherification pathways.^{¶¶} Instead, myrcene **2** was dihydroxylated with super AD-mix β ²⁸ and added phenyl boronic acid²² to give boronate ester **9** directly, also in 91% ee, as revealed by H₂O₂-mediated boronate deprotection²⁴ to diol **7**.^{§§} Here, not only does the addition of phenylboronic acid allow for the *in situ* protection of the newly installed 1,2-diol functionality, we also considered that the boronate ester would function as a uniquely effective protecting group in the subsequent bromination, where such diols otherwise protected in an additional synthetic step as *e.g.*, benzylidenes or as alkyl acetals may retain sufficient nucleophilicity to participate in otherwise competing intramolecular bromoetherifications reactions.²⁹

Much to our delight, *E*-selective 1,4-dibromination of the diene **9** proceeded smoothly with molecular bromine without interference from the protected alcohol groups to give dibromide **10** in quantitative yield.^{||||} The application of the citric acid buffered Upjohn reaction²⁵ (*cf.* dibromide **5** to diol **6**, Table 1, entry 7) to dibromide **10** did not provide diol **11**, but instead a moderate yield (45%) of inseparable bisboronates **12** and **13** was obtained. Here, under the conditions of reaction, evidently dihydroxylation is proceeding, but the isolation of the bisboronates implicates intermolecular boronate ester exchanges.





Scheme 3 Hexafunctionalisation of myrcene **2** via a dihydroxylation-dibromination-dihydroxylation sequence employing boronate esters as protecting groups.

Sharpless asymmetric dihydroxylation as well as all other relative and absolute configurations.

In conclusion we have demonstrated a successful asymmetric dihydroxylation-dibromination-dihydroxylation sequence employing *in situ* protection of diols as boronate esters during the dihydroxylation reactions to rapidly assemble the first enantiopure hexafunctionalised myrcene derivative in just four steps. This concise asymmetric sequence provides an advanced intermediate for the targeted synthesis of halomon **1** *via* subsequent stereospecific transformations (*vide supra*),¹⁴ where both stereogenic centres of the natural product have already been set. Such work is ongoing and will be reported in due course.

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Notes and references

[‡] However, to the best of our knowledge the formation of an enantiopure bromonium ion of a 1,1-disubstituted alkene has not yet been demonstrated.

[§] This ratio is comparable with that reported in literature at 92:8 (ref. 19).

[¶] See ESI[†] for details.

^{||} The putative epoxides proved to be volatile and only traces of material could be isolated after attempted column chromatography.

^{**} Small quantities of the (*R*^{*,}*S*^{*})-diol was also obtained (see ESI[†]). This arises from *syn*-dihydroxylation of the minor *Z*-dibromide **5**.

^{††} The reaction mixture under these acidic conditions was characteristically green in colour that faded as the reaction proceeded. See ref. 25 for the significance of this colour.

^{‡‡} The absolute configuration was assigned on the basis of the Sharpless mnemonic (ref. 16).

^{§§} The ee was calculated as 91% by comparison of the measured rotation with the reported rotation for (3*R*)-7 (ref. 27) (see ESI[†]).

^{¶¶} Complex product mixtures were obtained.

^{|||} As a 96:4 *E*:*Z* mixture.

^{***} H_2O_2 deprotection studies with the phenyl boronate ester of dibromodiol **6** (not shown) showed characteristic signals for epoxides in the ^1H NMR of the crude reaction mixtures. We invoke epoxide formation in the attempted H_2O_2 deprotection of boronates **12** and **13** also, and subsequent decomposition in the work-up and/or purification process (chromatography).

^{†††} The dibromotetroses were obtained as a *ca.* 1:1 mixture, and analytically pure samples of each could be obtained by careful column chromatography (see ESI[†]).

- 1 R. W. Fuller, J. H. Cardellina II, Y. Kato, L. S. Brinen, J. Clardy, K. M. Snader and M. R. Boyd, *J. Med. Chem.*, 1992, **35**, 3007–3011.
- 2 E. H. Andrianasolo, D. France, S. Cornell-Kennon and W. H. Gerwick, *J. Nat. Prod.*, 2006, **69**, 576–579.
- 3 (a) M. J. Egorin, D. L. Sentz, D. M. Rosen, M. F. Ballasteros, C. M. Kearns, P. S. Callery and J. L. Eiseman, *Cancer Chemother. Pharmacol.*, 1996, **39**, 51–60; (b) M. J. Egorin, D. M. Rosen, S. E. Benjamin, P. S. Callery, D. L. Sentz and J. L. Eiseman, *Cancer Chemother. Pharmacol.*, 1997, **41**, 9–14.
- 4 R. W. Fuller, J. H. Cardellina II, J. Jurek, P. J. Scheuer, B. Alvarado-Lindner, M. McGuire, G. N. Gray, J. R. Steiner, J. Clardy, E. Menez, R. H. Shoemaker, D. J. Newman, K. M. Snader and M. R. Boyd, *J. Med. Chem.*, 1994, **37**, 4407–4411.
- 5 T. Schlama, R. Baati, V. Gouverneur, A. Valleix, J. R. Falck and C. Mioskowski, *Angew. Chem., Int. Ed.*, 1998, **37**, 2085–2087.
- 6 T. Sotokawa, T. Noda, S. Pi and M. Hirama, *Angew. Chem., Int. Ed.*, 2000, **39**, 3430–3432.
- 7 The racemic synthesis of two naturally occurring halogenated monoterpenes of the halomon class have been reported: M. E. Jung and M. H. Parker, *J. Org. Chem.*, 1997, **62**, 7094–7095.
- 8 B. J. Burreson, F. X. Wooland and R. E. Moore, *Chem. Lett.*, 1975, 1111–1114.
- 9 Hirama and coworkers (ref. 6) employed a stepwise bromochlorination of myrcene to obtain 2,6-dibromo-3-(bromomethyl)-1,3,7-trichloro-7-methyloctane as a mixture of four diastereoisomers.

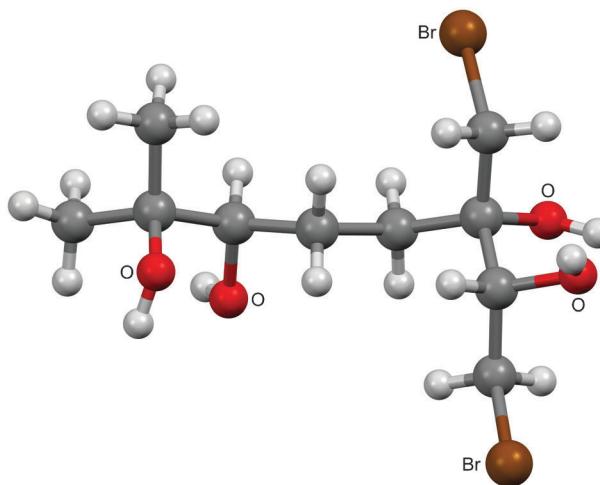


Fig. 1 The crystal structure of (3*R*,6*S*,7*S*)-3.

Accordingly, citric acid buffered Upjohn dihydroxylation of **10** with added phenylboronic acid – a further novel variation on the Upjohn reaction – gave diastereomeric bisboronates **12** and **13** as an approximate 1:1 mixture of diastereoisomers in 85% yield.^{††} However, in contrast to the facile deprotection of boronate **9** with hydrogen peroxide, attempted global deprotection of the bisboronate mix **12** and **13** under the same conditions²⁴ led only to low and variable mass recoveries (0–35% yield) of the two expected diastereomeric tetrols (3*R*,6*R*,7*R*)-3 and (3*R*,6*S*,7*S*)-3.^{***} Deprotection instead using modified conditions of Padwa,³⁰ gave the separable diastereomeric dibromotetroses (3*R*,6*S*,7*S*)-3 and (3*R*,6*R*,7*R*)-3 in 82% combined yield.^{†††} Dibromotetrol (3*R*,6*S*,7*S*)-3 proved to be crystalline, and the X-ray crystal structure (Fig. 1) confirmed the original sense of induction in the



However, all attempts to effect an elimination of HBr to yield halomon **1** were reported as unsuccessful.

10 Geranyl diphosphate has been proposed to be the common bio-
genetic precursor for the wider family of monoterpenes in macro-
phytic red algae: M. L. Wise and R. Croteau, in *Comprehensive
Natural Product Chemistry*, ed. D. H. R. Barton, K. Nakanishi and
O. Meth-Cohn, Pergamon, Elmsford, NY, 1999, vol. 2, pp. 97–153.

11 For a review on halogenating enzymes see: A. Butler and M. Sandy,
Nature, 2009, **460**, 848–854 and references cited therein.

12 For selected reviews see: (a) S. Zheng, C. M. Schienebeck, W. Zhang,
H.-Y. Wang and W. Tang, *Asian J. Org. Chem.*, 2014, **3**, 366–376;
(b) Y. A. Cheng, W. Z. Yu and Y.-Y. Yeung, *Org. Biomol. Chem.*, 2014,
12, 2333–2343; (c) K. Murai and H. Fujioka, *Heterocycles*, 2013, **87**,
763–805; (d) S. E. Denmark, W. E. Kuester and M. T. Burk, *Angew. Chem.,
Int. Ed.*, 2012, **51**, 10938–10953; (e) U. Hennecke, *Chem. – Asian J.*, 2012, **7**,
456–465; (f) C. K. Tan, L. Zhou and Y.-Y. Yeung, *Synlett*, 2011, 1335–1339;
(g) A. Castellanos and S. P. Fletcher, *Chem. – Eur. J.*, 2011, **17**, 5766–5776;
(h) G. Chen and S. Ma, *Angew. Chem., Int. Ed.*, 2010, **49**, 8306–8308.

13 For a review on asymmetric intermolecular halogenation of alkenes
see: J. Chen and L. Zhou, *Synthesis*, 2014, 586–595.

14 (a) D. C. Braddock, S. A. Hermitage, L. Kwok, R. Pouwer, J. M. Redmond
and A. J. P. White, *Chem. Commun.*, 2009, 1082–1084; (b) D. C. Braddock,
J. S. Marklew and A. J. F. Thomas, *Chem. Commun.*, 2011, **47**, 9051–9053;
(c) D. C. Braddock, J. S. Marklew, K. M. Foote and A. J. P. White, *Chirality*,
2013, **25**, 692–700.

15 S. E. Denmark, M. T. Burk and A. J. Hoover, *J. Am. Chem. Soc.*, 2010,
132, 1232–1233 and references cited therein.

16 K. B. Sharpless, W. Amberg, Y. L. Bennani, G. A. Crispino, J. Hartung,
K.-S. Jeong, H.-L. Kwong, K. Morikawa, Z.-M. Wang, D. Xu and X.-L.
Zhang, *J. Org. Chem.*, 1992, **57**, 2768–2771.

17 E. J. Corey, M. C. Noe and W.-C. Shieh, *Tetrahedron Lett.*, 1993, **34**,
5995–5998.

18 E. A. Couladouros and V. P. Vidali, *Chem. – Eur. J.*, 2004, **10**,
3822–3835.

19 C. A. Falciola, K. Tissot-Crosset, H. Reyneri and A. Alexakis, *Adv.
Synth. Catal.*, 2008, **350**, 1090–1100.

20 H. C. Kolb, Y. L. Bennani and K. B. Sharpless, *Tetrahedron: Asymmetry*,
1993, **4**, 133–141.

21 A Sharpless asymmetric dihydroxylation of a 1,6-dibromohexa-2,4-diene
under modified conditions has been reported: O. Hidestål,
R. Ding, A. Almesåker and U. M. Lindström, *Green Chem.*, 2005, **7**,
259–261.

22 C. H. Hövelmann and K. Muñiz, *Chem. – Eur. J.*, 2005, **11**, 3951–3958.

23 V. VanRheenen, R. C. Kelly and D. Y. Cha, *Tetrahedron Lett.*, 1976,
17, 1973–1976.

24 A. Gypser, D. Michel, D. S. Nirschl and K. B. Sharpless, *J. Org. Chem.*,
1998, **63**, 7322–7327 and references cited therein.

25 P. Dupau, R. Epple, A. A. Thomas, V. V. Fokin and K. B. Sharpless,
Adv. Synth. Catal., 2002, **344**, 421–433.

26 Dihydroxylation of myrcene using AD-mix α : J. Y. Wu, B. N. Stanzl
and T. Ritter, *J. Am. Chem. Soc.*, 2010, **132**, 13214–13216.

27 (3R)-7 has been reported via an alternative route: H. Hioki, H. Ooi,
M. Hamano, Y. Mimura, S. Yoshio, M. Kodama, S. Ohta, M. Yanai
and S. Ikegami, *Tetrahedron*, 2001, **57**, 1235–1246.

28 For 'super' AD-mix see footnote 76 in: H. C. Kolb, M. S. VanNieuwenhze
and K. B. Sharpless, *Chem. Rev.*, 1994, **94**, 2483–2547.

29 For recent representative examples of intramolecular bromoetherifications
of unsaturated ethers see: (a) D. C. Braddock, D. S. Millan,
Y. Perez-Fuertes, R. Pouwer, R. N. Sheppard, S. Solanki and A. J. P.
White, *J. Org. Chem.*, 2009, **74**, 1835–1841; (b) S. A. Synder, A. P.
Brucks, D. S. Treitler and I. Moga, *J. Am. Chem. Soc.*, 2012, **134**,
17714–17721 and references cited therein.

30 A. Padwa and Q. Wang, *J. Org. Chem.*, 2006, **71**, 7391–7402 and
reference cited therein.

