ChemComm

ROYAL SOCIETY OF CHEMISTRY

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2020, **56**, 12174

Received 7th August 2020,
Accepted 3rd September 2020

DOI: 10.1039/d0cc05396a

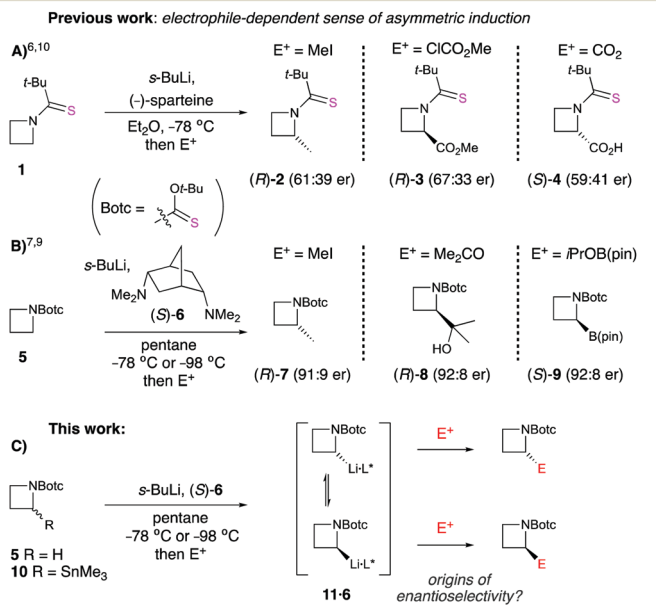
rsc.li/chemcomm

Electrophile dependent mechanisms in the asymmetric trapping of α-lithio-*N*-(*tert*-butoxythiocarbonyl)azetidine†

Pascal K. Delany, Claire L. Mortimer and David M. Hodgson *

Sn–Li exchange and 'poor man's Hoffmann tests' establish asymmetric trapping of α-lithio-*N*-(*tert*-butoxythiocarbonyl) (Botc) azetidine to be controlled by dynamic thermodynamic resolution or dynamic kinetic resolution, depending on the electrophile. Unusually, different configurational stability is seen for the anion generated by lithiation compared to transmetallation. Configurational stability of α-lithio-*N*-Boc azetidine indicates instability with the *N*-Botc system is due to the C=S group.

Saturated azacycles are pervasive motifs in pharmaceutically active compounds;[1] consequently, advances in their asymmetric synthesis are of significant interest.[2] Directed deprotonative lithiation—electrophile trapping sequences are synthetically powerful approaches in enantioselective synthesis,[3] especially for α-functionalisation of saturated azacycles.[4] Azetidines have recently received increased attention due to their desirable physiochemical properties and the emergence of highly bioactive azetidine containing compounds.[5] We have developed asymmetric α-lithiation—electrophile trapping of azetidines, enabled by a *N*-thiopivaloyl or -*tert*-butoxythiocarbonyl (Botc) directing group (Scheme 1A and B);[6–9] the latter being preferred owing to greater levels of asymmetric induction, ease of deprotection and accessibility to 2,4-disubstituted azetidines.[7,8] Knowledge of pathways for enantioinduction provides insight and rationalisation of previous observations and serves as valuable understanding to underpin future studies. O'Brien and co-workers reported the sense of asymmetric induction in α-lithiation—electrophile trapping of *N*-(thiopivaloyl)azetidine (**1**) was electrophile dependent (Scheme 1A),[10] a phenomenon rarely observed for non-benzylic sp^3 lithiated species.[11] On previous evaluation of our DIANANE (*S*)-**6**-mediated asymmetric α-lithiation—electrophile trapping of *N*-Botc azetidine **5**,[9] we also observed the sense of enantioinduction was electrophile dependent (Scheme 1B). This has prompted us to investigate the origins of asymmetric substitution of *N*-Botc azetidine through α-lithiation, with emphasis on how the process proceeds with respect to different electrophiles (Scheme 1C).

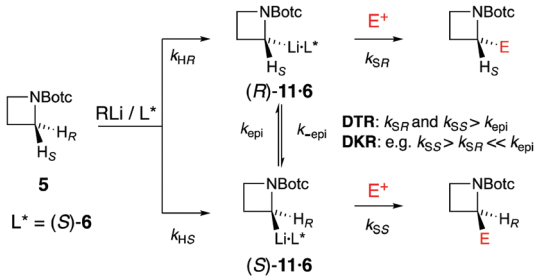


Scheme 1 Investigations of α-lithiated azetidines.

Enantioselectivity can originate from three distinct pathways (Scheme 2).[12] An organolithium base coordinated with a chiral ligand could preferentially remove the *pro-R* or *pro-S* hydrogen to give a configurationally stable anion; if an introduced electrophile reacts stereospecifically then asymmetric induction is controlled by the lithiation rate difference (*e.g.*, $k_{HS} \gg k_{HR}$). Enantioselectivity can also arise post-deprotonation when a configurationally unstable anion is formed (Scheme 2). Dynamic thermodynamic resolution (DTR) occurs if the lithiated complexes (*e.g.*, (*R*)-**11·6** and (*S*)-**11·6**) equilibrate to a thermodynamically controlled ratio and substitute with an electrophile at a rate faster

Department of Chemistry, Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford OX1 3TA, UK. E-mail: david.hodgson@chem.ox.ac.uk

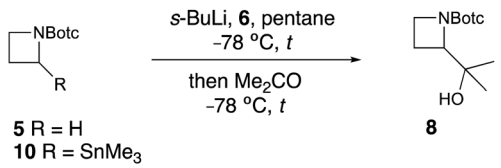
† Electronic supplementary information (ESI) available: Additional configurational stability studies, experimental procedures and ^{1}H and ^{13}C NMR spectra. CCDC 2027137. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0cc05396a



Scheme 2 Possible enantiodetermining steps.

than epimerisation (k_{SR} and k_{SS} > k_{epi}).[12] Alternatively, dynamic kinetic resolution (DKR) could operate, where the rate of epimerisation between diastereomeric complexes is faster than reaction with the electrophile (*e.g.*, k_{SR} > k_{SS} ≪ k_{epi}, Scheme 2); enantioselectivity is now determined by the difference in rate of reaction of the two diastereomeric complexes with the electrophile (*i.e.*, $\Delta\Delta G^{\ddagger}$).

We first examined the configurational stability of *N*-Botc azetidine complexes ((*R*)-**11·6** and (*S*)-**11·6**) with chiral diamine ligand DIANANE (*S*)-**6**,[13] when generated through α-deprotonation and Sn–Li exchange (Scheme 3). A control reaction using previously optimised conditions for lithiation (deuteration studies) and for enantioselectivity (pentane, 1 h, −78 °C) with acetone as the electrophile (3 equiv.),[7] gave alcohol (*R*)-**8** (61%) in 89 : 11 er (*cf.*, Scheme 1B). Sn–Li exchange, a process with considerable precedent for occurring in a stereoretentive manner,[14] with stannane (±)-**10** in the presence of (*S*)-**6** (1 h, −78 °C, then acetone) gave alcohol (*R*)-**8** in 90 : 10 er (57%). Matching levels of enantioenrichment from these two experiments show the intermediate organolithium complexes are configurationally unstable at −78 °C and enantioselectivity originates after anion formation. If DTR is occurring, then altering incubation time may influence enantioselectivity. Following Sn–Li exchange, decreasing incubation to 5 min gave alcohol (*R*)-**8** in essentially unchanged er (85 : 15, 64%), indicating either anion equilibration following transmetallation is effectively complete after 5 min at −78 °C, or a DKR process.



Scheme 3 Studies on the synthesis of alcohol **8** from deprotonation or Sn–Li exchange.

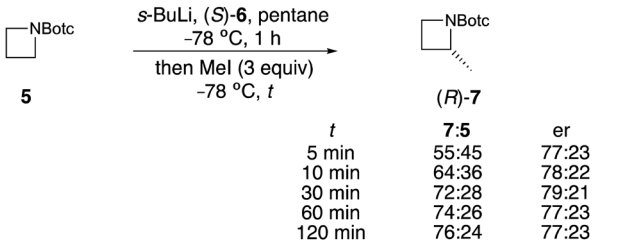
Although the enantiodetermining step occurs post-deprotonation, asymmetric deprotonation could still be occurring.[15] 1 min lithiation at −78 °C of azetidine **5** in the presence of DIANANE (*S*)-**6** before acetone trapping, gave alcohol (*R*)-**8** in 58 : 42 er (28%). The reduced er after 1 min indicates the lithiated diastereomeric complexes have not fully equilibrated (unlike after 1 h), and there is no favourable initial formation of one organolithium complex by asymmetric deprotonation that is then reduced on equilibration. Sn–Li exchange with enantioenriched stannane (*R*)-**10** (67 : 33 er) in the presence of racemic DIANANE (±)-**6** at −98 °C for 1 min before acetone trapping, resulted in essentially racemic alcohol **8** (51 : 49 er, 39%). Assuming stereoretentive Sn–Li exchange (although see below), this demonstrates configurational instability of the organolithium complexes even at −98 °C when the anion is formed by transmetallation. However, in contrast to anion generation through Sn–Li exchange, partial configurational stability was demonstrated in deprotonations with different incubation temperatures and times. Lithiation of azetidine **5** in the presence of DIANANE (*S*)-**6** and incubation for 1 h at −98 °C before trapping gave alcohol (*R*)-**8** with moderate enantioselectivity (65 : 35 er, 38%), showing incomplete equilibration. But when deprotonation and incubation were performed at −78 °C for 1 h, then cooling to −98 °C before trapping, this gave alcohol (*R*)-**8** with good enantioselectivity (88 : 12 er, 55%), indicating that high enantioselectivity can be achieved with trapping at −98 °C. Deprotonation and incubation at −98 °C for 3 h before trapping gave alcohol (*R*)-**8** in 86 : 14 er (51%), with the high er suggesting equilibration is almost complete at −98 °C after 3 h. These time dependent enantioselectivities imply DTR, with acetone (for a full table of acetone trapping studies and similar results obtained with aromatic aldehydes, see the ESI†), and indicate the organolithium complexes possess greater configurational stability at −98 °C when formed through deprotonation.

Remarkably, compared to 65 : 35 er obtained from deprotonation for 1 h at −98 °C, increased enantioselectivity was observed through Sn–Li exchange of stannane (±)-**10** when carried out under the same conditions in the presence of DIANANE (*S*)-**6**, giving alcohol (*R*)-**8** in 84 : 16 er (41%). This difference at −98 °C can be rationalised by 'unproductive' kinetic deprotonation (preferential generation of the thermodynamically less stable lithiated complex) and a longer equilibration time, relative to transmetallation. Alternatively, Sn–Li exchange with stananne (±)-**10** could be occurring non-stereospecifically in the presence of DIANANE (*S*)-**6**, although precedent for non-retentive Sn–Li exchange is very limited;[16] no transmetallation occurred without the ligand present. Non-retentive Sn–Li exchange could explain the rapid racemisation observed at −98 °C after 1 min with enantioenriched stannane (*R*)-**10**. The possibility of non-stereospecific Sn–Li exchange was probed using stannane (±)-**10** with DIANANE (*S*)-**6** and *in situ* acetone. This gave trace amounts (1%) of essentially racemic alcohol **8** (52 : 48 er), indicating Sn–Li exchange is occurring stereospecifically with some degree of 'microscopic'[17] configurational stability, relative to the rate of acetone trapping.

In a 'poor man's Hoffmann test',[12] azetidine **5** was deprotonated (1 h, −78 °C) and reacted with sub-stoichiometric acetone (0.5 and 0.1 equiv.) to give alcohol (*R*)-**8** in 61 : 39 er (29%) and 60 : 40 er (2%), respectively. Decreased enantioselectivity (compared with 89 : 11 er using 3 equiv. earlier) suggest the minor lithiated complex reacts marginally faster than the major complex[15] ((*R*)-**11·6** faster than (*S*)-**11·6**, assuming retentive substitution, $S_E2$ret, with acetone[11]). The difference in enantioselectivity shows epimerisation

is not occurring on the timescale of acetone trapping at −78 °C, confirming a DTR process.

A sacrificial electrophile has been previously used to improve enantioselectivity in a reaction where DTR operates.[18] Generation of α-lithio-*N*-Botc azetidine in the presence of DIANANE (*S*)-**6** at −78 °C, then reaction with MeI (0.2 equiv.) for 5 min before addition of acetone (3 equiv.) only led to alcohol (*R*)-**8** (58%) with a slight reduction in er (80 : 20). However, the enantioenrichment of the traces (1%) of isolated methylated azetidine (*S*)-**7** (73 : 27 er) is similar to that found at this temperature for (*S*)-**7** (77 : 23 er) using only MeI (3 equiv.), sampled as the reaction progressed (5–120 min, Scheme 4). While these results do not strictly discriminate between DTR and DKR (as potentially $k_{SR} \approx k_{SS}$, *cf.*, Scheme 2), enantioselectivity independent of reaction conversion and (also in contrast to acetone) improved enantioenrichment at −98 °C after 1 h (91 : 9 er),[7] support a DKR process with this slower reacting[19] electrophile.

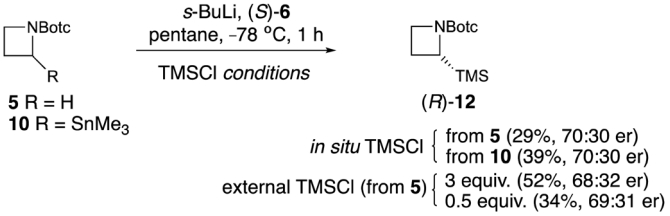


Scheme 4 Unchanging er during the methylation of *N*-Botc azetidine **5**.

With Me_3SnCl as the electrophile, both variation in reaction time and temperature altered asymmetric induction (Table 1).

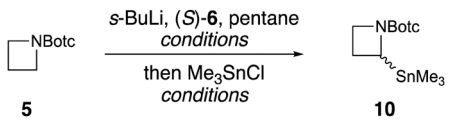
Lithiation of *N*-Botc azetidine **5** in the presence of DIANANE (*S*)-**6** at −78 °C for 1 h led to stannane (*S*)-**10** in 67 : 33 er (90%, Table 1, entry 1). An otherwise identical reaction, but without warming to rt following Me_3SnCl addition, resulted in stannane (*S*)-**10** in similar enantioselectivity (61 : 39 er, entry 2) in 80% yield. However, reducing the lithiation time to 5 min before stannylation inverted the sense of asymmetric induction, to give stannane (*R*)-**10** in 54 : 46 er (62%). Decreasing the lithiation temperature to −98 °C for 3 h before trapping at the same temperature gave stannane (*S*)-**10** in 64 : 36 er (77%, entry 4). However, reducing the lithiation time to 1 h at −98 °C again resulted in a change in the sense of asymmetric induction to 54 : 46 er (entry 5). The dependence of asymmetric induction on lithiation time at −78 °C and −98 °C indicates DTR in stannylation, similar to trapping with acetone. These results also suggest deprotonation-derived organolithium complex equilibration is incomplete after 5 min at −78 °C and reinforces the earlier observation with acetone of increased time required for complex equilibration at −98 °C, due to a less configurationally labile anion at this lower temperature. The reduced overall levels of enantioselectivity compared with optimised conditions for acetone trapping suggests either an interfering DKR mechanism in which the thermodynamically less stable complex reacts with at a faster rate with Me_3SnCl, or possible competing non-stereospecific electrophile trapping ($S_E2$ret and $S_E2$inv).[11]

Use of an internal electrophile such as TMSCl has been previously used to ascertain the degree of an asymmetric deprotonation.[15] Two parallel '*in situ*' trapping experiments were performed at −78 °C using *N*-Botc azetidine **5** and stannane (±)-**10** substrates (Scheme 5). These reactions gave silane (*R*)-**12** in identical enantioenrichment (70 : 30 er), showing the level of asymmetric induction with this electrophile is independent of the method of anion generation. TMSCl is a slower reacting electrophile[19] and the matching enantioselectivity could therefore be due to DKR. A deprotonation reaction with a 1 h incubation period at −78 °C before external addition of TMSCl gave silane (*R*)-**12** in 52% yield and essentially the same enantioselectivity (68 : 32 er). A 'poor man's Hoffmann test' with 0.5 equiv. of TMSCl, gave silane (*R*)-**12** in 69 : 31 er (34%), providing further evidence for DKR. With TMSOTf, a more reactive silylating agent, a change in the sense of asymmetric induction was observed, giving (*S*)-**12** in 58 : 42 er (28%); this is most likely a result of diminished influence of a DKR mechanism.



Scheme 5 Silylation studies.

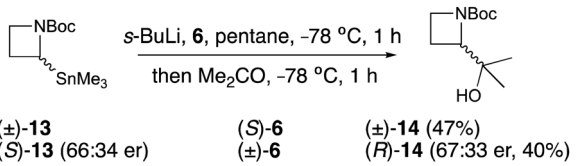
Table 1 Asymmetric stannylation of *N*-Botc azetidine **5**



Entry	Lithiation temp (time)	Stannylation temp (time)	Yield **10**	er (*R* : *S*)	Recovered **5**
1	−78 °C (1 h)	−78 °C (30 min) then rt (30 min)	90%	33 : 67	0%
2	−78 °C (1 h)	−78 °C (30 min)	80%	39 : 61	0%
3	−78 °C (5 min)	−78 °C (30 min) then rt (30 min)	62%	54 : 46	38%
4	−98 °C (3 h)	−98 °C (30 min)	77%	36 : 64	21%
5	−98 °C (1 h)	−98 °C (30 min)	70%	54 : 46	24%

For the two electrophiles which trap through DKR (MeI and TMSCl), the predominant sense of asymmetric induction is opposite to those electrophiles which proceed through DTR (acetone, benzaldehyde† and Me_3SnCl). This could be due either to preferential invertive S_E2inv trapping, not uncommon for mesomerically stabilised organolithiums reacting with alkyl halides,[15] or to retentive trapping in which the minor diastereomeric organolithium complex is the faster reacting species, as was observed earlier in the 'poor man's Hoffmann test' with acetone.

O'Brien and co-workers previously established with *N*-thiopivaloyl azetidine that asymmetric induction occurs post deprotonation; however, no distinction between DTR or DKR was made.[10] They also speculated the origin of configurational instability may due to the longer C═S bond leading to a weaker C–Li bond. To discriminate between the C═S group or azacycle size being responsible for the configurational instability of *N*-Botc azetidine lithiated complexes ((*R*)-**11**·**6** and (*S*)-**11**·**6**), we sought to access the lithiated *N*-Boc azetidine equivalents. We previously found that direct α-lithiation of *N*-Boc azetidine is problematic,[6] but access to α-lithiated *N*-Boc azetidine is achievable by Sn–Li exchange from *N*-Boc stannane **13** (Scheme 6). Stannane **13** was accessed by deprotection/reprotection of *N*-Botc stannane **10**, using TMSI for deprotection (66%). Under identical transmetallation conditions used for stannane **10** in the presence of DIANANE (*S*)-**6**, stannane (±)-**13** underwent Sn–Li exchange and trapping with acetone to give racemic *N*-Boc alcohol (±)-**14** (47%). Transmetallation of enantioenriched *N*-Boc stannane (*S*)-**13** (66 : 34 er) using *s*-BuLi with racemic DIANANE (±)-**6**, led to enantioenriched alcohol (*R*)-**14** in 67 : 33 er (40%). These results demonstrate, for the first time, access to a configurationally stable α-lithiated azetidine and indicate the C═S group is responsible for the configurational instability of α-lithio *N*-Botc azetidine.



Scheme 6 Transmetallation of *N*-Boc stannane **13**.

In summary, the present studies show configurational instability of α-lithiated *N*-Botc azetidine complexes ((*R*)-**11**·**6** and (*S*)-**11**·**6**). These diastereomeric complexes reach thermodynamic equilibrium after 1 h at −78 °C (3 h at −98 °C). They react with a fast trapping electrophile such as acetone *via* DTR, producing α-substituted azetidines with enantioselectivities (~90 : 10) that reflect the complexes dr. Slower trapping electrophiles (MeI and TMSCl) react by DKR; this provides an explanation as to why different enantioselectivities are observed when conditions for optimal DTR are used with these electrophiles and also rationalises the different sense of enantioinduction. This change in mechanism could also be occurring with *N*-thiopivaloyl azetidine. In the current work, an intriguing difference in configurational stability of the anion formed by lithiation *versus* transmetallation was also observed (further discussed in the ESI†). Finally, the origin of configurational instability was determined to be the presence of C═S group, as demonstrated by the configurational stability of α-lithiated *N*-Boc azetidine. The stereochemical lability may be due to the longer C═S bond and/or the greater polarisability of S, compared to O, allowing greater charge transfer from N to S.[8,20]

We thank the EPSRC for studentship support (to P. K. D.) and the EPSRC and Novartis for an Organic Synthesis Studentship (to C. L. M.). We also thank the Martin Smith group at Oxford for use of their HPLC equipment.

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 10257.
2 (*a*) M.-Y. Han, J.-Y. Jia and W. Wang, *Tetrahedron Lett.*, 2014, **55**, 784; (*b*) G.-Q. Liu and T. Opatz, *Adv. Heterocycl. Chem.*, 2018, **125**, 107.
3 (*a*) D. M. Hodgson, *Topics in Organometallic Chemistry: Organolithiums in Enantioselective Synthesis*, Springer-Verlag, Heidelberg, 2003, vol. 5; (*b*) L. Degennaro, B. Musio and R. Luisi, in *Lithium Compounds in Organic Synthesis – From Fundamentals to Applications*, ed. R. Luisi and V. Capriati, Wiley-VCH, Weinheim, Germany, 2014, p. 191.
4 K. Kasten, N. Seling and P. O'Brien, *Org. React.*, 2019, **100**, 255.
5 (*a*) D. Antermite, L. Degennaro and R. Luisi, *Org. Biomol. Chem.*, 2017, **15**, 34; (*b*) M. Maetani, N. Kato, V. A. P. Jabor, F. A. Calil, M. C. Nonato, C. A. Scherer and S. L. Schreiber, *ACS Med. Chem. Lett.*, 2017, **8**, 438; (*c*) T. W. Reidl and L. L. Anderson, *Asian J. Org. Chem.*, 2019, **8**, 931; (*d*) G. S. Singh, *Adv. Heterocycl. Chem.*, 2020, **130**, 1.
6 D. M. Hodgson and J. Kloesges, *Angew. Chem., Int. Ed.*, 2010, **49**, 2900.
7 D. M. Hodgson, C. L. Mortimer and J. M. McKenna, *Org. Lett.*, 2015, **17**, 330.
8 K. E. Jackson, C. L. Mortimer, B. Odell, J. M. McKenna, T. D. W. Claridge, R. S. Paton and D. M. Hodgson, *J. Org. Chem.*, 2015, **80**, 9838.
9 P. K. Delany and D. M. Hodgson, *Org. Lett.*, 2019, **21**, 9981.
10 P. J. Rayner, J. C. Smith, C. Denneval, P. O'Brien, P. A. Clarke and R. A. J. Horan, *Chem. Commun.*, 2016, **52**, 1354.
11 R. E. Gawley and Q. Zhang, *J. Org. Chem.*, 1995, **60**, 5763.
12 (*a*) A. Basu and S. Thayumanavan, *Angew. Chem., Int. Ed.*, 2002, **41**, 716; (*b*) R. E. Gawley, *Top. Stereochem.*, 2010, **26**, 93; (*c*) I. Coldham and N. S. Sheikh, *Top. Stereochem.*, 2010, **26**, 253.
13 J. Praz, L. Guenée, S. Aziz, A. Berkessel and A. Alexakis, *Adv. Synth. Catal.*, 2012, **354**, 1780.
14 J. Clayden, *Organolithiums: Selectivity for Synthesis*, Pergamon, Oxford, 2002, pp. 214–222.
15 K. Behrens, R. Fröhlich, O. Meyer and D. Hoppe, *Eur. J. Org. Chem.*, 1998, 2397.
16 J. Clayden, M. Helliwell, J. H. Pink and N. Westlund, *J. Am. Chem. Soc.*, 2001, **123**, 12449.
17 D. C. Kapeller and F. Hammerschmidt, *J. Org. Chem.*, 2009, **74**, 2380.
18 K. Tomooka, L.-F. Wang, N. Komine and T. Nakai, *Tetrahedron Lett.*, 1999, **40**, 6813.
19 (*a*) J. D. Firth, P. O'Brien and L. Ferris, *J. Am. Chem. Soc.*, 2016, **138**, 651; (*b*) J. D. Firth, PhD Thesis, University of York, 2014.
20 (*a*) K. B. Wiberg and P. R. Rablen, *J. Am. Chem. Soc.*, 1995, **117**, 2201; (*b*) K. B. Wiberg and D. J. Rush, *J. Am. Chem. Soc.*, 2001, **123**, 2038.