RSC Advances

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

RSC Advances

COMMUNICATION

Copper-Catalysed Cross-Coupling Affected by the Smiles Rearrangement: A New Chapter on Diversifying the Synthesis of Chiral Fluorinated 1,4-Benzoxazine Derivatives

Received 00th January 20xx,

Saba Alapour,[a] Deresh Ramjugernath[b] and Neil A. Koorbanally[a]*

Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Synthesis of different chiral fluorinated Boc-[1,4]benzoxazin from their open chain precursors were investigated. The NMR spectra and crystallographic data showed the presence of the Smiles Rearrangement (SR) followed by copper catalysed coupling. The influence of the Boc protecting group, solvent, base, catalyst and the conformational changes of adducts was explored in detail by careful reaction optimization. No product was obtained in the absence of Boc, indicating its crucial role. Finally, a new mechanism for the SR copper catalysed ring closure was proposed.

Benzoxazines exist in many drugs and herbicides, and are widely used as building blocks of bioactive molecules. They exhibit interesting biological and pharmaceutical properties such as progesterone receptor (PR) modulation, antianxiety, anti-HIV, agonist and antagonist activities.[1-4] Particularly, chiral dihydrobenzo[1,4]oxazines attracted much attention due to their interesting biological activities.[5, 6] Chiral dihydrobenzo[1,4]oxazines are also employed as catalysts for the asymmetric transfer hydrogenation of α,β-unsaturated aldehydes.[7]

Fluorine atoms contained in the core structure of a drug results in enhancement of several biological properties such as solubility, lipophilicity, metabolic stability and binding selectivity.[8] Levofloxacin, Ciprofloxacin, Norfloxacin and Efavirenz are examples of pharmaceutical drugs containing a fluorine atom together with dihydrobenzo[1,4]oxazines in the same molecule.[8-10]

Consequently, a wide range of synthetic procedures have been developed for the synthesis of these fluorinated chiral benzoxazines. These procedures include direct cyclization using a metal catalyst such as Pd in the Buchwald-Hartwig coupling reaction[11] and the copper-catalysed intramolecular direct ring closure,[12] a biocatalytic method[13] and several other older methods.[14-18]

Rearrangement reactions are generally undesired, but in many instances can be favourable since they are able to facilitate the synthesis of synthetically complicated chemicals.[19] Additionally, these reactions provide an opportunity to synthesise organic molecules that were not possible previously.

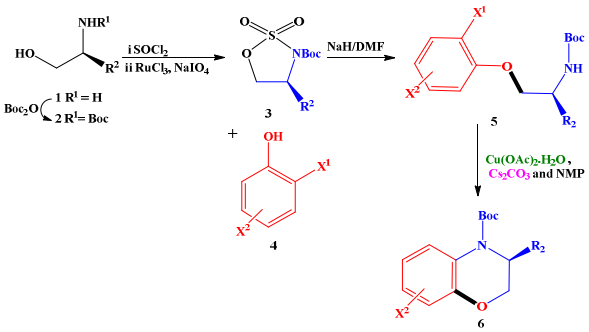
The Smiles Rearrangement (SR) has been used in the synthesis of different benzoxazinones.[20-23] To the best of our knowledge there have been no reports of this rearrangement in the synthesis of benzoxazines. In spite of the wealth of literature pertaining to SR, there is still a gap in the literature with regard to studies on the conformational effect on the copper catalysed ring closure via SR. It is well accepted that conformations of precursors can play a crucial role in chemical reactions and biological activity.[24-30] As such, there is a need to explore this aspect further.

The initial aim of our work was to synthesise Levofloxacin's precursor (**6fi**) via a copper catalysed ring closure, but surprisingly the interruption by the SR was detected in all derivatives. Further investigation led us to provide a new insight to this rearrangement. The effects of conformational change as well as the presence of fluorine in novel derivatives of benzoxazines were investigated by NMR and X-ray crystallography. These studies helped us to propose a new mechanism for the one pot SR-ring closure reaction of benzoxazine type compounds. Herein we report an operationally simple and economic technique for the synthesis of enantiomerically pure fluorinated [1,4]-benzoxazines assisted by the SR and involving a copper mediated intramolecular ring closure, which can be considered as a novel procedure in comparison to the existing literature.

a. *School of Chemistry, University of KwaZulu-Natal, Private Bag X54001, Durban 4000, South Africa. Email: koorbanally@ukzn.ac.za*
b. *School of Chemical Engineering, University of KwaZulu-Natal, Private Bag X54001, Durban 4000, South Africa*

† Electronic Supplementary Information (ESI) available: Experimental details, ^{1}H NMR spectra, ^{13}C NMR spectrum, 2D NMR spectra, HRMS profile and CIF files of crystallographic data. See DOI: 10.1039/x0xx00000x?????????????

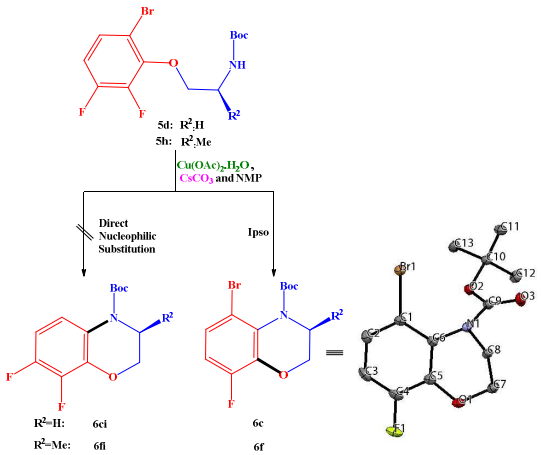
Scheme 1. Synthesis of Boc-[1,4]benzoxazin **6**



Commercially available alaninol **1** was protected with Boc via standard procedures[11] to give **2**, which was transformed to a cyclic sulfamidate **3** over two steps with 90% overall yield.[11] The reaction of **3** and phenol **4** afforded the product **5** by nucleophilic cleavage in 98% yield.[11] The reaction of **5** with a catalytic amount of copper (II) acetate (20 mol %,) at 90 °C in (undried) NMP in the presence of Cs_2CO_3 (3 *eq.*) provided Boc-[1,4]benzoxazin **6** by replacing the leaving group X^1 (either Br, I or F depending on the substrate) **(Scheme 1, Table 1)**.

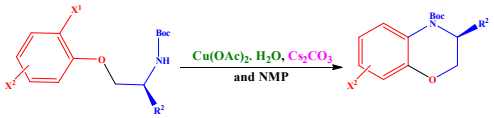
On inspection of the ^{13}C and ^{19}F NMR data of the product **6f** from the precursor **5h** (**available in the supplementary data**), it was apparent that the expected **6fi (Scheme 2)** did not form since there was a missing C-F resonance in the ^{13}C NMR spectrum and only a single fluorine resonance was observed in the ^{19}F NMR spectrum. The optimized reaction conditions were applied to **5d** and the same observation was found in the spectra of **6c**. Instead of **6ci (scheme 2)**, the rearranged compound (**6c**) was found to be the actual structure. This rearrangement, where the stronger F base acts as a leaving group, can be categorized as a SR that typically occurs in the presence of base in polar solvents.[6, 31, 32] Some reports have shown that Cu was essential for the SR ring closure to occur.[6, 33-36]

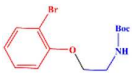
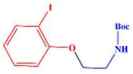
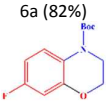
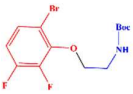
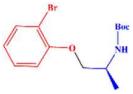
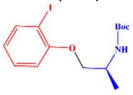
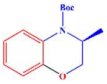
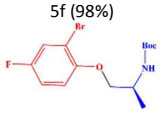
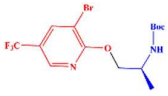
Scheme 2. Synthesis of Boc-[1,4]benzoxazin **6** interrupted by SR



Considerable optimization (**available in supplementary data**) showed that undried NMP (*N*-methyl-2-pyrrolidone) provided the best yield amongst other polar aprotic solvents. These results also indicated that $Cu(OAc)_2.H_2O$ was the best catalyst amongst other copper sources. Control experiments in the absence of ligand revealed that $Cu(OAc)_2.H_2O$ alone was capable of this catalytic performance and application of an external ligand poisoned the reactions. In addition, no product was formed in the absence of copper, indicating its importance in the mechanism of the reaction. Various bases were also tested and amongst these, Cs_2CO_3 showed the best results. This was in agreement with other reports.[6, 31, 35, 37]

Table 1. Synthesis of different Boc-benzoxazine via SR copper catalyzed ring closure. (Temperature: 90 °C).



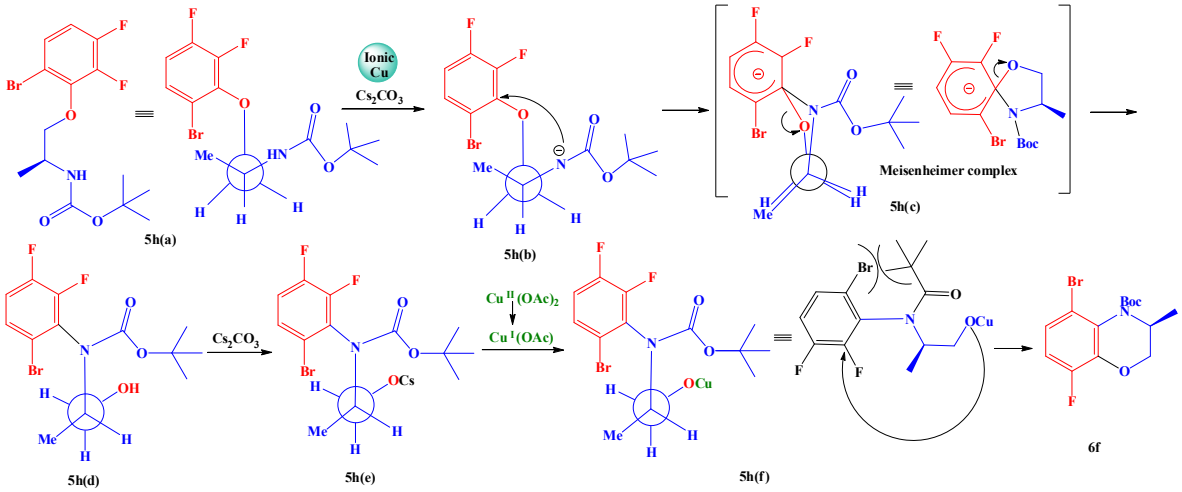
No.	Adduct (**5**) (Yield[a] %)	Boc-[1,4]benzoxazine (yield[a] %)[b,c]
1	 5a (99%)	 6a (84%)
2	 5b (99%)	 6a (82%)
3	 5c (99%)	 6b (NR)
4	 5d (99%)	 6c (96%)
5	 5e (98%)	 6d (87%)
6	 5f (98%)	 6d (82%)
7	 5g (99%)	 6e (NR)
8	 5h (99%)	 6f (98%)
9	 5i (99%)	 6g (NR)

[a] Isolated yield (%). [b] Temperature: 90 °C. [c] The reaction time for all reactions is 24 hours.

The reactions were repeated with the optimised conditions at room temperature instead of 90 °C. Surprisingly, the coupling reaction on **5d** and **5h** proceeded to **6c** and **6f** with 90 % yield at room temperature, while **5a** and **5b** proceeded to **6a**, and **5e** and **5f** to **6d**

at 90 °C only and no product was observed at room temperature (**Table 1**). With the precursors **5c**, **5g** and **5i**, the products **6b**, **6e** and **6g** could not be formed even at 90 °C. This observation prompted us to study the conformation of adducts in the reaction in order to gain an insight into how the products were formed.

Scheme 3. Plausible catalytic cycle for formation of Boc-[1,4]benzoxazin through the SR copper catalyzed ring closure reaction



The presence of an iodine or bromine atom in the *ortho* position to the oxygenated side without further substitution (**5a**, **5b**, **5e** and **5f**) provided almost the same yield for the cyclized products **6a** and **6d** (~85 %) (**Table 1**). The highest yield was obtained for **6e** (98%) with the **5h** precursor. The other precursor with an *ortho* positioned F atom, **5d** also had a similar yield of 96%. Therefore, it can be concluded that electron-withdrawing effect of fluorine in the *ortho*-position of the aromatic ring stabilizes the formed intermediate (Meisenheimer complex **5h(c)** in **Scheme 3**) and therefore, the highest yields were obtained for **6c** and **6f**.[38] Zhao *et al.* in 2012 also showed that strong electron-withdrawing groups on the aromatic rings increase the yields of SR.[31]

It is likely that the SR copper catalysed ring closure reaction in this study may follow the proposed mechanism in **scheme 3**. In this proposed mechanism, the proton of the amide was removed from **5h(a)** in the presence of Cs_2CO_3 as a base **(Scheme 3)**. This is followed by a nucleophilic substitution of the nitrogen onto the aromatic ring producing **5h(d)**. In the final step, the resulting nucleophilic oxygen in the side chain substitutes the *ortho* positioned F atom to yield the product **6f**.

The existence of different parameters seems to have a direct impact on the initiation of this reaction. The presence of the Boc protecting group seems to play a crucial role in the SR. [39] To prove this hypothesis, we applied the optimised reaction conditions on deprotected **5h** and observed that no cyclisation took place. Furthermore, it is suggested that the presence of a carbonyl group in the neighbouring NH (amide group) increases its nucleophilic effect in the SR.[39] It is highly likely that this is the reason why there are no reports on the presence of SR for 1,4-benzoxazine, while this rearrangement was frequently reported for benzoxazinones.

$Cu(OAc)_2$ and Cs_2CO_3 are two other important reagents needed for this rearrangement to occur. The presence of ionic Cu plays a role in increasing the acidity of the amide proton and makes its deprotonation via Cs_2CO_3 easier.[35, 40]

It is also well accepted that the localized negative charge on the nitrogen in our study increases its nucleophilic strength.[39] Polar aprotic solvents such as DMF and NMP are frequently used in the SR, which is in a good agreement with our optimized data.[34, 35] It is also suggested that these types of solvents stabilize the Meisenheimer complex and help improve the results.[35]

This copper catalysed coupling reaction is known to occur through the presence of Cu(I). This is supported by literature, which reports that Cu(II) and Cu(0) as a source of Cu will be transformed to Cu(I).[41, 42] There are also reports that Cu(II) performed better than Cu(I) based on the selected conditions of the reaction.[36, 43]

In addition, when there is competition between Br and F, the expected leaving group is assumed to be Br, the better of the two leaving groups. This did not occur in our experiments. The presence of steric hindrance between the Boc protecting group (**5h(f) scheme3**) and Br with a large atomic radius (in comparison to F) causes the oxygen to substitute the F instead of Br on the aromatic ring.

Based on the proposed mechanism in **Scheme 3**, this conformer (**5h**) facilitated the SR by shortening the distance between the nucleophile and the electrophile (ipso carbon) (**Figure 1**) for the occurrence of nucleophilic substitution. These desirable conformations of **5d** and **5h** assist these reactions, so much so that these reactions could proceed at room temperature with high yield.

As can be seen from **Figure 1**, **5h** (and probably **5d**) possess a folded structure. Based on a review published by O'Hagan[44], it can be proposed that the fluorine atoms in the aromatic ring of adduct **5g** (and **5d**) is situated in an ideal position for a dipole-dipole interaction, which results in the conformer shown in **Figures 1** and

2. Since fluorine atoms are well-known π donors, this interaction can be due to hyper-conjugation of the highly polarized C-F bonds, which is stabilized by the π system of the aromatic ring and provide the *gauche* conformer in **5g** (and **5d**) (**Figure 2(a)**).[45-47]

Figure 1. Crystal structure of **5e**, **5f** and **5h** and the distances between the ipso carbon and nitrogen

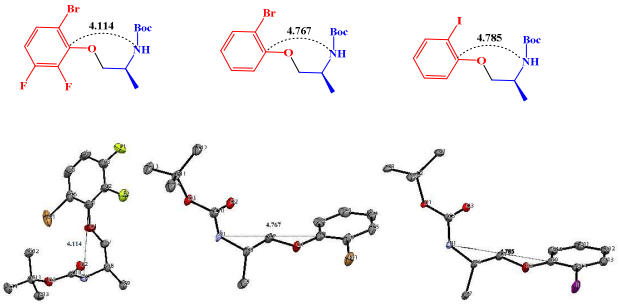
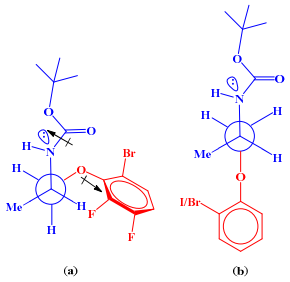


Figure 2. (a) *Gauche* conformer (from crystal structure of 5g) (b) *anti* conformer (from crystal structure of 5d and 5e)



Conclusions

The new synthesis procedure for chiral [1,4]-benzoxazin derivatives containing F atoms as well as other halogens in different positions of the aromatic ring via the copper catalyzed SR ring closure provided valuable information about the effect of the SR on the synthesis and diversification of these valuable chemicals. The optimization reaction conditions as well as the proposed mechanism indicated the importance of the Boc protecting group, since this reaction could not proceed in its absence. Application of polar aprotic solvents seems to facilitate this reaction and enhances the final yield. In addition, presence of both a copper source and Cs_2CO_3 is crucial for this reaction to occur (**Scheme 3**). Finally, the reaction of adducts **5d** and **5h (Figure 1)** with folded structures in the *gauche* conformation (from crystallographic data) made it possible for these reactions to occur at room temperature.

Acknowledgment

This research was supported by grants from the National Research Foundation (NRF), South Africa and was supported by the South African Research Chairs Initiative of the Department of Science and Technology. We thank Dr Bernard Owaga and Mr Sizwe Zamisa for assistance with X-Ray crystallography.

References

1. N. Dias, J. F. Goossens, B. Baldeyrou, A. Lansiaux, P. Colson, A. Di Salvo, J. Bernal, A. Turnbull, D. J. Mincher and C. Bailly, *Bioconjugate Chem.*, 2005, **16**, 949-958.
2. S. J. Hays, B. W. Caprathe, J. L. Gilmore, N. Amin, M. R. Emmerling, W. Michael, R. Nadimpalli, R. Nath, K. J. Raser, D. Stafford, D. Watson, K. Wang and J. C. Jaen, *J. Med. Chem.*, 1998, **41**, 1060-1067.
3. S. Jana, A. Ashokan, S. Kumar, A. Verma and S. Kumar, *Org. Biomol. Chem.*, 2015, **13**, 8411-8415.
4. P. Zhang, E. A. Terefenko, A. Fensome, Z. Zhang, Y. Zhu, J. Cohen, R. Winneker, J. Wrobel and J. Yardley, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 787-790.
5. B. Achari, S. B. Mandal, P. K. Dutta and C. Chowdhury, *Synlett*, 2004, 2449-2467.
6. E. Feng, H. Huang, Y. Zhou, D. Ye, H. Jiang and H. Liu, *J Org Chem*, 2009, **74**, 2846-2849.
7. C. Ebner and A. Pfaltz, *Tetrahedron*, 2011, **67**, 10287-10290.
8. S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320-330.
9. V. V. Komnatnyy, W.-C. Chiang, T. Tolker-Nielsen, M. Givskov and T. E. Nielsen, *Angew. Chem. Int. Ed.*, 2014, **53**, 439-441.
10. S. Atarashi, S. Yokohama, K. I. Yamazaki, K. I. Sakano, M. Imamura and I. Hayakawa, *Chem. Pharm. Bull.*, 1987, **35**, 1896-1902.
11. J. F. Bower, P. Szeto and T. Gallagher, *Org. Lett.*, 2007, **9**, 3283-3286.
12. M. K. Parai and G. Panda, *Tetrahedron Lett.*, 2009, **50**, 4703-4705.
13. M. Lopez-Iglesias, E. Busto, V. Gotor and V. Gotor-Fernandez, *J. Org. Chem.*, 2015, **80**, 3815-3824.
14. S. Atarashi, H. Tsurumi, T. Fujiwara and I. Hayakawa, *J. Heterocycl. Chem.*, 1991, **28**, 329-331.
15. J. Balint, G. Egri, E. Fogassy, Z. Bocskei, K. Simon, A. Gajary and A. Friesz, *Tetrahedron: Asymmetry*, 1999, **10**, 1079-1087.
16. S. B. Kang, E. J. Ahn, Y. Kim and Y. H. Kim, *Tetrahedron Lett.*, 1996, **37**, 9317-9320.
17. L. A. Mitscher, P. N. Sharma, D. T. W. Chu, L. L. Shen and A. G. Pernet, *J. Med. Chem.*, 1987, **30**, 2283-2286.
18. K. Satoh, M. Inenaga and K. Kanai, *Tetrahedron: Asymmetry*, 1998, **9**, 2657-2662.

19. T. J. Snape, *Chem. Soc. Rev.*, 2008, **37**, 2452-2458.
20. I. G. C. Coutts and M. R. Southcott, *J. Chem. Soc., Perkin Trans. 1*, 1990, 767-771.
21. J. Kang, K. H. Kam, M. Ghate, Z. Hua, T. H. Kim, C. R. Reddy, S. Chandrasekhar and D. S. Shin, *ARKIVOC*, 2008, 67-76.
22. S. Xia, J.-Q. Liu, X.-H. Wang, Y. Tian, Y. Wang, J.-H. Wang, L. Fang and H. Zuo, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 1479-1483.
23. H. Zuo, L. Meng, M. Ghate, K. H. Hwang, Y. K. Cho, S. Chandrasekhar, C. R. Reddy and D. S. Shin, *Tetrahedron Lett.*, 2008, **49**, 3827-3830.
24. J. I. Seeman, *Chem. Rev.*, 1983, **83**, 83-134.
25. L. Agocs, G. G. Briand, N. Burford, T. S. Cameron, W. Kwiatkowski and K. N. Robertson, *Inorg. Chem.*, 1997, **36**, 2855-2860.
26. C. M. Dobson, *Nature*, 2003, **426**, 884-890.
27. X.-B. Wang, J. Yang and L.-S. Wang, *J. Phys. Chem. A*, 2008, **112**, 172-175.
28. M. Nishizaka, T. Mori and Y. Inoue, *J. Phys. Chem. Lett.*, 2010, **1**, 2402-2405.
29. T. Lei, X. Xia, J.-Y. Wang, C.-J. Liu and J. Pei, *J. Am. Chem. Soc.*, 2014, **136**, 2135-2141.
30. M. D. Farahani, B. Honarparvar, F. Albericio, G. E. M. Maguire, T. Govender, P. I. Arvidsson and H. G. Kruger, *OBC*, 2014, **12**, 4479-4490.
31. Y. Zhao, Y. Wu, J. Jia, D. Zhang and C. Ma, *J. Org. Chem.*, 2012, **77**, 8501-8506.
32. T. J. Snape, *Chem. Soc. Rev.*, 2008, **37**, 2452-2458.
33. M. O. Kitching, T. E. Hurst and V. Snieckus, *Angew. Chem. Int. Ed.*, 2012, **51**, 2925-2929.
34. T. E. Hurst, M. O. Kitching, L. C. R. M. da Frota, K. G. Guimaraes, M. E. Dalziel and V. Snieckus, *Synlett*, 2015, **26**, 1455-1460.
35. N. C. Ganguly, P. Mondal, S. Roy and P. Mitra, *RSC Advances*, 2014, **4**, 55640-55648.
36. P. Sang, M. Yu, H. Tu, J. Zou and Y. Zhang, *Chem. Commun.*, 2013, **49**, 701-703.
37. L. Fang, H. Zuo, Z. B. Li, X. Y. He, L. Y. Wang, X. Tian, B. X. Zhao, J. Y. Miao and D. S. Shin, *Med. Chem. Res.*, 2011, **20**, 670-677.
38. J. Hornback, *Organic Chemistry*, Cengage Learning, 2005.
39. J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, 1951, **49**, 273-412.
40. B. F. G. Johnson, *Inorganic Chemistry of the Transition Elements*, Chemical Society, 1977.
41. X. Ribas and I. Gueell, *Pure Appl. Chem.*, 2014, **86**, 345-360.
42. C. Sambiagio, S. P. Marsden, A. J. Blacker and P. C. McGowan, *Chem. Soc. Rev.*, 2014, **43**, 3525-3550.
43. S. Li, Z. Li and J. Wu, *Adv. Synth. Catal.*, 2012, **354**, 3087-3094.
44. D. O'Hagan, *Chem. Soc. Rev.*, 2008, **37**, 308-319.
45. P. R. Rablen, R. W. Hoffmann, D. A. Hrovat and W. T. Borden, *J. Chem. Soc., Perkin Trans. 2*, 1999, 1719-1726.
46. L. Goodman, H. B. Gu and V. Pophristic, *J. Phys. Chem. A*, 2005, **109**, 1223-1229.
47. C. Sparr, E. Salamanova, W. B. Schweizer, H. M. Senn and R. Gilmour, *Chem. Eur. J.*, 2011, **17**, 8850-8857.