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LETTER

Unprecedented directed oxidative cross-coupling of sulfahydantoins with aldehydes *via* a radical sulfonate–sulfinate conversion†

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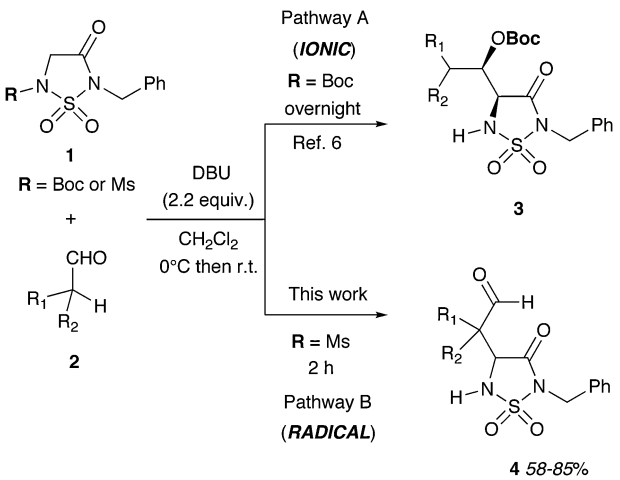
An unexpected C–C cross-coupling radical oxidation involving aldehydes and glycine enolate equivalents such as activated mesyl-sulfahydantoins leading to β,β′-disubstituted aspartate semialdehydes (ASA) instead of the expected threonine analogues was observed and various α-substituted non-proteinogenic amino acid analogues were synthesized. A radical mechanism was envisaged and supported by DFT calculations.

Non-proteinogenic amino acids and their derived peptides are important components of biological systems and attractive targets in synthetic chemistry because of the diverse range of physiological and therapeutic activities they display.[1,2] The sulfahydantoin (3-oxo-1,2,5-thiadiazole-1,1-dioxide) ring, a highly effective peptidomimetic scaffold where the non-hydrolyzable sulfonamide functionality can be exploited as a valuable candidate for the replacement of the amido group, is an emerging class of heterocycles in this respect. The sulfonamide functionality proved to be selective for the inhibition of proteases,[3,4] it constitutes the aglycone part in pseudonucleoside analogues,[5] or the substructure in constrained peptides.[6] On the other hand, the reactions of glycine derivatives, *via* their corresponding enolates, are some of the most versatile ways to introduce functional groups at the α-position of carbonyl and create a large variety of modified amino acids.[7] In this context, the sulfahydantoin **1**, activated in the *N*-5 position by an electron withdrawing group, can be considered a glycine enolate equivalent, able to promote the formation of new C–C bonds under basic conditions. We have recently reported[7] that threonine sulfahydantoin analogues **3** could be obtained in good yields by an ionic highly diastereoselective aldolisation reaction of Boc-activated sulfahydantoin **1** with aldehydes in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a base (pathway A, Scheme 1). We report herein a 'serendipitous' discovery: when the *N*-Boc protecting group was replaced by a methanesulfonyl (mesyl, Ms) group, an unexpected product was formed. Instead of the aldolisation product, the aspartate semialdehyde (ASA) derivative **4** was unequivocally obtained, provided that an aldehyde with an α-hydrogen such as **2** was used (pathway B, Scheme 1). The assembly of two carbonyl subunits by their α-carbon, which is undocumented to date, afforded 1,4-carbonyl derivatives through a direct oxidative cross-coupling reaction.



Scheme 1 Modulation of the reactivity of sulfahydantoin rings.

We speculated that formation of the 1,4-dicarbonyl derivative **4** would involve the spontaneous formation of radical intermediates, instead of ionic species. The radical directed oxidative cross-condensation reaction described here, named with the acronym •*docc*, allowed conversion of a sulfonate into a sulfinate group.‡ The radical sulfonate–sulfinate reduction was postulated to follow an oxidative coupling involving enolates. This original reaction led to a direct access to β,β′-disubstituted aspartate semialdehyde (ASA) derivatives **4**, which are important synthetic and biosynthetic precursors, involved in bacterial amino acid and peptidoglycan biosynthesis.[8] The ionic functionalization of the α-position of amino acids has been extensively described. In contrast, examples involving a radical C–C bond formation

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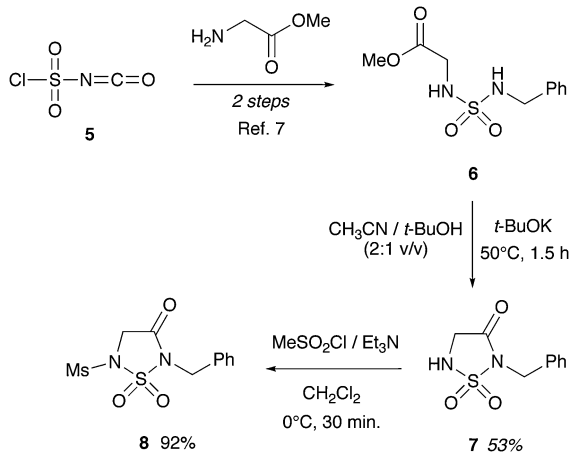
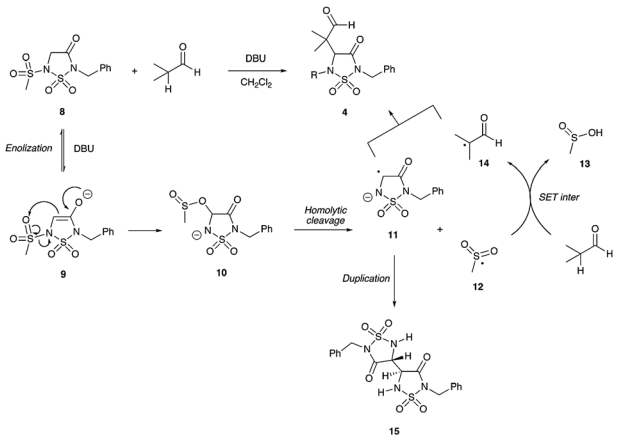
† Electronic supplementary information (ESI) available: Experimental procedures, ^{1}H and ^{13}C spectra and DFT calculations. See DOI: 10.1039/c2nj40294g



Scheme 2 Synthesis of *N*-mesylated sulfahydantoin **8**.



Scheme 3 Proposed reaction mechanism for radical •*docc* reaction.

mechanism are quite rare,[9] and in most cases duplication products are obtained.[10,11] To our knowledge, only one example in which glycine is alkylated *via* a visible light-induced intermolecular radical coupling reaction is reported in the literature.[12] In order to explore in detail the potential of our findings, we synthesized large quantities of *N*-mesylated sulfahydantoin **8**. The synthesis of *N*-benzyl-sulfamoyl methyl glycinate **6** was carried out in three steps as previously described,[7] *via* a *trans* sulfamoylation-ring closure pathway from chlorosulfonyl isocyanate (CSI) **5** and methyl glycinate (Scheme 2). Although the intramolecular cyclization of **6** leading to sulfahydantoin **7** could not be improved in terms of yield (53%) in comparison with the previously published procedure,[7] scale-up of **7** (5 g) was possible when acetonitrile was used as the co-solvent, instead of *t*-BuOH alone. *N*-5 mesylated sulfahydantoin **8** was obtained in the presence of methanesulfonyl chloride in very good yield after purification (Scheme 2).

At the beginning our goal was directed towards the aldolization reaction of *N*-Boc or *N*-Ms protected sulfahydantoins. Then, isobutyraldehyde was chosen as a model substrate and the reaction was carried out in the presence of two equivalents of DBU, in dichloromethane at 0 °C (Scheme 1, pathways A and B) under alkaline conditions. To our surprise, when the substrate was the *N*-mesylated ring **8**, full conversion of the starting material was observed within five minutes (instead of one night)[7] and a single product was obtained in 81% yield after purification. However, the careful interpretation of the ^{1}H-NMR, ^{13}C-NMR, coupled ^{13}C-NMR, COSY clearly indicated that the expected aldolization product was not formed, but a new compound was obtained. The ^{1}H NMR spectrum[13] showed a singlet at 9.36 ppm characteristic of an aldehyde proton. The benzylic protons became anisochrones (two doublets at 4.76 ppm) as the consequence of creation of a chiral center at the glycine α-position, suggesting that a new C–C bond was formed. Moreover, the presence of a broad singlet at 4.88 ppm characteristic of an exchangeable proton indicated that the *N*-5 nitrogen atom was not mesylated anymore. By analysing the coupling constants ^{n}J ($n > 1$) measured in the coupled ^{13}C-NMR spectrum,[13] we determined the presence (at 50 ppm) of an aliphatic quaternary carbon adjacent to the aldehyde, indicating that the hydrogen atom of the isopropyl group was not present. This aliphatic quaternary carbon coupled with the aldehydic hydrogen (^{2}J = 22.9 Hz), the six hydrogens of geminal methyl groups and the hydrogen at the α-position of glycine (^{2}J = 3.7 *Hz*), clearly indicating that the direct oxidative coupling was realized between these two sites. The α-carbon of glycine coupled with its geminal hydrogen atom (^{1}J = 146.3 Hz) and with the exchangeable proton at 4.88 ppm, confirming that the sulfahydantoin ring was not mesylated.[13] On the other hand, the sulfonate, which was liberated during the reaction pathway, has been detected by mass spectrometry in its reduced form as a sulfinate DBU salt, displaying a peak at m/z = 79 (FAB in negative mode).

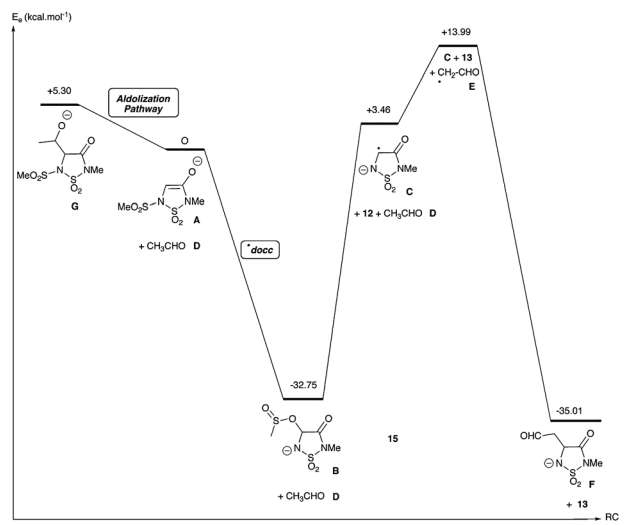
Starting from these experimental data and based on DFT calculations, we proposed that condensation proceeded through a homolytic mechanism (Scheme 3). The sulfonate group would play the role of the necessary oxidant with the particularity of being initially linked to the substrate. We proposed the reduction of the sulphur atom from oxidation state +4 (in **12**) to +2 (in **13**) through a radical-promoted pathway according to a general scheme in agreement with the cross-condensation observed experimentally, leading to **4** (Scheme 3). To date, the involvement of a sulfonyl group in such oxidative coupling has not been reported. However, the implication of the $PhSO_2^{\bullet}$ radical was highlighted in oxime substitutions.[14]

As originally proposed by Rathke and Lindert for the oxidative coupling of carboxylates,[15] the first step of this transformation involved enolization of **8**. The intramolecular rearrangement of enolate **9** to **10** was followed by radical extrusion *via* an homolytic cleavage leading to a persistent[9] α-carbon-centered anion radical **11** and a sulfonyl radical **12**. The radical sulfonate **12** was reduced by an intermolecular single electron transfer (SET inter) in the presence of the aldehyde, to afford sulfinic acid **13**, which formed a salt with the second DBU equivalent. The hydrogen-transfer reaction between the methanesulfonyl radical **12** and the aldehyde proceeded through the so-called polarity-reversal catalysis[16] mediated by $MeSO_2^{\bullet}$ species.[17] Moreover, it was demonstrated[18] that the unpaired electron in **12** was centered mainly on sulphur in an orbital predominantly of 3p character, with a pyramidal geometry with respect to the sulphur atom. The radical intermediate **14** collapsed with **11** by a radical–radical coupling mechanism

affording the observed •*docc* product **4** (Scheme 3). To get more insight into the mechanistic details of this coupling reaction, DFT calculations were undertaken, using the GAUSSIAN 09 program, at the B3LYP/6-31+G(d,p) or UB3LYP/6-31+G(d,p) (for radical and radical anion species) level of theory.[19,20] Stationary points for optimized geometries were determined to have zero imaginary vibrational frequencies. In the gas phase, optimization of the geometry of model enolate **A**, bearing a methyl group instead of a benzyl group on the *N*-2 nitrogen atom for calculation cost reasons, turned out to be very difficult. In spite of many efforts, it always led to the transfer of the sulfonyl group from *N*-5 to C-4. This apparent instability of the enolate anion led us to consider the mechanistic pathway involving a transfer such as the one proposed from **9** to **10** depicted in Scheme 3. It is well known that anions are quite sensitive to the polarity of the reaction medium. This effect was thus considered using the polarizable continuum model (PCM). When taking into account the effect of the dichloromethane dielectric constant, it became possible to optimize the geometry of the enolate anion **A**, which indeed proved to be less stable than sulfinate **B** (by 32.75 kcal mol^{-1}) (Scheme 4). The reaction pathway from **A** to **B** was evaluated by localization of the transition state (TS). The energy profile suggests a two step mechanism, involving, first, the dissociation of the enolate and, then, the attack of the sulfinate on the carbon atom of the enolate (see ESI†). As expected, homolytic cleavage of the C–O bond yielding radical anion **C** and radical sulfonate **12** was endothermic but the global process, modelled with acetaldehyde **D**, is thermodynamically favorable since the anion **F**, resulting from the coupling of radical anion **C** and radical **E**, was more stable. In contrast to this pathway, aldolization reaction was not favorable since it led to a less stable alkoxide **G** (Scheme 4).

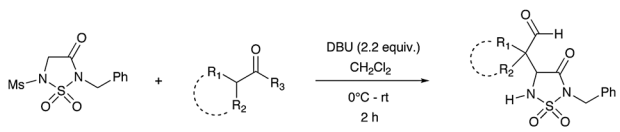
By performing the same type of calculations on the carbamate protected sulfahydantoins, which experimentally led to a classical aldol reaction, we found that the coupling pathway was not possible in this case since transfer of the carboxyl group from *N*-2 to C-4 would imply the formation of a carbene, a much less stable species (see ESI†). The dimerization of the radical sulfahydantoin **11** leading to **15** was demonstrated by NMR and mass spectrometry in separate experiments. It clearly proved the formation of radical species from **10** by a SET process. *N*-Mesylated sulfahydantoin **8** was suspended into a solution of DBU, in dry and previously degassed toluene under an argon atmosphere. The postulated radical intermediate **11** collapsed by a radical–radical coupling mechanism, leading to the duplication product **15** (Scheme 3). The ^{1}H NMR analysis of the duplication product **15** showed an AB system centered at 4.71 ppm for the diastereotopic benzyl protons and a sharp, well defined singlet at 5.01 ppm for the two magnetically equivalent α-CH protons of the glycine residue, allowing us to conclude that the dimer was in the *meso* form.[13] We extended our 'serendipitous' discovery to other different substrates bearing a mobile hydrogen in the α-position with respect to an electron withdrawing group (EWG) and susceptible to give radicals, when tested in the •*docc* reaction (Table 1).

As a general trend, in the aldehyde series better results were obtained when the α-position had a tertiary carbon substituted by electron rich alkyl chains (Table 1, entries 2, 4 and 5), leading to the expected •*docc* products in a very short time and good yields. However, linear aldehydes or electron withdrawing groups on the tertiary carbon (Table 1, entries 3 and 6 respectively) were completely unreactive. This could be explained by taking into account the electronic nature of the thiyl radical, particularly electrophilic and able to react with relatively high electron density centers. This behaviour was particularly enhanced by the ability of sulphur to use d orbitals to accommodate negative charges. Linear or branched ketones proved to be completely unreactive even after 24 hours or under prolonged heating (Table 1, entries 7–9). In contrast complex mixtures were obtained under the same reaction conditions with *tert*-butylacrylate or acrylonitrile maybe due to their instability in the presence of radical species (Table 1, entries 10 and 11). In order to succeed in the •*docc* coupling with the refractory substrates we speculate that dichloromethane, a



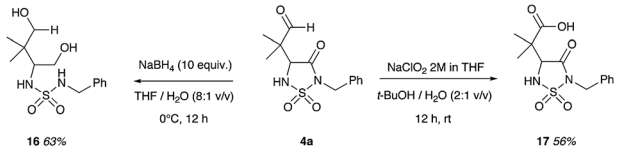
Scheme 4 Energetic diagram for the radical pathway.

Table 1 Selected data for the direct oxidative cross-coupling reaction (•*docc*)



Entry	R_1	R_2	R_3	Product	Yield[a,b] (%)
1	CH_3	CH_3	H	**4a**	80
2	CH_3CH_2	CH_3	H	**4b**	69[c]
3	$CH_3CH_2CH_2$	H	H	**4c**	0
4	—	*c*-Hex	H	**4d**	58
5	Ph	CH_3	H	**4e**	85[d]
6	BocNH[e,f]	CH_3[e,f]	H	**4f**	0
7	CH_3	CH_3	$CH(CH_3)_2$	**4g**	0
8	CH_3	CH_3	Ph	**4h**	0
9	CH_3CH_2	H	CH_3	**4i**	0
10	CH_3	CH_3	OCH_3	**4l**	n.d.
11	CH_3	CH_3	CN	**4m**	n.d.

[a] Isolated yields. [b] The diasteroisomeric ratio (*dr*) was determined by ^{1}H NMR. [c] The diasteroisomeric ratio was 2 : 1. [d] The diasteroisomeric ratio was 1 : 1. [e] Optically pure *S*-enantiomer. [f] The substrate was synthetized according to previously reported procedures.[22]



Scheme 5 ASA analogues **4** to access more complex derivatives.

hydrogen donor solvent, could be involved in the radical cascade, inhibiting the reaction. Therefore 1,2-dichloroethane, suitable for radical process studies, was selected as substitutive solvent and all the experiments were repeated under the same conditions as before. Unfortunately, the results were not improved, while increasing the temperature at reflux proved to be detrimental: a new product was detected in the crude mixture obtained from a side S_N2 reaction between the *N*-5 position of sulfahydantoin and the solvent. The potential access to a variety of polyfunctional non-proteinogenic and unnatural amino acids using ASA and its derivatives has already been described.[21] From this perspective, compounds **4** are important synthetic intermediates, as the aldehyde moiety can be functionalized leading to more complex structures. The reactivity of compound **4a** was tested in the reduction of aldehyde functions with $NaBH_4$ to afford functionalized 1,4-diol **16** and in the Pinnick oxidation,[22,23] leading to 1,4-ketoacid **17** in good yields (Scheme 5).

In conclusion, it has been possible to show that reactivity of the sulfonamide unit was governed by the nature of the protecting group, allowing otherwise 'impossible transformations' such as direct functionalization of the α-position of amino acids. We described a serendipitous synthesis of disubstituted aspartate semialdehydes *via* an oxidative cross condensation of glycine enolate equivalents. The elucidation of the radical mechanism was supported by DFT calculations. Optimization of the procedure and other mechanistic studies are in progress, as well as the extension of the new methodology to more complex synthetic goals leading to quaternary amino acids, which are often difficult to synthesize by ionic reactions.

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Notes and references

‡ Typical experimental procedure for the radical couplings of **8** with aldehydes (Table 1). To a solution containing Ms-sulfahydantoin **8** (1.65 mmol, 502 mg) and the suitable aldehyde (1.65 mmol, 502 mg) in CH_2Cl_2 (4 mL), DBU (3.63 mmol, 550 mg) was slowly added (1.82 mmol, 130 mg) at room temperature. The reaction mixture was stirred for 2 hours, then the reaction mixture was quenched with dilute HCl 0.1% (1 time) at 0 °C. The aqueous layer was extracted with CH_2Cl_2 (3 times). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was quickly purified by column chromatography on silica gel (3g) (gradient: AcOEt/CH_2Cl_2 (v/v), 5/95–20/80) to afford the title compounds **4a–b,d–e**.

1 R. O. Duthaler, *Tetrahedron*, 1994, **50**, 1539.
2 R. M. Williams, *Adv. Asymmetric Synth.*, 1995, **1**, 45.
3 W. C. Groutas, R. Kuang, R. Venkataraman, J. B. Epp, S. Ruan and O. Prakash, *Biochemistry*, 1997, **36**, 4739.
4 R. Kuang, J. B. Epp, S. Ruan, H. Yu, P. Huang, S. He, J. Tu, N. M. Schechter, J. Turbov, C. J. Froelich and W. C. Groutas, *J. Am. Chem. Soc.*, 1999, **121**, 8128.
5 (*a*) N. Aouf, G. Dewynter and J.-L. Montero, *Tetrahedron Lett.*, 1991, **32**, 6545; (*b*) G. Dewynter, N. Aouf, Z. Regaïna and J.-L. Montero, *Tetrahedron*, 1996, **52**, 993.
6 (*a*) S. Boudjabi, G. Dewynter, N. Voyer, L. Toupet and J.-L. Montero, *Eur. J. Org. Chem.*, 1999, 2275; (*b*) G. Dewynter, N. Aouf, M. Criton and J. L. Montero, *Tetrahedron*, 1993, **49**, 65.
7 (*a*) D. Bouchouk, E. Colacino, L. Toupet, N. Aouf, J. Martinez and G. Dewynter, *Tetrahedron Lett.*, 2009, **50**, 1100; (*b*) U. Schollkopf, *Top. Curr. Chem.*, 1983, **109**, 65; (*c*) D. Seebach, E. Juaristi, D. D. Miller, C. Schickli and T. Weber, *Helv. Chim. Acta*, 1987, **70**, 237.
8 P. Meffre, *Amino Acids*, 1999, **16**, 251–272.
9 C. J. Easton, *Radicals Organic Synthesis*, ed. P. Renaud and M. P. Sibi, Wiley VCH, Mannheim, 2001, vol. 2, pp. 505–522.
10 C. Alvarez-Ibarra, A. G. Csák, B. Colmenero and M. L. Quiroga, *J. Org. Chem.*, 1997, **62**, 2478.
11 A. G. Csàk and J. Plumet, *Chem. Soc. Rev.*, 2001, **30**, 313.
12 M. Schwarzberg, J. Sperling and D. Elad, *J. Am. Chem. Soc.*, 1973, **95**, 6418.
13 Refer to spectral data in the ESI†.
14 S. Kim and I. Y. Lee, *Tetrahedron Lett.*, 1998, **39**, 1587.
15 M. W. Rathke and A. Lindert, *J. Am. Chem. Soc.*, 1971, **93**, 4605.
16 B. P. Roberts, *Chem. Soc. Rev.*, 1999, **28**, 25.
17 D. Marković, A. Varela-Alvarez, J. A. Sordo and P. Vogel, *J. Am. Chem. Soc.*, 2006, **128**, 7782.
18 A. G. Davies, B. P. Roberts and B. R. Sanderson, *J. Chem. Soc., Perkin Trans. 2*, 1973, 626.
19 G. W T. M. J. Frisch, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski and D. J. Fox, Gaussian, Inc, Wallingford, CT, 2009.
20 This DFT method has been shown to be reliable for similar organic systems. See for instance: (*a*) I. Chataigner, C. Panel, H. Gérard and S. R. Piettre, *Chem. Commun.*, 2007, 3288; (*b*) Y. Zhou and W. H. Nelson, *J. Phys. Chem. A*, 2011, **115**, 11566; (*c*) K. Makarova, E. V. Rokhina, E. A. Golovina, H. Van As and J. Virkutyte, *J. Phys. Chem. A*, 2012, **116**, 443.
21 H. Lusch and H. C. Uzar, *Tetrahedron: Asymmetry*, 2000, **11**, 4965.
22 B. S. Bal, W. E. Childers and H. W. Pinnick, *Tetrahedron*, 1981, **37**, 2091.
23 S. Jiang, P. Li, C. C. Lai, J. A. Kelley and P. P. Roller, *J. Org. Chem.*, 2006, **71**, 7307.