Catalytic formation of aziridines from imines. Characterisation of an intermediate in $SnCl_4$-catalysed aziridination and mechanistic considerations

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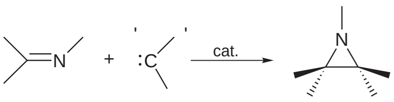
The tin(IV) catalysed aziridination of imines using ethyl diazoacetate as the carbene fragment donor has been investigated from a synthetic and mechanistic point of view. For imines substituted with aromatic substituents, an intermediate in the aziridination reaction has been isolated and characterised by X-ray diffraction. This intermediate is an octahedral complex with a *trans* coordination of two imines and in which the imines have isomerised from *trans* to *cis* by the reaction with/coordination to tin(IV). Tin(IV) is a very effective catalyst for the aziridination of various imines giving *cis*-aziridines as the major product. The aziridination can proceed with a very low catalyst load as 0.05 mol% of $SnCl_4$ is sufficient to achieve a high conversion. For the formation of aziridines a linear plot of the experimental data is obtained by means of the Hammett equation for a series of competition experiments. Based on the results the mechanism for the aziridination is discussed in terms of a Lewis acid activation of the imine for a nucleophilic attack of ethyl diazoacetate.

Introduction

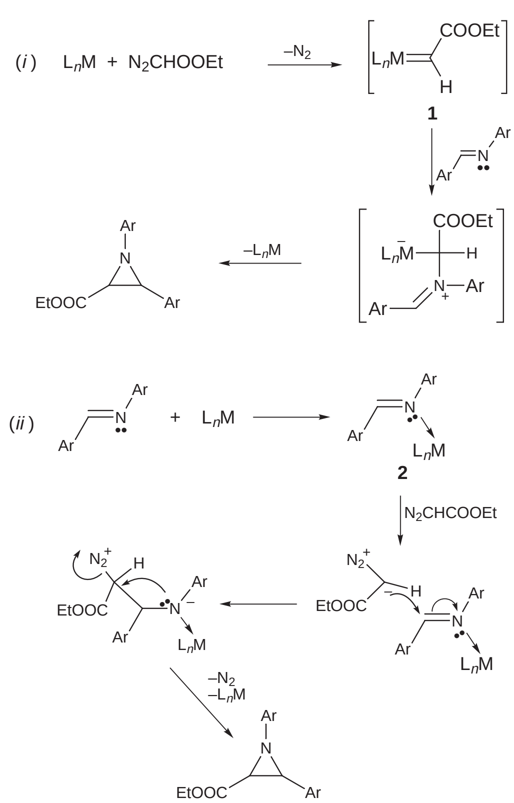
The reaction of imines with a carbene donor in the presence of a metal complex as a catalyst is a new entry for the formation of aziridines [eqn. (1)].[1–4]



(1)

Aziridines prepared by the reaction of imines with diazo compounds, such as ethyl diazoacetate (EDA), as the carbene-donor fragment in the presence of metal complexes can take place by two different reaction paths depending on the properties of the metal:[2] the metal complex can react with EDA under elimination of N_2 and the formation of a metal–carbene complex, **1**, which can transfer the carbene fragment to the imine as outlined in Scheme 1 (*i*). The other approach (*ii*) outlined in Scheme 1 is activation of the imine by the metal, the latter now acting as a Lewis acid, leading to intermediate **2**. The coordination of the imine to the Lewis acid activates the imine for a nucleophilic attack by EDA at the α-carbon atom followed by subsequent elimination of N_2.

Various Lewis acid complexes, such as titanium(IV),[2i,m] zinc(II),[2h,i] ytterbium(III),[2i] tin(IV),[2d,m,4] silicon(IV),[2j] boron(III),[2j,m] methylrhenium trioxide[2e] and rhodium- and manganese-exchanged montmorillonite K10 clays[2k] can catalyse the formation of aziridines from imines probably *via* the mechanism outlined as (*ii*) in Scheme 1.

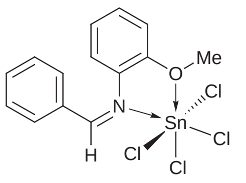


Scheme 1

Recently an imine–Lewis acid intermediate, **3**, in the tin(IV)-catalysed aziridination, consisting of the imine coordinated in a bidentate fashion to $SnCl_4$ has been isolated and characterised by X-ray diffraction.[4] The intermediate **3** was formed in the aziridination reaction of *N*-benzylidine-*o*-anisidine **4a** with EDA **5** in the presence of $SnCl_4$ as the catalyst [eqn. (2)].[2i,4] The reaction proceeds to give the *cis*-aziridine **6a** with high selectivity.[4]

The structure of the imine–$SnCl_4$ complex **3** shows that imine **4a** utilises both the nitrogen and oxygen lone-pair electrons for a bidentate coordination to the metal. Furthermore, the imine isomerises from a *trans* geometry in **4a** to a *cis* geometry by the reaction with/coordination to $SnCl_4$.[4]

In an attempt to develop highly effective catalytic aziridination reactions and to obtain further insight into Lewis-acid catalysed aziridination reactions [Scheme 1 (*ii*)] using Lewis acids as the catalyst, the attention has been focused on the reaction of imines, which can coordinate in a mainly monodentate fashion to the metal, with EDA [eqn. (3)]. The present work (*i*) presents a new imine–$SnCl_4$ intermediate for the aziridination reaction, (*ii*) shows that a *very low* catalyst load of $SnCl_4$ can be used and (*iii*) gives new mechanistic insight into the Lewis-acid



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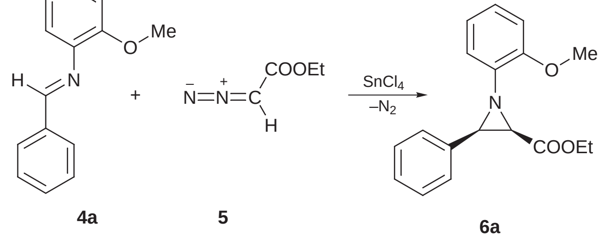
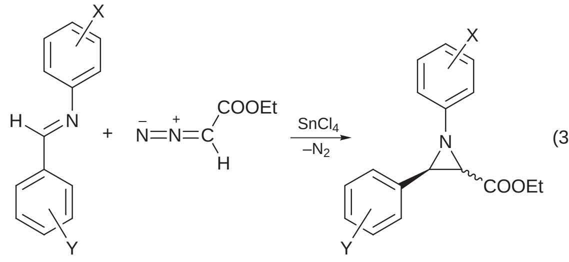


(2)

4a **5** **6a**



(3)

4a: X = *o*-OMe
4b: X = *p*-Cl
4c: X = *p*-H
4d: X = *p*-OMe
4e: Y = *p*-Me
4f: Y = *p*-Cl
4g: Y = *p*-CN
4h: Y = *p*-NO$_2$

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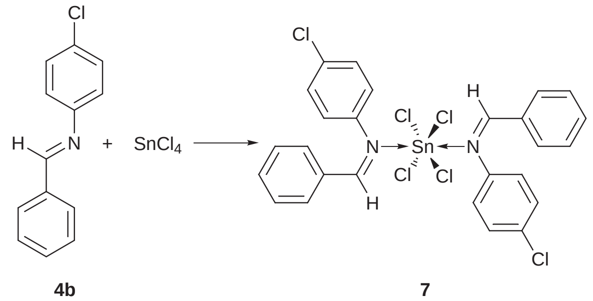
6a: X = *o*-OMe
6b: X = *p*-Cl
6c: X = *p*-H
6d: X = *p*-OMe
6e: Y = *p*-Me
6f: Y = *p*-Cl
6g: Y = *p*-CN
6h: Y = *p*-NO$_2$

catalysed aziridination reaction on the basis of competition studies.

Results and discussion

The reaction of *N*-benzylidene-4-chloroaniline **4b** with SnCl$_4$ in CDCl$_3$ under an argon atmosphere leads to the formation of an imine–SnCl$_4$ complex **7** formed as colourless crystals.



(4)

4b **7**

The structure of **7**, determined by X-ray diffraction, depicted in Fig. 1, shows an octahedral complex with a *trans*-coordination of two imines **4b** to tin. It appears from the X-ray structure of **7** that the imines isomerise from *trans* to *cis* by coordination to SnCl$_4$. The reason for the *trans* to *cis* isomerisation of **4b** is probably a reduction of the steric repulsion between the C-phenyl substituent of the imine and the equatorial chlorines of SnCl$_4$. This *trans* to *cis* change of **4b** is similar to the isomerisation observed for the reaction of **4a** with SnCl$_4$.[4] The Sn–N bond length in **7** is 2.267(2) Å which is slightly longer than the Sn–N bond length in **3** [2.222(5) Å]. The equatorial Sn–Cl bond length, Sn–Cl(1), is slightly longer than the axial one, Sn–Cl(2), 2.404(1) *vs.* 2.390(1) Å, respectively. The imine C(1)=N bond in **7** [1.288(2) Å] is not affected by the coordination to SnCl$_4$ and is similar to other imines characterised.[5] The two aromatic substituents are slightly twisted because of steric repulsion.

Table 1 Aziridination of various imines **4a**–**h** with ethyl diazoacetate as the terminal oxidant catalysed by SnCl$_4$ (1 mol%)

Entry	Imine	Conversion (%)	Aziridine, *cis*:*trans*
1	**4a**	>90	**6a**, >20:1
2	**4b**	>90	**6b**, >20:1
3	**4c**	>90	**6c**, 15:1
4	**4d**	88	**6d**, 13:1
5	**4e**	72	**6e**, 5:1
6	**4f**	>90	**6f**, >20:1
7	**4g**	>90	**6g**, 4:1
8	**4h**	>90	**6h**, 3:1

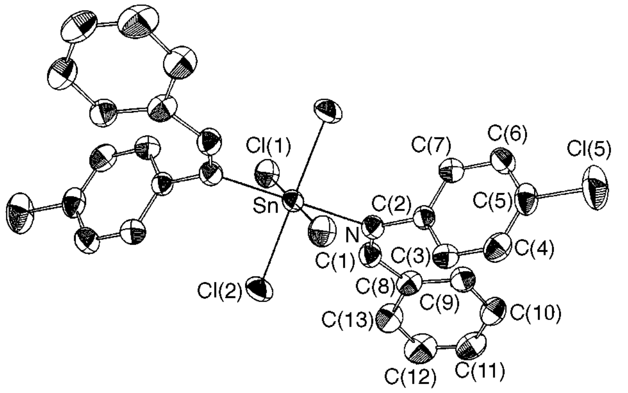


Fig. 1 Molecular structure of **7**. C–H hydrogen atoms are not shown. Selected distances (Å) and angles (°) for **7**: Sn–N 2.267(2), Sn–Cl(1) 2.404(1), Sn–Cl(2) 2.390(1), N–C(1) 1.288(2), N–C(2) 1.445(2), C(1)–C(8) 1.467(3); Sn–N–C(1) 117.3(1), Sn–N–C(2) 120.6(1), C(1)–N–C(2) 121.7, N–C(1)–C(8) 131.8(2), N–C(1)–C(8)–C(9) 14.8(4), C(3)–C(2)–N–C(1) 84.3(2), C(2)–N–C(1)–C(8) 3.4(3).

The complex **7** reacts with EDA **5** to give the *cis*-aziridine **6b**, while in the absence of SnCl$_4$ no reaction between the imine **4b** and **5** takes place. The results for the reaction of the various aromatic imines **4a**–**h** with **5** catalysed by SnCl$_4$ (1 mol%) are presented in Table 1.

It appears from Table 1 that a high conversion of all the imines **4a**–**h** to the aziridines **6a**–**h** takes place by application of only 1 mol% SnCl$_4$ as the catalyst, and in all cases the *cis*-aziridines are formed as the major isomer. For entries 1, 2 and 6 in Table 1 only the *cis*-isomer could be detected by ^{1}H NMR spectroscopy. It should also be noted that the aziridines prepared from the imines **4a**–**d**, lead to *cis*-aziridines with high selectivity (entries 1–4, 6), whereas aziridination of **4e**–**h** leads to variation in the *cis*:*trans* ratio (entries 5, 7, 8, *vide infra*).

The imines **4b**–**d** have been reacted with EDA **5** in the presence of SnCl$_4$ as the catalyst and studied as a function of time with various amounts of catalyst load. The results are shown in Fig. 2.

Independent of catalyst loading imine **4b** reacts significantly faster than **4c**,**d** with EDA **5** in the presence of SnCl$_4$ as the catalyst to give the corresponding aziridines **6b**–**d**. The reactivity of **4b**–**d** is **4b** > **4c** > **4d**, and for the latter the conversion is less than 5% after 50 min. It is also notable that the reactions proceed with very low catalyst loading and it appears from the conversions in Fig. 2 that only 0.05 mol% of SnCl$_4$ is sufficient to achieve a reasonable conversion, which, according to our knowledge, is the lowest catalyst load observed for catalytic formation of aziridines. The reaction is found to be first order in SnCl$_4$.

A series of competition experiments have been performed to investigate the product ratio of the aziridines **4c**,**e**–**h** formed by reaction of *p*-Y-C$_6$H$_4$CH=NPh *vs.* C$_6$H$_5$CH=NPh with EDA **5**

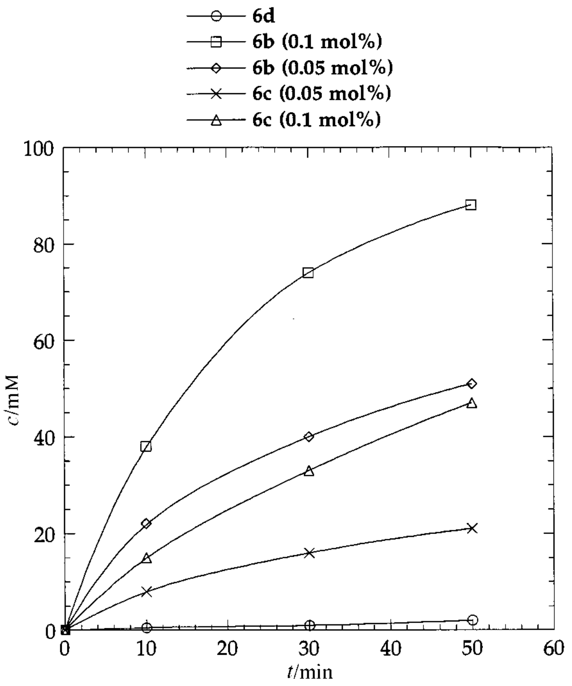


Fig. 2 The formation of the aziridines **6b–d** by reaction of the imines **4b–d** with EDA in the presence of $SnCl_4$ as the catalyst (0.1 and 0.05 mol%) as a function of time

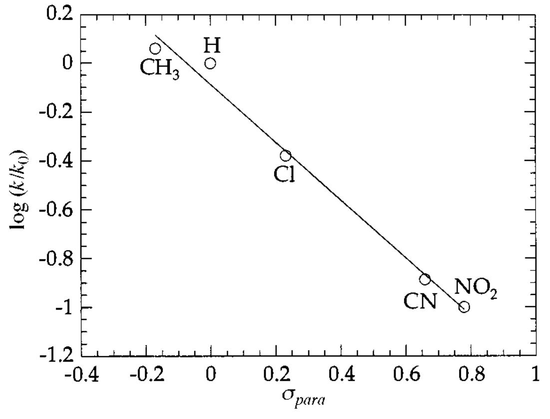


Fig. 3 Hammett plot for the formation of *cis*-aziridines **6c**,**e–h**

in the presence of $SnCl_4$ (imine : EDA : $SnCl_4$ = 100 : 50 : 1) as the catalyst. The ratios of the resulting aziridines **6c**,**e–h** were determined by ^1H NMR spectroscopy. The formation of *cis*-**6e–h**/*cis*-**6c** was found to correlate with the Hammett σ-values as shown in Fig. 3.

The Hammett plot in Fig. 3 shows that aziridines substituted with electron-donating substituents are formed faster than those substituted with electron-withdrawing substituents. The ρ-value is calculated to be -1.2 ($r^2 = -0.99$). The satisfactory Hammett $\sigma\rho$-correlation with a negative value for ρ supports a mechanism in which imines with electron-donating substituents coordinate better to $SnCl_4$ compared with imines having electron-withdrawing substituents. It is notable that opposite electron demands favour the two reaction steps in the $SnCl_4$-catalysed aziridination reaction; the coordination to the metal is favoured for imines having electron-donating substituents (see Fig. 3) while the addition-step of EDA proceeds faster for imines having electron-withdrawing substituents (see Fig. 2).

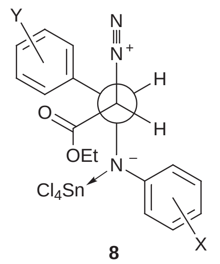
The interaction of the imines **4a**,**b**,**d** with both $SnCl_4$ and $BF_3{\cdot}OEt_2$ has been studied by ^{13}C NMR spectroscopy in an attempt to investigate the influence of a bidentate and a monodentate coordinating Lewis acid on the ^{13}C NMR shifts. The results are presented in Table 2.

Table 2 The influence of $SnCl_4$ and $BF_3{\cdot}OEt_2$ on the ^{13}C NMR chemical shifts (ppm) for imines **4a**,**b** and **d**

	δ_C		
Imine	Imine	Imine–$SnCl_4$	Imine–$BF_3{\cdot}OEt_2$
4a, N=*C*	161.3	168.7	169.2
4a, O-*C*H_3	55.8	58.1	55.8
4b, N=*C*	160.7	172.0	168.5
4c, N=*C*	160.4	171.4	168.0

From the ^{13}C NMR shifts it appears that for **4a** both $SnCl_4$ and $BF_3{\cdot}OEt_2$ coordinate to the imine nitrogen atom and that the latter is slightly more electron-withdrawing compared with the former. It is also notable that $SnCl_4$ coordinates in a bidentate fashion, while $BF_3{\cdot}OEt_2$ coordinates only to the imine nitrogen atom. Both the imine substituted with an electron-withdrawing substituent in the *para*-position (**4b**) and the unsubstituted imine (**4c**) coordinate to both Lewis acids in solution.

The present investigations have shown that catalytic aziridination of imines using $SnCl_4$ as the catalyst can proceed with a very low loading of catalyst, and according to our knowledge, the lowest found for aziridination reactions. The reaction course is dependent on two opposite electronic effects, the first step being the coordination of the imine to $SnCl_4$ and is faster for imines substituted with electron-donating substituents compared with imines having electron-withdrawing substituents, while the second step is favoured for imines having the reverse electron demand. The electronic nature of the imine has influence on the *cis* : *trans* ratio of the aziridines formed, however the present results indicate that there is no simple correlation between this ratio and the electronic structure of the imine. To account for the formation of the *cis*-aziridine as the major isomer intermediate **8** is proposed: nucleophilic attack of the nitrogen atom on the carbon atom with elimination of N_2 gives the observed stereochemistry. However, it is not possible on the basis of the present results to distinguish if there are one or two imines (as in intermediate **7**) coordinated to $SnCl_4$ during the reaction course.



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Experimental

The ^1H NMR and ^{13}C NMR spectra were obtained using a Varian Gemini at 300 MHz and 75 MHz, respectively. Chemical shifts for ^1H NMR and ^{13}C NMR are recorded in $CDCl_3$ and reported in ppm downfield from tetramethylsilane (TMS). *J* Values are given in Hz.

Materials

The imines were prepared from the corresponding amines and aldehydes.[7] The imines were recrystallised from EtOH. EDA, $SnCl_4$ and $BF_3{\cdot}OEt_2$ were commercially available from Aldrich and used as received. CH_2Cl_2 was dried over CaH_2 and distilled before use.

General procedure for the reaction of imines with EDA catalysed by $SnCl_4$

0.5 mmol of the imine **4** was added to a 5 ml Schlenk flask which was evacuated and filled twice with Ar. 4 ml CH_2Cl_2 was added followed by 0.05 mmol $SnCl_4$. The solution was cooled to 0 °C before the addition of 0.65 mmol EDA **5**. When the evolution of N_2 ceased the reaction mixture was poured onto ice and the resulting aqueous phase was extracted with 3 ml CH_2Cl_2. The organic phase was washed with 5% aqueous $NaHCO_3$, brine and dried with Na_2SO_4. The crude product can be purified by flash chromatography on silica gel using 5% EtOAc–light petroleum as eluent to give the pure aziridine **6**.

Procedure for aziridination competition experiments

0.5 mmol of imine **4c** and 0.5 mmol of the *para*-substituted *N*-benzylideneaniline **4e**–**h** were added to a Schlenk flask which was evacuated and filled twice with N_2. 4 ml CH_2Cl_2 was added followed by 50 µl of a 0.2 M solution of $SnCl_4$ in CH_2Cl_2 (0.01 mmol). The solution was cooled to 0 °C before the addition of 0.5 mmol EDA **5**. When the evolution of N_2 ceased the reaction mixture was poured onto ice and the resulting aqueous phase was extracted with 3 ml CH_2Cl_2. The organic phase was washed with 5% aqueous $NaHCO_3$, brine and dried with Na_2SO_4. The crude product was investigated by ^1H NMR spectroscopy and the ratios of the formation of *cis*-**6e**–**h** and *cis*-**6c** were obtained by integrating the proton resonance at positions 2 and 3 of the aziridine.

Procedure for the kinetic experiments

0.5 mmol of the appropriate imine was added to a 5 ml Schlenk flask which contained toluene (~0.1 M) as internal standard. The flask was evacuated and filled twice with Ar. 4 ml CH_2Cl_2 was added followed by 0.025 or 0.001 mmol $SnCl_4$. Samples of the reaction mixture were taken out at the appropriate times and quenched as above. The reaction mixture was analysed by ^1H NMR spectroscopy. The kinetic experiments were performed twice.

^1H and ^{13}C NMR data

The data for **6a**–**d** are available from the literature.[2i,4]

cis-**6e**: δ_H 1.06 (t, *J* 6.8, 3H), 2.36 (s, 3H), 3.20 (d, *J* 6.6, 1H), 3.58 (d, *J* 6.6, 1H), 3.95–4.10 (m, 2H), 7.00–7.33 (m, 7H), 7.41 (d, *J* 8.1, 2H); δ_C 14.0, 21.2, 45.6, 47.1, 61.0, 120.0, 123.4, 127.6, 128.8, 129.2, 131.6, 137.6. 152.5, 167.8.

cis-**6f**: δ_H 1.00 (t, *J* 7.2, 3H), 3.21 (d, *J* 6.9, 1H), 3.61 (d, *J* 6.6, 1H), 3.95–4.09 (m, 2H), 7.02–7.08 (m, 3H) 7.25–7.36 (m, 4H), 7.44–7.48 (m, 2H); δ_C 14.0, 45.6, 46.5, 61.2, 119.9, 123.6, 128.3, 129.1, 129.3, 133.2, 133.8, 152.0, 167.4.

cis-**6g**: δ_H 1.00 (t, *J* 7.2, 3H), 3.26 (d, *J* 6.6, 1H), 3.61 (d, *J* 6.6, 1H), 3.97–4.13 (m, 2H), 7.02–7.11 (m, 3H), 7.25–7.32 (m, 2H), 7.65 (s, 4H); δ_C 14.0, 45.7, 46.4, 61.3, 111.7, 114.4, 119.8, 123.9, 128.6, 129.4, 131.9, 140.1, 151.6, 167.0.

cis-**6h**: δ_H 1.06 (t, *J* 7.2, 3H), 3.29 (d, *J* 6.6, 1H), 3.65 (d, *J* 6.6, 1H), 3.99–4.14 (m, 2H), 7.04–7.56 (m, 5H), 7.71 (d, *J* 9.0, 2H), 8.23 (d, *J* 8.7, 2H); δ_C 14.1, 45.8, 46.2, 61.4, 119.8, 123.33, 124.0, 128.75, 129.4, 142.0, 147.6, 151.5, 166.9.

Crystallographic data for 7

$SnCl_4(C_{13}H_{10}NCl_2)_2$; monoclinic, space group $P2_1/c$, $a = 7.8265(4)$, $b = 14.7134(7)$, $c = 11.9493(1)$ Å, $\beta = 91.447(1)°$, $V = 1375.6(2)$ Å^3, $Z = 2$. 3633 independent reflections measured at 295 K on a Siemens SMART CCD diffractometer. Mo-Kα. 3024 reflections with $I > 3\sigma(I)$ and 200 variables yields $R = 0.022$, $R_w = 0.041$. Full crystallographic details, excluding structure factor tables, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 2*, available *via* the RSC Web page (http://www.rsc.org/authors). Any request to the CCDC for this material should quote the full literature citation and the reference number 188/129.

Acknowledgements

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