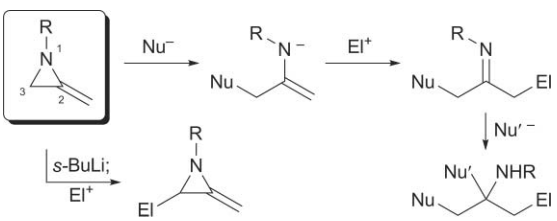
Structure and reactivity of bicyclic methylene aziridines prepared by intramolecular aziridination of allenes†

Jeremy Robertson,*[a] George C. Feast,[a] Louise V. White,[a] Victoria A. Steadman (née Doughty)‡[b] and Timothy D. W. Claridge[a]

Received 4th March 2010, Accepted 20th April 2010
First published as an Advance Article on the web 18th May 2010
DOI: 10.1039/c003693e

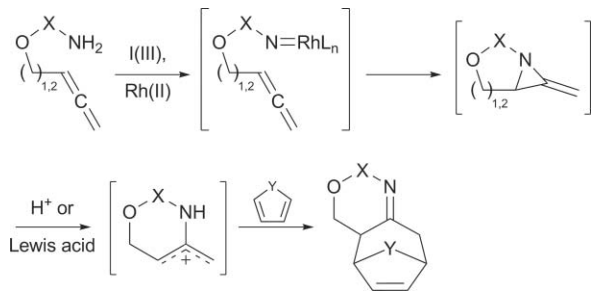
Unprecedented bicyclic methylene aziridines are prepared by rhodium(II)-catalyzed allene aziridination of buta-2,3-dienyl carbamates. Aspects of their NMR and X-ray data are described and a preliminary reactivity profile is given, including overall S_NV-mode ring-opening with organometallic reagents.

The chemistry of methylene aziridines (MAs) has been re-invigorated over the past 15 years by the series of reports from the Shipman group concerning their synthesis, by 2-bromoallylamine cyclization,[1] and derivatization by, for example, diastereoselective lithiation and alkylation.[2] Their importance as synthetic intermediates[3] has been extended by the general multi-component reaction summarized in Scheme 1.[4] The reactions initiate by nucleophilic ring-opening, alkylation of the so-formed metallo-enamine follows, and a second nucleophile quenches the imine. In these reactions, and others,[5] the ring-opening process occurs, unsurprisingly, at the allylic carbon, C(3). Reports describing direct cleavage of the C(2)–nitrogen bond by carbon nucleophiles[6] are confined to radical additions[7] and Pd-catalyzed insertion processes.[8]



Scheme 1 The reactivity of MAs illustrated by multicomponent processes initiated by nucleophilic ring-opening at C(3).

The preparation of MAs by intermolecular aziridination of allenes has been reported in single figure percentage yield.[9] MAs are implicated as intermediates in the thermal addition of ethyl azidoformate and tetramethyl allene,[10] and in the formation of a diazaspiro[2.2]pentane from methyl 2-methylbuta-2,3-dienoate.[11] However, in view of the emergence of reliable protocols for alkene aziridination by rhodium-bound nitrenoids,[12,13] we became interested in the potential of these recent reagent combinations to achieve more practical syntheses of MAs from allenyl substrates (Scheme 2). At the outset, and in view of the lack of precedent for bicyclic MAs of the type shown, we envisaged that these intermediates might not be readily isolable, and their further transformation *in situ*, for example by ring-opening and cycloaddition,[14] was planned as illustrated.



Scheme 2 A proposed one-pot allene aziridination, ring-opening and [4+3]-cycloaddition resulting in polycyclic products from acyclic precursors [X = CO, SO_2; Y = CH_2, O, NBoc].

We began this project with a study, described in this paper, of the reactions of buta-2,3-dienyl carbamates; our results with penta-3,4-dienyl sulfamates were quite different and have been reported separately.[15]

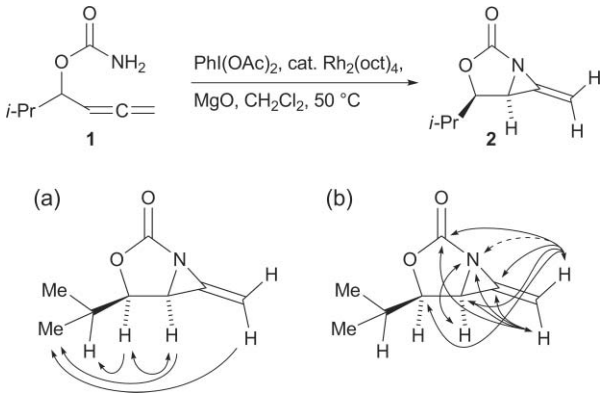
When readily-available carbamate **1** (Scheme 3) was subjected to Du Bois' standard conditions for rhodium-nitrenoid generation,[16] a slow reaction ensued resulting in a rather complex product mixture. Remarkably, we were able to isolate MA **2** by column chromatography and sufficient material was obtained to allow a full spectroscopic analysis in support of the unprecedented structure. Mass spectrometry confirmed the molecular formula and the infra-red spectrum showed a clear absorption for the bicyclic oxazolidinone carbonyl at 1792 cm^{-1}, significantly higher than typical for simple oxazolidinones. ^{1}H NMR data revealed the presence of a terminal methylene in the olefinic region (δ 5.18 and 5.39, 2 × 1 H, 2 × d, J 3.2 Hz), the loss of the internal alkene and a new resonance assigned as C*H*N (δ 3.64, 1 H, d, J 5.6 Hz). Resonances in the ^{13}C NMR spectrum at δ 91.4, 130.2 and 162.8 were assigned to the CH_2=*C*–N–*C*O carbons respectively. The NOE enhancements shown in Scheme 3(a) supported an *endo*-disposition for the *iso*-propyl substituent. Finally, following full

[a]*Department of Chemistry, Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford, OX1 3TA, UK. E-mail: jeremy.robertson@chem.ox.ac.uk; Fax: 44 1865 285002; Tel: 44 1865 275660*
[b]*GlaxoSmithKline, New Frontiers Science Park, Third Avenue, Harlow, Essex, CM19 5AW, UK*

† Electronic supplementary information (ESI) available: Selected experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra. CCDC reference numbers 767254 and 767255. For crystallographic data in CIF or other electronic format see DOI: 10.1039/c003693e

‡ Current address: Selcia Ltd., Fyfield Business & Research Park, Fyfield Road, Ongar, Essex, CM5 0GS, UK

^{1}H and ^{13}C NMR assignment by HSQC, the correct connectivity was established by HMBC experiments. In addition to the expected two- and three-bond correlations in the ^{1}H/^{13}C HMBC spectrum, one of the =CH_2 protons correlated to the *C*HO carbon, and both =CH_2 protons correlated with the carbonyl carbon. These four-bond couplings were initially disconcerting but such anomalies are precedented in certain conformationally defined systems.[17] The ^{1}H/^{15}N HMBC spectrum showed correlations between both =CH_2 protons and the nitrogen; as expected, the proton *trans*-disposed to the nitrogen showed a much stronger correlation. In this experiment the C*H*O proton did not correlate to the nitrogen, which we attribute to a (C–H)/(C–N) dihedral angle close to 90°.[18]



Scheme 3 Preparation of bicyclic MA **2** by intramolecular allene aziridination under Du Bois' conditions. Diagram (a) shows important NOE correlations; diagram (b) indicates key C–H and N–H HMBC correlations (dashed curve = weak).

Our first attempts to improve upon this result and to extend the substrate scope met with little success.[19] Thus, from substrate **3** (Fig. 1), only starting material was recovered in one run and a second attempt generated unidentified products not consistent with a MA. The penta-3,4-dienyl carbamates **4** and **5** afforded C–H insertion products **6** and **7** respectively.

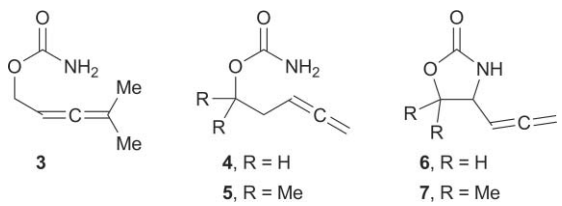
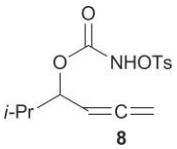
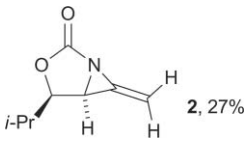
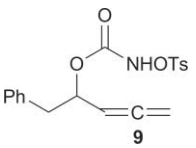
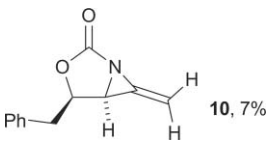
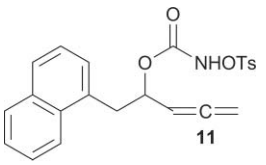
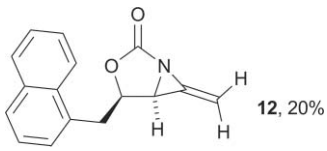
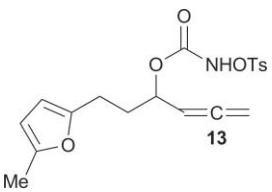
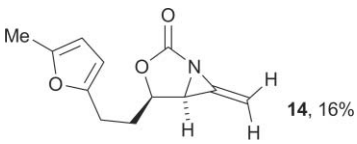
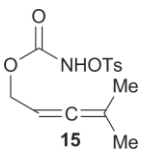
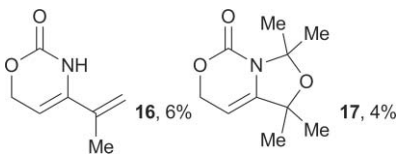
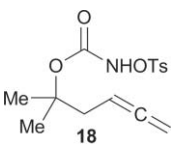
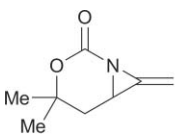


Fig. 1

We were concerned that AcOH generated during these reactions might lead to unproductive reactions of any MA products, therefore attention turned to Lebel's system in which the substrates are introduced into the reaction at the correct oxidation level, as *N*-tosyloxycarbamates.[13c] In this system, in addition to a source of Rh(II), only K_2CO_3 is required in order to effect elimination of TsOH. Application of these conditions to *iso*-propyl substrate **8** raised the yield of MA **2** to 27% which, whilst low,[20] was reproducible and sufficient to access usable quantities of MA for further experiments. MAs and other products prepared by this reaction are depicted in Table 1.[21]

The naphthyl-substituted MA (**12**) was crystalline and single crystals were grown that proved suitable for X-ray structural

Table 1 Rh(II)-catalyzed aziridinations of allenyl carbamate derivatives

Substrate	Major isolated product/s[a] and yields
	
	
	
	
	
	

[a] *Reagents and conditions*: $Rh_2(OAc)_4$ (0.05 equiv.), K_2CO_3, acetone, 20 °C, 18 h.

analysis (Fig. 2).[22] In this structure, the naphthylmethyl substituent is *endo*-disposed, in accordance with the relative stereochemistry assigned by NMR to MA **2**. As expected, the nitrogen atom is highly pyramidalized, being 0.79 Å out of the C2–C5–C6 plane (crystal numbering).

The two products (**16** and **17**) isolated from the reaction of dimethyl-substituted allenyl substrate **15** could result as secondary products from a first-formed MA. Alternatively, they could be derived from 2-aminoallyl intermediate[15,23] **20** by proton transfer or formal dipolar cycloaddition with the solvent (Scheme 4).

The structural information acquired for MAs **2** and **12** show that of the two C–N bonds in the aziridine, the HC–N bond is naturally antiperiplanar to the carbonyl bond (in **12**: (O=C)/(C–N) dihedral angle = 176°) whereas the =C–N bond is more closely orthogonal to the carbonyl (in **12**: (O=C)/(C–N) dihedral angle = 116°). In effect, cleavage by nucleophiles of the =C–N bond should be accompanied by delocalization of developing

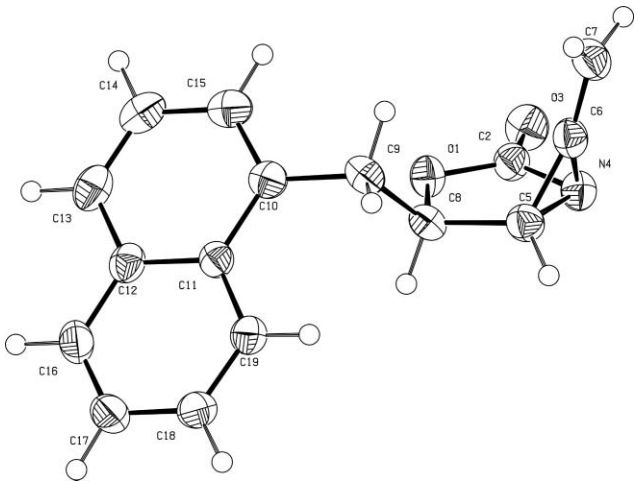
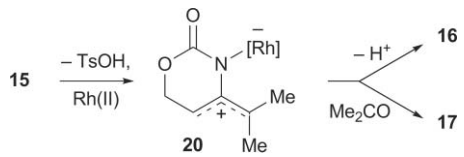


Fig. 2 Molecular structure of bicyclic MA **12**. Displacement ellipsoids are drawn at the 50% probability level.

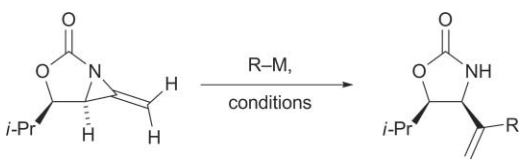


Scheme 4 Postulated reaction pathway for the formation of non-MA products from substrate **15**.

negative charge on nitrogen into the C=O π-system without significant conformational change. On this basis, we envisaged that appropriate nucleophiles would react with MAs such as **2** in an S_NV mode[24] rather than at the usual 'allylic' position.

In view of the precedent[4b,25] for both *N*-acyl and *N*-alkyl aziridine ring-opening by organolithium and Grignard reagents, mediated in some cases by Cu(I) and $BF_3{\cdot}OEt_2$ additives, we treated MA **2** with ethylmagnesium bromide under a variety of conditions, the best yield being obtained when CuI (0.05 equiv.) and $BF_3{\cdot}OEt_2$ (1.5 equiv.) were added to the Grignard (3.0 equiv.) prior to addition of the aziridine. The only identifiable product in this reaction was the formal S_NV product, the alkenyl oxazolidinone **21**,[26] isolated in 72% yield. Similar reactions[27] were achieved with *iso*-propyl, butyl,[28] phenyl, and vinyl nucleophiles as summarized in Table 2.[29]

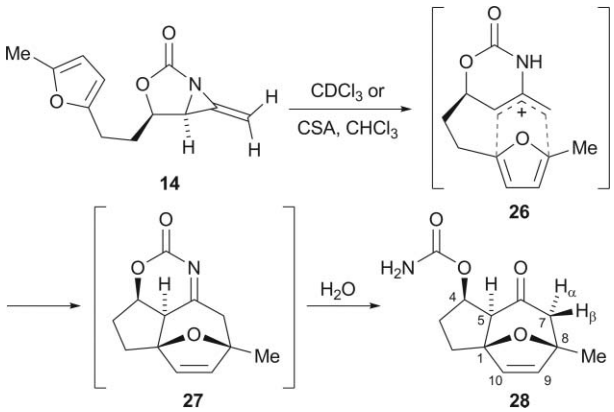
Table 2 Formal S_NV products by organometallic ring-opening of MA **2**



R–M (conditions)[a]	Major isolated product (yield)
EtMgBr (**A**)	**21**, R = Et (72%)
i-PrMgCl (**A**)	**22**, R = *i*-Pr (26%)
BuMgCl (**B**)	**23**, R = Bu (32%)
Ph_2CuLi (**C**)	**24**, R = Ph (45%)
Vinyl-MgBr (**B**)	**25**, R = vinyl (31%)

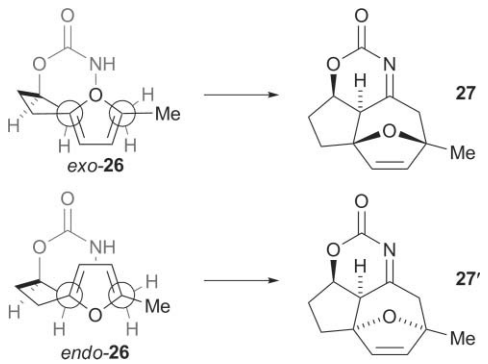
[a] **A**: cat. CuI, $BF_3{\cdot}OEt_2$, THF, –40 → 0 °C, 1 h; **B**: as **A**, omitting the $BF_3{\cdot}OEt_2$; **C**: Et_2O, 0 °C, 30 min.

Returning to the initial aim of this work, we were disappointed to find that the furan MA **14** could not be isolated cleanly and little material was available with which to test the ring-opening/cycloaddition proposal. However, it soon became clear that a major product was generated as the MA apparently decomposed. An NMR sample of MA **14** left at RT in $CDCl_3$ solution was monitored for an extended period and, after 28 d, little MA remained so the product was isolated by preparative TLC. We were pleased to find that all data supported the 11-oxatricyclo[6.2.1.$0^{1,5}$]undecenone derivative **28** (Scheme 5) arising by formal cycloaddition of aminoallyl cation **26** and hydrolysis of the imine (in **27**) *in situ*. The reaction time (**14** → **28**, 22%) was reduced to 48 h when camphorsulfonic acid was added as catalyst to a dilute chloroform solution.



Scheme 5 Aminoallyl cation cycloaddition from MA **14** under acidic conditions.

The stereochemical assignment of tricycle **28** was developed from a consideration of the two possible reasonable approaches of the furan to the 2-aminoallyl cation (Scheme 6) to generate imine **27** and its C(1)/C(8) diastereomer **27′**. In both products there is a *cis*- relationship between H(4) and H(5) which would be carried forward to **28**/**28′**. A NOESY experiment (on **28**) allowed H(9) to be distinguished from H(10) by its correlation to H(7_α) and the Me group. From this, correlation of H(10) to H(5) set the CH=CH bridge *syn*- to H(5) to complete the assignment.



Scheme 6 *Exo*- and *endo*- mode cycloadditions should afford products **27** and **27′** differing only in the stereochemistry of the –O– bridge.

In summary, we have described the first intramolecular aziridinations of allene carbamate derivatives and shown that the unprecedented, structurally fascinating and rather fragile products,

undergo interesting chemistry including formal S_NV ring-opening and acid-mediated [4+3]-cycloaddition. Future work will focus on increasing the efficiency of the aziridinations and clarifying the mechanistic and stereochemical details of the S_NV reaction.

The authors gratefully acknowledge GSK and the EPSRC for funding, and the Oxford Chemical Crystallography Service for use of the instruments.

Notes and references

1 (*a*) A. T. Bottini and R. E. Olsen, *Org. Synth. Coll. Vol. V*, 1973, 541; (*b*) J. J. Shiers, M. Shipman, J. F. Hayes and A. M. Z. Slawin, *J. Am. Chem. Soc.*, 2004, **126**, 6868; (*c*) see also N. De Kimpe, D. De Smaele and Z. Sakonyi, *J. Org. Chem.*, 1997, **62**, 2448, which also nicely summarizes the field.

2 (*a*) J. F. Hayes, N. Prévost, I. Prokes, M. Shipman, A. M. Z. Slawin and H. Twin, *Chem. Commun.*, 2003, 1344; (*b*) C. Montagne, N. Prévost, J. J. Shiers, G. Prié, S. Rahman, J. F. Hayes and M. Shipman, *Tetrahedron*, 2006, **62**, 8447.

3 (*a*) M. Shipman, *Synlett*, 2006, 3205; (*b*) K. A. Tehrani and N. De Kimpe, *Curr. Org. Chem.*, 2009, **13**, 854.

4 First reports: (*a*) J. Ince, M. Shipman and D. S. Ennis, *Tetrahedron Lett.*, 1997, **38**, 5887; (*b*) J. F. Hayes, M. Shipman and H. Twin, *Chem. Commun.*, 2000, 1791; (*c*) D. S. Ennis, J. Ince, S. Rahman and M. Shipman, *J. Chem. Soc., Perkin Trans. 1*, 2000, 2047.

5 For example: (*a*) A. T. Bottini and J. D. Roberts, *J. Am. Chem. Soc.*, 1957, **79**, 1462; (*b*) H. Quast and C. A. W. Vélez, *Angew. Chem., Int. Ed. Engl.*, 1974, **13**, 342.

6 Addition of phenol occurs at C(2) of MAs in a process that ultimately cleaves the C(2)–N bond: J. K. Crandall, L. C. Crawley and J. B. Komin, *J. Org. Chem.*, 1975, **40**, 2045.

7 (*a*) N. Prévost and M. Shipman, *Org. Lett.*, 2001, **3**, 2383; (*b*) N. Prévost and M. Shipman, *Tetrahedron*, 2002, **58**, 7165.

8 (*a*) H. Alper and N. Hamel, *Tetrahedron Lett.*, 1987, **28**, 3237; (*b*) see also B. H. Oh, I. Nakamura and Y. Yamamoto, *J. Org. Chem.*, 2004, **69**, 2856; (*c*) A. I. Siriwardana, K. K. A. D. S. Kathriarachchi, I. Nakamura, I. D. Gridnev and Y. Yamamoto, *J. Am. Chem. Soc.*, 2004, **126**, 13898; (*d*) K. K. A. D. S. Kathriarachchi, A. I. Siriwardana, I. Nakamura and Y. Yamamoto, *Tetrahedron Lett.*, 2007, **48**, 2267.

9 E. M. Bingham and J. C. Gilbert, *J. Org. Chem.*, 1975, **40**, 224.

10 R. F. Bleiholder and H. Schecter, *J. Am. Chem. Soc.*, 1968, **90**, 2131.

11 R. S. Atkinson and J. R. Malpass, *Tetrahedron Lett.*, 1975, **16**, 4305.

12 Sulfamates: (*a*) K. Guthikonda and J. DuBois, *J. Am. Chem. Soc.*, 2002, **124**, 13672; (*b*) P. M. Wehn, J. Lee and J. Du Bois, *Org. Lett.*, 2003, **5**, 4823; (*c*) K. W. Fiori, J. J. Fleming and J. Du Bois, *Angew. Chem., Int. Ed.*, 2004, **43**, 4349; (*d*) C. Fruit and P. Mueller, *Tetrahedron: Asymmetry*, 2004, **15**, 1019; (*e*) P. M. Wehn and J. Du Bois, *Org. Lett.*, 2005, **7**, 4685; (*f*) K. Guthikonda, P. M. Wehn, B. J. Caliando and J. Du Bois, *Tetrahedron*, 2006, **62**, 11331; (*g*) J. J. Fleming, M. D. McReynolds and J. Du Bois, *J. Am. Chem. Soc.*, 2007, **129**, 9964; (*h*) D. N. Zalatan and J. Du Bois, *J. Am. Chem. Soc.*, 2008, **130**, 9220; (*i*) K. W. Fiori, C. G. Espino, B. H. Brodsky and J. Du Bois, *Tetrahedron*, 2009, **65**, 3042; (*j*) S. Ranatunga and J. R. Del Valle, *Tetrahedron Lett.*, 2009, **50**, 2464; (*k*) P. M. Wehn and J. Du Bois, *Angew. Chem., Int. Ed.*, 2009, **48**, 3802.

13 Carbamates: (*a*) A. Padwa and T. Stengel, *Org. Lett.*, 2002, **4**, 2137; (*b*) A. Padwa, A. C. Flick, C. A. Leverett and T. Stengel, *J. Org. Chem.*, 2004, **69**, 6377; (*c*) H. Lebel, K. Huard and S. Lectard, *J. Am. Chem. Soc.*, 2005, **127**, 14198; (*d*) C. J. Hayes, P. W. Beavis and L. A. Humphries, *Chem. Commun.*, 2006, 4501.

14 *Cf.* G. Prié, N. Prévost, H. Twin, S. A. Fernandes, J. F. Hayes and M. Shipman, *Angew. Chem., Int. Ed.*, 2004, **43**, 6517.

15 G. C. Feast, L. W. Page and J. Robertson, *Chem. Commun.*, 2010, **46**, 2835.

16 (*a*) C. G. Espino and J. Du Bois, *Angew. Chem., Int. Ed.*, 2001, **40**, 598; (*b*) C. G. Espino, P. M. Wehn, J. Chow and J. Du Bois, *J. Am. Chem. Soc.*, 2001, **123**, 6935.

17 Examples are discussed in: R. Araya-Maturana, H. Pessoa-Mahana and B. Weiss-López, *Nat. Prod. Commun.*, 2008, **3**, 445.

18 M. Witanowski, L. Stefaniak and G. A. Webb, Nitrogen NMR Spectroscopy, in *Annual Reports on NMR Spectroscopy*, 1981, Academic Press, Vol 11B, 1–502.

19 L. V. White, *Chemistry Part II Thesis*, Oxford 2007.

20 The reactions to form this and other cyclic carbamate MAs afforded a number of unidentified side-products that could only be removed by exhaustive chromatography; inevitably, this resulted in some material loss and a reduction in isolated yield of reasonably pure product.

21 We note that the C*H*N–C*H*O vicinal coupling constant in the ^{1}H NMR spectrum of MAs **2**, **10**, **12** and **14** are all *ca.* 5.5 Hz and we assume that the oxazolidinyl substituent is *endo*-disposed in the whole series.

22 Crystallographic data (excluding structure factors) for structures of **12** and **23**[28] have been deposited with the Cambridge Crystallographic Data Centre (CCDC 767254 and 767255, respectively). Copies of these data can be obtained free of charge *via* www.ccdc.cam.ac.uk/data_request/cif. Crystal data for compound **12**: (clear, colourless plate, $0.20 \times 0.18 \times 0.10$ mm): $C_{16}H_{13}NO_2$ $M_r = 251.28$; monoclinic, $P2_1/n$; $a = 11.8660(3)$ Å, $b = 9.5726(3)$ Å, $c = 12.1209(4)$ Å, $\beta = 115.3492(11)°$, $V = 1244.23(7)$ Å^3; $Z = 4$; $\mu = 0.09$ mm^{-1}; $D_c = 1.341$ g cm^{-3}; reflections collected = 5213; independent reflections = 2766 ($R_{int} = 0.030$); R values [$I > 2\sigma(I)$, 1990 reflections]: $R_1 = 0.045$, w$R_2 = 0.140$; $\rho_{min/max} = -0.30/0.34$ e Å^{-3}.

23 A. H. Stoll and S. B. Blakey, *J. Am. Chem. Soc.*, 2010, **132**, 2108.

24 Lead references and recent reviews: (*a*) Z. Rappoport, *Acc. Chem. Res.*, 1981, **14**, 7; (*b*) Z. Rappoport, *Recl. Trav. Chim. Pays-Bas*, 1985, **104**, 309; (*c*) C. F. Bernasconi and Z. Rappoport, *Acc. Chem. Res.*, 2009, **42**, 993; (*d*) S. Chiba, K. Ando and K. Narasaka, *Synlett*, 2009, 2549.

25 For example: (*a*) A. Hassner and A. Kascheres, *Tetrahedron Lett.*, 1970, 462; (*b*) M. J. Eis and B. Ganem, *Tetrahedron Lett.*, 1985, **26**, 1153.

26 Such compounds have been prepared by Pd(II)- or Ag(I)-mediated cyclization of allenyl *N*-sulfonyl carbamates; see for example (*a*) M. Kimura, K. Fugami, S. Tanaka and Y. Tamaru, *J. Org. Chem.*, 1992, **57**, 6377; (*b*) M. Kimura, N. Saeki, S. Uchida, H. Harayama, S. Tanaka, K. Fugami and Y. Tamaru, *Tetrahedron Lett.*, 1993, **34**, 7611; (*c*) M. Kimura, S. Tanaka and Y. Tamaru, *J. Org. Chem.*, 1995, **60**, 3764; (*d*) M. Kimura, S. Tanaka and Y. Tamaru, *Bull. Chem. Soc. Jpn.*, 1995, **68**, 1689; (*e*) S. -K. Kang, T. -G. Baik and Y. Hur, *Tetrahedron Lett.*, 1999, **55**, 6863; (*f*) G. Lu and X. Lu, *Org. Lett.*, 2001, **3**, 3879.

27 Later experiments revealed that the addition of $BF_3{\cdot}OEt_2$ was unnecessary; in the reaction to form oxazolidinone **24**, the yield with Ph_2CuLi was slightly higher than obtained with conditions **A** or **B**.

28 The *cis*- stereochemistry in this compound (**23**) was confirmed by single crystal X-ray diffraction.[22] Crystal data for compound **23**: (clear, colourless plate, $0.30 \times 0.20 \times 0.08$ mm): $C_{12}H_{21}NO_2$ $M_r = 211.30$; monoclinic, $P2_1/a$; $a = 8.3937(4)$ Å, $b = 11.5174(7)$ Å, $c = 13.4324(6)$ Å, $\beta = 100.112(3)°$, $V = 1278.39(11)$ Å^3; $Z = 4$; $\mu = 0.07$ mm^{-1}; $D_c = 1.098$ g cm^{-3}; reflections collected = 5022; independent reflections = 2863 ($R_{int} = 0.053$); R values [$I > 2\sigma(I)$, 2076 reflections]: $R_1 = 0.053$, w$R_2 = 0.159$; $\rho_{min/max} = -0.24/0.24$ e Å^{-3}. The stereochemistry of the other vinyl oxazolidinones (**21**, **24** and **25**) was assigned by analogy and on the basis of the C*H*N–C*H*O vicinal coupling constant in the ^{1}H NMR spectrum ($^3J = 7.0$–8.0 Hz); the C*H*N and C*H*O resonances were coincident in the ^{1}H NMR spectrum for **22** however, given the support for the stereochemistry of the precursor (**2**), we believe this assignment to be reasonable.

29 The isolated yields of oxazolidinones **21**–**25** are lower than was expected on the basis of the ^{1}H NMR spectra of the crude products which revealed the presence of no other significant components. As with the MAs, there was evidence of product decomposition during isolation by chromatography on silica or alumina.