THE CHEMISTRY OF THE CARBON-TIN BOND: ANOTHER CHEMICAL CHAMELEON ?

Peter Quayle

Department of Chemistry, University of Manchester. Manchester M13 9PL UK
<peter.quayle@man.ac.uk> Fax: + 44 161 275 4598

Dedicated to Professor Barry M. Trost on the occasion of his 60th birthday.

Abstract: The use of organostannanes as latent carbanions is now well established although their use as carbocation equivalents is less well recognised. In this overview of the authors' work the preparation and synthetic applications of α -heterofunctionalised organostannanes (and other group 14 organometallics) is summarised. Recent results show that such intermediates can behave as capped carbocations, undergoing mild oxidation in the presence of Ce(IV) to form oxonium cations, which can be trapped in either an *inter-* or *intramolecular* manner.

INTRODUCTION

The term "chemical chameleon" was coined by Trost¹ to highlight the ability of the sulfone moiety to moderate its chemical reactivity in keeping with its environment. The sulfone moiety can behave as an electron sink, facilitating the generation of a negative charge on the α -carbon when treated with a base or can, on exposure to a Lewis acid, act as a nucleofuge generating a carbocation. This dual role makes the sulfone group an extremely useful temporary activating group (or virtual functional group) and is a property which has found numerous synthetic applications. The sulfone moiety is not alone in its ability to change the colour of its chemical coat in order to blend in with its chemical background but is a property shared by certain group 14 organometallics, most notably those of tin.

RESULTS AND DISCUSSION

Vinyl Stannanes: Ipso-Substitution vs. Acylation

Some time ago we wished to investigate a new approach to the synthesis of β -lactams related to thienamycin² which relied on an umpolung of the usual reactivity pattern associated with C₄ in monocyclic β -lactams. It is well known³ that nucleofugal groups at C₄ in monocyclic β -lactams are susceptible to displacement by a wide range of nucleophiles: we wished to see if would be possible to generate a carbanion at C₄ - which is in fact a homoenolate⁴ - and trap it with an electrophile (**Scheme 1**).

This approach necessitated the synthesis of stannanes such as **1**, which we anticipated could undergo transmetallation to the organolithiums **2** upon reaction with a suitable organolithium reagent. After much experimentation the synthesis of stannanes such as **3** was indeed accomplished⁵ by reaction of the readily available β -lactams **4** with tin-centred anions. In addition the generation of an homoenolate from **3c** and its trapping *in situ* was also observed, **Scheme 1**. Unfortunately the displacement reactions involved in the preparation of **3a,b** were capricious so it was decided, somewhat naively, to investigate a more direct approach to these intermediates based upon a [2+2]-cycloaddition strategy which has been used extensively for the synthesis of monocyclic β -lactams.⁶ In the event treatment of vinyltributylstannane with chlorosulfonyl isocyanate (CSI) afforded none of the desired tin-substituted β -lactam **5**.

Undeterred by this result the reaction between CSI and the more electron rich stannane **6** was pursued. Although the desired β -lactam **7** was not obtained from this reaction it did however generate the acrylamide **8** as a single geometrical isomer in 85% yield (**Scheme 2**), the double bond stereochemistry being assigned upon the magnitude of the ^{117,119}Sn-H _{β} coupling constant ($J = 72,76\text{Hz}$). We were a little surprised at these results on two counts, firstly why didn't these *electron rich* vinyl stannanes undergo *ipso*-substitution⁷ with CSI and secondly what factors controlled the double bond geometry observed in the product?

We quickly established that the reaction of electron rich stannanes (acylic or cyclic enol ethers or thioenol ethers) with a variety of isocyanates, sulfonyl halides, sulfonylating agents and trichloroacetyl chloride proceeded *without loss* of the tin moiety by attack at C _{β} . Presumably in these examples the mesomeric effect of the heterosubstituent outweighs the normal propensity of the tin to direct electrophilic attack at the *ipso*-carbon. In order to explain the double bond stereochemistry observed in these acylation reactions we invoke the formation of chelated intermediates, such as **9**, in which the weakly Lewis basic tin co-ordinates with the electrophile prior to loss of a proton in the final stage of the reaction.

THIENAMYCIN: Retrosynthetic Analysis

Synthesis of aminostannanes

(cf Quintard *et al*, *Synthesis*, 1984, 495)

Homoenolate generation

Scheme 1

Synthesis of aminostannanes: [2+2] Cycloaddition route

Scheme 2

Ipso*-substitution**(Eaborn *et al*) β* - Functionalisation** **Scheme 3**

These results are to be compared with the reaction of the thioether **10** with tosyl isocyanate which affords a 1:1 mixture of acrylamides **11** in 72% isolated yield. The formation of trichloroketones **12**, **13** and **14** by reaction of the appropriate stannane with trichloroacetyl chloride under Effenberger⁶ conditions (Cl_3CCOCl ; Hünig's base; CH_2Cl_2 ; 20°C) is also noteworthy as these intermediates undergo high-yielding haloform-type reactions (ROH ; cat. RONa ; 20°C) with a variety of alcohols providing a general route to tin-

substituted esters (e.g. **15**). We have also briefly investigated the reactivity of the silanes, **16** germane **17** and plumbane **18** towards acylation with trichloroacetyl chloride or tosyl isocyanate. The silanes **16a** and germane **17** exhibit similar reactivity to the analogous stannane in their acylation with tosyl isocyanate (reflux in Et₂O or THF), affording the tosamides **19** and **21** in good isolated yields (65% and 61%). The more hindered TBDMS-derivative, **16b**, however undergoes functionalisation much less efficiently affording **20** in ca. 20% when using trichloro acetylchloride as the acylating agent. In this case, a competing reaction, namely ring opening to the acyl silane **22** (ca. 20% yield) is also observed. Unfortunately, whilst the plumbane **18** is also readily available, the lability of the carbon-lead bond precludes its functionalisation with these reagents (Scheme 3).

Ionic Reduction of Functionalised Vinyl Stannanes (Silanes and Germanes)

As one of the major objectives of this work was to develop general methods for the preparation of heterofunctionalised organostannanes possessing a stereogenic centre at the α -carbon atom we now wished to see if the functionalised vinyl stannanes described above could be reduced to their saturated analogues. A search of the literature revealed that the reduction of vinyl stannanes had little precedent although diimide¹⁰ had been employed successfully for the reduction of non-polarised systems. Unfortunately catalytic hydrogenation generally appears to be marred by competing destannylation reactions, although exceptions to this generalisation are known.^{11,12} Not wishing to prejudge the issue we subjected the vinyl stannane **15** to a battery of reduction procedures: unfortunately **15** proved resistant towards reduction by diimide, nucleophilic hydride, "copper hydrides" and catalytic hydrogenation.

A procedure which has met with some success for the reduction of polarised alkenes utilises the "ionic" reduction methodology developed by Parnes.¹³ To our delight we found that a wide range of heterofunctionalised vinylstannanes are reduced by triethylsilane in the presence of a strong Brønsted acid (TFA) or Lewis acid (TMS triflate; BF₃·Et₂O) in CH₂Cl₂.¹⁴ Weaker Brønsted acids such as acetic acid are ineffective as promoters for this reaction. Somewhat surprising is the observation that reduction takes place without the loss of the tin moiety, even when the promoter for the reduction is TFA. The reduction takes place at low temperatures, typically on warming up from -78°C to 0°C and is tolerant of a wide range of functionality. In the case of cyclic substrates such as **15** the reduction is highly diastereoselective, affording the *trans*-diastereoisomer **23a** (ds > 95:5). Poly(methylhydrosiloxane) or triphenylsilane can be substituted for triethylsilane although yields are diminished; reduction of **15** in the presence of Et₃SiH/TFA-d affords **23b** regiospecifically. In certain cases competing reactions are observed other than simple reduction such as in the reduction of **24** which affords **25**. In addition attempted reduction of **26** results in the formation of **27**, thereby lending credence to our rational for the stereochemical course observed in the acylation reactions depicted in Scheme 3; vinyltributyltin is inert to reduction by this procedure. Other group 14 organometallics such as **21**, **28** and **29** also undergo reduction, again without loss of the metal,¹⁵ in moderate to excellent yields (32-90%), Scheme 4.

Alternate Routes to alkoxymethylsilanes: Birch Reduction of 2-trialkylsilylfuran-3-carboxylic acids

Given that the acylation of silanes **16a,b** was dependent to some degree on the silicon-substituent an alternate route for the preparation of silanes **30** was sought. It occurred to us that one route, namely Birch reduction of furan-3-carboxylic acid derivatives **32**, would not only enable the introduction of the silicon moiety by well defined DOM metallation chemistry from readily available furans, but would have the added bonus of introducing an additional function group, the $\Delta^{4,5}$ -double bond, which would provide a handle for further functionalisation. Silanes **31** were conveniently prepared either by the di-anion chemistry developed by Knight¹⁶ (for **31a-e**) or *via* the silyl esters **33** as described by Keay.¹⁷ The rearrangement route starting from the esters **33** (*i.* LDA; DMPU; THF; -78°C; *ii* 1,5-silatropic shift; -78°C to 0°C) proved especially useful for the synthesis of the sterically congested silanes **31f,g** which could not be accessed using the di-anion chemistry; the synthesis of stannane **34** was also accomplished by this route. To our satisfaction, reduction of the carboxylic acids **31** using standard Birch conditions (Na; liquid NH₃; propan-2-ol) afforded the silanes **32** which on esterification and catalytic reduction provided access to the desired silanes **30** in multigram quantities.¹⁸ It is to be noted that both the phenyl substituted silane **31e** and the stannane **34** suffered decomposition during the course of the Birch reduction step, Scheme 5.

Stereoselective Synthesis of Tetrahydrofurans

Having developed a general method for the synthesis of heterofunctionalised stannanes their functional group chemistry was next investigated. In the case of the ester **23a** we soon discovered that enolate generation proceeded without mishap under standard conditions (THF, LDA, -78°C) to afford an enolate **35**, which was resistant towards β -elimination at temperatures up to ca -20°C.

Ionic reduction of Gp 14 organometallics

Scheme 4

Birch Reduction of furans

Reagents and conditions: (i) LDA, 2.2 eq.; THF; -78°C ; 30 mins.; (ii) a. R_3SiCl ; b. 2M HCl; (iii) a. Na, 3 eq.; NH_3 , propan-2-ol; -35°C , b. NH_4Cl ; -33°C ; (iv) CH_2N_2 , Et_2O ; (v) 10% Pd/C; EtOH; H_2 , 1 atm.; (vi) R_3SiCl , 1.1 eq.; DBU, 1 eq.; CH_2Cl_2 ; 20°C or R_3SiCl , 1.2 eq.; imidazole, 2 eq.; DMF; 100°C ; (vii) LDA, 1.2 eq.; THF - HMPA (1:1; v/v); -78°C .

Scheme 5

In passing it should be noted that enolisation of the parent ester **36** under analogous conditions generates an unstable enolate, **37**, which undergoes very rapid decomposition to afford, amongst other products, the dimeric species **38** (ca. 20 yield; 1:1 mixture of diastereoisomers). Interception of the enolate **35** with a variety of electrophiles proceeds with uniformly high levels of stereoselectivity (ds > 95:5) affording tri-substituted tetrahydrofurans in good yields. The sense of induction is presumably dictated by steric approach control, in which the incoming electrophile approaches the *re* face of enolate **35**, i.e. approach on the face away the bulky tin residue. A similar situation is also observed in the case of the silicon-substituted enolate **39**, although the facial selectivity is not as pronounced (ds ca. 2:1). The generation of α -akoxymethyl lithium reagents from the corresponding organostannanes is a well documented reaction, and proceeded without mishap in our case on a range of diastereoisomerically pure stannanes readily prepared from the corresponding ester precursors (Scheme 6), affording, after reaction with a suitable electrophile, access to a series of di- and trisubstituted tetrahydrofurans. As to be expected, the overall transmetalation-alkylation sequence was stereochemically retentive.¹⁹

Enolate generation

Scheme 6

Aldol Sequences

The aldol reaction represents a special case of the alkylation sequence described above. Trapping of the enolate **35** with aldehydes again proceeded with high levels of facial selectivity, from the on the *re* face of the enolate affording the aldol products **40** in a *syn*-selective manner. The aldol stereochemistry may be rationalised in terms of a chair transition state, **TS₂**, in which the ester enolate has *E*-stereochemistry and the bulky R group of the aldehyde adopts an axial orientation in order to minimise non-bonded interactions with C₃. The stereochemical outcome of the enolisation step, depicted as generating the *E*-enolate, derives from the model put forward some time ago by Ireland.²⁰ **TS₁**. We initially considered that the enolate may have been generated as the chelated *Z*-isomer, or “ate”-complex **41** although this notion has now been discounted as the aldol reactions of the enolates **43** and **44** are also *syn*-selective and in the case of **43** at least there is not the possibility of forming a *Z*-enolate stabilised as an “ate”-complex.^{21a} An unfortunate aspect of much of this chemistry, especially in the tri-*n*-butylstannane series, is the reluctance of these compounds to form crystalline derivatives. Elucidation of the stereochemical course of these reactions was therefore determined, in part, by a sequence which utilises the precedented transmetallation chemistry of alkoxymethylstannanes. Hence conversion of the aldol product **45** to the acetal **46**, followed by transmetallation (*n*-BuLi; THF; -78°C) and alkylation with benzophenone afforded the crystalline adduct **47** whose structure could be determined unambiguously by X-ray diffraction.^{21b} That the initial transmetallation-alkylation sequence proceeded in an overall retentive manner was corroborated by extensive nmr investigations on the stannane **46** and the adduct **47**.

The nucleophilicity of the carbon tin bond can also be unleashed under Lewis acid conditions in an adaptation of a reaction first reported by Davis.²² Hence treatment of the *syn*-aldol products **40** with a Lewis acid afforded the *exo*-cyclopropanes **48** whilst the *anti*-aldol products **41** afforded the *endo*-cyclopropanes **49**. The stereostructure of these cyclopropanes was based upon detailed nmr studies and unambiguously assigned in the case of **48** (R = *t*-Bu) by X-ray crystallography.²¹ In these cyclisation reactions the overall stereochemical outcome is one of inversion at both reacting centres and is in accord with the “W”- transition state, **TS₃**, originally adumbrated by Davis, **Scheme 7**.

Michael Reactions

Treatment of the enolate **35** with a range of electron deficient alkenes at -78°C affords the Michael adducts **50**. Again, these reactions proceed with high levels of facial bias, and in the case of substituted acrylates generate adducts with good 1,2-asymmetric induction, in which the *syn*-isomer predominates (*ds* > 95:5). Our working model for the simple Michael reactions invokes a “closed-*E-s-cis*” transition state, **TS₄**, in which the R group of the acrylate is equatorially disposed. Examination of molecular models indicates that if the R group on the acrylate is axially disposed it would encounter unfavourable diaxial interactions with the -OMe group on the enolate and solvent molecules around the lithium cation (**TS₅**), which presumably outweighs the A_{1,3}-type interaction between the R group of the acrylate and C₃ when R is equatorially disposed. The reaction of enolate **35** with lactone **51** presents a rather nice example of a double diastereodifferentiating reaction which proceeds *via* mutual kinetic resolution. We have not been able, as of yet, to fully confirm then stereochemistry of **52**, but suggest that it possesses the relative stereochemistry as shown which may arise by way of the transition state **TS₆**, **Scheme 8**.²⁴

Oxidative Removal of the Tin Moiety

We have already seen how the tin moiety can be removed in a productive sense enabling the formation of a new carbon-carbon bond. In seeking to extend the synthetic potential of these intermediates we wished to find alternate methods for removal of the tin moiety which would incorporate introduce other functional groups in the unmasking step. An early pointer to this possibility is provided in the work of Still²⁵ who showed that the carbon-tin bond could be cleaved oxidatively using CrO₃-pyridine complex. We were in fact able to convert the stannane **53** into the lactone **54** using an excess of this reagent (15 eq.) albeit in low isolated yield (26%). A more promising possibility arose from a more recent publication from Lindermann's group⁶ who found that ozone effected cleavage of the carbon-tin bond under mild conditions. We have subsequently shown²⁷ that that ozone is in fact the reagent of choice for the oxidative removal of the tin moiety in ethers of the type **23**. These reaction conditions are very mild (CH₂Cl₂; -78°C) and proceed in a chemoselective manner providing rapid access to a variety of functionalised lactones (**Scheme 9**). Abnormal ozonolysis of the furan **55** to the furano-furan stannane **56** and the observation that other group 14 organometallics appear to be unaffected by this reagent, as demonstrated by the selective oxidation²⁸ of the carbon-tin bond of the bi-metallic intermediate **57**, augurs well for the development of further methodology in this area.

Oxidation of the C-Sn bond

Conditions: CrO_3 /pyridine;
 CH_2Cl_2 , 9 hrs. (26%)

Conditions: CrO_3 /pyridine; (4%);
 O_3 , CH_2Cl_2 ; -78°C (63%)

Scheme 9. Lactone preparation: ozonolytic cleavage of C-Sn bond

Scheme 10: oxonium cation generation

The electrochemistry of the carbon-metal bond of group 14 organometallics has been extensively investigated most notably by Yoshida and his group,³⁰ however the chemical oxidation of such intermediates has met with scant attention.¹¹ We surmised that treatment of substrates such as **23** with a suitable oxidant (e.g. CAN) would generate an oxonium cation, which could then be trapped by a suitable nucleophile thereby effecting an oxidative substitution of the carbon-tin bond. In the event, exposure of substrates such as **59**, which were readily prepared from the Michael adduct **58**, to CAN in CH₃CN resulted in the formation of the furano-pyran **60** in 74% isolated yield. This oxidative unmasking is quite general and occurs readily in the presence of a number of functional groups. Not unexpectedly the redox potential of these substrates is dependent on the metal and the ease of oxidation, at least qualitatively, is found to be in the order Sn>Ge>Si. The organostannane **59** undergoes oxidation under very mild conditions (CAN; CH₃CN; 25°C; 25 min.) whereas the analogous silane **61** is only oxidised at an appreciable rate in hot (70°C) acetic acid. Oxidation of the germane **21** proceeds at a somewhat slower rate than stannane **59**, affording 2:1 mixture of acetals **62** after 6 hours at ambient temperature using a methanolic solution of CAN,²⁸ Scheme 10.

CONCLUSION

Clearly the tin moiety is pivotal to a number of the reaction sequences developed in our group: it stabilises otherwise labile ester enolates, controls enolate geometry and dictates the facial selectivity in their alkylation reactions. The enolate geometry imposed in the enolisation step controls the sense of 1,2-induction in aldol and Michael reactions. Unmasking the latent nucleophilic character of the carbon-tin bond can be realised under either basic or Lewis acidic conditions, the manner of activation controlling the stereochemical consequences of the final alkylation sequence. Alternatively redox activation of the carbon-tin bond using simple chemical oxidants such as ozone or Ce(IV) proceeds in a unpoled fashion, generating oxonium cations which may be captured by suitable nucleophilic entities. It is to be hoped that the chemistry highlighted in this article can now be applied to the synthesis of a variety of heterocyclic systems.

ACKNOWLEDGEMENTS

I would like to thank all my co-workers for their enthusiasm practical skills and intellectual input and to the funding agencies who have generously supported this programme.

REFERENCES

1. B. M. Trost and R. M. Ghadiri, *J. Am. Chem. Soc.*, 1984, **106**, 7260.
2. M. Sunagawa and A. Sasaki, Akira, *Heterocycles*, 2001, **54**, 497.
3. K. Clauss, D. Grim and G. Prossel, *Annalen*, 1974, 539.
4. e.g. I. Kadota, I.; H. Takamura, H.; K. Sato, K. and Y. Yamamoto, Y., *Tetrahedron Lett.* 2001, 4228, 4729-4731 and refs. therein.
5. D. MacLeod, P. Quayle and G. M. Davies, *Tetrahedron Lett.*, 1990, **31**, 4927.
6. C. Palomo, J. M. Aizpurua, I. Ganboa, M. Oiarbide, *Pure Appl. Chem.* 2000, **72**, 1763.
7. H. Imanieh, D. MacLeod, P. Quayle and G. M. Davies, *Tetrahedron Lett.*, 1989, **30**, 2689.
8. e.g. A. A. Alvanipour, C. Eaborn and D. R. M. Walton, *J. Organomet. Chem.*, 1980, **201**, 233.
9. F. Effenberger, *Angew. Chem., Int. Ed. Engl.*, 1969, **8**, 295.
10. A. Rahm, J. Grimeau, M. Petraud and B. Barbe, *J. Organomet. Chem.*, 1985, **286**, 297.
11. M. Lautens and H. M. Patrick, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 2448.
12. M. Lautens, C. H. Zhang, B. Goh, C. M. Crudden and M. J. R. Johnson, *J. Org. Chem.*, 1994, **59**, 6208.
13. *Ionic Hydrogenation and Related Reactions*, D. N. Kursave, Z. N. Parnes, M. I. Kalinkin, N. M. Loim, OPA, Amsterdam, 1985.
14. Y. Zhao, P. Quayle and E. A. Mason, *Tetrahedron Lett.*, 1994, **35**, 4179.
15. S. P. Thompson, PhD Thesis, University of Manchester, 1998.
16. D. W. Knight and A. P. Knott, *J. Chem. Soc., Perkin Trans 1*, 1981, 1125.
17. G. Beese and B. A. Keay, *Synlett*, 1991, 33.
18. R. L. Beddoes, M. L. Lewis, P. Gilbert, P. Quayle, S. P. Thompson, S. Wang and K. Mills, *Tetrahedron Lett.*, 1996, **37**, 9119.
19. Y. Zhao, R. L. Beddoes, and P. Quayle, *Tetrahedron Lett.*, 1994, **35**, 4183; Y. Zhao, R. L. Beddoes, and P. Quayle, *Tetrahedron Lett.*, 1994, **35**, 4187.
20. R. E. Ireland, R. H. Mueller and A. K. Willard, *J. Am. Chem. Soc.*, 1976, **98**, 2868.
21. a. R. L. Beddoes, M. L. Lewis, P. Quayle, Y. Zhao, M. Attwood and D. Hurst, *Tetrahedron Lett.*, 1994, **35**, 2641; b. R. L. Beddoes, M. L. Lewis, P. Quayle, Y. Zhao and M. Attwood, *Tetrahedron Lett.*, 1994, **35**, 4189.

22. D. D. Davis and H. T. Johnson, *J. Organomet. Chem.*, 1974, **96**, 7576.
23. R. L. Beddoes, M. L. Lewis, P. Quayle, S. Johal, M. Attwood and D. Hurst, *Tetrahedron Lett.*, 1995, **36**, 471.
24. P. Gilbert and P. Quayle, unpublished observations. For a pertinent discussion see D. A. Oare and C. H. Heathcock, *J. Org. Chem.*, 1990, **55**, 157.
25. W. C. Still, *J. Am. Chem. Soc.*, 1977, **99**, 4836.
26. R. J. Lindermann and M. Jaber, *Tetrahedron Lett.*, 1994, **35**, 5993.
27. P. Gilbert, M. L. Lewis, P. Quayle, Y. Zhao and K. Mills, *Tetrahedron Lett.*, 1996, **37**, 9115.
28. P. Quayle and S. P. Thompson, *unpublished observations*.
29. e.g. J. Yoshida, Y. Morita, Y. Ishichi and S. Isoe, *Tetrahedron Lett.*, 1994, **35**, 5247; J. Yoshida, *Topics in Current Chemistry*, 1994, **170**, 39.
30. For related examples see: Y. Kohno and K. Narasaka, *Bull. Chem. Soc. Jpn.*, 1996, **69**, 2063; C. Chen and P. S. Mariano, *J. Org. Chem.*, 2000, **65**, 3252 and ref. 18.