Pergamon

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Tetrahedron Letters 44 (2003) 7735–7740

TETRAHEDRON
LETTERS

A comparison of the Still–Gennari and Ando HWE-methodologies with α,β-unsaturated aldehydes; unexpected results with stannyl substituted systems

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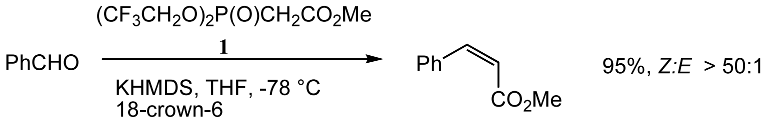
Received 5 August 2003; accepted 21 August 2003

Abstract—Still–Gennari reactions have been carried out on a range of *E*- and *Z*-3-substituted propenals. In all cases, with the exception of *Z*-3-stannyl systems, good *Z*-stereoselectivity was observed. By contrast, the Ando procedure gives reasonable *Z*-stereoselectivity with all systems studied, including those with a *cis*-disposed stannyl substituent.

The Horner–Wadsworth–Emmons (HWE) reaction,[1] which is used for the homologation of aldehydes to obtain *E*-α,β-unsaturated esters and related systems, is a fundamental construction tool in synthetic organic chemistry.[2] In recent years, a great deal of attention has been devoted to variants of the HWE process which produce *Z*-α,β-unsaturated esters and related systems with a high degree of stereocontrol. The Still–Gennari procedure,[3] which utilises the bis(2,2,2-trifluoroethyl)phosphonoester **1** (Eq. (1)) has been most commonly employed for this transformation. However, the recently introduced Ando procedure,[4] which employs the bis(phenyl)phosphonoester **2** (Eq. (2)), also has a number of attractive features, not least the lower overall cost.

In connection with a natural product synthesis project, we needed to prepare the *Z*,*E*- and *Z*,*Z*-5-stannyldienoates **5** and **7** (Scheme 1). To this end, the 3-stannylpropenals **3**[5] and **6**[5] were subjected to the Still–Gennari reaction using [bis(2,2,2-trifluoroethyl)phosphono]-2-propanoate **4**[6] under standard conditions. As expected, the *E*-stannane **3** gave the required adduct Z,*E*-**5** with complete *Z*-stereocontrol.[7] However, to our surprise, under the same conditions the corresponding *Z*-stannane **6** gave a mixture in which the expected *Z*,*Z*-product **7** was the minor component, with the *E*,*Z*-isomer **8** predominating (**7**:**8** = 1:9). To confirm this unexpected result we repeated these reactions using the unsubstituted phosphonate **1** (Scheme 2). Once again, the *E*-stannane **3** gave the required adduct *Z*,*E*-**9** with complete *Z*-stereocontrol, whereas the corresponding *Z*-stannane **6** gave predominantly the *E*-adduct isomer **11** (**10**:**11** = 23:77; **10**, *J* 11.5 Hz; **11**, *J* 14 Hz for the newly formed alkenes).[8]

The predominance of the *E*-isomer under Still–Gennari conditions appears to be unprecedented. However, we were unsure as to whether this unexpected result was due to the *syn*-orientated tin substituent, or the fact that we



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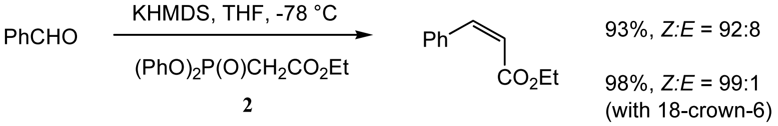

(2)

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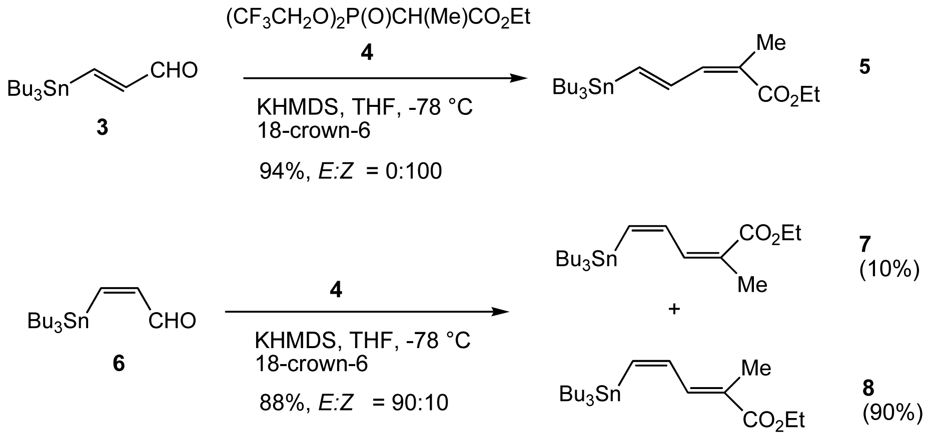
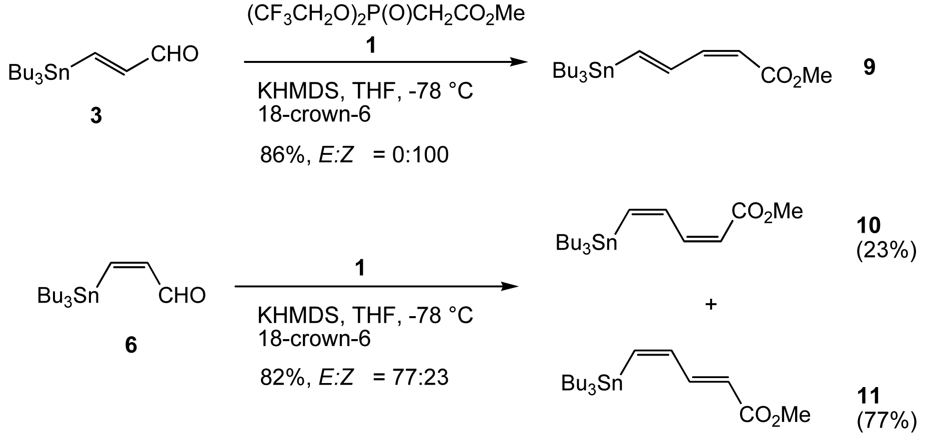
doi:10.1016/j.tetlet.2003.08.095



Scheme 1.



Scheme 2.

were using a *cis*-α,β-unsaturated aldehyde—certainly we were only able to find a small number of literature examples[9] in which Z-enals have been converted into Z,Z-dienes under Still–Gennari conditions. We therefore explored Still–Gennari reactions of phosphonates **4** and **1** with a range of known and novel unsaturated aldehydes variously substituted at the γ-position (Table 1).[10] Thus, in addition to the stannanes (entry i), enals with a range of γ-carbon substituents were studied (entries ii–iv). In all of these examples, the Still–Gennari reactions of phosphonates **4** and **1** proceeded with the expected Z-selectivity, even with sterically demanding, *cis*-disposed phenyl and *tert*-butyl substituents. These results appear to suggest that the anomalous result with stannane **6** may not be purely steric in origin.

In order to investigate a possible γ-heteroatom effect, we therefore made the 3-silyl enals shown in Table 1 (entries v and vi). With the trimethylsilyl system (entry v), the Z-alkene adducts were obtained as the sole or major products with both the *trans*- and the *cis*-enals. To ensure that the smaller size of the alkyl substituents was not a factor, the corresponding Z-3-tributylsilylpropenal was investigated (entry vi); once again, almost complete Z-stereocontrol was seen in the Still–Gennari reaction with phosphonate **1**.

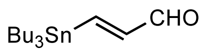
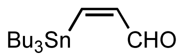
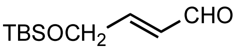
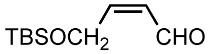
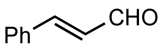
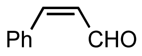
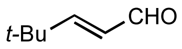
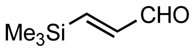
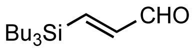
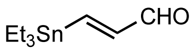
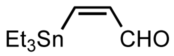
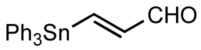
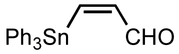
Finally, in this series, we looked at reactions of Z-3-triethyl- and Z-3-triphenyl-stannylpropenal (entries vii and viii) in order to confirm that the 'tin-effect' was not limited to the tributylstannyl system **6**. As can be seen, in both of these additional examples a predominance of the E-adduct was again observed.

In order to overcome this problem and prepare the target systems, we moved on to study the use of the Ando-variant of the HWE reaction in the key transformations (Scheme 3). Thus, using Z-3-(tributylstannyl)propenal **6** and the methyl-substituted Ando reagent **12**, we were delighted to observe that the desired Z,Z-diene **7** was obtained in good yield and with good stereoselectivity (Z:E=87:13). In a similar manner, use of the phosphonate **2** gave a predominance of Z,Z-diene **13** in 63% yield;[11] it should be noted that, in this system, the addition of sodium iodide did not lead to an improvement in the Z-selectivity.[12]

The Ando reagents were also tested on other systems (Table 2). As can be seen, with both tin (entries i and ii) and carbon (entry iii) substituents, the expected Z-preference was observed.

We are carrying out further practical and theoretical studies to rationalise this unexpected result. Our current

Table 1. Reactions of *E*- and *Z*-enals with phosphonates **4** and **1**[a]

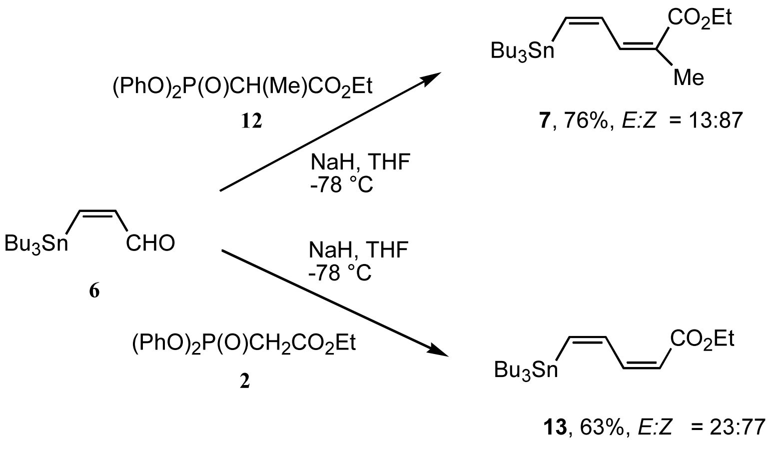
	E-Enal	with **4** Yield (*E*:*Z*)	with **1** Yield (*E*:*Z*)	*Z*-Enal	with **4** Yield (*E*:*Z*)	with **1** Yield (*E*:*Z*)
i	 **3**	94% (0:100)	86% (0:100)	 **6**	88% (90:10)	82% (77:23)
ii		89% (0:100)	-		88% (4:96)	-
iii		96% (0:100)	80% (0:100)		66% (0:100)	-
iv		-	-		33% (0:100)	-
v		95% (0:100)	-		91% (15:85)[b]	-
vi		-	-		-	94% (6:94)[b]
vii		-	-		54% (100:0)	37% (84:16)
viii		-	-		92% (89:11)	-

[a] In THF at −78°C with phosphonate **1** or **4** (1.3 equiv.), KHMDS (0.5 M in toluene, 1.2 equiv.), 18-crown-6 (4 equiv.) followed by aldehyde (1 equiv.).

[b] These aldehydes were contaminated by (ca. 10%) of the *E*-isomer.

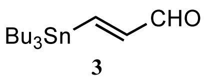
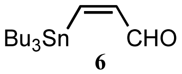
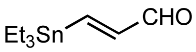
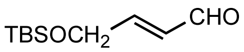
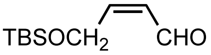
model assumes that the *cis*-disposed tin group stabilises the intermediate betaine **14** as shown, thus preventing the normally fast conversion into the oxaphosphetane intermediate leading to the *Z*-alkene, and allowing equilibration in the case of the **14**, R = CF_3CH_2. However, other possibilities, such as the fact that the *cis*-disposed tin group favours the direct generation of the oxaphosphetane intermediate leading to the *E*-alkene, are under consideration.

To probe the hypothesis that interactions between the alkoxide oxygen and the tin centre in **14** may play a role in the reaction, we have performed a series of density functional calculations on the *E*- and *Z*-isomers **15** of $H_3M{-}CH{=}CH{-}CH_2O^-$, M = C, Si and Sn. All calculations were performed using the Gaussian 98 package,[13] with the B3LYP functional. The 6-31G* basis set was used for H, C and O, while Si and Sn were modelled using the LANL2DZ basis (and associated



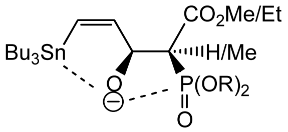
Scheme 3.

Table 2. Reactions of *E*- and *Z*-enals with phosphonates **12** and **2**[a]

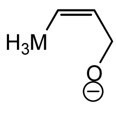
	E-Enal	with **12** Yield (*E*:*Z*)	with **2** Yield (*E*:*Z*)	*Z*-Enal	with **12** Yield (*E*:*Z*)	with **2** Yield (*E*:*Z*)
i	 **3**	55% (10:90)	75% (17:83)	 **6**	76% (13:87)	63%[11] (23:77)
ii		-	-		70% (11:89)	-
iii		92% (8:92)	-		86% (9:91)	-

[a] In THF at 0°C with phosphonate **2** or **12** (1.5 equiv.) and NaH (1.4 equiv.). After cooling to −78°C, the aldehyde (1 equiv.) was added dropwise over 10 min.[11]

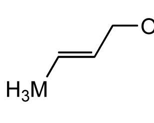
pseudopotential), augmented by a single d polarisation function.[14] These molecules represent a highly simplified model of the initial betaine formed by nucleophilic attack (in this case by hydride) on the α,β-unsaturated aldehydes H_3M–CH=CH–CHO. In the case of Si and Sn, the *Z*-isomer shows clear evidence for an expansion of the octet at M, forming a five-membered ring with a relatively short M–O bond length in each case. No such expansion is possible in *Z*-H_3C–CH=CH–CH_2O^- and there is no evidence for C–O formation, although the intermediate **15*Z*** is stabilised to some extent by electrostatic interactions between the alkoxide and the methyl protons. The orientation of the groups in the *E*-isomers **15*E*** precludes any similar M–O interactions, and so the relative energies of the two isomers affords an estimate of the extent to which M–O bond formation may stabilise the intermediate betaine. The energetic separation between the *Z*- and *E*-isomers increases dramatically from C (36 kJ mol^{-1}) to Si (120 kJ mol^{-1}) to Sn (158 kJ mol^{-1}), the tin case indicating a substantial stabilisation of the *Z*-isomeric betaine due to formation of a five-membered ring. The



14



15*Z*



15*E*

value for Si, whilst still large, is much lower than for Sn, suggesting that this stabilisation may be the cause of the observed differences in reactivity. Previous studies[15] have shown that the regioselectivity of the HWE reaction is determined by the relative energies of two transition states, one leading to formation of the betaine and the other connecting the betaine and phosphetane intermediates. Further investigations are underway to probe the effect of the stabilisation of the betaine on each of these transition states. These studies may indicate why the above effect is more important in **14**, $R = CF_3CH_2$ than in **14**, R = Ph.

In summary, we have shown that a range of *E*- and *Z*-3-substituted propenals undergo the Still–Gennari variant of the HWE reactions with excellent *Z*-stereoselectivity. However, *Z*-3-stannylpropenals proved to be exceptional cases in that a predominance of the *E*-isomeric product is observed. By contrast, the Ando procedure gives reasonable *Z*-stereoselectivity with all systems studied, including those with a *cis*-orientated stannyl substituent. Natural product syntheses using products obtained from this study are also underway.

Acknowledgements

We are grateful to the EPSRC for postdoctoral funding (X.F.; GR/R14552), and to Yorkshire Cancer Research (S.L.X.M.; Y244) and the EPSRC (M.R.W.; Industrial CASE) for studentship support. We also thank Dr. S. A. Raw for helpful discussions and advice.

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6. Patois, C.; Savignac, P.; Aboujaudet, E.; Collignon, N. *Synth. Commun.* **1991**, *21*, 2391–2396.
7. All novel compounds were fully characterised (including by high field ^1H and ^{13}C NMR spectroscopy and high resolution mass spectrometry); NOE studies were employed to assign alkene stereochemistries.
8. Counterion effects were also studied. The reaction between *Z*-enal **6** and phosphonate **4** using KHMDS (with 18-crown-6), KHMDS, LiHMDS, NaHMDS and NaH gave the products **7** and **8** in high yields with the following *E*:*Z* ratios, 90:10, 100:0, 72:28, 50:50, 60:40.
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10. The α,β-unsaturated aldehydes are commercially available or were prepared using standard methods (see Refs. 5 and 9 and (a) Bestmann, H. J.; Roth, K.; Ettlinger, M. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 687; (b) Sakai, T.; Kohda, K.; Tsuboi, S.; Utaka, M.; Takeda, A. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 2911–2915; (c) Michel, P.; Rassat, A.; Daly, J. W.; Spande, T. F. *J. Org. Chem.* **2000**, *65*, 8908–8918).
11. Representative procedure for the Ando reaction on aldehyde **6**: To a stirred suspension of sodium hydride (60% w/w in mineral oil, 15 mg, 0.38 mmol) in THF (3 mL) at 0°C was added a solution of phosphonate **2** (130 mg, 0.40 mmol) in THF (1 mL). The reaction mixture was stirred at 0°C for 20 min, and then cooled down to −78°C. After 30 min at −78°C, aldehyde **6** (93 mg, 0.27 mmol) in THF (1 mL) was added dropwise over a period of 10 min. The reaction mixture was stirred at −78°C for 2 h then allowed to gradually warm up to rt overnight. The reaction mixture was then quenched with saturated aqueous NH_4Cl (10 mL) and extracted with ether (3×10 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether–diethyl ether, 40:1) to afford **13** (71 mg, 63%, *E*:*Z* = 23:77) as a yellow oil Found (CI): MH^+, 413.1807. $C_{19}H_{36}O_2{}^{116}Sn$ requires MH^+, 413.1811, 1.0 ppm error; R_f 0.35 (petroleum ether–diethyl ether, 40:1); ν_{max}/cm^{-1} (thin film) 2958, 2927, 2872, 2853, 1719, 1615, 1463, 1261, 1201, 1162; δ_H (270 MHz; $CDCl_3$, major isomer) 8.18 (1H, dd, *J* 12.5, 11.5, H-2), 6.73 (1H, d, *J* 12.5, H-1), 6.43 (1H, t, *J* 11.5, H-3), 5.73 (1H, d, *J* 11.5, H-4), 4.19 (2H, q, *J* 7.0, OCH_2), 1.57–1.42 (6H, m), 1.37–1.23 (9H, m), 1.00–0.84 (15H, m); δ_C (100 MHz; $CDCl_3$, major isomer) 166.5 (C=O), 148.1 (CH), 146.7 (CH), 142.7 (CH), 116.0 (C-4), 60.1 (CH_2), 29.2 (CH_2), 27.2 (CH_2), 14.5 (CH_3), 13.8 (CH_3), 9.8 (CH_2); *m*/*z* (CI) 417, 376, 359, 308 (100%), 291, 127.
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