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Palladium Catalysed Coupling of Imidazoles to Alkynyl and Vinyl Substrates

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Abstract: Methods for preparing 4-substituted imidazoles from the palladium(0) catalysed couplings of N-protected 4-haloimidazoles with alkynes or alkynyl- and vinyltrialkyltin derivatives or from the coupling reactions of 4-trimethylstannylimidazole 9 with aryl and vinyltoidides and bromides under Stille conditions is reported. Copyright © 1996 Elsevier Science Ltd

Imidazole based compounds form a biologically important series of molecules. Histamine, a simple monosubstituted compound is released by tissue during an allergic reaction.¹ More recently other imidazoles have been discovered with varying biological properties. Urocanic acid^{2,3} and azothioprine⁴ have been shown to effect the immune competence of laboratory animals. Azothioprine also displays antitumor activity.⁴ A third substituted imidazole, THI, produces lymphopenia in laboratory rats^{5,6,7} and has been reported to prevent spontaneous and cyclophosphamide-induced diabetes in non-obese diabetic mice.⁸

As part of a larger synthetic project involving the synthesis of new imidazoles, 9,10 a means of introducing unsaturated side-chains onto the 4-position of the imidazole ring was required. Previous methods for preparing 4-substituted imidazoles have involved the use of transmetallation reactions of protected 4-haloimidazoles, using either lithium¹¹ or Grignard reagents.^{12,13} Neither of these methods were practical for our purposes, however, as we required the introduction of unsaturated side-chains for use in subsequent reactions. Palladium catalysed coupling reactions of *N*-protected 4-haloimidazoles with alkenes, alkynes and their trialkyltin derivatives were therefore examined and the results of this investigation are presented here.

Under Heck-type coupling conditions, the reaction¹⁴ of protected 4-iodoimidazoles and terminal alkenes failed to give the desired 4-vinyl-imidazole products due to a facile homo-coupling of the heterocycle to give 4,4'-bisimidazoles.¹⁵ The palladium catalysed reactions of 4-iodoimidazoles and alkynes $2a-c^{16}$ however, gave the cross-coupled products 3a-e in moderate to good yields (Scheme 1). In the cases were phenylacetylene was used the yields were only moderate irrespective of the nature of the *N*-protecting groups on the imidazole 1-position. In contrast, good yields of the cross-coupled imidazole products 3b and 3c were obtained using the non-aromatic alkynes 2b and 2c respectively.¹⁷

Scheme 1

$$R^{1}N \xrightarrow{I} H C \equiv CR^{2} \xrightarrow{Pd(Ph_{3}P)_{4}} DMF, 80 \ ^{\circ}C$$

$$R^{1}N \xrightarrow{I} R^{1} = Ts$$

$$2a; R^{2} = Ph$$

$$b; R^{1} = PhSO_{2}$$

$$2b; R^{2} = CH_{2}OTBDMS$$

$$1c; R^{1} = EtOCH_{2}$$

$$2c; R^{2} = (CH_{2})_{2}OTBDMS$$

$$1d; R^{1} = Tr$$

$$3a; R^{1} = Ts, R^{2} = Ph$$

$$3b; R^{1} = PhSO_{2}, R^{2} = CH_{2}OTBDMS$$

$$3c; R^{1} = PhSO_{2}, R^{2} = (CH_{2})_{2}OTBDMS$$

$$3d; R^{1} = EtOCH_{2}, R^{2} = Ph$$

$$3e; R^{1} = Ts, R^{2} = Ph$$

$$3e; R^{1} = Ts, R^{2} = Ph$$

$$3e; R^{1} = Ts, R^{2} = Ph$$

$$3f; R^{1} = Ts, R^{2} = (CH_{2})_{4}CH_{3}$$

Table 1	. Palladium	catalysed	alkyne	coupling	to imidazoles	1a-d.
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Imidazole	Alkyne	Product	Yield(%)	
1a	2a	3a	51	
1b	2b	3b	89	
1b	2c	3c	72	
1c	2a	3d	42	
1d	2a	3e	47	

Significant improvements in the yields of the 4-phenylethynyl-imidazoles **3a** and **3d** could be realised from the reaction of the related 1-tributylstannane **4a** with the 4-iodoimidazoles **1a** and **1c** under Stille type coupling conditions (Scheme 2 and Table 2).¹⁸ Significant improvements in yield was noted in several cases upon the use of 1-alkynylstannanes (Table 2, **3a** and **3d**). In two cases, however, the use of trimethylstannanes resulted in a decrease in product yield (Table 2, **3b** and **3c**) when compared to that obtained *via* direct palladium catalysed alkyne coupling.

Scheme 2

$$R^{1}N = N + R^{3}{}_{3}SnC \equiv CR^{2} \xrightarrow{a, b \text{ or } c} R^{-}N = R + N = N$$
1a-c
4a; R² = Ph, R³ = Bu
4b; R² = CH₂OTBDMS, R³ = Me
4c; R² = (CH₂)₂OTBDMS, R³ = Me
4d; R₂ = (CH₂)₄CH₃, R³ = Me

a: $Pd_2(dba)_3$, AsPh₃, Cul, THF, reflux, b: $Pd_2(dba)_3$, AsPh₃, Cul, DMF, 80 °C,c: $Pd(Ph_3P)_4$, THF, reflux

Imidazole	Stannane	R'	R"	Conditions*	Product	Yield
1a	4a	Bu	Ph	a	3a	85%
1b	4 b	Me	CH ₂ OTBDMS	b	3b	50%
1b	4 c	Me	(CH ₂) ₂ OTBDMS	ь	3c	47%
1c	4a	Bu	Ph	с	3d	69%
1a	4d	Me	(CH ₂) ₄ CH ₃	b	3f	53%

Table 2. Stille coupling of alkynylstannanes to imidazoles 1a-c.

* a: 5 mol % Pd₂(dba)₃, 10 mol % AsPh₃, 10 mol % CuI, THF, reflux. b: 5 mol % Pd₂(dba)₃, 10 mol % AsPh₃, 10 mol % CuI, DMF, 80 °C. c: Pd(Ph₃P)₄, THF, reflux.

Stille cross-coupling also allowed for the successful introduction of vinyl moieties which were previously unobtainable under Heck coupling conditions. Reaction of 1a with vinylstannane 5 (E : Z = 9 : 1) using the Pd₂(dba)₃/AsPh₃/CuI catalyst system¹⁹ resulted in both E and Z coupled products **6a** and **6b** in 55% and 10% yields respectively. Similarly, reaction of 1b with stannane 7 (E : Z = 87 : 13) under identical conditions gave **8a** and **8b** in 47% and 5% yields respectively (Scheme 3). Other palladium catalysts (eg Pd(Ph₃P)₄) gave poorer yields of **7** and **8**.

Scheme 3



As an alternative to using N-protected iodoimidazoles, 4-trimethylstannylimidazole 9 was prepared and was found to successfully undergo cross-coupling to aryl and vinyliodides and bromides under Stille conditions. Treatment of 1c with ethylmagnesium bromide in anhydrous dichloromethane¹² followed by quenching with trimethyltin chloride gave stannane 9 in 66% yield, plus reduced imidazole 10 in 16% yield (Scheme 4). Reaction of 9 with iodobenzene using the Pd₂(dba)₃/AsPh₃/CuI catalyst system gave the cross-coupled product 11 in 59% yield, while coupling with β -bromostyrene (E: Z = 10: 1) resulted in the E- and Z-isomers 12a and 12b in 68% and 12% yields respectively (Scheme 5).



The use of 9 in this manner is particularly attractive for reactions that involve valuable aryl, alkynyl and vinylhalides, where conversion to the equivalent stannane and coupling to imidazoles of type 1 would present an unviable option. Treatment of vinyliodide 13 (E: Z = 9: 1) with an excess of the stannane 9 for 16 h at 80 °C in the presence of PdCl₂(Ph₃P)₂ gave 14a and 14b in 60% and 13% yields respectively, plus a third unidentified product (Scheme 6).



In summary, the application of palladium(0) cross-coupling reactions to various N-protected imidazoles has been demonstrated. Heck coupling of vinyl substrates to iodoimidazoles fails, resulting in the isolation of homocoupled material only. The introduction of alkene moieties, however, is readily achieved using vinylstannanes under Stille conditions. Alkyne groupings can be introduced either by a direct coupling reaction or by use of alkynylstannanes.

Experimental

All ¹H NMR and ¹³C NMR were run in CDCl₃ solution. All organic extracts were dried over MgSO₄. Column chromatography was performed on silica gel (70-230 mesh). Compounds 1a,¹⁰ 1c,¹⁰ 1d,²⁰ 4c,¹⁰ and 5^{10} were prepared by known procedures.

4-(*t*-Butyldimethylsilyloxy)-1-propyne (2b). A solution of imidazole (3.62 g, 53.2 mmol) and TBDMS-Cl (4.0 g, 26.7 mmol) in anhydrous DMF (15 mL) was cooled to 0 °C under an N₂ atmosphere. Propargyl alcohol (1.36 g, 24.2 mmol) was added dropwise and the solution was stirred at rt for 16 h. The solution was then diluted with ether (70 mL) and washed with water (3 x 10 mL). The ether phase was dried and concentrated to give a pale oil. Purification by vacuum distillation (40 °C/8 mmHg) gave the title alkyne as a clear oil (3.14 g, 76%). ¹H NMR δ 4.31 (2H, d, J = 2.4 Hz), 2.39 (1H, t, J = 2.4 Hz), 0.91 (9H, s), 0.13 (6H, s). ¹³C NMR δ 82.4, 72.8, 51.5, 25.8, 18.3, -5.2. MS (ES +ve) m/z 158 (22%), 142 (100%).

4-(*t*-Butyldimethylsilyloxy)-1-butyne (2c). Using the general procedure described above for the synthesis of 4-(*t*-butyldimethylsilyloxy)-1-propyne, the title compound was obtained as a clear oil (94%) after purification by fractional distillation (70 °C/10 mmHg). ¹H NMR δ 3.74 (2H, t, J = 7.2 Hz), 2.40 (2H, dt, J = 2.4, 7.2 Hz), 1.96 (1H, t, J = 2.4 Hz), 0.89 (9H, s), 0.07 (6H, s). ¹³C NMR δ 81.5, 69.2, 61.7, 25.6, 22.8, 18.3, -5.3. MS (CI+ve) m/z 170 (M-CH₃+, 4%), 128 (M-^{*i*}Bu, 58%), 110 (12%), 98 (83%). IR (neat) 3313, 2120, 1472, 1256, 1115 cm⁻¹. HRMS calcd for C₉H₁₇OSi (M-CH₃+) 169.1049, found 169.1047.

1-Benzenesulfonyl-4-iodoimidazole (1b). To a solution of 4(5)-iodoimidazole²¹ (3.0 g, 15.5 mmol) and benzenesulfonyl chloride (2.74 g, 15.5 mmol) in anhydrous THF (40 mL) under N₂ was added triethylamine (1.57 g, 15.5 mmol) and the solution was stirred at rt for 16 h. The mixture was filtered and the solvent removed. Recrystallisation from ethanol gave the title compound as a white solid (4.85 g, 78%), mp 124-126 °C. ¹H NMR δ 7.95 (1H, d, J = 8.4 Hz), 7.90 (1H, t, J = 1.2 Hz), 7.75-7.71 (1H, m), 7.63-7.58 (2H, m), 7.40

(1H, t, J = 1.2 Hz). ¹³C NMR δ 137.6, 137.1, 135.2, 129.9, 127.4, 122.3, 85.4. MS (ES +ve) m/z 335 (M+H⁺, 100%), 141 (PhSO₂⁺, 22%). IR (nujol) 3140, 1175, 1143, 1072, 920 cm⁻¹. HRMS calcd for C₉H₇N₂O₂I 333.9273, found 333.9268. Anal. calcd for C₉H₇N₂O₂SI: C, 32.35; H, 2.11; N, 8.38. Found: C, 32.39; H, 2.07; N, 8.44.

4-(2'-Phenylethynyl)-1-*p*-tosylimidazole (3a). A representative palladium catalysed alkyne coupling procedure: A solution of imidazole 1a (200 mg, 0.58 mmol), phenylacetylene (88 mg, 0.86 mmol), Et₃N (0.58 g, 5.8 mmol), 10 mol % CuI (11 mg, 5.79×10^{-5} mol) and 5 mol % Pd(Ph₃P)₄ (33 mg, 2.89 x 10⁻⁵ mol) in anhydrous DMF (5 mL) was heated at 80 °C under N₂ for 3 h. The mixture was cooled, diluted with ether (25 mL) and washed with H₂O (3 x 5 mL). The organics were dried, concentrated and purified by column chromatography (20% ethyl acetate / hexane) to give the title compound as a light tan solid (95 mg, 51%), mp 144-145 °C. An analytical sample was recrystallised from ethyl acetate to give a white solid.

¹H NMR δ 7.98 (1H, d, J = 1.2 Hz), 7.85 (2H, d, J = 8.4 Hz), 7.51-7.49 (2H, m), 7.48 (1H, d, J = 1.5 Hz), 7.38 (2H, d, J = 8.1 Hz), 7.34-7.32 (3H, m), 2.46 (3H, s). ¹³C NMR δ 146.7, 136.5, 134.6, 131.6, 130.6, 128.7, 128.3, 127.5, 127.2, 122.3, 120.2, 91.0, 80.9, 21.7. MS (ES +ve) m/z 323 (M+H⁺, 31%), 284 (39%), 256 (100%). HRMS calcd for C₁₈H₁₄N₂O₂S 322.0781, found 322.0776. Anal. calcd for C₁₈H₁₄N₂O₂S: C, 67.09; H, 4.34; N, 8.69. Found: C, 67.09; H, 4.31; N, 8.54.

1-Benzenesulfonyl-4-(3'-(t-butyldimethylsilyloxy)prop-1'-ynyl)imidazole (3b). Using the general procedure described above for the synthesis of 3a, the title compound was obtained as a yellow oil (89%) after purification by column chromatography (15% ethyl acetate / hexane). ¹H NMR δ 7.96-7.93 (3H, m), 7.74-7.68 (1H, m), 7.62-7.56 (2H, m), 7.40 (1H, d, J = 1.2 Hz), 4.48 (2H, s), 0.90 (9H, s), 0.13 (6H, s). ¹³C NMR δ 137.5, 136.3, 135.1, 129.9, 127.4, 126.8, 120.3, 90.0, 76.4, 52.0, 25.8, 18.2, -5.2. MS (ES +ve) *m/z* 399 (M+Na⁺, 47%), 377 (M+H⁺, 100%).

1-Benzenesulfonyl-4-(4'-(t-butyldimethylsilyloxy)but-1'-ynyl)imidazole (3c). Using the general procedure described above for the synthesis of **3a**, the title compound was obtained as a light yellow solid (72%) after purification by column chromatography (20% ethyl acetate / hexane), mp 67-69 °C. ¹H NMR δ 7.94 (1H, d, J = 0.8 Hz), 7.93-7.92 (2H, m), 7.72-7.68 (1H, m), 7.61-7.56 (1H, m), 7.33 (1H, d, J = 0.8 Hz), 3.78 (2H, t, J = 7.2 Hz), 2.58 (2H, t, J = 7.2 Hz), 0.89 (9H, s), 0.06 (6H, s). ¹³C NMR δ 137.7, 136.1, 135.0, 129.9, 127.5, 127.4, 119.6, 89.5, 73.3, 61.4, 25.9, 23.7, 18.3, -5.3. MS (ES +ve) 391 (M+H⁺, 100%).

1-Ethoxymethyl-4-(2'-phenylethynyl)imidazole (3d). Using the general procedure described above for the synthesis of **3a**, the title compound was obtained as a tan oil (42%) after purification by column chromatography (50% ethyl acetate / hexane). ¹H NMR δ 7.58 (1H, d, J = 1.2 Hz), 7.54-7.52 (2H, m), 7.34-7.32 (3H, m), 7.30 (1H, d, J = 1.2 Hz), 5.27 (2H, s), 3.47 (2H, q, J = 7.2 Hz), 1.20 (3H, t, J = 7.2 Hz). ¹³C NMR δ 137.3, 131.4, 128.1, 128.0, 125.2, 123.1, 89.1, 82.8, 76.4, 64.5, 14.5. MS (ES +ve) 227 (M+H⁺, 100%), 197 (M-Et⁺, 6%), 183 (C₁₂H₁₁N₂⁺, 10%), 59 (EtOCH₂⁺, 20%), 42 (42%). HRMS calcd for C₁₄H₁₄N₂O 226.1106, found 226.1114.

4-(2'-Phenylethynyl)-1-tritylimidazole (3e). Using the general procedure described above for the synthesis of **3a**, the title compound was obtained as a white solid (47%) after recrystallisation from 1:1 ethyl acetate / chloroform, mp 244-245 °C. ¹H NMR δ 7.50-7.48 (2H, m), 7.44 (1H, d, J = 1.2 Hz), 7.37-7.35 (9H, m), 7.31-7.29 (3H, m), 7.16-7.14 (6H, m), 7.11 (1H, d, J = 1.6 Hz). ¹³C NMR δ 142.0, 139.1, 131.4, 129.7, 128.22, 128.19, 128.16, 127.99, 125.6, 123.4, 123.2, 89.3, 83.2, 75.8. MS (ES +ve) *m/z* 411 (M+H⁺, 2%), 243 (CPh₃⁺,

100%). IR (nujol) 1297, 1107, 979, 865, 742, 701, 665 cm⁻¹. HRMS calcd for $C_{30}H_{22}N_2$ 410.1783, found 410.1785.

1-[4-(*t*-Butyldimethylsilyloxy)]propynyltrimethylstannane (4b). To a solution of TBDMS protected propargyl alcohol (1.0 g, 5.88 mmol) in anhydrous THF (10 mL) at -78 °C under N₂ was added *n*-BuLi in hexanes (5.88 mmol) and the reaction stirred for 30 min at -78 °C. A 1M solution of Me₃SnCl in THF (5.94 mmol) was then added dropwise and the mixture was stirred for 30 min at -78 °C and 16 h at rt. The mixture was diluted with ether (50 mL) and the solution was washed with H₂O (2 x 10 mL), dried and concentrated. Purification by bulb-to-bulb distillation (95 °C/8 mmHg) gave the title stannane as a clear oil (1.72 g, 88%). ¹H NMR δ 4.30-4.26 (2H, m), 0.88 (9H, s), 0.24 (9H, s, ²J (¹¹⁹Sn, H) = 60.3 Hz, ²J (¹¹⁷Sn, H) = 57.6 Hz), 0.09 (6H, s). MS (ES +ve) *m*/z 373* (M+K⁺, 8%), 165* (Me₃Sn⁺, 100%).

* ¹²⁰Sn isotope.

1-Heptynyltrimethylstannane (4d). Using the general procedure described above for the synthesis of 4b, the title compound was obtained as a pale oil (93%) after purification by bulb-to-bulb distillation (110 °C/10 mmHg). ¹H NMR δ 2.22 (2H, t, J = 7.2 Hz), 1.54-1.25 (6H, m), 0.89 (3H, t, J = 6.6 Hz), 0.25 (9H, s, ²J (¹¹⁹Sn, H) = 60.3 Hz, ²J (¹¹⁷Sn, H) = 57.6 Hz).

4-(2'-Phenylethynyl)-1-*p*-tosylimidazole (3a) *via* Stille coupling: A representative Stille coupling procedure: A solution of iodoimidazole 1a (0.3 g, 0.86 mmol), (phenylethynyl)tributylstannane 4a (0.34 g, 0.86 mmol), 5 mol % Pd₂(dba)₃ (40 mg, 4.37 x 10⁻⁵ mol), 10 mol % AsPh₃ (26 mg, 8.6 x 10⁻⁵ mol) and 10 mol % CuI (17 mg, 8.6 x 10⁻⁵ mol) in anhydrous THF (8 mL) under N₂ was heated to reflux for 7 h. The mixture was then cooled to rt and poured into H₂O (10 mL). The aqueous solution was extracted with CH₂Cl₂ (3 x 15 mL) and the combined extracts were dried and concentrated. Purification by column chromatography (15% ethyl acetate / hexane) gave the title compound as a light tan solid (235 mg, 85%).

1-Benzenesulfonyl-4-(3'-(t-butyldimethylsilyloxy)prop-1'-ynyl)imidazole (3b) via Stille coupling. Using the general Stille coupling procedure described above for the synthesis of 3a with imidazole 1b, stannane 4b and anhydrous DMF as reaction solvent, the title compound was obtained as a yellow oil (50%) after purification by column chromatography (15% ethyl acetate / hexane).

1-Benzenesulfonyl-4-(4'-(t-butyldimethylsilyloxy)but-1'-ynyl)imidazole (3c) via Stille coupling. Using the general Stille coupling procedure described above for the synthesis of 3a with imidazole 1b, stannane 4c and anhydrous DMF as reaction solvent, the title compound was obtained as a light yellow solid (47%) after purification by column chromatography (15% ethyl acetate / hexane).

1-Ethoxymethyl-4-(2'-phenylethynyl)imidazole (3d) *via* Stille coupling. Using the general Stille coupling procedure described above for the synthesis of 3a with imidazole 1c, stannane 4a and 5 mol % Pd(Ph₃P)₄, the title compound was obtained as a light yellow solid (47%) after purification by column chromatography (15% ethyl acetate / hexane).

4-(Hept-1'-ynyl)-1-*p*-tosylimidazole (3f). Using the general Stille coupling procedure described above for the synthesis of 3a with imidazole 1a, stannane 4d and anhydrous DMF as reaction solvent, the title compound was obtained as a light yellow solid (53%, mp 75-77 °C) after purification by column chromatography (15% ethyl acetate / hexane). ¹H NMR δ 7.90 (1H, d, J = 1.5 Hz), 7.81 (2H, d, J = 8.4 Hz), 7.36 (2H, d, J = 8.4 Hz), 7.31 (1H, d, J = 1.5 Hz), 2.44 (3H, s), 2.35 (2H, d, J = 7.2 Hz), 1.61-1.51 (2H, m), 1.43-1.26 (4H, m), 0.89 (3H, t, J = 7.2 Hz). ¹³C NMR δ 146.4, 137.5, 135.9, 134.5, 130.3, 127.3, 119.1, 92.5, 72.1, 30.9, 27.9, 22.0, 21.5, 19.1, 13.7. MS (ES +ve) *m/z* 195 (14%), 163 (MH+-tosyl, 100%).

(E)-(1'-Heptenyl)tributylstannane and (Z)-(1'-heptenyl)tributyl stannane (7). A neat mixture of heptyne (730 mg, 7.56 mmol) and a catalytic amount of AIBN was stirred at 120 °C under an N₂ atmosphere. Tributyltin hydride (2.00 g, 6.87 mmol) was then added and the reaction was stirred at 120 °C for 3 h, cooled to ambient temperature and placed under high vacuum to remove excess heptyne. The title isomeric stannanes were obtained in quantitative yield as a pale oil (E: Z = 87: 13). (E)-Isomer: ¹H NMR δ 6.01-5.88 (2H, m), 2.16-2.09 (2H, m), 1.58-1.27 (22H, m), 0.92-0.83 (12H, m). (Z)-Isomer: ¹H NMR δ 6.51 (1H, dt, J = 6.9, 12.3 Hz), 5.77 (1H, dt, J = 1.2, 12.3 Hz), 2.05-1.98 (2H, m), 1.58-1.27 (22H, m), 0.92-0.83 (12H, m). (E)-4-[4'-(t-Butyldimethylsilyloxy)but-1'-enyl]-1-p-tosylimidazole (6a) and (Z)-4-[4'-(tbutyldimethylsilyloxy)but-1'-enyl]-1-p-tosylimidazole (6b). A solution of iodoimidazole 1a (300 mg, 0.86 mmol), vinnylstannane 5 (400 mg, 0.86 mmol, E : Z = 9 : 1), 5 mol % Pd₂(dba)₃ (39 mg, 4.3 x 10⁻⁵ mol), 10 mol % AsPh₃ (27 mg, 8.6 x 10⁻⁵ mol) and 10 mol % CuI (16 mg, 8.6 x 10⁻⁵ mol) in anhydrous DMF (8 mL) was degassed with a stream of N₂ and sealed in a thick walled tube under N₂. The solution was then stirred at 80 °C for 3 h. The mixture was diluted with ether (30 mL) and washed with H2O (3 x 8 mL). The organic phase was then stirred with a sat. aqueous solution of KF (10 mL) for 1 h, the phases separated and the organics filtered, dried and concentrated. Purification by column chromatography (12% ethyl acetate / hexane) gave **6a** (191 mg, 55%) and **6b** (34 mg, 10%) both as yellow oils. **6a**: ¹H NMR δ 7.92 (1H, d, J = 1.2 Hz), 7.80 (2H, d, J = 8.7 Hz), 7.34 (2H, d, J = 8.7 Hz), 7.07 (1H, d, J = 1.2 Hz), 6.40 (1H, dt, J = 7.2, 15.6 Hz), 6.22 (1H, d, J = 15.6 Hz), 3.68 (2H, t, J = 6.9 Hz), 2.43 (3H, s), 2.42-2.35 (2H, m), 0.87 (9H, s), 0.04 (6H, s). ¹³C NMR δ 146.1, 142.8, 136.6, 135.0, 130.3, 129.3, 127.2, 121.7, 112.5, 62.6, 36.4, 25.9, 21.6, 18.3, -5.3. MS (ES +ve) m/z 407 (M+H⁺, 100%), 254 (14%), 142 (22%). HRMS calcd for C₁₉H₂₇N₂O₃SSi (M-CH₃) 391.1512, found 391.1490. 6b: ¹H NMR d 7.95 (1H, d, J = 1.2 Hz), 7.82 (2H, d, J = 8.4 Hz), 7.35 (2H, d, J = 8.1 Hz), 7.21 (1H, s), 6.26 (1H, d, J = 11.7 Hz), 5.74 (1H, dt, J = 7.2, 11.7 Hz), 3.73 (2H, t, J = 6.6 Hz), 2.67-2.60 (2H, m), 2.43 (3H, s), 0.88 (9H, s), 0.05 (6H, s). ¹³C NMR δ 146.2, 142.0, 136.0, 135.1, 130.6, 130.4, 127.3, 121.0, 114.7, 62.5, 32.9, 25.9, 21.7, 18.3, -5.3. MS (ES +ve) m/z 407 (M+H+, 100%), 313 (24%), 288 (E)-4-(1'-Heptenyl)-1-benzenesulfonylimidazole (8a) and (Z)-4-(1'-heptenyl)-1-benzenesulfonylimidazole (8b). Using the coupling procedure described above for the synthesis of 6a and 6b with imidazole 1b and stannane 7, compounds 8a and 8b were obtained as pale oils in 47% and 5% yields respectively after purification by column chromatography (10% ethyl acetate / hexane). 8a: ¹H NMR δ 7.95-7.91 (2H, m), 7.70-7.65 (1H, m), 7.59-7.53 (2H, m), 7.07 (1H, d, J = 1.2 Hz), 6.45 (1H, dt, J = 6.9, 15.6 Hz), 6.16 (1H, d, J = 1.2 Hz), 6.45 (1H, dt, J = 6.9, 15.6 Hz), 6.16 (1H, d, J = 1.2 Hz), 6.45 (1H, dt, J = 6.9, 15.6 Hz), 6.16 (1H, dt, J = 1.2 Hz), 6.45 (1H, dt, J = 6.9, 15.6 Hz), 6.16 (1H, dt, J = 1.2 Hz), 6.45 (1H, dt, J = 6.9, 15.6 Hz), 6.16 (1H, dt, J = 1.2 Hz), 6.45 (1H, dt, J = 6.9, 15.6 Hz), 6.16 (1H, dt, J = 1.2 Hz), 6.45 (1H, dt, J = 6.9, 15.6 Hz), 6.16 (1H, dt, J = 6.9, 15.6 Hz), 6.16 (1H, dt, J = 1.2 Hz), 6.45 (1H, dt, J = 6.9, 15.6 Hz), 6.16 (1H, dt, J = 1.2 Hz), 6.45 (1H, dt, J = 6.9, 15.6 Hz), 6.16 (1H, dt, J = 1.2 Hz), 6.45 (1H, dt, J = 1.2 Hz), 7.55 (1H, dt, J = 1.2 Hz), 8.55 (1H, dt, J = 15.9 Hz), 2.19-2.12 (2H, m), 1.45-1.26 (6H, m), 0.87 (3H, t, J = 6.9 Hz). ¹³C NMR δ 143.1, 138.1, 136.6, 134,7, 133.8, 129.8, 127.2, 119.7, 112.3, 32.7, 31.4, 28.7, 22.5, 14.0. MS (ES +ve) m/z 305 (M+H+, 100%). 8b: ¹H NMR δ 7.97-7.92 (3H, m), 7.70-7.65 (1H, m), 7.60-7.53 (2H, m), 7.17 (1H, s), 6.20-6.16 (1H, m), 5.70 (1H, dt, J = 6.9, 11.7 Hz), 2.43-2.35 (2H, m), 1.47-1.26 (6H, m), 0.89-0.85 (3H, m). ¹³C NMR (In part) δ 142.1, 135.8, 134.8, 134.6, 129.7, 127.1, 119.9, 114.4, 32.6, 31.2, 28.6, 22.4, 13.9. MS (EI +ve) m/z 304 (M+, 8%), 259 (51%), 197 (38%), 163 (100%). HRMS calcd for C₁₆H₂₀N₂O₂S 304.1246, found 304.1249.

1-Ethoxymethyl-4-(trimethylstannyl)imidazole (9) and 1-ethoxy methylimidazole (10). To a solution of iodoimidazole 1c (1.5 g, 5.95 mmol) in anhydrous CH_2Cl_2 (10 mL) under N₂ was added EtMgBr in ether (6.55 mmol) and the mixture was stirred for 30 min at rt. The solution was then cooled to 0 °C, trimethyltin chloride (1.43 g, 7.14 mmol) in anhydrous CH_2Cl_2 (5 mL) was added dropwise and the mixture was then warmed to rt and stirred for 2 h. The mixture was then diluted with CH_2Cl_2 (20 mL), washed with a half sat. aqueous solution of NaCl (2 x 10 mL), dried and the solvent was removed to leave a yellow oil. Purification

by bulb-to-bulb distillation (70 °C/0.2 mmHg) gave the title stannane 9 (1.13 g, 66%), plus deiodinated 10 (120 mg, 16%) as clear oils. 9: ¹H NMR δ 7.79 (1H, d, J = 0.9 Hz), 7.07 (1H, d, J = 1.2 Hz), 5.29 (2H, s), 3.46 (2H, q, J = 7.8 Hz), 1.19 (3H, t, J = 6.9 Hz), 0.302 (9H, s, ^{2}J (117 Sn, H) = 54.6 Hz, ^{2}J (119 Sn, H) = 57 Hz). ¹³C NMR δ 141.5, 139.6 (J (Sn, C) = 59.5 Hz), 126.5 (J (Sn, C) = 109.6 Hz), 75.6, 64.2, 14.6, -9.6 (J $(^{117}Sn, C) = 349.9 \text{ Hz}, J (^{119}Sn, C) = 366.0 \text{ Hz}). \text{ MS (ES +ve) } m/z 291* (M+H^+, 100\%). HRMS calcd for$ C9H18N2O120Sn 290.0440, found 290.0438 (* 120Sn isotope peak). 10: 1H NMR d 7.60 (1H, s), 7.10 (1H, s), 7.06 (1H, t, J = 1.2 Hz), 5.29 (2H, s), 3.45 (2H, q, J = 7.2 Hz), 1.19 (3H, t, J = 7.2 Hz). ¹³C NMR d 137.3, 129.9, 118.7, 76.1, 64.2, 14.6. MS (ES +ve) m/z 127 (M+H+, 100%). IR (nujol) 3108, 2980, 1221, 1111 cm⁻¹. 1-Ethoxymethyl-4-phenylimidazole (11). Using the general Stille coupling procedure described above for the synthesis of 3a and anhydrous DMF as reaction solvent, the title compound was obtained as a red solid (59%, mp 60-62 °C) after purification by column chromatography (40% ethyl acetate / hexane). ¹H NMR δ 7.79-7.75 (2H, m), 7.70 (1H, d, J = 1.2 Hz), 7.39-7.32 (3H, m), 7.27-7.21 (1H, m), 5.30 (2H, s), 3.49 (2H, q, J = 6.9 Hz), 1.21 (3H, t, J = 6.9 Hz). ¹³C NMR (In part) δ 137.7, 133.8, 128.5, 127.0, 124.9, 114.4, 76.5, 64.4, 14.7. MS (ES +ve) m/z 203 (M+H+, 100%). HRMS calcd for C12H14N2O 202.1106, found 202.1117. (E)-1-Ethoxymethyl-4-(2'-phenylethenyl)imidazole (12a) and (Z)-1-Ethoxymethyl-4-(2'-phenylethenyl) imidazole (12b). Using the general Stille coupling procedure described above for the synthesis of 3a and anhydrous DMF as reaction solvent, the title compounds 12a (68%, mp 96-98 °C) and 12b (12%) were obtained as cream solids after purification by column chromatography (40% ethyl acetate / hexane). 12a: ¹H NMR δ 7.59 (1H, d, J = 0.9 Hz), 7.51-7.47 (2H, m), 7.36-7.27 (3H, m), 7.25-7.19 (1H, m), 7.08 (1H, d, J = 0.9 Hz), 7.51-7.47 (2H, m), 7.36-7.27 (3H, m), 7.25-7.19 (1H, m), 7.08 (1H, d, J = 0.9 Hz), 7.51-7.47 (2H, m), 7.36-7.27 (3H, m), 7.25-7.19 (1H, m), 7.08 (1H, d, J = 0.9 Hz), 7.51-7.47 (2H, m), 7.36-7.27 (3H, m), 7.25-7.19 (1H, m), 7.08 (1H, d, J = 0.9 Hz), 7.51-7.47 (2H, m), 7.36-7.27 (3H, m), 7.25-7.19 (1H, m), 7.08 (1H, d, J = 0.9 Hz), 7.51-7.47 (2H, m), 7.36-7.27 (3H, m), 7.25-7.19 (1H, m), 7.08 (1H, d, J = 0.9 Hz), 7.51-7.47 (2H, m), 7.36-7.27 (3H, m), 7.25-7.19 (1H, m), 7.08 (1H, d, J = 0.9 Hz), 7.51-7.47 (2H, m), 7.36-7.27 (3H, m), 7.25-7.19 (1H, m), 7.08 (1H, d, J = 0.9 Hz), 7.51-7.47 (2H, m), 7.51-7.57 (2H, m), 7.51-7 1.2 Hz), 6.99 (1H, d, J = 16.2 Hz), 5.26 (2H, s), 3.47 (2H, q, J = 6.9 Hz), 1.20 (3H, t, J = 6.9 Hz). ¹³C NMR δ 141.5, 137.7, 137.6, 128.6, 127.7, 127.2, 126.3, 120.0, 116.7, 76.5, 64.4, 14.7. MS (ES +ve) m/z 229 (M+H+, 100%). HRMS calcd for C14H16N2O 228.1263, found 228.1272. 12b: ¹H NMR (In part) d 7.45-7.42 (2H, m), 7.35-7.19 (4H, m), 6.69 (1H, d, J = 1.2 Hz), 6.68-6.49 (1H, m), 5.11 (2H, s), 3.36 (2H, q, J = 6.9 Hz), 1.34 (3H, t, *J* = 6.9 Hz). ¹³C NMR δ 139.4, 138.3, 136.3, 128.7, 128.4, 128.3, 127.1, 123.6, 117.4, 76.1, 64.2, 14.6. MS (ES +ve) m/z 229 (M+H⁺, 100%). HRMS calcd for C₁₄H₁₆N₂O 228.1263, found 228.1252. (4S)-(E)-2,2-Diethyl-4-(2'-iodoethenyl)-1,3-dioxolane and (4S)-(Z)-2,2-diethyl-4-(2'-iodoethenyl)-1,3dioxolane (13). To a solution of (45)-2,2-diethyl-4-(2'-tributylstannylethenyl)-1,3-dioxolane²² (2.67 g, 6.10 mmol, E: Z = 81: 19) in anhydrous CH₂Cl₂ (10 mL) under N₂ was added iodine (1.47 g, 5.79 mmol) in CH₂Cl₂ dropwise and the mixture stirred for 30 min. The solution was then washed with a sat. aqueous solution of Na₂S₂O₃ (10 mL) and the organic extract was concentrated. The residual oil was taken into ether (10 mL) and stirred vigorously with a sat. aqueous solution of KF (10 mL) for 1 h. Precipitated Bu₃SnF was removed by filtration, the layers were separated and the organic extract dried and concentrated. Purification by bulb-to-bulb distillation (110 °C/10 mmHg) gave the title vinyliodides as a pale oil (0.9 g, 52%, ratio E : Z = 9: 1). (E)-Isomer: ¹H NMR δ 6.59-6.52 (2H, m), 4.51-4.44 (1H, m), 4.11 (1H, dd, J = 6.3, 8.1 Hz), 3.60 (1H, t, J = 7.8 Hz), 1.71-1.60 (4H, m), 0.96-0.88 (6H, m). MS (ES +ve) m/z 253 (M-Et⁺, 100%), 179 (16%). HRMS calcd for $C_7H_{10}O_{21}$ (M-Et⁺) 252.9726, found 252.9727. (Z)-Isomer: ¹H NMR δ 6.48-6.36 (2H, m), 4.82-4.74 (1H, m), 4.25 (1H, dd, J = 6.3, 7.8 Hz), 4.20 (1H, dd, J = 6.6, 8.4 Hz), 1.71-1.60 (4H, m), 0.96-0.88 (6H, m). (3'S)-(E)-4-[3',4'-O-(3'-Pentylidene)-3',4'-dihydroxybut-1'-enyl]-1-ethoxymethylimidazole (14a) and (3'S)-(Z)-4-[3',4'-O-(3'-Pentylidene)-3',4'-dihydroxybut-1'-enyl]-1-ethoxymethyl imidazole (14b). A solution of imidazole 9 (180 mg, 0.62 mmol), vinyliodide 13 (207 mg, 0.73 mmol, E: Z = 9: 1) and PdCl₂(PPh₃)₂ (26 mg, 3.1 x 10⁻⁵ mol) in anhydrous DMF (2 mL) in a thick walled tube was flushed with argon, sealed and stirred at 80 °C for 8 h. The reaction was then cooled to rt, diluted with CH₂Cl₂ (10 mL), washed with a half sat. aqueous solution of NaCl (2 x 5 mL), dried and concentrated to leave a yellow oil. Purification by column chromatography (40% ethyl acetate / hexane) gave the coupled imidazoles 14a (90 mg, 60%) and 14b (20 mg, 13%), plus a third unidentified coupled product (10 mg) all as tan oils. 14a: ¹H NMR δ 7.54 (1H, d, J = 1.2 Hz), 6.95 (1H, d, J = 1.6 Hz), 6.58 (1H, d, J = 15.6 Hz), 6.31 (1H, dd, J = 8.0, 16.0 Hz), 5.24 (2H, s), 4.67-4.61 (1H, m), 4.14 (1H, dd, J = 6.0, 8.0 Hz), 3.65 (1H, t, J = 8.0 Hz), 3.44 (2H, q, J = 7.2 Hz), 1.73-1.65 (4H, m), 1.18 (3H, t, J = 7.2 Hz), 0.944, 0.935 (2 x 3H, 2 x t, J = 7.2 Hz). ¹³C NMR δ 140.0, 137.3, 125.2, 124.4, 116.6, 112.9, 77.3, 76.0, 69.8, 64.1, 29.8, 29.6, 14.4, 7.9, 7.8. MS (ES +ve) *m/z* 281 (M+H⁺, 100%). HRMS calcd for C₁₅H₂₄O₃N₂ 280.1787, found 280.1793. 14b: ¹H NMR δ 7.55 (1H, d, J = 1.2 Hz), 6.41 (1H, d, J = 11.6 Hz), 5.64 (1H, dd, J = 8.0, 11.6 Hz), 5.62-5.52 (1H, m), 5.26 (2H, s), 4.35 (1H, dd, J = 6.0, 8.0 Hz), 3.60 (1H, t, J = 8.0 Hz), 3.45 (2H, q, J = 10.8 Hz), 1.74-1.67 (4H, m), 1.19 (3H, t, J = 7.2 Hz), 0.953, 0.951 (2 x 3H, 2 x t, J = 7.2 Hz).

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