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Palladium Catalysed Coupling of Imidazoles to Alkynyl and Vinyl Substrates

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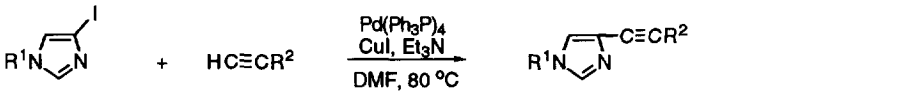
Abstract: Methods for preparing 4-substituted imidazoles from the palladium(0) catalysed couplings of *N*-protected 4-haloimidazoles with alkynes or alkynyl- and vinyltrialkyltin derivatives or from the coupling reactions of 4-trimethylstannylimidazole **9** with aryl and vinyliodides and bromides under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

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 azothioprine[4] 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 lithium[11] 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 reaction[14] 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



1a: R^1 = Ts
1b: R^1 = $PhSO_2$
1c: R^1 = $EtOCH_2$
1d: R^1 = Tr

2a; R^2 = Ph
2b; R^2 = $CH_2OTBDMS$
2c; R^2 = $(CH_2)_2OTBDMS$

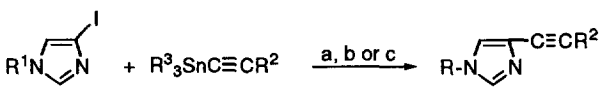
3a; R^1 = Ts, R^2 = Ph
3b; R^1 = $PhSO_2$, R^2 = $CH_2OTBDMS$
3c; R^1 = $PhSO_2$, R^2 = $(CH_2)_2OTBDMS$
3d; R^1 = $EtOCH_2$, R^2 = Ph
3e; R^1 = Tr, R^2 = Ph
3f; R^1 = Ts, R^2 = $(CH_2)_4CH_3$

Table 1. Palladium catalysed alkyne coupling to imidazoles 1a-d.

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



1a-c

4a; R^2 = Ph, R^3 = Bu
4b; R^2 = $CH_2OTBDMS$, R^3 = Me
4c; R^2 = $(CH_2)_2OTBDMS$, R^3 = Me
4d; R_2 = $(CH_2)_4CH_3$, R^3 = Me

3a-f

a: $Pd_2(dba)_3$, $AsPh_3$, CuI, THF, reflux, b: $Pd_2(dba)_3$, $AsPh_3$, CuI, DMF, 80 °C,c: $Pd(Ph_3P)_4$,THF, reflux

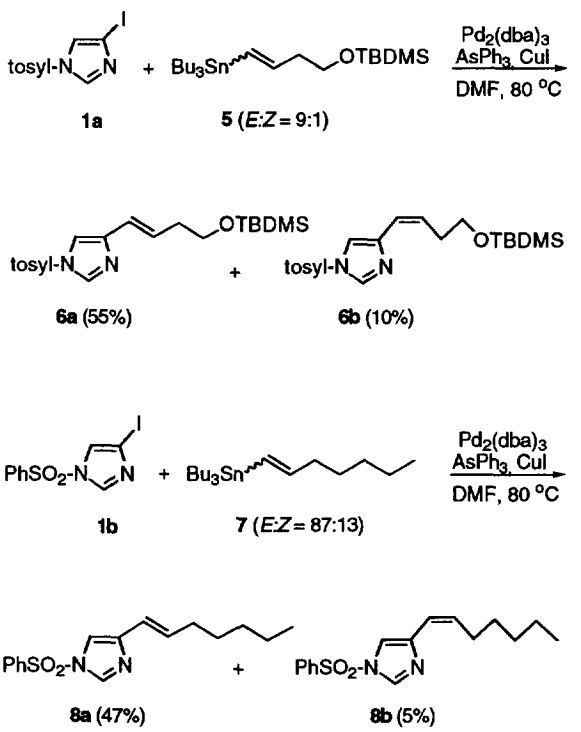
Table 2. Stille coupling of alkynylstannanes to imidazoles 1a-c.

Imidazole	Stannane	R'	R"	Conditions*	Product	Yield
1a	**4a**	Bu	Ph	a	**3a**	85%
1b	**4b**	Me	$CH_2OTBDMS$	b	**3b**	50%
1b	**4c**	Me	$(CH_2)_2OTBDMS$	b	**3c**	47%
1c	**4a**	Bu	Ph	c	**3d**	69%
1a	**4d**	Me	$(CH_2)_4CH_3$	b	**3f**	53%

* a: 5 mol % $Pd_2(dba)_3$, 10 mol % $AsPh_3$, 10 mol % CuI, THF, reflux. b: 5 mol % $Pd_2(dba)_3$, 10 mol % $AsPh_3$, 10 mol % CuI, DMF, 80 °C. c: $Pd(Ph_3P)_4$, THF, reflux.

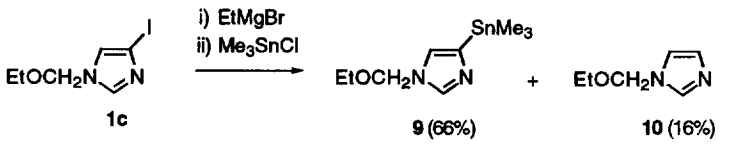
Stille cross-coupling also allowed for the successful introduction of vinyl moieties which were previously unobtainable under Heck coupling conditions. Reaction of **1a** with vinylstannane **5** (*E* : *Z* = 9 : 1) using the $Pd_2(dba)_3/AsPh_3/CuI$ catalyst system[19] resulted in both *E* and *Z* coupled 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 $Pd(Ph_3P)_4$) gave poorer yields of **7** and **8**.

Scheme 3

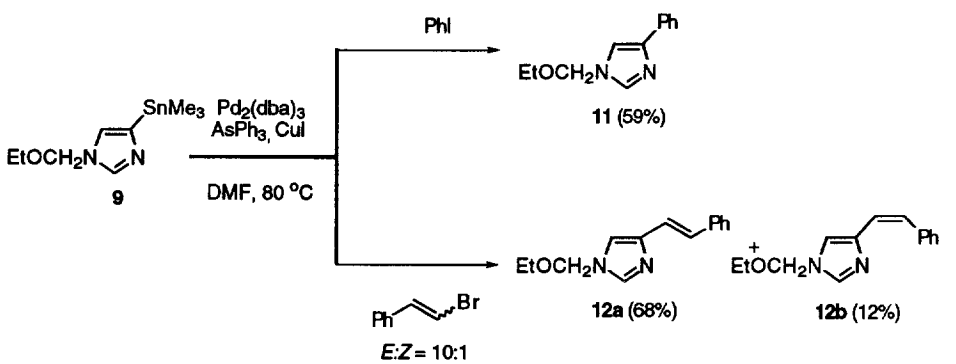


As an alternative to using *N*-protected iodoimidazoles, 4-trimethylstannylimidazole **9** was prepared and was found to successfully undergo cross-coupling to aryl and vinyliodides and bromides under Stille conditions. Treatment of **1c** with ethylmagnesium bromide in anhydrous dichloromethane[12] 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 $Pd_2(dba)_3/AsPh_3/CuI$ 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).

Scheme 4

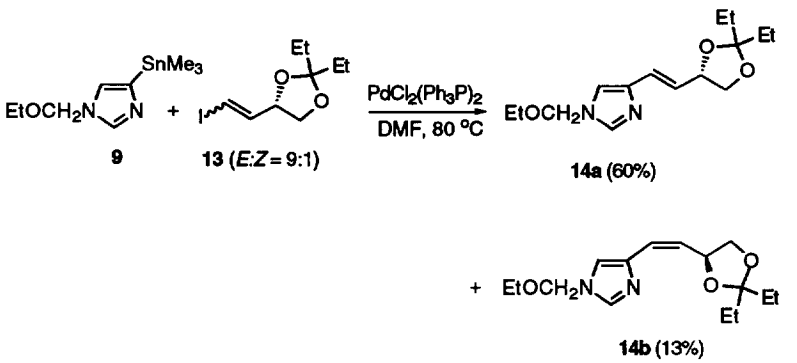


Scheme 5



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 $PdCl_2(Ph_3P)_2$ gave **14a** and **14b** in 60% and 13% yields respectively, plus a third unidentified product (Scheme 6).

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 ^{1}H NMR and ^{13}C NMR were run in $CDCl_3$ solution. All organic extracts were dried over $MgSO_4$. 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 N_2 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%). ^{1}H 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). ^{13}C 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). ^{1}H 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). ^{13}C NMR δ 81.5, 69.2, 61.7, 25.6, 22.8, 18.3, -5.3. MS (CI+ve) *m/z* 170 (M-CH_3^+, 4%), 128 (M-^{t}Bu, 58%), 110 (12%), 98 (83%). IR (neat) 3313, 2120, 1472, 1256, 1115 cm^{-1}. HRMS calcd for $C_9H_{17}OSi$ (M-CH_3^+) 169.1049, found 169.1047.

1-Benzenesulfonyl-4-iodoimidazole (1b). To a solution of 4(5)-iodoimidazole[21] (3.0 g, 15.5 mmol) and benzenesulfonyl chloride (2.74 g, 15.5 mmol) in anhydrous THF (40 mL) under N_2 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. ^{1}H 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). ^{13}C 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 ($PhSO_2^+$, 22%). IR (nujol) 3140, 1175, 1143, 1072, 920 cm^{-1}. HRMS calcd for $C_9H_7N_2O_2I$ 333.9273, found 333.9268. Anal. calcd for $C_9H_7N_2O_2SI$: 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), Et_3N (0.58 g, 5.8 mmol), 10 mol % CuI (11 mg, 5.79 x 10^{-5} mol) and 5 mol % $Pd(Ph_3P)_4$ (33 mg, 2.89 x 10^{-5} mol) in anhydrous DMF (5 mL) was heated at 80 °C under N_2 for 3 h. The mixture was cooled, diluted with ether (25 mL) and washed with H_2O (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.

^{1}H 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). ^{13}C 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 $C_{18}H_{14}N_2O_2S$ 322.0781, found 322.0776. Anal. calcd for $C_{18}H_{14}N_2O_2S$: 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). ^{1}H 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). ^{13}C 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. ^{1}H 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). ^{13}C 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). ^{1}H 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). ^{13}C 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 ($C_{12}H_{11}N_2^+$, 10%), 59 ($EtOCH_2^+$, 20%), 42 (42%). HRMS calcd for $C_{14}H_{14}N_2O$ 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. ^{1}H 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). ^{13}C 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 (CPh_3^+,

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 N_2 was added *n*-BuLi in hexanes (5.88 mmol) and the reaction stirred for 30 min at -78 °C. A 1M solution of Me_3SnCl 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 H_2O (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 (^{119}Sn, H) = 60.3 Hz, ^2J (^{117}Sn, H) = 57.6 Hz), 0.09 (6H, s). MS (ES +ve) *m/z* 373* ($M+K^+$, 8%), 165* (Me_3Sn^+, 100%).

* ^{120}Sn 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 (^{119}Sn, H) = 60.3 Hz, ^2J (^{117}Sn, 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 % $Pd_2(dba)_3$ (40 mg, 4.37 x 10^{-5} mol), 10 mol % $AsPh_3$ (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 N_2 was heated to reflux for 7 h. The mixture was then cooled to rt and poured into H_2O (10 mL). The aqueous solution was extracted with CH_2Cl_2 (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 % $Pd(Ph_3P)_4$, 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). ^{13}C 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 N_2 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:** ^{1}H 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:** ^{1}H 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'-(*t*-butyldimethylsilyloxy)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 % $Pd_2(dba)_3$ (39 mg, 4.3 x 10^{-5} mol), 10 mol % $AsPh_3$ (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 N_2 and sealed in a thick walled tube under N_2. The solution was then stirred at 80 °C for 3 h. The mixture was diluted with ether (30 mL) and washed with H_2O (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:** ^{1}H 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). ^{13}C 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 $C_{19}H_{27}N_2O_3SSi$ ($M-CH_3$) 391.1512, found 391.1490. **6b:** ^{1}H 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). ^{13}C 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:** ^{1}H 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* = 15.9 Hz), 2.19-2.12 (2H, m), 1.45-1.26 (6H, m), 0.87 (3H, t, *J* = 6.9 Hz). ^{13}C 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:** ^{1}H 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). ^{13}C 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 $C_{16}H_{20}N_2O_2S$ 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 N_2 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:** ^{1}H 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, ^2J (^{117}Sn, H) = 54.6 Hz, ^2J (^{119}Sn, H) = 57 Hz). ^{13}C 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 Hz, *J* (^{119}Sn, C) = 366.0 Hz). MS (ES +ve) *m/z* 291* ($M+H^+$, 100%). HRMS calcd for $C_9H_{18}N_2O^{120}Sn$ 290.0440, found 290.0438 (* ^{120}Sn isotope peak). **10:** ^{1}H 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). ^{13}C 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). ^{1}H 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). ^{13}C 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 $C_{12}H_{14}N_2O$ 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:** ^{1}H 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* = 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). ^{13}C 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 $C_{14}H_{16}N_2O$ 228.1263, found 228.1272. **12b:** ^{1}H 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). ^{13}C 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 $C_{14}H_{16}N_2O$ 228.1263, found 228.1252.

(4*S*)-(*E*)-2,2-Diethyl-4-(2'-iodoethenyl)-1,3-dioxolane and (4*S*)-(*Z*)-2,2-diethyl-4-(2'-iodoethenyl)-1,3-dioxolane (13). To a solution of (4*S*)-2,2-diethyl-4-(2'-tributylstannylethenyl)-1,3-dioxolane[22] (2.67 g, 6.10 mmol, *E* : *Z* = 81 : 19) in anhydrous CH_2Cl_2 (10 mL) under N_2 was added iodine (1.47 g, 5.79 mmol) in CH_2Cl_2 dropwise and the mixture stirred for 30 min. The solution was then washed with a sat. aqueous solution of $Na_2S_2O_3$ (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 Bu_3SnF 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:** ^{1}H 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 $C_7H_{10}O_2I$ ($M-Et^+$) 252.9726, found 252.9727. **(*Z*)-Isomer:** ^{1}H 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 $PdCl_2(PPh_3)_2$ (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 CH_2Cl_2 (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:** ^{1}H 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). ^{13}C 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 $C_{15}H_{24}O_3N_2$ 280.1787, found 280.1793. **14b:** ^{1}H NMR δ 7.55 (1H, d, *J* = 1.2 Hz), 7.05 (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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