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Alternation of Chemoselective Control in Stille–Heck and Heck–Stille Reaction Sequences

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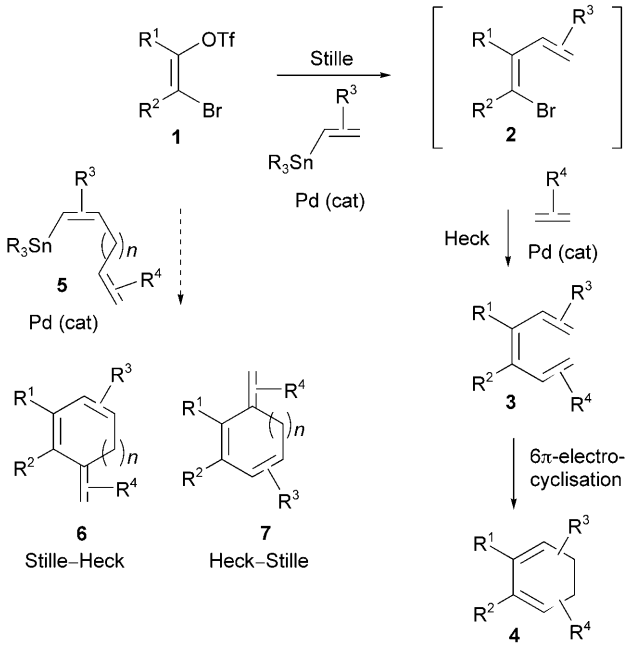
Abstract: Sequential and one-pot Stille–Heck and Heck–Stille reaction processes have been invoked to give divergent access to polycyclic ring systems. Both reaction conditions and substrate structure are important in determining the nature of the reaction products formed. The Heck–Stille reactions have involved a reversal of the usual Heck regioselectivity and both *cine*- and *ipso*-substitutions have been observed in the Stille reaction.

Keywords: Heck reaction; one-pot process; palladium coupling; Stille reaction

In recent years, de Meijere and co-workers have demonstrated the utility of 2-bromoalkenyl trifluoromethanesulfonates **1** as substrates in sequential palladium-mediated reaction processes.[1] For example, Stille–Heck reaction sequences can be conducted in one-pot, where **1** reacts with a vinylstannane selectively at the triflate to give **2**, then with a Heck acceptor at the bromide to give a 1,3,5-hexatriene **3** (Scheme 1). Conjugated hexatrienes **3** can then be converted to 6-membered rings **4** by 6π-electrocyclisation. In building on this methodology, we were interested in linking the organostannane of the Stille reaction to the alkene of the Heck reaction with a tether, as in **5**. Palladium-catalysed reaction of **1** with **5** can then give cyclic structures **6** and **7** directly *via* a Stille–Heck or Heck–Stille process, respectively. Unlike the one-pot, three-component process developed by de Meijere and co-workers, where the order of addition of the Stille and Heck substrates determines the regioselectivity of their incorporation into the product (temporal control), tethering the Stille and Heck substrates means that the relative rates of the two reactions will determine the nature and level



Scheme 1. Stille and Heck reaction sequences.

of regioselectivity of the annulated product (conditional control). In this preliminary report we describe how reaction conditions can be manipulated to achieve either outcome, Stille–Heck or Heck–Stille, in a highly selective manner.[2]

For the purpose of this study we prepared 2-bromo(and chloro)-3,4-dihydronaphthalenyl triflates **10** and **11** from the known 2-bromo- (and chloro-)tetralones **8**[3] and **9**,[4] respectively (Scheme 2). The 2-halotetralone was deprotonated with KHMDS in THF at −78 °C, then treated with *N*-2-pyridyltriflimide.[2] It was found that further addition of triflic anhydride to the reaction mixture after 2 h resulted in a higher yield of triflate than with either reagent by itself.[5]

Two Stille–Heck "acceptor" compounds **16** and **17** were prepared from readily available (**12**) and 2-

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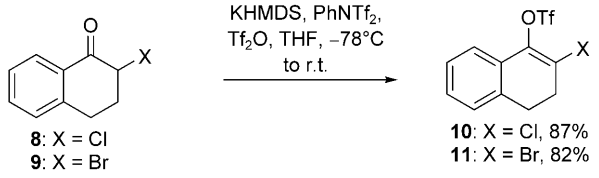


Scheme 2. Synthesis of 1,2-diactivated alkenes.

(buten-4-yl)-1,3-cyclahexadione (**13**), respectively.[2,6] Diones **12** and **13** were converted to bromoenones **14** and **15**, by treatment with $Ph_3P.Br_2$.[2,6] These were in turn converted to the alkenylstannanes **16** and **17** upon reaction with $Me_3SnCu{\cdot}LiCN$ in THF/HMPA.[2,7]

For a regioselective, one-pot Stille–Heck reaction we employed a combination of $Pd(dba)_2$, tri-(2-furyl)-phosphine (TFP) and copper(I) thiophene carboxylate (CuTC) co-catalyst with LiCl and K_2CO_3 as additives, the latter was added to ensure continual cycling of the catalyst in the intramolecular Heck reaction of intermediate **18** (Conditions A). When the reaction of **11** and **16** under Conditions A was heated at 55 °C for 4 h the Stille product **18** was the only product isolated (75%). However, heating at 85 °C for 3 h gave the annulated Stille–Heck product **19**, with *in situ* aromatisation, in reasonable yield (54% from **11**).

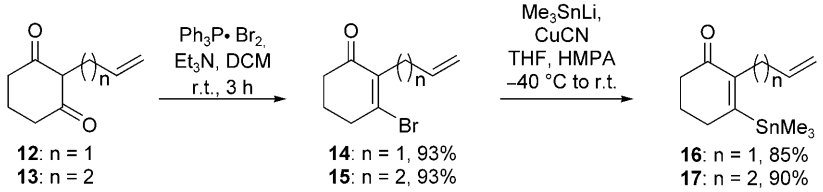
Also, when **11** and **17** were subjected to Conditions A at 85 °C for 4 h the Stille–Heck product **21a/b** (mixture of double bond isomers 1:2) was obtained in good yield (69%). Interestingly, even when the reaction was performed at a lower temperature, for a shorter time it was not possible to isolate **20** since **21a/b** had already begun to form, prior to complete consumption of the starting materials **11** and **17**. When the mixture of double bond isomers **21a/b** was allowed to stand in $CDCl_3$ for 48 h at room temperature quantitative conversion to **21b** was observed. Presumably, trace quantities of acid in the $CDCl_3$ catalyses this reaction.

We were also interested to see if we could access tetracycle **21** from 2-chloroalkenyl triflate **10** as well. We considered that the doubly vinylogous acid chloride in the Stille product **22** may be suitably reactive to also proceed through to tetracyle **21**, however, under standard Conditions A the reaction stopped at **22** (74%). Increasing the reaction temperature and time did not assist in converting **22** to **21** under these conditions. Nonetheless, we were able to convert **22** to **21** in a separate step using the more reactive catalyst $Pd(0)(t\text{-}Bu_3P)_2$ and Cs_2CO_3 in NMP at 90 °C for 7 h, giving **21a/b** in good yield (67%; Scheme 5).[2]

We next turned to see if the chemoselectivity of this process could be reversed, such that the Heck preceeds the Stille reaction (Heck–Stille reaction). By reacting **11** and **16** under typical Heck conditions, palladium tetrakistriphenylphosphine with dry NaOAc in 1,2-dichloroethane (DCE) at 80 °C (Conditions B), we were able to isolate the Heck product **23** in good yield (72%), with excellent regioselectivity. Interestingly, the regioselectivity of this reaction is the opposite to that expected for a Heck reaction involving an alkenyl triflate and terminal olefin in the absence of a bidendate ligand.[8] In a one-pot Heck–Stille process, Conditions B were again employed until completion of the Heck reaction, the DCE was then evaporated and LiCl, CuTC, additional palladium catalyst and NMP (solvent) were added (Conditions C), and the mixture further heated to give the unexpected spirocycle **24** in reasonable overall yield (51% from **11**). The same product was isolated in an 81% yield when the Stille reaction was performed directly on isolated **23** (Conditions D). Compound **24** appears to have resulted from unprecedented intramolecular *cine*-substitution of the stannane.[9] Remarkably, the Heck–Stille product, compound **24**, has resulted from two palladium-mediated processes with unusual regioselectivity.

When **11** and **17** were employed in a Heck reaction using Conditions B, again the product of unusual regioselectivity **25** (58%) was obtained. When the one-pot Heck–Stille conditions were employed (Conditions C) the major product isolated from the reaction mixture was **26**, albeit only in a modest yield (32%, from **11**). Notwithstanding the modest yield of **26** isolated from this reaction sequence, it was the only discernable product formed in this reaction.

A key difference in the reaction conditions that give rise to an initial Stille coupling (Conditions A, Scheme 3) as opposed to those that give an initial Heck reaction (Conditions B and C, Scheme 4) is most likely the use CuTC in the former, which activates the stannane to transmetalation. Presumably, in the absence of CuTC, where the Stille reaction is slower, the Heck reaction becomes a more competi-



Scheme 3. Synthesis of Stille–Heck acceptors.

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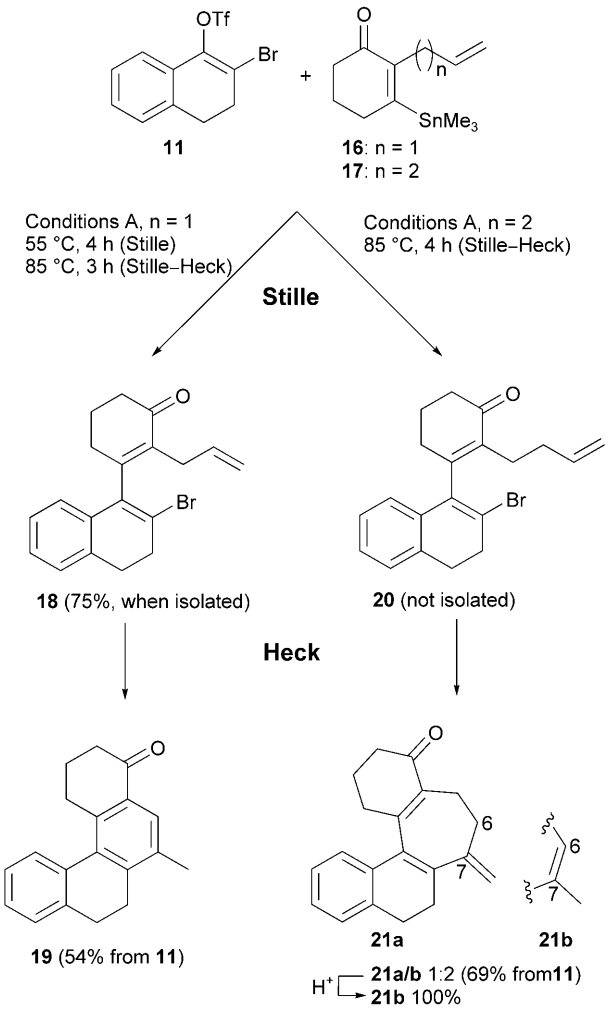
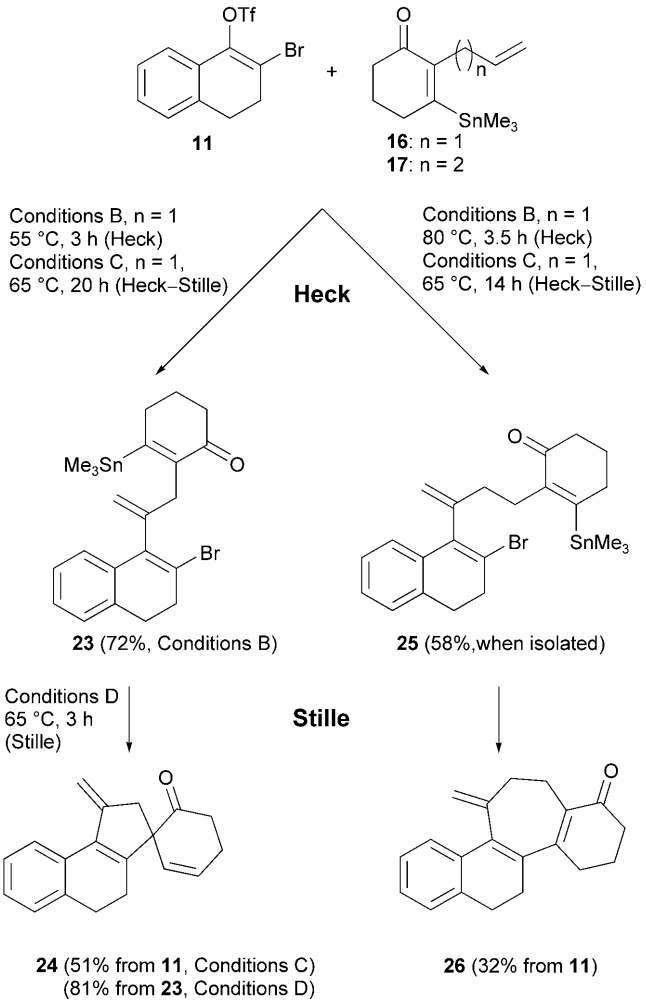


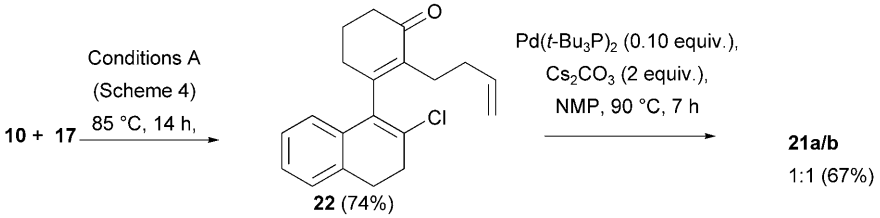
Scheme 4. Stille–Heck reaction sequences of **11**, **16** and **17**. *Conditions A:* $Pd(dba)_2$ (0.06 equiv.), TFP (0.12 equiv.), LiCl (5 equiv.), CuTC (0.10 equiv.), K_2CO_3 (4 equiv.), NMP.



Scheme 6. Heck–Stille reaction sequences. *Conditions B:* $Pd(PPh_3)_4$, (0.10 equiv.), NaOAc (2 equiv.), DCE. *Conditions C:* Reaction under conditions B, then remove DCE and add $Pd(dba)_2$ (0.05 equiv.), TFP (0.10 equiv.), LiCl (3 equiv.), CuTC (0.10 equiv.), NMP. *Conditions D:* $Pd(dba)_2$ (0.05 equiv.), TFP (0.10 equiv.), LiCl (3 equiv.), CuTC (0.10 equiv.), NMP.

tive pathway and in the case of Conditions B the dominating process.

A surprising feature of the Heck reactions was the observed regiochemistry, which is highly selective for the reverse orientation to that usually seen for Heck reactions involving simple terminal olefins and monodendate ligands (PAr_3).[8] Two tentative explanations are provided here for this unexpected regiochemistry (Scheme 7). In the standard Heck reaction of a terminal olefin, the regiochemistry is determined by the orientation of the two substituents on palladium prior to carbopalladation.[9,10] Usually the σ-bound substituent (from the alkenyltriflate or halide) sterically repels the substituent on the π-complexed olefin **27**. This arrangement leads to delivery of the σ-bound substituent to the terminal end of the olefin **28**, which



Scheme 5. Stille–Heck reaction sequence of **10** and **17**.

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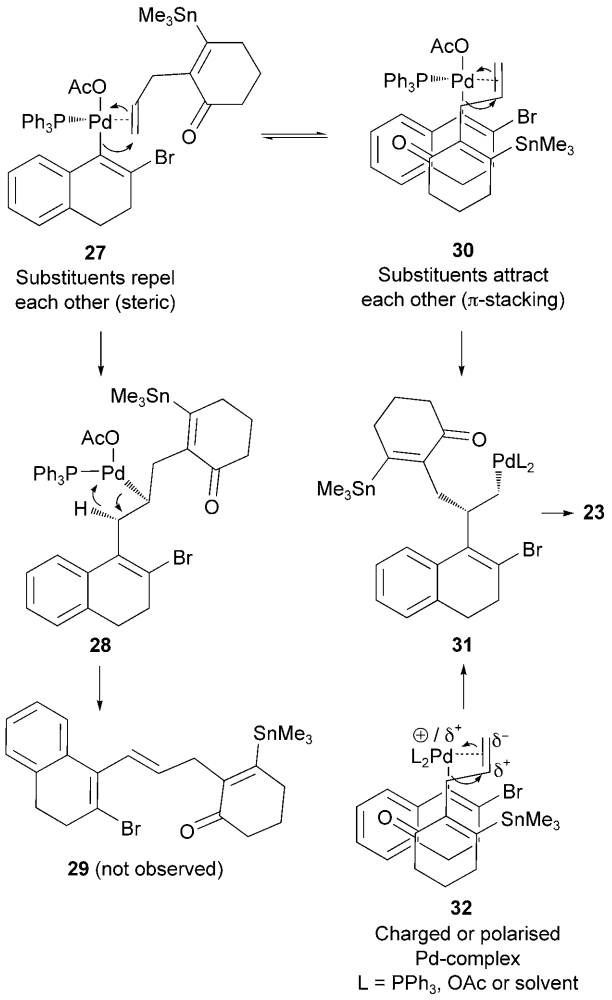
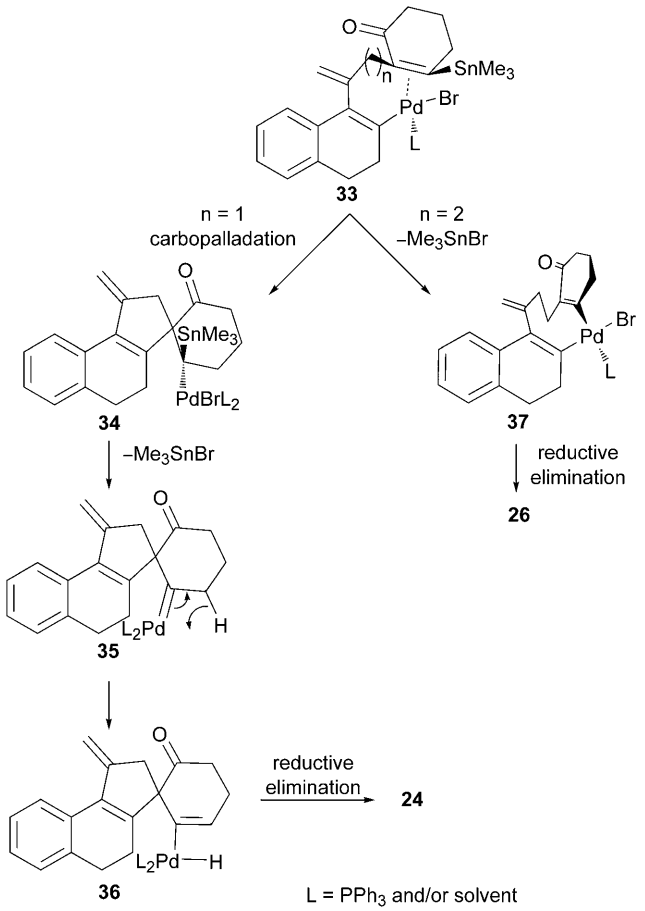


Scheme 7. Proposed mechanism for Heck regioselectivity.

gives a *trans*-vicinally substituted alkene **29** (unobserved regioisomer of **23**) upon β-hydride elmination. One possible explanation of the reversal of the regioselectivity seen in **23** and **25** is that a favourable, nonbonding interaction exists between the σ-bound group and the substituent on the π-complexed olefin, in the case of **30** this interaction may be a π-stacking interaction between the dihydronaphthyl group and the enone and/or a positive interaction between the bromide and the stannane. Subsequent carbopalladation gives complex **31**, which gives **23** upon β-hydride elimination. Alternatively, the reaction conditions and or the nature of the substrates used may lend themselves to the attainment of a charged or polarised palladium complex **32**, despite the fact that the usual reaction conditions required for the formation of such intermediates have not been employed.[8] Such complexes tend to undergo carbopalladation in a manner that directs the accumulating positive charge onto the most substituted carbon of the olefin, directing the palladium towards terminal end of the olefin, again giving **31** then **23**.

The same explanation(s) would apply to the homologous Heck product **25**.

The intramolecular Stille reaction of **23** also gave an unusual outcome in the *cine*-substituted product **24** (Scheme 6). Whereas the intramolecular Stille reaction of the homologous substrate **25** gave the usual, *ipso*-substituted product **26**. Based on previous mechanistic proposals for the *cine*- and *ipso*-Stille reactions, it is likely that the common σ,π-complexed intermediate **33** represent the branch point between these two reaction pathways (Scheme 8).[11] Presumably, intermediate **33** ($n=1$) prefers to undergo carbopalladation to give **34**, which then loses Me_3SnBr to give carbenoid **35**. Subsequent 1,3-hydride shift (**36**) and reductive elimination gives **24**.[1] Complex **33** ($n=2$), on the other hand, prefers to undergo transmetalation to give palladacycle **37** and reductive elimination to give **25**. This chemoselective difference in the fate of **33** ($n=1$) versus **33** ($n=2$) is difficult to explain but may arise from a better accommodation of the 90° angle in the square planar 8-membered palladacycle of **37** than in the seven-membered equivalent (not shown), where the additional methylene allows a reduction of strain in **37** and in the transition state leading to this structure from **33** ($n=2$). The CuTC present in the re-



Scheme 8. Proposed mechanism for Stille regioselectivity.

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action mixture is likely to facilitate one or both of these processes, most likely through interaction with **33** ($n=2$) and **34** to faciltate loss of Me_3SnBr.

The reaction processes described here offer new possibilities for accessing polycyclic ring systems in a manner that can afford significant scaffold diversity from a discrete set of substrates. In our ongoing studies in this area we will seek to better define the substrate and reaction condition requirements for the unusual regioselectivity observed in the Heck and Stille reaction processes performed in this work.

Experimental Section

General Remarks

Tetrahydrofuran (THF) was distilled from sodium wire and benzophenone (sodium benzophenone ketyl) and dichloroethane (DCE) from CaH_2 under $N_{2(g)}$. Petroleum spirit (PS, 40–60 °C fraction) was distilled prior to use. *N*-Methylpyrrolidinone (NMP), dichloromethane (DCM), ethyl acetate (EtOAc), and diethyl ether (Et_2O) were used as commercially supplied (anhydrous/reagent grade). Thin layer chromatography (TLC) was performed with 0.25 mm silica gel 60F plates with 254 nm fluorescent indicator (Merck) and plates were visualised with UV light and vanillin or anisaldehyde dip and heating. Products were isolated using silica gel 60, 230–400 mesh (Merck) or alumina (neutral, Brockmann grades I or II). Nuclear magnetic resonance (NMR) spectra were recorded at 300.1 MHz for ^{1}H and 75.5 MHz for ^{13}C and referenced to residual protonated solvent. ^{13}C NMR spectra assignments were made on the basis of a *J*-modulated spin echo (J-MOD) experiment. Infrared spectra (IR) were obtained on an FT-IR spectrometer. Low resolution mass spectrometry (LR-MS) and high resolution mass spectrometry (HR-MS) were performed using an EI, ESI or APCI ion source. Melting points were determined with an electrothermal melting point apparatus and are uncorrected.

Degas procedure: A typical degassing procedure is as follows: The solvent was stirred vigorously and a high vacuum [<5 mbar] was applied for 0.1 h. The flask was then backfilled with $N_{2(g)}$, and the procedure repeated ($\times 3$) in order to remove all dissolved gases. For volatile solvents (e.g., DCE) the procedure was performed at -40 °C.

2-Allyl-3-(2-bromo-3,4-dihydronaphthalen-1-yl)cyclohex-2-enone (18)

Conditions A: Lithium chloride (106 mg, 2.50 mmol) and sodium carbonate (Na_2CO_3, 160 mg, 1.50 mmol) were flame dried carefully in a round-bottomed flask under vacuum and cooled under $N_{2(g)}$. NMP (4 mL) and 2-bromoalkenyl triflate **11** (179 mg, 0.50 mmol) were added the suspension degassed (General Remarks). $Pd(dba)_2$ (28.4 mg, 0.05 mmol), TFP (23.2 mg, 0.10 mmol), stannane **16** (200 mg, 0.67 mmol) and CuTC (9.5 mg, 0.05 mmol) were added and the degas procedure repeated. The reaction mixture was heated to 55 °C for 4 h, after this time **11** was completely consumed (TLC). The reaction mixture was cooled and poured onto a plug of alumina (neutral, Brockmann grade I) and washed through with Et_2O (20 mL). The organics were then extracted with H_2O (2×20 mL), the combined aqueous washings extracted with Et_2O (20 mL), the combined organics washed with H_2O (2×20 mL), dried over $MgSO_4$ and the volatiles removed under reduced pressure. Column chromatography of the resulting brown crude on silica gel with EtOAc-PS (1:24 then 7:93) delivered bromide **18** as a pale yellow gum; yield: 129 mg (0.375 mmol, 75%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.17$ (m_c, 3H), 6.89 (d, $J=7.5$ Hz, 1H), 5.71 (m_c, 1H), 4.86–4.81 (m, 2H), 3.02–2.97 (m, 2H), 2.92–2.78 (m, 2H), 2.70–2.61 (m, 1H), 2.56 (t, $J=6.6$ Hz, 2H), 2.45–2.35 (m, 1H), 2.19–2.08 (tt, $J=6.6$, 6.9 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta=195.2$ (C=O), 155.5 (C), 137.4 (C), 136.1 (C), 135.2 (CH), 134.0 (C), 132.4 (C), 127.9 ($2\times$ signals, CH), 127.0 (CH), 124.4 (CH), 121.4 (C), 115.7 (CH_2), 38.3 (CH_2), 34.3 (CH_2), 31.9 (CH_2), 30.5 (CH_2), 29.3 (CH_2), 22.7 (CH_2); HR-MS (+ESI): $m/z=365.0509$ (^{79}Br), 367.0498 (^{81}Br); calcd. for $[C_{19}H_{19}BrNaO]^+$ (M+Na$^+$) (^{79}Br): 365.0512, (^{81}Br): 367.0491.

6-Methyl-2,3,7,8-tetrahydrobenzo[*c*]phenanthren-4(1*H*)-one (19)

This reaction was performed as described above for the coupling of **11** and **16** to give **18** (Conditions A) except the reaction mixture was heated to 85 °C for 3 h. The reaction vessel was cooled and the contents poured onto a plug of alumina (neutral, Brockmann grade I), and washed through with Et_2O (20 mL). The organics were then washed with H_2O (2×20 mL), the aqueous layer extracted with Et_2O (20 mL), the combined organics washed with H_2O (2×10 mL), dried over $MgSO_4$ and the volatiles removed under reduced pressure. Column chromatography of the crude on silica gel with EtOAc-PS (3:47 then 7:93) delivered tetracycle **19** as a pale yellow solid; yield: 43 mg (0.164 mmol, 54%); mp 128–129 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.97$ (s, 1H), 7.63 (d, $J=6.6$ Hz, 1H), 7.31–7.38 (m, 3H), 3.30 (t, $J=5.7$ Hz, 2H), 2.81 (s, 4H), 2.75 (t, $J=6.0$ Hz, 2H), 2.44 (s, 3H), 2.07 (tt, $J=6.0$, 5.7 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta=$ 198.9 (C=O), 144.4 (C), 139.7 (C), 138.8 (C), 134.7 (C), 134.0 (C), 133.3 (C), 131.7 (C), 128.7 (CH), 128.0 (CH), 127.4 (CH), 127.2 (CH), 125.8 (CH), 39.1 (CH_2), 30.6 (CH_2), 29.1 (CH_2), 26.8 (CH_2), 24.1 (CH_2), 19.8 (CH_3); HR-MS (EI): $m/z=262.1352$, calcd. for $[C_{19}H_{18}O]^+$ (M$^+$): 262.1352.

7-Methyl-5,6,9,11,12,13-hexahydrobenzo[6,7]cyclohepta[1,2-*a*]naphthalen-10-one (21b)

Substrates **11** and **17** were coupled as described for **19** (Conditions A, **17** replaces **16**) except that the reaction was heated to 85 °C for 4 h. After this time the reaction mixture was cooled and diluted with EtOAc (20 mL), washed with brine (10 mL), H_2O (3×10 mL), dried over $MgSO_4$ and the volatiles removed under reduced pressure. Column chromatography of the crude product on silica gel with EtOAc-PS (1:24) delivered tetracycles **21a/b** as a yellow gum; yield: 69%. This product was isolated as a mixture of the terminal olefin (direct Heck product) **21a** and the double-bond internalised species **21b** (1:1), which converted entirely to the thermodynamically more stable olefin **21b** upon standing in $CDCl_3$ for 48 h. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.23$–7.14

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(m, 3H), 7.00 (d, $J=7.2$ Hz, 1H), 5.73 (dt, $J=7.8$, 1.2 Hz, 1H), 3.52 (ddd, $J=12.6$, 7.5, 1.2 Hz, 1H), 2.88 (m, 1H), 2.82 (m, 1H), 2.82–2.71 (m, 2H), 2.62–2.53 (m, 1H), 2.41–2.30 (m, 1H), 2.28–2.21 (m, 1H), 2.14–2.08 (m, 1H), 2.05–2.02 (m, 1H), 1.93 (d, $J=1.2$ Hz, 3H), 1.97–1.88 (m, 1H), 1.66 (dd, $J=12.6$, 6.6 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta=$ 197.7 (C=O), 149.1 (C), 142.3 (C), 137.7 (C), 136.5 (C), 134.7 (C), 134.1 (C), 133.7 (C), 128.4 (CH), 127.9 (CH), 127.1 (CH), 126.8 (CH), 126.3 (CH), 38.2 (CH_2), 29.8 (CH_2), 28.2 (CH_2), 26.2 (CH_2), 23.87 (CH_2), 23.6 (CH_2), 22.0 (CH_3); LR-MS (+ESI); $m/z=277.3$ (100%, $M+H^+$), 259.3 (13%, $M+H^+-H_2O$); HR-MS (ESI): $m/z=299.1407$, calcd. $[C_{20}H_{20}NaO]^+$ ($M+Na^+$): 299.1412.

2-[2-(2-Bromo-3,4-dihydronapthylen-1-yl)allyl]-3-(trimethylstannyl)cyclohex-2-enone (23)

Conditions B: A Schlenk tube with NaOAc (33 mg, 0.40 mmol) was flame dried under vacuum, cooled under $N_{2(g)}$ and 2-bromoalkenyl triflate **11** (72.0 mg, 0.20 mmol) then stannane **16** (32 mg, 0.12 mmol) were added. Dichloroethane (DCE, 2 mL) was added by syringe, the reaction mixture cooled to −40 °C and degassed (see General Remarks), then $Pd(PPh_3)_4$ (32 mg, 0.02 mmol) added and the degas procedure repeated. The reaction mixture was heated at 80 °C for 1 h, after which time another portion of stannane **16** (32 mg, 0.12 mmol) was added, heating continued for 1 h, then another portion of stannane **16** (32 mg, 0.12 mmol) added and heating continued for 1 h. After this time the solution was cooled to room temperature, diluted with Et_2O (30 mL) and washed with H_2O (3×10 mL). The organics were combined, dried with $MgSO_4$ and the volatiles removed under reduced pressure. Chromatography of the crude on silica gel with EtOAc-PS (3.5:96.5) delivered **23** as a yellow solid; yield: 73 mg (0.144 mmol, 72%); mp 110–112 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.51$ (d, $J=7.8$ Hz, 1H), 7.23 (t, $J=7.8$ Hz, 1H), 7.16 (t, $J=7.2$ Hz, 1H), 7.10 (d, $J=7.2$ Hz), 5.20 (s, 1H), 4.98 (s, 1H), 3.3–3.1 (s_{br}, 2H), 2.90–2.82 (s_{br}, 4H), 2.53 (t, $J=5.4$ Hz, 2H), 2.38 (t, $J=$ 6.6 Hz, 2H), 1.90 (m_c, 2H), 0.29 (s, $SnMe_3$, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta=194.4$ (C=O), 169.3 (C), 145.5 (C), 144.9 (C), 139.5 (C), 134.2 [2× non-equivalent (C) signals], 127.2 (CH), 127.2 (CH), 126.8 (CH), 126.2 (CH), 121.3 (C), 116.6 (CH_2), 38.7 (CH_2), 38.4 (CH_2), 35.1 (CH_2), 34.1 (CH_2), 29.6 (CH_2), 24.1 (CH_2); $SnMe_3$ not visible in the spectrum (need lower than 0 ppm); HR-MS (+APCI): $m/z=$ 507.0341, calcd. for $[C_{22}H_{28}BrOSn]^+$ ($M+H^+$): 507.0340.

1′-Methylene-1′,3′,4′,5′-tetrahydrospiro[cyclohex-2-ene-1′,2′-cyclopenta[*a*]naphthalene]-6-one (24)

Conditions D: LiCl (6 mg, 0.14 mmol) was flame-dried in a Schlenk flask under vacuum and back-filled with $N_{2(g)}$, then NMP (1 mL) was added and the solution degassed (see General Remarks). To this solution bromostannane **23** (24.0 mg, 0.047 mmol), $Pd(dba)_2$ (2.7 mg, 0.005 mmol), TFP (2.3 mg, 0.01 mmol) and CuTC (1.0 mg, 0.005 mmol) were added and the degas procedure repeated. The reaction mixture was stirred at 65 °C for 3 h, during which time **23** was completely consumed by TLC. The reaction mixture was cooled then poured on a plug of alumina (Brockmann grade II), washed through with Et_2O (10 mL), the organics washed with H_2O (3×10 mL), the combined aqueous washings extracted with Et_2O (10 mL), the combined organics washed with brine (10 mL), dried with $MgSO_4$ and the volatiles removed under reduced pressure. Chromatography of the crude on silica gel chromatography with DCM-EtOAc-PS (50:3:47) delivered tetracycle **24** as a brown gum; yield: 10.1 mg (0.038 mmol, 81%).

Conditions C: As per the procedure for **23** above however prior to work-up the solvent (DCE) was carefully removed under vacuum and replaced with NMP (1.5 mL) which was degassed (see General Remarks). $Pd(dba)_2$ (2.7 mg, 0.005 mmol), TFP (18.5 mg, 0.08 mmol) and CuTC (3.8 mg, 0.02 mmol) were added and the degas procedure repeated. The reaction mixture was stirred at 65 °C for 20 h. After this time the reaction mixture was cooled and passed through a plug of alumina (neutral, Brockmann grade I), the organics were flushed through with Et_2O (30 mL) and washed with H_2O (3×30 mL). The combined aqueous washings were extracted with Et_2O (10 mL), the combined organics washed with H_2O (10 mL), dried over $MgSO_4$ and the solvent removed under reduced pressure. Planar chromatography of the crude on silica gel with DCM-EtOAc-PS (50:3:47) delivered tetracycle **24** as a brown gum; yield: 26.8 mg (0.102 mmol, 51% from 2-bromoalkenyl triflate **11**). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.62$ (d, $J=7.2$ Hz, 1H), 7.14 (m_c, 3H), 5.94–5.88 (m_c, 1H), 5.61 (d, $J=8.1$ Hz, 1H), 5.36 (s, 1H), 4.95 (s, 1H), 3.13 (d, $J=15.9$ Hz, 1H), 2.90–2.74 (m, 2H), 2.72–2.64 (m, 2H), 2.58–2.45 (m, 3H), 2.22 (t, $J=7.5$ Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta=211.0$ (C=O), 150.4 (C), 147.8 (C), 137.2 (C), 136.7 (C), 132.7 (CH), 131.6 (C), 127.8 (CH), 127.1 (CH), 127.1 (CH), 126.3 (CH), 124.2 (CH), 103.2 (CH_2), 60.7 (C), 45.1 (CH_2), 38.4 (CH_2), 29.2 (CH_2), 26.1 (CH_2), 22.8 (CH_2); LR-MS (+ESI): $m/z=$ 263.4, ($M+H^+$); HR-MS (+ESI): $m/z=263.1426$, calcd. for $[C_{19}H_{19}O]^+$ ($M+H^+$): 263.1436.

2-[3-(2-Bromo-3,4-dihydronapthylen-1-yl)but-3-enyl]-3-(trimethylstannyl)cyclohex-2-enone (25)

Subtrates **11** and **17** were coupled as described for compound **23** above (Conditions B) except that the reaction was heated to 80 °C for 3.5 h. Planar chromatography of the crude reaction mixture on silica gel with EtOAc-PS (1:9) delivered stannane **25** as a yellow oil; yield: 58%. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.28$ (m_c, 1H), 7.20 (m_c, 2H), 7.15 (m_c, 1H), 5.47 (d, $J=1.2$ Hz, 1H), 5.07 (d, $J=1.2$ Hz, 1H), 2.90 (s_{br}, 4H), 2.51 (t, $J=5.7$ Hz, 2H), 2.51 (br m, 2H), 2.41 (t, $J=6.6$ Hz, 2H), 2.27 (br m, 2H), 2.17–2.02 (dt, $J=6.6$, 5.7 Hz, 2H), 0.26 (s, $SnMe_3$, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta=196.5$ (C=O), 166.6 (C), 147.6 (C), 146.7 (C), 139.2 (C), 138.3 (C), 134.03 (C), 127.4 (CH), 127.2 (CH), 126.7 (CH), 125.2 (CH), 121.5 (C), 116.1 (CH_2), 38.8 (CH_2), 36.3 (CH_2), 34.9 (CH_2), 33.6 (CH_2), 32.4 (CH_2), 29.5 (CH_2), 24.1 (CH_2), −8.4 $Sn(CH_3)$; HR-MS (EI): $m/z=543.0297$, calculated $[C_{23}H_{29}BrNaOSn]^+$ ($M+Na^+$): 543.0316.

11-Methylene-2,34,5,6,11,12,13-octahydrobenzo[3,4]-cyclohepta[1,2-*a*]naphthalene-1-one (26)

Subtrates **11** and **17** were coupled as described for compound **24** above (Conditions C, **17** replaces **16**) except that the reaction was heated at 65 °C for 14 h. Planar chromatog-

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raphy of the crude on silica gel with DCM-EtOAc-PS (50:3:47) delivered tetracycle **26** as a pale yellow oil which became a white solid upon standing; yield: 32% (from 2-bromoalkenyl triflate **11**):mp 84–86 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.45$ (m_c, 1H), 7.18 (m_c, 3H), 5.14 (d, $J = 1.5$ Hz, 1H), 4.73 (d, $J = 1.5$ Hz, 1H), 2.87 (t, $J = 7.5$ Hz, 2H), 2.87 (t, $J = 6.9$ Hz, 2H), 2.45 (m_c, 8H), 2.02 (m_c, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 198.1$ (C=O), 158.9 (C), 145.0 (C), 138.2 (C), 136.0 (C), 135.1 (C), 133.8 (C), 128.9 (C), 127.6 (CH), 127.5 (CH), 126.6 (CH), 126.1 (CH), 114.1 (CH_2), 45.5 (CH_2), 38.0 (CH_2), 28.5 (CH_2), 28.15 (CH_2), 24.9 (CH_2), 23.0 (CH_2), 22.1 (CH_2); LR-MS (+APCI): $m/z = 277.0$; HR-MS (+ESI): $m/z = 299.1414$, calcd. for $[C_{20}H_{20}NaO]^+$ ($M+H^+$): 299.1406.

Supporting Information

Detailed experimental procedures for all other compounds and spectral data are provided as Supporting Information.

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