Short Communication

Regioselective Control in Pd(0)-Catalyzed Allylations of 3-Stannylallyl Alcohol Derivatives

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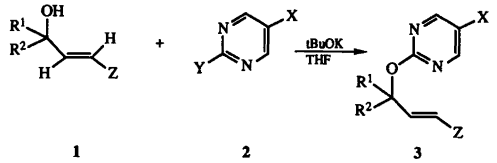
Palladium-catalyzed rearrangements of allyl derivatives is a useful method for directed alkylation.[1,2] The rearrangement approach may be complementary to direct alkylation using π-allylpalladium complexes.[1,3] We recently reported a study on Pd(0)- and Pd(II)-catalysis in rearrangements of 2-propenyloxypyrimidines which shows that the Claisen 3,3-rearrangement is effected by Pd(II)-catalysis whereas Pd(0)-catalysis, which involves a π-allylpalladium complex, gives rise to a 1,3- and/or a 3,3-rearrangement depending on reaction conditions and the substitution pattern in the allyl ligand.[4] The *N*-allyl product initially formed in the Pd(0)-catalyzed reaction may undergo a second allylic rearrangement with re-allylation of the same nitrogen. In the equilibrium set up, the thermodynamically favoured product has the less substituted allyl terminus attached to the nitrogen of the ring.[4]

The Pd(II)-catalyzed rearrangement is a Claisen 3,3-rearrangement (*vide supra*) and therefore regiospecific in the allylic moiety. Unfortunately this rearrangement does not work with highly substituted allylic systems.[2b,4] On the other hand, the more 'reactive' Pd(0)-catalyzed rearrangement is not regiospecific (*vide supra*). It should, however, be possible to make it regioselective for α-alkylation if the allyl ligand were to carry an α-directing substituent on its γ-carbon which is readily removable once the rearrangement is complete. It has been found that a trimethylsilyl group can be used to direct nucleophilic attack on π-allylpalladium complexes onto the other allyl terminus, the directing effect being attributed to both steric and electronic factors.[5] A similar regio-directing effect has been reported for α-substituted-γ-trimethylsilylallyl carbonates where the carbon nucleophile will attack the α-carbon in the π-allyl ligand.[6] The strong directing effect of the silyl group was also found to be true in the Pd(0)-catalyzed rearrangement of the 2-α-pentyl-γ-trimethylsilylallyl 2-pyrimidinyl ether **3a** which resulted in the selective formation of the desired 1-α-pentyl derivative **4a** (Scheme 2).[4] Protolytic substitution of the silyl group, however, was difficult to effect without hydrolytic cleavage of the allyl group (*vide infra*), and we therefore turned to more reactive stannyl derivatives (**3b–3d**).

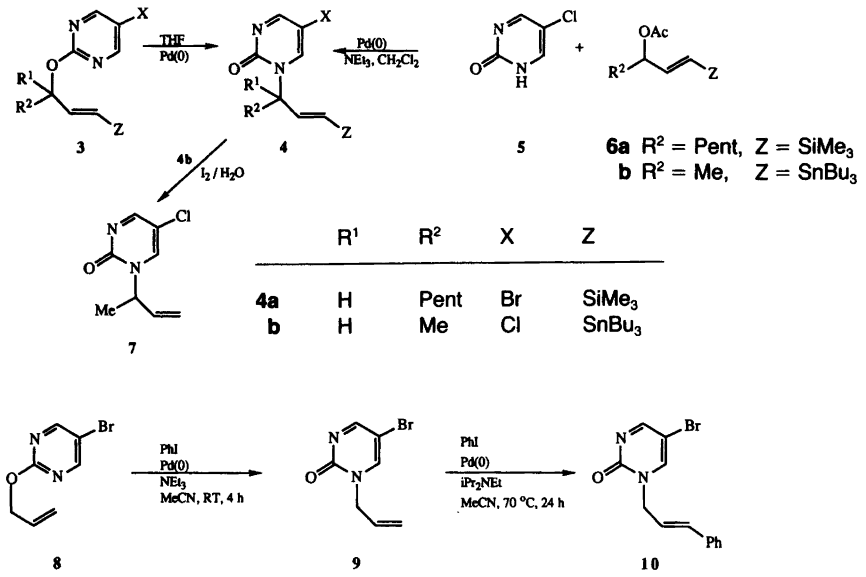
The γ-stannylated allylic alcohols **1** (R^1 = H, Me; R^2 = H, Me) to be used as substrates for the preparation of the 2-propenyloxypyrimidines **3** were prepared from the corresponding propargylic alcohols by the addition of tributyltin hydride with azoisobutyronitrile (AIBN) as the radical initiator.[7] The primary and secondary allylic alcohols with potassium *tert*-butoxide as the base gave the propenyl ethers in ca. 70 % yield from either the 2-chloro- or the 2-sulfonyl-pyrimidine **2** (Scheme 1). The tertiary alcohol **1** (R^1 = R^2 = Me) failed to react with the chloropyrimidine but furnished the 2-propenyloxypyrimidine **3d** in 27 % yield with the more reactive 2-sulfonylpyrimidine.

The γ-silyl (**3a**) or γ-stannyl (**3b**) derivatives were unaffected by Pd(II)-catalysts, but the rearrangement proceeded readily in THF under the influence of Pd(0)-catalysis. The product resulted from attack by the nitrogen nucleophile on the π-allylpalladium complex in the α-position despite steric interference from the α-alkyl group. Only the parent pyrimidinone **5** was isolated from the attempted rearrangement of the α,α-dimethyl derivative **3d**.



Product	R^1	R^2	X	Y	Z	Yield (%)
3a	H	Pent	Br	Cl	$SiMe_3$	67
b	H	Me	Cl	Cl	$SnBu_3$	68
b	H	Me	Cl	SO_2Me	$SnBu_3$	73
b	H	Me	Cl	SO_2CH_2Cl	$SnBu_3$	61
c	H	H	Br	Cl	$SnBu_3$	72
d	Me	Me	Cl	SO_2Me	$SnBu_3$	27

Scheme 1.



Scheme 2.

Direct allylation of 5-chloro-2(1*H*)-pyrimidinone (**5**) with the allylic acetates **6** and Pd(0)-catalysis also gave the product **4** with the same regioselectivity, *viz.* attachment of the α-carbon in the allyl ligand to the annular nitrogen, but the yields were inferior to the yields in the rearrangement reactions.

Having established the regiochemical possibilities in the Pd(0)-catalyzed allylic reactions it remained to remove the metallic substituent from the γ-carbon. Hydrogen iodide or a mixture of iodine and water has been used to remove the trimethylsilyl group by protolysis on sp^2-hybridized carbon.[8] The silyl group in **4a**, however, was resistant to these conditions. With acids such as *p*-toluenesulfonic acid[9] or hydrochloric acid[10] in catalytic amounts the allyl group was cleaved off to yield the parent pyrimidinone **5**. This problem was overcome in the case of the stannyl derivative **4b** which was protolyzed to form **7** in almost quantitative yield using iodine in water.

Both 2-allyloxypyrimidines (**3**) and *N*-allylpyrimidinones (**4**) are potential substrates for the Heck vinylation reaction.[11] Reaction conditions for the Heck reaction were set up to effect a reaction between the allyl 2-pyrimidinyl ether **8** and iodobenzene with tetrakis(triisopropyl phosphite) palladium(0) as the catalyst and triethylamine as the base. Competition between the Heck reaction and allylic rearrangement was expected. The reaction was run at ambient temperature in acetonitrile, and consumption of the substrate was complete after 4 h. The Heck reaction did not proceed to any significant extent, the faster reaction being the allylic rearrangement whereby the *N*-allyl derivative **9** was formed. However, when the *N*-allyl derivative **9** was heated together with iodobenzene, ethyldiisopropylamine and tetrakis(triisopropyl phosphite)palladium(0) as the catalyst, vinylation of iodobenzene took place, the yield of the Heck product being 35 %. The yield in this reaction was boosted to 77 % when the ligand for the Pd(0)-catalyst was changed to tri-(*o*-tolyl)phosphine. Arylation occurred exclusively at the terminal position in both cases.

Experimental

The ^{1}H NMR spectra were recorded at 300 MHz with either a Varian XL-300 (manual) or at 200 MHz with a Varian Gemini 200 instrument. The ^{13}C NMR spectra were recorded at 75 or 50 MHz on the same instruments. The mass spectra under electron impact conditions were recorded at 70 eV ionizing potential and ammonia was used for chemical ionization (CI); the spectra are presented as *m/z* (% rel. int.).

Compounds available by literature methods: (*E*)-5-Bromo-2-(1-pentyl-3-trimethylsilyl-2-propenyloxy)pyrimidine (**3a**);[4] (*E*)-bromo-1-(1-pentyl-3-trimethylsilyl-2-propenyl)-2(1*H*)-pyrimidinone (**4a**);[4] (*E*)-1-pentyl-3-trimethylsilyl-2-propenyl acetate (**6a**).[4]

Preparation of substituted 5-halo-2-(3-tributylstannyl-2-propenyloxy)pyrimidines (**3**). A solution of the allylic alcohol **1**[7] (2.28 mmol) in dry THF (5 ml) was added dropwise with stirring to potassium *tert*-butoxide (0.279 g, 2.49 mmol) in dry THF (5 ml) under N_2 at 0 °C. The mixture was stirred at 0 °C for 15 min before a solution of the pyrimidine **2** (2.08 mmol) in dry THF (5 ml) was added dropwise at 0 °C. The resulting solution was stirred overnight at ambient temperature, diluted with diethyl ether and washed with water (3×). The dried ($MgSO_4$) solution was evaporated and the residue was subjected to flash chromatography on silica gel using hexane–EtOAc 6:1 (v/v).

(E)-*5-Chloro-2-(1-methyl-3-tributylstannyl-2-propenyloxy)-pyrimidine* (**3b**). Compound **3b** was obtained from (*E*)-4-tributylstannyl-3-buten-2-ol[7a] and 5-chloro-2-methylsulfo-

nylpyrimidine.[12] Oily substance; yield 73%. Anal. $C_{20}H_{35}ClN_2OSn$: C, H. ^{1}H NMR ($CDCl_3$): δ 0.76–0.99 / 1.24–1.51 (Bu_3Sn and Me, m), 5.50–5.54 (CHO, m), 6.08 (CH=, dd, *J* 5, 19 Hz), 6.25 (CH=, d, *J* 19 Hz), 8.42 (H-4,6, s). ^{13}C NMR ($CDCl_3$): δ 9.3 / 13.5 / 27.2 / 28.9 (Bu_3Sn), 20.1 (Me), 76.5 (CHO), 123.4 (C-5), 129.6 (CH=), 146.8 (CH=), 157.2 (C-4,6), 163.0 (C-2).

Compound **3b** was also obtained from (*E*)-4-tributylstannyl-3-buten-2-ol and 5-chloro-2-chloromethylsulfonylpyrimidine[12] by the same procedure.

(E)-*5-Bromo-2-(3-tributylstannyl-2-propenyloxy)pyrimidine* (**3c**). Compound **3c** was obtained from (*E*)-3-tributylstannyl-2-propen-1-ol[7b] and 5-bromo-2-chloropyrimidine.[13] Oily substance; yield 72%. Anal. $C_{19}H_{33}BrN_2OSn$: C, H. ^{1}H NMR ($CDCl_3$): δ 0.82–0.99 / 1.23–1.54 (Bu_3Sn, m), 4.88 (CH_2, d, *J* 5 Hz), 6.14–6.24 (CH=, m), 6.38 (SnCH=, d, *J* 19 Hz), 8.52 (H-4,6, s). ^{13}C NMR ($CDCl_3$): δ 9.3 / 13.5 / 27.1 / 28.9 (Bu_3Sn), 71.0 (CH_2), 111.6 (C-5), 132.8 (CH=), 141.2 (CH=), 159.4 (C-4,6), 163.5 (C-2).

(E)-*5-Chloro-2-(1,1-dimethyl-3-tributylstannyl-2-propenyloxy)pyrimidine* (**3d**). Compound **3d** was obtained from (*E*)-4-tributylstannyl-2-methyl-3-buten-2-ol[7c] and 5-chloro-2-methylsulfonylpyrimidine.[12] Oily substance; yield 27%. Anal: $C_{21}H_{37}ClN_2OSn$: C, H. ^{1}H NMR ($CDCl_3$): δ 0.84–0.95 / 1.21–1.53 (Bu_3Sn, m), 1.67 (2 × Me, s), 6.14 (CH=, d, *J* 19.5 Hz), 6.28 (CH=, d, *J* 19.5 Hz), 8.36 (H-4,6, s). ^{13}C NMR ($CDCl_3$): δ 9.3 / 13.5 / 27.0 / 28.9 (Bu_3Sn), 26.9 (2 × Me), 83.4 (CO), 123.3 (C-5), 125.9 (CH=), 151.7 (CH=), 156.9 (C-4,6), 162.7 (C-2).

(E)-*5-Chloro-1-(1-methyl-3-tributylstanyl-2-propenyl)-2(1H)-pyrimidinone* (**4b**). Compound **4b** was prepared by Pd(0)-catalyzed rearrangement of (*E*)-5-chloro-2-(1-methyl-3-tributylstannyl-2-propenyloxy)pyrimidine (procedure A) in 44% yield, and also by Pd(0)-catalyzed reaction of (*E*)-1-methyl-4-tributylstannyl-2-propenyl acetate and 5-chloro-2(1*H*)-pyrimidinone (procedure B) in 19% yield.

Procedure A. (*E*)-5-Chloro-2-(1-methyl-3-tributylstannyl-2-propenyloxy)pyrimidine (0.9 g, 1.97 mmol), palladium(II) acetate (0.03 g, 1.34×10^{-4} mol) and triisopropyl phosphite (0.204 g, 9.81×10^{-4} mol) were dissolved in dry THF (20 ml) under N_2. The mixture was stirred at ambient temperature for 24 h, and the solvent was removed at reduced pressure. The residue was subjected to flash chromatography on silica gel eluting with EtOAc.

Procedure B. Triethylamine (0.39 g, 3.86 mmol) in dry dichloromethane (10 ml) was added to a suspension of 5-chloro-2(1*H*)-pyrimidinone (0.5 g, 3.86 mmol) in dry dichloromethane (10 ml) and the mixture was stirred under N_2 at ambient temperature for 15 min before (*E*)-1-methyl-3-tributylstannyl-2-propenyl acetate (0.679 g, 3.86 mmol), palladium(II) acetate (0.043 g, 0.192 mmol) and triisopropyl phosphite (0.321 g, 1.54 mmol) were added. The mixture was stirred overnight, diluted with dichloromethane and washed with saturated, aqueous sodium chloride. The dried ($MgSO_4$) solution was evaporated and the product was purified by flash chromatography on silica gel eluting with EtOAc. Oily substance. ^{1}H NMR ($CDCl_3$): δ 0.83–1.00 / 1.23–1.53 (Bu_3Sn and Me, m), 5.46–5.51 (CHN, m), 6.05 (CH=, dd, *J* 4.5, 19 Hz), 6.41 (CH=, d, *J* 19 Hz), 7.67 (H-6, d, *J* 3.3 Hz), 8.50 (H-4, d, *J* 3.3 Hz). ^{13}C NMR ($CDCl_3$): δ 9.2 / 13.2 / 26.7 / 28.6 (Bu_3Sn), 17.7 (Me), 56.5 (CHN), 110.7 (C-5), 134.2 (CH=), 141.9 (CH=), 144.0 (C-6), 153.9 (C-2), 163.7 (C-4). MS(CI-NH_3): 475/473 (0.1/0.1, *M*+1), 226 (9), 225 (100), 187 (32), 186 (8), 185 (80), 148 (8), 131 (12).

(E)-*1-Methyl-3-tributylstannyl-2-propenyl acetate* (**6b**). Acetic anhydride (1.36 g, 13.3 mmol) in dry dichloromethane (20 ml) was added dropwise to a solution of (*E*)-4-tributylstannyl-3-buten-2-ol (4 g, 11.08 mmol) and 4-dimethylaminopyridine (1.69 g, 13.85 mmol) in dry dichloromethane (20 ml) under N_2 at 0°C. The mixture was stirred for 3 h at 0°C, diluted with dichloromethane and shaken with aqueous $CuSO_4$ (4 ×), $NaHCO_3$ (2 ×) and with saturated aqueous sodium chloride (1 ×). The dried ($MgSO_4$) solution was evaporated and the residual material was subjected to flash chromatography on silica gel eluting with EtOAc–hexane 1:10 (v/v). Oily substance; yield 4.180 g (82%). ^{1}H NMR ($CDCl_3$): δ 0.84–0.99 / 1.27–1.55 (Bu_3Sn, m), 2.02 (Me, d, *J* 5 Hz), 2.05 (MeCO, s), 5.29–5.33 (CH, m), 5.96 (CH=, dd, *J* 5, 20 Hz), 6.17 (SnCH=, d, *J* 20 Hz). ^{13}C NMR ($CDCl_3$): δ 9.2 / 13.4 / 27.0 / 28.8 (Bu_3Sn), 19.7 (Me), 21.1 (Me), 72.8 (CHO), 129.2 (CH=), 146.8 (CH=), 169.9 (C=O). MS (CI-NH_3): 405/403 (3.4/2.7, *M*+1), 347 (200), 345 (24), 308 (100), 307 (36), 306 (78), 305 (30), 304 (47).

5-Chloro-1-(1-methyl-2-propenyl)-2(1H)-pyrimidinone (**7**). (*E*)-5-Chloro-1-(1-methyl-3-tributylstannyl-2-propenyl)-2(1*H*)-pyrimidinone (0.144 g, 3.14×10^{-4} mol), I_2 (8 mg, 3.14×10^{-5} mol) and water (0.5 ml) were dissolved in benzene (7 ml). The solution was heated to 70°C and stirred overnight. The mixture was washed with aqueous sodium sulfite, dried ($MgSO_4$), and the solvent was removed at reduced pressure. The product was purified on a silica gel flash column using EtOAc for elution; yield 52 mg (90%). Anal. $C_8H_9ClN_2O$: C, H. ^{1}H NMR ($CDCl_3$): δ 1.49 (Me, d, *J* 7 Hz), 5.38–5.51 ($CH=CH_2$, m), 5.90–6.00 (NCH, m), 7.62 (H-6, d, *J* 3.3 Hz), 8.51 (H-4, d, *J* 3.3 Hz). ^{13}C NMR ($CDCl_3$): δ 18.2 (Me), 55.2 (CHN), 111.5 (C-5), 120.2 (CH_2=), 136.2 (C=), 142.6 (C-6), 155.2 (C-2), 165.0 (C-4).

1-Allyl-5-bromo-2(1H)-pyrimidinone (**9**). 2-Allyloxy-5-bromopyrimidine[4] (0.5 g, 2.33 mmol) and triethylamine (0.282 g, 2.79 mmol) were added to a solution of iodobenzene (0.474 g, 2.33 mmol), palladium(II) acetate (0.037 g, 0.16 mmol) and triisopropyl phosphite (0.19 g, 0.93 mmol) in dry MeCN (5 ml) under argon. The solution was stirred for 4 h at ambient temperature, the solvent evaporated off,

chloroform added and the solution washed with water (2 ×). The dried ($MgSO_4$) solution was evaporated, and the residue was subjected to flash chromatography on silica gel eluting with hexane–EtOAc 4:1 (v/v); yield 386 mg (77 %). The assigned structure was verified by comparison with an authentic sample.[4]

(E)-*5-Bromo-1-(3-phenyl-2-propenyl)-2(1H)-pyrimidinone* (**10**). 1-Allyl-5-bromo-2(1*H*)-pyrimidinone (114 mg, 5.3×10^{-4} mol) and diisopropylethylamine (82 mg, 6.36×10^{-4} mol) were added to a solution of iodobenzene (108 mg, 5.3×10^{-4} mol), palladium(II) acetate (8 mg, 3.71×10^{-5} mol) and tri(*o*-tolyl)phosphine (45 mg, 1.48×10^{-4} mmol) in dry MeCN (2 ml) under argon. The solution was refluxed for 24 h, the solvent evaporated off, chloroform added and the solution washed with water (2 ×). The dried ($MgSO_4$) solution was evaporated and the residue was subjected to flash chromatography on silica gel eluting with EtOAc; yield 118 mg (77 %). The structure of the product was verified by comparison with an authentic sample.[4]

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