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CROSS-COUPLING REACTION OF ALLYL BROMIDES WITH ORGANOTIN REAGENTS CATALYZED BY ZINC CHLORIDE

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Abstract: Myrcene and β-farnesene have been synthesized by the zinc chloride catalyzed coupling reaction of (2-methylene-3-butenyl)trimethyltin with prenyl bromide and geranyl bromide, respectively; vitamin K_1 was synthesized by a similar coupling reaction.

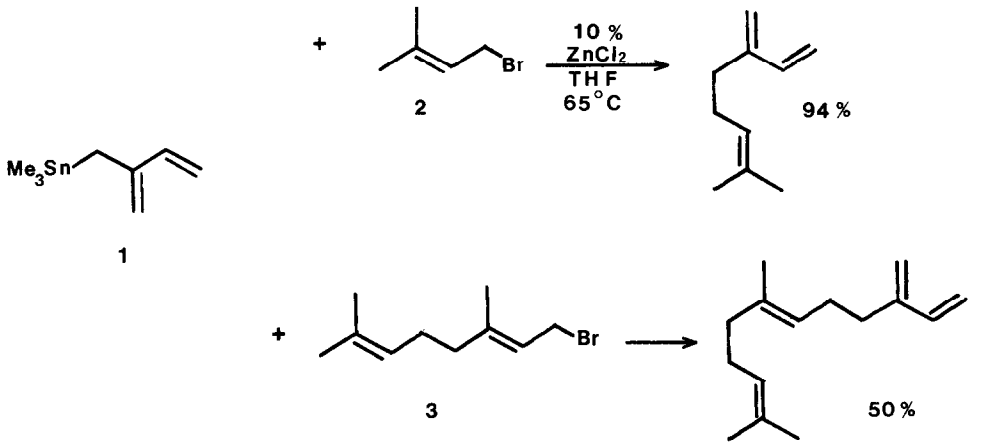
The palladium catalyzed cross-coupling reaction of allyl halides with allyltin reagents yields 1,5-dienes in which the predominate isomer is that resulting from coupling of the allyl bromide without allylic rearrangement, but with predominate allylic rearrangement in the allyltin partner.[1] Whereas minor rearrangement does occur in the allyl halide, no allylic transposition is observed when a Lewis acid catalyst, zinc chloride, is utilized in the coupling reactions with this partner. High yields of coupled product (~80%) could be realized either at 65°C or at ambient temperatures in THF.

We now have used this coupling reaction to advantage in the synthesis of myrcene and β-farnesene (Scheme 1) as well as in the synthesis of vitamin K_1 (Scheme 2). The key organotin reagent in the synthesis of both myrcene and β-farnesene was (2-methylene-3-butenyl)-trimethyltin (1),[2] which was prepared (70% yield after distillation) by the addition of trimethyltinlithium[3] to α-bromoisoprene.[4] Allylic rearrangement was not expected in the allyl bromide partners, and allylic transposition in the tin reagent is redundant.

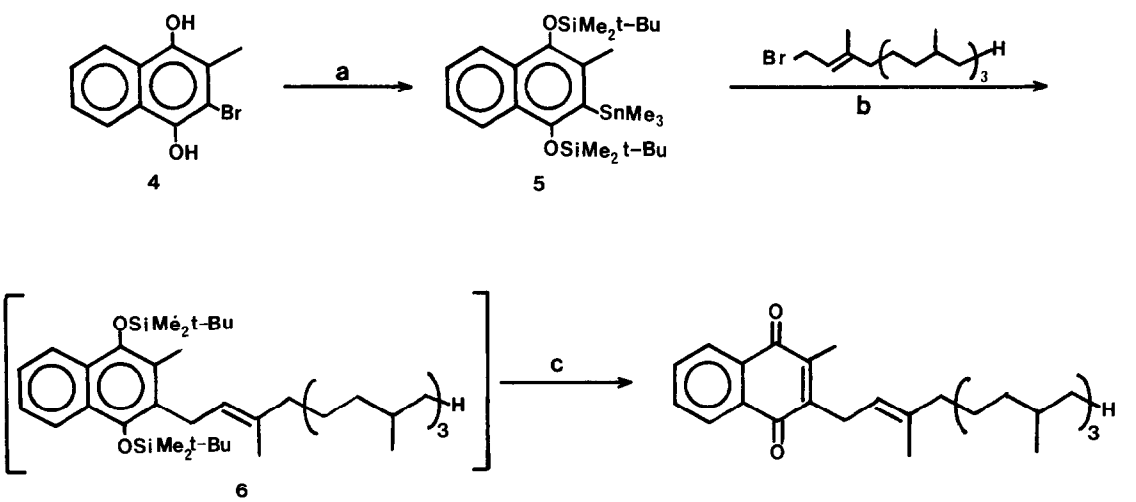
Thus, the cross-coupling reaction provided the desired products under the following conditions: Into a Schlenk tube were charged 2.2 mmol of prenyl bromide (2),[5] 3.2 mmol of 1 and 0.22 mmol of zinc chloride dissolved in 1 mL THF, in that order. The tube was stoppered and placed in an oil bath at 65°C to yield myrcene[6,7] in 94% yield. Similarly, β-farnesene[6,7] was obtained from 1 and geranyl bromide (3).[5]

The key intermediate in the synthesis of vitamin K_1 was the tin derivative (5). The precursor to 5, 3-bromo-2-methyl-4,4-bis(dimethyl-t-butylsilyl)-1,4-dihydroxyphthalene[8] was obtained by the reaction of the corresponding phenol[9] with t-butyldimethylsilyl chloride. This protected phenol (6.23 mmol) was converted to 5[10] by its reaction with t-butyllithium at -78°C in ether followed by the addition of trimethyltin chloride (6.23 mmol). The coupling reaction of 5 was carried out by allowing a solution of 2.2 mmol of 5 in 1 mL of ether to react with 2.2 mmol of phytyl bromide[11] at -78°C for 24 h by adding 60 mg of zinc chloride in 2 mL of ether. The crude reaction product in 28 mL of methylene chloride was oxidized by

Scheme 1



Scheme 2



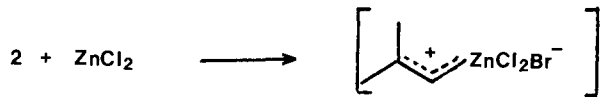
a. i. t-BuMe$_2$SiCl, imidazole, DMF (95%). ii. 2 t-BuLi. iii. Me$_3$SnCl (77% ii, iii).

b. 10% ZnCl$_2$, Et$_2$O.

c. Pyridiniumchlorochromate, CH$_2$Cl$_2$, 25° (40% b plus c).

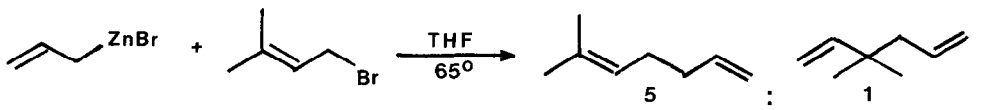
4.4 mmol of PCC. The crude vitamin K_1, was purified by column chromatography, and was identical (^1H and ^{13}C NMR) to an authentic sample.

Two possible mechanisms for the cross-coupling reaction catalyzed by zinc chloride involve the synthesis of an allyl zinc compound. First, the zinc chloride could react with the allylic halide to yield a carbocation which acts as an electrophile to cleave the carbon-tin bond and yield the cross-coupled product. Electrophilic cleavage of a carbon-tin bond is a well documented reaction for organotins.[12]



Eq 1

Second, the allyl tin reagent could react with zinc chloride to yield an allyl zinc reagent which would then couple with the allylic halide. This mechanism is entirely possible, since the reaction of allyl zinc bromide with 5 under the typical reaction conditions gave the 1,5-diene in good yield.



Eq 2

An allylic rearrangement product could be expected from the first reaction pathway (Eq. 1), if indeed an allylic cation, as depicted, were formed. The fact that 20% of the product of the reaction of allyl zinc bromide with prenyl bromide is the rearranged product (Eq. 2) suggests that the zinc choride catalyzed coupling reaction does not occur by this pathway, since allylic transposition of prenyl bromide is not observed in this type of coupling catalyzed by zinc bromide, for example in the synthesis of myrcene. Thus, the mechanism of the reaction is open to question.

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8. ^1H NMR ($CDCl_3$) δ 0.23 (s, 6 H), 0.36 (s, 6 H), 1.21 (s, 9 H), 1.22 (s, 9 H), 2.55 (s, 3 H), 7.48 (m, 2 H), 8.09 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ -3.05, -2.29, 18.79, 19.08, 26.26, 26.50, 114.72, 122.95, 123.71, 124.70, 125.05, 126.98, 127.50, 143.15, 143.38; mp

95.5-96.5°C. Anal. Calcd for $C_{23}H_{37}O_2Si_2Br$: C, 57.36; H, 7.74. Found: C, 57.59; H, 7.72.

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10. ^1H NMR ($CDCl_3$) δ 0.03 (s, 6 H), 0.21 (s, 6 H), 0.48 (s, 9 H), 1.16 (s, 9 H), 1.20 (s, 9 H), 2.48 (s, 3 H), 7.3 (m, 2 H), 8.05 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ -4.10, -2.93, 18.91, 20.31, 26.38, 27.08, 122.54, 123.24, 123.59, 124.93, 127.21, 128.32, 129.08, 129.25, 143.21, 150.86; mp 91-92°C. Anal. Calcd for $C_{26}H_{46}O_2Si_2Sn$: C, 55.22; H, 8.20. Found: C, 55.53; H, 8.32.
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