Regioselective Joining of Prenyl Units. A Simple Strategy for Geometry Control in Pd Catalyzed Allylic Alkylations

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Summary: Either E,E-3,9-dimethylundecadien-1,11-diol or its E,Z-isomer is selectively available via Pd catalyzed allylic alkylation as a function of alkylating agent and catalyst - an observation that establishes that reactions of vinyl epoxides and their related vinyl carbonates do not proceed through a common intermediate.

The recent emergence of an insect pheromone^{1,2} which can be viewed as arising by regioselective joining of two prenyl units to a C-1 unit induced us to develop such a coupling based upon a lynchpin strategy using neutral alkylations according to eq. 1.³ We



wish to record the unusual effects of leaving group on olefin geometry and of experimental parameters for mono- versus di-alkylation. These results also provide mechanistic insight into the reactions of vinyl carbonates⁴ as electrophiles in π -allylpalladium chemistry.

Exposure of bis(benzenesulfonyl)methane 1 and excess vinyl epoxide 2^5 to Pd(0) catalysts led cleanly to the monoalkylated products 5a and 6 with no dialkylation even



a) R = H, b) R = TMS, c) R = TBDMS

a) X = 0, b) X = 000₂

after prolonged reaction times. As expected, the E isomer dominated with some dependence on catalyst [4.2:1 with $(dba)_3Pd_2$ CHCl₃, dppe, THF, rt, 66%; 9.7:1 with $(Ph_3P)_4Pd$, dppp, THF, rt, 77%].

The high reactivity of the vinyl epoxide 2 towards the Pd(0) complexes led us to speculate that the failure of the second alkylation lay in the more sluggish proton transfer from the monoalkylated 5a to the reactive intermediate 7a. The self decomposition of the vinyl epoxide then prevented its being effectively captured. Believing that

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stabilizing the alkoxide in 7a would prolong the lifetime of the reactive intermediate led us to investigate alkylations with the vinyl carbonate 8, a synthetic equivalent of the epoxide. The latter was readily derived from the epoxide 2 using Pd(0) catalysts [2 atm CO_2 , 3 mol% Pd(OAc)_2, 22 mol% (iC_3H_7O)_3P, THF, rt, 85%].⁶ The reaction still refused to go beyond monoalkylation upon subjecting the bis-sulfone 1 to an excess of cyclic carbonate 8 in the presence of Pd(0) catalysts. Surprisingly, the major geometrical isomer was the 2olefin 6 [Pd(OAc)_2, (iC_3H_7O)_3P, THF, 70°, 78%, 1:1.2 E:Z]. Thus, addition of the vinylepoxide 2 to a pronucleophile leads to a preference for the E-olefin product but condensation with the carbonate 8 leads to a preference for the Z-isomer of the product.

The second alkylation dramatically demonstrates this phenomenon. The initial failures to effect the second alkylation apparently stemmed from the presence of a free hydroxyl group since the silylated monoalkylated products 5b or 5c smoothly participated in the second alkylation. For example, condensation of 5b with the vinyl carbonate 8 led to a 1:8 mixture of the E,E and E,Z isomers 3 and 9 in 58% yield (eq. 2). Use of the TBDMS ether of



a) R=H, b) R=TMS, c) R=TBDMS

5 (i.e. 5c) gave the E,Z isomer 9c exclusively in 85% yield! The reaction was conveniently performed in a single operation from the epoxide 2. A 0.5 M solution of the epoxide and catalyst derived from 2 mol% $Pd(OAc)_2$ and 15 mol% $(iC_3H_7O)_3P$ in THF was exposed to CO_2 at 2 atm at rt for 4 h. After release of the pressure, the bis-sulfone 5c and BSA were added and the reaction heated at 70° for 1.5 h. Standard work-up gave the product 9c.⁷

Alternatively, exposing 5a or 5b to the vinyl epoxide 2 in the presence of BSA and a Pd(0) catalyst gave the E,E-diene 3 as the major product after desilylation upon work-up. The formation of 3 was conveniently performed in a single operation from the bis-sulfone 1 if BSA is added after the first stage. Thus, a 1.1:1 mixture of the vinylepoxide 2 and bis-sulfone 1 in THF containing 5 mol% of $(dba)_3Pd_2$ · CHCl₃ and 22 mol% dppe was stirred 2 h at rt. BSA and a second portion (1.2 eq) of vinyl epoxide were added and the reaction mixture warmed to 70°. Work-up followed by recrystallization (ethyl acetate) gave the pure E,E-isomer 3,⁷ mp 126-8°, in 74% yield in addition to 17% of the E,Z isomer 9.

NMR spectroscopy clearly reveals the nature of the olefin geometry. ¹H decoupled 13 C nmr spectroscopy⁷ shows only 9 peaks for the product from the vinyl epoxide alkylation - a fact that indicates the symmetrical nature of the product. The appearance of the signals

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for the vinyl methyl groups in the 1 H (δ 1.68) and 13 C (δ 18.2) nmr spectra suggests the E,E geometry. The product from alkylation with the vinyl carbonate for the second step exhibits 15 peaks in the 13 C spectrum⁷ - a fact consistent with only the E,Z-isomer. The appearance of the signals for the vinyl methyl groups in the 1 H (δ 1.63 and 1.76) and 13 C (δ 18.5 and 25.5) nmr spectra supports this conclusion.

Why should the choice of leaving group affect the olefin geometry of the product in such a dramatic fashion? The data indicate that the syn complex 7a is the main product determining intermediate from the epoxide but that the anti complex 10b is the main product determining intermediate from the carbonate. Since all current data supports the notion



that the leaving group departs on the face of the π -allyl unit distal from palladium, 8 it appears unlikely this observation reflects a kinetic preference for the syn complex from the epoxide and the anti complex from the carbonate. Such di-substituted systems normally show a kinetic preference for the syn complex.⁹ Further, the selectivity depended upon the nucleophile - increasing dramatically by going from the anion derived from the simple bissulfone 1 to that derived from the alkylated bis-sulfone 5. This observation suggests that both species can form under the reaction conditions. The kinetic preference for 7 even from the carbonate is indicated by the larger amount of the E product with the sterically less hindered bis-sulfone 1. Slowing the alkylation rate by using the mono-alkyl pronucleophile 5 allows equilibration to the anti complex and production of the Z-product. Therefore, the results support the notion that in the case of the carbonate, an equilibration between the syn and anti forms can occur and that the latter is thermodynamically preferred. The source of the thermodynamic preference for 10b may derive from a destabilization of 7b due to an increased peri-like interaction between the methyl group and a sterically larger X group or to a stabilization of 10b due to a coordination between the negative X substitutent and palladium. In any event, the results clearly demonstrate that the same intermediate does not form from the vinyl epoxide 2 and the vinyl carbonate 8. A plausible explanation suggests that disengagement of carbon dioxide does not accompany ionization.

Thus, either the E.E- or E.Z-diene 3 or 9 is clearly available simply by choosing the appropriate electrophile. To complete the synthesis of the simple diol 4, bis-sulfone 3

was desulfonylated using buffered sodium amalgam¹⁰ [6% Na(Hg), Na₂HPO₄, CH₃OH, -10°] to provide the desired tail, tail joined product 4 in 95% yield. Thus, a simple two step protocol provides this useful building block.

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- Kamija, M.; Fukuzawa, S.; Sakai, S. *Chem.* Lert. **1985**, 199. **3** IR(KBr): 3433, 1656, 1447, 1334cm.⁻¹ ¹H NMR(400MHz, CDC1₃): *88.02* (dd, J-7.4, 1.3Hz, 4H), 7.69 (t, J-7.4Hz, 2H), 7.56 (T, J-7.4Hz, 4H), 5.72 (tq, J-6.5, 1.1Hz, 2H), 4.13 (d, J-6.0Hz, 4H), 3.19 (s, 4H), 1.68 (bs, 6H). ¹³C NMR(100MHz, CDC1₃): *6137.8*, 7. 134.6, 131.8, 131.0, 128.5, 93.7, 59.1, 39.3, 18.2, Anal. C,H,S. 9c IR(CDCl₃): 3612, 3540, 1658, 1602, 1584, 1474, 1448, 1397, 1333cm.¹ ¹H $\begin{array}{c} J=7.7 \text{Hz}, \ 1\text{H}), \ 4.16 \ (\text{d}, \ J=6.6 \text{Hz}, 2\text{H}), \ 4.11 \ (\text{d}, \ J=7.7 \text{Hz}, 2\text{H}), \ 3.30 \ (\text{s}, 2\text{H}), \ 3.18 \ (\text{s}, 2\text{H}), \ 1.76 \ (\text{bs}, 3\text{H}), \ 1.63 \ (\text{bs}, 3\text{H}), \ 1^{3}\text{C} \ \text{NMR}(100\text{MHz}, \ \text{CDC1}_{3}): \ \$137.7, \ 134.8, \ 133.5, \ 132.8, \ 132.1, \ 131.9, \ 131.3, \ 128.7, \ 93.9, \ 59.2, \ 58.8, \ 41.0, \ 31.7, \ 25.5, \ 18.5. \ \text{Anal}. \end{array}$ C,H,S. 4 IR(CDCl₃): 3614, 3442, 1667, 1443, 1384, 1353cm.⁻¹ ¹H NMR(400MHz, CDCl₃): *5*5.40 (t,

C11H17(M-H2O-OH): 149.1330, Found: 149.1318.

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