anti-Stereospecificity in the Palladium-catalysed Reactions of Alkenyl- or Aryl-metal Derivatives with Allylic Electrophiles†

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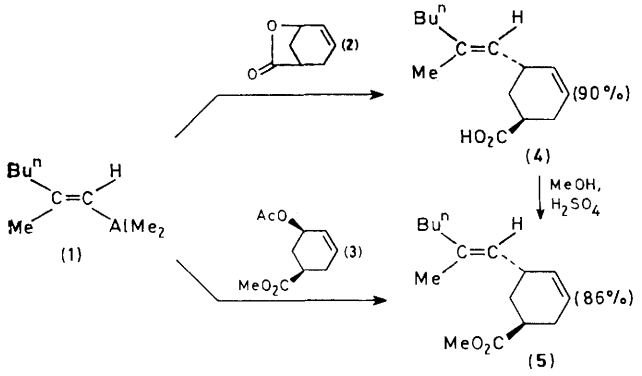
Palladium-catalysed alkenyl–allyl or aryl–allyl cross-coupling, such as the reaction of the alkenylalane (**1**) with (**2**), can proceed with nearly complete (98%) inversion of configuration at the participating allylic carbon centre.

Palladium-catalysed alkenyl–allyl or aryl–allyl coupling[1] can proceed with essentially complete retention of the stereo- and regiochemistry of the participating olefin groups. For a clarification of the mechanism of this reaction and its application to selective carbon–carbon bond formation, it is necessary to establish the stereochemistry about the participating allylic carbon atom.

We now report that the reactions of (*E*)-(2-methylhex-1-

† For Part 23 of the series Selective Carbon–Carbon Bond Formation via Transition Metal Catalysis, see E. Negishi, C. L. Rand, and K. P. Jadhav, *J. Org. Chem.*, in the press.

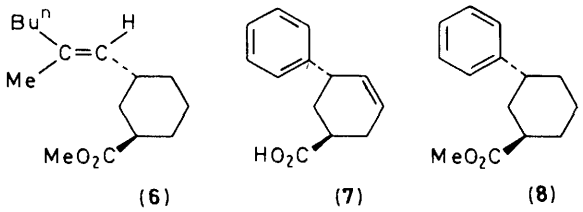


Scheme 1

enyl)dimethylalane[2] (**1**) with 7-oxabicyclo[3.2.1]oct-2-en-6-one[3] (**2**) and with methyl (*Z*)-5-acetoxycyclohex-3-enecarboxylate[3] (**3**) in the presence of 5 mol % of $Pd(PPh_3)_4$ proceed with *ca.* 98 and 90% inversion of configuration, respectively, at the participating allylic carbon centre (Scheme 1). These results represent the first demonstration of nearly complete inversion at the participating allylic carbon centre in the Pd-catalysed allylation of carbon nucleophiles. The observed stereochemistry is opposite to that found in the Pd-catalysed reaction of stabilized enolates with (**2**) and (**3**).[3] However, it is in accord with that observed recently in the stoicheiometric reaction of preformed π-allylpalladium derivatives with organozirconium reagents.[4] *anti*-Stereospecificity has also been observed recently in the reaction of MeMgI with allylic alcohols in the presence of a Ni catalyst.[5]

The reaction of (**1**) with 1 equiv. of (**2**)[3] in tetrahydrofuran (THF) in the presence of 5 mol % of $Pd(PPh_3)_4$ was carried out as reported recently by us[2] and is complete within 3 h at room temperature. After protolytic work-up and evaporation of volatile compounds, (**4**) was obtained in 90% isolated yield: ^{1}H n.m.r. ($CDCl_3$; Me_4Si) δ 0.87 (t, *J* 7 Hz, 3H), 1.0—1.5 (m, 4H), 1.62 (s, 3H), 1.7—2.1 (m, 4H), 2.1—2.4 (m, 2H), 2.55—2.9 (m, 1H), 2.9—3.3 (m, 1H), 5.02 (d, *J* 8 Hz, 1H), 5.4—5.8 (m with a peak at δ 5.57, 2H), and 11.52 (s, 1H); ^{13}C n.m.r. ($CDCl_3$; Me_4Si) δ 14.05, 16.10, 22.45, 26.99, 30.31, 31.22, 32.62, 36.41, 39.54, 124.19, 127.19, 130.51, 135.69, and 182.65 p.p.m.; M^+, *m/e* 222.162; calc. 222.162. The ^{13}C n.m.r. spectrum indicated that the product was *ca.* 98% pure, even with no attempt to separate isomeric by-products. The corresponding reaction of (**1**) with (**3**)[3] gave (**5**) and its stereoisomer in a 90:10 ratio (by g.l.c.) in essentially 100% combined yield by g.l.c. (86% isolated). In addition to the expected fifteen ^{13}C n.m.r. signals at δ 14.03, 16.09, 22.41, 27.21, 30.26, 31.44, 32.69, 36.27, 39.50, 51.51, 124.32, 127.24, 130.36, 135.54, and 176.16 p.p.m., a group of minor peaks appeared at δ 27.59, 31.04, 32.52, 35.45, 39.79, 124.89, 127.82, 131.34, and 135.98 p.p.m. Since there is no indication that sidechain stereoisomers., regioisomers, or any other by-products (^{1}H n.m.r. and i.r.), are formed these minor peaks must be due to the ring stereoisomer of (**5**). Esterification of (**4**) with MeOH and H_2SO_4 also produced (**5**) in $\geqslant$98% isomeric purity, indicating that both (**4**) and (**5**) have the same stereochemistry.

That both (**4**) and (**5**) are the *trans*-ring stereoisomers was established as follows. Hydrogenation of (**5**) using $ClRh(PPh_3)_3$ as a catalyst for 24 h at atmospheric pressure and room temperature gave the essentially pure ring-hydrogenated product (**6**) in 94% isolated yield. The corresponding reaction of (**4**) is much slower under these conditions and the ring-reduced carboxylic acid was obtained only in 25% yield after 48 h. Oxidation of (**6**) with $KMnO_4$–KOH produced cyclohexane-1,3-dicarboxylic acid as a waxy solid in 88% yield, whose spectral data and m.p. were compared with those of the



pure *cis*-cyclohexane-1,3-dicarboxylic acid, m.p. 166—167 °C,[6] prepared by the $KMnO_4$ oxidation of *cis*-cyclohexane-1,3-dimethanol as well as those of a mixture of the *cis*- and *trans*-isomers (*cis*/*trans* = 75/25) obtained by hydrogenation of isophthalic acid over PtO_2. These data, especially the ^{13}C n.m.r. information, established that the dicarboxylic acid derived from (**5**) is the *trans*-isomer. Moreover, the fact that both *cis*- and *trans*-cyclohexane-1,3-dicarboxylic acids can be obtained as essentially pure isomers *via* oxidation with $KMnO_4$–KOH precludes the occurrence of isomerization during the oxidation. The overall *anti*-stereochemistry of the reaction shown in Scheme 1 is therefore unequivocally established.

The reaction of phenylzinc chloride, prepared *in situ* by treating phenylmagnesium bromide with 1 equiv. of anhydrous $ZnCl_2$, with (**2**) in the presence of 5 mol % of $Pd(PPh_3)_4$ produced (**7**) in 94% isolated yield: ^{1}H n.m.r. ($CDCl_3$; Me_4Si) δ 1.8—2.8 (m, 5H), 3.45—3.75 (m, 1H), 5.65—6.1 (m, 2H), 7.27 br. (s, 5H), and 11.2 (s, 1H); ^{13}C n.m.r. ($CDCl_3$; Me_4Si) δ 27.12, 33.18, 35.51, 39.37, 126.37, 126.53, 128.08, 128.42, 128.91, 144.68, and 182.22 p.p.m.

To establish the stereochemistry of (**7**) it was first hydrogenated in EtOH over Pd/C and then treated with MeOH and H_2SO_4 to produce (**8**) in essentially 100% overall yield. The ^{1}H and ^{13}C n.m.r. spectra as well as g.l.c. analysis of (**8**) clearly indicate that it is $\geqslant$98% pure. Treatment of (**8**) with $KOBu^t$ in refluxing MeOH for 3 h produced a *ca.* 15:85 mixture of (**8**) and its epimer. The results strongly indicate that (**8**) is the *trans*-isomer, which, on epimerization, is converted into the more stable *cis*-isomer.

While additional studies are necessary to establish the mechanism of the Pd-catalysed allylation of alkenyl- or arylmetal compounds, the results herein presented can be nicely accommodated by a sequence[1] consisting of (i) formation of allylpalladium(II) derivatives by the interaction of allylic esters with $Pd(PPh_3)_4$, which has been reported to proceed with inversion,[7] (ii) transmetallation with retention, and (iii) reductive elimination with retention.

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