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Preliminary Communication

Near Absolute Regio-, Diastereo-, and Enantioselectivity in a Palladium Catalyzed Alkylation Using an Uncommon Chiral Auxiliary

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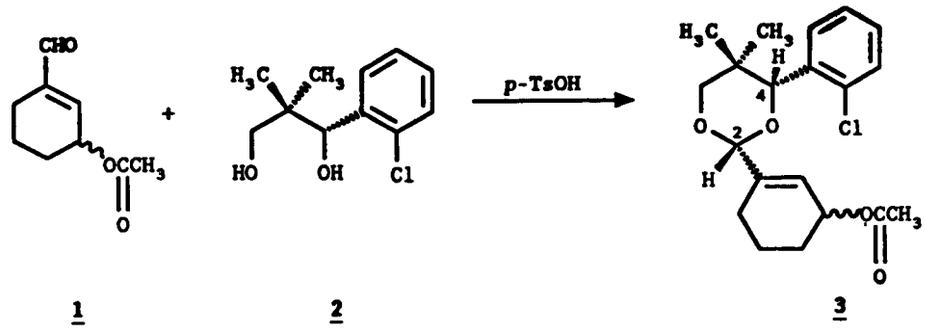
Abstract Condensation of R-(+)-1-(2-chlorophenyl)-2,2-dimethyl-propan-1,3-diol (**2**) with a derivative (**1**) of 1-formylcyclohexene substituted in the 3-position with an acetoxy group proceeded with absolute stereospecificity at the acetal center. Catalytic alkylation of the π-allyl complex obtained upon reaction with Pd with the anion of dimethylmalonate proceeded at the 3-position of the cyclohexyl ring with complete stereocontrol.

Attainment of high diastereo- and/or enantiocontrol in palladium catalyzed alkylations of π-allyl complexes is not easy.[1] We report here an encouraging result obtained using a chiral auxiliary not commonly used. The high stereocontrol obtained may well have further useful ramifications. Aldehyde **1**, prepared as described by Ogura[2] (2-cyclohexenone with the lithium salt of $CH_3SCH_2SOCH_3$ followed by hydrolysis in 2N H_2SO_4 and then treatment with CH_3COCl), condensed smoothly with R-(+)-1-(2-chlorophenyl)-2,2-dimethyl-propan-1,3-diol[3] (**2**) to afford **3** as shown in Scheme 1.

Scheme 1



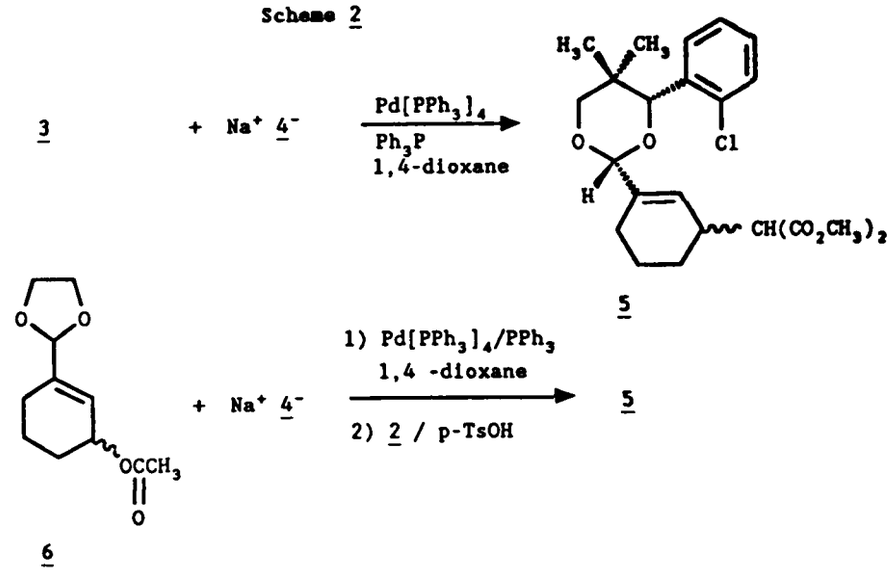
1 **2** **3**

Proton and ^{13}C NMR spectra clearly reveal that compound **3** consists of two diastereomers in roughly equal amounts; these arise from both possible configurations at the acetoxy bearing carbon. This conclusion is based on the following considerations. First, we have shown previously that the condensation of various cyclic and acyclic aldehydes with **2** produces exclusively 1,3-dioxanes with the substituents at C2 and C4 **cis** as illustrated.[4] This appears to be the thermodynamically most stable arrangement. The stereochemical assignment was based[4] on the consistent appearance of a cross peak between the protons at C2 and C4 in the NOESY spectra; this is only possible if both protons are axial as indicated. A similar cross peak is observed in **3**. There is thus absolute stereochemical control at C2 in **3** but, in accord with expectation, not at the acetoxy bearing carbon.

Of the two diastereomers of **3** one can be partially purified (80:20 mixture) by recrystallization.[5] Qualitative kinetic experiments established that both diastereomers react at the same rate (10% error) in the catalytic alkylation described in the following paragraph. The diastereomerically enriched crystalline material was used for preparative experiments without fear for kinetic selection between the diastereomers.

Catalytic alkylation with the sodium salt of dimethyl malonate (**4**) in dry 1,4-dioxane (3 eqv. **4** with 3

Scheme 2

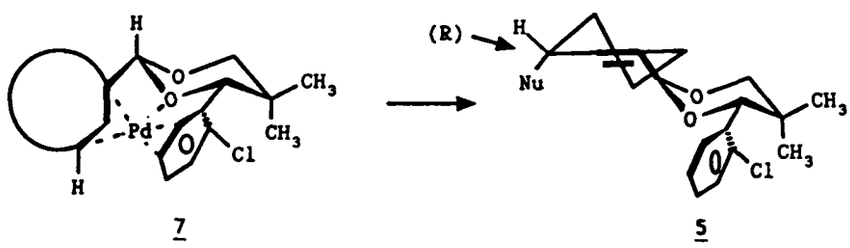


eqv. NaH to which a solution of 1 eqv. diastereomerically enriched **3**, 1 eqv. $(C_6H_5)_3P$ and 0.05 eqv. $Pd(O)[P(C_6H_5)_3]_4$ had been added followed by reflux for 48 h) delivered exclusively **5** (Scheme 2) in 80% yield.[6] Regioselective addition of malonate to the terminal end of the allyl system is anticipated on steric grounds; with various acyclic analogs of **1** condensed with **2** we have also consistently observed the same regioselectivity.[6]

Proton and ^{13}C spectra of **5** were consistent with the formation of a single diastereomer.[7] To verify this conclusion racemic **6** was alkylated as described for the preparation of **5**. The ethylene glycol bridge was then exchanged for **2** under acidic conditions (cat. $CH_3C_6H_5SO_3H$ in benzene, 48 h reflux) to generate **5** (Scheme 2) that, on the basis of ^1H NMR spectra, was clearly an almost 50:50 mixture of diasteromers.[8] The catalytic allylation of **3** is thus >95% (limits of NMR detection) regio- and **dia**stereoselective. The newly generated chiral center in **5** is thus **enantiomerically** pure.

Stereogenic centers 4 and 6 atoms removed from the center of substitution have thus exerted absolute (as far as can be measured) regio- and stereocontrol. The following interpretation is given tentatively. In the π-allyl complex (7) leading to **5** the π-orbitals are arranged perpendicularly to the the acetal C-H bond.[9] This creates a pocket on the **si** face of the allyl system to which Pd is bonded as well as to (probably) an acetal oxygen and the 2-chlorophenyl ring. The malonate anion attacks from the **re** face to generate **5** with an R configuration at the newly formed stereogenic center (Scheme 3). This stereochemical prediction remains to be proved. This as well as further work on the applications of this methodology is being undertaken.

Scheme 3



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5. Recrystallization from n-hexane; repeated recrystallization failed to lead to further purification. Both diastereomers showed cross peaks between H2 and H4 (Scheme 1) in the NOESY spectrum.