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A PALLADIUM-CATALYZED ROUTE TO MONO- AND DIPROTECTED CIS-2-CYCLOPENTENE-1,4-DIOLS[1]

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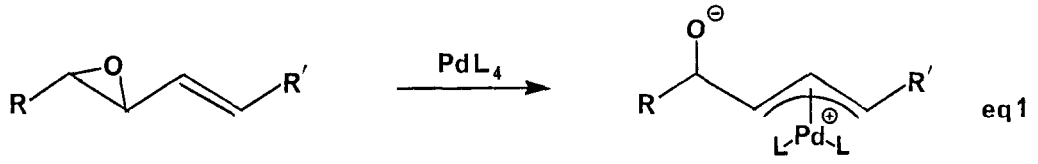
ABSTRACT - The π-allylpalladium complex arising from cyclopentadiene monoepoxide has been shown to react with carboxylic acids and derivatives both as a nucleophile and an electrophile. This reaction represents an attractive synthetic route to protected versions of cis-2-cyclopentene-1,4-diol.

We were intrigued by the synthetic potential inherent in zwitterions (2) generated by the opening of vinyl epoxides (1) with palladium(0) catalysts (eq 1). Unlike other π-allyl-palladium complexes, these dipolar intermediates harbor both a nucleophilic and an



eq 1

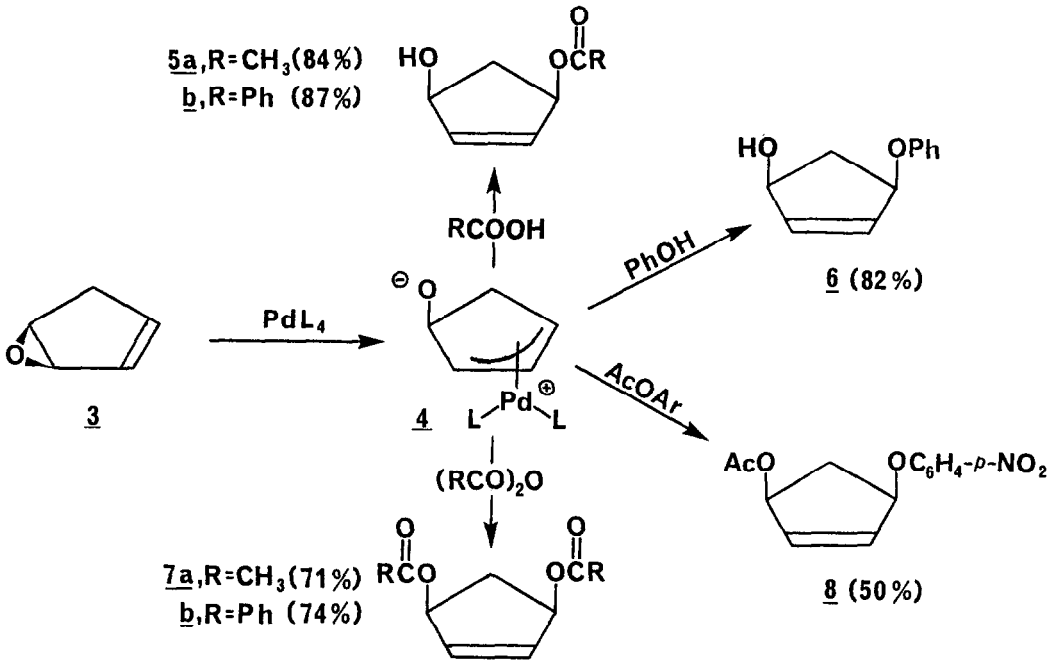
1 2

electrophilic center. Trost[2] and Tsuji[3] have shown that the oxygen in 2 can function as an alkoxide base while the electron deficient allylic system reacts with nucleophiles in a manner analogous to normal π-allylpalladium complexes. Product analysis suggests that 2 prefers to add neutral nucleophiles in a 1,4-sense such that the incoming group appends to the face of the molecule syn to the oxygen moiety.[2]

We envisioned that the zwitterionic species (4) derived from cyclopentadiene monoepoxide (3) would prove an ideal synthon for the stereo- and regiospecific construction of substituted cyclopentanoids. Initially, we hoped that 4 would react with carboxylic acids to give the corresponding cis-1,4-adducts. Products obtained via this route would undoubtedly be useful in the preparation of prostaglandins and other similarly functionalized natural products.[5]

As expected, treatment of cyclopentadiene monoepoxide[6,7] (3) with 0.5 mol % of tetrakis-(triphenylphosphine)palladium(0) in the presence of acetic or benzoic acid (1.1 equiv) cleanly affords cis-1,4-addition products 5a and b (Scheme 1) in excellent isolated yields (84% and

Scheme I



87%, respectively). A similar reaction with phenol, another acidic substrate, produces phenoxy adduct 6 in equally good yield (82%). The cis stereochemistry was unambiguously assigned using ^{1}H NMR techniques.[8] The observed ^{1}H NMR spectra were found to be fully consistent with the literature values or in accordance with other cyclopentenes having similar substitution patterns.[9]

In each of the above examples, the reaction is presumably initiated through proton abstraction by the basic oxygen atom in 4. A subsequent trans attack by the freshly liberated phenoxide or carboxylate anion on the distal end of the π-allyl system (external delivery mechanism[10]) insures the cis stereochemistry. Since no trans 1,4-isomer is observed, it may be concluded that a reductive elimination mechanism (internal delivery)[10] is probably not in operation. This stereochemical result is in perfect agreement with that obtained by Bäckvall who has studied the palladium(II)-catalyzed diacetoxylation of cyclopentadiene.[11]

It occurred to us that we might also be able to exploit the native nucleophilicity of the oxygen in 4 to generate the nucleophile which ultimately attacks the π-allylpalladium complex. We were pleased to discover that exposure of 3 to acetic anhydride in the presence of palladium(0) furnishes cis-diacetate 7a in 71% yield. Since monoacetate 5a is not acylated under the identical conditions, this clearly demonstrates that initiation must have occurred by acylation of the alkoxide moiety. Benzoic anhydride was also found to react under the analogous conditions to give the expected dibenzoate 7b in a slightly better yield (74%).

In view of these encouraging results, we wanted to extend the scope of this reaction to include esters. Success on this front has unfortunately been limited to only the more reactive cases. For example, whereas 4 rapidly reacts with p-nitrophenyl acetate (1.1 equiv) to afford the corresponding cis-aryloxy acetate (8; 50%[12]), its comparable reaction with phenyl acetate only results in a disappointing mixture of unidentified products.

The ease with which the reported reactions may be carried out is remarkable. An illustrative example is as follows:

> A solution of cyclopentadiene monoepoxide (4.0 g, 49 mmol) in THF (10 mL) was added dropwise over 8 minutes to an ice-cooled, stirred solution of tetrakis-(triphenylphosphine)palladium(0) (0.25 g, 0.22 mmol, 0.5 mol %) and benzoic acid (6.25 g, 51 mmol) in THF (50 mL). After 10 minutes, the reaction was judged complete by TLC assay (1:1; hexane:ethyl acetate). The mixture was passed through a silica gel plug with ether, concentrated under reduced pressure, and chromatographed over silica gel (200 g) to afford 8.7 g (87%) of 5b. Yields range from 72% to 87% depending on reaction scale.

In sum, these reactions offer a novel, highly stereo- and regioselective route to functionalized cyclopentanoids in good to excellent yields.[13] Since this methodology is compatible with numerous functional groups, its potential synthetic applicability may be widespread. Our studies on acyclic vinyl epoxides will appear in a separate communication.

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