Observations on the Intramolecular Palladium(0) Catalysed [3 + 2] Cycloaddition of Diphenylmethylenecyclopropanes

Richard T. Lewis, William B. Motherwell,*† and Michael Shipman

Department of Chemistry, Imperial College, South Kensington, London SW7 2AY, U.K.

The intramolecular variant of the palladium(0) catalysed cycloaddition of diphenylmethylenecyclopropanes with olefinic and acetylenic acceptors provides a regiocontrolled route to highly functionalised bicyclo[3.3.0]octane derivatives.

The discovery by Noyori[1] of the formal transition metal catalysed [2π + 2σ] cycloaddition of an alkylidene cyclopropane with an olefin to yield an alkylidene cyclopentane represented a significant step towards the elaboration of a useful [3 + 2] 'Diels–Alder' like strategy for the construction of cyclopentanoids. Extensive and elegant studies by Binger[2] have not only confirmed the initial concept but have also highlighted the facts that the reaction does not proceed *via* the Trost[3] palladium(0)trimethylenemethane complex and that simple olefinic partners may be used as well as the more conventional electron deficient alkenes and alkynes. Nevertheless, competing reactions[2] such as co-dimerisation of the alkylidene cyclopropane, and ring cleavage to dienes or rearrangements of alkyl substituted cyclopropanes can often compete with the desired pathway. Even more significantly, in the case of synthetically useful unsymmetrical substituted partners, both possible regioisomers may be formed.

We reasoned that many of these undesirable complications could be simply resolved by employing the constraints of the intramolecular mode, as illustrated in Figure 1 for prototypical cleavages *via* the distal and proximal modes. Here we report our initial studies on the construction of highly functionalised bicyclo[3.3.0]octanes by such an approach.

Compound (**1**) was selected for initial study, in order to benefit not only from the classical Thorpe–Ingold effect[4] of the *gem*-dimethyl group in ring forming reactions, but also by virtue of the diphenylmethylene group, to facilitate and ensure a palladium(0) catalysed distal cleavage. The latter group also functions as a latent ketonic functionality.

The synthetic route is outlined in Scheme 1. Protection of aldehyde (**2**)[5] as its dimethyl acetal followed by cuprous triflate catalysed addition of diethyl diazomethyl phosphonate and elaboration of the resultant cyclopropyl phosphonate (**3**) in a Wadsworth–Emmons reaction with benzophenone smoothly provided, after deprotection of the dimethyl acetal, the key diphenylmethylene cyclopropane (**5**).‡ Isolation of the

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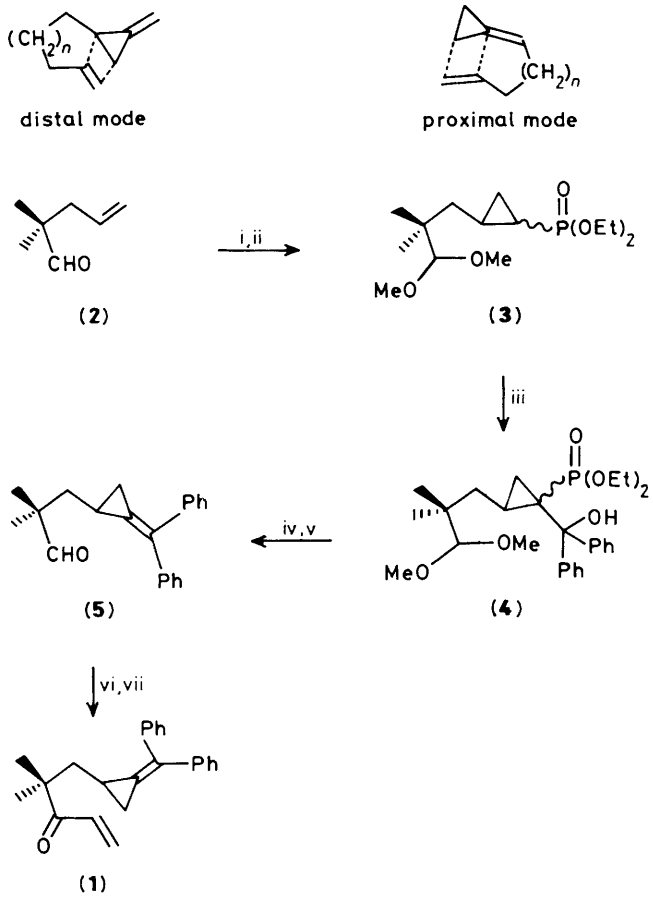
‡ Details of this route from olefins to a variety of functionalised mono and diphenylmethylene cyclopropanes will be published separately.

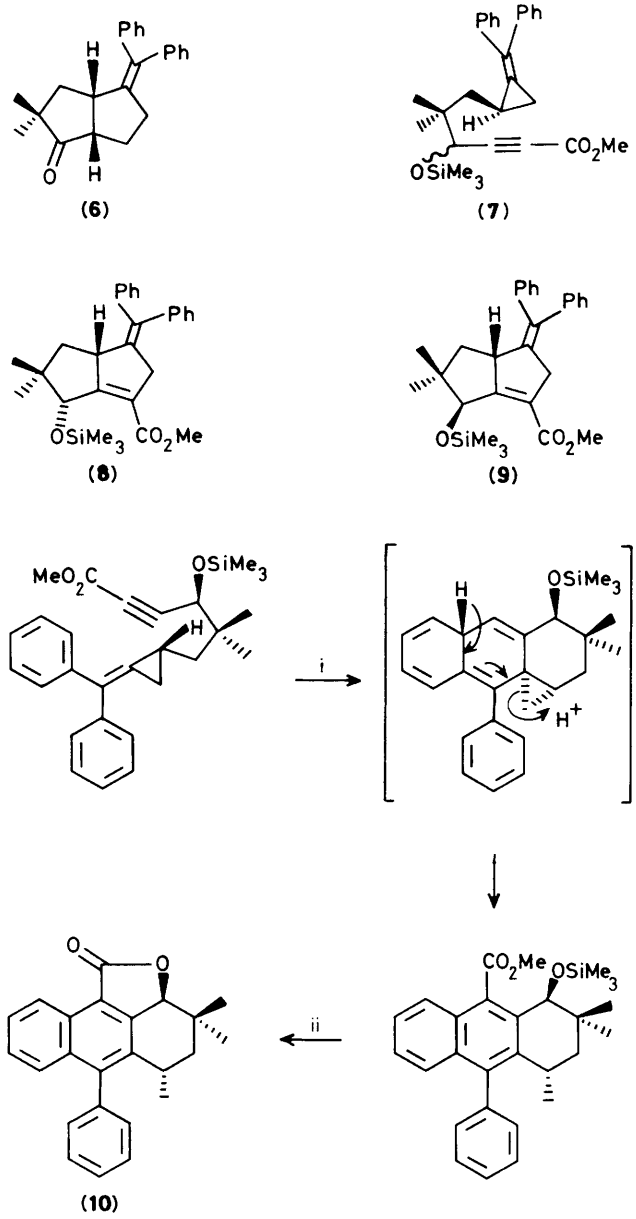


Scheme 1. *Reagents and conditions*: i, MeOH, Amberlyst 15; ii, diethyl diazomethyl phosphonate (DAMP), $[Cu^{I}\ SO_3CF_3]_2$· PhH, CH_2Cl_2, 0 °C, 72 h [44% yield from (2)]; iii, Bu^nLi, tetrahydrofuran (THF) −78 °C, Ph_2CO, then AcOH quench (76% yield); iv, NaH, dimethylformamide (DMF), 90 °C, 5 h; v, 10% HCl, 18 h [67% yield from (4)]; vi, vinylmagnesium bromide, 0 °C, Et_2O; vii, pyridinium chlorochromate (PCC), CH_2Cl_2, r.t. [46% yield from (5)].

β-hydroxy phosphonate intermediate (**4**) and counterion exchange was necessary in order to obtain a high yield in this sequence. Subsequent Grignard reaction of the resultant aldehyde (**5**) with vinylmagnesium bromide followed by pyridinium chlorochromate oxidation furnished enone (**1**).

Initially, reaction of enone (**1**) with bis(dibenzylideneacetone)palladium (11 mole%) in the presence of tri-isopropyl phosphite [1 equiv. with respect to palladium(0)] in degassed toluene at 110 °C for 42 h afforded the desired bicyclic ketone (**6**) in 31% yield, together with formation of a co-dimer. Increased substrate dilution (three fold) led, as expected, to an improved yield of the monomer (47%), thus demonstrating our objective that regioselective control may be achieved through selection of the intramolecular mode. A significant feature of interest in this reaction is the use of a simple acyclic enone as the olefinic acceptor. In the intermolecular counterpart,[2] molecules such as acrolein, which can adopt the *cisoid* conformation, generally fail to give cycloadducts, since the alkene forms a strongly bonded ligand to palladium(0) and prevents interaction of the metal with the alkylidene cyclopropane.

We have also examined the cyclisation of the acetylenic ester (**7**), which was simply prepared as a 1 : 1 mixture of diastereoisomers by addition of lithium methoxycarbonylacetylide to aldehyde (**5**) followed by silylation. In this case, the



Scheme 2. *Reagents and conditions*: i, toluene, 140—150 °C, sealed tube; ii, tetrabutylammonium fluoride (TBAF), tetrahydrofuran (THF).

regiochemistry of the electron deficient acceptor is reversed relative to the situation obtaining in enone (**1**). Use of this substrate in a similar thermal cycloaddition catalysed by bis(dibenzylideneacetone)palladium(0) gave a 1 : 1 mixture of the two bicyclic esters (**8**) and (**9**) isolated in 38 and 41% yield respectively, together with some unreacted starting material. No dimeric products were formed. From the experimental standpoint, it is important to note that identical yields can also be obtained using tetrakis(triphenylphosphine)palladium(0) as a catalyst under the conditions of mild sonication. While this catalyst is not normally considered[2] to be one of the more reactive in this area, the temperature and pressure effects induced by cavitation may well be responsible for more facile ligand expulsion and/or reductive elimination from a metallacycle intermediate. The obtention of a 1 : 1 mixture of diastereoisomeric cycloadducts (**8**) and (**9**) not only reaffirms

the concept of regioisomeric control in unsymmetrically substituted cycloadditions but also provides strong presumptive evidence that such cyclisations are highly stereoselective with respect to the relative configurations of peripheral substituents.

It was also of interest to compare the results of the palladium(0) catalysed cycloaddition of ester (**7**) with those obtained in a purely thermal reaction. This latter case led, after deprotection of the silyl ether, to isolation of the novel lignan (**10**) (20% yield based on the indicated diastereoisomer), whose structure was determined by *X*-ray crystallography. A rational mechanism, similar to that proposed in the intermolecular reaction of diphenylmethylenecyclopropane with tetracyanoethylene,[6] would involve intramolecular Diels–Alder reaction followed by prototropic migration (Scheme 2).

From the synthetic viewpoint, the foregoing results clearly demonstrate that controlled and predictable regioselectivity may be obtained in the intramolecular mode. This, when allied with the previously demonstrated[2] facets of stereochemical control in intermolecular reactions, combine to provide a highly convergent and useful strategy for natural product synthesis, particularly in the important polyquinane area.[7]

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