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REGIOSPECIFIC INTRAMOLECULAR [2π+2σ] CYCLOADDITIONS OF METHYLENE CYCLOPROPANES

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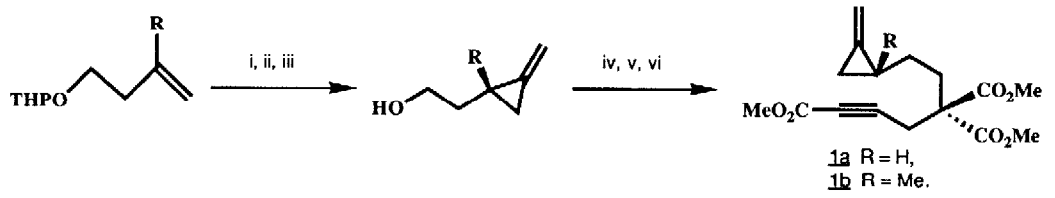
Summary: Intramolecular cyclisation of methylene cyclopropanes with acetylenic acceptors affords highly functionalised bicyclononane derivatives. The regiospecificity of these cyclisations is dependent on the nature of the transition metal employed.

We have recently described[1] the first examples of the intramolecular variant of the transition metal catalysed [2π+2σ] cycloaddition of diphenylmethylene cyclopropanes to electron deficient olefinic and acetylenic acceptors. Further to our work, elegant studies by Nakamura[2] have served to confirm the idea that selection of the intramolecular mode may be used not only to control regioselectivity, but also to minimise the problems of competing codimerisation, rearrangement, and ring opening of cyclopropanes observed in the intermolecular reaction.[3] In our initial report,[1] the selection of an arylidene cyclopropane and the use of a palladium(0) catalyst combined to ensure that exclusive cleavage of the distal bond of the cyclopropane was achieved and accordingly that a single regioisomer was formed. In this letter, we address the problem of regioselectivity in the more energetically demanding case of simple methylene cyclopropanes.

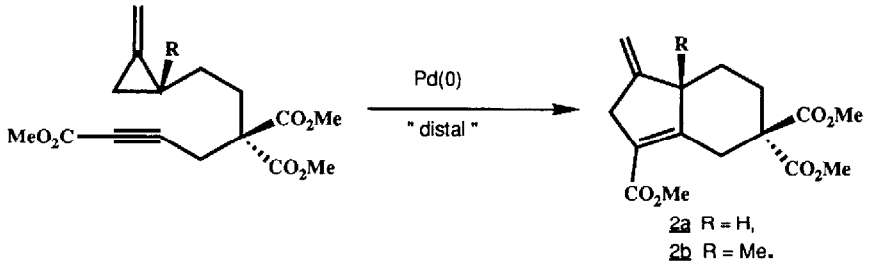
A suitable test of the anticipated regiocontrol involved the preparation of acyclic precursors (1) for the transition metal mediated construction of a highly functionalised hydrindane skeleton. The general synthetic sequence is outlined in Scheme 1. Preparation of the appropriate alkylidene cyclopropane building blocks was simply achieved by reaction of the protected but-3-en-1-ol derivatives with methyl chlorocarbene followed by dehydrohalogenation[4] and deprotection. Subsequent conversion to the iodide, and alkylation with dimethyl monopropargyl malonate then methyl chloroformate proceeded smoothly to furnish the required acyclic acetylenes (1 a,b).



Scheme 1. *Reagents and conditions:* i, ^{n}BuLi, CH_3CHCl_2, -35°C, Et_2O (R=H, 76% yield ; R=Me, 79% yield); ii, KO^{t}Bu, DMSO, 70°C; iii, p-TsOH, MeOH (R=H, 76% yield; R=Me, 68% yield); iv, PPh_3, I_2, imidazole, Et_2O, MeCN; v, dimethyl monopropargylmalonate, NaH, DMF; vi, ^{n}BuLi, THF, -78°C, MeOCOCl (R=H, 46% yield; R=Me, 57% yield).

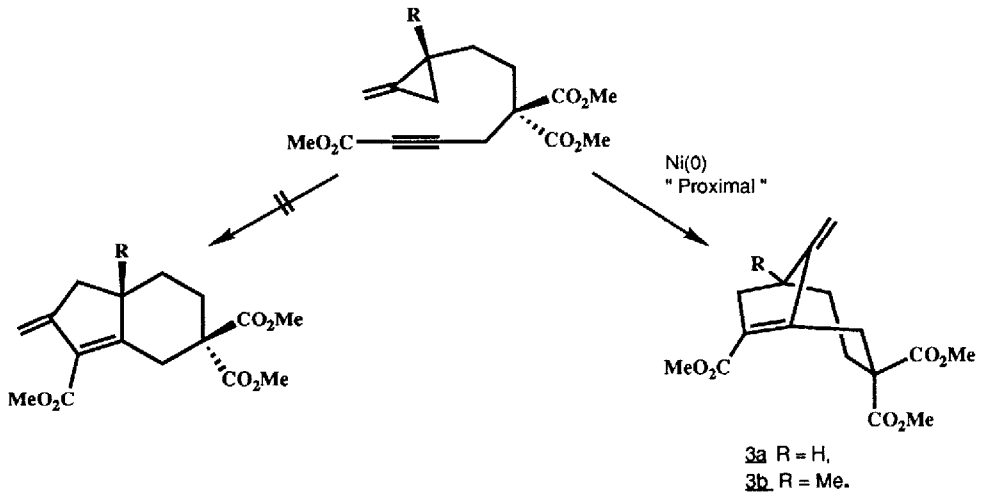
Initial studies focussed on the palladium(0) catalysed reactions, which gave the substituted hydrindanes (2) resulting from distal cleavage of the alkylidene cyclopropane ring (Scheme 2). Thus, in a typical reaction of the acetylenic ester (1b) with a catalyst prepared from 10 mol% of bis(dibenzylideneacetone)palladium in the presence of tri-isopropyl phosphite (4 equivalents with respect to metal) in degassed toluene at 110 °C for 42 hours, the bicyclic product (2b) was isolated in 59% yield.[5] Similarly, the nor methyl analogue (1a) gave the bicyclic hydrindane (2a) in 40% yield. A feature of mechanistic relevance and considerable preparative utility in these reactions, stems from the observation that a much higher relative concentration of ancillary phosphite ligand may be employed in the intramolecular mode than is the case in the intermolecular reactions, where phosphorus ligand concentrations in excess of one molar equivalent with respect to palladium often lead to inhibition of reaction.[6] Thus, in the case of a possible trimethylenemethane-like[7] derived metallocyclic intermediate (see figure 1), the presence of additional ligands around the metal would be expected to promote reductive elimination to give product (2 a,b).[8]

Scheme 2



We then turned our attention to the intriguing possibility that use of the same substrate (1) in a nickel(0) catalysed reaction could result in the formation of a different regioisomer (3), through cleavage of the proximal bond of the methylene cyclopropane, as observed in the original work of Noyori[9] using an acrylate ester as the olefinic acceptor. Thus, an initial experiment using ester (1a) as substrate and bis(cycloocta-1,5-diene)nickel(0) as catalyst afforded the anti-Bredt diene (3a) in 20% yield, (32% based on recovered starting material). A higher conversion was established in the case of the methyl analogue (1b), where use of 40mol% of the nickel(0) catalyst and a 0.05M solution with respect to substrate in toluene at 0 °C afforded the analogous bicyclic adduct (3b) in 50% yield (63% based on recovered starting material)[5]. Addition of 1,5-cyclooctadiene (2 molar equivalents with respect to substrate) to the reaction mixture did not enhance catalytic turnover; similarly use of stoichiometric nickel(0) failed to increase the yield. It is of particular interest to note that the reaction proceeds exclusively via a proximal cleavage in which the acetylenic carbon bearing the ester grouping becomes bonded to the less substituted vinylic carbon atom of the alkylidene cyclopropane. This result is in accord with the proven regioselectivity observed in the first intermolecular example by Noyori[9] (see figure 2).

Scheme 3



3a R = H,
3b R = Me.

From the synthetic standpoint, the foregoing results clearly demonstrate that the selection of metal catalyst may be used in a predictable way to govern the regiochemical outcome of the reaction, and this feature, when allied with the previously demonstrated facets of control induced by operating in the intramolecular mode, combine to give a flexible and useful strategy for synthesis of a wide variety of structural types incorporating a cyclopentanoid.

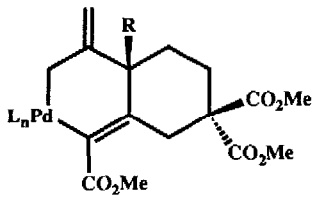


FIGURE 1

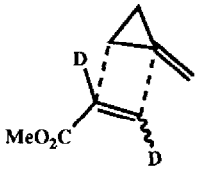


FIGURE 2

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