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CONJUGATE NUCLEOPHILIC RING OPENING OF ACTIVATED VINYLCYCLOPROPANES FACILITATED BY HOMOGENOUS PALLADIUM CATALYSIS

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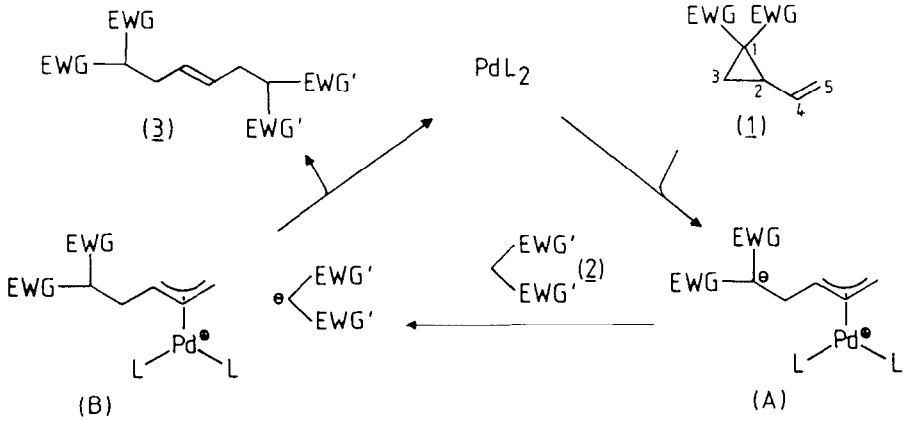
Summary: 1,1-Diactivated-2-vinylcyclopropanes (1) add carbon nucleophiles (2) regiospecifically in a conjugate sense in the presence of a catalytic amount of a zerovalent palladium complex.

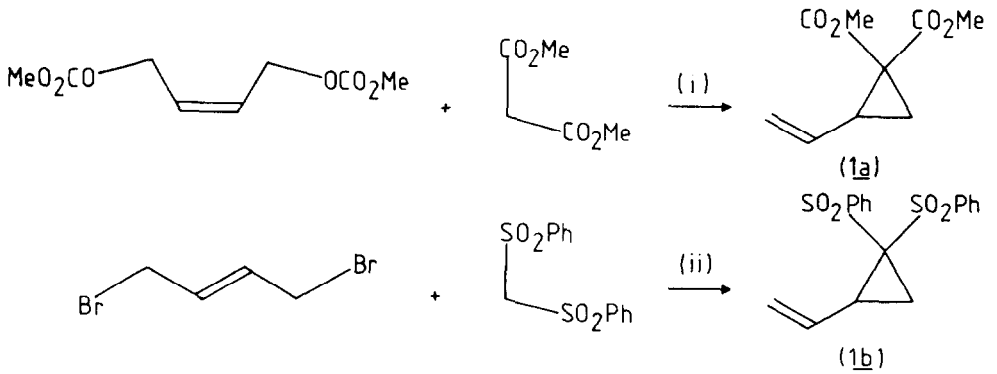
Nucleophilic ring opening of cyclopropanes activated by two electron withdrawing groups is an established proceedure in organic synthesis.[1] Ring cleavage of vinylcyclopropanes has comparable potential if the regiochemistry of nucleophilic attack can be controlled. Activated vinylcyclopropanes add amines and thioalkoxides at C2, lithium dimethylcuprate adds in a conjugate sense, but stabilized carbanions, e.g. sodiodimethylmalonate, give a mixture of products resulting from both these modes of addition occuring at similar rates.[1]

Scheme 1



Reported here is a method for achieving regiospecific conjugate addition of active methylene compounds to activated vinylcyclopropanes under mild, neutral conditions. It was envisaged that a palladium (0) complex might cleave the 1,2 bond of a cyclopropane to form a zwitterionic π-allyl intermediate (A); this could deprotonate an active methylene compound so producing a stabilised enolate which would be free to add to the π-allyl terminus (Scheme 1). Such a process is reminiscent of conjugate nucleophilic addition to vinylepoxides catalysed by zerovalent palladium compounds.[2]

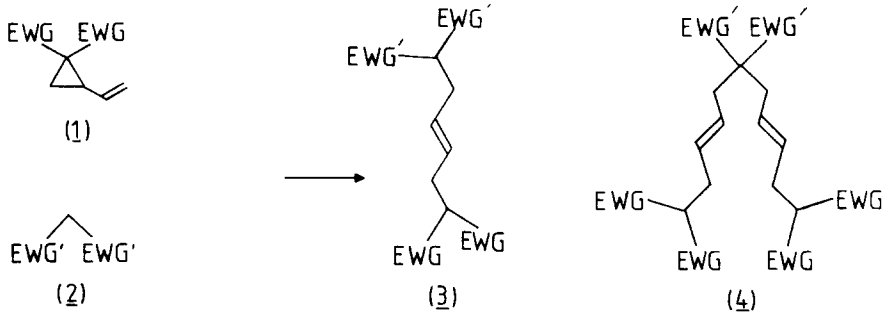
The dimethylmalonate derivative (1a) can be synthesised by a known[3] method or by a palladium catalysed reaction (eq. 1) (32% yield, unoptimized) which does not require added base because the carbonate leaving groups collapse to alkoxide.[4] Formation of cyclopropanes via stepwise palladium catalysed allylic substitution has been reported and used in syntheses of chrysanthmic acid derivatives.[5] The sulphone (1b) was accessible in 74% yield by a phase transfer reaction (eq. 2) similar to that used for the preparation of cyclopropanes from 1,2-dibromides.[6]



Conditions: (i) 2 mol% $Pd(PPh_3)_4$, THF, 20°C, 12h; (ii) 2.1 NBu_4OH 40% aq., CH_2Cl_2, 20°C, 4 days.

Results for the palladium catalysed ring cleavage vinylcylopropanes, (eq. 3) are shown in the Table. The procedure for opening of the dimethylmalonate derivative (1a) with 2,4-pentandione (entry 1) is illustrative. 2,4-Pentandione (0.100 g, 1.0 mmol), (1a) (0.184 g, 1.0mmol), $Pd(PPh_3)_4$ (0.023 g, 2 mol%), and then THF (2 cm^3) were added under dinitrogen to a reaction vessel cooled to ca. -190°C. The mixture was freeze-thaw degassed twice[7] then stirred at 20°C for 8 h. The solvent was removed in vacuo and the residue flash chromatographed on silica using 25% ethyl acetate/hexane eluant increased to 40% ethyl acetate in stages. The first fraction was (3a), rf 0.3 in 25% ethyl acetate/hexane, 0.084 g, 30%; and the second fraction was (4a), rf 0.1 in 25% ethyl acetate/hexane, 0.139 g, 59%.[8]

No base was necessary in these reactions presumably because the nucleophile is deprotonated by the carbanion functionality of the postulated intermediate (A) formed in the ring opening step. Yields are low in entries 7-9 probably because pKa differences disfavour proton transfer. The regioselectivity of these reactions is high, none of the compounds derived from attack at C2 could be detected in any of these examples. Entries 1-3 and 4-6 show that the product distribution can be biased by towards monoalkylation or dialkylation by adjusting the (1):(2) ratio. It is noteworthy that the dialkylated product (4b) (entry 5) is formed implying that a second electrophilic attack at the more hindered, sulphone, end of the monoalkylated intermediate is preferred.



eq. 3

Table[a]

Entry	EWG	EWG'	Ratio (1):(2)	Time h	Isolated Yields %(3)	%(4)
1	CO_2Me	MeCO	1:1	8.0	30	59
2	CO_2Me	MeCO	2:1	8.0	5	91
3	CO_2Me	MeCO	1:3	8.0	58	30
4[b]	CO_2Me	SO_2Ph	1:1	4.75	94	-
5	CO_2Me	SO_2Ph	2:1	3.0	-	96
6	CO_2Me	SO_2Ph	1:3	4.75	98	-
7[c]	SO_2Ph	CO_2Me	1:3	5.5	18	-
8	CO_2Et	CO_2Me	1:1	2.0	23	-
9	CO_2Et	CO_2Me	1:3	8.0	26	-
10	SO_2Ph	MeCO	1:1	5.75	62	32
11[c]	SO_2Ph	MeCO	2:1	5.0	52	-
12	SO_2Ph	MeCO	1:3	6.75	76	16
13[b]	SO_2Ph	SO_2Ph	1:3	5.0	61	-

[a] 2 mol%$Pd(PPh_3)_4$, THF at 0.5 M conc. of (1), 20°C unless otherwise specified. [b] At 65°C. [c] A complex mixture formed, only the products indicated were separable by flash chromatography.

Ring opening of vinylcyclopropanes by transition metal complexes is a well documented process.[9] Most significantly it has been shown that activated vinylcyclopropanes add amines in a conjugate sense in the presence of palladium (0) complexes.[10] It has also been reported that dienylcyclopropanes rearrange to vinylcyclopentenes, in the presence of palladium (0) catalysts, whereas vinylcyclopropanes do not isomerise under similar conditions[11] presumably because such a reaction would involve a geometrically unfavourable ring closure.

The potential of this methodology in reactions similar to the macrocyclization of vinylepoxides[12] is apparent but, as yet, unexplored.

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References and Notes

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7 This degassing proceedure is not absolutely necessary if the usual measures to exclude dioxygen are taken; this technique was used as a precaution here to ensure absolutely reproducable results.

8 All the compounds reported here were characterized by i.r., ^{1}H n.m.r., ^{13}C n.m.r., accurate mass spectral data and/or combustion analysis. ^{1}H coupling constants and/or i.r. data indicates the double bond geometry was trans for all products.

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