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Palladium-catalysed Alkylative Cyclisation of 2,3-Butadienylmalonates to γ-Lactones

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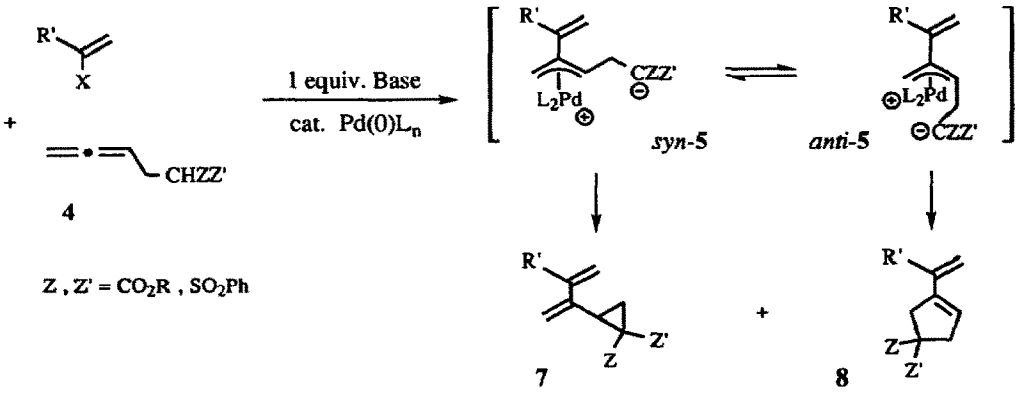
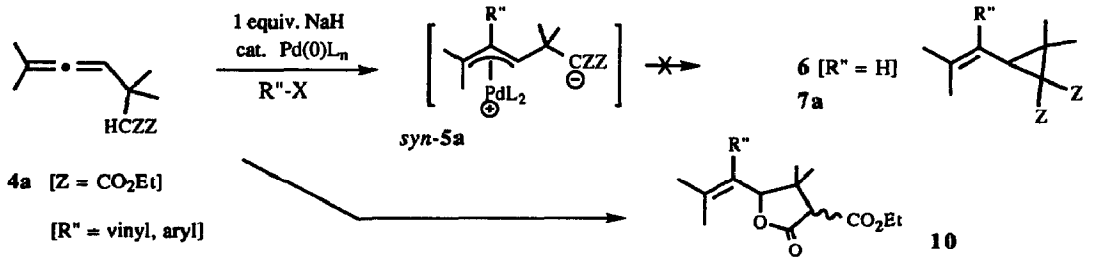
Abstract : The palladium-catalysed reaction of vinyl halides with the anions of 1,1-dimethyl-2,3-butadienylmalonates leads to 4-dienyl γ-lactones through an unexpected alkylative O-cyclisation pathway due to the steric demand of the α-allenic gem-dimethyl group.

Carbopalladation of allenic compounds by vinyl type organopalladium species is a general process which leads to unsaturated π-allyl palladium complexes[1], and is the key step of a palladium-catalysed synthesis of functionalysed dienic (or styryl) compounds from allenes.[2-4] Further studies in this area demonstrated that an intramolecular reaction from functionalysed allenes which include a potential nucleophilic pole as 2,3-butadienylmalonates **4** was leading to vinylcyclopropanes **7** and/or cyclopentenes **8**.[3,5] The regioselectivity of these competitive cyclisations was dependent on the substitution patterns of both the allenic substrate and the unsaturated halide and was tentatively rationalised through the *syn* and *anti* π-allyl palladium intermediates **5** : the cyclisation to vinylcyclopropanes **7**, which has numerous precedents in the literature[6], would arise from the π-allyl complex *syn*-**5** , while the cyclopentene **8** would be formed from the cyclisation of the isomer complex *anti*-**5**.[5]



As a part of our on-going research about palladium-mediated cyclisation processes from allenes, we envisioned the alkylative cyclisation of the tetrasubstituted 2,3-butadienylmalonate **4a**[7] as a possible route to substituted vinylcyclopropanes **7a** [R" = vinyl, aryl] related to the "chrysanthemyl" structure **6** [R" = H], the three-membered ring closure being expected because of an anticipated larger stability of the intermediate

syn π-allyl complex **5a** which would more easily accommodate the steric demand of the vicinal gem-dimethyl group. This C3 cyclisation was not observed from malonate **4a** and we report herein our results on an alternative ring closure to substituted γ-lactones **10**.

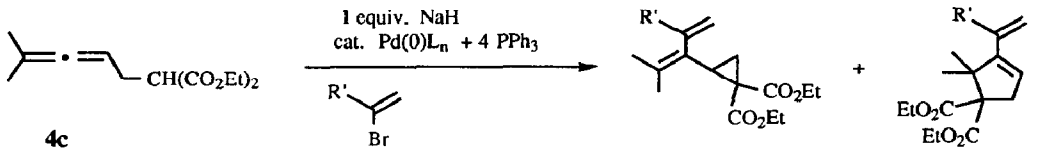


In a preliminary experiment malonate **4a** was treated in DMSO with sodium hydride NaH (1 equiv.) and vinyl bromide (2 equiv.) in the presence of the catalytic system $Pd(dba)_2$ + 4 $P(Ph)_3$ [4% molar equivalent] at 80°C for 48 hours (Table, entry 1). Four compounds could be isolated from this reaction, the unreacted malonate **4a**, the γ-allenic ethyl ester **9a** and the two lactones **10a1** (cis and trans[8]) and **11a1** ; obviously the formation of **9a** and **11a1** is easily explained through the in situ decarboxylation of **4a** and lactone **10a1** respectively.[9]

The results of similar reactions with other unsaturated halides **2** and **3** in various experimental conditions chosen to minimize the decarboxylative side reactions (lower temperature, longer times) are listed in the Table (entries 1-7). In each case the only isolated cyclised products were the two lactones **10a** and **11a**, the presence of minute amounts of vinylcyclopropane **7a** and/or cyclopentene **8a** being undetected through GLC-SM chromatography. The best cumulative yield (**10a** + **11a**) was about 60% at 40°C (entries 3 and 5) except with the use of iodobenzene (entries 6 and 7).

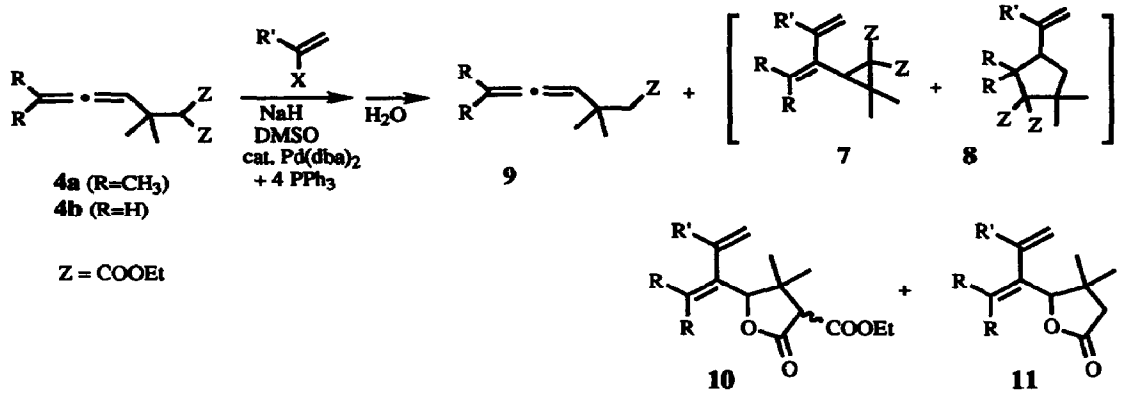
The occurence of O-cyclisation products from β-ketoesters via palladium-mediated ring closures to enolethers is not unprecedented[10] ; however these cyclisations are often reversible and lead easily to the thermodynamically more stable C-alkylated products.[11] Thus, the reasons of this unusual ring closure to lactones **10a** from malonate **4a** were not obvious and the actual nature of the putative palladium intermediates was questioned ; however the presence of the two gem-dimethyl groups in malonate **4a** was logically responsible of this cyclisation to lactone.

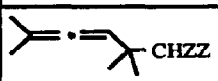
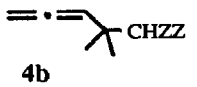
In order to clarify the consequence of each gem-dimethyl group on the ring closure selectivity, two other malonates[12] **4b** and **4c** were tested in similar conditions. Malonate **4b** had an identical behavior and led to lactones **10b** and **11b** (table 1, entries 8 and 9). On the contrary malonate **4c** led to mixtures of vinylcyclopropane **7c** and cyclopentene **8c**, this last one being favored by the use of a bulky vinyl halide as isopropenyl bromide **2**.



1	(R' = H)	60%	**7c1**	70 / 30	**8c1**
2	(R' = CH_3)	60%	**7c2**	5 / 95	**8c2**

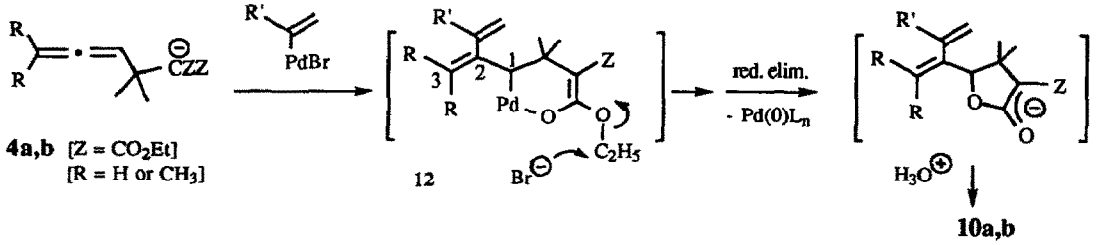
Table :



entry	4	Halide 1, 2, 3	Conditions	Yield (%) 4	9	10 (d.r *)		11
	 4a			4a	9a	10a		11a
1		 1	80°C - 48 h	20	20	10a1	38 (60/40)	- 11a1
2			40°C - 90 h	40	8		38 (60/40)	6
3			40°C - 200 h	30	8		58 (67/33)	6
4		 2	40°C - 48 h	48		10a2	38 (80/20)	- 11a2
5			40°C - 72 h	13	13		53 (82/18)	7
6		 3	80°C - 37 h	23	35	10a3	11 (100/0)	17 11a3
7			40°C - 160 h	2	72		15 (100/0)	3
	 4b							
8		 1	60°C - 60 h			10b1	52 (60/40)	6 11b1
9		 2	60°C - 60 h			10b2	48 (60/40)	2 11b2

* Diastereomeric ratios were obtained by GC and ^{1}H NMR analysis.[10]

Thus it seems clear that the only presence of a gem-dimethyl group in α position of the allenic unit is responsible of the clear-cut change of the ring closure from C3 or C5 cyclisations to O-cyclisation leading to lactone **10**. This could be explained by the impossibility of the classically involved *syn* and *anti* π-allyl **5** to accommodate the bulkyness of this gem-dimethyl group. A likely mechanistic pathway might involve a more favored carbopalladation step leading to an oxapalladacycle **12**, the steric requirements of which are smaller because of a free rotation along the C_1-C_2 bond of the allyl unit. This oxapalladacycle **12** would evolve through the nucleophilic cleavage of the O-C_2H_5 bond and reductive elimination to the anion of lactone **10a**, which gives this lactone on hydrolysis. Recently, the formation of C-O bonds from vinylpalladium intermediates, leading to isocoumarins[13] and pyrones[14], has been rationalised by a related route.



4a,b [Z = CO_2Et] [R = H or CH_3]

Further investigations towards the mechanistic aspect of this new palladium-mediated O-cyclisation to lactones are in progress.

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