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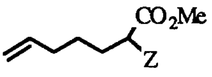
PALLADIUM-MEDIATED CYCLOPENTANATION OF ALKENES BEARING A NUCLEOPHILIC SUBSTITUENT. STEREOCHEMISTRY AND MECHANISM.

Didier BOUYSSI, Geneviève BALME, Guy FOURNET, Nuno MONTEIRO and Jacques GORE,
Laboratoire de Chimie Organique 1, associé au CNRS, Université Claude Bernard, ESCIL
43 Bd du 11 Novembre 1918, 69622 Villeurbanne, France.

Abstract. The increased facility of the reaction 1 ⟶ 2 simultaneously with the increased nucleophilicity of the malonate, as well as the stereospecificity observed in the case of 3, led to the conclusion that the cyclisation proceeds by a nucleophilic attack on the double bond activated by a palladium(II) species.

Recently [1], we described a new palladium-catalyzed cyclisation (1 ⟶ 2) which occured when the anion of 1 (prepared by reaction of 1 with HNa) was treated with vinylic or arylic halides in the presence of a Pd(0) complex (DMSO, 85°C, 1-4 hours).

Only cyclopentanes were formed by this reaction, the homologs of 1 giving preferentially a Heck reaction, namely carbopalladation of the double bond followed by β-elimination of a palladium hydride.



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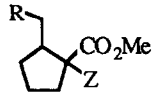
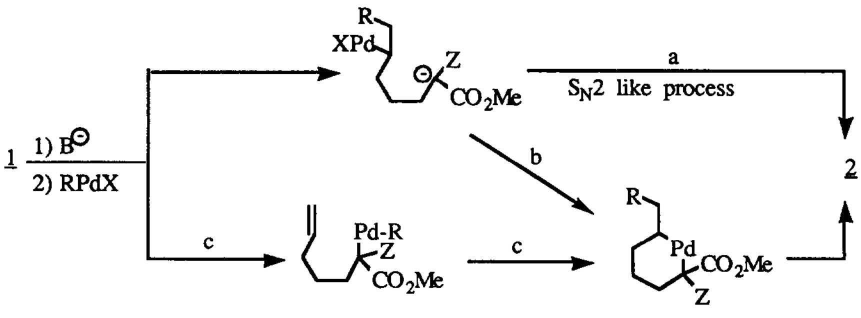


2

Z = CO_2Me , COMe or SO_2Ph
R = vinyl or aryl group

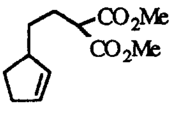
Initially, we considered that this reaction was a two-step process in which carbopalladation of the double bond first takes place and is then followed by cyclisation (or β-elimination). Three pathways a , b , c could be imagined for the cyclisation (scheme 1).



Scheme 1

To get more information about the mechanism of this reaction, it was studied with an aryl iodide and substrate 3 , easily prepared from the commercially available acid 4 . With the hypothesis that in processes a and b the carbopalladation would first take place preferentially by the less hindered diastereoface of the double bond, it was possible to predict :

- that process a would lead to diastereoisomer 5a
- that process b would be difficult to follow because it would produce the strained 5b
- that 5c would be the product of process c



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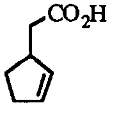

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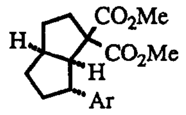
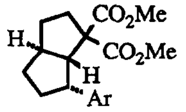
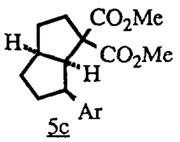


5a Ar = phenyl
6a Ar = p-tolyl



5b



5c

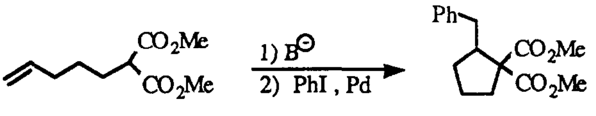
Unfortunately, when 3 was treated successively with 1.1 equivalent of sodium hydride and phenyl iodide in the presence of 0.04 equivalent of the palladium-diphos complex [2] in DMSO at 85°C, no reaction occurred except a slow degradation. We then turned our attention to conditions known to accelerate the Heck reaction [3] by varying several parameters : nature of the solvant, of the palladium ligands, of the base etc. and (or) addition to the reaction mixture of ammonium salts (phase transfer reagents) or anionic activators. The results summarized in table 1 show that :

* the yield of the reaction, and the amount of transformed 3, are fairly dependent on these reaction parameters, with the counter-ion of the enolate (K in place of Na) being the most influent.

* in every case, the reaction is stereospecific leading exclusively to 5a, the structure of which was deduced from NMR [4], and confirmed by X-Ray [5] of its homolog 6a obtained in the same reaction using p-iodotoluene (conditions of entry 4; recovered 3 : 22%, yield of 6a : 48%).

* in no case was it possible to complete the reaction, even by adding fresh catalyst or excess base to the reaction mixture after several hours.

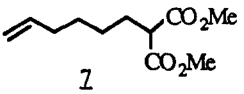
Having shown, in the case of 3, the great influence of the reaction conditions on the course of the annelation (rate and yield), we came back to the basic reaction 1a ⟶ 2a and repeated it with different solvents, diverse catalysts and eventually anionic activators. Some of the results obtained are listed in Table 2.



1a 2a

From these results, it becomes again evident that the main effect is due to the increase of the nucleophilicity of the enolate by i) the use of potassium as counter-ion ii) the presence of cation chelating additives such as 18-Crown-6 (entry 8) or TDA 1 [6] (entry 6). The nature of the solvent and the presence of phosphine have only a limited effect on the facility of the reaction that can be run with a high yield in only one hour at room temperature [7].

Unfortunately, even under these conditions, the reaction remains limited to the formation of a five membered ring : the treatment of 7 successively by 1,1 equivalent of tBuOK, and then by phenyl iodide (1,1 equivalent) $Pd(OAc)_2$ (0.04 equivalent) in NMP at 20° in the presence of aliquat 336 (0.1 equivalent) leads exclusively to 8 in 24 hours and 75 % yield.



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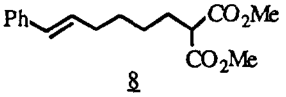

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entry n°	solvent	base	additive [a]	reaction conditions	Recovered [b] 4	Yield of 6a [b]
1	DMF	HNa	Aliquat 336 (1 eq.)	80°- 22 h	70%	15%
2	NMP[c]	"	"	" - 46 h	60%	25%
3	"	tBuOK	"	50° - 9 h	30%	47%
4	"	"	18-Crown-6 (0.2 éq.)	" - 6h30	15%	53%
5	"	"	TEBA (1 eq.)	" "	"	"

All the reactions were performed with $Pd(OAc)_2$ as catalyst (0.04 eq.) 1.1 eq. of base , 1.1 eq. of phenyl iodide on a millimole scale.

a : aliquat 336 = tricaprylylmethylammonium chloride

b : 4 and 6 were purified by flash-chromatography. The yield of 6a refers to the quantity of starting 4

c : NMP = N-methylpyrrolidone

Table 1

entry n°	solvent	base	catalyst	additive[a]	Reaction Conditions	Yield of 2a [b]
1	DMSO	HNa	$Pd(dba)_2$+dppe	-	85° - 1h30	75%
2	NMP	tBuOK	Pd(dppe)	-	20° - 3 h	82%
3	THF	"	"	-	" - 2 h	80%
4	NMP	"	$Pd(OAc)_2$	-	25° - 24 h	60%
5	"	"	"	Aliquat 336 (0.1 eq)	" "	80%
6	"	"	"	TDA 1 (0.1 eq)	" - 1h30	78%
7	Toluene	"	"	-	" - 100h	d
8	"	"	"	18 crown-6 (0.2 eq)	" - 1h	79%

All the reactions were performed on a millimole scale with 1.1 eq. of base , 1.1 eq. of phenyl iodide and 0.04 eq. of catalyst.

a : TDA 1 = tris (3.6 dioxaheptyl) amine.

b : based on quantities of 2a purified by flash-chromatography

c : The crude product contains several unidentified products

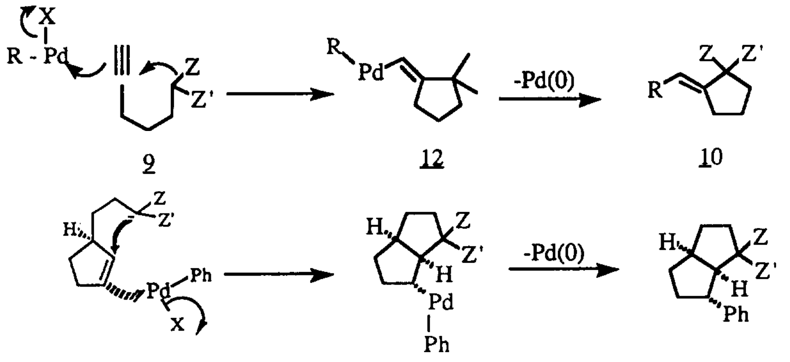
d : only 30% of 1a is engaged. The transformed product consists essentially of 2a.

Table 2

As regards the mechanism of the reaction it appears :

* that the nucleophilicity of the enolate is the most important factor in determining the rate of the reaction. This can fit with all processes a , b , c depicted before.

* that the stereospecificity of the reaction (3 → 5a) would suppose, in the case of mechanism a , a surprisingly complete addition of the σ-aryl-palladium species on the less hindered diastereoface of the double bond (no trace of 5b or 5c was ever detected). This, and mainly the ANTI stereospecific process which was observed in the case of the acetylenic homologs [8] (9 gives exclusively 10), led us to conclude that the annelation is an attack, by the enolate, of the unsaturation electrophilically activated by the σ-aryl (or vinyl) palladium species (scheme 2). In the case of ethylenic substrates, this cyclisation is favored only if the formation of a cyclopentane ring can occur ; if this process cannot occur, it is replaced by a normal Heck reaction. Finally, a reductive elimination from the resulting σ-bonded palladium species 11 or 12 leads to the reaction products 5a (or 2a) and 10.



9 12 10

11 5a

(R = aryl or vinyl)

Scheme 2

References and notes

1. Fournet, G. ; Balme, G. and Gore, J. ;
   a) Tetrahedron Lett. **1989** , 30 , 69.
   b) Tetrahedron, **1990** , 46 , 7763.
2. This complex is made "in situ" by the reduction of $Pd(OAc)_2$ in the presence of dppe (bis-diphenylphosphinoethane) and 1-heptene.
3. See inter alia :
   a) Jeffery, T. ; J.Chem.Soc.Chem.Comm. **1984**, 1287 and Tetrahedron Lett. **1985**, 26, 2667.
   b) Larock, R.C. and Baker, B.E. ; Tetrahedron Lett., **1988**, 29, 905.
   c) Larock, R.C. and Babu, S. ; Tetrahedron Lett., **1987** , 28 , 5291.
   d) Larock, R.C. and Gong, W.H. ; J. Org. Chem., **1990**, 55, 407.
4. 400 MHz experiments. The chemical shift of all the protons where determined by 2D spectra and the relative configuration of the asymetric carbons by differencial NOE measurements. Thanks are due to J.J.Barieux and B.Van Hemelryck (Atochem Pierre Bénite) for their efficient help.
5. The assistance of R. Faure from our University is greatly acknowledged.
6. Soula, G. ; J. Org. Chem., **1985** , 50 , 3717.
7. It is also possible to run the reaction at -20°C (conditions of Table 2, entry 2) but in 48 hours.
8. Fournet, G. ; Balme, G. and Gore, J. ; Tetrahedron Lett. **1990** , 31, 5147.

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