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A Steric Control of Regioselectivity in Palladium-Catalyzed Cyclizations of Alkenes Bearing Arylbromides and Nucleophiles

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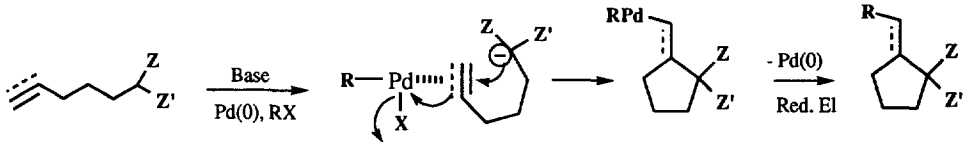
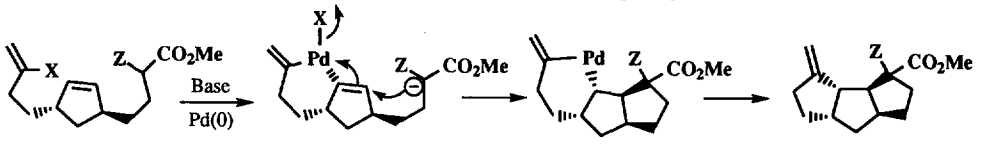
Abstract : The stereocontrolled synthesis of tricyclic compounds through an efficient and highly regioselective 5-exo-trig palladium catalyzed biscyclization process is reported, starting from compounds **1**. The 6-endo competing cyclization can also be the only pathway leading to *trans*-octahydrophenanthrene. In this finely balanced competition , it appeared that the 6-endo to 5-exo ratio is dependent upon the size of the nucleophilic part of the starting material.

For several years, we have been exploring the synthetic potential of a new palladium-mediated cyclization of unsaturated substrates bearing a nucleophilic substituent [1](*Scheme 1*).



Scheme 1

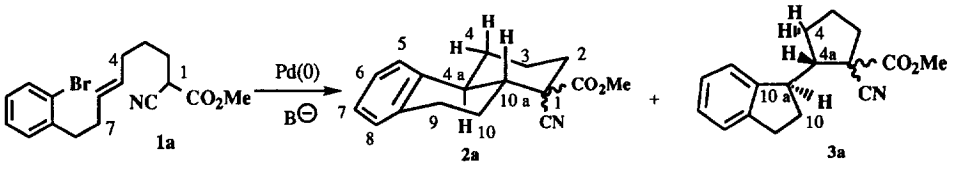
By using an intramolecular version of this process, we have recently reported a method for the construction of fused tricyclopentanoids [2] (*Scheme 2)* . We found that the nature of the nucleophile (Z = CN) and of the vinylic halogen (X = Br) were determinent to avoid the competing Heck reaction.



Scheme 2

It is noteworthy that these cyclizations proceed in a completely stereoselective *trans* manner since they involve an attack by the carbon nucleophile onto the unsaturation electrophilically activated by the palladium species.

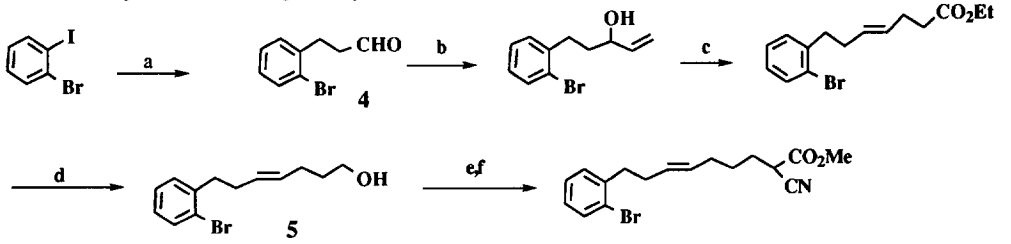
In our continuous efforts on the development of "one step" synthesis of tricyclic system [3] and on the basis of the above results, we became interested to study the palladium biscyclization of the linear (E)-**1a**. Indeed, it was anticipated that this cyclization could proceed by either a 5-exo- or 6-endo-trig process leading respectively to tricyclic compounds **2a** or **3a**. In compound **2a**, the ring fusion must be trans because of the stereochemistry of the initial double bond substrate; the relative configuration of **3a** would be fixed for the same reason *(scheme 3)*.



Scheme 3

The required E-**1a** was easily prepared from the readily available 3-(2-bromo-phenyl)propanal **4**, the key step being a stereoselective Claisen-Johnson rearrangement [4] *(scheme 4)*.

The aldehyde was previously prepared [5] in five steps from *o*-bromobenzyl bromide by a malonic ester synthesis. We found that **4** can be obtained in one step by the palladium-catalyzed reaction of 2-bromo-iodo benzene with allylic alcohol using Jeffery's conditions [6].



a) allyl alcohol, $Pd(OAc)_2$, $NaHCO_3$, TEBA, DMF, 50°C; b) vinyl magnesium bromide ; c)$MeC(OEt)_3$, $EtCO_2H$ cat, Δ ; d) $LiAlH_4$; e) MsCl, Et_3N ; f) methylcyanoacetate, NaH, KI cat, DMF/THF, 70°C

Scheme 4

When **1a** was subjected to biscyclization reaction conditions (1.1 equivalent of tBuOK, 0.2 equivalent of 18-crown-6, 5 mole % Pd(dppe)[7], THF, room temperature) the starting material was not consumed. After a screening of various solvents and temperatures, we found that substrate **1a** cyclized in 1-methyl-2-pyrrolidinone, at 50°C, to give in 70% yield a 1:1 mixture of two tricyclic compounds. The ^1H NMR spectrum of the crude reaction product showed no traces of bicyclic substrates resulting from the competing Heck reaction.

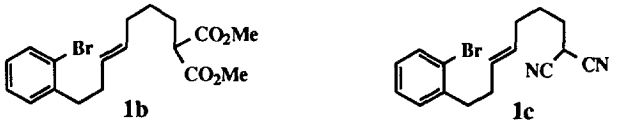
These two tricyclic compounds were readily separated by careful medium pressure liquid chromatography and their structures were assigned on the basis of spectral data [8].

The solid less polar product was identified as one epimer of **2a** by a 400 MHz two dimensional DQF COSY spectra and ^1H-^{13}C HMQC experiment recorded in the phase-sensitive mode [9]. The $J_{4a\text{-}10a}$, $J_{4a\text{-}4ax}$ and $J_{4a\text{-}4eq}$ constant were respectively 12.1, 11.3 and 3.9 Hz and consistant with the expected two $J_{ax\text{-}ax}$, one $J_{ax\text{-}eq}$ of a *trans*- octahydrophenanthrene [10].

The structure assigned to the liquid more polar product was one epimer of **3a** by arguments analogous to those made for assigment of **2a**. In the ^1H NMR spectrum, the double doublet of doublets at 3.4 is assigned to the H_{10a} angular proton. It is coupled to the adjacent H_{10} et $H_{10'}$ protons by coupling constants $J_{10a\text{-}10} = 8.3$, $J_{10a\text{-}10'} = 7.1$ Hz typical of a five-membered ring. The splitting of the H_{10a} signal due to its coupling with the adjacent angular proton H_{4a} ($J_{10a\text{-}4a} = 11.5$ Hz) confirms the expected anti relationship between them.

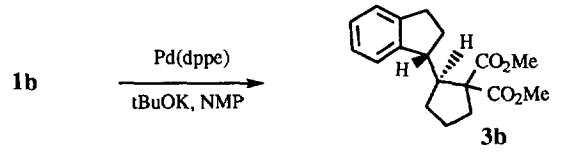
As expected, the palladium induced cyclization of **1a** proceeded via both exo- and endo- pathway, but surprisingly, only one diastereomer of **2a** and **3a** were formed in which the configuration of the quaternary center was not determined.

At this stage of our work, we decided to study the cyclization selectivity (5-exo- versus 6-endo-trig) of this reaction. The examination of molecular models led us to think that the factor controlling the regioselectivity would be the steric hindrance of the nucleophile. Indeed, because of the strain generated by the double bond, 6-endo trig cyclization would be preferred over 5-exo-trig cyclization in the absence of severe steric effects between the nucleophile and one of the hydrogen (H_7) of the linear substrate and five-membered ring formation would be favoured over six-membered ring formation in the presence of a bulky nucleophile. On the basis of the above discussion, we believed that it would be possible to control the regioselectivity of the reaction by changing the size of the nucleophile. Substrates **1b** and **1c** seemed to be perfect candidates to test the viability of this approach. They were readily obtained from alcohol **5** by conventional manners[11]. *(Scheme 5)*



Scheme 5

1b was submitted to the experimental conditions used for **1a**, the evolution of the reaction being monitored conveniently by GPC and TLC. Much to our delight, the starting material underwent a regiospecific 5-exo-trig cyclization to give, after 15 hours at 60°C, exclusively the compound **3b** isolated in 55% yield after chromatographic purification. No traces of formation of the other regioisomer or of the product of a classical Heck reaction were observed in the limits of ^1H NMR and capillary GC sensivities. The structure of the liquid **3b** was deduced from the same arguments than that of **3a**.*(Scheme 6)*



Scheme 6

We can see here **the beneficial influence of a bulky nucleophile on the regioselectivity** of this palladium-biscyclization process yielding exclusively the cyclopentanic compound **3b** via the 5-exo-trig pathway.

Having solded the problem of controlling the 5-exo-cyclization we turned our attention to the palladobiscyclization of **1c** having a less bulky nucleophile . Using the procedure mentioned above, we observed that the cyclization rate is slower than that of **1a** and **1b** since all the starting material was consumed after 65 hours

at 60°C [12]. Only the crystalline regioisomer **2c** resulting from the 6-endo-trig cyclization process was isolated in 52% yield after flash-chromatography. Its structure was confirmed by the observation that the signals of the rings carbons of compounds **2a** and **2c** showed very similar chemical shifts [13] *(Scheme 7)*

Scheme 7

This last result shows that the tandem carbopalladation-cyclization sequence proceeds here with **complete regio- and stereoselectivity** leading to the *trans* perhydrophenantrene ring. This system is very common in natural products in particular in the carbon framework of steroids and triterpenoids.

In conclusion, we have shown that it is possible to control the regioselectivity of the biscyclization of linear substrates of type **1** by varying the size of the nucleophile. Clearly, exo-cyclization is preferable with the bulkier substituents at nucleophilic center leading to cyclopentanic compounds. On the other hand, endo-cyclization leading to fused *trans* 6-membered ring is only observed with a thiner nucleophile. Application of this chemistry to the synthesis of natural products is currently under investigation.

References and notes

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5 Cooke, M.P. and Widener R.K. *J. Org. Chem.*, **1987**, *52*, 1381-139 . See also : Beak P. and Selling, G. W. *J.Org.Chem.* , **1989**, *54*, 5574-5580.
6. To our knowlege this aldehyde was not previously prepared using a Heck reaction . We used here the Jeffery's conditions ; Jeffery, T. *Tetrahedron Lett.* , **1991**, *32*, 2121-2124.
7 The palladium diphenylphosphinoethane was preformed by heating $Pd(OAc)_2$ (0.05 mol.eq.) and dppe (0.05 mol.eq.) in the presence of 1-heptene (0.1eq., NMP, 50°C) until homogeneous dark red solution is obtained.
8 Full spectroscopic data, consistent with the structures given, have been obtained for all compounds reported herein and the ratio of isomers was determined by capillary G.C. analysis.
9. J couplings were best measured on the 1D after assigment from the 2D spectra.
10. Funk, R. L. and Vollhardt, K. P. C. *J. Am. Chem. Soc.* , **1980**, *102*, 5245-5253.
11. Substrate **1b** was prepared by alkylation of methylmalonate with the mesylate derived from alcohol **5** and **1c** by alkylation of malononitrile with the iodide derived from alcohol **5**.
12. The difference in the rate of cyclization beetwen a malononitrile and a methylmalonate or a methylcyano-acetate derivative was already observed see : Bouyssi, D. , Coudanne, I., Uriot, H., Goré J. and Balme G. *Tetrahedron Lett.* , **1995** , *36*, 8019-8022.
13. ^{13}C ($CDCl_3$) data of the non CH benzylic carbons and of CH_2 carbons for compounds:
2a : 44,5 (CH), 38,8 (CH), 34,4 (CH_2), 30,1 (CH_2), 29,3 (CH_2), 26,0 (CH_2), 22,6 (CH_2),
2c : 45,7 (CH), 38,6 (CH), 34,8 (CH_2), 29,3 (CH_2), 28,9 (CH_2), 26,3 (CH_2), 21,9 (CH_2),

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