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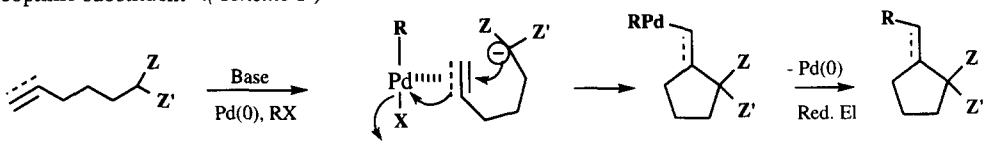
# Three Partners for a One Pot Palladium-Mediated Synthesis of Various Tetrahydrofurans.

**M. Cavicchioli, E. Sixdenier, A. Derrey, D. Bouyssi and G. Balme***
*Laboratoire de Chimie Organique 1 , associé au CNRS, Université Claude Bernard, CPE, 43 Bd du 11 Novembre 1918, 69622 Villeurbanne Cédex.*

***Abstract :*** Substituted furans are obtained in a one step procedure from addition of allylic alkoxides to Michael acceptors followed by a palladium catalysed cyclisation involving iodo-aryl compounds.

Due to their widespread occurence in nature and biological properties, cyclic ethers represent important targets for organic chemists [1]. Over the last twenty years, many synthetic methodologies have been developed in their direction. Original strategies in this area are still emerging [2] and powerful new synthetic routes involve appropriate combinations of different reactions in a " one-pot" operation [3].

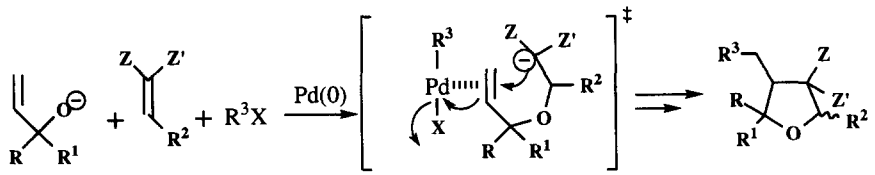
As part of our ongoing interest in palladium chemistry, particularly for the construction of various carbocycles, we recently described a new palladium mediated cyclisation of unsaturated substrates bearing a nucleophilic substituent [4].*( scheme 1 )*




Z , Z' = electrowithdrawing groups ; R = aryl, alkenyl, alkynyl

*scheme 1*

Therefore, we became interested in the application of this new carbopalladation-cyclisation process to the "**one pot synthesis**" of functionalized heterocyclic compounds using three commercial or readily available starting materials *( scheme 2 ).*




*scheme 2*

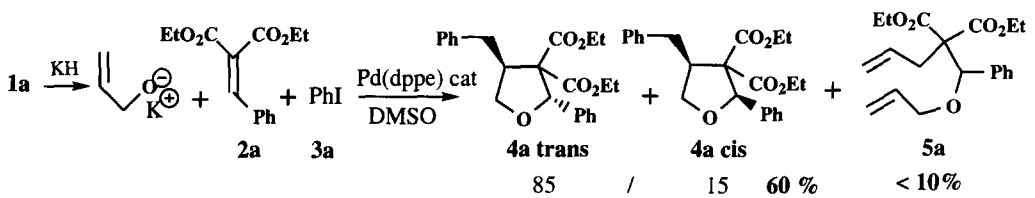
* E-mail : balme@univ-lyon1.fr ; Fax : 04.72.43.12.14

This simple approach to five membered ring oxygen heterocycles first involves an intermolecular conjugate addition of an oxygen nucleophile to a Michael acceptor. This generates an enolate intermediate which can then attack the unsaturation electrophilically activated by the organopalladium species.

Because of its intermolecularity, the success of these " cascade addition-cyclisation-coupling processes " depends on the order in which the three components react one with each other since competitive side reactions may occur. Among these, the Heck reaction between Michael acceptors and unsaturated halides could be anticipated [5]. The reaction of alkoxides with organopalladium species is also a known process [6] and indeed, it appeared to be a major problem at the early stage of our studies. ( vide infra )

To test the viability of our approach, we initially chose allylic alcool **1a**, diethylbenzylidenemalonate **2a** and phenyliodide **3a** as test substrates. Treatment of the potassioalkoxide generated from **1a** ( using KH as base ) with **2a** in the presence of **3a** and 0. 05 % mol of Pd(dppe) as catalyst in various solvents, led mainly to a premature trapping of the alkoxide by the organopalladium species.

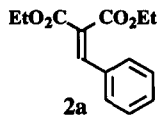
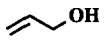
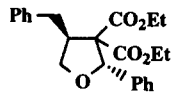
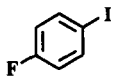
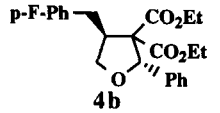
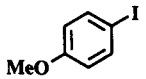
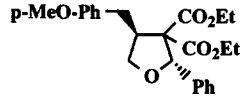
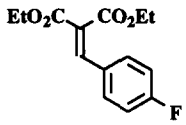
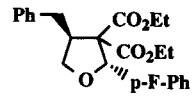
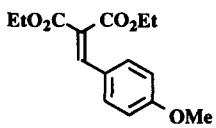
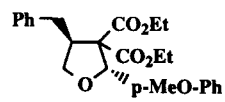
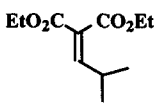
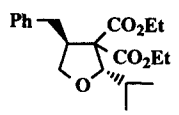
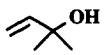
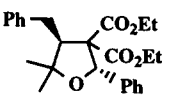
In order to avoid this undesirable side reaction, we decided to add slowly the alkoxide via a syringe pump. Indeed, we found that, under optimized conditions, slow addition of an excess of potassioalkoxide ( 2 equiv, 1M in DMSO ) at a rate of 0.7 mL / hour to a DMSO solution of the Michael acceptor ( 1 equiv ), phenyliodide ( 1.5 equiv ) and 0.05 mol % of preformed Pd(dppe) at 50°C, gave the target tetrahydrofuran **4a** as a 85:15 mixture of trans and cis diastereomers and in 60% yield ( based on **2a** ) .The cyclised product **4a** is accompanied by small amounts ( < 10 % ) of an uncyclised compound [7] identified as **5a** by $^1H$ and $^{13}C$ NMR spectroscopy. Estimation of isomeric ratios, measured on the crude reaction mixture, was based on capillary GLC analysis and on the integrals of the $^1H$ NMR signals corresponding to the o-methine proton at $C_2$. The stereochemistry assignment is based on the NOESY spectrum of the isolated [8] major isomer which clearly indicates that the $C_2$ methine proton correlates with the two benzylic protons. Furthermore, no correlation was observed between the $C_2$ and $C_4$ methine protons.*( scheme 3 )*




*scheme 3*

During the optimization of the protocol, various bases and solvents were tested and the combination of potassium hydride and DMSO proved to be the best for this reaction. The use of sodium hydride led to a decrease in the yields of **4a** but surprisingly, butyllithium provided better results. ( see table I entry 1, 2 and 3 ). The nature of the palladium complex was found to be essential for the reaction to proceed : employing $PPh_3$, P(o-tol)$_3$, tri(furyl)phosphine instead of the bidentate ligand dppe, led only to small amounts of cyclised product. When the reaction was carried out in THF, DMF, acetonitrile, THF/DMSO, little or no furan derivative **4a** was obtained. In order to explore the scope of this tetrahydrofuran synthesis, we examined the cyclization of several Michael acceptors in the presence of different aryl halides and allylic alcools using the procedure outlined above. ( see table I )

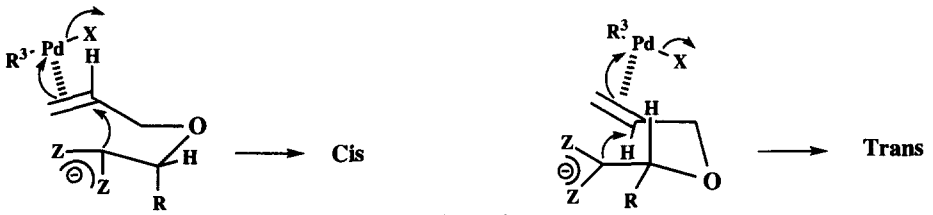
**Table 1** : Synthesis of furans (scheme 2) [a]

| entry | Michael acceptor | iodoarene | alcohol | Base | product [b] | yield (%)[c] |
|---|---|---|---|---|---|---|
| 1 |  |  |  | KH |  | 60 |
| 2 | | | | NaH | | 30 |
| 3 | **2a** | **3a** | **1a** | BuLi | **4a** | 50 |
| 4 | **2a** |  | **1a** | KH |  | 70 |
| 5 | | | | BuLi | **4b** | 40 |
| 6 | **2a** |  | **1a** | KH |  | 66 |
| 7 | | | | BuLi | **4c** | 35 |
| 8 |  | **3a** | **1a** | KH |  | 60 |
| 9 | | | | BuLi | **4d** | 30 |
| 10 |  | **3a** | **1a** | KH |  | 66 |
| 11 | | | | BuLi | **4e** | 35 |
| 12 |  | **3a** | **1a** | KH |  | 60 |
| 13 | | | | BuLi | **4f** | 40 |
| 14 | **2a** | **3a** |  | KH |  | 10 |
| 15 | | | | BuLi | **4g** | 30 |

a) All reactions were carried out at 50 °C on a 2 mmol scale ( referred to Michael acceptors ) . b) Major diastereomer shown (Cis/ Trans : ca : 15 / 85). c) Isolated yield of diastereomeric mixture after chromatography.

Fair isolated yields of furans were obtained with both electon-rich (entry 6) and electron-poor ( entry 4) organopalladium precursors in the presence of diethylbenzylidenemalonate **2a** or with phenyliodide as arylhalide while varying $R_3$ substituent on the Michael acceptors [9]( entry 8, 10, 12 ). The effect of substituents at the α position of the allylic alcool was briefly examined. The hindered 2-methyl-3-buten-2-ol **1b** reacted with

**2a** and **3a** to afford trans 2-4 furan **4g** as the sole tetrahydrofuran diastereomer but in low yields.The assigned stereochemistry was deduced from NOESY studies. In all cases studied, the substituted furans **4a-4g** were always accompanied by undesired adducts of type **5** ( 5 to 10%). Furthermore, there was high selectivity for the trans isomer and the observed isomeric ratio appeared independent of the nature of the enolate counterion and of steric factors arising from $C_2$ substituents and aryl halides. This can be rationalized by invoking a chairlike transition state for the ring closure whith the $C_2$ substituent preferentially located at pseudo equatorial position, the product was a trans isomer. *( scheme 4)*




*(scheme 4)*

In summary, a conceptually new and convergent synthetic route to substituted tetrahydrofurans has been developed using a one-pot " three components " Michael-carbopalladation-cyclisation process. We are currently investigating the extension of this methodology to the synthesis of other heteroatomic analogs as well as that of natural products.

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7. Further work is underway to elucidate the mechanism of formation of compounds of type **5**
8. trans-**4a** was obtained by careful flash chromatography on silicagel (petroleum ether/$Et_2O$: 85/15); $^1H$ NMR of compound trans-**4a** ( 300 MHz, $CDCl_3$) (assignment facilitated by selective irradiations) : 0.8 (t, 3H, J=7.1Hz, $CH_3$ ); 1.3 (t, 3H, J=7.1Hz, $CH_3$ ); 2.36 (dxd, 1H, J= 13.0, 12.9 Hz ,CH*H*Ph); 3.07 (dxd, 1H, 3.6; 13.1 Hz, C*H*HPh); 3.35-3.52 (m, 2H, ,$H_4$ and one H of the four $CO_2CH_2CH_3$ ); 3.75 (dxd, 1H, J=8.3, 8.2 Hz, one of the two $H_5$); 3.75-3.85 (1H, one H of the four $CO_2CH_2CH_3$ ); 4.2-4.3 (m, 1H, one H of the four $CO_2CH_2CH_3$ ); 4.3-4.4 (m, 1H, one H of the four $CO_2CH_2CH_3$ ); 5.75 (s, 1H, $H_2$); 7.1-7.5 (m, 10H, ArH)
9 Prepared by a Knoevenagel condensation between diethylmalonate and commercial 4-fluorobenzaldehyde, p-anisaldehyde and isobutyraldehyde.

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