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Palladium-Mediated Stereo- and Regioselective Tandem-Cyclization- Carbonylations of 1,3-dienes.

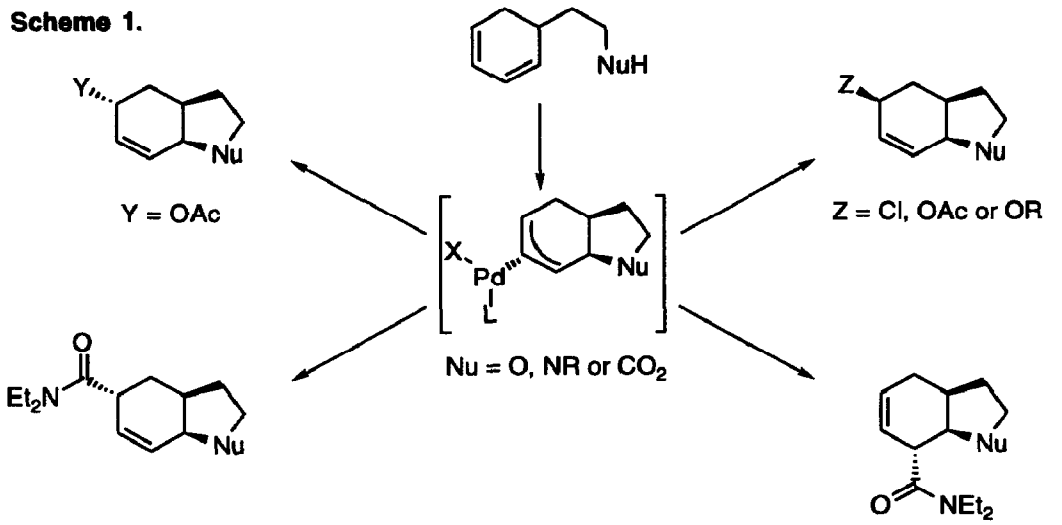
Pher G. Andersson * and Attila Aranyos

Department of Organic Chemistry, University of Uppsala
Box 531, S-751 21 Uppsala, Sweden

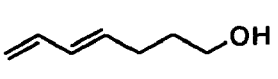
Abstract: A new palladium-mediated tandem cyclization-carbonylation of 1,3-dienes is described. The reaction proceeds via an intramolecular nucleophilic addition on the diene to give an intermediate π-allyl palladium complex which is subsequently carbonylated to give either a overall 1,2- or 1,4-addition over the diene. By proper choice of reaction conditions control of the regiochemical outcome of the reaction was obtained.

We have earlier reported on the palladium-catalyzed 1,4-oxidation of 1,3-dienes possessing an intramolecular nucleophile which gives rise to various heterocycles in a regio- and stereoselective manner.[1] An interesting feature of these cyclizations is that the external nucleophile can be directed to give *either* an overall *cis* or *trans* addition over the diene. Furthermore, the products obtained can be further functionalized thanks to the versatility of the allylic chlorides or acetates in organic synthesis.[1d,2]

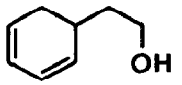
Scheme 1.



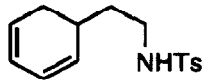
It occurred to us that the intermediate π-allyl palladium complex could be trapped by carbon monoxide insertion into a palladium carbon bond and subsequent aminolysis. If successful, this tandem cyclization-carbonylation would lead to the regio- and stereoselective formation of one heterocycle and one carbon-carbon bond in one operation. Although the insertion of carbon monoxide into the metal-carbon σ-bonds of vinyl- and alkylpalladium species has found several uses in organic synthesis,[3] the corresponding examples of insertion into palladium π-allyl complexes are relatively few.[4]



1

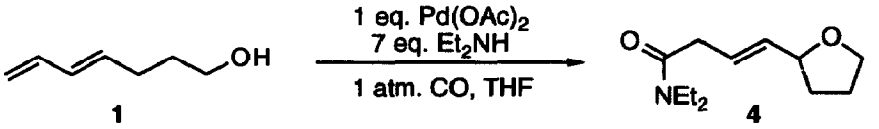


2



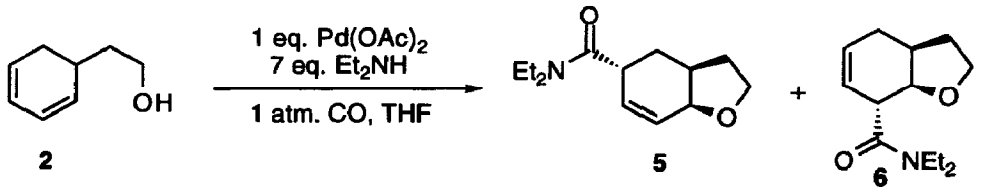
3

The starting materials (1-3) were all synthesized according to literature procedures. Compound **1** was readily available via a Johnson-Claisen rearrangement of divinylcarbinol[5] and subsequent reduction of the ethyl ester[6] while **2** and **3** were synthesized via organo-palladium routes.[1b,2] When **1** was treated with 1 eq. of $Pd(OAc)_2$ and 7 eq. diethylamine in THF under an atmospheric pressure of CO the tetrahydrofuran **4** was obtained in 80% yield. The selectivity for the 1,4- contra 1,2-addition was 95 : 5.



1 **4** (Eq. 1.)

Encouraged by this result we turned our attention to diene-alcohol **2**. With this substrate however, a substantial decrease in regioselectivity was obtained. Performing the reaction of **2** under same reaction conditions as for **1** resulted in a 3.3 : 1 mixture of the 1,4- and 1,2-adducts **5** and **6**. In order to optimize the regio-selectivity of the reaction several different conditions were tried. It was found that the solvent had some influence on the regiochemical outcome of the reaction. Changing the solvent from THF to DMF gave a 5 : 1 mixture of **5** and **6** while using methylene chloride resulted in a 6 : 1 mixture although in low yield. Interestingly, it was also found that the regiochemical outcome of the reaction depends on the pressure of the CO. When the reaction of diene alcohol **2** was performed at an atmospheric pressure of carbon monoxide in THF the ratio between **5** and **6** was 3.3 : 1. Performing the same reaction at a slightly elevated pressure (3 atm.) resulted in a ratio of 1.5 : 1 while running the reaction at 30 atmospheres gave a 1 : 1 mixture of the two amides **5** and **6**. Further increase of the pressure did not result in any significant change of this ratio.



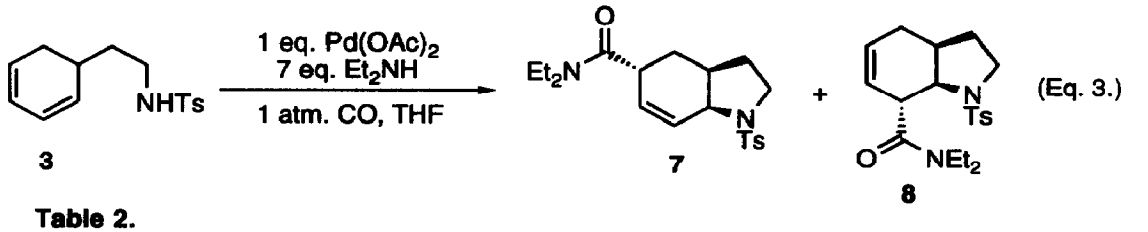
2 **5** **6** (Eq. 2.)

Table 1.

Entry	Solvent	CO Pressure	1,4-addition		1,2-addition	Yield[1]
1	THF	1 atm	77	:	23	72 %
2	THF	3 atm.	60	:	40	81 %
3	THF	30 atm.	50	:	50	52 %
4	THF	65 atm.	50	:	50	82 %
5	Toluene	1 atm.	---	---	---	0 %
6	CH_3CN	1 atm.	70	:	30	37 %
7	CH_2Cl_2	1 atm.	86	:	14	40 %
8	DMF	1 atm.	83	:	17	53 %
9	THF:DMF 1:1	1 atm.	80	:	20	74 %

[1]Determined by ^1H NMR on the reaction mixture.

With these results in hand we investigated the cyclization of the diene amide **3**. When **3** was reacted with $Pd(OAc)_2$ and diethyl amine in THF at one atmosphere of CO, a 1 : 1 mixture of the two amides **7** and **8** was formed in high yield.[7,8] When the CO pressure was increased to 90 atmospheres the ratio between **7** and **8** changed to 1 : 2. The selectivity could be changed towards the 1,4-adduct **7** by changing the solvent. If the reaction was performed in DMF the ratio of 1,4- to 1,2-adduct was altered to 4 : 1 and if methylene chloride was used this ratio changed to 6 : 1.



3 7 8 (Eq. 3.)

Table 2.

Entry	Solvent	CO Pressure	1,4-addition		1,2-addition	Yield[1]
1	THF	1 atm	50	:	50	76 %
2	THF	90 atm.	33	:	67	82 %
3	DMF	1 atm.	80	:	20	79 %
4	CH_2Cl_2	1 atm.	86	:	14	72 %

[1] Isolated yields.

Thus, in the case of amides **7** and **8** it was possible to change the selectivity from 67 % 1,2- to 85 % 1,4-addition over the diene system by altering the solvent and CO pressure. All attempts to turn the tandem cyclization-carbonylation into a catalytic process with respect to palladium were unsuccessful. This is possibly due to difficulties with reoxidizing Pd(0) to Pd(II) in the presence of carbon monoxide. Attempts were also made to insert isonitrile instead of carbon monoxide in the intermediate π-allyl palladium complex since it is known that this is a very facile process for palladium σ-bonds.[9] However, all attempts to insert *t*-butylisonitrile in the reaction of **2** failed and no cyclized products could be isolated.

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7. General Procedure (for **3**): K_2CO_3 (60 mg, 0.423 mmol) and $Pd(CH_3CN)_2Cl_2$ (110 mg, 0.423 mmol) were dissolved in THF (5 ml), and **3** (50 mg, 0.404 mmol) was added. The reaction vessel was sealed with a septum and the mixture was stirred at room temperature for 5 minutes (NMR spectroscopy showed that the Pd-(π-allyl) complex was formed immediately.) To the stirred solution $HNEt_2$ (315 µl, 3.03 mmol) was added and the mixture was subjected to CO (bubbling through the solution at 1atm, or charged in an autoclave) and the reaction mixture was stirred overnight. Ether (15 ml) was added, the resulting mixture was filtered through celite, washed with water (4 ml) and brine (4 ml) and the organic phase was dried over $MgSO_4$. The solvent was removed in vacuo and the product ratio was checked by NMR and HPLC. The two isomers were separated via preparative HLPC using a 1:1 mixture of hexane and ethyl acetate as eluent.

   Spectral data for compound **7**: ^1H NMR (300 MHz in $CDCl_3$) 7.72 (d, J = 10.7 Hz, 2H), 7.31 (d J = 10.7 Hz, 2H), 5.98-6.04 (dtd, J = 10, 2.3, 0.3 Hz, 1H), 5.61-5.67 (dm, J = 10 Hz, 1H), 3.99-4.04 (m, 1H), 3,48-3.56 (m, 1H) 3.3-3.41 (m, 4H), 3.22-3.30 (m, 1H), 3.06-3.16(m, 1H) 2.42 (s, 3H), 2.17-2.28 (m, 1H), 1.95-2.07 (m, 1H), 1.65-1.79 (m, 1H), 1.19 (t, J = 7.2 Hz, 3H) 1.09 (t, J = 7.2 Hz, 3H).; ^{13}C NMR:(75.42 MHz in $CDCl_3$) 172.58, 143.41, 134.28, 129.84, 129.67, 127.53, 126.15, 56.73, 47.40, 41.95, 40.35, 35.29, 27.99, 26.63, 21.52, 14.88, 13.00.; MS e/m (%) 223 (2.5), 222 (11.6), 221 (80), 155 (9.8), 148 (8.2), 139 (5.3), 121 (8.3), 120 (38.2), 118 (8), 100 (85.6), 91 (100), 72 (69.9), 65 (30).; IR (in $CDCl_3$ solution) 2978, 2256, 1628, 1460, 1448, 1434, 1344,1214, 1161,1092.

   Spectral data for compoud **8**: ^1H NMR (300 MHz, $CDCl_3$) :7.69 (d, J = 10.6 Hz, 2H), 7.29 (d, J = 10.6 Hz, 2H), 5.8-5.87 (m, 1H), 5.5-5.57 (ap .dqd, J = 10.0, 1.9, 0.8 Hz 1H), 4.11-4.16 (dd, J = 7.2, 4 Hz, 1H), 3.72-3.77 (m, 1H), 3.33-3.65 (m, 5H), 3.09-3.17 (m, 1H), 2.41 (s, 3H), 2.27-2.38 (dm, J = 17 Hz, 1H), 2.0-2.11 (m, 1H), 1.83-1.94 (dm, J = 17 Hz, 1H), 1.49-1.73 (m, 2H), 1.28(t, J = 7 Hz, 3H), 1.18(t, J = 7 Hz 3H).; ^{13}C NMR (75.42 MHz in $CDCl_3$):172.49, 143.34, 133.79, 129.63, 127.69, 127.11, 123.5, 59.40, 47.55, 43.61, 42.45, 40.74, 35.48, 30.21, 25.52, 21.50, 14.80, 12.92.; MS e/m (%) 223 (5.3), 222 (9.2), 221 (54.5), 155 (11.4), 148 (23.2), 121 (10.2), 120 (24), 118 (10.3) 100 (88.67), 92 (20.3), 91 (100), 77 (20.1), 65 (40.3).; IR (in $CDCl_3$ solution) 2977, 2253, 2242, 1733, 1630, 1599, 1461 1435, 1342, 1286, 1216, 1161, 1090, 1046, 936.
8. The regio- and stereochemistry of products **4**, **5**, **6**, **7** and **8** was established by COSY and NOE experiments.
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