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Unusual Palladium-Mediated Methylene-Addition to the Carbonyl of a Homochiral Polyfunctionalized Cyclohexenone, and Intramolecular Oxirane-Ring Opening. Efficient Synthesis of Novel Enantiopure 3a,4,5,7a-Tetrahydrobenzoxazole Derivatives.

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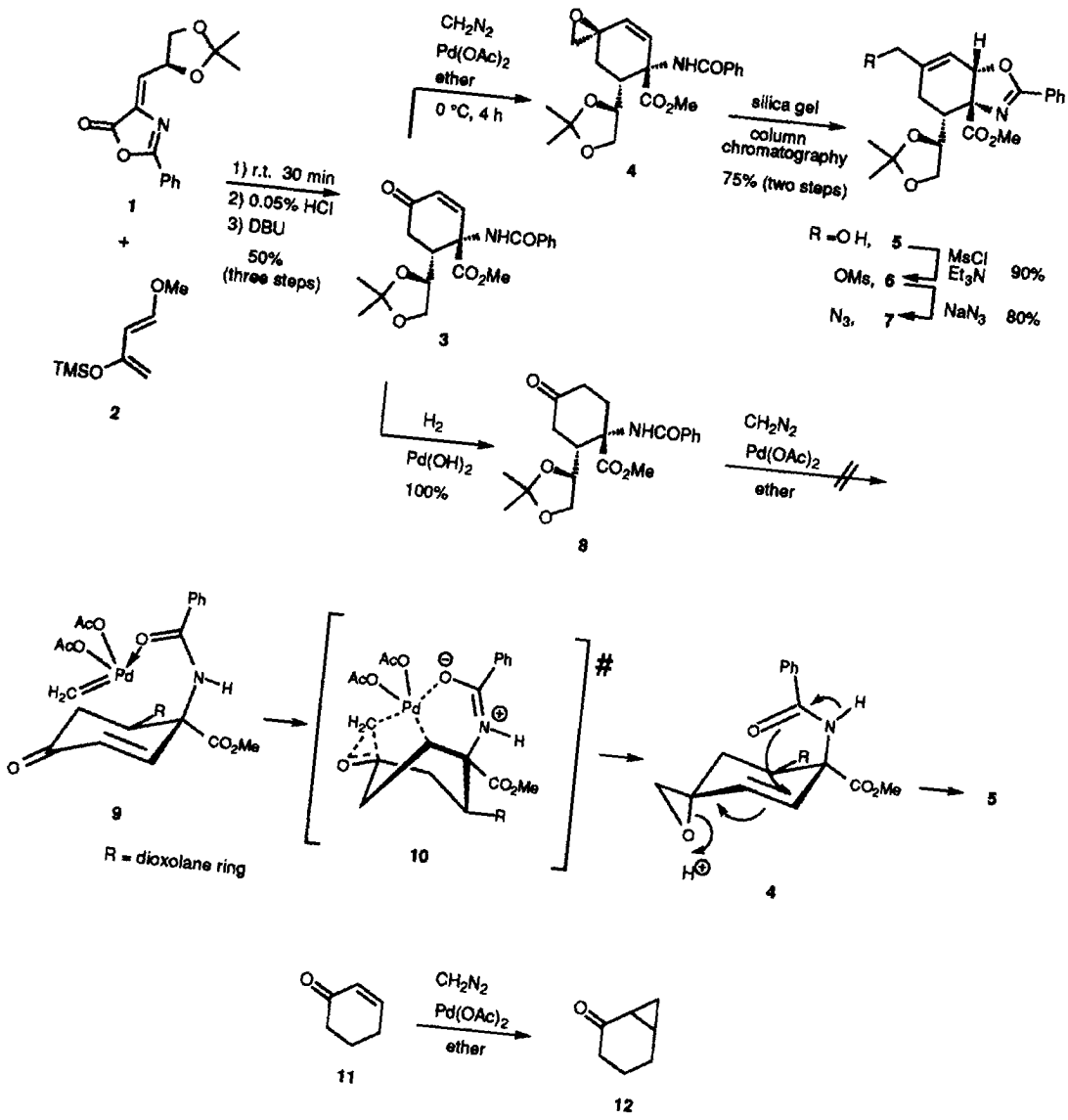
Abstract. *Three new enantiopure oxazoline derivatives have been synthesized in good yields from a homochiral 4-benzamido 2-cyclohexenone. The key step involves the unusual palladium-catalyzed methylene-addition to the carbonyl, giving a conjugated epoxide, and subsequent acid-promoted intramolecular oxirane-ring opening via an S_N2'-type process.* Copyright © 1996 Elsevier Science Ltd

Diazomethane usually adds to conjugated C-C double bonds in unsaturated ketones and esters affording cyclopropanes, the reaction being catalyzed by palladium(II), rhodium(II) or copper(II) salts.[1,2] Nevertheless, treatment of enone **3** with excess diazomethane in the presence of $Pd(OAc)_2$ resulted in the chemoselective methylene-addition to the carbonyl group giving conjugated oxirane **4**, as a single stereoisomer, which easily rearranged to oxazoline **5** (Scheme 1). As far as we know, this is the first example described on the preferential methylene-addition to carbonyl in an unsaturated ketone, under these conditions.

Structurally close oxazolines, although in racemic form, are the key intermediates in the syntheses of carbocyclic analogues and other kinds of derivatives of *N*-acetylneuraminic acid (NANA), recently published by Glaxo.[3] Some of these products are potent anti-neuraminidase inhibitors[3,4] and are currently under development as potential drugs for the prophylaxis and treatment of disease caused by the influenza A and B viruses.[3] These facts, jointly with the observation that there are rather scarce examples on the asymmetric synthesis of oxazolines,[5] prompted us to report our method to prepare new enantiopure tetrahydrobenzoxazole derivatives in a simple and efficient manner.

Homochiral polyfunctionalized enone **3** was prepared in 50% overall yield through a Diels-Alder cycloaddition of azlactone **1**[6] to the Danishefsky's diene **2** and subsequent acid hydrolysis followed by base-promoted elimination (Scheme 1).[7] Treatment of **3** according to the Corey-Chaykovsky protocol or with diazomethane in absence of any catalyst resulted in recovering the starting material. Epoxide **4** was produced in 75-80% yield, however, when an ethereal solution of **3** was reacted with excess diazomethane in the presence of one equivalent of $Pd(OAc)_2$ at 0 °C for 4 hours. A lower conversion was observed when



Scheme 1

0.2 equivalents of catalyst was used. Solvent played an important role since addition was less efficient when the reaction was performed in THF and was not observed to occur in dichloromethane. These results point to a solvated polar transtion state for this process being also noticeable the influence of steric factors (reaction in ether *vs* reaction in THF). On the other hand, palladium was crucial for the addition, since the use of $Rh_2(OAc)_4$ either in ether or in dichloromethane let enone **3** unaltered. The same result was obtained when $Cu(OTf)_2$ was employed.

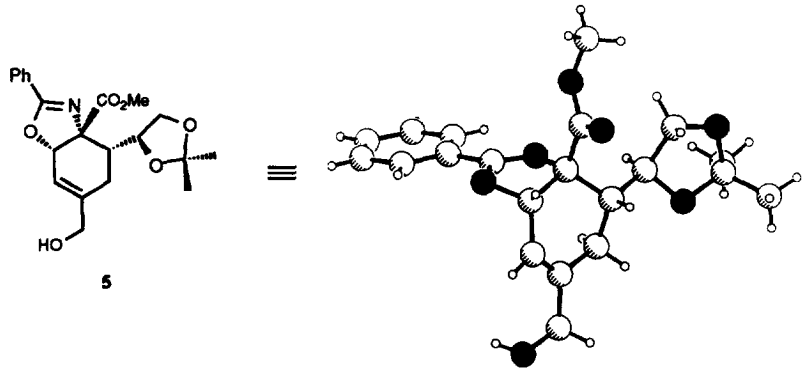
Some remarkable features of this reaction related to the assistance of the further functional groups were also investigated. For instance, the double bond was essential to achieve methylene-addition since ketone **8**, resultant of catalytic hydrogenation of **3**, remained unreacted when treated under the conditions described above for **3** producing **4**.

Moreover, since metal-catalyzed addition of diazomethane to cyclohexenone, **11**, was not previously described, we have performed several experiments in order to compare its behaviour with that of polyfunctionalized enone **3**. In no case addition to carbonyl was observed, cyclopropane derivative **12** being the only defined product when $Pd(OAc)_2$ in ether (80% yield) or $Rh_2(OAc)_2$ in dichloromethane (60% yield) were used as catalysts (Scheme 1). $Cu(OTf)_2$ induced only a very low conversion (*ca* 10%).

These results evidence the influence that the neighbouring groups in **3** exert on the preferential attack of carbene to the carbonyl prior to the C-C double bond. It is well known that palladium coordinates to amides.[8] In our case, owing all the results mentioned above, we assumed a coordination mechanism for this process,[2] involving the formation of such a substrate-palladium-carbene complex as **9**. From this species, carbene would be delivered intramolecularly and stereospecifically through a highly ordered tetracyclic transition state, **10**, in which palladium would coordinate simultaneously to the double bond and to the benzamide oxygen, as represented in Scheme 1. This intramolecular transfer is sterically favoured by conformational bias of the dioxolane ring to be equatorial with respect to the cyclohexene, either in a *chair-like* or in a *boat-like* conformation, thus determining benzamide to be axial. Moreover, the role of the double bond would consist in anchoring palladium and, consequently, lowering the activation-energy barrier.

Epoxide **4** is an unstable oil that was purified by flash-column chromatography on Florisil®, NMR accounting for its stereochemical homogeneity since only one set of signals was observed both in ^{13}C and ^{1}H NMR spectra, respectively.[9] Although the configuration at the new quaternary stereogenic center could not be established by spectroscopic techniques, it must be that represented in Scheme 1, as the result of carbene addition on the same diastereotopic π-face that contains the benzamide group.

Furthermore, when epoxide **4** was cromatographed on ordinary silica gel, oxazoline **5** was the only eluted product. This compound is produced by acid-catalyzed oxirane-ring opening assisted by nucleophilic attack of the benzamide oxygen to the double bond, according to an intramolecular S_N2'-type process as depicted in Scheme 1. This mechanism also agrees with the proposed configuration for oxirane **4**.[5c] Oxazoline **5** is a solid, identity of which was unambiguously established by X-ray structural analysis of a single crystal[10] (Figure 1). In turn, alcohol **5** reacted cleany with mesyl chloride in triethylamine to afford



5

Fig 1. Structure of oxazoline 5 as determined by X-ray structural analysis.

mesylate **6**, as a solid in 90% yield. This product was treated with sodium azide in DMF giving the oily azido compound **7** in 80% yield, showing the versatility of **5** to prepare new functional oxazoline derivatives.[9] Other synthetic applications of these molecules are currently under investigation in our laboratory.

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9. All new products were fully characterized by their physical constants and spectral data. Compounds **5**, **6**, and **8** gave satisfactory microanalysis. Some selected data for the most representative compounds synthesized follow.
   Compound **4**: Unstable oil; MS, m/e 387 (M), 372 (M-15). 62.5-MHz ^{13}C NMR (acetone d_6): δ 24.6, 25.7, 26.3, 41.2, 53.8, 54.1, 61.2, 65.6, 67.3, 74.5, 109.9, 127.3, 127.6, 128.9, 129.0, 131.9, 134.9, 166.8, 172.3. 250-MHz ^1H NMR (acetone d_6): Olefinic protons at 6.78 and 5.44 ppm (d, J=10.2 Hz), oxirane protons at 2.94 and 2.86 ppm, (d, J=5.1 Hz). Compound **5**: Crystals, m.p. 41-43 °C (from ethyl acetate-pentane); $[\alpha]_D$ -96.5 (c=1.14, $CHCl_3$). Compound **6**: Crystals, m.p. 67-69°C (from ethyl acetate-pentane); $[\alpha]_D$ -66.1 (c=3.45, $CHCl_3$). Compound **7**: Oil, $[\alpha]_D$ -102.6 (c=1.56, $CHCl_3$).
10. The atomic coordinates and thermal parameters for structure **5** are available on request from the Director of the Cambridge Crystallographic Data Centre. Any request should be accompanied by a full literature citation of this paper.

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