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Stereoselective synthesis of chiral polyfunctionalized cyclohexane derivatives. Palladium(II)-mediated reaction between cyclohexenones and diazomethane

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Abstract—Several chiral polyfunctionalyzed cyclohexanones and cyclohexenones have been synthesized through Diels–Alder cycloadditions, stereoselectivity being stated by X-ray structural analysis and NOE experiments. The chemoselectivity in the palladium(II)-catalyzed reaction between cyclohexenones and diazomethane has been investigated. Thus, in those enones bearing an amide function on the γ-carbon, the preferential addition occurs at the carbonyl giving epoxides which, under acid conditions, rearrange to tetrahydrobenzoxazoles. The other cyclohexenones afford cyclopropanes as a result of addition to the C=C bond. A mechanistic approach to explain the whole process is proposed.

1. Introduction

Polyfunctional cyclohexenones and cyclohexanones have been used as powerful building blocks in the synthesis of a wide variety of compounds including terpenes,[1] amino acids,[2] and cyclohexene carbocyclic nucleosides.[3] In particular, chiral cyclohexenones can undergo, among other reactions, thermal[4] or photochemical[5] cycloadditions, to afford cyclohexanone derivatives in which the configuration of the new stereogenic centers is determined by the chirality of the precursors. Moreover, a highly functionalized cyclohexenone unit has been recently described to be the common structural feature of many natural products with antibiotic and antitumor activity.[6]

According to our research project on the synthesis of carbocyclic compounds,[7] we envisaged the stereoselective synthesis of polyfunctional cyclohexane derivatives as precursors to a variety of products with potential biological activity. One of our synthetic goals was the creation of bicylo[3.1.0]hexane[8] and bicyclo[4.1.0]heptane skeletons. To synthesize the later, we intended the cyclopropanation of enone **1** (Scheme 1) by using the Corey–Chaykovsky protocol,[9] which led, in our case, to the total recovery of the starting material. The same result was obtained when **1** was treated with diazomethane trying to produce a pyrazoline that, under photolysis, would provide the corresponding cyclopropane. Then, we performed the reaction of cyclohexenone **1** with excess diazomethane under catalysis of palladium(II) acetate. Surprisingly, conjugated epoxide **2**, in a single isomeric form, was obtained instead of the expected cyclopropane (Scheme 1). Compound **2** was an unstable product that rearranged during chromatography on silica gel, with concomitant formation of an oxazolidine ring, to afford **3** in 75% yield for the two steps (Scheme 1).[10] On the other hand, we realized that the presence of the C=C bond was required since treatment of the saturated ketone **4** with diazomethane, under similar conditions, led to the total recovery of the starting material.

Palladium-catalyzed reactions between diazoalkanes and olefinic substrates have been used as an efficient method for the cyclopropanation of α,β-unsaturated carbonyl compounds including cyclohexenones[11,12] and cyclopentenones.[11] The generally accepted mechanism involves the formation of a metal-carbene complex as intermediate which adds to the C=C bonds.[12–14] Nevertheless, there was not precedent in the literature on the chemoselective methylenation of carbonyls in cyclohexenones by using this procedure.

Therefore, owing to the novelty of this process and the interest of the resulting oxazolidine derivative as a versatile synthetic intermediate,[15,16] we decided to investigate this reaction from different points of view. We report in this paper the obtained results. The first goal was to study the

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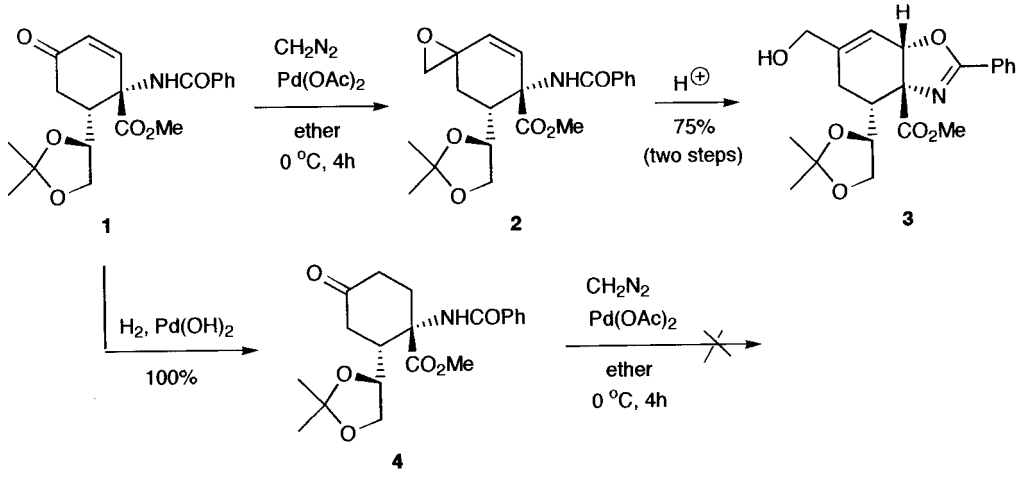


Scheme 1.

influence on the reactivity of several conditions, such as the metal used as catalyst, the substrate-catalyst stoichiometry, solvent, and temperature. Secondly, we investigated the effect of the neighboring substituents on the chemoselective approach of the reagent, that is, the scope of the process. The third objective was to postulate a mechanistic pathway according to the experimental findings. To achieve these purposes, we chose cyclohexenones **5**–**11** as convenient substrates (Chart 1). Compounds **5**–**7**, as well as **1**, bear the benzamide and ester functions at *C*-4, but differ in the substituents at *C*-5 which are of increasing size from **5** to **7**. Cyclohexenone **8** shows the same substitution as **1** but only the dioxolane ring is in the same relative position. Compounds **9** and **10** should be useful to discern if the presence of the amide, the ester or both is required for the chemoselective methylenation of the carbonyl. Finally, the obtained results were contrasted with the reaction of cyclohexenone itself, **11**. The synthesis of compounds **1**, **5**–**10** was carried out through Diels–Alder cycloadditions of heterosubstituted dienes to suitable dienophiles. Compounds **5**, **6**, **8**, and **9** were previously unknown. Regarding their synthesis, *endo*/*exo* diastereoselectivity of the corresponding reactions is not relevant since the corresponding stereogenic center is destroyed concomitantly to the formation of the C=C bond. Nevertheless, we investigated the stereoselectivity of these cycloadditions since the alcohols or ethers, precursors to the enones, present a great synthetic interest because they are highly functionalized

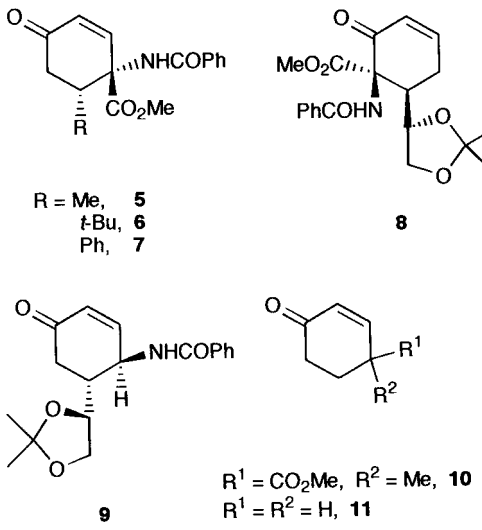
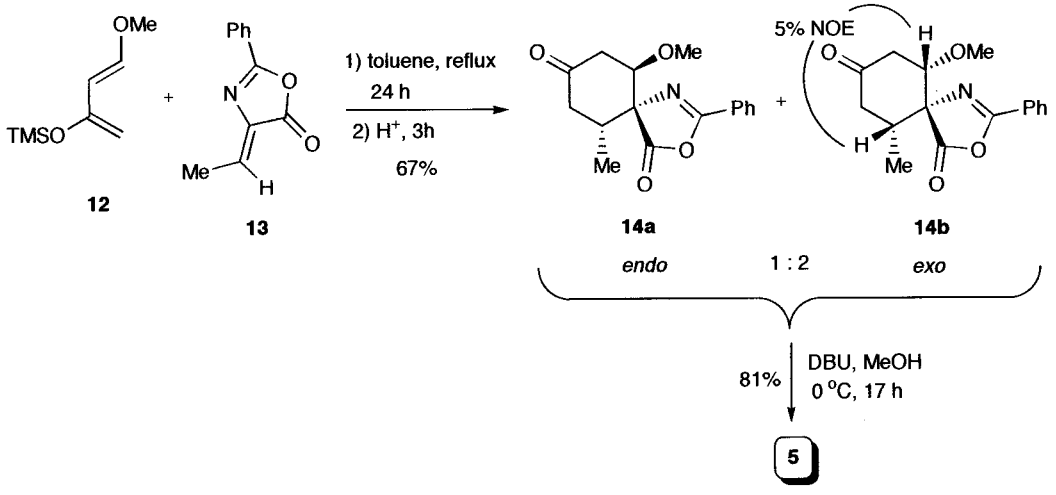
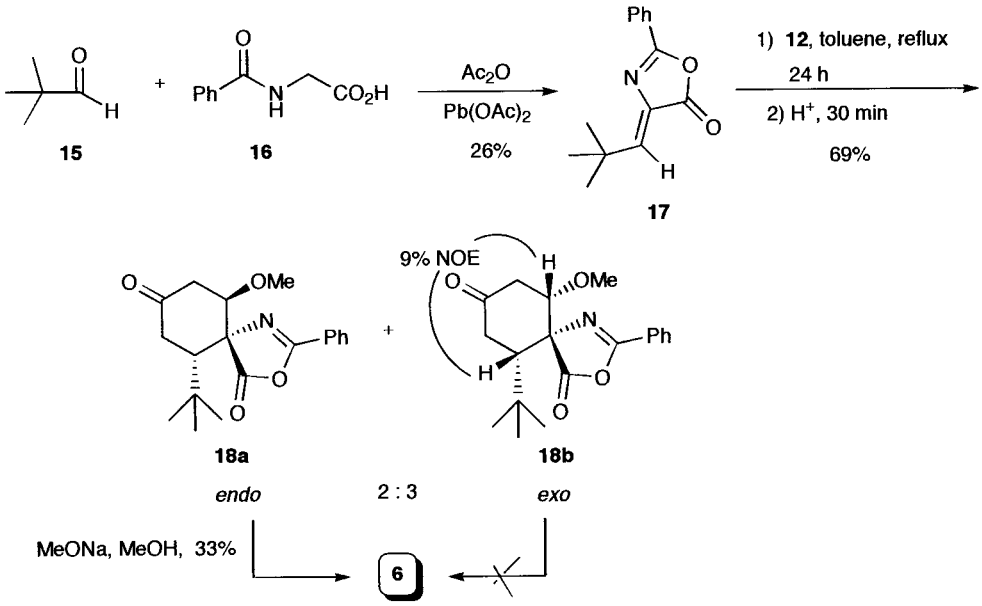


Chart 1.

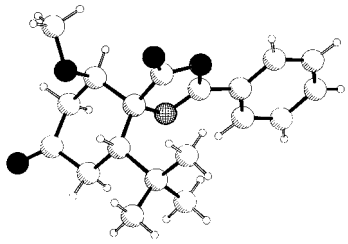


Scheme 2.



Scheme 3.

cyclohexanes bearing three chiral centers of determined relative configuration. Moreover, facial diastereoselection in the cycloadditions of chiral dienophiles leading to optically pure ketones, **1**,[17] **8**, and **9** was unambiguously established by X-ray structural analysis of these compounds.



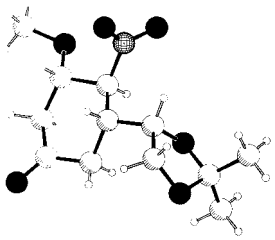


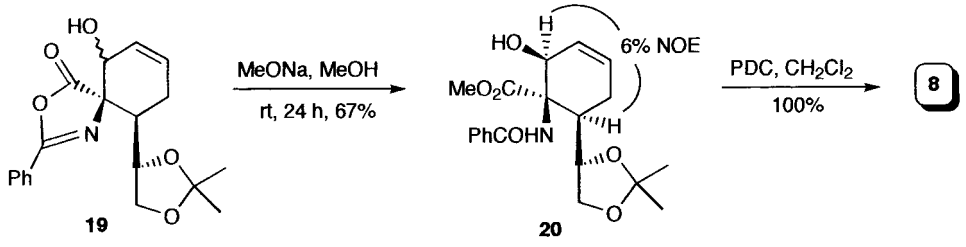
Figure 1. Structure of compounds **18a** and **22** as determined by X-ray structural analysis.

2. Results and discussion

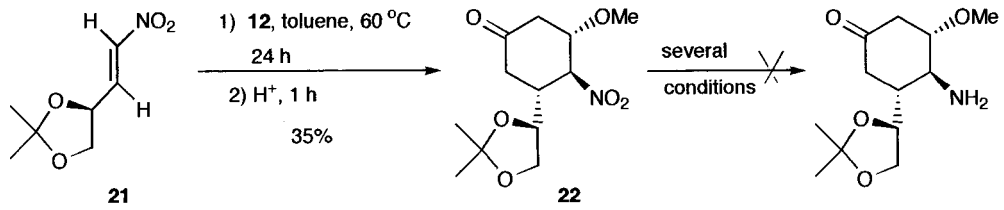
2.1. Synthesis of the cyclohexenones and the precursor cyclohexanones

Ketone **1** had been previously synthesized in our laboratory,[17] and the syntheses of **7**[18] and **10**[19] were described in the literature. Ketones **5** and **6** resulted from Diels–Alder cycloaddition of Danishefsky diene, **12,** to (*Z*)-methyl- and (*Z*)-*t*-butylazlactone, **13** and **17**, respectively (Schemes 2 and 3). Thus, reaction between **12** and known azlactone **13**[20] in boiling toluene for 24 h, followed by acid hydrolysis, afforded a 1:2 mixture of *endo*/*exo* diastereomers **14a**,**b** (67% yield) whose configuration was elucidated by differential NOE experiments. Treatment of the mixture with DBU in dry methanol at 0°C overnight allowed methanol elimination to produce the C=C bond, as well as methanolysis of the azlactone, giving cyclohexenone **5** in 81% yield.

Azlactone **17** was prepared in 26% yield following a modification of the Erlenmeyer–Plöchl method[21] (Scheme 3). Thus, reaction of pivalaldehyde, **15**, with hippuric acid **16**, in the presence of acetic anhydride and lead diacetate, afforded **17** in 26% yield. The *Z* configuration of **17** was assessed by spectroscopic methods by comparison with **13**.



Scheme 4.



Scheme 5.

Subsequent cycloaddition of diene **12** to azlactone **17** led, in 69% yield, to a 2:3 mixture of *endo*/*exo* diastereomers **18a,b**. Stereochemistry was unambiguously stated by X-ray structural analysis of **18a** (Fig. 1) and corroborated by significant NOE enhancements in **18b** (Scheme 3). Reaction of these compounds with DBU in methanol, as above, failed. *exo* Isomer **18b** was inert under treatment with MeONa/MeOH, whereas *endo* **18a** afforded cyclohexenone **6** in only 33% yield. In **18b**, the steric congestion induced by the bulky *t*-butyl group precludes a conformation suitable for methanol elimination through a E_2-mechanism, since it would force both methoxyl and *t*-butyl groups to be axial.

The synthesis of ketone **8** was undertaken from alcohol **19** (Scheme 4). This compound, as a mixture of *endo*/*exo* isomers, resulted from the Diels–Alder cycloaddition of 1-trimethylsilyloxy-1,3-butadiene to a chiral azlactone.[17] Treatment of **19** with sodium methoxide in methanol, at room temperature for 24 h, afforded **20** in 67% yield as the single *exo* isomer, as established by NMR. This is, presumably, the thermodynamically most stable diastereomer. Oxidation of allylic alcohol **20** with PDC in dichloromethane produced quantitatively ketone **8**.

Finally, the synthesis of enone **9** was envisioned as depicted in Scheme 5. Thus, reaction between diene **12** and the nitroolefin **21**,[22] in toluene at 60°C for 24 h, and subsequent acid hydrolysis, afforded compound **22** in 35% yield, as a single isomer whose stereochemistry was assigned by X-ray crystallography (Fig. 1). Attempts to reduce the nitro group by reaction with hydrogen, in the presence of $Pd(OH)_2$ and under several atmospheres pressure, failed. The use of ammonium formate or cyclohexene, as sources of hydrogen, did not afford satisfactory results neither. These facts, jointly with the low yield in the cycloaddition and hydrolysis steps, prompted us to give up the attempted synthesis of **9**.

2.2. Reactions of the cyclohexenones with diazomethane

Table 1 summarizes the experiments carried out on ketone **1**. Firstly, we realized that the presence of a catalyst was required for reaction to take place. Solvent played an important role since addition was less efficient in THF and was not observed to occur in dichloromethane, these results pointing towards a solvated polar transition state for this process where the steric factors should be noticeable. Addition was not observed when $Rh_2(OAc)_4$, either in ether or in dichloromethane, was used as catalyst. The same result was obtained when $Cu(OTf)_2$ was employed.

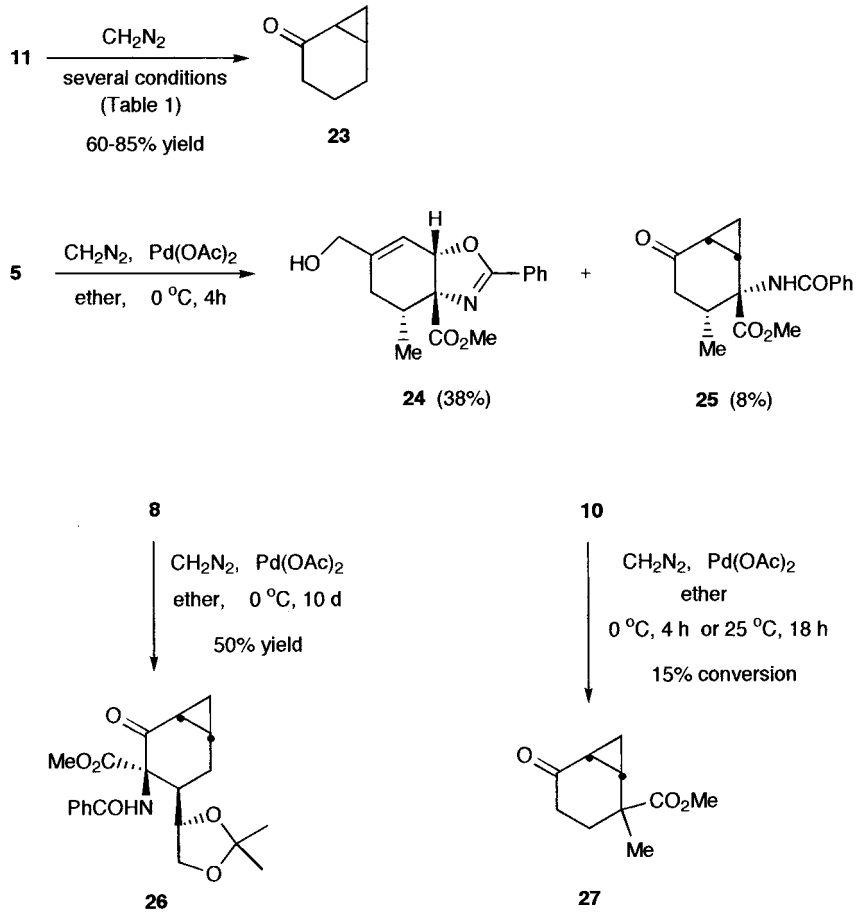
Then, we decided to explore the behavior of the parent compound **11**. After a preliminary communication on this work was published,[10] Denmark described the cyclopropanation of **11** with diazomethane and a bis(oxazoline)palladium(II) complex to afford **23** (Scheme 6) in 71% yield as the only reaction product.[12] Our most significant results are listed in Table 1. In no case addition to carbonyl was observed, compound **23** being the only defined product when $Pd(OAc)_2$ in ether (85% yield) or $Rh_2(OAc)_4$ in dichloromethane (60% yield) were used as catalysts, whereas $Cu(OTf)_2$ promoted only a very low conversion. Another noticeable difference between the behaviour of **1** and **11** lies on the fact that the substrate/catalyst ratio, as well as solvent and temperature, does not have a remarkable effect on the reactivity of **11** towards cyclopropanation (entries 5–8, Table 1).

From all these results, we concluded that $Pd(OAc)_2$ was the catalyst of choice, in good agreement with Denmark's findings,[12] ether being the best solvent for addition to the carbonyl group. The reagent addition order was also crucial. For instance, cyclopropane derivative **23** was obtained from cyclohexenone, **11**, in ca 10% yield, when diazomethane was added to a suspension of $Pd(OAc)_2$ in ether, the mixture

Table 1. Selected reactions of enones **1** and **11** with diazomethane under several conditions

Entry	Enone	Catalyst (eq)	Solvent	Temperature (°C)	Time (h)	Product	Yield
1	**1**	$Pd(OAc)_2$ (0.02)	ether	0	4	**2**	57
2	**1**	$Pd(OAc)_2$ (1)	ether	0	4	**2**	70
3	**1**	$Pd(OAc)_2$ (1)	THF	0	4	**2**	63
4	**1**	$Pd(OAc)_2$ (1)	CH_2Cl_2	0	4	–[a]	–
5	**11**	$Pd(OAc)_2$ (0.02)	ether	0	2	**23**	77
6	**11**	$Pd(OAc)_2$ (0.02)	ether	25[b]	2	**23**	85
7	**11**	$Pd(OAc)_2$ (1)	ether	0	2	**23**	76
8	**11**	$Pd(OAc)_2$ (0.02)	CH_2Cl_2	25[b]	2	**23**	88
9	**11**	$Rh_2(OAc)_4$ (0.01)	ether	25[b]	2	**23**	10
10	**11**	$Rh_2(OAc)_4$ (0.01)	CH_2Cl_2	25[b]	2	**23**	60

[a] Enone **1** is recovered.
[b] Diazomethane was added at 0°C, then the reaction mixture was warmed to 25°C.



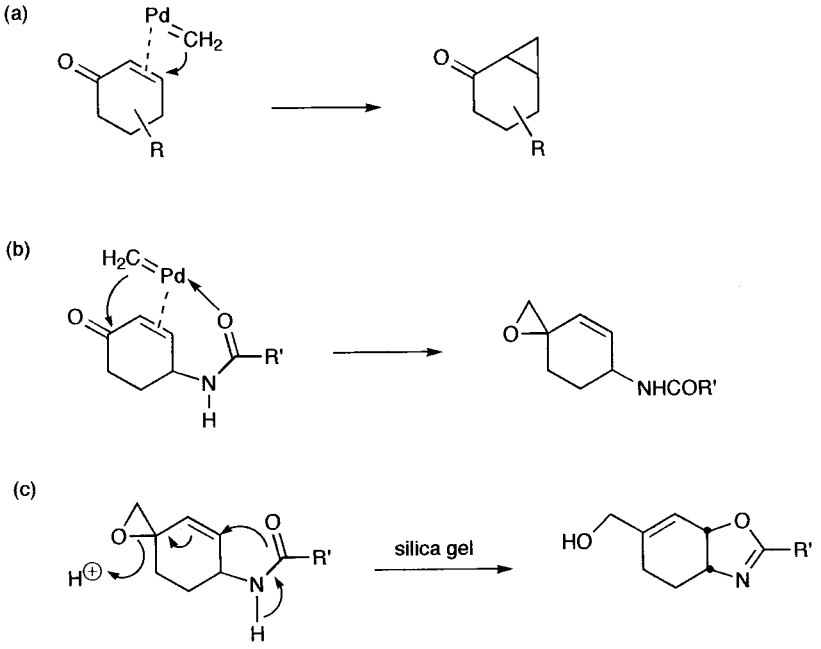
Scheme 6.

was stirred for 15 min, then enone **11** was added and the final mixture was stirred for 16 h at room temperature. In contrast, compound **23** was obtained in 90% yield when the enone was added prior to diazomethane.

The study of this process was also extended to the other cyclohexenones. The obtained results can be grouped in two sets, depending on the presence or the absence of the amide group at the allylic γ-position. Thus, ketone **5** was reacted with diazomethane and 1 equiv. $Pd(OAc)_2$ in ether at 0°C for 4 h affording, after flash chromatography on silica gel, a mixture of oxazolidine **24** (38% yield) and cyclopropane **25** (8% yield). Ketones **6** and **7** remained unaltered under similar conditions suggesting that steric hindrance prevents these substrates to react.

On the other hand, cyclopropanation products (mixtures of stereoisomers) were the only compounds obtained from ketones **8** and **10** under similar conditions (Scheme 6). Thus, **26** resulted from enone **8** in 50% yield, after 10 days reaction with excess diazomethane. Enone **10** reacted very smoothly to afford compound **27**, but conversion was never higher than ca 15%, either at 0°C for 4 h or at 25°C overnight. This low reactivity may be attributed to the steric congestion produced by the presence of the methyl group at the allylic γ-position of **10**. The presence of compound **27** in the reaction mixture was detected by ^1H NMR and MS. The former showed a complex absorption between 1.1 and 1.3 ppm, attributable to the cyclopropane-ring protons, and two singlets at 1.35 and 1.37 ppm due to the methoxyl group in each isomer. GC–MS showed two peaks that produced the same molecular ion (182) and identical ionic fragments, being relevant those at *m/e* 123 (loss of CO_2Me) and 81 (C_6H_9).

All these results reinforce the hypothesis that the neighboring benzamide group assists the methylene addition to the carbonyl of enones **1** and **5** reversing the chemoselectivity from the C=C attack to the C=O attack. This is an example of 1,2-/1,4-dichotomy, presumably controlled by chelation. Thus, it is reasonable to assume that, under normal circumstances, the metallocarbene $Pd{=}CH_2$ species[12–14] attacks the conjugated double bond with Pd approaching the α-carbon (and the CH_2 group approaching the β-carbon) (Scheme 7a).[23] In enones such as **1** and **5**, it may well be that coordination of the electrophilic palladium to the Lewis-basic amide carbonyl will actually alter the geometry of approach, forcing Pd to approach the β-carbon (Scheme 7b). Then, palladium would coordinate simultaneously to the amide carbonyl and to the double bond. Several conformations of enone **8** have been studied through theoretical calculations using the semiempirical PM3 method[24] implemented in the CHEM3D program.[25] Fig. 2 presents the most stable structure obtained in this study. The relative orientation of the C=C and amide C=O groups shows that the formation of a chelate Pd complex seems feasible. From this species, methylene can be delivered intramolecularly through the attack of the



Scheme 7.

metallocarbene carbon to the electrophilic carbon of the C═O group (rather than to the α-carbon). In this way, the formation of the oxirane-ring is diastereoselective and the presence of the C═C bond is required to link the palladium species. In contrast, when the benzamido group is absent, the cyclopropanation of the C═C bond occurs in the usual way. Steric hindrance produced by the substituents can prevent the attack of the reagents. Thus, reactivity of enones **8** and **10** is decreased with respect to cyclohexenone **11**.

Finally, in the cases of addition to carbonyl, rearrangement of the resultant conjugated epoxide takes place under acid catalysis to afford the tetrahydrobenzoxazole nucleus (Scheme 7c).

3. Concluding remarks

Several chiral polyfunctionalized cyclohexanones and cyclohexenones have been synthesized through stereoselective Diels–Alder cycloadditions. The transition-metal catalyzed reactions of some cyclohexenones with diazomethane have been investigated. Thus, while cyclohexenone itself reacts fairly under rhodium(II) or palladium(II) catalysis, affording the corresponding cyclopropane derivative in good yield, the other cyclohexenones led to cyclopropanes or oxiranes as the main products, depending on the substitution at the γ-carbon. Thus, those cyclohexenones bearing an amide function at γ-position underwent addition to the carbonyl to give a conjugated epoxide which rearranged under acid conditions to a tetrahydrobenzoxazole derivative. The other cyclohexenones gave cyclopropanes in variable yields, as a result of addition to the C═C bond. In both cases, steric hindrance markedly decreased the reactivity of the substrates considered.

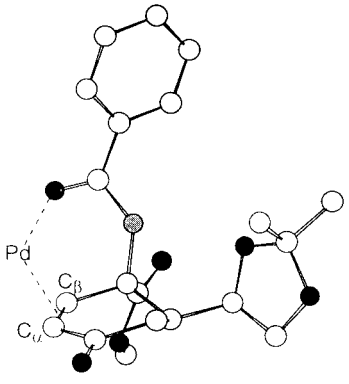


Figure 2. PM3 optimized structure of enone **8** indicating the approximate position that Pd would occupy in a chelate complex. Hydrogen atoms have been omitted for clarity.

4. Experimental

4.1. General

Flash column chromatography was carried out on silica gel (240–400 mesh) unless otherwise stated. Melting points were determined on a hot stage and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at 250 and 62.5 MHz, respectively, unless otherwise stated.

Ketones **1**,[17] **7**,[18] and **10**[19] were synthesized according to the previously described procedures. Commercially available palladium(II) acetate and dimeric rhodium(II) acetate were used without further treatment.

4.1.1. X-Ray diffraction analysis of 18a. Suitable crystals were obtained by crystallization from EtOAc–pentane. Crystal dimensions: 0.18×0.14×0.14 mm. Empirical formula $C_{19}H_{23}NO_4$. Molecular weight 329.38. Crystal system: monoclinic. Space group Cc (No. 9). Lattice parameters: a=18.020(6) Å, b=8.293(4) Å, c=12.844(6) Å,

β=116.60(4)°, V=1716.2(13) Å^3. Z=4. Calculated density 1.275 g cm^{-3}. F(000)=704. Data were collected at 293(2) K on an Enraf Nonius CAD4 diffractometer using MoKα radiation (λ=0.71069 Å) yielding 1504 independent reflections. The structure was solved by direct methods (SHELXS-86)[26] and refined by least-squares on F^2 for all reflections (SHELXL-97).[27] Non-hydrogen atoms were refined anisotropically. Hydrogen were placed in calculated positions with isotropic displacement parameters 1.5 (methyl H) or 1.2 (the rest) times the U_{eq} values of corresponding carbons. Refined parameters 217. Goodness-of-fit on F^2: 0.818. $R(F)$=0.071 for reflections with $I>2\sigma(I)$, $R_w(F^2)$= 0.172 for all data.

4.1.2. X-Ray diffraction analysis of 22. Suitable crystals were obtained by crystallization from EtOAc–pentane. Crystal dimensions: 0.58×0.36×0.25 mm. Empirical formula $C_{12}H_{19}NO_6$. Molecular weight 273.28. Crystal system: orthorhombic. Space group $P2_12_12_1$ (No. 19). Lattice parameters: a=7.561(3) Å, b=9.571(3) Å, c=19.425(10) Å, V=1405.7(10) Å^3. Z=4. Calculated density 1.291 g cm^{-3}. F(000)=584. Data were collected at 293(2) K on an Enraf Nonius CAD4 diffractometer using MoKα radiation (λ=0.71069 Å) yielding 1442 independent reflections. The structure was solved by direct methods (SHELXS-86)[26] and refined by least-squares on F^2 for all reflections (SHELXL-97).[27] Non-hydrogen atoms were refined anisotropically. Hydrogen were placed in calculated positions with isotropic displacement parameters 1.5 (methyl H) or 1.2 (the rest) times the U_{eq} values of corresponding carbons. Refined parameters 172. Goodness-of-fit on F^2: 0.927. $R(F)$= 0.040 for reflections with $I>2\sigma(I)$, $R_w(F^2)$=0.103 for all data.

4.1.3. Methyl (1*S*,2*R*)-1-benzoylamino-2-[(4′*S*)-4′-(2′,2′-dimethyl-1′,3′-dioxolo)]-4-oxocyclohexane-1-carboxylate, 4. Enone **1**[17] (396 mg, 1,1 mmol) in methanol (35 mL) was hydrogenated at atmospheric pressure in the presence of 20% Pd(OH)$_2$/C (20 mg). The suspension was filtered through *celite*, solvent was evaporated under vacuo and the residue was chromatographed (4:1 ethyl acetate–hexane) to afford quantitatively ketone **4** (398 mg) as a dense oil, $[\alpha]_D$=−48.6 (*c* 0.37, $CHCl_3$); IR (film) 1735, 1715, 1673 cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.35 (s, CH_3), 1.48 (s, CH_3), 2.25–2.46 (complex absorption, 5H), 2.68 (dd, J=16.0 Hz, J'=13.1 Hz, 1H), 3.46 (m, 1H), 3.65 (dd, J=8.8 Hz, J'=5.8 Hz, 1H), 3.75 (s, OCH_3), 4.02 (dd, J=J'=8.8 Hz, 1H), 4.34 (m, 1H), 7.38–7.54 (complex absorption, 3H), 7.78–7.82 (complex absorption, 2H), 7.90 (broad s, 1H); ^{13}C NMR ($CDCl_3$) 24.6, 25.8, 30.6, 35.5, 36.4, 45.0, 52.9, 63.3, 66.8, 74.5, 110.5, 126.9, 128.5, 131.8, 134.3, 168.3, 172.7, 208.6. Anal. Calcd for $C_{20}H_{25}NO_6$: C, 64.06; H, 6.72; N, 3.74. Found: C, 64.12; H, 6.70; N, 3.68

4.1.4. Diels–Alder reaction between diene 12 and azlactone 13, and subsequent hydrolysis of adducts: Compounds 14a and 14b. Diene **12** (500 mg, 2.9 mmol) and azlactone **13** (500 mg, 2.7 mmol) in anhydrous toluene (30 mL) were heated to reflux for 24 h under nitrogen atmosphere. Solvent was evaporated at reduced pressure, a 4:1 mixture of 0.05% HCl–THF (20 mL) was added, and the solution was stirred for 3 h. After concentration to dryness, the residue was poured into dichloromethane (20 mL). The resultant solution was washed with brine (2×20 mL), and with saturated aqueous sodium bicarbonate (20 mL). The organic phase was dried ($MgSO_4$) and solvent was removed to afford a 1:2 mixture of **14a/14b** (500 mg, 67% yield) as determined from its ^{1}H NMR spectrum: ^{1}H NMR ($CDCl_3$) 0.82 (d, 3H); 0.90 (d, 3H); 2.13–2.95 (complex absorption, 10H), 3.24 (s, 3H); 3.34 (s, 3H); 3.70 (m, 1H); 3.79 (m, 1H); 7.4–8.1 (m, 10H). Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.89. Found: C, 66.74; H, 6.13; N, 4.75.

Column chromatography (mixtures of ethyl acetate–hexane) of the mixture **14a/14b** allowed the isolation and characterization of the major isomer, **(3*S*,4*S*,5*R*)-5-methyl-4-spiro{4′[2′-phenyl-5′(4*H*)-oxazolone]}-3-methoxycyclohexan-1-one, 14b,** as a solid. Crystals, mp 118–119°C (from EtOAc–pentane); IR (KBr) 1845, 1812, 1727 cm^{-1}; 400-MHz ^{1}H NMR ($CDCl_3$) 0.82 (d, $J_{Me\text{-}5}$=4.1, CH_3); 2.30 (m, H_5+H_{6ax}); 2.60 (t, $J_{6eq-6ax}$=J_{6eq-5}=14.7 Hz, H_{6eq}); 2.81 (m, H_{2ax}+H_{2eq}); 3.24 (s, OCH_3); 3.79 (dd, J_{3-2eq}=11.5 Hz, J_{3-2ax}=5.7 Hz, H_3); 7.3–8.1 (m, Ph); 100-MHz ^{13}C NMR ($CDCl_3$) 17.2 (CH_3); 36.3 (C_5); 44.6, 46.7 (C_2+C_6); 59.4 (OCH_3); 82.8 (C_4); 127.4, 130.2, 130.7, 134.9 (Ph); 163.7 (NC(Ph)O); 180.8 (*C*OO); 207.9 (*C*O). Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.89. Found: C, 66.84; H, 6.03; N, 4.67.

4.1.5. Methyl (1*R*,6*R*)-1-benzoylamino-6-methyl-4-oxo-2-cyclohexene-1-carboxylate, 5. A mixture of **14a/14b** (500 mg, 1.8 mmol) and DBU (0.3 g, 1.8 mmol) in methanol (36 mL) was stirred at 0°C for 17 h. Solvent was removed and the residue was chromatographed (1:1 ethyl acetate–hexane) to afford enone **5** as a white solid (405 mg, 81% yield). Crystals, mp 125–126°C (from EtOAc–pentane); IR (KBr) 1740, 1694, 1635, 1607 cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.06 (d, $J_{Me\text{-}6}$=6.58 Hz, CH_3); 2.52 (m, H_{5ax}+H_{5eq}); 2.75 (m, H_6); 3.74 (s, OCH_3); 6.03 (d, J_{2-3}=10.25 Hz, H_3); 7.05 (broad s, N*H*); 7.13 (d, J_{3-2}=10.25 Hz, H_2); 7.3–7.9 (m, Ph); ^{13}C NMR ($CDCl_3$) 15.8 (CH_3); 35.8 (C_6); 41.7 (C_5); 53.2 (OCH_3); 61.2 (C_1); 127.1, 128.6, 129.5, 132.0, 133.4 (Ph+C_2); 145.8 (C_3); 167.7 (*C*ONH), 171.5 (*C*OO); 197.8 (*C*O). Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.88. Found: C, 66.78; H, 5.97; N, 4.88.

4.1.6. Synthesis of azlactone 17 and its Diels–Alder reaction with diene 12: Compounds 18a and 18b. A mixture of pivalaldehyde, **15** (600 mg, 7.4 mmol), hippuric acid, **16** (900 mg, 4.9 mmol), lead diacetate (900 mg, 2.5 mmol) and acetic anhydride (2 mL) was stirred at 130°C for 72 h. Then, absolute ethanol (100 mL) was added and the resultant azeotropic mixture was distilled. The residue was chromatographed (1:4 ethyl acetate–hexane) to afford **(*Z*)-2-phenyl-4-*tert*-butyliden-(4*H*)-oxazolone, 17** (300 mg, 26% yield) which was identified by its spectral data. IR (KBr) 1807, 1747, 1720, 1665, 1597 cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.35 (s, 3×CH_3); 6.65 (s, 1H), 7.4–8.0 (complex absorption, Ph); ^{13}C NMR ($CDCl_3$) 29.88 (*t*-Bu); 34.8 (q, *t*-Bu); 125.8, 128.1, 128.8, 133.0, 133.8 (C_2+Ph); 148.2 (C_1), 161.8 (NH(*C*O)Ph); 167.6 (*C*OO); 203.6 (*C*O).

A solution of azlactone **17** (400 mg, 1.5 mmol) and diene **12**

(300 mg, 1.5 mmol) in anhydrous toluene (20 mL) was heated to reflux for 24 h. Solvent was removed and a 4:1 solution of 0.05% HCl–THF was added. The resultant mixture was stirred at rt for 30 min, solvent was evaporated and the residue was diluted with dichloromethane (20 mL). The solution was washed with brine (2×20 mL) and saturated aqueous sodium bicarbonate (20 mL), and dried ($MgSO_4$). Solvent was removed to afford a 2:3 mixture of diastereomeric ketones **18a** and **18b** (500 mg, 69% yield) which were isolated after column chromatography (1:3 ethyl acetate–hexane). **(3*S*,4*S*,5*R*)-5-*tert*-Butyl-4-spiro-{4′[2′-phenyl—5′(4*H*)-oxazolone]}-3-methoxycyclohexan-1-one, 18a.** Crystals, mp 138–139°C (from EtOAc–pentane); IR (KBr) 1817, 1723, 1653 cm^{-1}; 400-MHz ^1H NMR ($CDCl_3$) 0.90 (s, 3×CH_3); 2.54–2.90 (complex absorption, H_{2ax}, H_{2eq}, H_5, H_{6ax}, H_{6eq}); 3.32 (s, OCH_3); 3.50 (dd, J_{3-2eq}=6.6 Hz, J_{3-2ax}=3.6 Hz, H_3); 7.4–8.0 (m, Ph); 100-MHz ^{13}C NMR ($CDCl_3$) 30.5 (*t*-Bu); 36.0 (q, *t*-Bu); 41.5, 41.6 (C_2+C_6); 49.1 (C_5); 60.3 (OCH_3); 75.7 (C_4); 84.3 (C_3); 127.7, 130.0, 130.8, 135.0 (Ph); 163.1 (N*C*(Ph)O); 180.1 (*C*OO); 210.2 (*C*O); MS, *m/e* (%) 329 (M^+, 1), 77 (27), 105 (100). **(3*R*,4*S*,5*R*)-5-*tert*-Butyl-4-spiro{4′[2′-phenyl—5′(4*H*)-oxazolone]}-3-methoxycyclohexan-1-one, 18b.** Oil; IR (film) 1827, 1713, 1618, 1579 cm^{-1}; 400-MHz ^1H NMR ($CDCl_3$) 0.87 (s, 3×CH_3); 2.14 (dd, J_{5-6ax}=4.38 Hz, J_{5-6eq}=13.25 Hz, H_5); 2.53 (dd, J_{6ax-5}=4.38 Hz, $J_{6ax-6eq}$=13.8 Hz, H_{6ax}); 2.77 (d, $J_{2ax-2eq}$=J_{2-3}=8.75 Hz, H_{2ax}+H_{2eq}); 2.87 (dd, $J_{6eq-6ax}$=14.0 Hz, J_{6eq-5}=14.0 Hz, H_{6eq}); 3.21 (s, OCH_3), 3.67 (dd, J_{3-2eq}=J_{3-2ax}=8.75 Hz, H_3); 7.4–8.1 (m, Ph). 100-MHz ^{13}C NMR ($CDCl_3$): 28.8 (*t*-Bu); 34.2 (q,*t*-Bu); 40.2 (C_6); 42.4 (C_2); 47.8 (C_5); 57.8 (OCH_3); 76.1 (C_4); 83.0 (C_3); 125.8, 128.1, 128.7, 132.7 (Ph); 161.0 (N*C*(Ph)O); 180.1 (*C*OO); 206.8 (*C*O); MS, *m/e* (%) 329 (M^+, 1), 77 (24), 105 (100). Anal of the mixture **18a/18b**. Calcd for $C_{19}H_{23}NO_4$: 69.28; H, 7.04; N, 4.25. Found: C, 69.13; H, 6.99; N, 4.28.

4.1.7. Methyl (1*R*,6*R*)-1-benzoylamino-6-*tert*-butyl-4-oxo-2-cyclohexene-1-carboxylate, 6. Compound **18a** (300 mg, 1.0 mmol), and NaOMe (100 mg, 2.0 mmol) in anhydrous methanol (40 mL) were stirred at 0°C for 72 h. Then 0.1% HCl was added to reach neutral pH, and the mixture was concentrated to dryness. The residue was poured into dichloromethane (50 mL), filtered, and the solvent was removed. After column chromatography (mixtures of ethyl acetate–hexane), pure enone **6** was obtained in 33% yield (g) as a solid. Crystals, 124–125°C (from EtOAc–pentane); IR (KBr) 1732, 1675, 1581 cm^{-1}; ^1H NMR ($CDCl_3$) 0.93 (s, 3×CH_3); 2.63 (dd, J_{6-5eq}=17.5 Hz, J_{6-5ax}=5.1 Hz, H_6); 2.76 (complex absorption, H_{5eq}); 3.43 (dd, $J_{5ax-5eq}$=13.8 Hz, J_{5ax-6}=5.1 Hz, H_{ax}); 3.81 (s, OCH_3); 6.17 (m, H_2), 6.60 (m, H_3); 7.3–7.9 (m, Ph); ^{13}C NMR ($CDCl_3$) 28.65 (*t*-Bu); 34.2 (q, *t*-Bu); 37 (C_5); 47.4 (C_6); 53.6 (OCH_3); 63.2 (C_1), 126.8, 128.6, 129.7, 131.9, 133.8 (Ph+C_3); 150.9 (C_2); 165.14 (*C*ONH); 171.3 (*C*OO); 198.9 (*C*O). Anal. Calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.14; H, 6.95; N, 4.30.

4.1.8. Methyl (1*S*,2*S*,6*R*)-1-benzoylamino-2-hydroxy-6-[(4′*S*)-4′-(2′,2′-dimethyl-1′,3′-dioxolo)]cyclohex-3-ene-1-carboxylate, 20. Azlactone **19** (100 mg, 0.3 mmol) and NaOMe (10 mg) in methanol (15 mL) was stirred at rt for 24 h. Solvent was removed and the residue was chromatographed (1:7 ethyl acetate–hexane) to afford **20** as a solid in a single isomeric form (70 mg, 67% yield). Crystals, mp 154–155°C (from EtOAc–pentane); $[\alpha]_D$=−68.0 (*c* 1.79, $CHCl_3$); IR (KBr) 3374, 3253, 1746, 1736 1661, 1602 cm^{-1}; ^1H NMR ($CDCl_3$) 1.36 (s, CH_3), 1.46 (s, CH_3), 2.29–2.33 (m, H_{5ax},H_{5eq}), 2.70 (dd, J_{6-5ax}=J_{6-5eq}=1.5 Hz, H_6), 3.76 (dd, $J_{5'a,5'b}$=6.6 Hz, $J_{5'a,4'}$=3.7 Hz, $H_{5'a}$), 3.80 (s, OCH_3), 4.05 (dd, $J_{5'b,5'a}$=7.3 Hz, $J_{5'b,4'}$=7.1, $H_{5'b}$), 4.28 (t, $J_{4',5'a}$=$J_{4',5'b}$=6.6 Hz, $H_{4'}$), 4.72 (m, H_2), 5.69 (complex absorption, H_3,H_4), 6.98 (broad, N*H*), 7.38–7.83 (m, Ph); ^{13}C NMR ($CDCl_3$) 21.9, 24.9, 27.0, 29.6, 40.3, 53.0, 66.8, 68.9, 71.8, 75.3, 110.3, 125.6, 127.9, 128.5, 129.7, 131.9, 134.3, 168.4, 171.8. Anal. Calcd for $C_{20}H_{25}NO_6$: C, 63.99; H, 6.71; N, 3.73. Found: C, 64.00; H, 6.61; N, 3.72.

4.1.9. Methyl (1*S*,6*R*)-1-benzoylamino-6-[(4′*S*)-4′-(2′,2′-dimethyl-1′,3′-dioxolo)]-2-oxocyclohex-3-ene-1-carboxylate, 8. A mixture of alcohol **20** (200 mg, 0.5 mmol) and PDC (300 mg, 0.7 mmol) in dry dichloromethane (25 mL) was stirred at 40°C for 70 h. Solvent was removed and the residue was chromatographed (1:1 ethyl acetate–hexane) to afford 19 mg of recovered **20** and 180 mg of **8** (100% yield on reacted **20**) as a solid. Crystals, mp 123–124°C (from EtOAc–pentane); $[\alpha]_D$=−186.3 (*c* 1.1, $CHCl_3$); IR (KBr) 3385, 1745, 1702, 1674 cm^{-1}; ^1H NMR ($CDCl_3$) 1.19 (s, CH_3), 1.29 (s, CH_3), 2.69 (m, H_{5a}), 3.20 (m, H_{5b}), 3.49 (m, H_6), 3.66 (dd, $J_{5'a,5'b}$=$J_{5'a,4'}$=8.9 Hz, $H_{5'a}$), 3.66 (s, OCH_3), 3.98 (dd, $J_{5'b,5'a}$=$J_{5'b,4'}$=8.8 Hz, $H_{5'b}$), 4.23 (m, $H_{4'}$), 6.08 (m, H_3), 6.94 (m, H_4), 7.41–7.85 (m, Ph), 7.94 (s, 1H, N*H*); ^{13}C NMR ($CDCl_3$) 24.3, 25.0, 25.9, 41.1, 53.2, 67.3, 67.9, 73.9, 109.4, 125.3, 127.2, 128.6, 132.1, 133.1, 151.5, 166.9, 167.8, 189.6. Anal. Calcd for $C_{20}H_{23}NO_6$: C, 64.33; N, 3.75; H, 6.21. Found: C, 64.37; N, 3.53; H, 6.11.

4.1.10. (3*S*,4*S*)-3-Methoxy-5-[(4′*S*)-4′-(2′,2′-dimethyl-1′,3′-dioxolo)]-4-nitrocyclohexan-1-one, 22. Nitroolefin **21** (170 mg, 10. 0 mmol) and diene **12** (200 mg, 10.9 mmol) in toluene (40 mL) were stirred at 60°C for 24 h. Solvent was removed and a 1:4 solution of 0.05% HCl–THF was added to the residue. The mixture was stirred at room temperature for 1 h, then concentrated to dryness. The residue was chromatographed (1:2 ethyl acetate–hexane) to afford ketone **22** as a white solid (65 mg, 35% yield). Crystals, mp 117–118°C (from EtOAc–pentane); $[\alpha]_D$=−25.5 (*c* 1.02, $CHCl_3$); ^1H NMR ($CDCl_3$) 1.28 (s, CH_3); 1.39 (s, CH_3); 2.37–2.48 (complex absorption, H_{2a},H_3,H_{6a},H_{6b}); 2.93 (dd, $J_{2a,2b}$=14.8 Hz, J_{2b-3}=4.9 Hz, H_{2b}); 3.32 (s, OCH_3); 3.60 (dd, $J_{5'a,5'b}$=8.3 Hz, $J_{5'a,4'}$=5.1 Hz, $H_{5'a}$); 4.10–3.89 (complex absorption, $H_{4'}$,$H_{5'b}$,H_3); 4.85–4.78 (m, H_4); ^{13}C NMR ($CDCl_3$) 24.3 and 25.7 (2×*C*H_3), 37.4 (C_6), 39.1 (C_3), 43.7 (C_2), 57.4 (OCH_3), 65.9 ($C_{5'}$), 73.1 ($C_{4'}$), 78.3 (C_3), 89.8 (C_4), 100.0 ($C_{2'}$). Anal. Calcd for $C_{12}H_{19}NO_6$: C, 52.74; H, 7.01; N, 5.13. Found: C, 52.88; H, 6.90; N, 5.14.

4.1.11. Reaction of enone 1 with diazomethane and palladium acetate: Methyl (1*S*,4*R*,6*R*)-1-benzoylamino-6-[(4′*S*)-4-(2′,2′-dimethyl-1′,3′-dioxolo)]-4-oxaspiro[2.5]-2-octene-1-carboxylate, 2, and [(3*aR*,4*R*,7*aS*)]-4-[(4′*S*)-4′-(2′,2′-dimethyl-1′,3′-dioxolo)]-6-hydroxymethyl-3*a*-methoxycarbonyl-2-phenyl-3*a*,4,5,7*a*-tetrahydrobenzoxazole, 3. Palladium diacetate (79 mg, 0.3 mmol) was added to an ice-cooled solution of enone **1** (130 mg, 0.35 mmol) in

ether (10 mL). On the resultant suspension was distilled an ethereal solution of diazomethane (prepared from *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (2.2 g, 10.0 mmol) and KOH (0.4 g, 7.1 mmol) in 30 mL ether). The light-protected mixture was stirred at 0°C for 4 h, then filtered through *celite*, and concentrated to dryness. The residue was flash-chromatographed on *florisil* (3:1 ether–hexane) to afford 17 mg of alcohol **3** and 81 mg of epoxide **2** (75% total yield) as an oil which was identified by its spectroscopic data, as follows. IR (film) 3381, 1743, 1665 cm^{-1}; ^1H NMR ($CDCl_3$) 1.35 (s, CH_3), 1.47 (s, CH_3), 2.32–2.57 (complex absorption, H_5,H_{4a},H_{4b}), 2.87 (d, $J_{6a,6b}$=5.1 Hz, H_{6a}), 2.92 (d, $J_{6b,6a}$=5.1 Hz, H_{6b}), 3.71–3.77 (complex absorption, OCH_3+$H_{5'a}$), 4.08 (m, $H_{5'b}$), 4.59 (m, $H_{4'}$), 5.39 (d, $J_{3,2}$=10.2 Hz, H_3), 6.91 (d, $J_{2,3}$=10.2 Hz, H_2), 7.43 (m, 3H) and 7.77 (m, 2H) (Ph), 8.23 (broad s, N*H*); ^1H NMR (acetone-d_6) 1.36 (s, CH_3), 1.51 (s, CH_3), 2.45–2.58 (complex absorption, H_{4a},H_{4b}), 2.86 (d, $J_{6a,6b}$=5.1 Hz, H_{6a}), 2.94 (d, $J_{6b,6a}$=5.1 Hz, H_{6b}), 3.40 (m, H_5), 3.70–3.85 (complex absorption, OCH_3+$H_{5'a}$), 4.15 (dd, $J_{5'b,5'a}$= 8.2 Hz, $J_{5'b,4'}$=5.9 Hz, $H_{5'b}$), 4.70 (m, $H_{4'}$), 5.44 (d, $J_{3,2}$= 10.2 Hz, H_3), 6.75 (d, $J_{2,3}$=10.2 Hz, H_2), 7.50 (m, 3H) and 7.84 (m, 2H) (Ph), 8.35 (broad s, N*H*); ^{13}C NMR (acetone-d_6) 24.5, 25.7, 26.3, 41.2, 53.8, 54.1, 61.2, 65.6, 67.7, 74.5, 109.9, 127.3, 127.6, 128.9, 131.9, 134.9, 166.8, 172.3, MS, *m/e* (%) 387 (M, 6), 372 (M-15, 6), 329 (43), 122 (35), 105 (100), 77 (31).

When epoxide **2** was eluted through a silica gel column (3:1 ether–hexane), alcohol **3** was obtained and fully characterized. Crystals, mp 41–43°C (from ethyl acetate–pentane); $[\alpha]_D$=−96.5 (*c* 1.14, $CHCl_3$); IR (KBr) 3451–3381 (broad), 1729, 1644 cm^{-1}; ^1H NMR ($CDCl_3$) 1.24 (s, CH_3), 1.34 (s, CH_3), 2.06 (dd, $J_{5a,5b}$=16.8 Hz, $J_{5a,4}$=4.4 Hz, H_{5a}), 2.30 (dd, $J_{5b,5a}$=16.8 Hz, H_{5b}), 2.66 (m, H_4), 3.71–3.78 (complex absorption, OCH_3+$H_{5'a}$), 3.97 (dd, $J_{5'b,5'a}$=8.0 Hz, $J_{5'b,4'}$= 5.8 Hz, $H_{5'b}$), 4.07–4.11 (complex absorption, $H_{4'}$, H_{8a},H_{8b}), 5.29 (d, $J_{7a,7}$=4.4 Hz, H_{7a}), 5.95 (m, H_7), 7.41 (m, 3H) and 7.93 (m, 2H) (Ph); ^1H NMR (acetone-d_6) 1.25 (s, CH_3), 1.31 (s, CH_3), 2.11–2.17 (complex absorption, $H_{5a,5b}$), 2.66 (m, H_4), 2.86 (broad s, O*H*), 3.70 (dd, $J_{5'a,5'b}$=8.1 Hz, $J_{5'a,4'}$= 5.1 Hz, $H_{5'a}$), 3.77 (s, OCH_3), 3.93 (dd, $J_{5'b,5'a}$=8.1 Hz, $J_{5'b,4'}$=5.8 Hz, $H_{5'b}$), 4.04 (broad s, 2×H_8), 4.20 (m, $H_{4'}$), 5.31 (d, $J_{7a,7}$=4.4 Hz, H_{7a}), 5.93 (m, H_7), 7.59 (m, 3H) and (7.98 (m, 2H) (Ph); ^{13}C NMR (acetone-d_6) 25.4, 26.1, 26.9, 43.2, 53.0, 65.2, 69.0, 76.9, 77.7, 80.9, 107.9, 116.3, 128.5, 129.1, 129.3, 132.7, 145.9, 165.7, 174.8; MS, *m/e* (%) 372 (M-15, 3), 105 (100), 77 (38), 43 (33). Anal. Calcd for $C_{21}H_{25}NO_6$: C, 65.18; H, 6.51; N, 3.62. Found: C, 65.15; H, 6.59; N, 3.56.

4.1.12. Metal-catalyzed reaction of cyclohexenone, 11, with diazomethane: Bicyclo[4.1.0]heptan-2-one, 23.[28] *Method A: Pd(II) as a catalyst and ether as a solvent*. Working as described above, reaction of **11** (200 mg, 2.1 mmol) in ether (20 mL) with excess diazomethane in the presence of palladium acetate (10 mg, 0.04 mmol) at 0°C for 2 h afforded, after chromatography (mixtures of ethyl acetate–hexane), 185 mg (80% yield) of cyclopropane **23**. *Method B: Rh(II) as a catalyst and dichloromethane as a solvent*. Rhodium diacetate (5.0 mg, 0.02 mmol) was added to a solution of cyclohexenone, **11**, (200 mg, 2.1 mmol) in dichloromethane (20 mL). Then, an ethereal solution of excess diazomethane was distilled onto the mixture, previously cooled at 0°C. The resultant solution was allowed to warm to rt and stirred for 2 h, then filtered through *celite*, and concentrated to dryness. The residue was chromatographed (mixtures of ethyl acetate–hexane) to afford **23** (130 mg, 57% yield). Compound **23** was identified by its spectroscopic data, as follows. ^1H NMR ($CDCl_3$) 0.98 (m, 1H), 1.10 (m, 1H), 1.49–1.66 (complex absorption, 3H), 1.78–2.01 (complex absorption, 3H), 2.14 (dd, J= J'=4.4 Hz, 1H), 2.21 (dd, J=5.1 Hz, J'=4.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) 10.0, 17.3, 17.6, 21.1, 25.6, 36.6, 209.1. MS, *m/e* (%) 110 (M, 61), 82 (43), 81 (37), 68 (34), 67 (72), 55 (71), 54 (100).

4.1.13. Palladium(II)-catalyzed reaction of enone 5 with diazomethane. A light-protected ethereal-solution of enone **5** (100 mg, 3.5 mmol), $Pd(OAc)_2$ (80 mg, 3.5 mmol) and excess diazomethane (prepared from 3.0 g of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide) was stirred at 0°C for 4 h. After the usual working-up and chromatography (1:2 ethyl acetate–hexane), fractions enriched in oxazole **24** (43 mg, 38%) and in cyclopropane **25** (10 mg, 8%) were obtained and identified by their spectroscopic data. **(3*aR*,4*R*,7*aS*)-4-Methyl-3a-methoxycarbonyl-2-phenyl-6-hydroxymethyl-3a,4,5,7a-tetrahydrobenzoxazole, 24.** IR (film) 3381, 1732, 1644 cm^{-1}; ^1H NMR ($CDCl_3$) 1.17 (d, J=7.3 Hz, CH_3); 1.61 (m, 2×H_5); 2.51 (m, H_4); 3.76 (s, OCH_3); 4.02 (broad s, CH_2OH); 5.28 (m, H_{7a}); 5.79 (broad s, H_7); 7.65 (m, Ph); ^{13}C NMR ($CDCl_3$) ; GC-MS, *m/e* (%) 301 (M, 1), 242 (83), 139 (98), 105 (100), 104 (27), 93 (44), 77 (77). **(1*R**,2*R*,3*R*,6*S**)-2-Benzoylamino-3-methyl-6-methoxycarbonylbicyclo[4.1.0]heptan-5-one, 25.** ^1H NMR ($CDCl_3$) 0.95 (d, J=7.2 Hz, CH_3); 1.26 (complex absorption, 2×H_7), 2.44 (m, H_1, H_3, H_{4eq},H_{4ax}, H_6); 7.55 (m, Ph); ^{13}C NMR ($CDCl_3$) 16.1, 30.7, 32.4, 41.6; 44.4, 45.1, 53.44, 70.7, 129.1, 129.3, 129.8, 132., 162.2, 175.5, 206.1; GC-MS, *m/e* (%) 301 (M, 1), 212 (74), 105 8100), 77 (42).

4.1.14. Palladium(II)-catalyzed reaction of enone 10 with diazomethane: (1*R,3*R*,4*R*,6*R**)-3-Benzoylamino-4-[(4′*S*)-4′-(2′,2′-dimethyl-1′,3′-dioxolo)]-3-methoxycarbonylbicyclo[4.1.0]heptan-2-one, 26.** An ethereal solution of excess diazomethane was distilled onto a stirred mixture of enone **8** (110 mg, 3.2 mmol) and $Pd(OAc)_2$ (65 mg, 3.2 mmol) in ether (15 mL) for five times throughout a 2.5 days period. Each time, the reaction mixture was cooled at 0°C before diazomethane addition, later stirred at room temperature. The mixture was filtered through *celite*, solvent was removed and the residue was chromatographed (mixtures of ethyl acetate–hexane) to afford compound **26** as a 4:1 diastereoisomeric mixture (56 mg, 50% yield). The major isomer was an oil which could be characterized by its spectroscopic data. ^1H NMR ($CDCl_3$) 1.19 (m, H_{7a}), 1.25 (s, CH_3), 1.36 (s, CH_3), 1.50 (m, H_{7b}), 1.93 (m, H_6), 2.26–2.07 (complex absorption, 2×H_5), 2.42 (m, H_1), 2.70 (m, H_4), 3.24 (m, $H_{5'a}$), 3.78 (s, OCH_3), 3.94 (m, $H_{5'b}$), 4.08 (m, $H_{4'}$), 7.70 (m, Ph), 8.24 (broad s, N*H*). ^{13}C NMR ($CDCl_3$) 13.3, 19.0, 20.9, 21.5, 25.6, 25.7, 26.4, 26.9, 27.1, 30.6, 39.2, 42.5, 47.6, 54.0, 54.8, 68.0, 68,1, 68.7, 74.4, 76.4, 109.4, 128.1, 128.2, 129.6, 129.7, 132.9, 133.0, 134.1, 134.3, 167.8, 201.8. MS, *m/e* (%) 387 (M, 1), 105 (100), 77 (26). Calcd for $C_{21}H_{25}NO_6$×1/2H_2O: C, 63.32; H, 6.61; N, 3.53. Found: C, 63.09; H, 6.55; N, 3.14.

4.1.15. Palladium(II)-catalyzed reaction of enone 10 with diazomethane. Several experiments were carried out in order to state the influence of the temperature and the reaction time. In all cases, results were similar and conversion never was higher than ca 15%. For instance, an ice-cooled ethereal solution of **10** (80 mg, 0.48 mmol), palladium acetate (108 mg, 0.48 mmol) and excess diazomethane was stirred for 4 h. After the usual working-up and subsequent chromatography, 65 mg (85% recovery) of **10** and 16 mg (15% total yield) of a 1:1 diastereomeric mixture of **27a/27b** were obtained. Significant selected ^{1}H NMR data for the mixture **27a/27b** and **10** ($CDCl_3$): 1.10–1.30 (complex absorption, 4H, cyclopropane-ring protons, **27a**+**27b**), 1.35 (s, CH_3, **27a**), 1.37 (s, CH_3, **27b**), 1.44 (s, CH_3, **10**). GC-MS, (a) Compound **27a**, retention time 6.68 min, *m/e* (%) 182 (M, 40), 150 (52), 123 (100), 122 (51), 95 (83), 94 (36), 81 (92), 79 (50), 67 (47), 55 (68), 41 (36). (b) Compound **27b**, retention time 6.80 min, *m/e* (%) 182 (M, 68), 154 (61), 126 (42), 123 (88), 122 (51), 95 (94), 94 (47), 81 (100), 79 (56), 67 (53), 55 (78), 41 (35).

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