$Rh_2(OAc)_4$-Catalyzed reactions of methyl diazoacetate with 1,3-oxazolidines and 1,3-oxathiolanes

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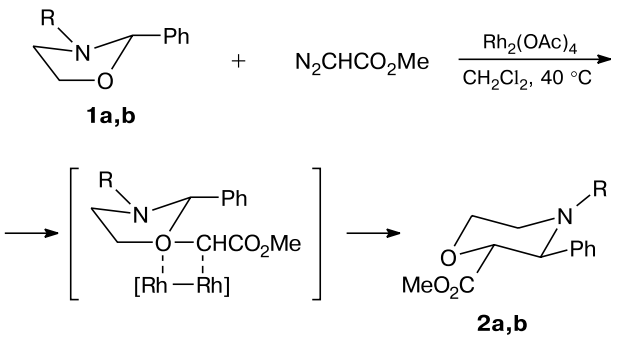
Methoxycarbonylcarbene generated by catalytic decomposition of methyl diazoacetate in the presence of $Rh_2(OAc)_4$, is regioselectively inserted into the C(2)—O bond of 3-alkyl-2-phenyl-1,3-oxazolidines and into the C(2)—S bond of 2-phenyl-1,3-oxathiolane. Study by the competitive reaction method demonstrated that the relative reactivity toward the insertion of the methoxycarbonylcarbene fragment into the C—heteroatom bond increases in the series of 1,3-dioxolane, 1,3-oxazolidine, and 1,3-oxathiolane.

Key words: 1,3-oxazolidines, 2-phenyl-1,3-oxathiolane, methyl diazoacetate, morpholines, oxathianes, catalysis, insertion reaction.

In recent years, much attention has been focused on developing new regio- and stereoselective methods for the synthesis of 1,4-diheteracyclohexanes.[1—9] This is primarily due to high and various physiological activities of these heterocyclic compounds. For example, the morpholine fragment is involved as a structural element in many pharmacological drugs.[10] Tagetitoxin containing the 1,4-oxathiane fragment is an RNA polymerase inhibitor.[11,12] One of convenient procedures for the synthesis of 1,3-dioxane, morpholine, and oxathiane derivatives is based on the intramolecular rearrangement of oxonium, ammonium, and sulfonium ylides, respectively, in the catalytic reactions of diazo compounds with 1,3-diheteracyclopentanes.[1—5] In the reactions with 3-ethyl-2-phenyl- and 2,3-diphenyloxazolidines, methoxycarbonylcarbene, which is generated by thermocatalytic decomposition of methyl diazoacetate (MDA) in the presence of copper bronze, was demonstrated[13] to be predominantly inserted into the C—N bond of the oxazolidine ring to give morpholine-3-carboxylic acid esters. It was also noted[13] that insertion products of carbene neither into the C—N bond nor into the C—O bond are formed in the presence of $Rh_2(OAc)_4$, although it is highly probable that insertion might occur into the C—O bond in the presence of a rhodium catalyst. For example, the reaction of MDA with 1,3-dioxanes in the presence of $Rh_2(OAc)_4$ produces 1,4-dioxepanes, the *cis* isomer being the major product in the reactions with 1,3-dioxane containing a substituent at position 2.[14]

In the present study, we examined the catalytic reactions of 3-alkyl-2-phenyl-1,3-oxazolidines (**1a,b**) and 2-phenyl-1,3-oxathiolane (**1c**) with MDA in the presence of $Rh_2(OAc)_4$. It appeared that the reactions of oxazolidines **1a,b** with MDA in dichloromethane in the presence of 0.4 mol.% of the catalyst at 40 °C produced methyl 4-alkyl-3-phenylmorpholine-2-carboxylates **2a** and **2b** in 50 and 46% yields, respectively (the reaction time was 2 h). In both cases, the ring enlargement of the heterocycle due to the insertions of the carbene fragment into the C—O bond occurs to give *trans* isomers **2a,b**.

Scheme 1



R = Et (**a**), Bu^i (**b**)

Morpholine derivatives **2a,b** are generated apparently through the attack of methoxycarbonylcarbene on the oxy-

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gen atom of oxazolidines **1a,b** to form *O*-ylides, which undergo the Stevens rearrangement accompanied by the ring enlargement.[15] It should be noted that thermocatalytic decomposition of MDA (120 °C, copper bronze)[13] with oxazolidine **1a** affords a complex mixture of compounds, in which the percentage of morpholine **2a** is lower than 13%, the spectroscopic characteristics typical of *trans* isomer **2a** being unobserved.

The stereochemical compositions of compounds **2a,b** were determined by analyzing the chemical shifts and spin-spin coupling constants in the ^{1}H NMR spectra and performing quantum chemical calculations of the NMR spectra for the compounds under study with the use of the GAUSSIAN program.[16] The ^{1}H NMR spectrum of compound **2a** shows doublets at δ 3.36 and 3.95 ($^3J_{2,3}$ = 8.9 Hz) corresponding to the methine protons at the C(3) and C(2) atoms, respectively, of the morpholine ring. The spin-spin coupling constant is indicative of the *trans* arrangement of the substituents at the adjacent carbon atoms. The COLOC 2D NMR spectrum of ester **2a** shows a cross-peak between the signal for the carbonyl carbon atom (δ 169.6) and a low-field signal for the methine proton at the C(2) atom (δ 3.95), which confirms that methoxycarbonylcarbene is inserted into the C(2)—O bond of oxazolidine **1a**.

The NMR spectra of methyl *trans*- and *cis*-4-ethylmorpholine-3-phenyl-2-carboxylates (**2a,d**) and regioisomeric *trans*- and *cis*-4-ethylmorpholine-2-phenyl-3-carboxylic acid esters (**3a,b**) were simulated by the CSGT method[17] in the MPW1PW91/6-311G(2d,p) approximation with the use of the geometric parameters of the compounds determined at the B3LYP/6-31G(d,p) level of theory. The solvent (chloroform) effect was taken into account using the COSMO polarized continuum model.[18] Chloroform has approximately the same effect on all four isomers. It was found that the best agreement between the calculated and experimental ^{13}C NMR spectra is observed for isomer **2a**. The chemical shifts of all carbon nuclei are linearly related to each other with a high correlation coefficient:

$$\delta_{exp} = (0.982\pm0.008)\delta_{calc} - (2.09\pm0.87) \quad (r = 0.9996).$$

The calculated spectra of morpholines **2d** and **3b** containing the *cis*-arranged Ph and CO_2Me substituents are in poorer agreement with experiment due primarily to small chemical shifts of the carbon nuclei of the morpholine ring. The insertion product into the C—N bond of molecule **3a** with the *trans* arrangement of these substituents is characterized by a somewhat lower correlation coefficient for the dependence $\delta_{exp} \sim \delta_{calc}$, but this coefficient is nevertheless sufficiently high (r = 0.9991) to confirm the agreement between the calculated and experimental spectra. The chemical shifts for compounds **2a** and **3a** corrected with the use of the correlation dependence are given in Table 1. The average absolute errors are 1.0 and 1.4 ppm, respectively.

An analogous situation is observed when comparing the calculated ^{1}H NMR spectra of these compounds with experiment. The best agreement is observed for isomer **2a**, which is characterized by the following correlation dependence:

$$\delta_{exp} = (0.958\pm0.015)\delta_{calc} + (0.41\pm0.07) \quad (r = 0.998).$$

Therefore, a comparison of the calculated ^{1}H and ^{13}C NMR spectra with the experimental data demonstrated that the $Rh_2(OAc)_4$-catalyzed reaction of 3-ethyl-2-phenyl-1,3-oxazolidine with MDA affords the insertion product of carbene into the C—O bond of oxazolidine, *viz.*, *trans* isomer **2a**.

The fact that carbene is inserted into the C—N or C—O bond of oxazolidines is additionally confirmed by

Table 1. Experimental and calculated ^{1}H and ^{13}C NMR spectra of compounds **2a** and **3a** ($CDCl_3$, δ)

Fragment	^{13}C NMR			^{1}H NMR		
	Calculations		Experiment	Calculations		Experiment
	2a	**3a**		**2a**	**3a**	
HC(2)	83.92	80.81	82.1	3.77	2.72	3.95
HC(3)	68.00	73.72	68.6	3.36	4.52	3.36
$H_2C(5)$	48.81	47.47	50.2	2.27 (H_{ax}), 3.00 (H_{eq})	2.12 (H_{ax}), 2.90 (H_{eq})	2.50 (H_{ax}), 3.00 (H_{eq})
$H_2C(6)$	66.22	65.89	67.1	3.78 (H_{ax}), 3.91 (H_{eq})	3.82 (H_{ax}), 3.92 (H_{eq})	3.82 (H_{ax}), 4.05 (H_{eq})
CH_2	48.03	49.36	48.2	1.92, 2.63	2.19, 2.45	2.08, 2.55
Me	12.29	12.26	10.8	1.01—1.44	1.14—1.44	1.05
CO_2	167.09	170.33	169.6	—	—	—
OMe	50.15	49.96	51.6	3.43—3.50	3.48—3.53	3.35
Ph	127.8—129.6, 138.50	126.6—128.7, 138.47	127.6—128.5, 137.5	7.15—7.68	7.04—7.54	7.20—7.50

the results of theoretical modeling of the reaction under consideration. The most probable pathway of the process and, consequently, the major reaction product were chosen by calculating the relative energy of the possible product and determining which reaction pathway is thermodynamically more favorable. Based on the relative energies of the conformers, conclusions were drawn about the thermodynamic probability of the formation of a particular compound. To reduce the calculation time, we performed theoretical analysis for morpholine derivatives containing the ethyl substituent at the nitrogen atom. In preliminary calculations, the optimal arrangement of the Et, Ph, and COOMe substituents relative to the plane of the six-membered ring was determined with consideration for the possibility of free rotation of the substituents and their fragments about to C—C and C—O single bonds.

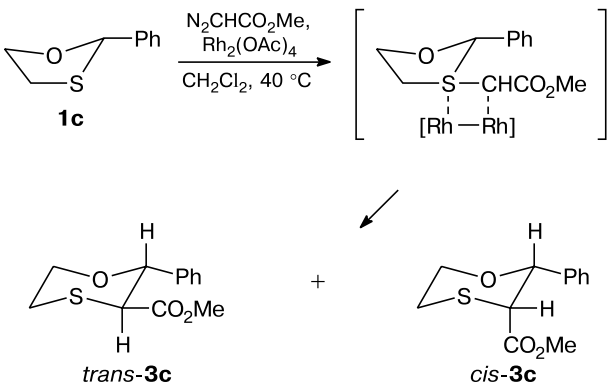
Based on calculations at the RHF/3-21G level of theory, the diaxial and diequatorial morpholine derivatives, which are insertion products into the C—O and C—N bonds, were found to be the most stable compounds. The energies of these compounds were refined by geometry optimization of their structures at the B3LYP/6-31G(d,p) level, and the temperature corrections for the enthalpy were calculated. The temperature correction includes the zero-point energy and the enthalpy change for the compound upon heating from 0 to 298 K and is calculated by the equations of statistical thermodynamics. Finally, the solvent effect on H°_{298} was taken into account with the use of the COSMO polarized continuum model. The calculated standard enthalpies of these compounds are given in Table 2. According to these data, the isomers corresponding to the insertion of carbene into the C—N bond are thermodynamically more stable and their formation is more probable, all other factors being the same. However, a drawback of the thermodynamic approach is that it ignores the kinetic parameters of the reactions.

The reaction of 2-phenyl-1,3-oxathiolane (**1c**) with MDA in CH_2Cl_2 in the presence of $Rh_2(OAc)_4$ produced methyl 2-phenyl-1,4-oxathiane-3-carboxylate (**3c**) in 72% yield (Scheme 2). In this case, as opposed to the reaction of 1,3-oxazolidines, the carbene fragment is inserted into the C—S bond of the heterocycle, oxathiane **3c** being formed as a mixture of the *trans* and *cis* isomers in a ratio of 1.5 : 1. Earlier, it has been noted[19,20] that the reaction of ethyl diazoacetate with heterocycle **1c** proceeds in the presence of $Cu(acac)_2$ as well, but the corresponding *trans* and *cis* isomers of ethyl 2-phenyl-1,4-oxathiane-3-carboxylate were synthesized only in 18% yield (the isomer ratio was ~2 : 1).

Table 2. Absolute enthalpies (H°_{298}) and relative energies (ΔH°) of stereoisomers of methyl 4-ethylmorpholine-3-phenyl-2-carboxylate (**2a,d**) and 4-ethylmorpholine-2-phenyl-3-carboxylate (**3a,b**) in the gas phase (I) and in chloroform (II)

Compound	$-H^\circ_{298}$/Hartree		ΔH°/kJ mol^{-1}	
	I	II	I	II
2a	825.031878	825.033941	3.5	4.3
2d	825.030569	825.032975	7.0	6.8
3a	825.033222	825.035577	0.0	0.0
3b	825.032180	825.034205	2.7	3.6

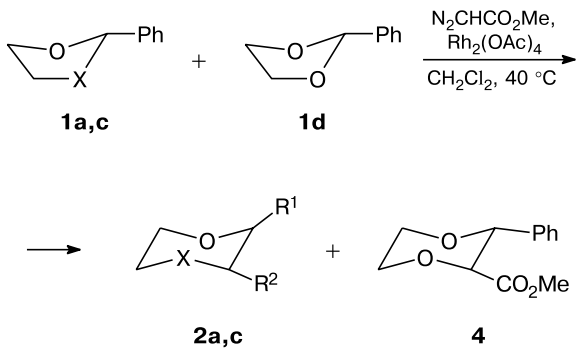
Scheme 2



The resulting mixture of esters *trans*- and *cis*-**3c** was characterized by ^{1}H, ^{13}C, and 2D NMR spectroscopy. The spectra of both isomers are very similar and each is indicative of the presence of the OCH(Ph)CH(CO_2Me)S fragment in the six-membered heterocycle and, consequently, of the insertion of methoxycarbonylcarbene into the C—S bond of oxathiolane **1c**. The direction of the attack of carbene on the sulfur atom is, apparently, attributed to higher stability of the transition state of the resulting *S*-ylides compared to *O*-ylides.[21] In the ^{1}H NMR spectra of isomeric oxathianes **3c**, the vicinal spin-spin coupling constants $^3J_{2,3}$ of the methine protons are 2.8 and 9.5 Hz. The large coupling constant is indicative of the axial positions of the H(2) and H(3) protons in the *trans* isomer of **3c**. In the ^{13}C NMR spectra of isomeric oxathianes **3c**, the signals for the C(2) and C(3) atoms of the *trans* isomer are observed at lower field compared to the signals for the analogous atoms in the *cis* isomer (the chemical shifts of the C(2) and C(3) atoms in *trans*- and *cis*-**3c** are 82.1, 48.5 and 79.5, 42.0 ppm, respectively) due to the α and β effects of the equatorial substituents. The presence of the phenyl and methoxy groups at positions 2 and 3 of the heterocycle was established based on the NOE effects between the low-field signal for the protons at the C(2) atom and the signal for the aromatic protons. For example, irradiation of the H(2) atom in *cis*-**3c** at the protons of the phenyl ring gives the NOE effect of 6.2%, which is absent upon irradiation of the H(3) proton.

To reveal the relationships between the structure of 1,3-diheteracyclopentanes and the rate of insertion of methoxycarbonylcarbene into the carbon—heteroatom bond, the reactions of compounds **1a,c,d** with MDA in the presence of $Rh_2(OAc)_4$ were studied by the competitive reaction method (Scheme 3). The relative reactivities were determined at 40 °C by adding a solution of MDA in dichloromethane to a mixture containing dioxolane **1d** and its heteroanalog **1a** or **1c** in a molar ratio **1d** : **1a** (or **1c**) : MDA : $Rh_2(OAc)_4$ = 250 : 250 : 100 : 1.

Scheme 3



X = NEt, R^1 = CO_2Me, R^2 = Ph (**1a, 2a**),
X = S, R^1 = Ph, R^2 = CO_2Me (**1c, 2c**)

As expected, 2-phenyl-1,3-oxathiolane **1c** showed the highest reactivity (k_{rel}(**1c**/**1d**) = 9.8), whereas oxazolidine **1a** appeared to be only slightly reactive than 1,3-dioxolane **1d** (k_{rel}(**1a**/**1d**) = 1.7) although it is characterized by the insertion of the carbene fragment into the C—O bond rather than into the C—N bond. This fact is apparently attributed to the additional replacement at the nitrogen atom, which hinders the intermediate formation of *N*-ylide. Therefore, both the electronic character of the heteroatom and the degree of its shielding should be taken into account when considering the insertion of alkoxycarbonylcarbene into the C—heteroatom bond in 1,3-diheteracyclopentanes.

Experimental

The ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer (300.13 and 75.47 MHz, respectively) in $CDCl_3$ with $SiMe_4$ as the internal standard. The IR spectra were measured on a Specord M82-63 instrument in a thin layer. The mass spectra were obtained on an MX-1320 instrument; the ionizing electron energy was 70 eV; the temperature of the ionization chamber was 50—70 °C. The GLC analysis was carried out on a Chrom-5 chromatograph equipped with a flame ionization detector (a 1200×5 mm column with 5% SE-30 on Inerton N-AW DMCS (0.125—0.160 mm)) using helium as the carrier gas. The TLC analysis was performed on Silufol chromatographic plates (Merck). Preparative separation was performed by column chromatography on silica gel Chemapol (60 L, 100/160 μm). Starting 1,3-diheterocyclopentanes **1a—d** were synthesized according to known procedures,[22,23] distilled under a stream of argon, and stored under an inert atmosphere over metallic sodium, because storage of these compounds leads to their decomposition to form the starting aldehydes and ketones. The solvents (CH_2Cl_2, diethyl ether, benzene, hexane, and petroleum ether) were purified according to standard procedures.[24]

Quantum chemical calculations of the structures and the ^1H and ^{13}C NMR spectra of the morpholines were performed with the use of the GAUSSIAN-98 program.[16] The preliminary geometry optimization of the molecules and limited conformational analysis were performed by the HF/3-21G method. Of all theoretically possible structures, four thermodynamically most stable structures of morpholine derivatives **2a,d** and **3a,b** were chosen, and the total energies of the latter were refined by density functional theory. The B3LYP functional and the 6-31G(d,p) valence-split basis set were used as the main method for geometry optimization. This approximation was used to solve the vibrational problem as well as to calculate the zero-point energies and the temperature corrections for the enthalpy for estimation of the relative energies of the compounds under study at 298 K. The solvent ($CDCl_3$) effect was taken into account using the COSMO polarized continuum model.[17] The chemical shifts of the hydrogen and carbon atoms in compounds **2a,d** were calculated relative to Me_4Si by the CSGT method[18] in the MPW1PW91/6-311+G(2d,p) approximation with the use of the geometric parameters of the most stable conformers evaluated by the B3LYP/6-31G(d,p) quantum chemical method.

Reactions of 1,3-diheteracyclopentanes 1a—c with methyl diazoacetate (general procedure). A solution of MDA (1.10 g, 11 mmol) in CH_2Cl_2 (15 mL) was added to a stirred solution of 1,3-diheteracyclopentane (13 mmol) and $Rh_2(OAc)_4$ (24 mg, 0.054 mmol) in CH_2Cl_2 (35 mL) at 40 °C for 1 h. The reaction mixture was additionally stirred for 1 h. Then the solvent was removed, and the residue was dissolved in Et_2O (10 mL). The solution was passed through a thin layer of Al_2O_3, the solvent was removed *in vacuo*, and the residue was distilled off or chromatographed on silica gel.

Methyl *trans*-4-ethylmorpholine-3-phenyl-2-carboxylate (2a) was synthesized by the reaction of MDA with 3-ethyl-2-phenyl-1,3-oxazolidine (**1a**). The product was isolated by column chromatography in 50% yield, R_f 0.5 (hexane—Et_2O, 1 : 1, as the eluent). Found (%): C, 67.88; H, 7.51; N, 5.69. $C_{14}H_{19}NO_3$. Calculated (%): C, 67.45; H, 7.68; N, 5.62. ^1H NMR, δ: 1.05 (t, 3 H, Me, ^3J = 7.2 Hz); 2.08 and 2.55 (both m, 1 H each, C$\underline{H}_2$Me); 2.50 (m, 1 H, H_{ax}(5)); 3.00 (d, 1 H, H_{ex}(5)); 3.35 (s, 3 H, OMe); 3.36 (d, 1 H, H(3), ^3J = 8.9 Hz); 3.82 (td, 1 H, H_{ax}(6), $^3J_{5_{ax},6_{ax}}$ = 11.6 Hz, $^3J_{5_{eq},6_{ax}}$ = 2.4 Hz); 3.95 (d, 1 H, H(2), ^3J = 8.9 Hz); 4.05 (m, 1 H, H_{eq}(6)); 7.21—7.50 (m, 5 H, Ph). ^{13}C NMR, δ: 10.8 (Me); 48.2 (C$\underline{H}_2$Me); 50.2 (C(5)); 51.6 (OMe); 67.1 (C(6)); 68.6 (C(3)); 82.1 (C(2)); 127.6, 128.2, 128.5, 137.5 (Ph); 169.6 (COO). MS (EI, 70 eV), *m/z* (I_{rel} (%)): 249 $[M]^+$ (24), 234 $[M - Me]^+$ (4), 190 $[M - CO_2Me]^+$ (15), 172 $[M - Ph]^+$ (4), 160 $[M - CO_2Me - C_2H_6]^+$ (100), 146 (22), 132 (82), 118 (88), 104 (58), 103 (29), 91 $[C_7H_7]^+$ (71), 77 $[Ph]^+$ (37).

Methyl 4-isobutyl-3-phenylmorpholine-2-carboxylate (2b) was synthesized by the reaction of MDA with 3-isobutyl-2-phenyl-1,3-oxazolidine (**1b**). The product (yellow oil) was iso-

lated by vacuum distillation, the yield was 46%, b.p. 144—146 °C (2 Torr). Found (%): C, 69.10; H, 8.25; N, 5.00. $C_{16}H_{23}NO_3$. Calculated (%): C, 69.29; H, 8.36; N, 5.05. IR, ν/cm^{-1}: 710, 770, 1095, 1120, 1180, 1220, 1290, 1390, 1465, 1495, 1645, 1750, 2750—3100. ^{1}H NMR, δ: 0.62 and 0.74 (both d, 3 H each, Me, ^3J = 6.4 Hz); 1.70 (m, 1 H, $\underline{H}CMe_2$); 1.71—2.00 (m, 2 H, H(5)); 2.20—3.20 (m, 2 H, $\underline{H}_2CCH$); 3.22 (d, 1 H, H(3), ^3J = 9.1 Hz); 3.3 (s, 3 H, OMe); 3.75 (td, 1 H, $H_{ax}(6)$, $^3J_{5_{ax},6_{ax}}$ = 11.5 Hz, $^3J_{5_{eq},6_{ax}}$ = 2.3 Hz); 3.95 (m, 1 H, $H_{eq}(6)$); 3.95 (d, 1 H, H(2), ^3J = 9.1 Hz); 7.29—7.60 (m, 5 H, Ph). ^{13}C NMR, δ: 20.0, 20.9 (2 Me); 24.9 ($\underline{C}HMe_2$); 51.2 ($\underline{C}H_2CH$); 51.6 (OMe); 62.4 (C(5)); 67.1 (C(6)); 69.4 (C(3)); 82.2 (C(2)); 127.9, 128.2, 128.6, 137.8 (Ph); 169.6 (COO). MS (EI, 70 eV), *m/z*: 277 $[M]^+$, 262 $[M - Me]^+$, 246 $[M - OMe]^+$, 234 $[M - C_3H_7]^+$, 218 $[M - CO_2Me]^+$, 206, 202, 188, 174, 160.

Methyl 2-phenyl-1,4-oxathiane-3-carboxylate (3c) was synthesized by the reaction of MDA with 2-phenyl-1,3-oxathiolane (**1c**). The product (yellow oil) was isolated by vacuum distillation, the yield was 72%, b.p. 128—130 °C (1 Torr). This product is a mixture of isomers *trans*- and *cis*-**3c** in a ratio of ~1.5 : 1 (^{1}H NMR spectroscopic data). Found (%): C, 59.89; H, 5.65; S, 13.28. $C_{12}H_{14}O_3S$. Calculated (%): C, 60.48; H, 5.92; S, 13.46. IR, ν/cm^{-1}: 704, 756, 1000, 1095, 1152, 1290, 1336, 1730, 2860—3065. MS (EI, 70 eV), *m/z*: 238 $[M]^+$, 220 $[M - H_2O]^+$, 210 $[M - C_2H_4]^+$, 179 $[M - CO_2Me]^+$, 161 $[M - Ph]^+$, 121, 107, 104, 91, 77.

Compound *trans*-**3c**. ^{1}H NMR, δ: 2.34—4.51 (m, CH_2CH_2); 3.40 (s, OMe); 3.92 (d, H(3), ^3J = 9.5 Hz); 4.75 (d, H(2), ^3J = 9.5 Hz); 7.31—7.62 (m, Ph). ^{13}C NMR, δ: 26.6 (C(5)); 48.1 (C(3)); 51.8 (OMe); 68.8 (C(6)); 81.7 (C(2)); 125.1, 126.5, 128.0, 138.9 (Ph); 169.0 (COO).

Compound *cis*-**3c**. ^{1}H NMR, δ: 2.50—4.35 (m, CH_2CH_2); 3.38 (d, H(3), ^3J = 2.8 Hz); 3.40 (s, OMe); 4.93 (d, H(2), ^3J = 2.8 Hz); 7.31—7.62 (m, Ph). ^{13}C NMR, δ: 22.7 (C(5)); 41.5 (C(3)); 51.2 (OMe); 69.3 (C(6)); 79.1 (C(2)); 126.3, 127.9, 128.2, 139.4 (Ph); 170.0 (COO).

Competitive reactions of methyl diazoacetate with 2-phenyl-1,3-dioxolane (1d) and 1,3-diheteracyclopentanes 1a and 1c. A solution of MDA (1 g, 10 mmol) in CH_2Cl_2 (15 mL; the molar ratio **1d** : **1a** (or **1c**) : MDA : $Rh_2(OAc)_4$ = 250 : 250 : 100 : 1) was added to a stirred solution of dioxolane **1d** (3.77 g, 25 mmol), 1,3-oxazolidine **1a** (or **1c**) (25 mmol), and $Rh_2(OAc)_4$ (44.2 mg, 0.1 mmol) in CH_2Cl_2 (50 mL) at 40 °C for 2 h. After completion of the reaction, samples were withdrawn three times and GLC analysis was performed. The relative reactivities of 1,3-diheteracyclopentanes were calculated by the equation $k_{rel} = aS^1/S^0$, where S^0 is the peak area of methyl 3-phenyl-1,4-dioxane-2-carboxylate (**4**), S^1 is the peak area of the insertion product of methoxycarbonylcarbene into the C—heteroatom bond of 1,3-diheteracyclopentane **1a** or **1b**, and *a* is the calibration factor (*a* = 1.14 and 1.08 for **2a** and **3c**, respectively). Based on the experimental data, k_{rel}(**1c**/**1d**) = 9.8 and k_{rel}(**1a**/**1d**) = 1.7.

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