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Supplementary Material Available: Region of P.COSY spectrum used for simulations and table including $J_{2'3'}$ and $J_{2''3'}$ from simulation (5 pages). Ordering information is given on any current masthead page.

Functionalization of Saturated Hydrocarbons: Selective Insertion Reactions of Dihalocarbenes into Carbon-Hydrogen Bonds Adjacent to Cyclopropane Rings†

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Attempts to selectively functionalize saturated hydrocarbons[1] have been called "the search for the chemist's Holy Grail".[2] The fact that dihalocarbenes can insert into C-H bonds was recognized 30 years ago.[3] Since then, a number of different C-H insertions of dihalocarbenes have been discovered.[4,5] Moderate yields for insertion of dihalocarbenes into *tertiary* C-H bonds of saturated hydrocarbons have been obtained, however, only from ball-shaped molecules, such as adamantane[5h,o] and dodecahedrane.[5v] In contrast, insertions of dihalocarbenes into *secondary* and *tertiary* C-H bonds of other saturated hydrocarbons ordinarily afford only very low yields.[5j,l,p]

Table I. Insertion Reactions of $:CX_2$ into Carbon-Hydrogen Bonds of Small Ring Compounds

small ring compd	X	products (ratios, %)[a]	yield (%)[b]
1	Cl	**2a** (81), **2b** (19)	83
	Br[c]	**3a** (80), **3b** (20)	27
4	Cl	**5a** (26), **5b** (74)	40
	Br[c]	**6a** (20), **6b** (80)	18
7	Cl	**8a** (83), **8b** (17)	57
9	Cl	three isomers[d]	2
10	Cl	no reaction	0
11	Cl	**12**	90

[a] Relative ratios measured by ^1H NMR spectroscopy. [b] Total yields of two isomers. [c] Stereochemical assignment based on similarity of NMR spectra with the corresponding chloro compounds. [d] Ratios = 5:1:1 based on ^1H NMR of signals of $CHCl_2$ groups.

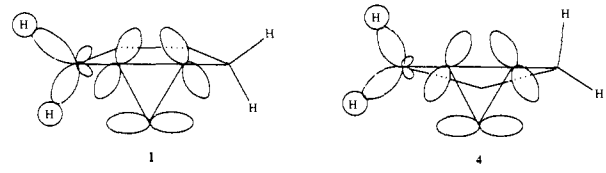
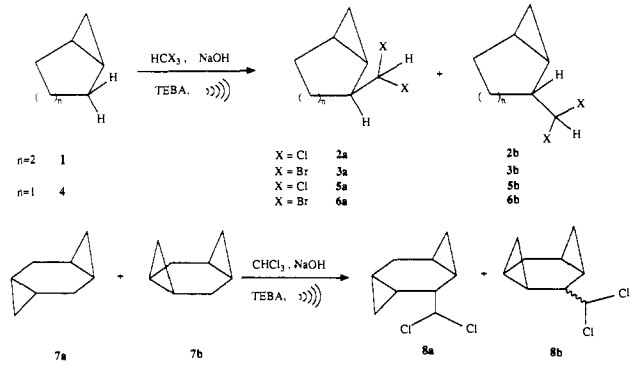


Figure 1.

Scheme I



Although reactions of dihalocarbenes with strained compounds containing three-membered rings have been studied for about 25 years,[6,7] C-H insertion reactions of dihalocarbenes with hydrocarbons containing three- or four-membered rings have not been reported. We sought evidence to support the premise that C-H bonds α to a three-membered ring could be inserted because of the possibility of an interaction of the Walsh orbitals of the cyclopropane ring with suitable C-H bond orbitals.

The reactions of dihalocarbenes with olefins in solid-liquid two-phase systems under ultrasonication usually afford high yields of double-bond addition products.[8,9] When a mixture of bicyclo[4.1.0]heptane (**1**),[10] chloroform, powdered sodium hydroxide, and 0.5% of TEBA (triethylbenzylammonium chloride) was ultrasonicated in the water bath of an ultrasonic cleaner (35 kHz, 120 W) for 3 h, 2-(dichloromethyl)bicyclo[4.1.0]heptanes **2a** and **2b** were obtained in a yield of 83% (ratio = 4.3:1; see Table I). As determined by NOE experiments,[11] the dichloromethyl group

† Carbene Rearrangements. Part 38. Part 37: Xu, L.; Miebach, T.; Smith, W. B.; Brinker, U. H. *Tetrahedron Lett.* **1991**, *32*, 4461-4.

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(7) When investigating reactions of bicyclo[2.1.0]pentane with dicarbomethoxycarbene and phenylcarbene generated by photolysis of the corresponding diazo precursors, Jones et al. found exo:endo isomers resulting from C-H insertions (ratios: ca. 1:2.7 and 1:2.4). With difluorocarbene, however, no C-H insertion product was found. See: Shiue, G.-H.; Misslitz, U.; Ding, X.; Jones, M., Jr.; de Meijere, A. *Tetrahedron Lett.* **1985**, *26*, 5399-402.

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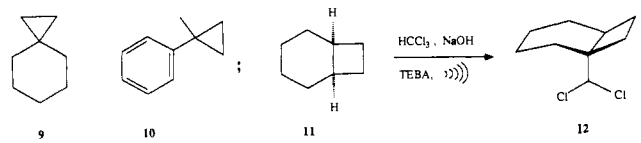
Scheme II



9 10 11 12

in the major isomer **2a** is located at the endo position. No reaction with **1** took place if dichlorocarbene was generated by the Doering–Hoffmann method[12] ($HCCl_3$, $KOBu^t$). Under normal phase-transfer-catalysis conditions[4d] ($HCCl_3$, 50% NaOH, 5% TEBA, 9 h), a 15% yield of **2a** and **2b** was obtained (ratio = ca. 4:1). When bromoform in dichloromethane was used,[9b] the C–H insertion products **3a** and **3b** were formed in 27% yield. Thus, dichloro- and dibromocarbene insert *selectively* into the C–H bonds adjacent to the three-membered ring of **1** (Scheme I).[13]

Similarly, dichlorocarbene insertion into the C–H bonds at C2 or C4 of bicyclo[3.1.0]hexane (**4**) afforded **5a** and **5b** in 40% yield. The exo product **5b**[11] is favored in this reaction (endo:exo = 1:3), rather than the endo product found from **1** (endo:exo = 4:1)! In the corresponding dibromocarbene insertion reaction, **6a** and **6b** were formed in a ratio of 1:4.

The insertion reactions of dichlorocarbene with **7a**[14] and **7b** (ratio = 7:1) yielded 57% of **8a** and **8b**. The syn isomer **7b** was found to be more reactive than the anti isomer **7a** by gas chromatographic monitoring of the reaction progress. Like the formation of the endo isomer **2a** in the reaction of **1**, the insertion reaction with **7b** leads to the formation of endo **8b**[11] as the major isomer. In addition to **8a** and **8b**, as indicated by ^1H NMR, ^{13}C NMR, and GC–MS, five bis-insertion products were detected. These products obviously derive from two dichlorocarbene insertions into *one* secondary C–H bond at C2 and *one* at C5 each. The "double activation" caused by the presence of two cyclopropane rings might be responsible for the formation of the bis-insertion products.

It is interesting to note that only ca. 2% of insertion products was detected in the reaction of dichlorocarbene with spiro[2.5]-octane (**9**), while 1-methyl-1-phenylcyclopropane (**10**) did not react at all under ultrasonication. One possible explanation for the observed endo/exo selectivities in the reactions of **1**, **4**, and **7b** is that only those C–H bonds whose orbitals can effectively interact with the Walsh orbitals of three-membered rings can be inserted by the dihalocarbene. Inspection of molecular models[15] reveals that in **1** the "conjugations" of the σ orbitals of the endo C–H bonds at the α positions with the Walsh orbitals seem to be better than those with the exo C–H bonds. In **4**, the σ orbitals of the exo and endo C–H bonds seem to interact with the Walsh orbitals to roughly the same extent. However, due to steric interactions with the endo hydrogens at both C3 and C6, preferential attack of dihalocarbenes should take place from the exo side (see Figure 1). Thus, the reactions of compounds **1** and **4** differently favor ratios of endo to exo isomers. In contrast, the four C–H bonds adjacent to the cyclopropane ring in spiro compound **9** cannot take on geometries favorable for sufficient "conjugations" with the Walsh orbitals. Consequently, dichlorocarbene insertion products are formed only in very low yield (ca. 2%). Thus, the reactivity of **9** is comparable with that of cyclohexane under ultrasonication, which affords a dichlorocarbene C–H bond insertion product in trace amounts (Scheme II).

In stark contrast, in the reaction of dichlorocarbene with *cis*-bicyclo[4.2.0]octane (**11**),[16] containing a cyclo*butane* ring, the C–H insertion reaction took place at the *tertiary* C–H bonds at the bridgehead position to afford **12** in a yield of 90%. No products resulting from insertion into C–H bonds adjacent to the cyclobutane ring were found. This suggests that the interactions between the Walsh orbitals of cyclopropane rings and the orbitals of suitably positioned adjacent C–H bonds are quite different from those of cyclobutane rings. While some cyclopropane rings "activate" *adjacent* C–H bonds, the cyclobutane ring in **11** does not.

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Supplementary Material Available: Details of experimental procedures and spectral data of the products, including NOE spectra of **2a** and **5b** (23 pages). Ordering information is given on any current masthead page.

(11) For **2a**, **5b**, and **8b** the stereochemistry of the $CHCl_2$ group was ascertained by 1D NOE difference spectroscopy. The syn and anti cyclopropane methylenes were assigned on the basis of spin simulation treating the cyclopropane protons as a four-spin system.

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Vibrational Raman Optical Activity of Proteins

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Although vibrational Raman optical activity (ROA) was first observed nearly 20 years ago,[1,2] its widespread application has been hampered by a lack of sensitivity with studies restricted to favorable samples.[3-5] We recently reported a major breakthrough in ROA instrumentation based on backscattering with CCD detection[6] which we have now developed sufficiently (by graduating to a *backthinned* CCD and employing an $f/4.1$ single-stage spectrograph fitted with an ion-etched holographic grating and a holographic edge filter) to render most biological molecules in aqueous solution, in particular proteins, accessible to ROA studies.[7] Preliminary results indicate that ROA provides a valuable new perspective on protein conformation complementing that obtained from its sibling technique, vibrational circular dichroism (VCD).[8]

Peptide and protein ROA spectra covering ~1100–1500 cm^{-1} obtained at an early stage of instrument development were presented and discussed previously.[9,10] The new instrument extends the range to ~600–1750 cm^{-1} and provides ROA spectra with much higher signal-to-noise ratios. Some typical protein ROA spectra are collected in Figure 1, with the tripeptide L-

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