



## PROBLEM 47

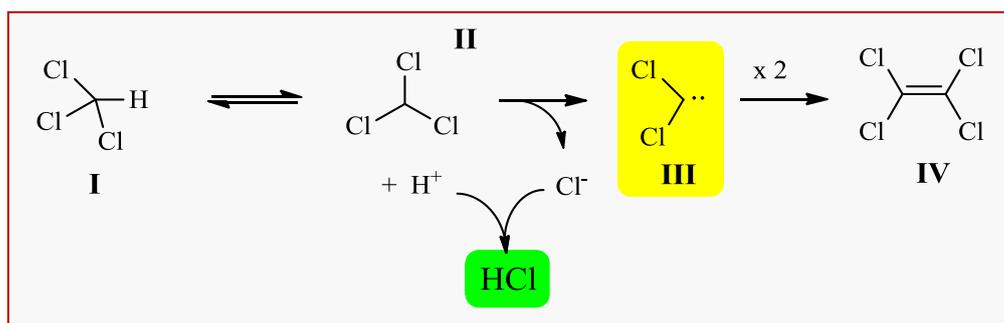
[SUPPL Problem 47 # 2°]

Arabic compound numbers in TAPSOC,  
Roman numerals in Supplementary material

### Pull-pull and push-pull carbenes

Have you ever wondered why chloroform standing in a bottle for some time is generally acidic? So much so, sometimes, that once every while cleaning up the proton accumulation is of the essence for dissolving acid-sensitive compounds in it.

The reason is an intrinsic property of haloforms:  $\alpha$ -elimination of HCl, with concomitant genesis of dihalorocarbene. With only six valence electrons carbenes are fundamentally unstable although there are incredible stable carbenes which can stand for several weeks in a bottle [1]. Hence, carbenes do whatever it takes to complete valence octets. A handy thing: dimerize. Indeed, tetrachloroethylene is the second peak one finds in the GC of analytical grade (according to bottle label) chloroform (there is a third small peak, derived also from dichlorocarbene; who this might be?[2]):



SCHEME SP47.2.1

As one can surmise, Li/Na/K/Cs hydroxides in water (and a phase transfer catalyst) prompt dihalorocarbene production.

Carbenes can be a very small and simple species ( $\text{H}_2\text{C}:$ ) with a complicated chemistry (entire books are dedicated to it [3]). These complications arise on four grounds:

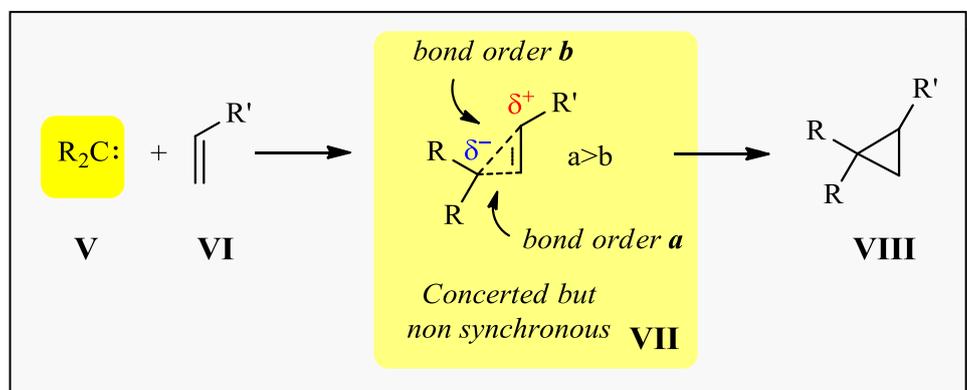
- 1) How is the carbene formed (UV radiation, heat, strong base) and source.
- 2) The transition metal associated with it in metal carbenoids.
- 3) The substrate it reacts with.
- 4) The companion substituents replacing H in methylene.

Let us discuss *briefly* the last two issues within the context of TAPSOC problem 47.

### I.- Substrates

Six valence electrons means an inherent LEDZ character for non substituted carbene ( $\text{CH}_2:$ ). That is, susceptible substrates will be those capable of providing a pair of bonding electrons.  $\text{R}_3\text{C-H}$ ,  $\text{RO-H}$ ,  $\text{R}_2\text{N-H}$  are examples of the so well known C-H insertions of carbenes. Some TAPSOC problems take account of such reactions.

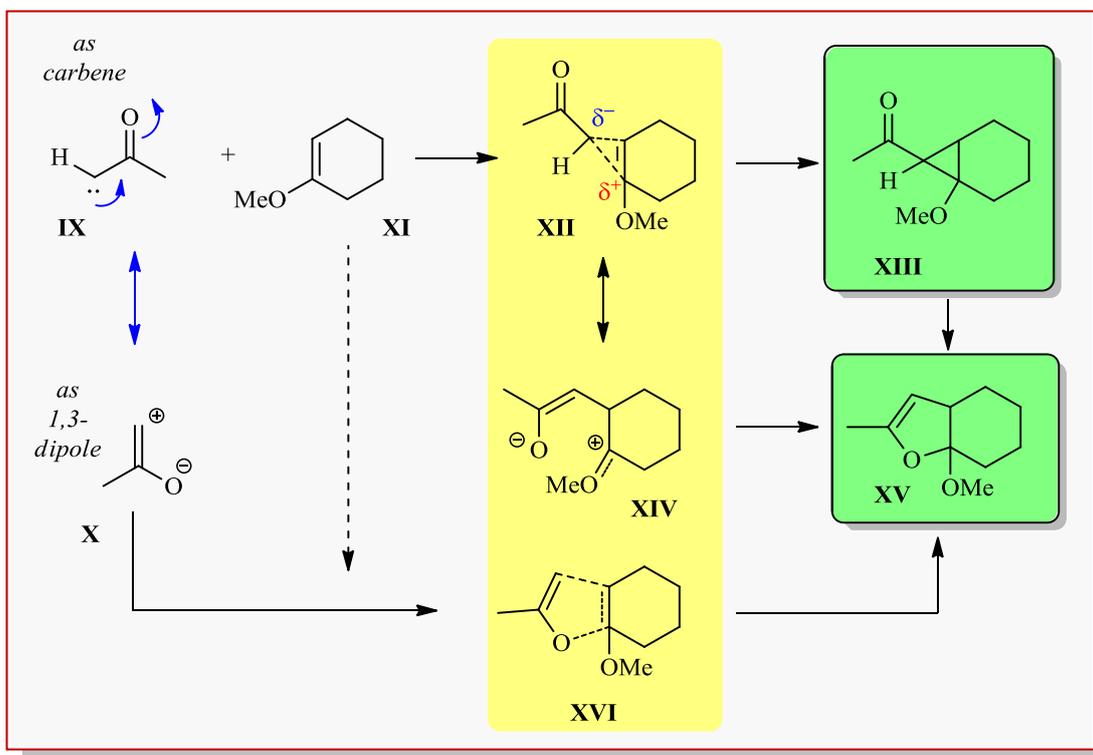
$\text{C}=\text{X}$  ( $\text{X} = \text{C}$ , heteroatoms)  $\pi$ -electrons can play the same role to provide bonding electrons. A three-center transition state (TS **VII**) develops. Two bonds are being formed between carbene and  $\text{C}=\text{X}$  substrate in a *concerted* but *non synchronous* fashion. Although this sounds paradoxical, the concept involves two separate issues: *concert* conveys the formation of two bonds not in tandem, whereas *non synchronous* expresses the new bonds being formed to a different extent in the transition state (partial bond orders are not equal) [4].



SCHEME SP47.2.2

This basic design gives rise to a polar TS. Buildup of partial charges varies according to substituents R (on the carbene side) and R' on the substrate. This poses limitations to the substrates susceptible to carbene addition: those with R' = EWG (strong) react slowly or not at all. Reduction of alkene character by extended conjugation as in stylobenes (Ph-CH=CH-Ph) are also unreactive. By the same token, R' = EDG increases substantially reaction rates. The same rationale can be applied on the carbene side in TS. EW substituents enhance reactivity, but EDGs do not inhibit the reaction. They just make the carbene more nucleophilic.

In the event that these charges may be delocalized extreme situations can be attained. Rearrangement products, or adducts equivalent to 1,3-dipolar cycloadditions arise. To illustrate this point, let's take a polar substrate (enol ether) and a  $\alpha$ -ketocarbene (Scheme SP47.2.3). The cycloaddition does not take the expected cyclopropanation course, but O-heterocycles like dihydrofurans (**XV**) are formed [5]. As well, O-cyclopropane aldehydes and ketones (**XIII**) prepared under controlled conditions rearrange quantitatively to the same dihydrofurans upon contact with silica gel or alumina III in a chromatographic column [6,7].  $\alpha$ -Ketocarbene **IX** may also operate as a true 1,3-dipole **X**.



SCHEME SP7.2.3

Reaction rates depend strongly on the substrate electronic character and steric encumbrance. For example, the relative rate of dibromocarbene cyclopropanation with 2-methylbutene vs isobutylene (di- vs monosubstituted alkene) is 3.2, presumably because of  $\pi$ -electron density differences and HOMO energy levels.

Further reaction cascades may be observed in carbene – alkene/alkyne interactions, with or without mediation of cyclopropyl primary adducts (see below). In fact, TAPSOC problem 47 is one such event.

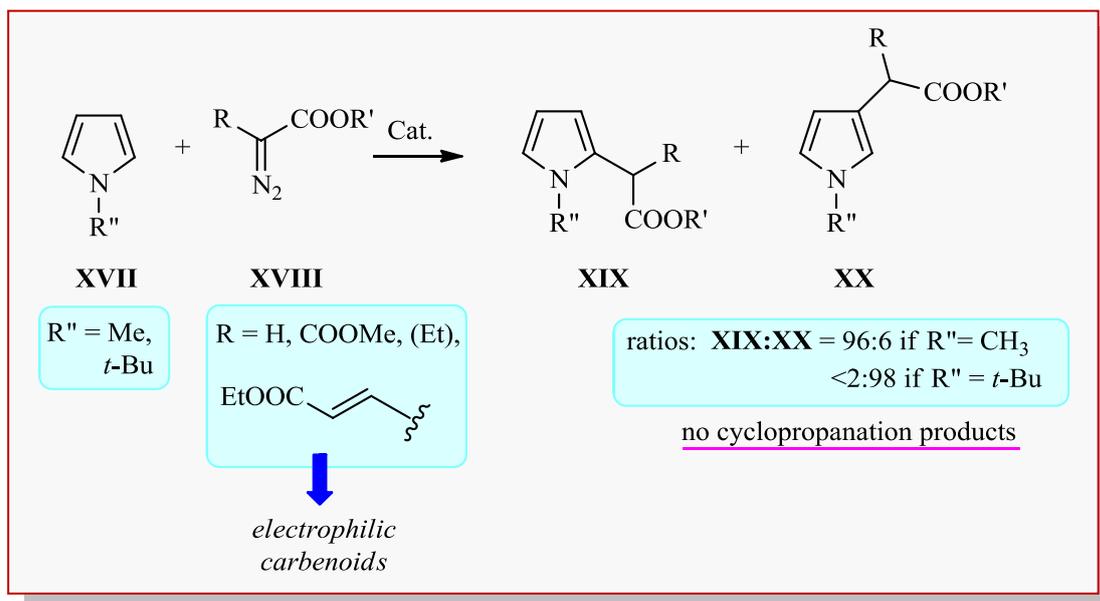
## II.- Carbenes and their substituents

Having two substituents on the carbene, there are four electronically different combinations providing a range of electronic density on the carbene orbital set:

- 1.- Natural carbene:  $\text{H}_2\text{C}$ :
- 2.- Electron-deficient carbenes (electrophilic):  $\text{HC}(\cdot)\text{-EWG}$  or  $\text{EWG-C}(\cdot)\text{-EWG}$
- 3.- Electron rich carbenes (nucleophilic):  $\text{HC}(\cdot)\text{-EDG}$  or  $\text{EDG-C}(\cdot)\text{-EDG}$
- 4.- Ambiphilic carbenes (push-pull):  $\text{EDG-C}(\cdot)\text{-EWG}$

As prof. Davies discovered long ago, pyrroles are fascinating substrates to work with to measure the effect of these four types of carbenes or metal carbenoids [8]. Not only are these compounds HEDZ  $\pi$  systems, but electron density in the ring can be regulated by EWGs on N.

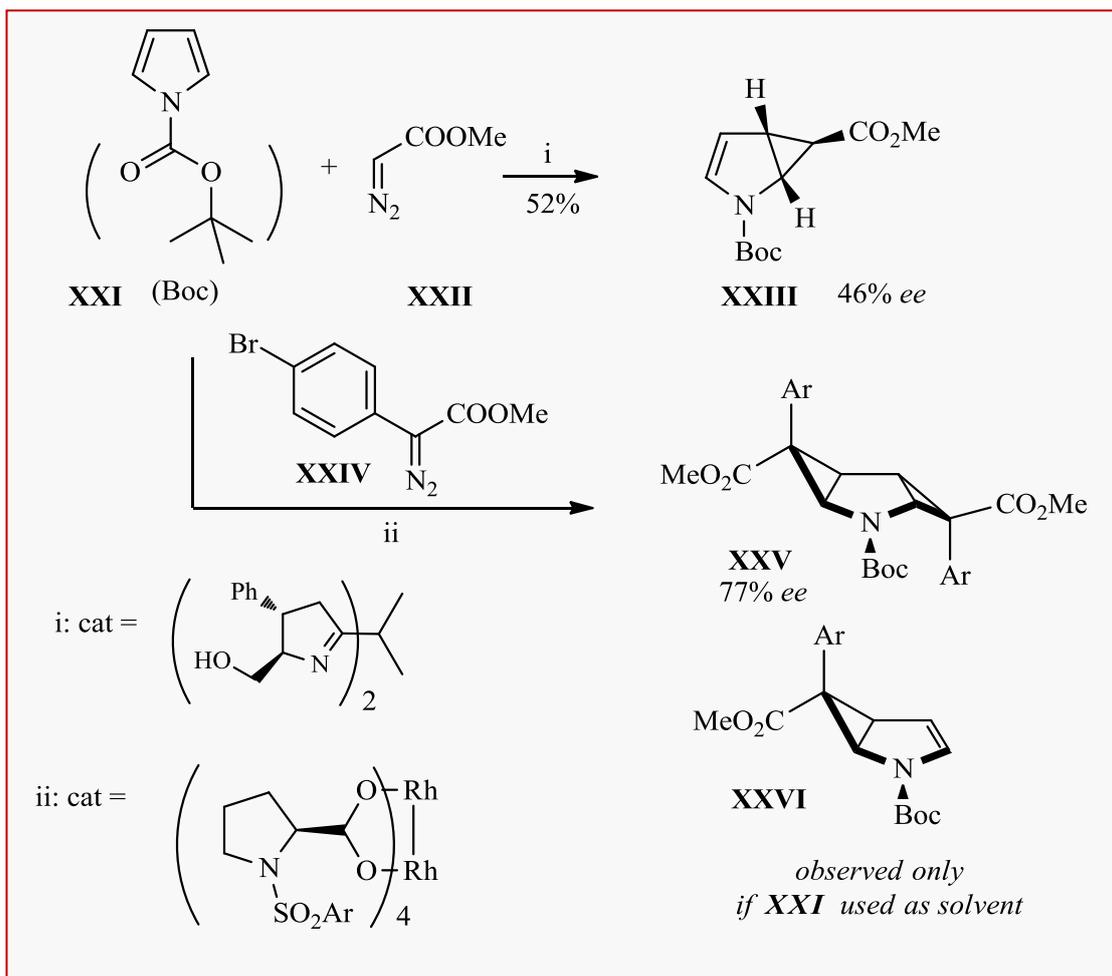
Compare for example the reactions of Scheme SP47.2.4, where diazocarbonyls are the source of the metal carbenoid using  $\text{Cu}^{\text{(II)}}$  and/or  $\text{Rh}^{\text{(II)}}$  catalysts (catalyst choice is critical for the reaction success). Aside from no cyclopropanation, the **XVII** + **XVIII** (metal carbenoid) coupling is highly regioselective on  $\text{C}^2$ . It can only be swerved to the  $\text{C}^3$  position (as in **XX**) by steric inhibition of  $\text{C}^2$  owing to the N-*t*-Bu group.



SCHEME SP47.2.4

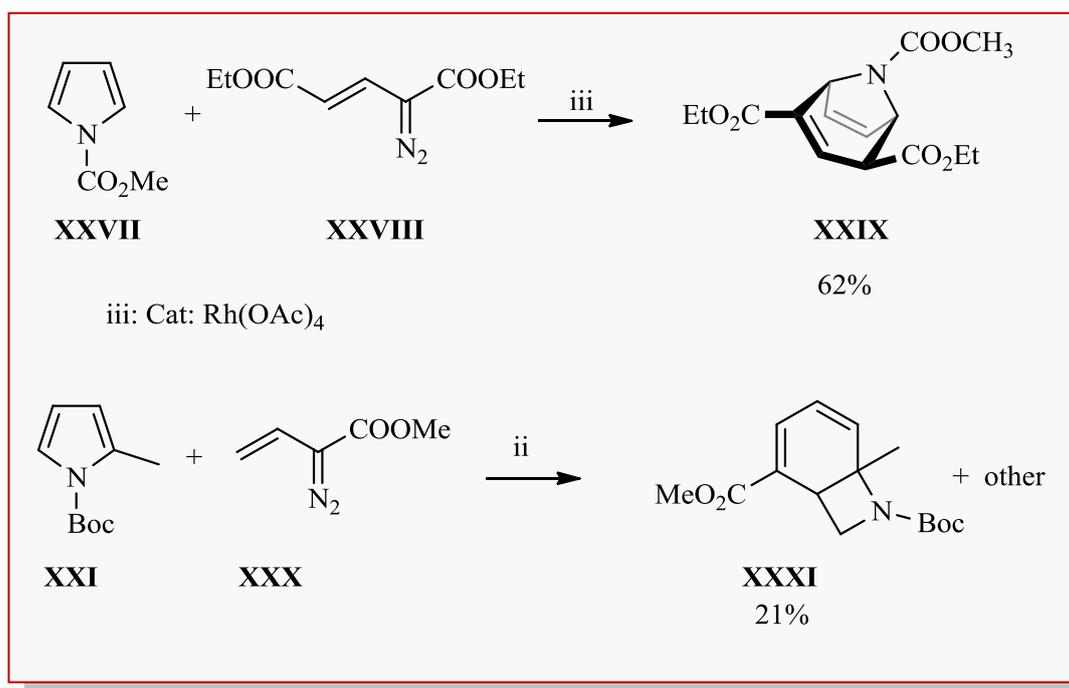
The nucleophilic reactivity of the pyrrole ring can be appeased by EWGs (benzoyl, acyl) on N-R<sup>''</sup>. The extension of the  $\pi$  MO over this substituent confers an enhanced non aromatic diene character to the pyrrole ring. Polarization of the TS decreases on account of this and carbene addition turns to cyclopropanation (Scheme SP47.2.5). The enantiomeric excess in **XXIII** results from the stereoelectronic through-space induction of the peculiar chiral catalyst employed (**XXII**), whereas the *trans* configuration of ester and pyrrole sections reflects intense steric effects of the bulky catalyst in the transition state.

A similar rationale (less polarization) can be applied by control over the other end: the diazocarbonyl carbenoid precursor with a general EDG-C(:)-EWG structure (e.g. **XXIV**). These species are known as donor-acceptor (push-pull) carbenes. Stabilization of partial negative charge here is stymied and cyclopropanation is dominant (Scheme SP47.2.5). Runaway reactions up to dicyclopropanation of N-Boc pyrroles occur (**XXI**  $\rightarrow$  **XXV**) because the second cycloaddition is faster than the first. Monocyclopropanation can only be witnessed with an infinite excess of pyrrole (used as solvent). Chiral catalysts i and ii induce moderate enantioselectivity.



SCHEME SP47.2.5

Additional functional groups on the carbene side may create complications in the final addition product(s) as a result of further reaction cascades taking place after the primary pyrrole-carbene interaction. Examples shown in Scheme SP47.2.6 make interesting and accessible reactions for you to work out the mechanism [9,10].



SCHEME SP47.2.6

## REFERENCES AND NOTES

- [1] Solé S, Gornitzka H, Schoeller WW, Bourissou D, Bertrand G. *Science* 2001;292:1901-1903.
- [2] Highly poisonous phosgene (Cl<sub>2</sub>C=O) is another decomposition product of chloroform, also producing HCl. This compound stems from dichlorocarbene trapping dissolved oxygen. It only can be removed by Ca(OH)<sub>2</sub> or alumina, not by distillation. Ethanol (0.5%) is generally used as stabilizer of industrial haloforms.
- [3] Here are two books on carbene chemistry I'd recommend: For well established concepts, good for beginners: Wolfgang Kirmse, *Carbene Chemistry*, 2<sup>nd</sup> Ed. Academic Press, New York, 636 p., 1971. For an updated comprehensive vision: Robert A. Moss & Michael P. Doyle. *Contemporary Carbene Chemistry (Wiley Series of Reactive Intermediates in Chemistry and Biology)*, Wiley, Hoboken NJ, 584 p., 2013 (released in 2014).

[4] This is not a semantic question. For experimental evaluation see, inter alia: Alonso-Amelot ME, Morales-Izquierdo A, Chitty AW. *J. Org. Chem.* 1982;47:3747-3754.

[5] Wenkert E, Alonso ME, Buckwalter BL, Sánchez EL. *J. Am. Chem. Soc.* 1983;105:2021-2029. Alonso-Amelot ME, Jano P, Hernández MI, Greenberg RS, Wenkert E. *J. Org. Chem.* 1983;48:3047-3050.

[6] Alonso-Amelot, ME, Morales-Izquierdo A. *J. Org. Chem.* 1980;45:4530-4532. Alonso-Amelot ME, Gómez M, Pekerar S. *J. Heterocyclic Chem.* 1982;19:369-371.

[7] The 1,3-dipolar cycloaddition, either from properly fashioned carbenes and metal carbenoids and polar substrates or other sources has become a powerful synthetic approach to a number of heterocycles. See: Albert Padwa & William H. Pearson (Eds.). *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products. The Chemistry of Heterocyclic Compounds, Vol 59.* Wiley-Interscience, Hoboken NJ, 952 p., 2002.

[8] For a review, see: Davies HML, Hedley SJ. *Chem. Soc. Rev.* 2007;36:1109-1119.

[9] Davies HML, Young WB, Smith HD. *Tetrahedron Lett* 1989;30:4653-4656.

[10] Davies HML, Matasi JJ, Hodges LM, Huby NJS, Thornley C, Kong N, Houser JH. *J. Org. Chem.* 1997;62:1095-1105.