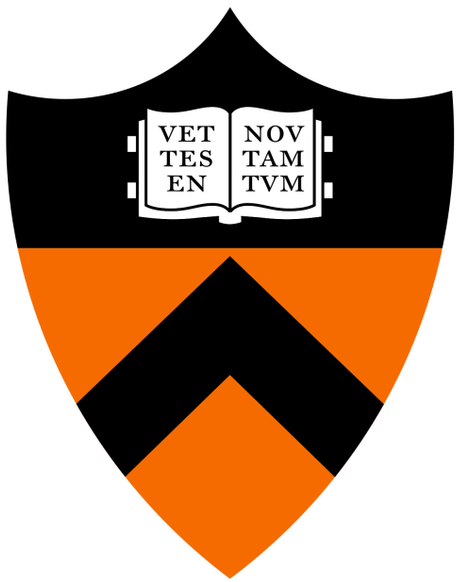
Carbenes: multiplicity and reactivity

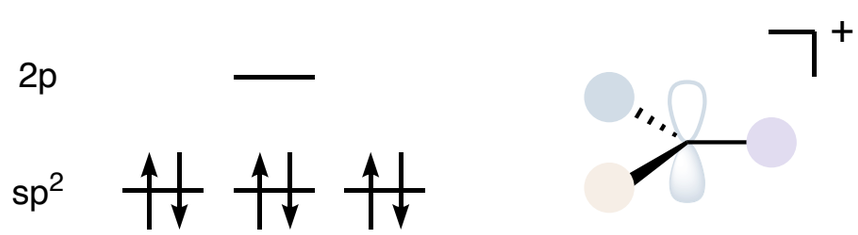


Beryl X. Li

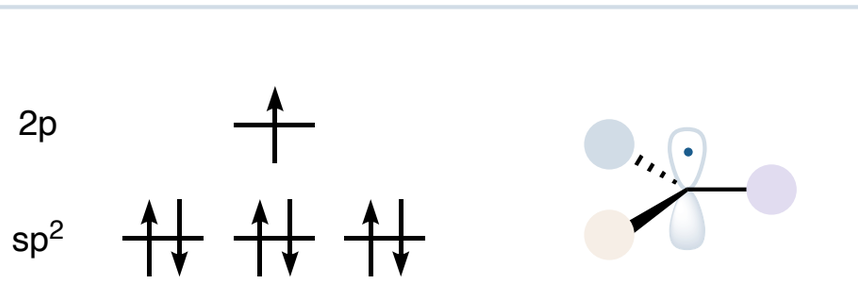
December 4th, 2019

Carbenes: multiplicity and reactivity

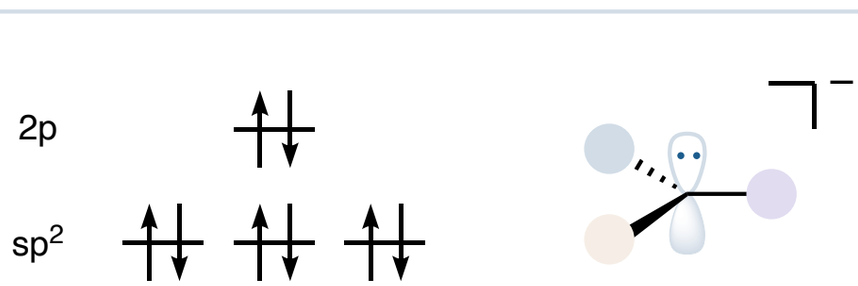
Introduction



carbocation



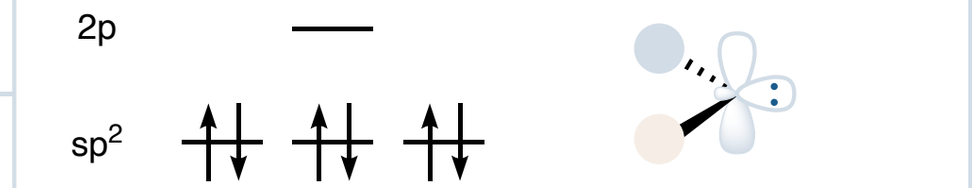
carbon radical



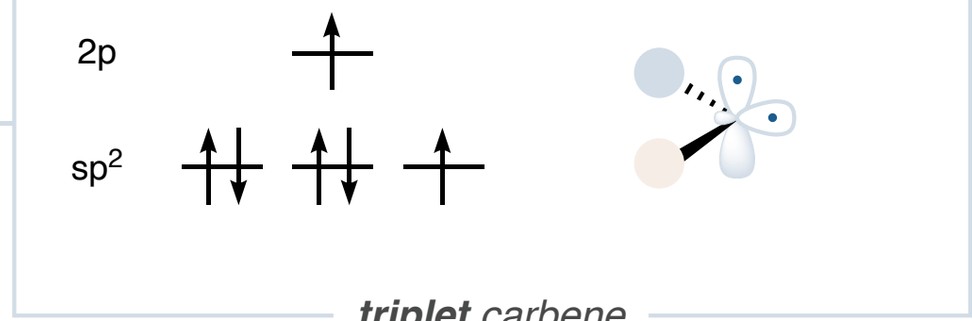
carbanion

6
C
Carbon
12.011

Divalent species, similar to CO and R–CN



***singlet** carbene*



***triplet** carbene*

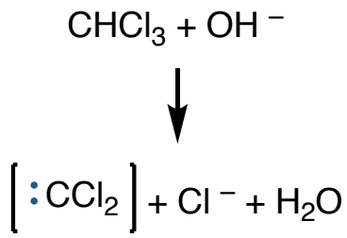
Very reactive: cyclopropanation, dimerization, ylide formation, X–H bond insertion, among others

Anslyn, E.V.; Dougherty, D.A *Modern Physical Organic Chemistry,* 1st ed; University Science Books, 2006.

Carbenes: multiplicity and reactivity

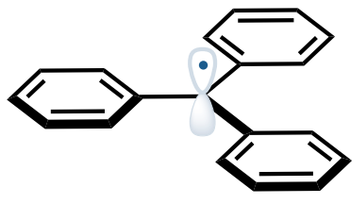
A brief history

Geuther & Hermann — 1855



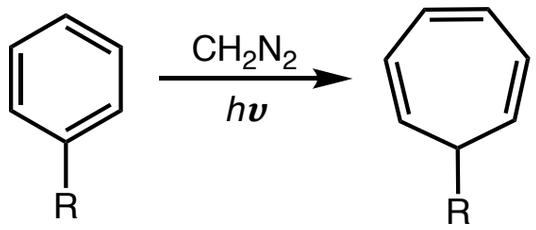
first to propose a carbenoid intermediate

Gomberg — 1900



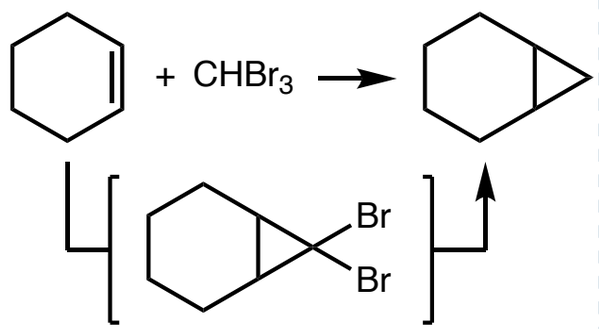
characterized the first example of a free radical

Doering & Knox — 1953



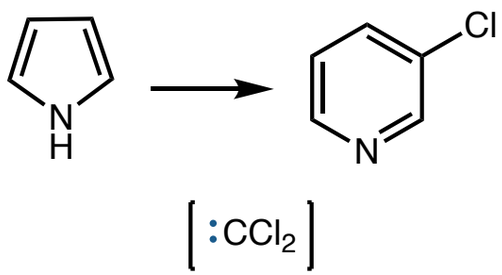
synthesis of tropolone derivatives

1954



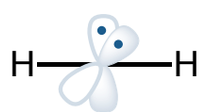
dibromomethylene intermediate

Nef — 1897



similar intermediate in a Ciamician-Dennstedt rearrangement

common belief — 1920s and 1930s



necessarily triplet

linear with degenerate p orbitals

Lennard-Jones & Pople — 1951

propose two ground states for the CH_2 carbene

Duschenne & Burnelle — 1953

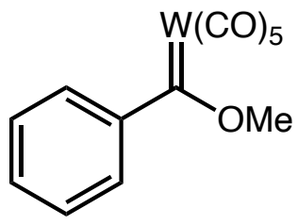
CF_2 is sp^2 hybridized, with a singlet ground state

Hopkinson, M.N.; Richter, C.; Schedler, M; Glorius, F. *Nature* **2014**, *510*, 485–96.
Fremont, P.; Marion, N.; Nolan, S.P. *Coord. Chem.* **2009**, *253*, 862–92.

Carbenes: multiplicity and reactivity

A brief history

Fischer
1964



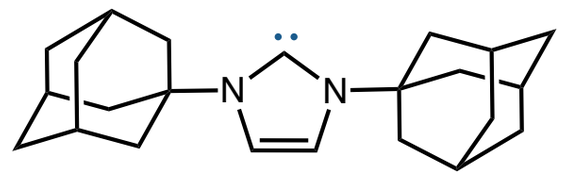
first metal-carbene complex

numerous research
1970s and 1980s

Ground state: singlet or triplet?

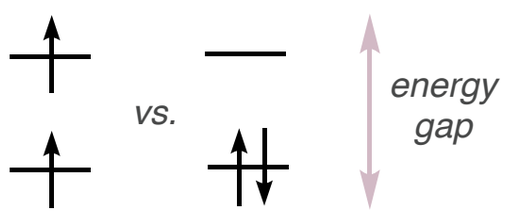
mesomeric and inductive effects considered

Arduengo
1991



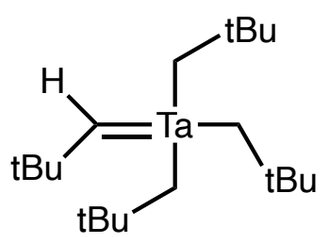
stable, isolable N-heterocyclic cabene

Hoffman
1968



min. splitting energy for CH_2 to have a GS singlet

Schrock
1974



first synthesis of a d^0 metal-alkylidene complex

present day

***Carbenes**: high energy intermediate with comprehensible reactivity*

Hopkinson, M.N.; Richter, C.; Schedler, M; Glorius, F. *Nature* **2014**, *510*, 485–96.
Fremont, P.; Marion, N.; Nolan, S.P. *Coord. Chem.* **2009**, *253*, 862–92.

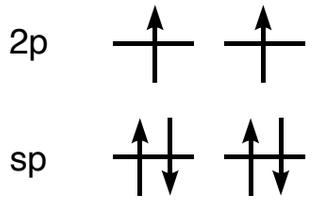
Carbenes: multiplicity and reactivity

Multiplicity overview

Hypothetically…

(as were believed in 1930s)

degenerate 2p orbitals

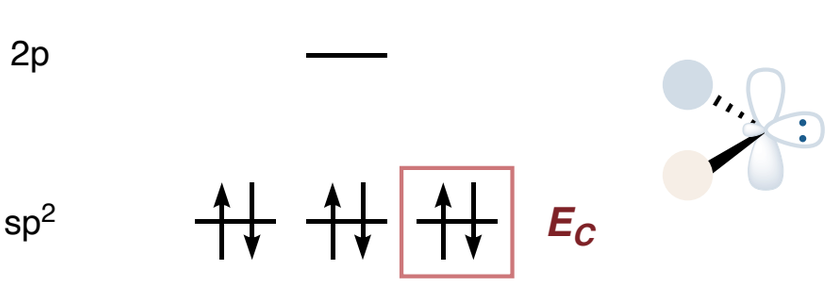


*linear carbenes would have a **triplet** ground state*

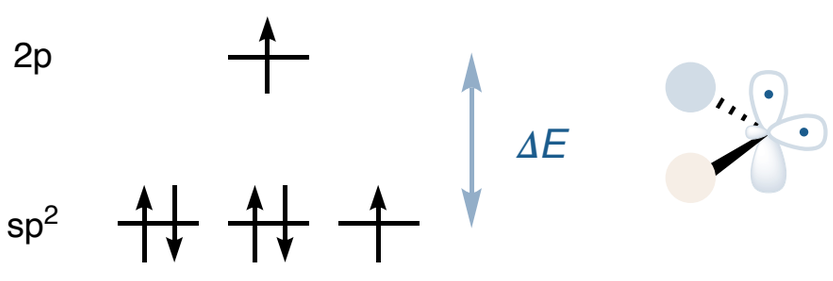
Today, carbenes are understood to be bent…

coulombic repulsion (E_C) *vs.* ***sp_2 – 2p energy difference (ΔE)***

Singlet-triplet splitting $\Delta G_{ST} = E_C - \Delta E$



singlet *carbene*



triplet *carbene*

Baird, N.C.; Taylor, K.F. *J. Am. Chem. Soc.* **1978**, *100* (5), 1333–8.

Carbenes: multiplicity and reactivity

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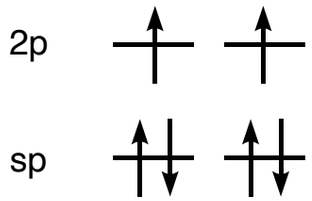

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Today, carbenes are understood to be (mostly) bent…

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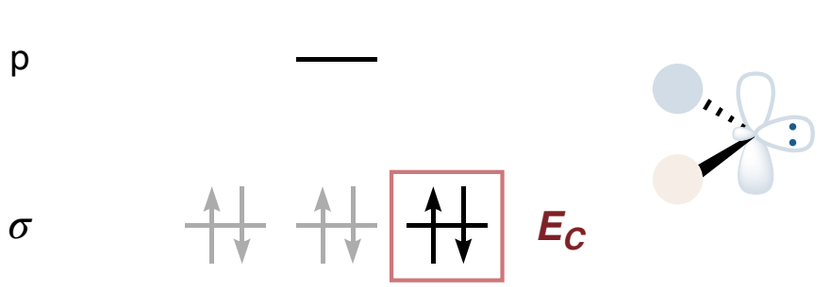
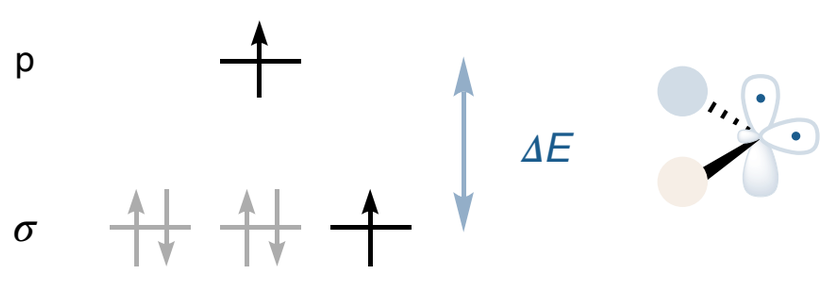
Singlet-triplet splitting $\Delta G_{ST} = E_C - \Delta E$



***singlet** carbene*



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Carbenes: multiplicity and reactivity

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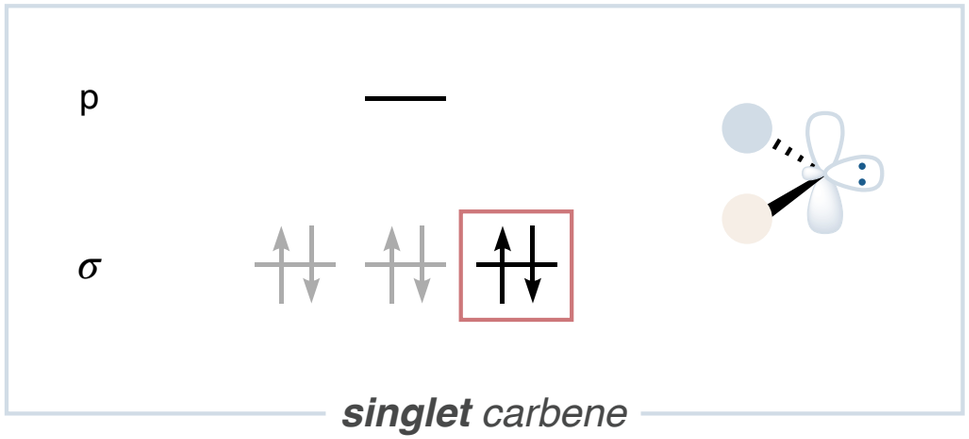
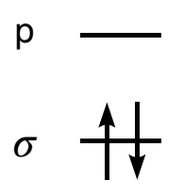
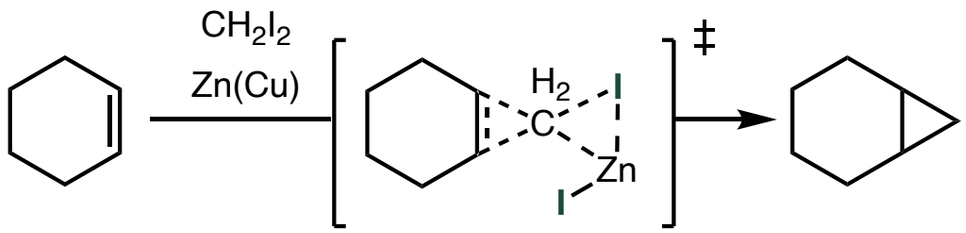


***singlet** carbene*

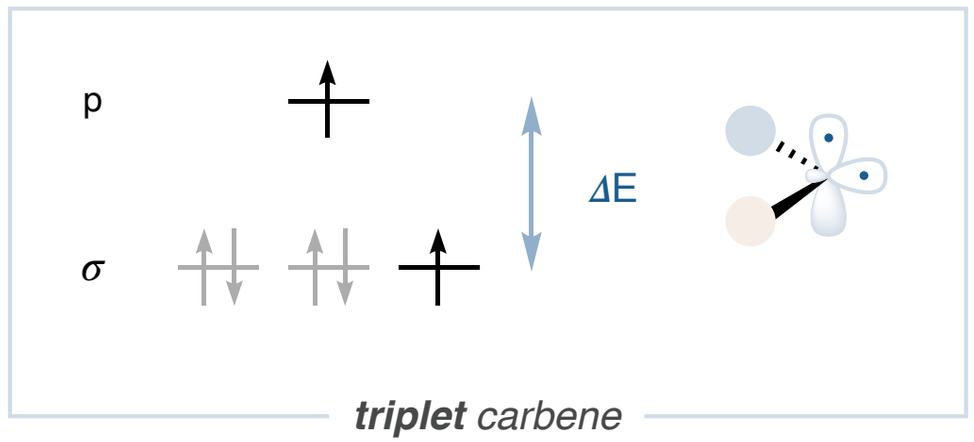
- Spin quantum number (S) = 1/2 + (–1/2) = 0
  - Multiplicity = 2S + 1 = 1 (hence “singlet”)



- Nucleophile/electrophile
- Chelotropic reactions, stereospecific

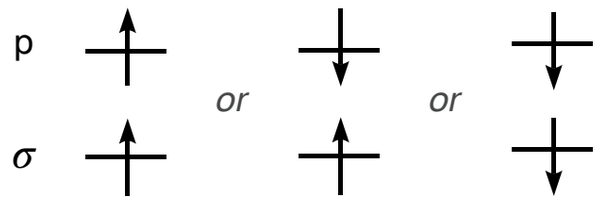


e.g. Simmons-Smith reaction

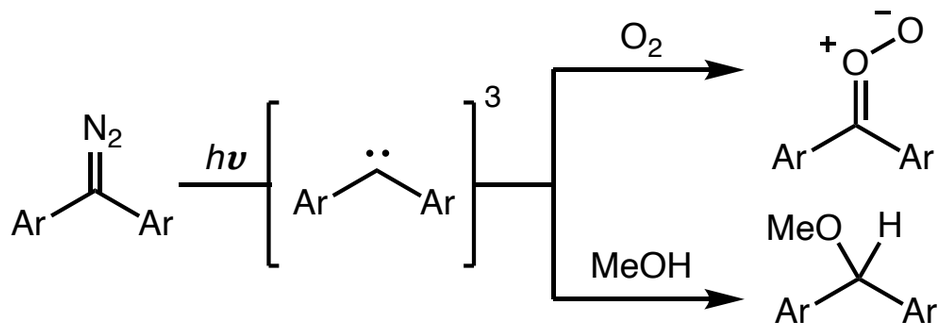


***triplet** carbene*

- Spin quantum number (S) = 1/2 + 1/2 = 1
  - Multiplicity = 2S + 1 = 3 (hence “triplet”)



- Diradicals
- Stepwise radical additions, potentially stereoselective



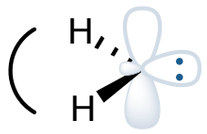
Simmons, H.E.; Smith, R.D. *J. Am. Chem. Soc.* **1958**, *80* (19), 5323–4.
Bourisson, D.; Guerret, O.; Gabbais, F.P.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39–91.

Carbenes: multiplicity and reactivity

Factors that determine multiplicity: parent CH_2

H–C–H

∡ 102 °



singlet state

p

σ

E_C

Factors

- mesomeric interactions
- inductive effects
- hyperconjugation
- steric effects
- solvent environment

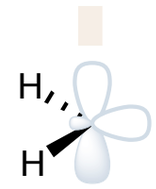
coulombic repulsion (E_C)

vs.

sp_2 / 2p energy difference (ΔE)

Singlet-triplet splitting

$\Delta G_{ST} = E_C - \Delta E$



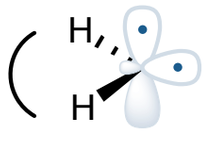
ΔG_{ST} = 9 kcal/mol

postive number indicates triplet is lowest energy ground state

energy increases

H–C–H

∡ 137 °



triplet state

p

σ

ΔE

Hoffman, R. *J. Am. Chem. Soc.*, **1968**, *90*, 1475–85.

Baird, N.C.; Taylor, K.F. *J. Am. Chem. Soc.* **1978**, *100* (5), 1333–8.

Carbenes: multiplicity and reactivity

Factors that determine multiplicity: mesomeric interactions

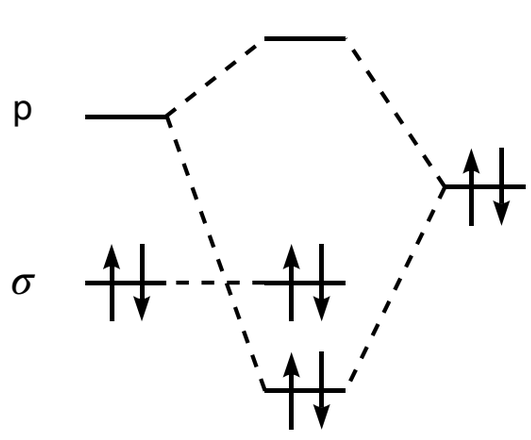
Mesomeric effects on carbene ground state multiplicity

electron donating or withdrawing substituents (essentially resonance)

Factors

- mesomeric interactions
- inductive effects
- hyperconjugation
- steric effects
- solvent environment

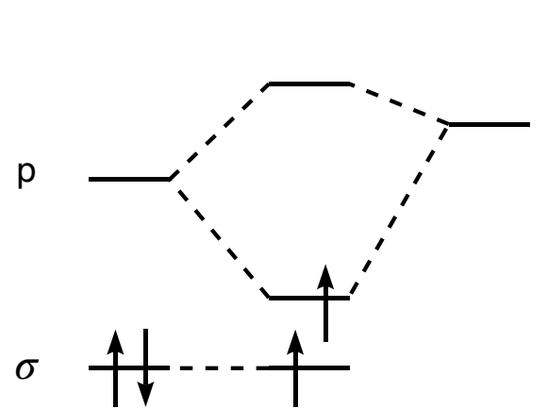
X-type interactions



π-electron donors raise p orbital
(e.g., –NR_2, –OR, –F, –Cl, –Br, –I)

*ground state **singlet***

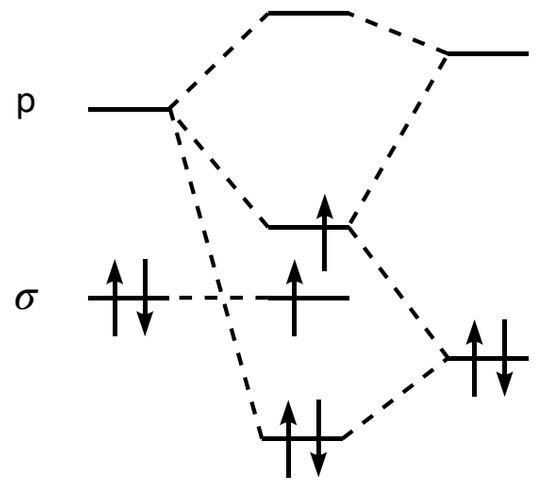
Z-type interactions



π-electron acceptors lower/
unaffect **σ**–p gap
(e.g., carbonyls, –SO_2R, –NO, –NO_2)

*ground state **triplet***

C-type interactions



conjugated groups lower/
unaffect **σ**–p gap
(e.g., alkenes, alkynes, aryl groups)

*ground state **triplet***

Hirai, K.; Itoh, T.; Tomioka, H. *Chem. Rev.* **2009**, *109*, 3275–332.

Carbenes: multiplicity and reactivity

Factors that determine multiplicity: mesomeric interactions

Factors

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- hyperconjugation
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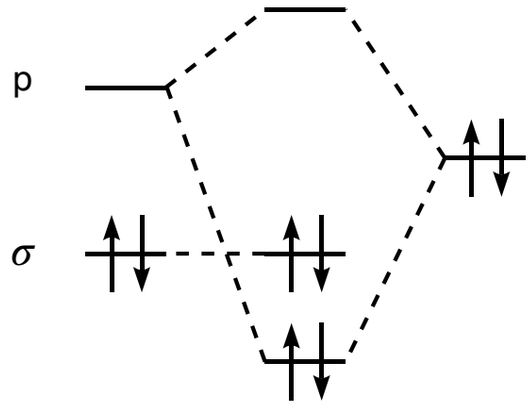
- solvent environment

Mesomeric effects on carbene ground state multiplicity

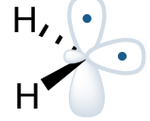
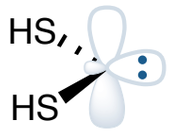
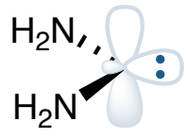
electron donating or withdrawing substituents (essentially resonance)

X-type interactions



π-electron donors raise p orbital
(e.g., –NR_2, –OR, –F, –Cl, –Br, –I)

*ground state **singlet***

carbenoid species	*ΔG_{ST}*
	9 kcal/mol
	–28.0 kcal/mol
	–52.6 kcal/mol

*negative ⊿GST indicates **singlet** is lowest energy ground state*

Matus, M. H.; Nguyen, M. T.; Dixon, D. A. *J. Phys. Chem. A* **2006**, *110*, 8864–71.
Alder, R. W.; Blake, M. E.; Oliva, J. M. *J. Phys. Chem. A* **1999**, *103*, 11200–11.
Hirai, K.; Itoh, T.; Tomioka, H. *Chem. Rev.* **2009**, *109*, 3275–332.

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- inductive effects
- hyperconjugation
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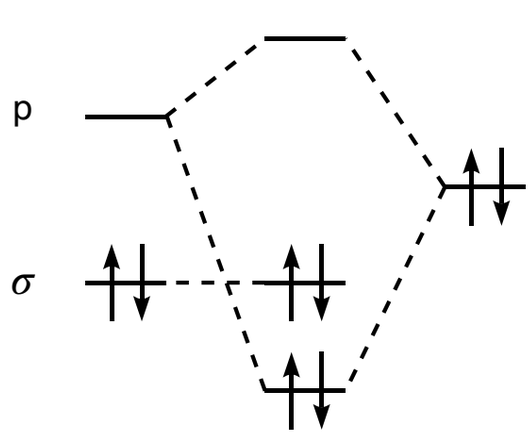
- solvent environment

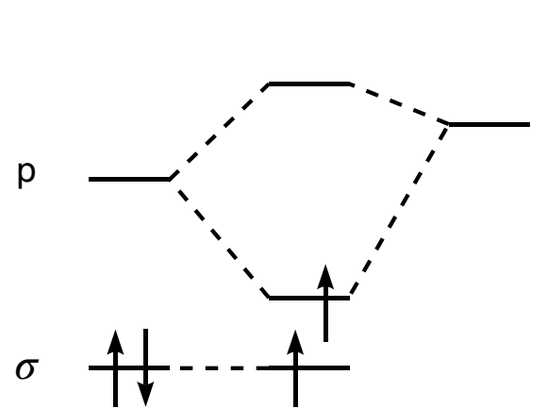
X-type interactions



π-electron donors raise p orbital
(e.g., –NR_2, –OR, –F, –Cl, –Br, –I)

*ground state **singlet***

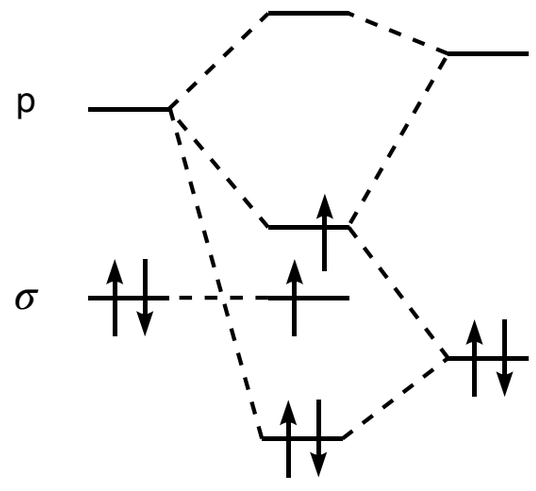
Z-type interactions



π-electron acceptors lower/
unaffect **σ**–p gap
(e.g., carbonyls, –SO_2R, –NO, –NO_2)

*ground state **triplet***

C-type interactions



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(e.g., alkenes, alkynes, aryl groups)

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Hirai, K.; Itoh, T.; Tomioka, H. *Chem. Rev.* **2009**, *109*, 3275–332.

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Factors that determine multiplicity: mesomeric interactions

Mesomeric effects on carbene ground state multiplicity

electron donating or withdrawing substituents (essentially resonance)

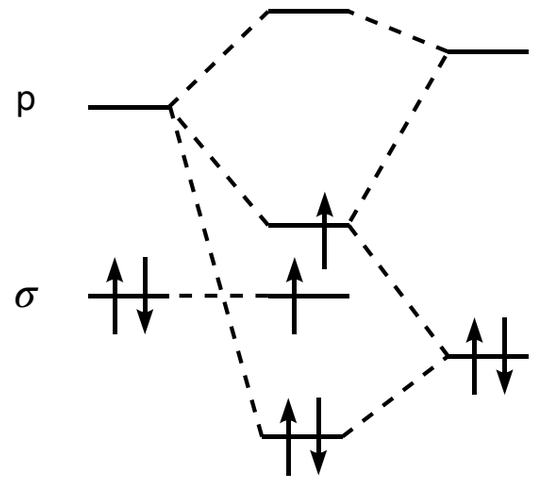
Carbene	E_{sub}/S (kcal/mol)	E_{sub}/T (kcal/mol)	ΔE_{sub} (kcal/mol)
Ph–C̈–H (**5a**)	24.4	18.1	6.3
(*E*)-1-Naph–C̈–H (*E*-α-**6a**)	26.6	20.9	5.7
9-Anth–C̈–H (**7a**)	30.5	26.8	3.7
Ph–C̈–Ph (**8a**)	15.8	16.0	-0.2
1-Naph–C̈–Naph-1 (α-**9a**)	18.6	19.0	-0.4
9-Anth–C̈–Anth-9 (**10a**)	21.5	-	-

aryl groups generally stabilize both the singlet state (E_{sub}/S) and the triplet state (E_{sub}/T)

Factors

- mesomeric interactions
- inductive effects
- hyperconjugation
- steric effects
- solvent environment

C-type interactions



conjugated groups lower/
unaffect **σ**–p gap
(e.g., alkenes, alkynes, aryl groups)

*ground state **triplet***

Woodcock, H. L.; Moran, D.; Brooks, B. R.; Schleyer, P. v. R.; Schaefer, H. F., III. *J. Am. Chem. Soc.* **2007**, *129*, 3763–70.
Hirai, K.; Itoh, T.; Tomioka, H. *Chem. Rev.* **2009**, *109*, 3275–332.

Carbenes: multiplicity and reactivity

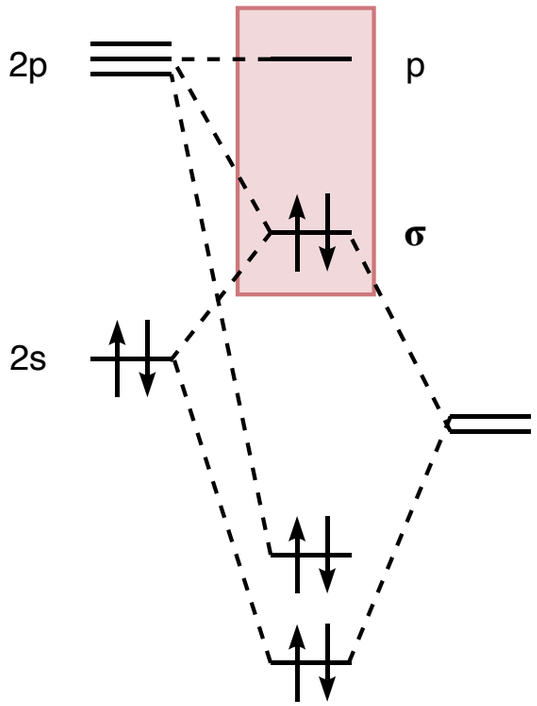
Factors that determine multiplicity: inductive effects

Factors

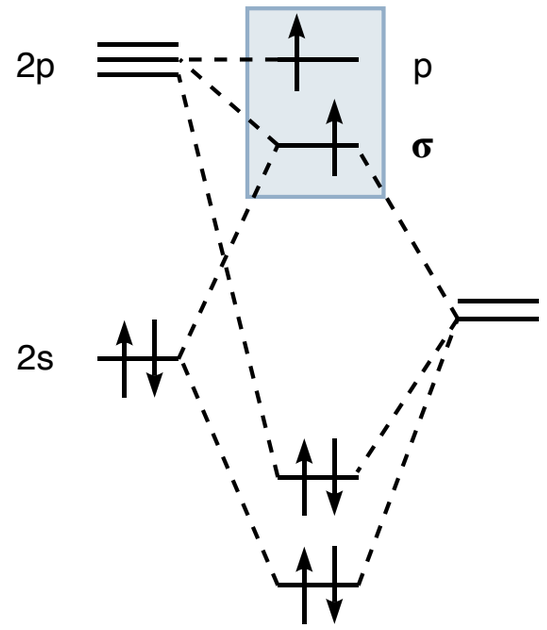
- mesomeric interactions
- inductive effects
- hyperconjugation
- steric effects
- solvent environment

Inductive effects

inductively electron-donating or -withdrawing groups intereact selectively with carbon orbitals, which changes the **σ**–*p gap*



σ*-EWG stabilizes* **σ***-nonbonding orbital thus increasing* **σ**–*p gap to favor* ***singlet***



σ*-EDG induces a smaller* **σ**–*p gap, therefore favoring* ***triplet***

Irikura, K.K.; Goddard III., W.A.; Beauchamp, J.L. *J. Am. Chem. Soc.* **1992**, *114*, 48–51.
Hirai, K.; Itoh, T.; Tomioka, H. *Chem. Rev.* **2009**, *109*, 3275–332.

Carbenes: multiplicity and reactivity

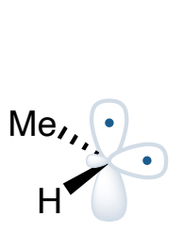
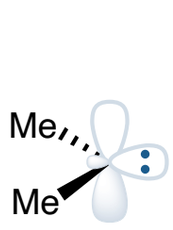
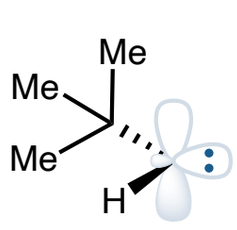
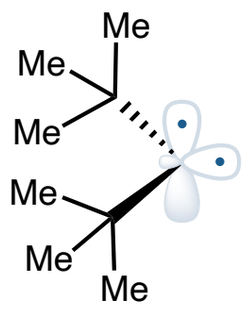
Factors that determine multiplicity: hyperconjugation

Hyperconjugation

Singlets**, which are isoelectric with carbocations, are more stabilized by hyperconjugative effects compared to the radical-like **triplets

Factors

- mesomeric interactions
- inductive effects
- hyperconjugation
- steric effects
- solvent environment

carbenoid species					
ΔG_{ST}	9.05 kcal/mol	2.26 kcal/mol	–2.47 kcal/mol	–0.17 kcal/mol	2.65 kcal/mol

more hyperconjugation → ***(favor singlet ground state)***

more steric bulk → ***(favor triplet ground state)***

Sulzbach, H. M.; Bolton, E.; Lenoir, D.; Schleyer, P. v. R.; Schaefer, H. F., III. *J. Am. Chem. Soc.* **1996**, *118*, 9908–14.
Gallo, M. M.; Schaefer, H. F., III. *J. Phys. Chem.* **1992**, *96*, 1515–7.
Richards, C. A., Jr.; Kim, S.-J.; Yamaguchi, Y.; Schaefer, H. F., III. *J. Am. Chem. Soc.* **1995**, *117*, 10104–7.
Hirai, K.; Itoh, T.; Tomioka, H. *Chem. Rev.* **2009**, *109*, 3275–332.

Carbenes: multiplicity and reactivity

Factors that determine multiplicity: steric effects

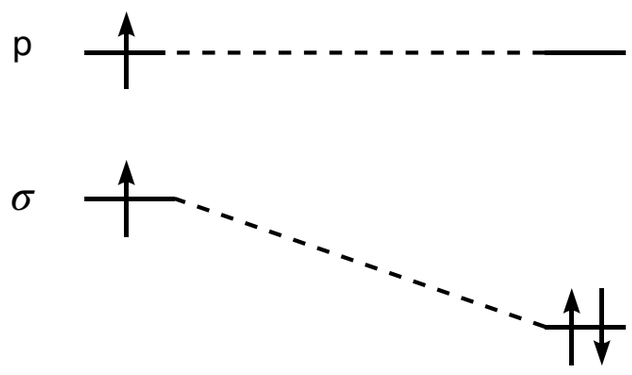
Steric effects

*Large angles favor the **triplet** state*

*Smaller angles (i.e. bulky substituents) favor the **singlet** state*

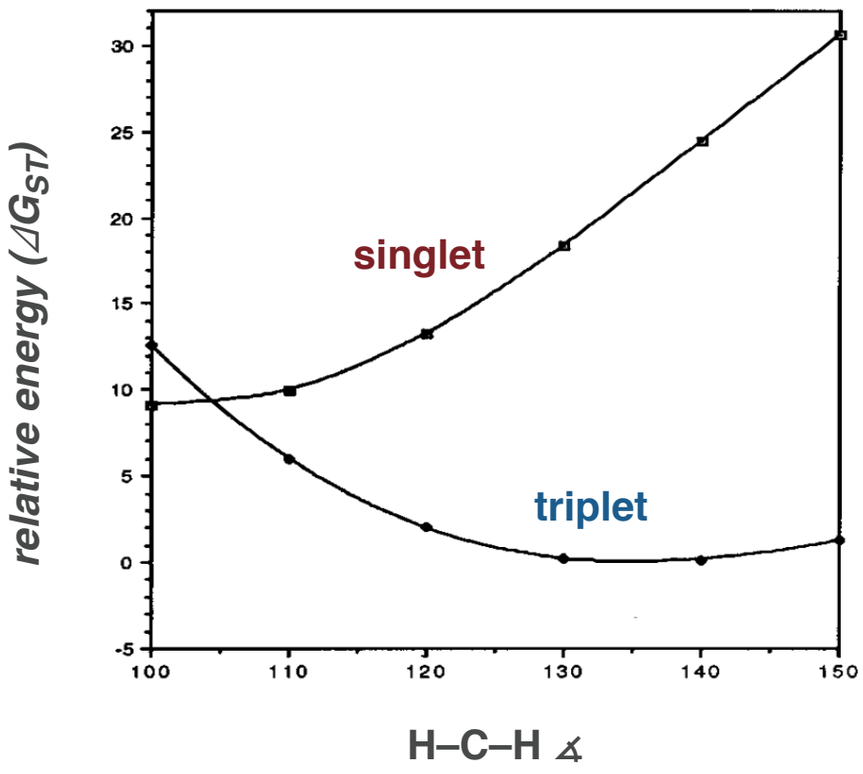
triplet state

singlet state



Factors

- mesomeric interactions
- inductive effects
- hyperconjugation
- steric effects
- solvent environment



As the carbon bond angle decreases, the **σ** *orbital gains more s character and moves lower in energy, increasing the* **σ***–p gap*

Sulzbach, H.M.; Bolton, E.; Lenoir, D.; Schyler, P.v.R.; Schaefer, H.F. *J. Am. Chem. Soc.* **1996**, *118* (41), 9908–14.

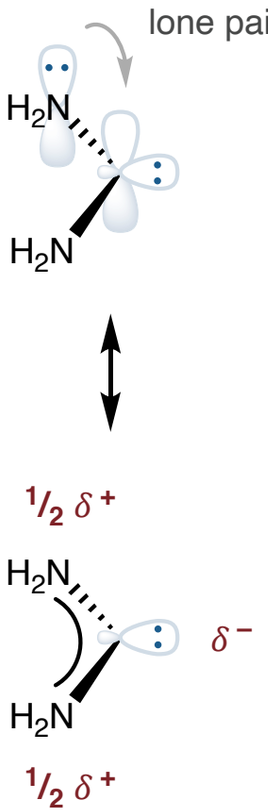
Hirai, K.; Itoh, T.; Tomioka, H. *Chem. Rev.* **2009**, *109*, 3275–332.

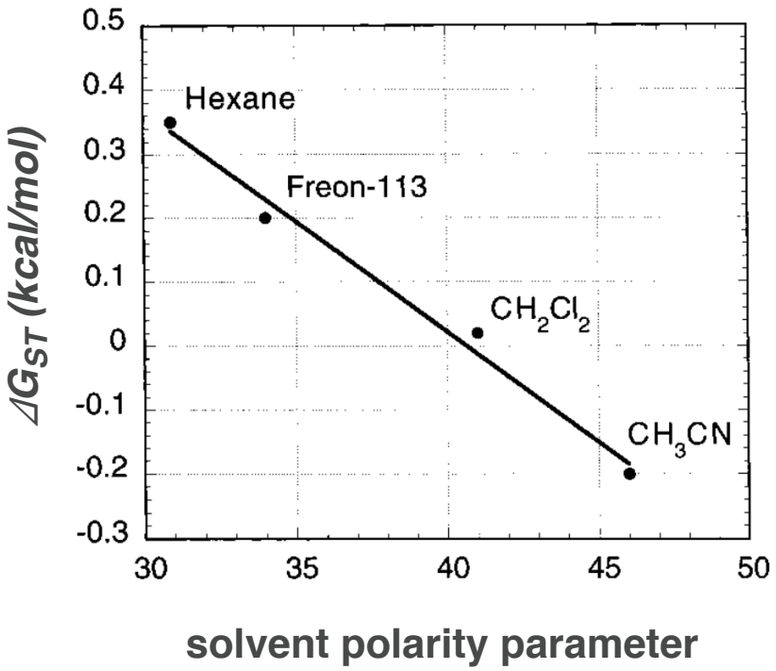
Carbenes: multiplicity and reactivity

Factors that determine multiplicity: solvent enviroment

Solvation of carbenoid

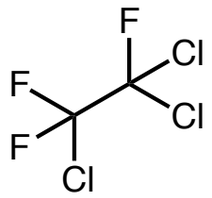
***Singlet** carbenes are stablized in polar solvents*





Factors

- mesomeric interactions
- inductive effects
- hyperconjugation
- steric effects
- solvent environment



Freon-113

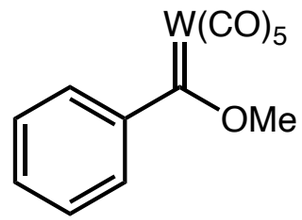
Singlet carbenes have zwitterionic character, allowing them to be stablized in polar solvents

Wang, Y.; Hadad, C.; Toscano, J.P. *J. Am. Chem. Soc.* **2002**, *124* (8), 1761–7.
Hirai, K.; Itoh, T.; Tomioka, H. *Chem. Rev.* **2009**, *109*, 3275–332.

Carbenes: multiplicity and reactivity

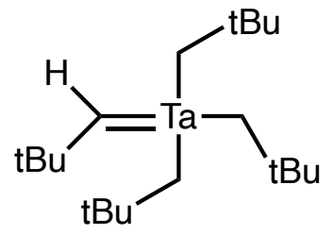
Fischer vs. Schrock metal carbenoids

Fischer
1964



first metal-carbene complex

Schrock
1974

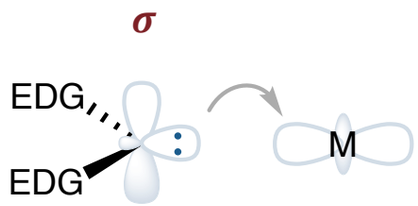


first synthesis of a d^0 metal-alkylidene complex

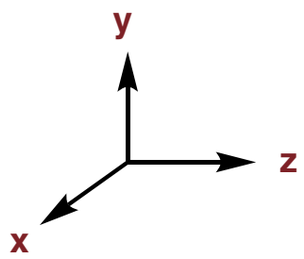
Hartwig, J. F. *Organotransition Metal Chemistry: From Bonding to Catalysis,* 1st ed; University Science Books, 2010.

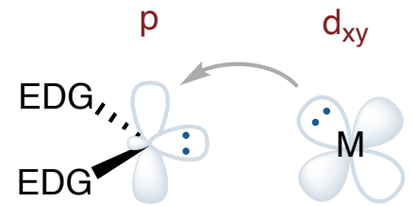
Carbenes: multiplicity and reactivity

Fischer metal-carbene complex: singlet carbenoid



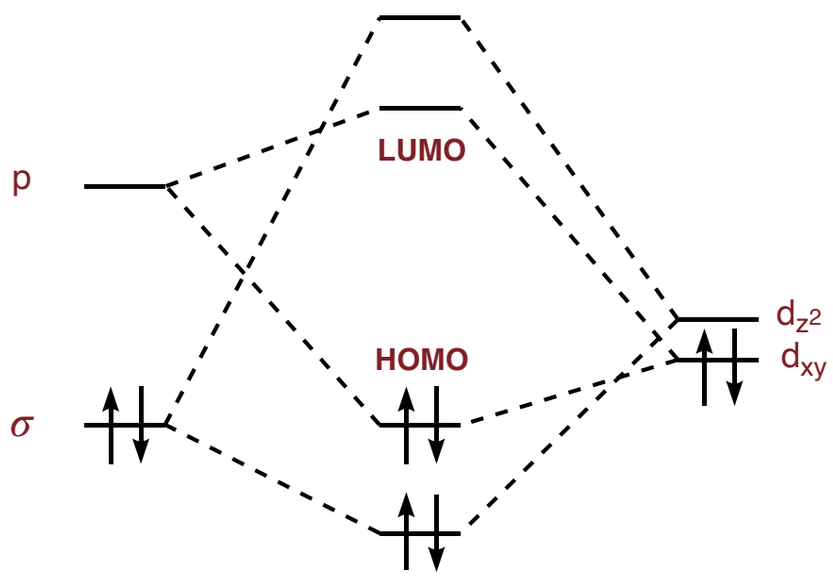
σ-bonding





π-backbonding

singlet
carbenoid

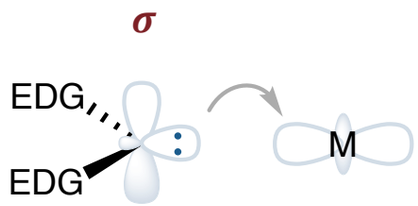


low oxidation state
transition metal
(low energy d orbitals)

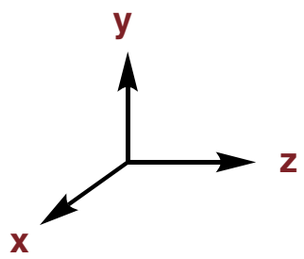
Hartwig, J. F. *Organotransition Metal Chemistry: From Bonding to Catalysis,* 1st ed; University Science Books, 2010.

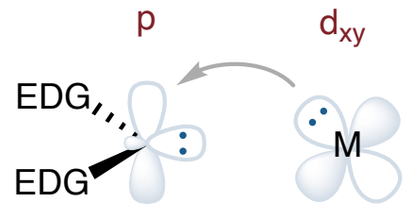
Carbenes: multiplicity and reactivity

Fischer metal-carbene complex: singlet carbenoid



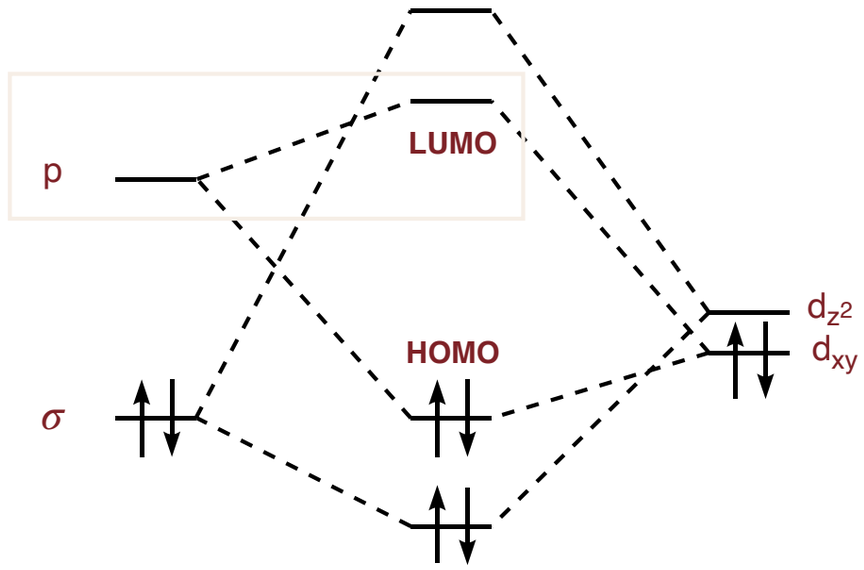
σ-bonding





π-backbonding

singlet
carbenoid



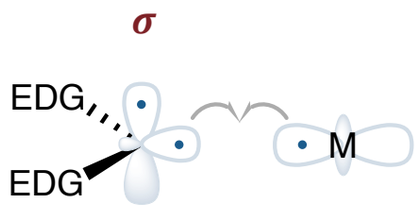
low oxidation state
transition metal
(low energy d orbitals)

LUMO closer to carbene, rendering it more electrophilic

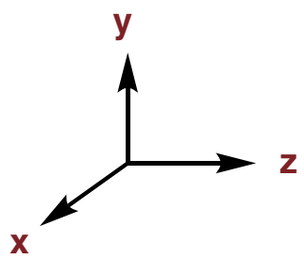
Hartwig, J. F. *Organotransition Metal Chemistry: From Bonding to Catalysis,* 1st ed; University Science Books, 2010.

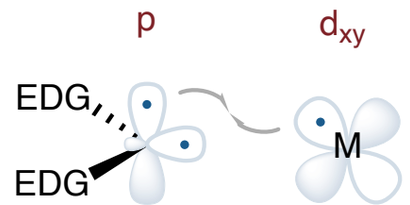
Carbenes: multiplicity and reactivity

Schrock metal-alkylidene complex: triplet carbenoid



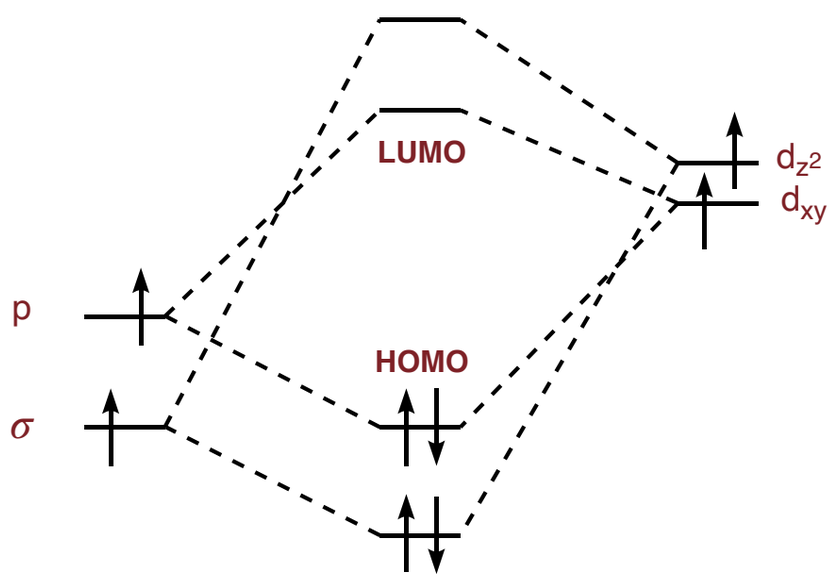
σ-bonding





π-bonding

triplet
carbenoid

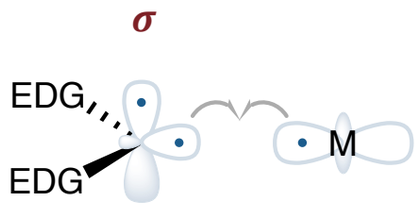


high oxidation state
transition metal
(high energy d orbitals)

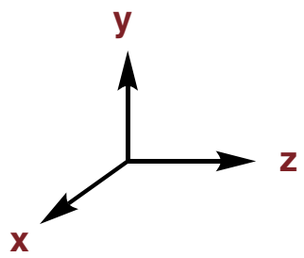
Hartwig, J. F. *Organotransition Metal Chemistry: From Bonding to Catalysis,* 1st ed; University Science Books, 2010.

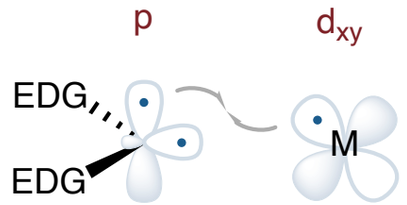
Carbenes: multiplicity and reactivity

Schrock metal-alkylidene complex: triplet carbenoid



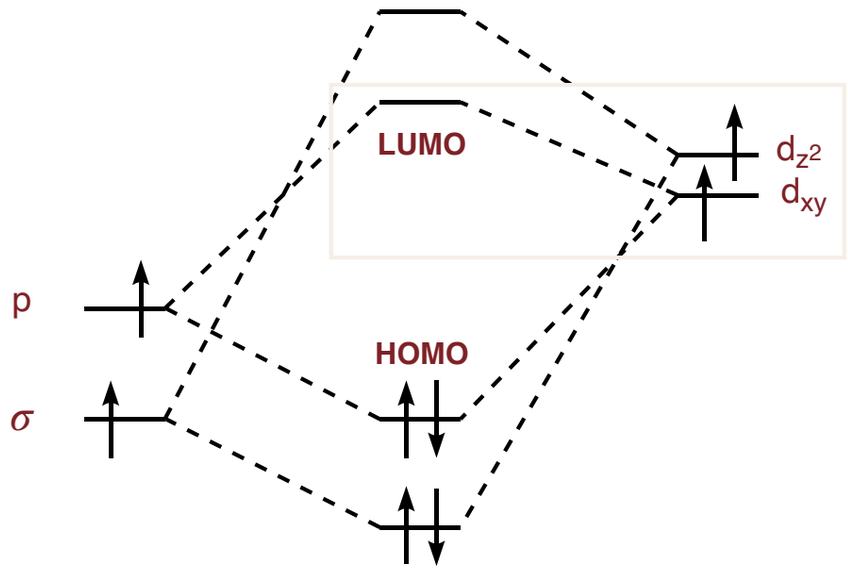
σ-bonding





π-bonding

triplet
carbenoid



high oxidation state
transition metal
(high energy d orbitals)

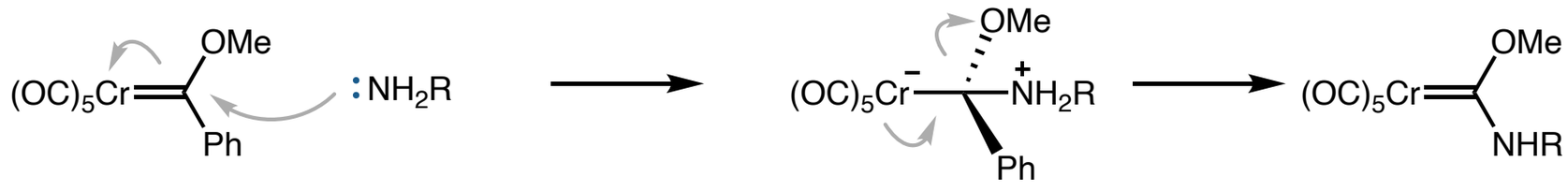
LUMO closer to metal center, rendering the carbene more nucleophilic

Hartwig, J. F. *Organotransition Metal Chemistry: From Bonding to Catalysis,* 1st ed; University Science Books, 2010.

Carbenes: multiplicity and reactivity

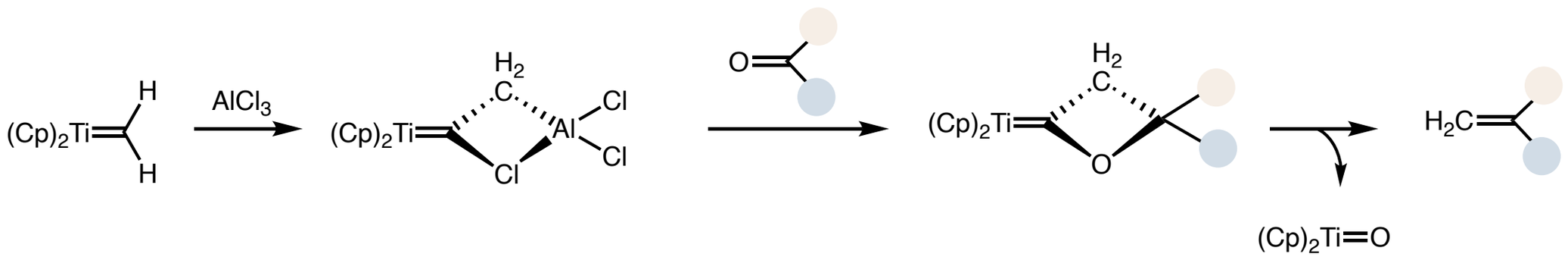
Fischer carbene vs. Schrock alkylidene: sample reactivities

Fischer carbene



nucleophilic substitution

Schrock alkylidene

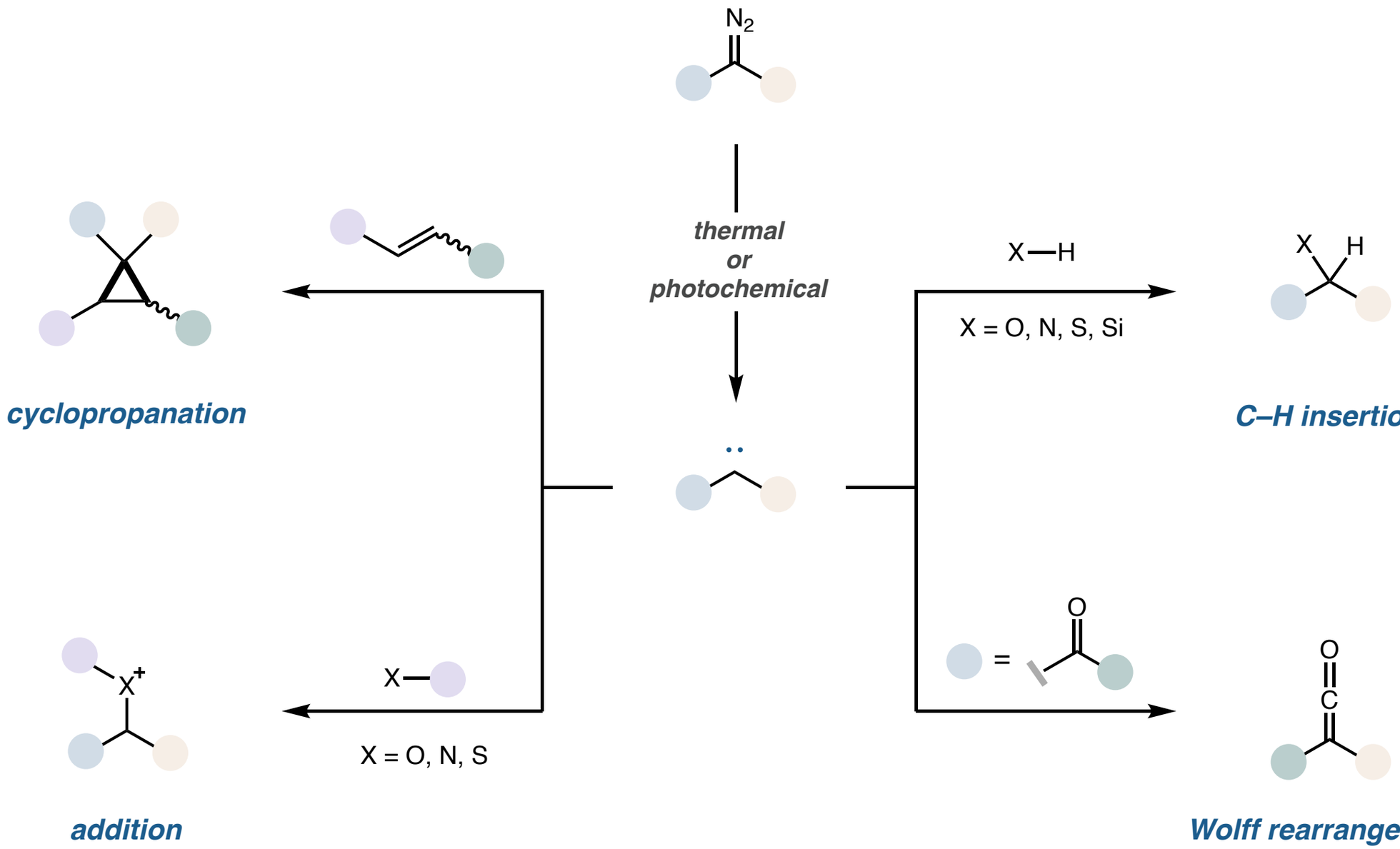


Tebb's reagent

Barluengal, J.; Montserrat, J.M.; l *J. Chem. Soc., Chem. Commun.* **1993**, *13*, 1068–70.
Tebbe, F.N.; Parshall, G.W.; Reddy, G.S. *J. Am. Chem. Soc.* **1978**, *100* (11), 3611–3613.

Carbenes: multiplicity and reactivity

Diazo compounds: reactivity overview

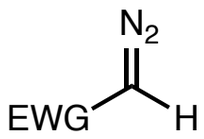


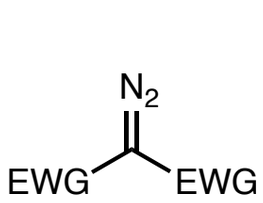
Ciszewski, L.W.; Rybicka-Jasinska, K.; Gryoko, D. *Org. Biomol. Chem.* **2019**, *17*, 432–48.

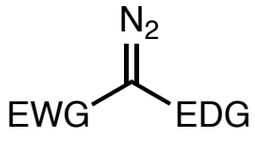
Carbenes: multiplicity and reactivity

Diazo compounds: precursor and carbene multiplicity

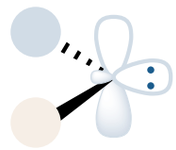
Precursors for stable (enough) carbenes





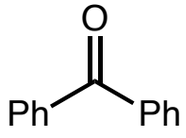


direct excitation

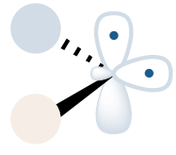


singlet *carbene*

intersystem crossing (ISC)



w/ photosensitizer

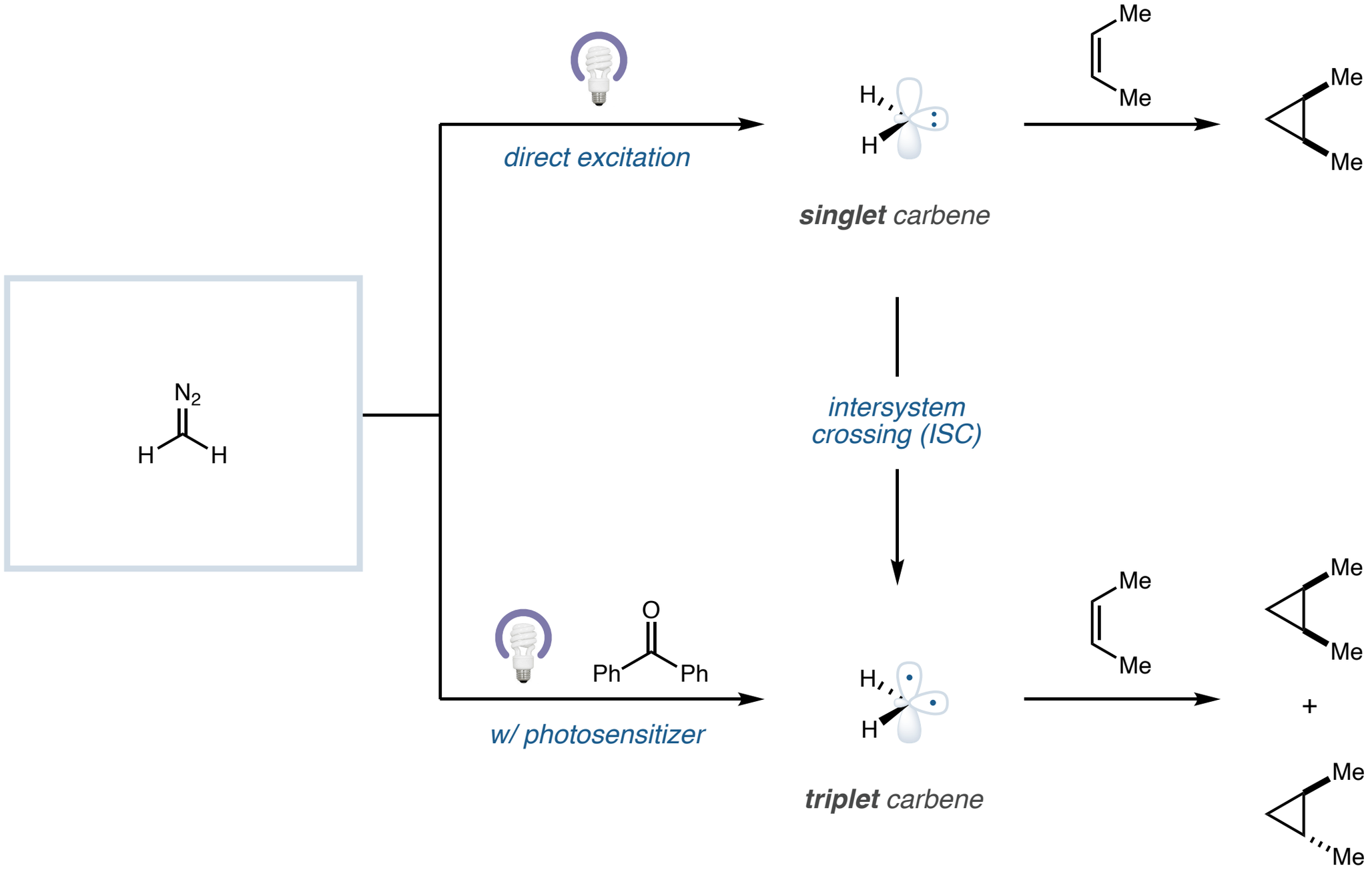


triplet *carbene*

Ciszewski, L.W.; Rybicka-Jasinska, K.; Gryoko, D. *Org. Biomol. Chem.* **2019**, *17*, 432–48.

Carbenes: multiplicity and reactivity

Diazo compounds: precursor and carbene multiplicity



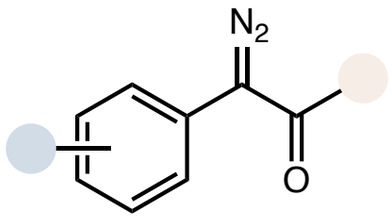
L'Esperance, R.P.; Ford, T.M.; Jones Jr., M. *J. Am. Chem. Soc.* **1988**, *110*, 209–13.
Ciszewski, L.W.; Rybicka-Jasinska, K.; Gryoko, D. *Org. Biomol. Chem.* **2019**, *17*, 432–48.

Carbenes: multiplicity and reactivity

Diazo compounds: visible-light excitation of aryldiazoacetates

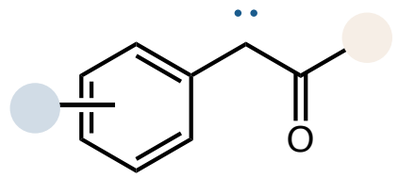
most diazo compounds

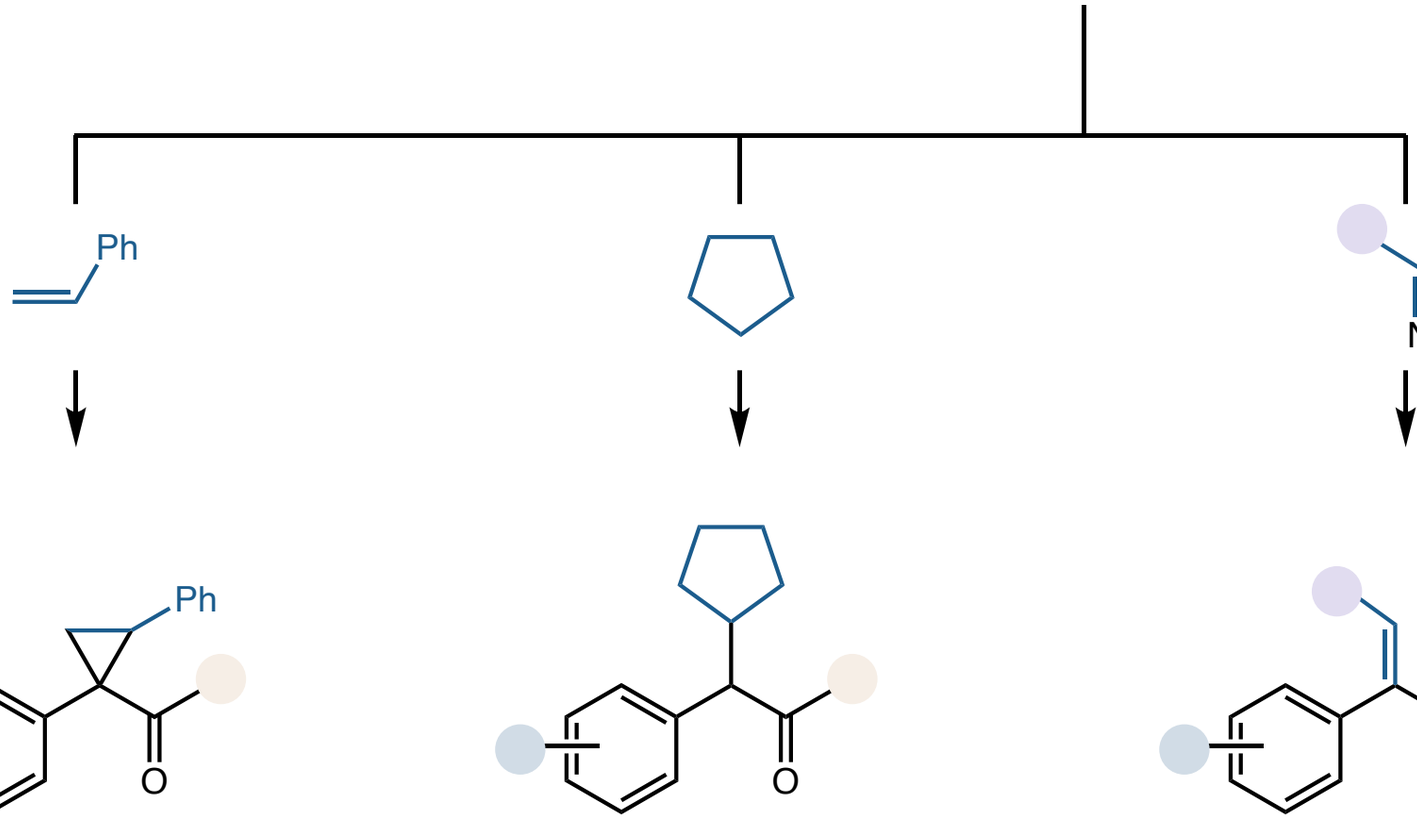
UV light



aryldiazoacetates

400–500 nm
visible light

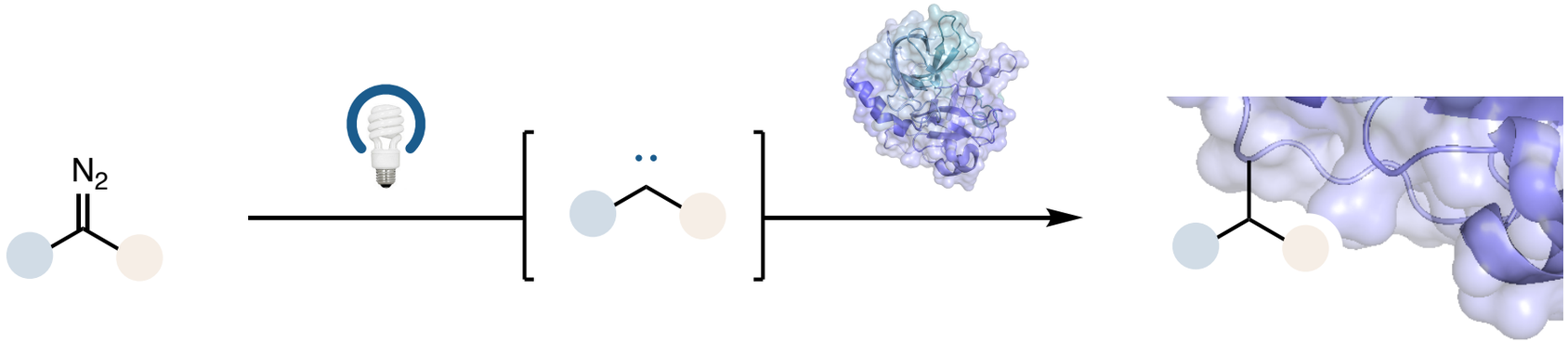




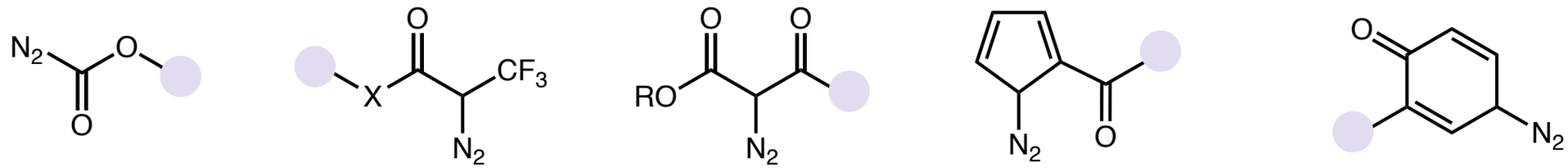
Jurberg, I.D.; Davies, H.M.L. *Chem. Sci.* **2018**, *9*, 5112–8.
Xiao, T.; Mei, M; He, Y.; Zhou, L. *Chem. Commun.* **2018**, *54*, 8865–8.
Ciszewski, L.W.; Rybicka-Jasinska, K.; Gryoko, D. *Org. Biomol. Chem.* **2019**, *17*, 432–48.

Carbenes: multiplicity and reactivity

Diazo compounds: applications to photoaffinity labeling



certain reported precursors in photoaffinity labeling



diazo acetals | **diazotrifluoroproprionyl** | **diazomalonyl** | **diazocyclopentadienyl** | **diazocyclohexadienone**

highly reactive carbenes are attractive tools for protein affinity labeling

$k_2 = 10^7 – 10^9\ M^{-1}s^{-1}$

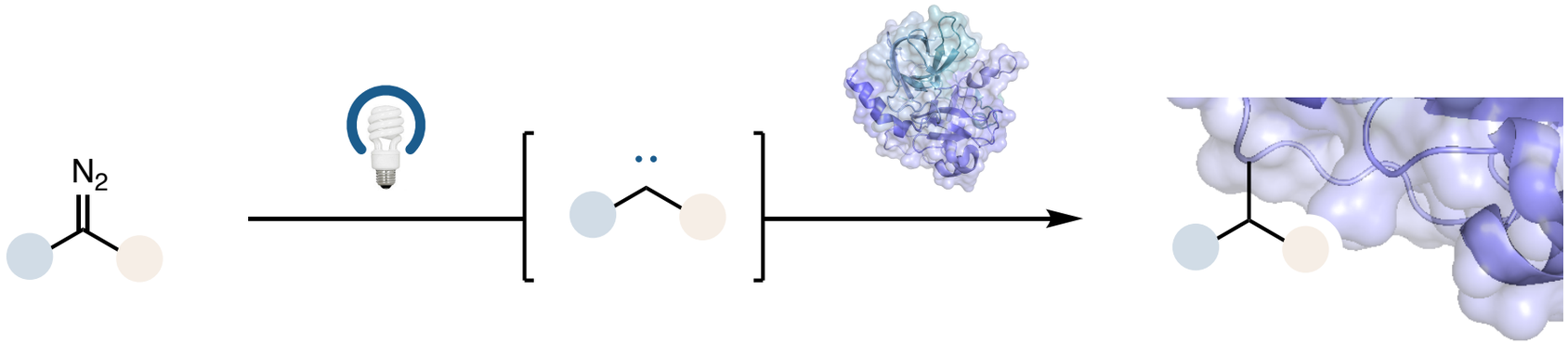
caveats

- alkyl diazo compounds may have β-hydride elimination
- α-keto diazo compounds may lead to Wolff rearrangement
- triplet carbenes are poor labels (dimerization, few radicals in proteins)

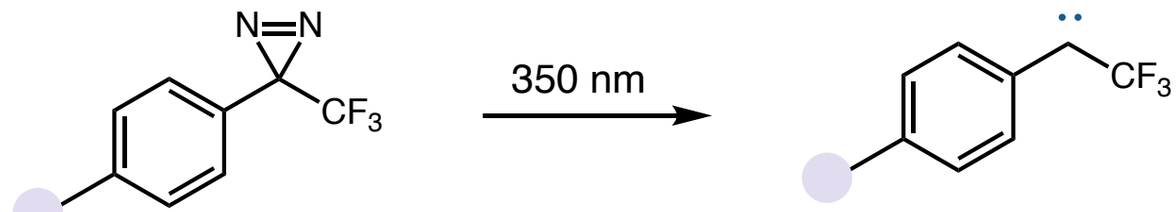
Holland, J.P; Gut, M.; Klinger, S.; Fay, R.; Guillo, A. *Chem. Eur. J.* **2019**, *25*, early view.

Carbenes: multiplicity and reactivity

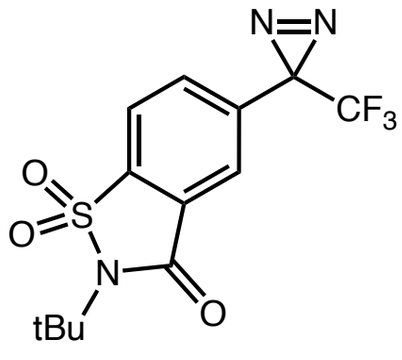
Aryl diazirine in photoaffinity labeling



Trifluoromethyl phenyl diazirines



singlet *carbene*



Photoactive saccharin

artificial sweetener to investigate

gustatory (taste) receptors

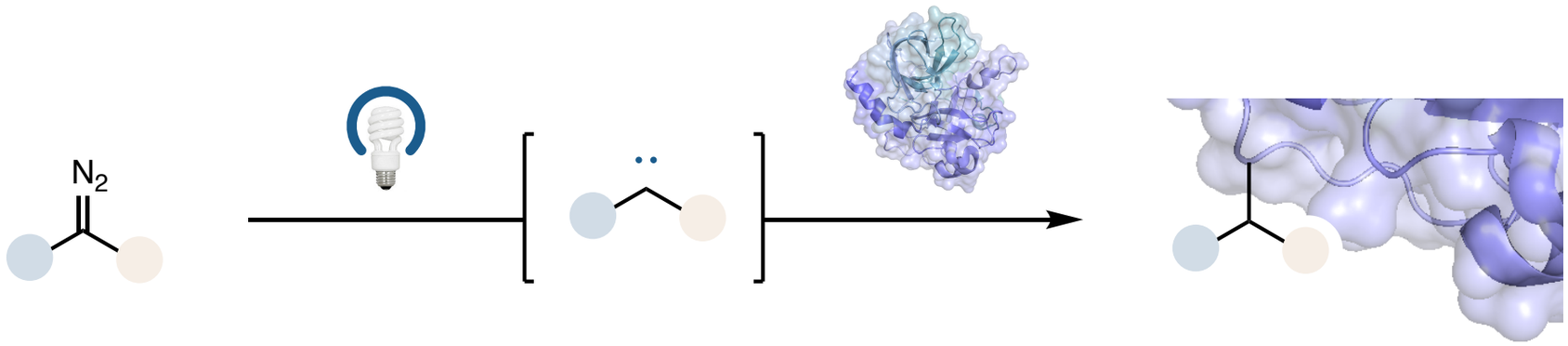
Brunner, J.; Senn, H.; Richards, F.M. *J. Biol. Chem.* **1980**, *255*, 3313–8.

Wang, L. *et al. Eur. J. Org. Chem.* **2015**, *14*, 3129–34.

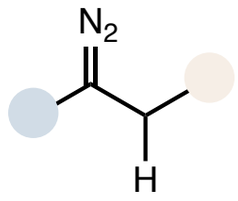
Holland, J.P; Gut, M.; Klinger, S.; Fay, R.; Guillo, A. *Chem. Eur. J.* **2019**, *25*, early view.

Carbenes: multiplicity and reactivity

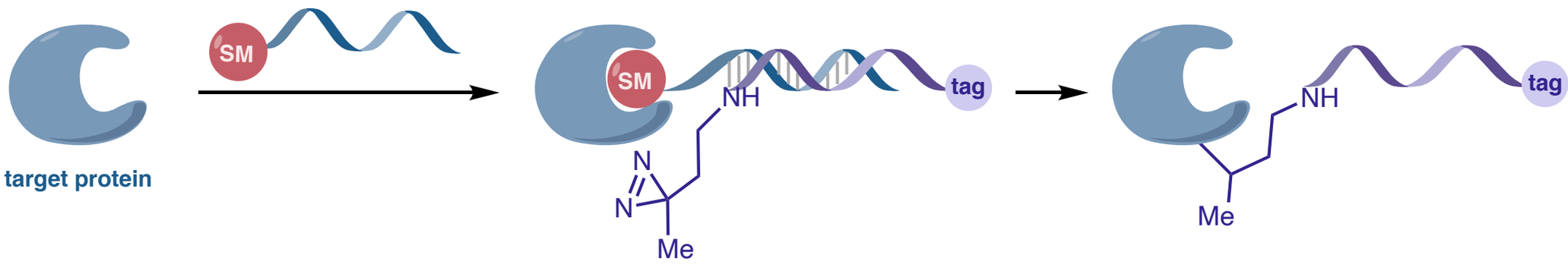
Aliphatic diazirine in photoaffinity labeling



Challenges with aliphatic diazirines



- *β*-hydride elimination
- intramolecular C–H insertion
- too long-lived (diffusion)

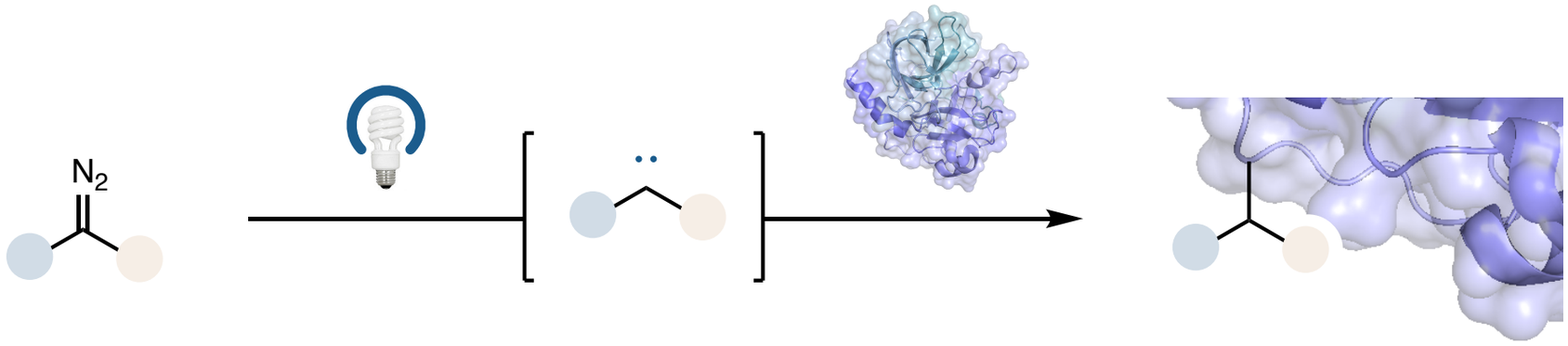


reduces non-specific crosslinking *by taking advantage of specific base pairing*

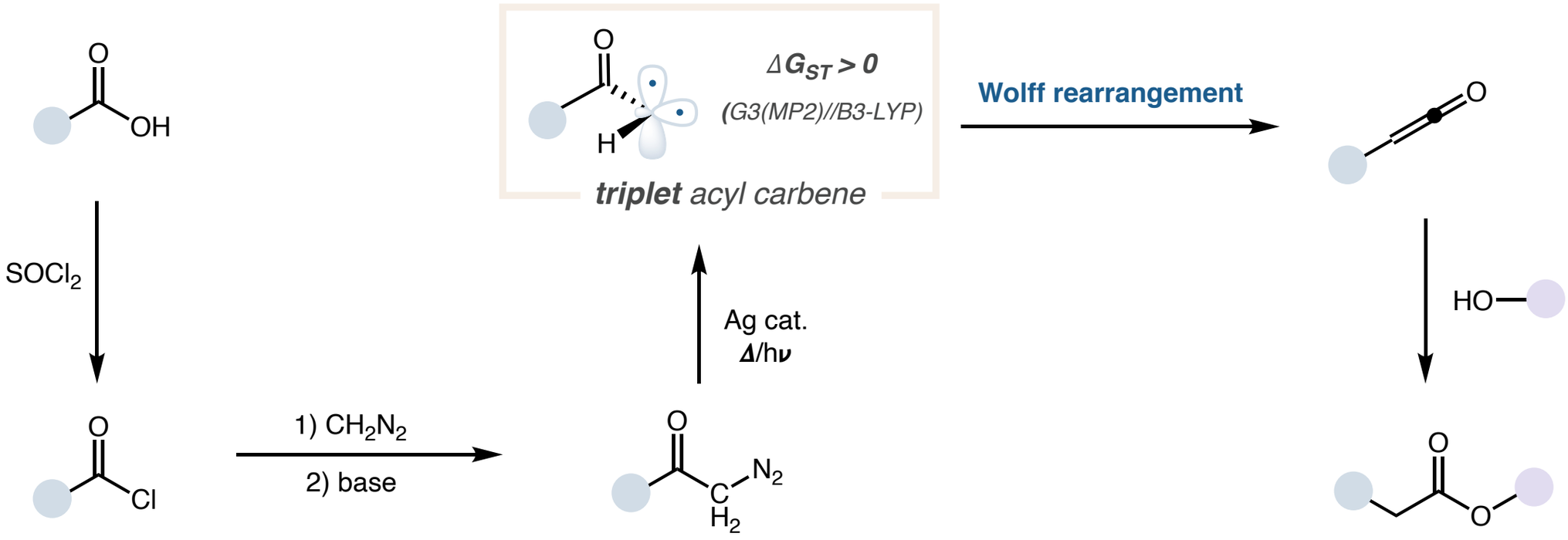
Li, G.; Liu, Y.; Chen, L.; Wu, S.; Liu, Y.; Li, X. *Angew. Chem. Int. Ed.* **2013**, *52*, 9544–49.
Holland, J.P; Gut, M.; Klinger, S.; Fay, R.; Guillo, A. *Chem. Eur. J.* **2019**, *25*, early view.

Carbenes: multiplicity and reactivity

Acyl diazirines are poor affinity labels



Arndt-Eistert procedure



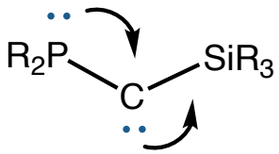
- triplet acyl carbene challenging to react with target in biological enviroment
- competitive Wolff rearrangement

Arndt, F.; Eistert, B. *Eur. J. Inorg.* **1935**, *1*, 200–8.
Scott, A.P.; Platz, M.S.; Radom, L. *J. Am. Chem. Soc.* **2001**, *123* (25), 6069–76.

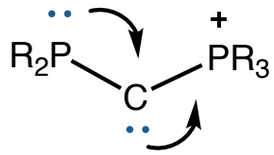
Carbenes: multiplicity and reactivity

Other stable singlet carbenes

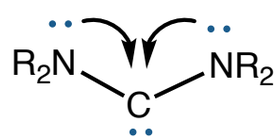
either phosphino or amino groups can serve as a sufficient π-doner to stabilize singlet carbenes



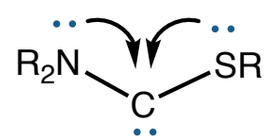
phosphino-silyl



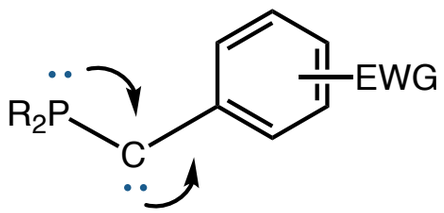
phosphino-phosphino

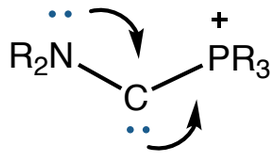


diamino

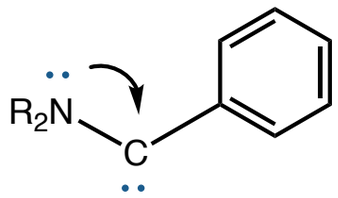


amino-thio

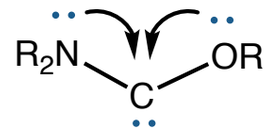




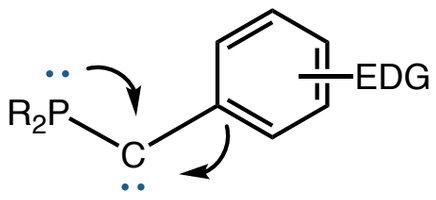
phosphino-phosphino



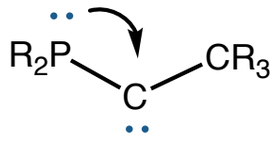
amino-aryl



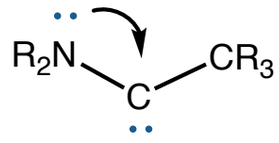
amino-oxy



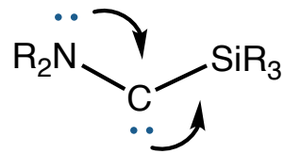
phosphino-aryl



phosphino-alkyl



amino-alkyl



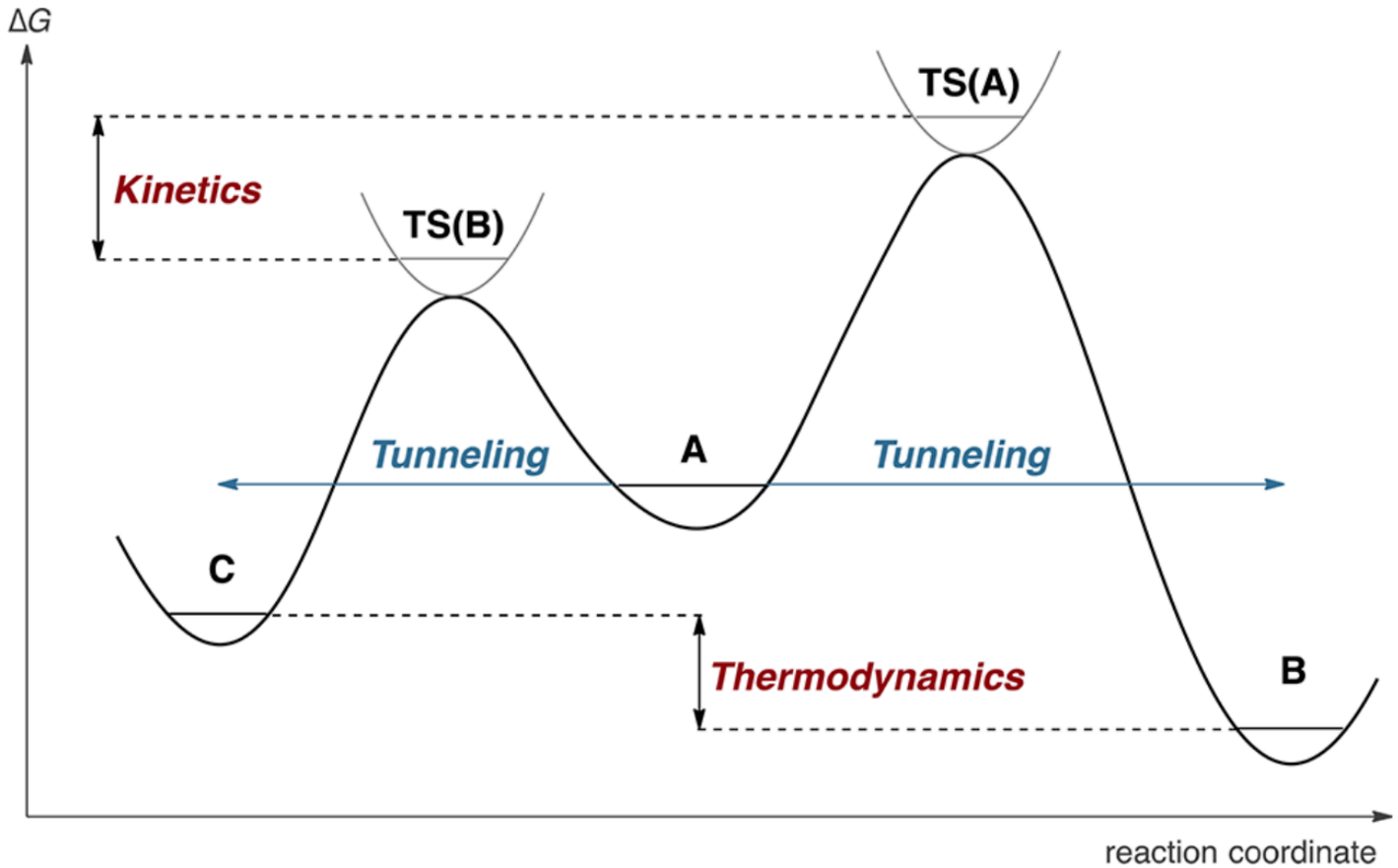
amino-silyl

Kapp, J.; Schade, C.; El-Nahasa, A. M.; Schleyer, P. v. R. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2236–8.
Vignolle, J.; Cattoen, X.; Bourissou, D. *Chem. Rev.* **2009**, *109*, 3333–84.

Carbenes: multiplicity and reactivity

Quantum mechanical tunneling (QMT)

Wave nature of particles allow it to travel through reaction barriers



1) Thermodynamics
2) Kinetics
3) Tunneling

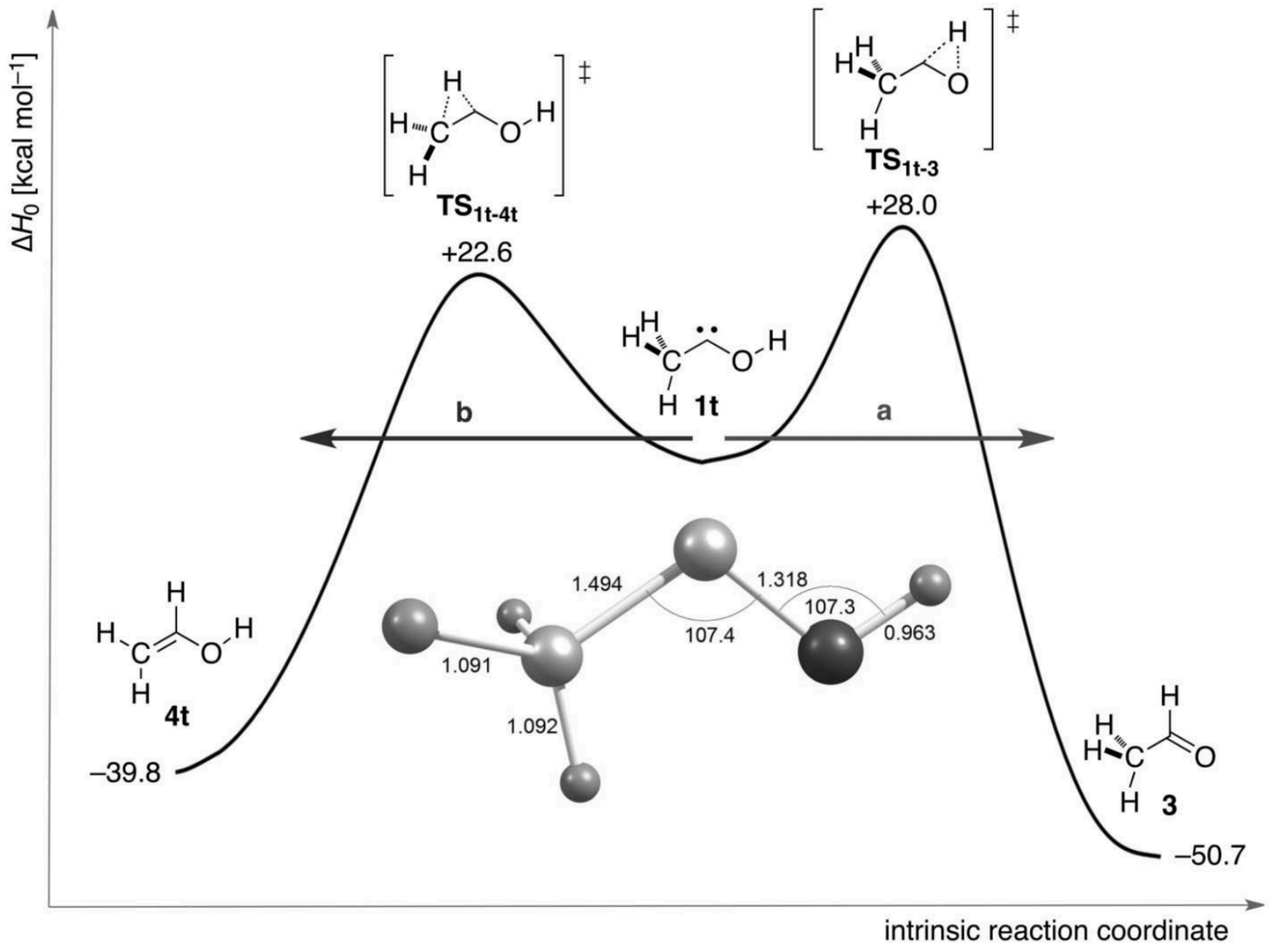
*Relevant when **de Broglie wavelength of the moving particle** is comparable to **width of reaction barrier***

Schreiner, P.R. *J. Am. Chem. Soc.*, **2017**, *139*, 15276–83.

Carbenes: multiplicity and reactivity

Quantum mechanical tunneling (QMT)

Carbenes can undergo H-shifts and C–H insertions under cryogentic temperatures due to QMT



barrier widths computed at AE-CCSD(T)/ cc-pCVQZ level of theory

- $t_{1/2}$ at 11 K for formadehyde = 70 min (similar to experimental value)
  - $t_{1/2}$ for vinyl alcohol = 190 days
  - $t_{1/2}$ from H3COD = 4000 years

QMT mechanism operative

Schreiner, P.R.; Reisenauer, H. P.; Ley, D.; Gerbig, D.; Wu, C.-H.; Allen, W.D. *Science* **2011**, *332*, 1300–1303.
Schreiner, P.R. *J. Am. Chem. Soc.* **2017**, *139*, 15276–83.

Carbenes: multiplicity and reactivity

Conclusion

1855

$CHCl_3 + OH^-$

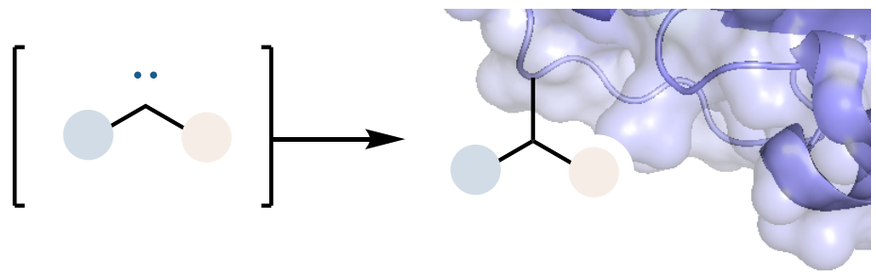
$\downarrow$

$[:CCl_2] + Cl^- + H_2O$

first to propose a carbenoid intermediate

***Carbenes**: high energy intermediate with comprehensible reactivity*

2019



tuning electronic structure to react in complex enviroments