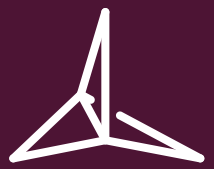
HISTORY OF [1.1.1]PROPELLANES AND BICYCLO[1.1.1]PENTANES

KIMBERLY HILBY

10/29/2019



OUTLINE OF TALK

- Synthesis of bicyclo**[1.1.1]**pentanes and **[1.1.1]**propellanes
- Properties of **[1.1.1]**propellanes and bicyclo**[1.1.1]**pentanes
- Reactivity of bicyclo**[1.1.1]**pentanes and **[1.1.1]**propellanes

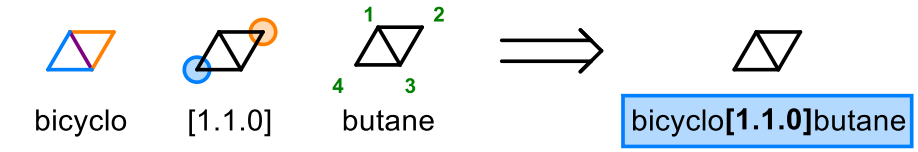
  -Carbanion

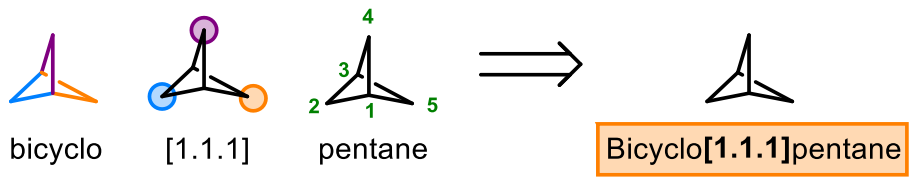
  -Radical

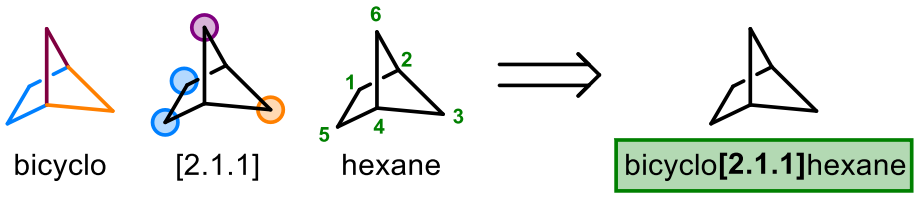
  -Carbocation
- Relevance in Pharmaceuticals
- Conclusions/Future Directions

COMPOUND NAMING PRIMER

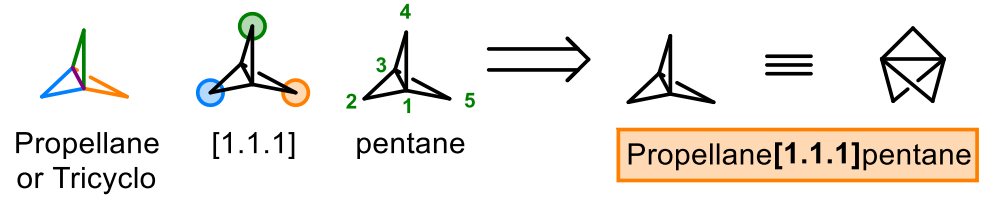
Naming Bicyclic Compounds

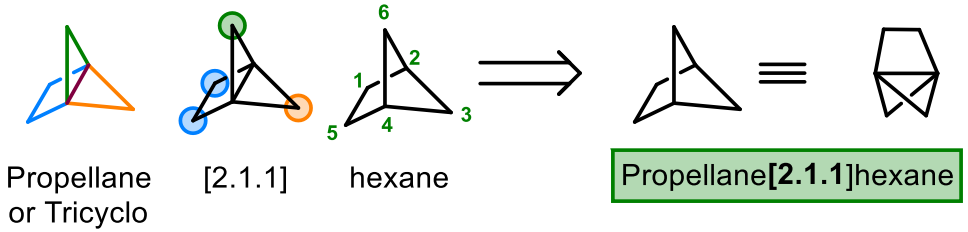






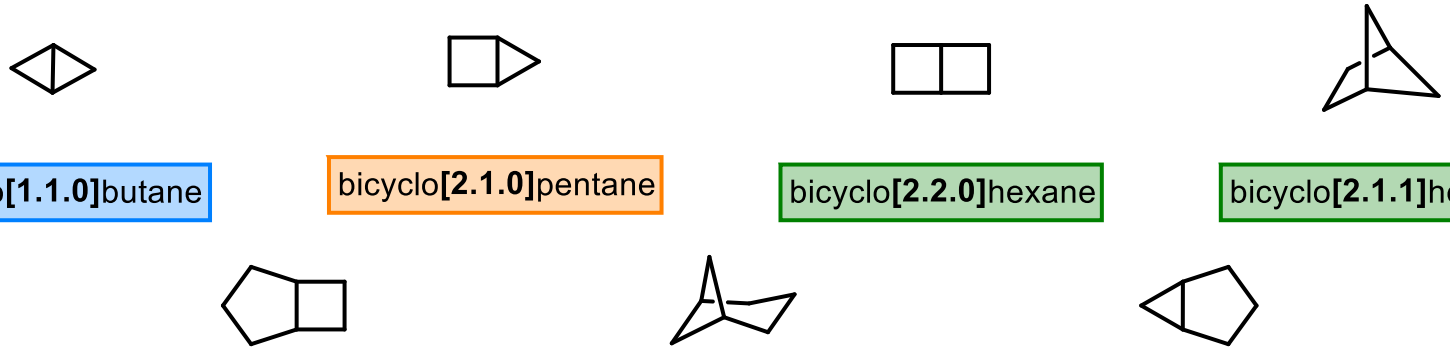
Naming Tricyclic Compounds





DISCOVERY OF BICYCLO[1.1.1]PENTANE

In 1964 bicyclic small ring compounds were interesting synthetic targets and a variety had been made:



bicyclo**[1.1.0]**butane

bicyclo**[2.1.0]**pentane

bicyclo**[2.2.0]**hexane

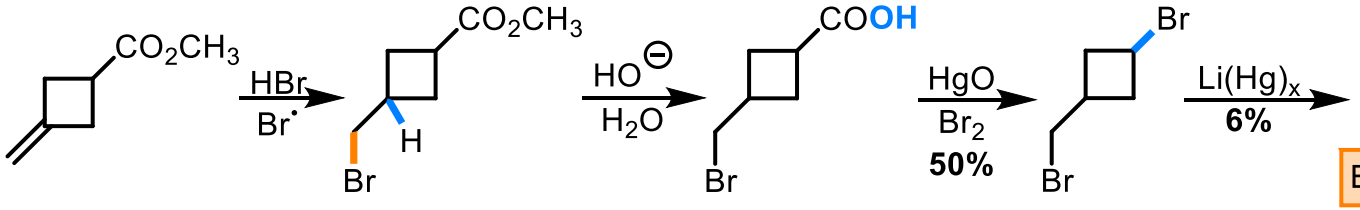
bicyclo**[2.1.1]**hexane

bicyclo**[3.2.0]**heptane

bicyclo**[3.1.1]**heptane

bicyclo**[3.1.0]**hexane

Kenneth Wiberg (1964): Synthesized and Characterized the first Bicyclo[1.1.1]pentane



Bicyclo**[1.1.1]**pentane

TETRAHEDRON LETTERS 1964, 10, 531-534

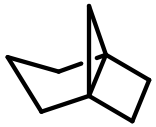
THE ULTIMATE STRAINED RING

- After synthesis of bicyclo[1.1.1]pentane physical organic chemists became interested in making propellanes due to the strained ring system and the hypothesized "inverted" carbon:

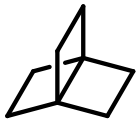
Propellane**[2.1.1]**hexane

Propellane**[3.1.1]**heptane

Propellane**[2.2.1]**heptane



Propellane**[3.2.1]**octane



Propellane**[2.2.2]**octane

Propellane**[4.1.1]**octane

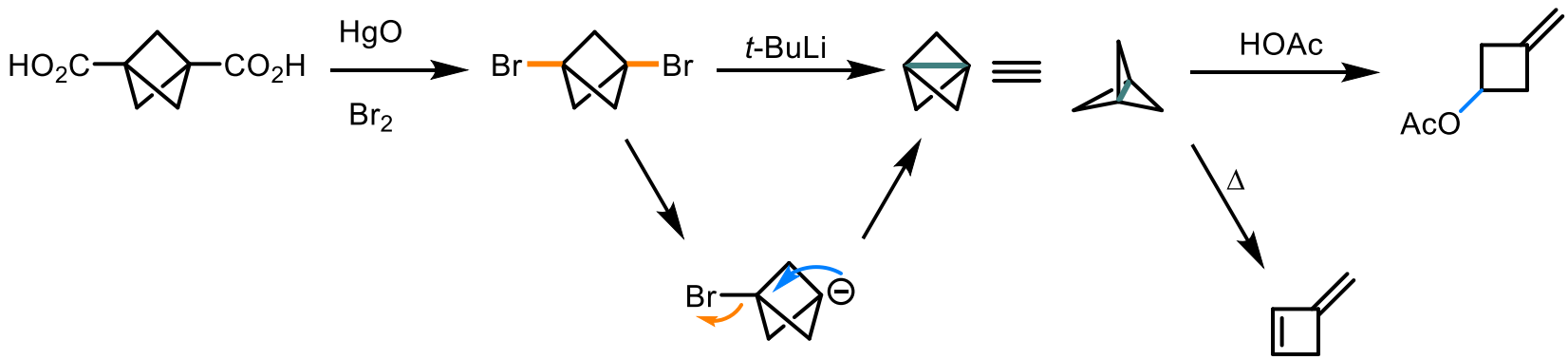
Propellane**[1.1.1]**pentane

Certainly, [1.1.1] propellane would be the least stable of these molecules. Indeed, as Newton and Schulman[16] have pointed out, the strain in this compound would be greater than the strongest of carbon–carbon single bonds.

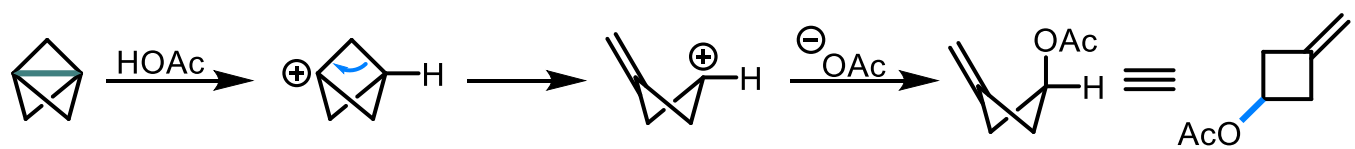
TETRAHEDRON 1977, 33, 1897

INITIAL SYNTHESIS OF PROPELLANE[1.1.1]PENTANE

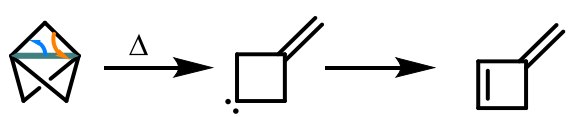
- Synthesized by Wilberg(1982):



- Mechanism for Acetoxylation:



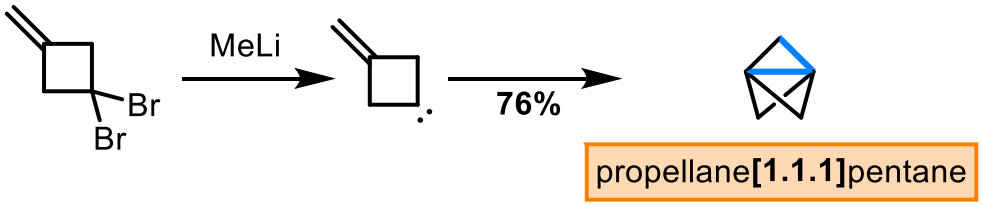
- Mechanism for Formation of Butylidene:



J. AM. CHEM. SOC. 1982, 104, 5239; ACC. CHEM RES. 1984, 17, 379-386

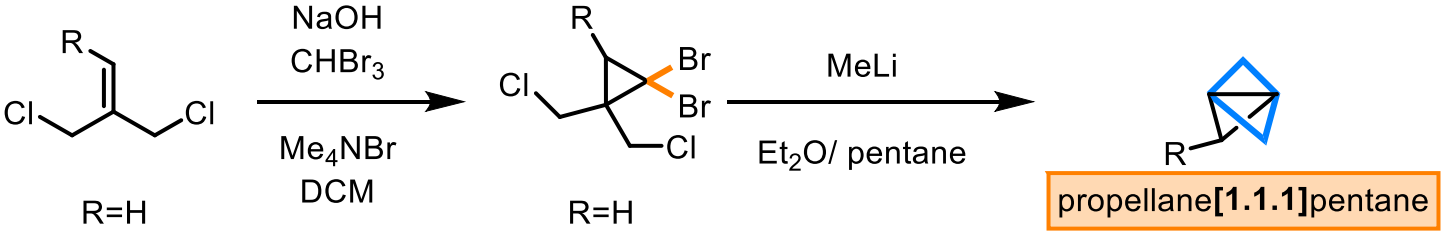
SYNTHETICALLY USEFUL SYNTHESIS

Szeimies(1988): Carbene approach to give Propellane:



Could be used to generate a variety of substituted [1.1.1]propellanes in good yields

Szeimies (1989): Anionic Cyclization to give Propellane:



R=H
$4.8/ 1 g
Oakwood

R=H
$8.5 / 1 g
Millipore-Sigma

Considered best way to make **[1.1.1]**propellane derivatives

R	Yield (%)
H	70%
n-C_5H_{11}	34-60%
$(CH_2)_3OCH_3$	57

J. AM. CHEM. SOC. 1988, 110, 5588; CHEM. BER. 1989, 122, 397

COMPARING PROPERTIES OF BICYCLO[1.1.1]PENTANE AND PROPELLANE

bicyclo**[1.1.1]**pentane

- Bicyclo**[1.1.1]**pentanes derivatives are solids
- Similar boiling point as n-pentane put melts 100 °C higher
- Thermally stable up to 300 °C
- Strain Energy of 65-68 kcal/mol

propellane**[1.1.1]**pentane

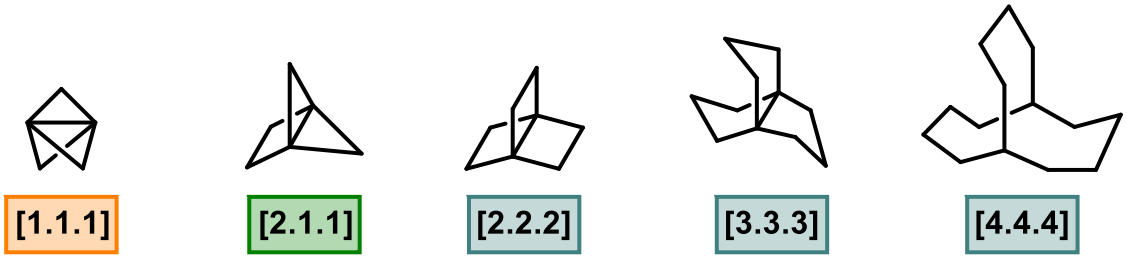
- If not diluted will spontaneously polymerize
- Diluted solutions must be kept below 0 °C or will polymerize
- Can be stored as a solid in liquid nitrogen
- Strain Energy of 98 kcal/mol

Relative stability due to breaking of central bond releasing less than a third of the strain energy and breaking the peripheral bonds is symmetry forbidden

CHEM REV 2000, 100, 169-234

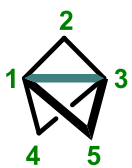
RING STRAIN IN RELATED SMALL RINGS

Structure	Actual Strain Energy	Calculated Strain Energy [kcal/mol^{-1}]		
		B3LYP/6-31G*	B3LYP/cc-pVTZ	MM/2
cyclopropane	27.5 kcal/mol	-	-	-
cyclobutane	26.5 kcal/mol	-	-	-
[1.1.1]	-	98.2	100.6	113.2
[2.1.1]	-	98.1	100.1	94.4
[2.2.2]	-	90.2	95.6	78.7
[3.3.3]		-	11.2	21.4
[4.4.4]	-	-	-	18.8



X-RAY CRYSTAL STRUCTURE OF PROPELLANE

- Seiler(1990): Obtained the X-RAY crystal structure of parent compound propellane at 138 °K (-135 °C)



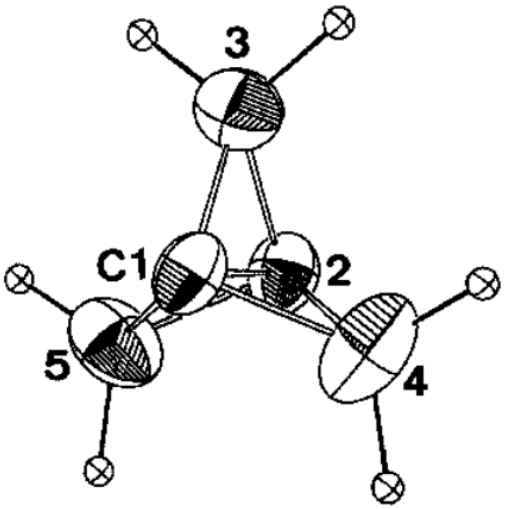


Table 1. *Experimental Details of the X-Ray Diffraction Measurements of [1.1.1]Propellane*

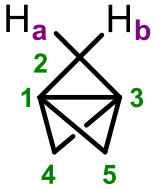
Temperature of data collection [K]	138
Melting point [K]	263
Approximate crystal dimensions [mm]	0.5×0.5×0.5
Space group	*C*2
Cell dimensions	
a [Å]	18.228(5)
b [Å]	10.833(3)
c [Å]	11.109(3)
β [°]	128.44(2)
Unit cell contents	$16\times C_5H_6$
D_c [g/cm^3]	1.022
2 sin θ/λ range [Å^{-1}]	1.10
No. of symmetry equivalent orientations measured	2
No. of measured reflections	2573
$R_{int} = (\sum_{\mathbf{H}}\sum_{\mathbf{N}} \mid I_{H,i} - \langle I_H \rangle \mid)/\sum_{\mathbf{H}} N \langle I_H \rangle$	0.017
No. of unique reflections	1267
No. of observed reflections ($I > 3\ \sigma(I)$)	845
No. of variables in final least-squares analysis	233
Type of refinement	*F*
Scan mode	ω/θ
Weight	1.0
Extinction correction	non
$R(F)$	0.038

Unfortunately, the crystal structure was low quality and some of the measurements had to be by calculation.

HELV. CHIM. ACTA. 1990, 73, 1574-1585; ANGEW. CHEM INT. ED. 2017, 56, 5684-5718

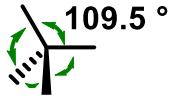
STRUCTURE OF PROPELLANE

- Based on X-Ray Crystallography and Gas-Phase Electron Diffraction able to determine bond lengths and angles

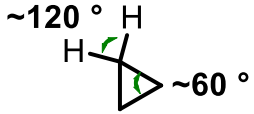


Distance [Å]		Angle[°]	
C(2)-H_a	1.09[a]	H_aC(2)H_b	116[a]
C(1)-C(2)	1.52[b]	C(1)C(2)C(3)	63.8[b]
C(1)-C(3)	1.58[b]	C(1)C(3)C(2)	58.8[b]
		C(3)C(1)C(4)	92.9[b]

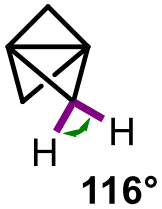
[a]- From Gas-Phase Electron Diffraction. [b]-From X-Ray crystallography analysis.

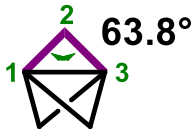


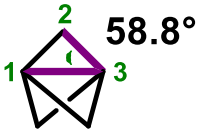
tetrahedral carbon

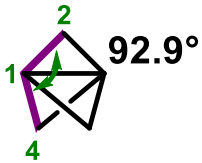


Cyclopropane





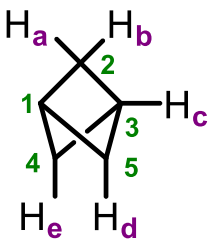




HELV. CHIM. ACTA. 1990, 73, 1574-1585; J. AM. CHEM. SOC. 1985, 107, 7257-7260; ANGEW. CHEM INT. ED. 2017, 56, 5684-5718

STRUCTURE OF BICYCLO[1.1.1]PENTANE

- X-Ray diffraction, electron diffraction and microwave spectroscopy have been used to characterize the compound.



C(1)-C(3)-2.14 Å

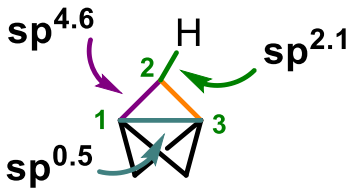
Distance [Å]		Angle[°]	
C(1)-C(3)	1.845	$H_aC(2)H_b$	103.9
C(1)-C(2)	1.545	C(1)C(2)C(3)	73.3
C(4)-C(5)	2.157	C(2)C(3)C(5)	87.5*
C(3)-H_c	1.10		
H_a-H_b	1.732		
H_e-H_d	2.455		
H_b-H_c	2.918		

*Measurement was made with (Ph and $OCONHC_6H_4Br$) at H_a and H_b

J. AM. CHEM. SOC. 1970, 92, 1614

HYBRIDIZATION OF PROPELLANE

- Jarret (1990): Published the hybridization of carbon atoms of [1.1.1]propellane using ^{1}H-^{13}C/^{13}C-^{13}C correlation



$$J_{CH} = 500(\%s)$$
$$\frac{J_{CH}}{500} = \%s$$
$$\%s = 32.6\%$$
$$\%p = 67.4\%$$

$$J = \frac{7.3(\%s_a \%s_b)}{100} - 17$$
$$\%s = \sqrt{\frac{(J+17)(100)}{7.3}}$$
$$\%s = 19\%$$
$$\%p = 81\%$$

1

C1-C2	9.9[a]	(10-17)
C1/C3		(69)
C-H	163.7	(33)

[a] ± 0.1 Hz, average taken from both carbon signals (acetone-d_6, -50 °C)

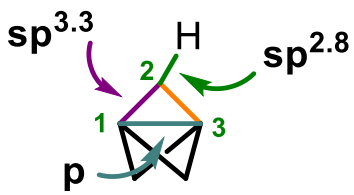
Hypothesizes ~70% s character for bond between bridged C(1)-C(3)

TETRAHEDRON LETT. 1990, 31, 171

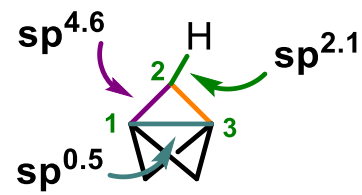
HYBRIDIZATION DETERMINED BY CALCULATION

- Michl (1995): Obtained calculations of the orbitals in [1.1.1]propellane using HF/6-311G** (NBO/ Weinhold's natural hybrid orbitals)

Determined by Calculation



Determined by NMR Correlation



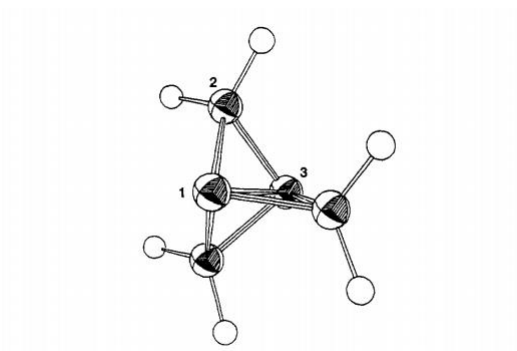


Figure 1. 6-31G* TCSCF D_{3h} geometry of [1.1.1]propellane: R_{13} = 1.57, R_{12} = 1.50, and R_{CH} = 1.08 Å; HCH = 114.5°; E = −192.7241.

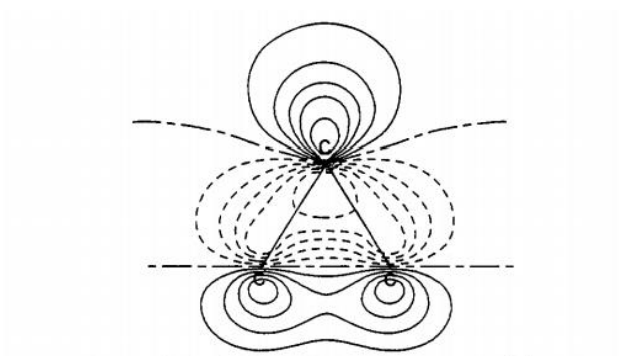


Figure 9. 6-31G* TCSCF 4e′ orbital at the geometry of Figure 1.

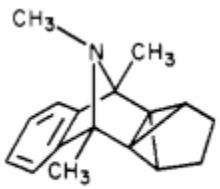
Calculations- Suggested that bridging bond is "two coaxial staggered planar methyl radicals bound by their p orbitals"

Calculations suggested that bridging bond was almost entirely "p" in character

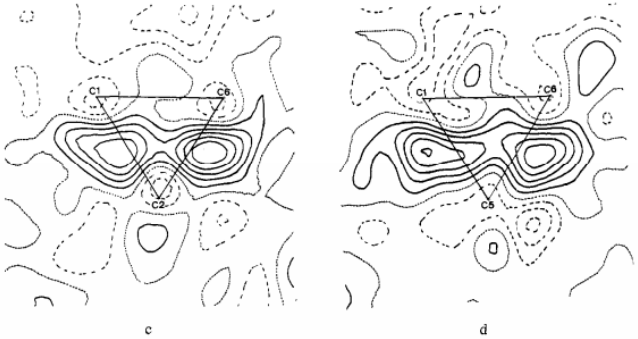
"THE CHEMISTRY OF THE CYCLOPROPYL GROUP." VOLUME 2. COPYRIGHT 1995 JOHN WILEY & SONS, LTD.; HELV CHEM ACTA. 1988, 71, 2100

NATURE OF THE BRIDGING BOND

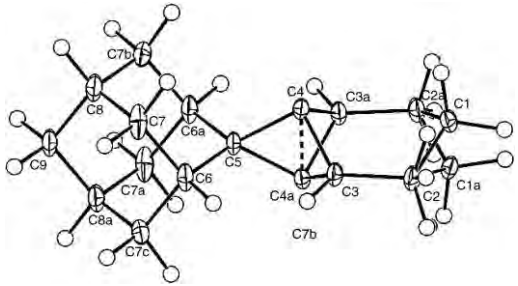
- Dunitz (1981): Exhibited using electron diffraction on a related compound that there was not electron density in central bond

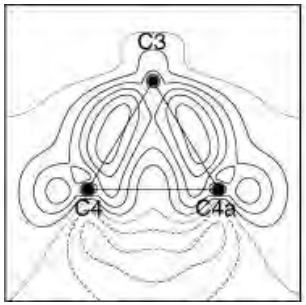


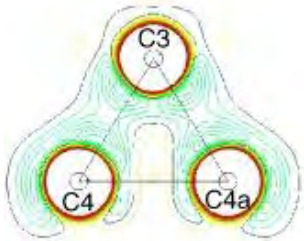
1



- Luger (2005): Used High-Resolution Refraction to obtain a Laplacian distribution for electron density







"This bond is unusual according to topological analysis: it has a bond path with a bond critical point of significant density, as is characteristic for a covalent bond, but no charge accumulation is evident at the bond critical point where the Laplacian is positive"

J. AM. CHEM. SOC. 1981, 103, 8778-8780; ANGEW CHEM. INT. ED. 2005, 44, 3925

CHARGE SHIFT BONDING

- Charge-Shift bond is a non-classical type of bonding in which the covalent-ionic resonance energy plays a major role

The charge shift bond derives its stability from the resonance of ionic forms rather than the covalent sharing of electrons.

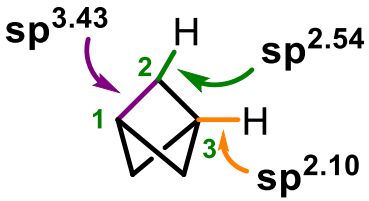
$$\Psi(Bonding) = a\omega_c(covalent) + b\omega_I(A^+B^-) + c\omega_2(A^-B^+)$$

ω – Reflects contribution of bonding character
In **covalent bond** ω_c is high(close to 1) and ω_1 and ω_2 are low
In **ionic bond** ω_1 or ω_2 is high and ω_c/ω_1 or ω_c/ω_2 is low
In **charge-shift bond** ω_1 and ω_2 are high and ω_c is low

NAT. CHEM. 2009, 1, 443

HYBRIDIZATION OF BICYCLO[1.1.1]PENTANE

- The hybridizations of $^{1}J_{CH}$ spin-spin coupling constant analysis agreed with *ab initio* and semiempirical calculations



Position of Substituent	Substituent: H Gas phase	CO_2H pK_a (H_2O)	NH_3Cl pK_a (50% aq EtOH)	NO_2 pK_a (50% aq EtOH)
1	411±3.5	4.09	8.2	-
2	-	4.27	8.90	11.20±.11

- Bicyclo[1.1.1]pentylcarboxylic acid is more acidic then pivalic acid (pKa=5.5)
- Bicyclo[1.1.1]pentylamine is less basic than ammonia

J. ORG CHEM. 1970, 35, 369; J. ORG. CHEM. 1993, 58, 1372; J. MAGN. RES. 1984, 59, 282.

BONDING OF BICYCLO[1.1.1]PENTANE

Electron density confirmed no bond between bridgehead carbons

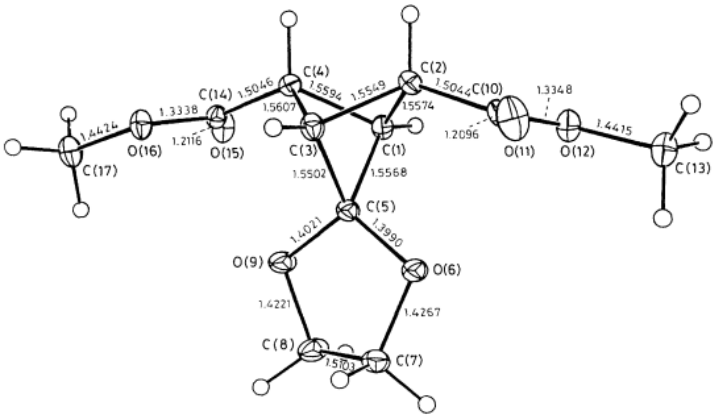
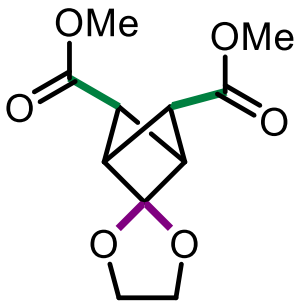
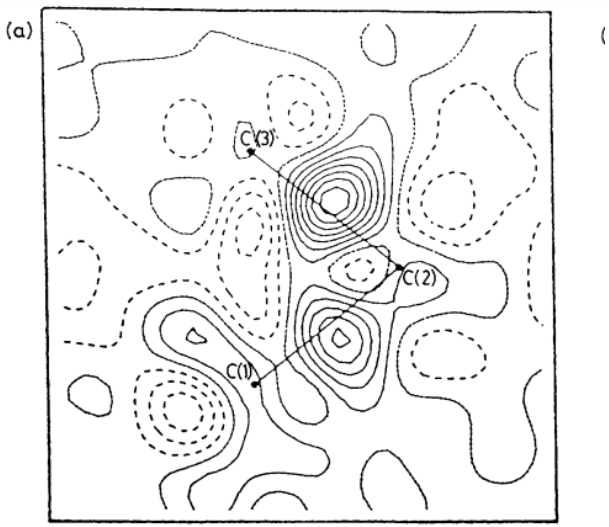


Figure 1. Structure of (1) and bond lengths (Å) at 100 K. Standard deviations 0.0006—0.0008 Å.





Difference Electron Density showed presence of bent bonds and absence of bond between bridgehead

J. AM. CHEM. SOC. 1970, 92, 1614

INTERBRIDGEHEAD INTERACTIONS

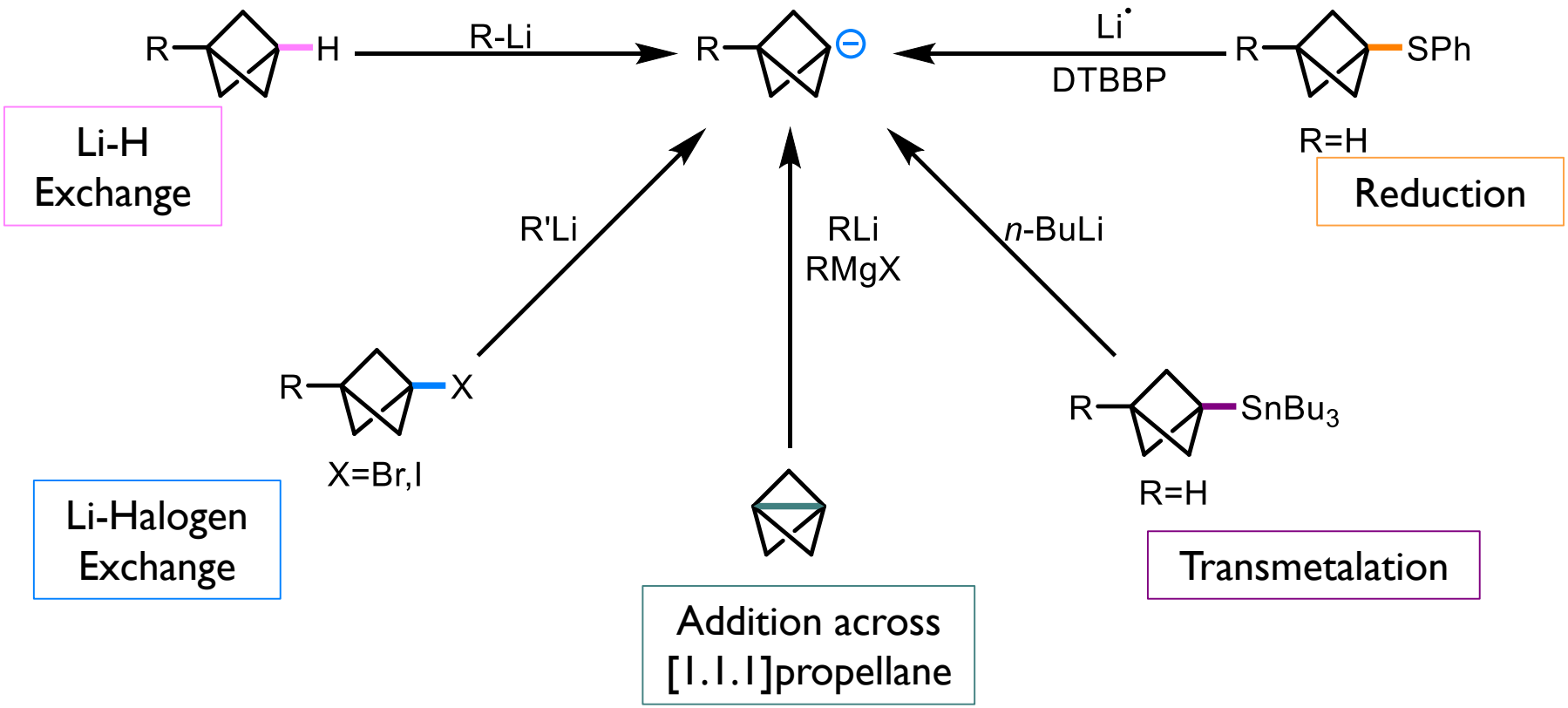
- Short interbridgehead distance providesa strong 1-3 nonbonded interaction between the two high s character hybrids on carbon. This has been proposed to be main contributor of strain energy.

Substituent	Calculated C(1)-C(3) distance (Å)
F	1.826
Cl	1.836
OH	1.849
H	1.872
CH_3	1.878
SiH_3	1.890

This strain energy is mitigated by EWG substituents.

J. AM. CHEM. SOC. 1994, 116, 11990; J. AM CHEM. SOC. 1994, 116, 4653; CHEM REV 2000, 100, 169-234

GENERATION OF BICYCLO[1.1.1]PENTYL ANION

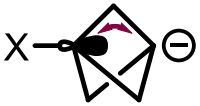


THE BICYCLO[1.1.1]PENTYL ANION

- The proton affinity for Bicyclo[1.1.1]pentlyl anion has been measured.

Anion	Proton Affinity
	411±3.5 kcal/mol
	408±3.0 kcal/mol
	407±3.0 kcal/mol

1.970 Å distance has been calculated



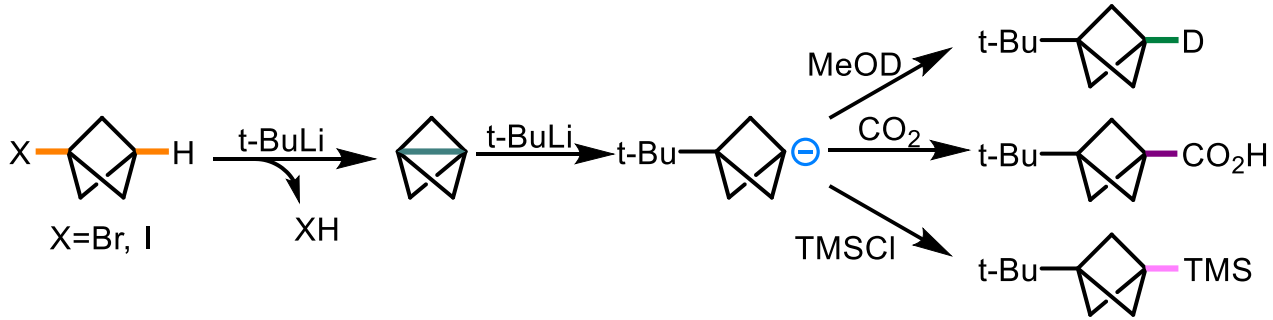
EWG stabilizes anion by allowing donation into antibonding orbital

- While high level of s character at C(1)/C(3) should lead to higher acidities and more stabilized anions- calculations show that transannular interaction between the back lobe of bridgehead carbon causes destabilization

J. AM. CHEM. SOC. 1989, 111, 1968; CHEM REV 2000, 100, 169-234

LITHIUM-HALOGEN /LITHIUM-H EXCHANGE AND TRANSMETALATION

Li-H Exchange-

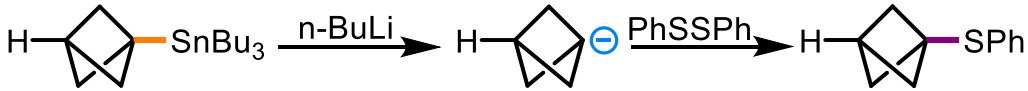


Li-Halogen Exchange-

R=Me, X= I
R=4-OMePh, X=I
R=Ph, X=Br

R=Me, 90%
R=4-OMePh, 93%
R=Ph, 94%

Transmetalation-

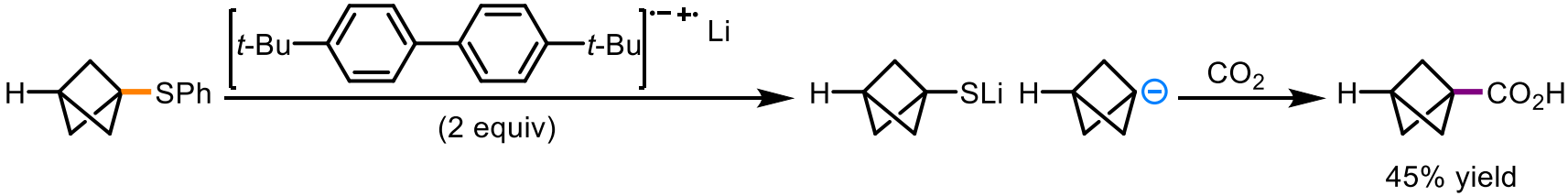


40% Yield

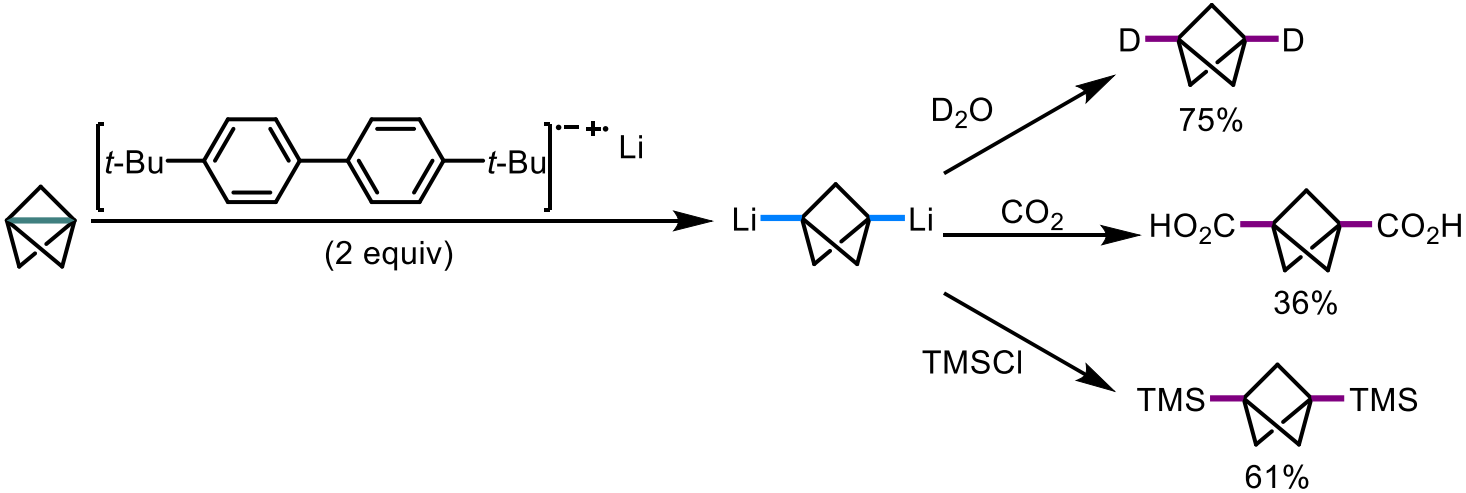
ORG. PREP & PROC. 1996, 28, 411-441; J. ORG. CHEM 1994, 59, 2986; J. ORG. CHEM 1993, 58 6505

REDUCTION TO FORM AN ANION

Reduction of SPh substituted Bicyclo[1.1.1]pentane to form an anion-



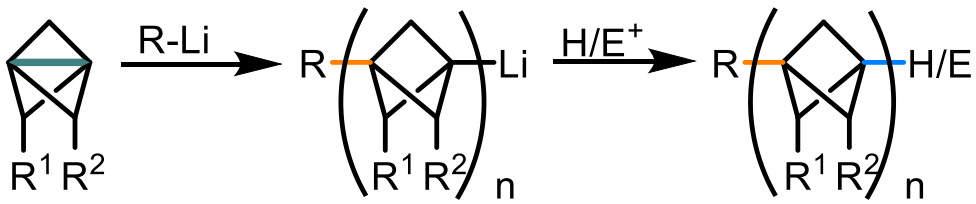
Reduction of [1.1.1]propellane to form a dianion-



ORG. PREP & PROC. 1996, 28, 411-441; CHEM REV 2000, 100, 169-234

[1.1.1] PROPELLANE REACTIVITY TO FORM CARBANIONS

- Michl (1988)- Formation of the carbanion from [1.1.1]propellane using lithium reagents causes oligmerization/polymerization



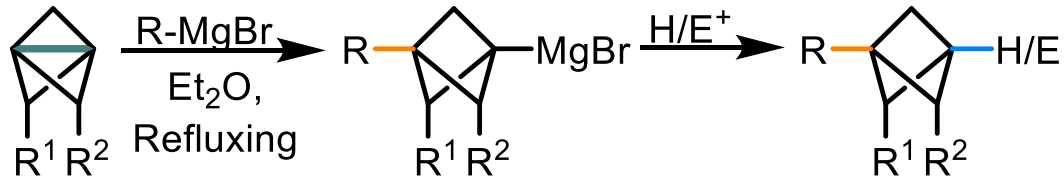
R^1, R^2	R-Li	H/E	Yield
H,H	*t*-Bu	H	78%
H,H	*n*-Bu	CO_2	60%
H, H	Ph	TMSCl	92%
H, $(CH_2)_4CH_3$	*t*-Bu	H	Polymerizes

In the presence of n-BuLi [1.1.1]propellanes will oligomerize to form [n]Staffanes.

"THE CHEMISTRY OF THE CYCLOPROPYL GROUP." VOLUME 2. COPYRIGHT 1995 JOHN WILEY & SONS, LTD.; CHEM REV 2000, 1000, 169-234; J. AM. CHEM. SOC. 1988, 110, 5225

FUNCTIONALIZATION OF [1.1.1]PROPELLANES USING GRIGNARD'S

- Wiberg (1994)- Addition of a Gringard Reagent across bridgehead bond leads to no oligermization/polymerization.



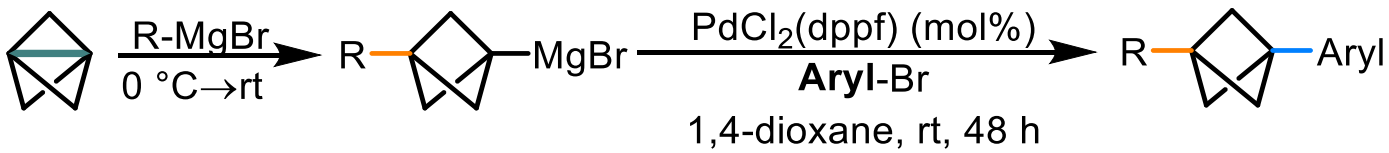
R^1, R^2	R-MgBr	H	Yield
$-(CH_2)_3-$	Et	H	21%
$-(CH_2)_3-$	i-Pr	H	46%
$-(CH_2)_3-$	t-Bu	H	32%
$-(CH_2)_3-$	Ph	H	67%
H, H	C_6H_5	CO_2	6%
H, H	MeC_6H_5	CO_2	18%

Grignard reagents do not oligomerize/polymerize [1.1.1]propellanes, they require harsh conditions and give poor yields of the bicyclo[1.1.1]pentanes.

"THE CHEMISTRY OF THE CYCLOPROPYL GROUP." VOLUME 2. COPYRIGHT 1995 JOHN WILEY & SONS, LTD.; CHEM REV 2000, 1000, 169-234; J. AM. CHEM. SOC. 1994,112, 2194

KUMADA COUPLING INTERMEDIATE

- Szeimies (1999)- The product of the addition of a Grignard Reagent was shown to be viable in a Kumada cross-coupling.

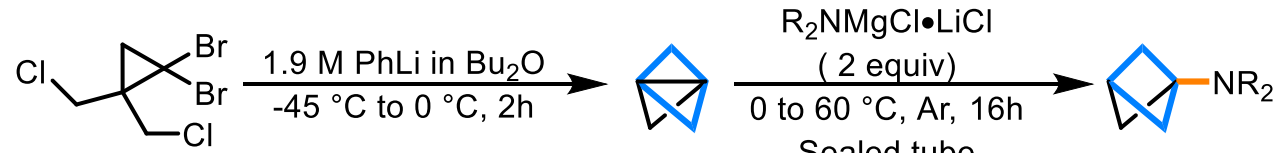


R-Mg	Aryl Bromide	$PdCl_2$(dppf) (mol%)	Yield
t-Bu	Ph	1.3%	88%(37%)
t-Bu	2-Naphthyl	1.3%	93%(42%)
t-Bu	4-ClC_6H_4	1.3%	90%(40%)
t-Bu	4-$MeOC_6H_4$	2.8%	97%(37%)
Cy	4-ClC_6H_4	2.6%	89%(38%)
i-Pr	4-$TMSC_6H_4$	3.0%	91%(36%)
Ph	4-ClC_6H_4	2.2%	87%(39%)

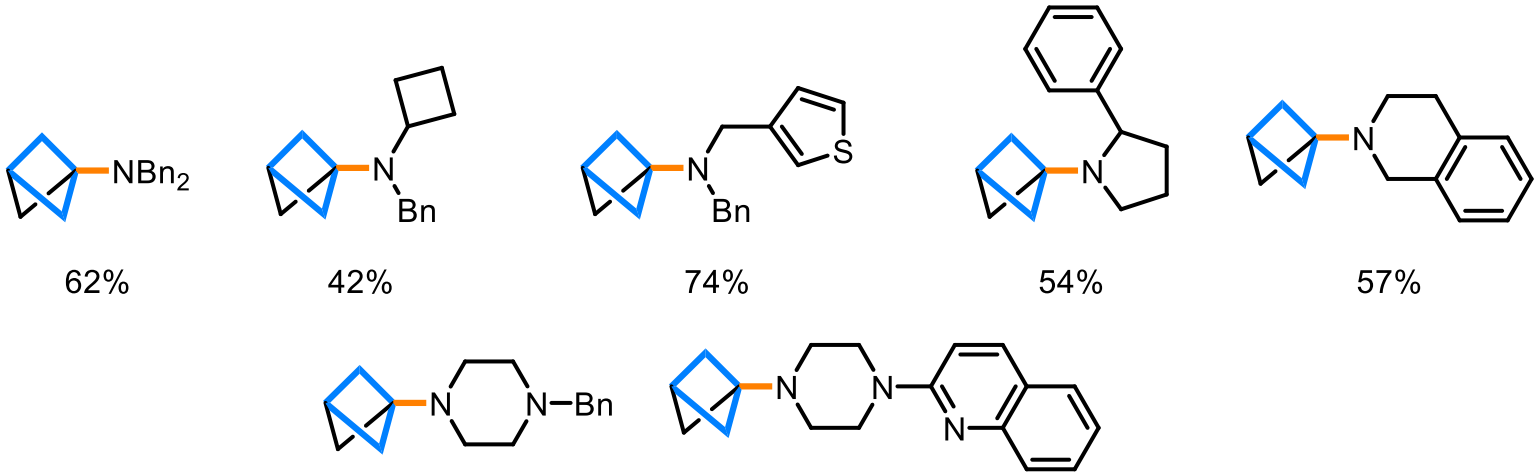
EUR. J. ORG. CHEM. 1999, 2079-2085

AMINE FUNCTIONALIZATION

- Baran (2016)- Developed a method for adding amines across the bridgehead bond by making the Davies type amine nucleophiles.



$8.5 / 1 g
Millipore-Sigma

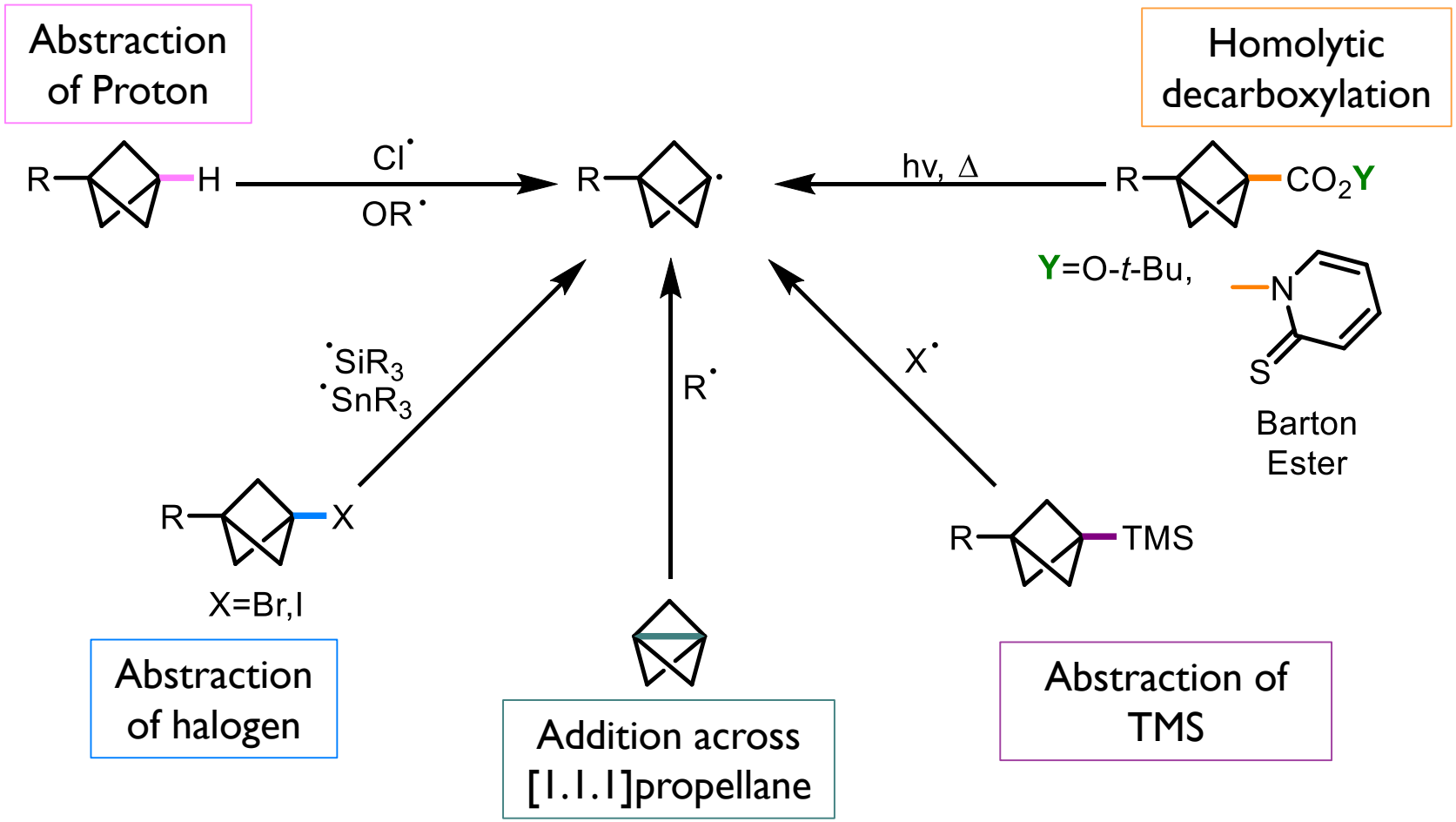


62% 42% 74% 54% 57%

67%

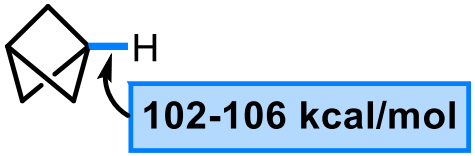
"propellerized" quipazine 81%

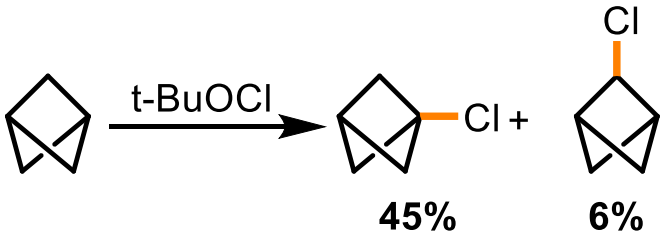
GENERATION OF BICYCLO[1.1.1]PENTYL RADICAL



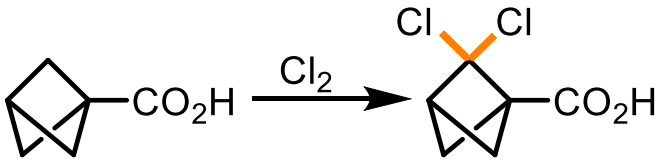
ABSTRACTION OF HYDROGEN

- Wiberg (1966)-Abstraction of proton is complicated by fact that both bridgehead and exocyclic hydrogen can be abstracted





Due to s character in the adjacent carbon the radical can donate into the σ* which leads to stabilization.

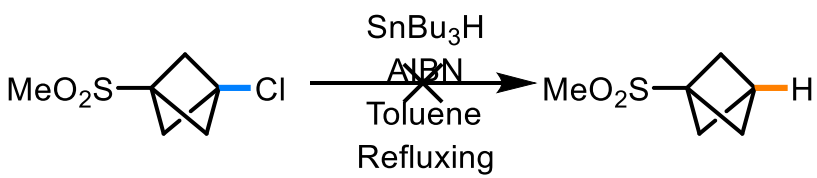


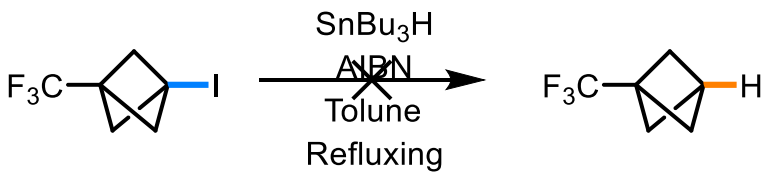
Selectivity maybe due to EWG substituent destabilizing positive charge on the bridgehead carbon in the transition state

J. AM. CHEM. SOC. 1966, 88, 4437; J. ORG. CHEM 1970, 35, 369

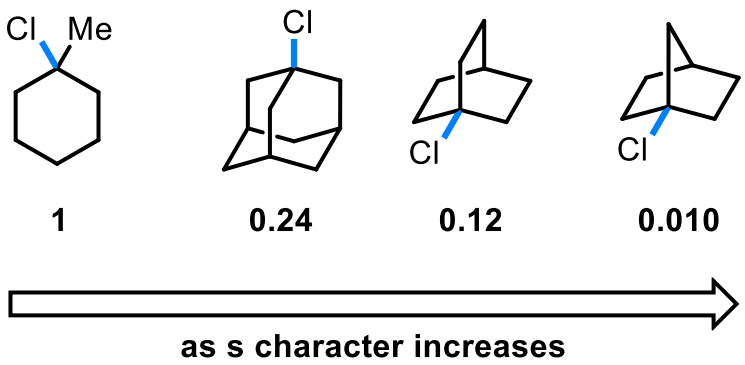
ABSTRACTION OF HALOGEN AND ABSTRACTION OF TMS GROUP

Abstraction of Halogen-



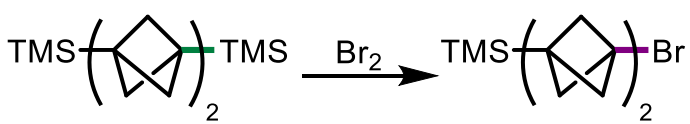


Examples that are successful are shown in [n]staffanes



Relative rate of chlorine abstraction

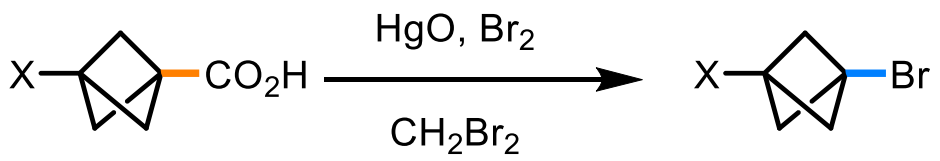
Abstraction of TMS Group-



Limited examples but using [n]staffanes this has been successful

HOMOLYTIC DECARBOXYLATION

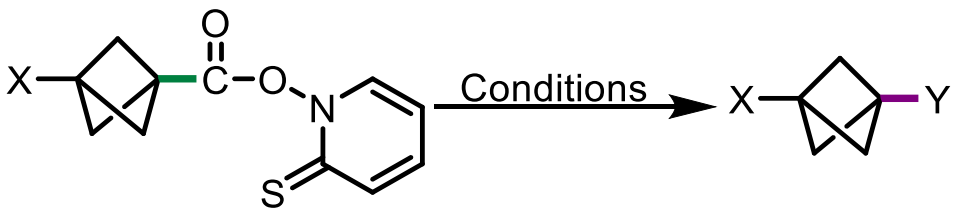
Hunsdiecker Decarboxylation-



X=CO_2Me
X=CO_2H

X=CO_2Me, 68%
X=Br, 68%

Barton Ester Decarboxylation-

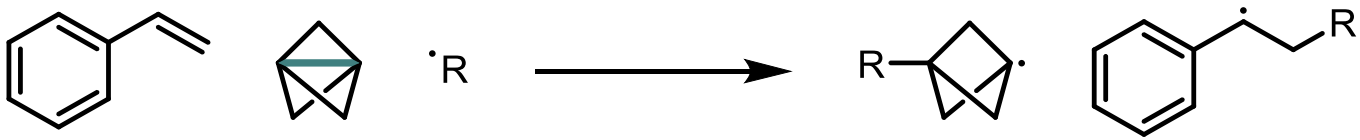


X,Y	Conditions	Yield
H, Cl	$CFCl_3$, hv, 1.5 h, rt	87%
CH_3, Br	$CF_3CHBrCl$, hv, 1 hr, rt	81%
F, Br	$CF_3CHBrCl$, hv, 40 min, rt	83
I, Br	CF_3CH_2I, hv, 1 hr, rt	0%

ORG. PREP & PROC. 1996, 28, 411-441; CHEM REV 2000, 1000, 169-234

[1.1.1] PROPELLANE REACTIVITY TO FORM RADICAL

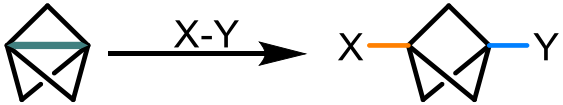
- Radicals add over [1.1.1]propellane very rapidly.



	Rate Constant [$M^{-1}s^{-1}$] at Rt	
Radical	[1.1.1]Propellane	Styrene
t-BuO•	2.8×10^6	0.91×10^6
PhS•	6.2×10^7	2.2×10^7
Et_3Si•	6.0×10^8	Complex Mixture
p-$MeOC_6H_4COO$•	1.0×10^7	5.5×10^6

REACTION OF PROPELLANES[1.1.1]

- Radicals add over [1.1.1]propellane to give functionalized bicyclo[1.1.1]pentanes



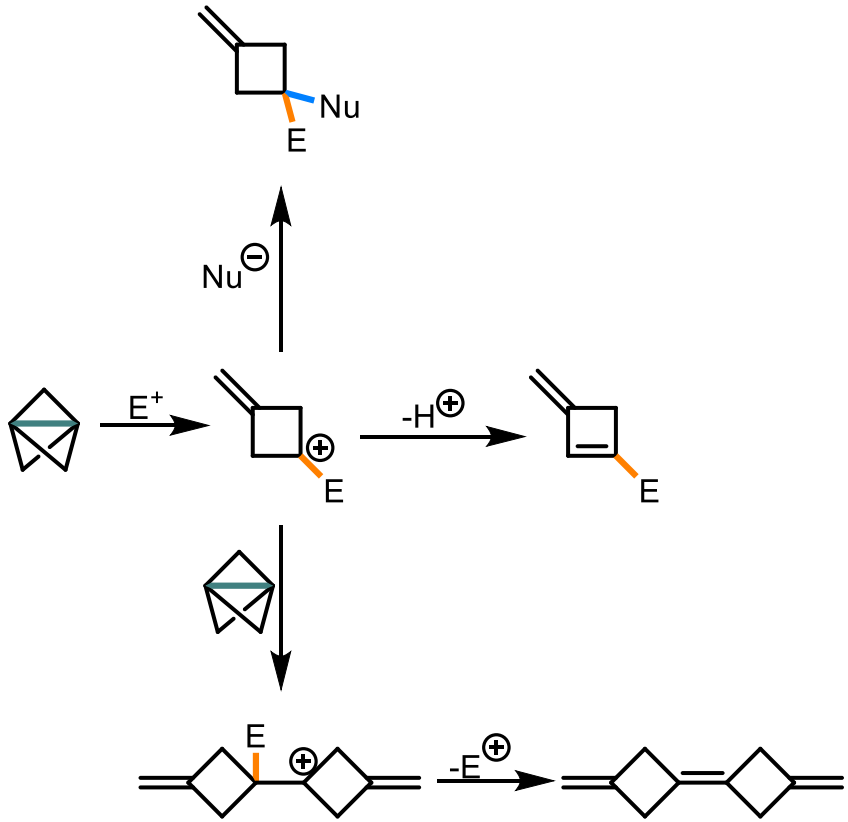
X-Y	Conditions	Yield
I-I	Et_2O/hexane, rt	100%
Br-Br	Et_2O/pentane, hv, -25°C	36%[a]
Me-I	Et_2O, hv, 30 min, 0°C	68%
CF_3-I	Et_2O, 3 days, rt	75%
Ph_3Sn-H, $(t\text{-BuO})_2$	Et_2O, hv, 1 hr, rt	68%
$(PhS)_2$	Et_2O/hexane, hv, 4 hrs	45%
PhCHO, $(t\text{-BuO})_2$	hv, 15 min, rt	52%
HCOOMe, $(t\text{-BuO})_2$	hv, 15 min, rt	45%

[a]From Propellane Precursor

ORG. PREP & PROC. 1996, 28, 411-441

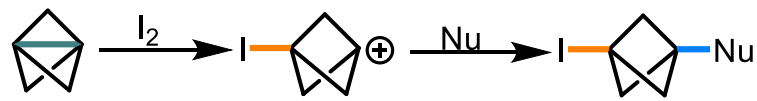
[1.1.1]PROPELLANE TO FORM CARBOCATIONS

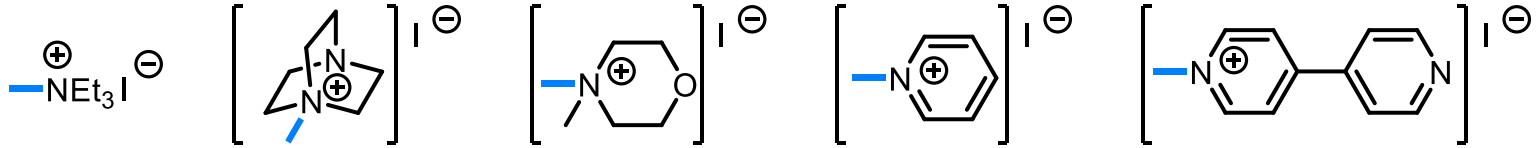
- Typically formations of carbocations will cause ring rearrangement.



PROPELLANE[1.1.1] REACTIVITY TO FORM CARBOCATIONS

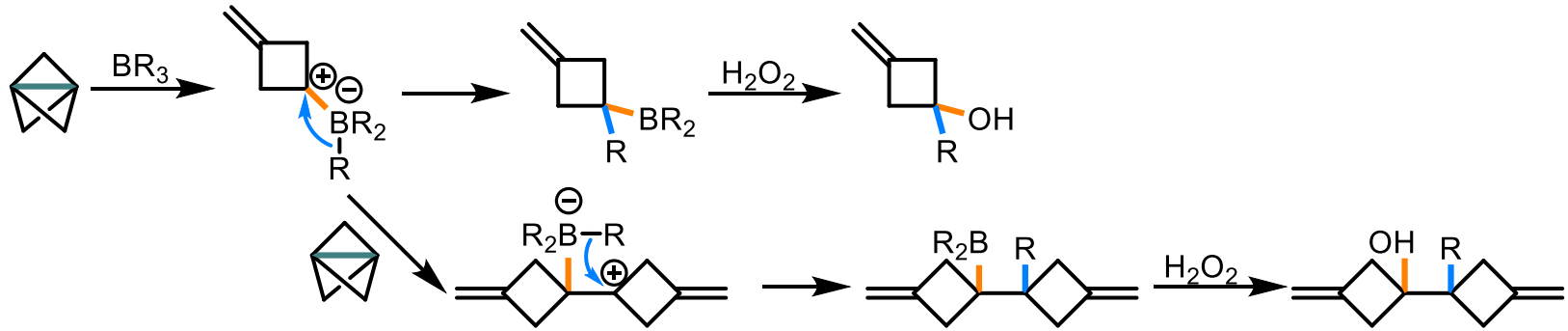
- If stabilized carbocation is formed will get addition across bridgehead bond





63% 31% 76% 67% 73%

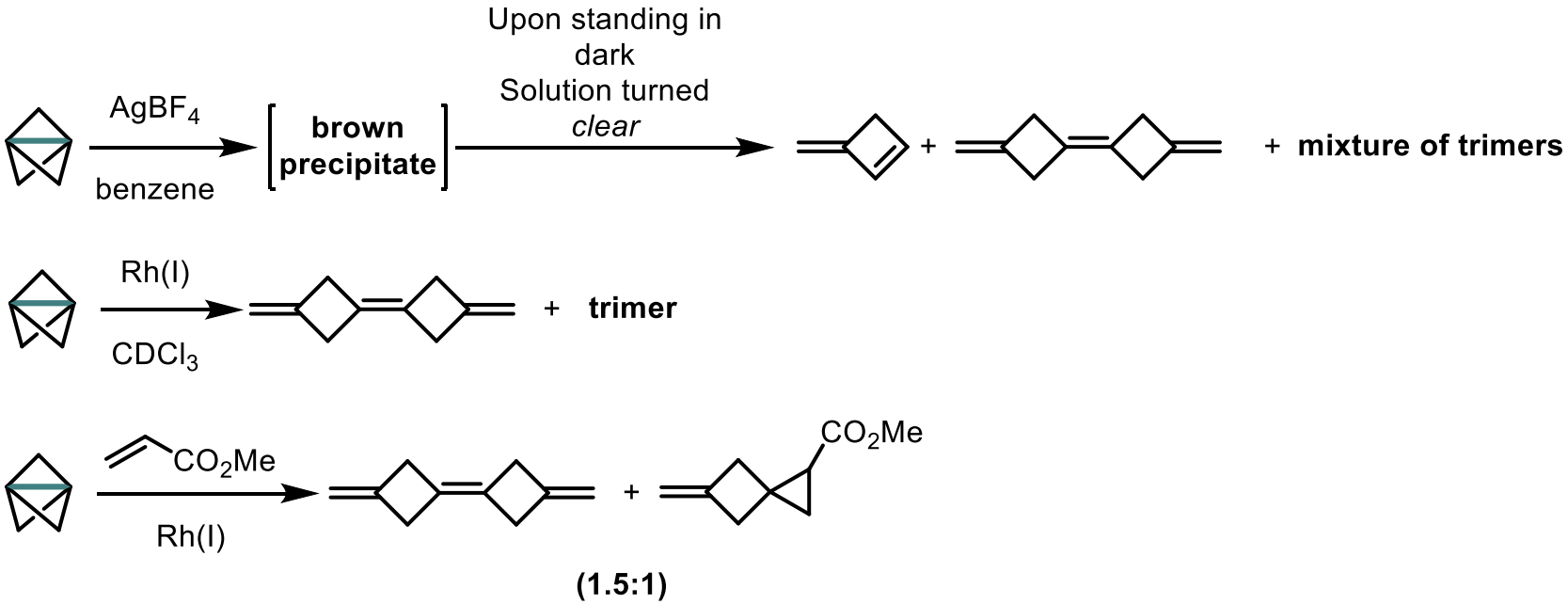
- Rearrangement can be used to make interesting structures



J. AM. CHEM. SOC. 1994, 116, 11990; J. ORG. CHEM. USSR 1999, 26, 2002.

TRANSITION METAL INSERTION IN [1.1.1]PROPELLANES

- Wiberg (1990)- Showed that in the presence of metals that the [1.1.1]propellanes ring opened and rearranged.

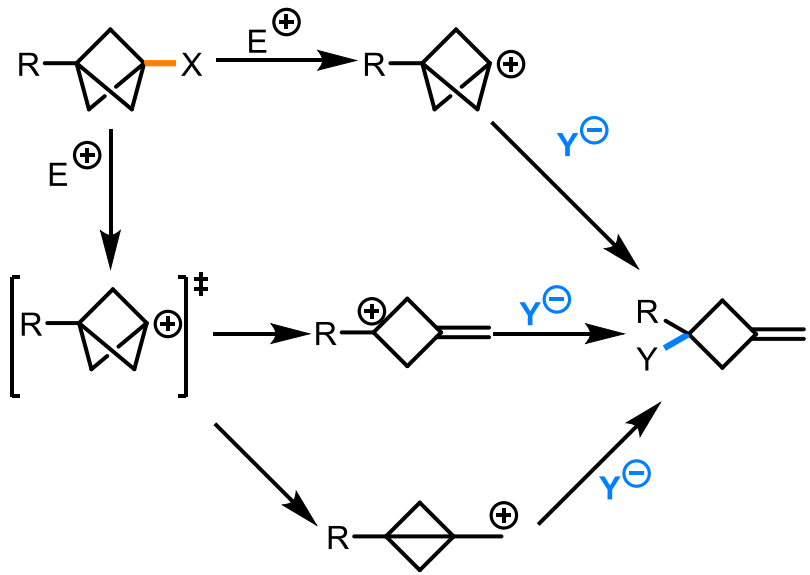


- In the presence of Pd(II) showed similar products as with rhodium
- In the presence of Pt(0), Pt(II) and Ir(I) gave methylecylcobutene and dimer

J. AM. CHEM SOC. 1990, 112, 2194-2216

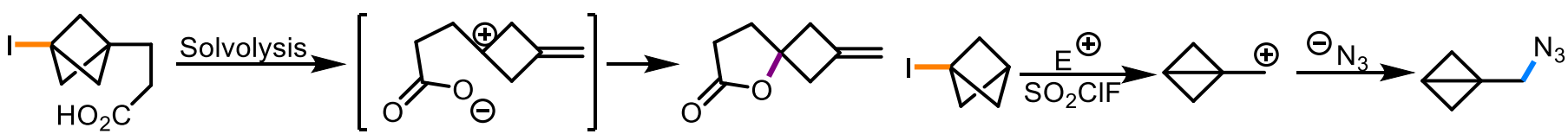
GENERATION OF CARBOCATION FROM BICYCLO[1.1.1]PENTANE

Possible Intermediates in Carbocation formation-



- Evidence that this intermediate rearranges to either more stabilized bicyclo[1.1.0]butyl-1-ylcarbinyl cation or the 3-methylenecyclobutyl cation

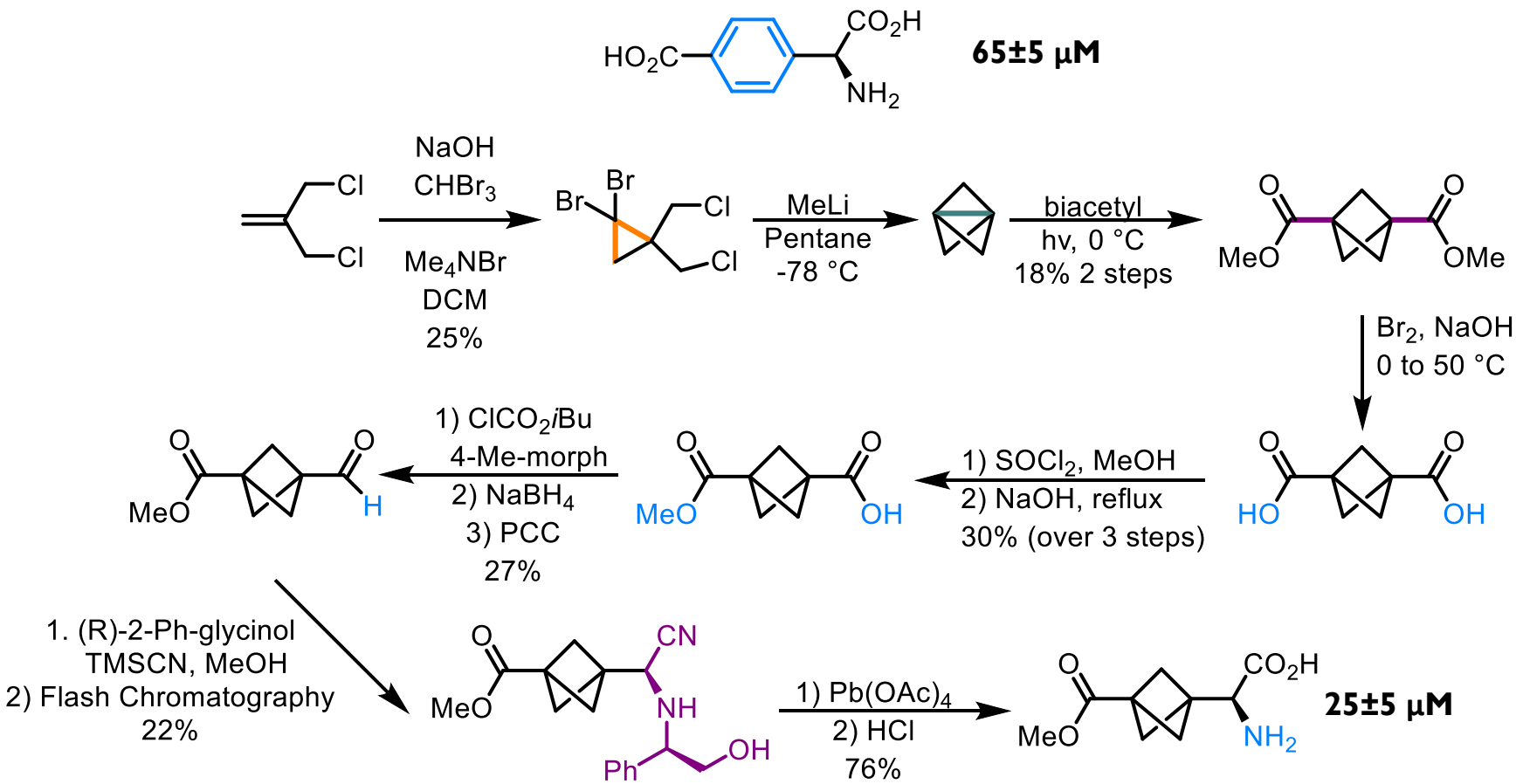
Solvolysis Reactions-



CHEM REV 2000, 100, 169-234; J. AM. CHEM. SOC. 1994, 116, 11990; J. ORG. CHEM. 1991, 56, 307

INITIAL USE AS AN ISOSTERE

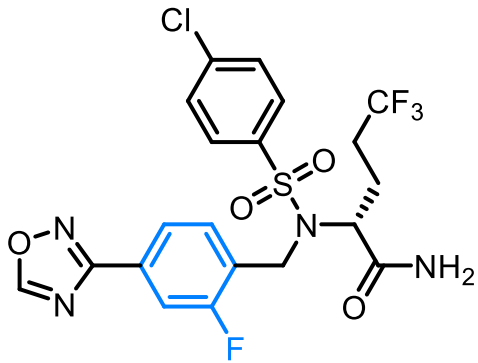
Pellicciari (1998)- Studying agonists of the metabolic glutamate receptor.



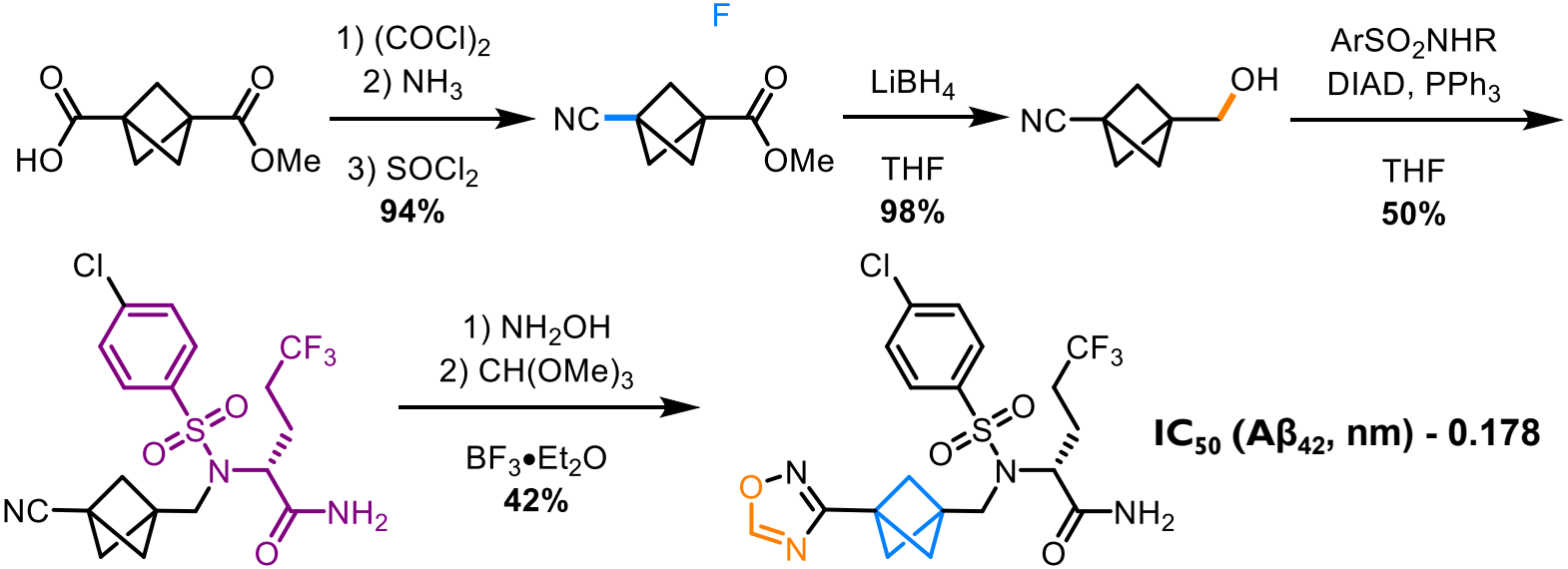
BIOORG. MED. CHEM. LETT. 1998, 8, 1569; ORG. PROC. RES. DEV. 2013, 17, 1503

Γ-secretase Inhibitor

Stepan (2012)-Replaced Phenyl group in known γ-secretase inhibitor with bicyclo[1.1.1]pentane.



IC_{50} ($A\beta_{42}$, nm) - 0.225



IC_{50} ($A\beta_{42}$, nm) - 0.178

CONCLUSIONS/FUTURE DIRECTIONS

- [1.1.1]propellanes and bicyclo[1.1.1]pentanes have interesting structures and properties
- Example of why researching "esoteric" topics can be important
- Bicyclo[1.1.1]pentanes and [n]Staffanes (oligermized) have found important uses in materials and pharmaceutical applications
- Research still needs to be done into synthesizing functionalized bicyclo[1.1.1]pentanes.
- Since 2016 over >100 patents filed on bicyclo[1.1.1]pentanes but yet to have drug on market with this moiety

REVIEWS

- Structure/Reactivity- Chem Rev 2000, 100, 169-234; Org. Proc. Res. Dev. 2013, 17, 1503
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