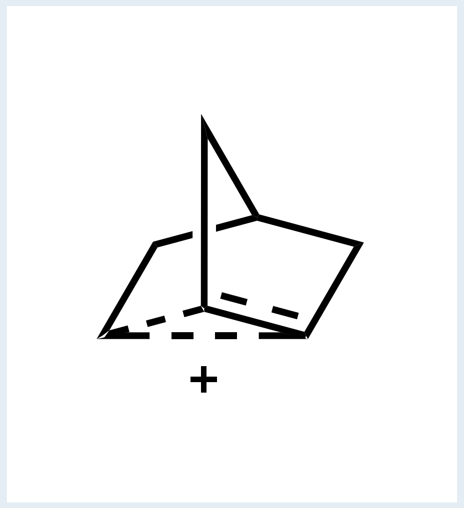
Non-Classical Carbocations



Nate Dow

Group Meeting Literature Talk

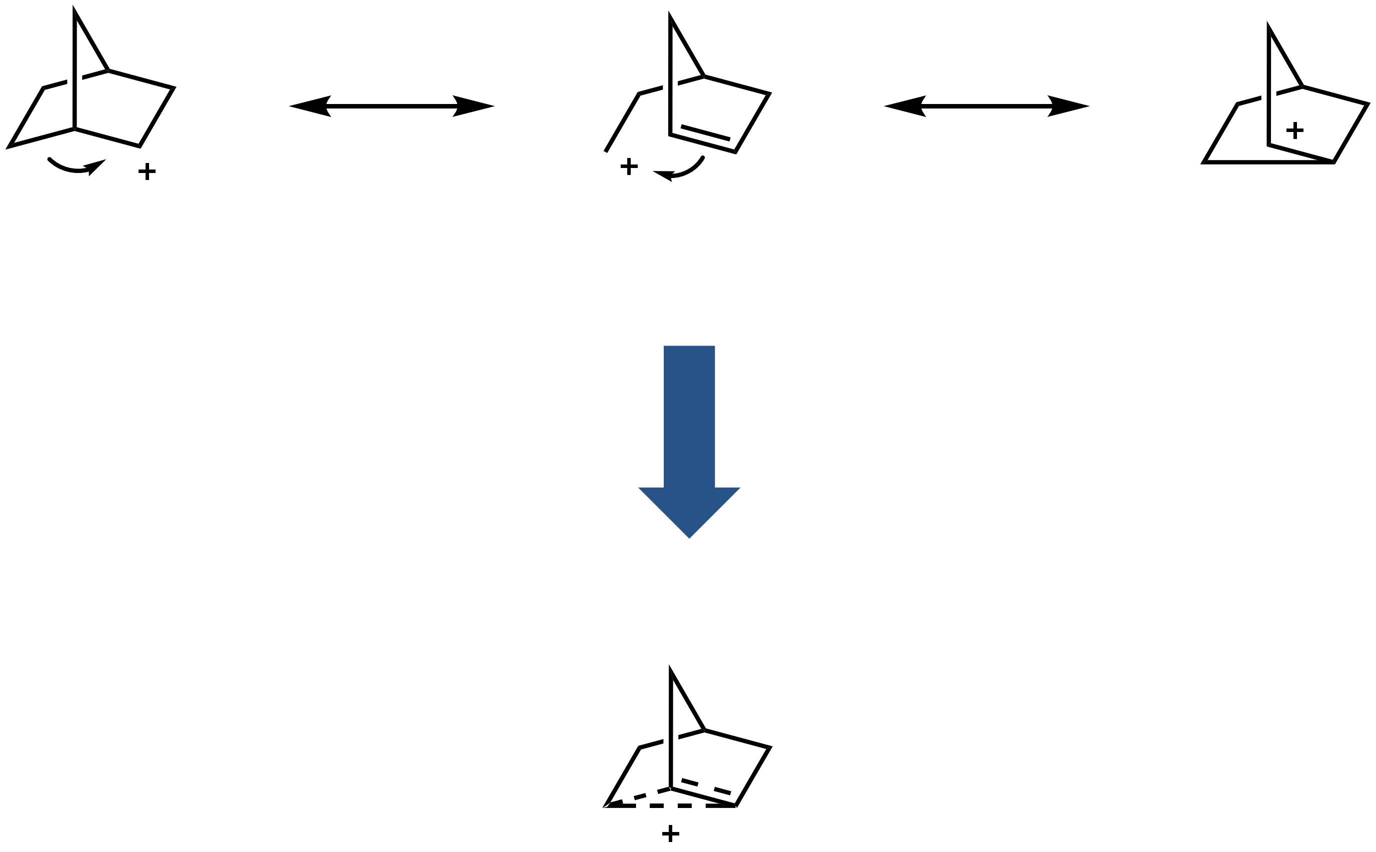
June 30th, 2021

Outline

- *Fundamentals of non-classical carbocations: bonding, reactivity and common examples*
- *How it all began: the 2-norbornyl cation debate*
- *Non-classical reactivity in action: biosynthesis and reactions of complex molecules*
- *Modern developments in non-classical carbocation chemistry*
  - *enantioselective transformations (List/Schreiner)*
  - *intermolecular non-classical interactions in C–H activation (Nelson)*

Non-classical carbocations: the basics

***non-classical carbocation**: cations that receive stabilization via charge delocalization into adjacent C–H or C–C σ-bonds*

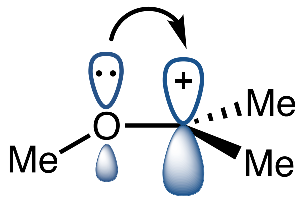


P. D. Bartlett. *Nonclassical Ions,* W.A. Benjamin, New York, 1965.

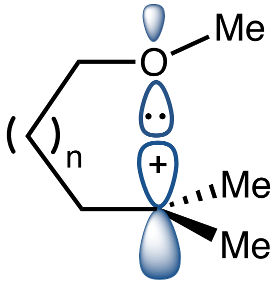
Non-classical carbocations: the basics

commonly encountered forms of carbocation stabilization

lone pair stabilization

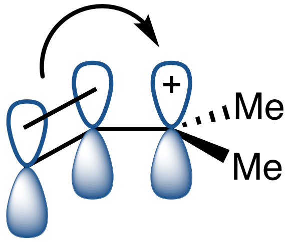


traditional
resonance



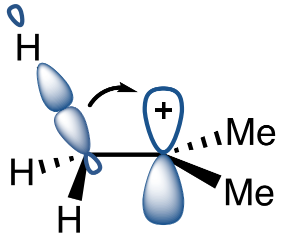
anchimeric
assistance

π-bond stabilization

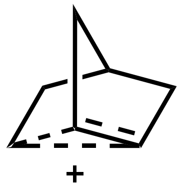


allylic + benzylic
resonance

σ-bond stabilization



C–H + C–C
hyperconjugation



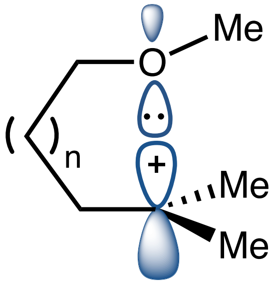
non-classical
stabilization

P. D. Bartlett. *Nonclassical Ions,* W.A. Benjamin, New York, 1965.

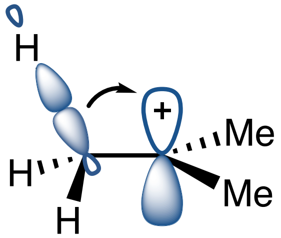
Non-classical carbocations: the basics

- *applies specifically to C–C and C–H σ-bond donation*

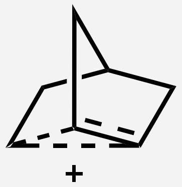
- *full charge delocalization across participating filled/empty orbitals;*
  all atoms involved bear charge and electrophilic character



anchimeric assistance



C–H + C–C hyperconjugation



non-classical stabilization

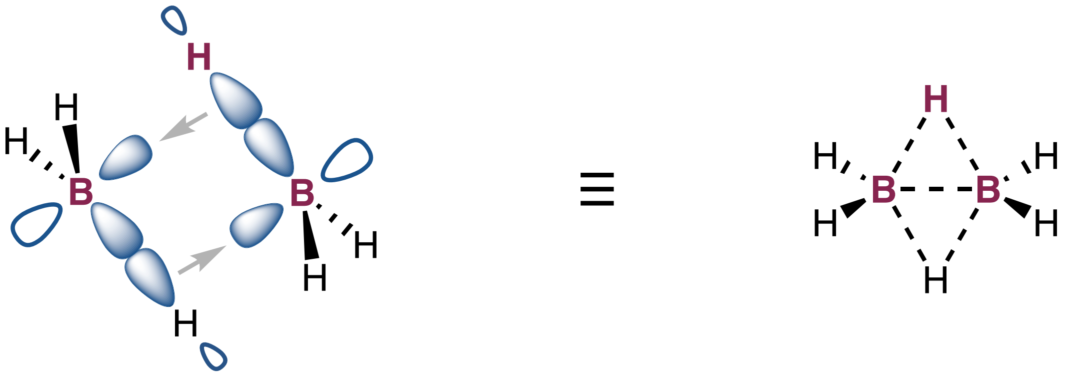
single sites of reactivity

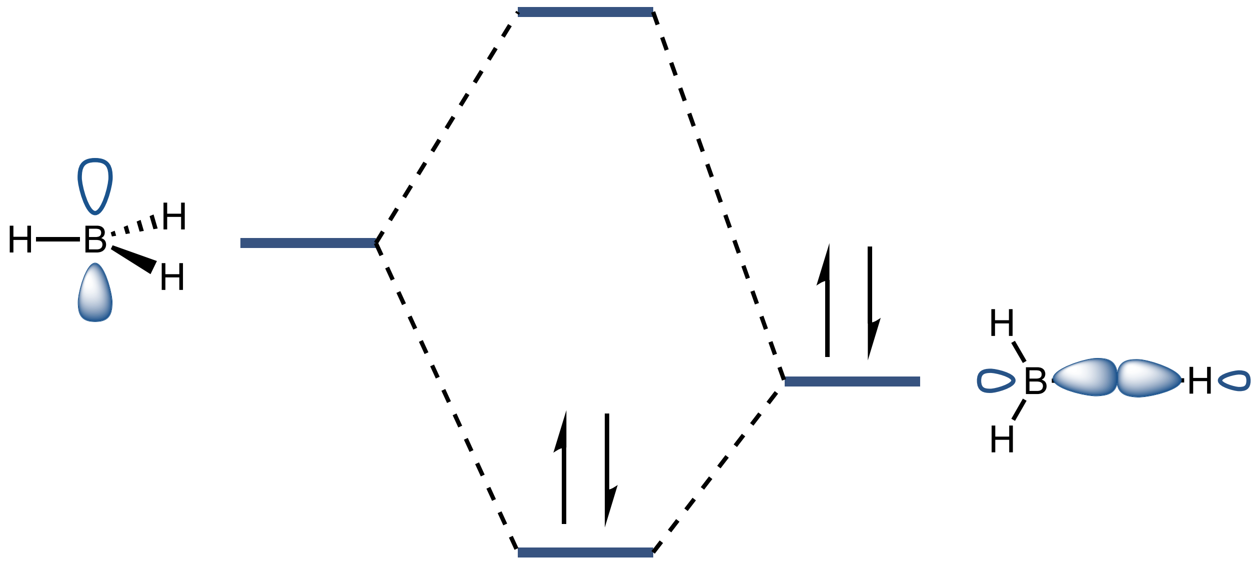
multiple reactive sites

P. D. Bartlett. *Nonclassical Ions,* W.A. Benjamin, New York, 1965.

The 3-center, 2-electron bond

diborane: prototypical example of 3-center, 2-electron bonding





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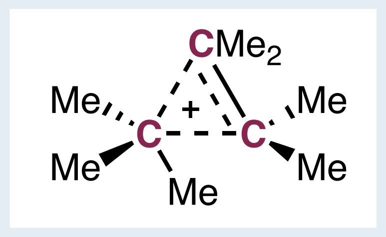

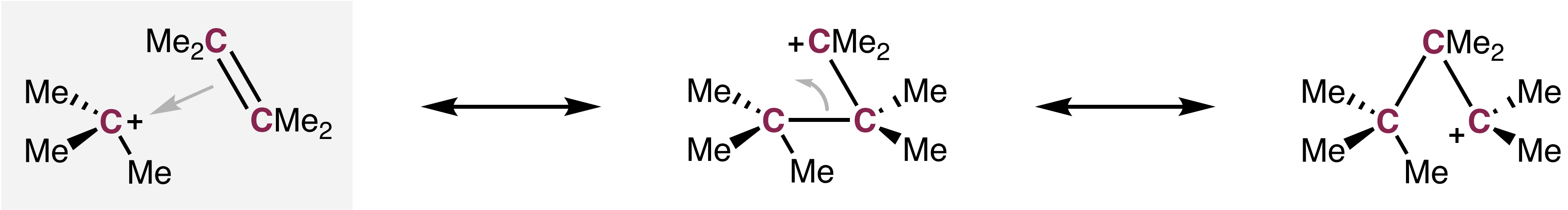

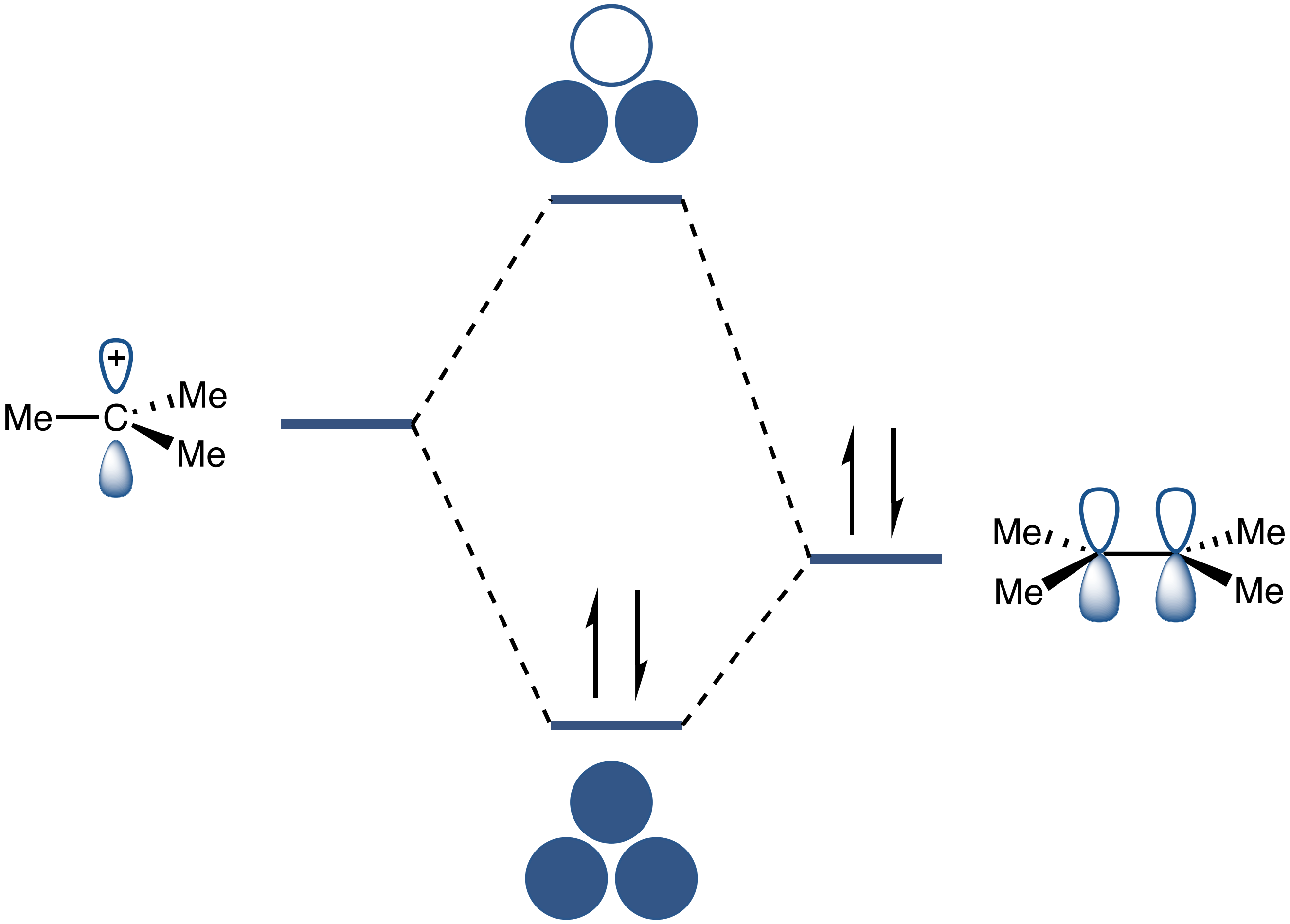

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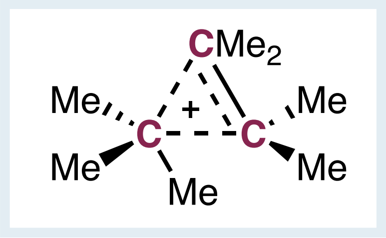

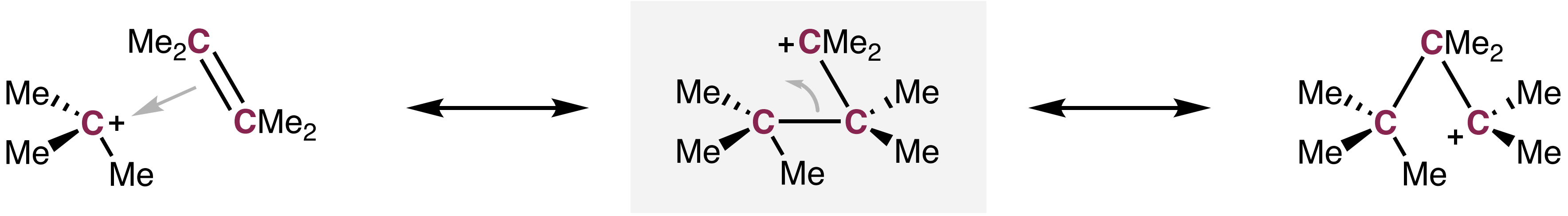

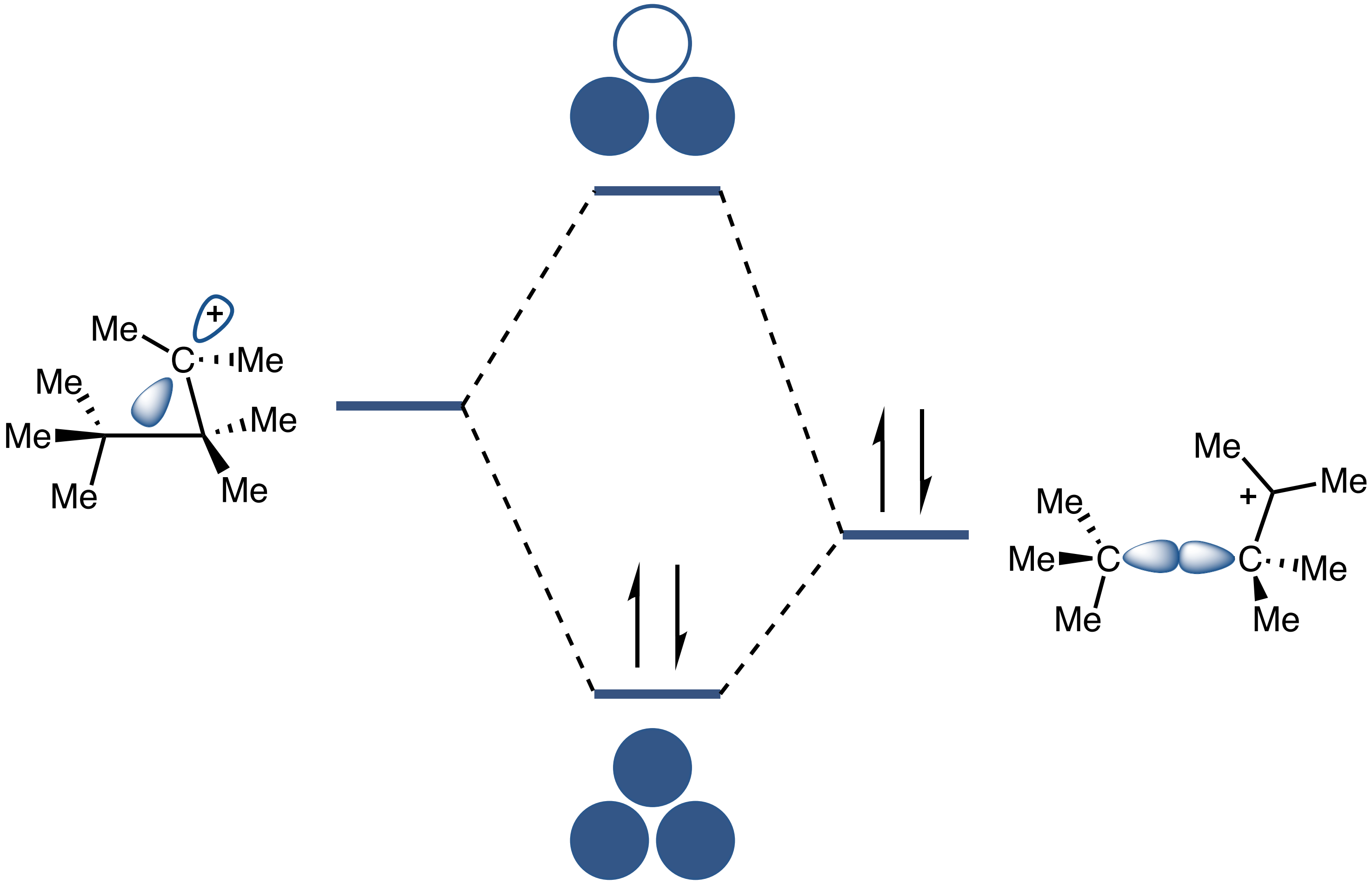

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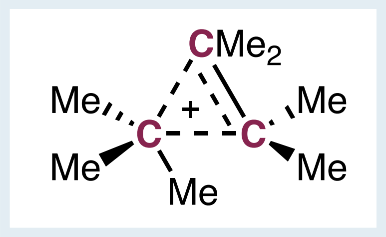
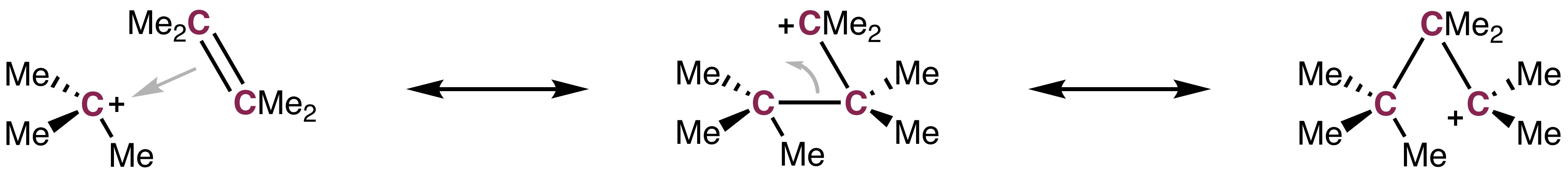
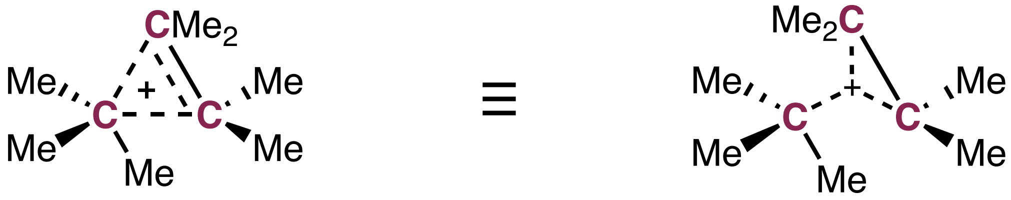




- *best described as 3-center, 2-electron bonding in all resonance forms*
- *all participating C atoms are pentavalent AND electron-deficient*

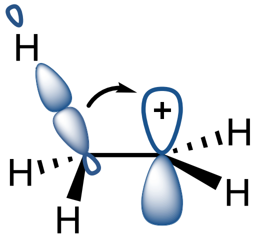


P. D. Bartlett. *Nonclassical Ions,* W.A. Benjamin, New York, 1965.

Carbenium vs. carbonium ions for simple systems

3-center, 2-electron bonding description applies to numerous cases that ***appear to be*** *carbenium ions*

carbenium: trivalent C-centered cation ***vs.*** *carbonium: pentavalent C-centered cation*



case study: ethyl cation

expectation: hyperconjugation moderately stabilizes carbenium ion

Ausloos, P.; Rebbert, R. E.; Sieck, L. W.; Tiernan, T. O. *J. Am. Chem. Soc.* **1972**, *94*, 8939.

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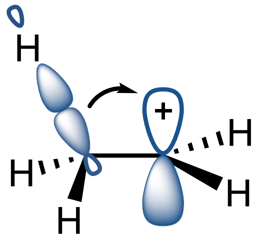

$C_2H_3D_2^+$	+	Alk–D	$\longrightarrow$	$C_2H_3D_3$
$C_2H_2D_3^+$		Alk–H		*various isomers*
ethyl cation precursor		*H^-/D^- donor*		
CD_3CH_2I		*i*-C_4H_{10}		*if carbenium predominates, direct H^-/D^- transfer should provide one isomer*
CH_3CD_2I		*i*-C_4D_{10}		
CD_3CH_2Br		c-C_5H_{10}		$H_3C{-}CD_3$

Ausloos, P.; Rebbert, R. E.; Sieck, L. W.; Tiernan, T. O. *J. Am. Chem. Soc.* **1972**, *94*, 8939.

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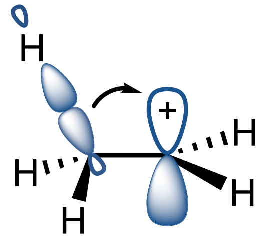

$$\left.\begin{matrix} C_2H_3D_2^+ \\ C_2H_2D_3^+ \end{matrix}\right. + \left.\begin{matrix} \text{Alk–D} \\ \text{Alk–H} \end{matrix}\right. \longrightarrow \begin{matrix} C_2H_3D_3 \\ \textit{various isomers} \end{matrix}$$

ethyl cation precursor	*H^-/D^- donor*	*% CD_2HCDH_2*	*% CD_3CH_3*
CD_3CH_2I	*i*-C_4H_{10}	89%	11%
CH_3CD_2I	*i*-C_4D_{10}	90%	10%
CD_3CH_2Br	c-C_5H_{10}	90%	10%
$CD_3CH_2CD_3$ (via electron-beam radiolysis)	c-C_4H_8	90%	10%

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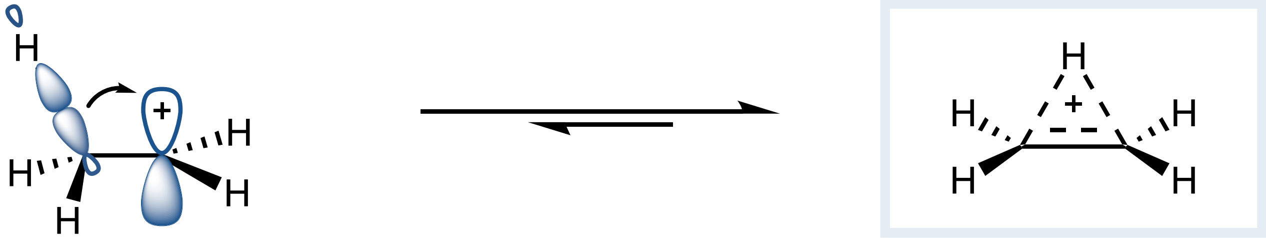
isotopic scrambling consistent with hypervalence, delocalized intermediate



low barrier carbenium/carbonium interconversion

ethyl cation precursor	*H^-/D^- donor*	*% CD_2HCDH_2*	*% CD_3CH_3*
CD_3CH_2I	*i*-C_4H_{10}	89%	11%
CH_3CD_2I	*i*-C_4D_{10}	90%	10%
CD_3CH_2Br	c-C_5H_{10}	90%	10%
$CD_3CH_2CD_3$ (via electron-beam radiolysis)	c-C_4H_8	90%	10%

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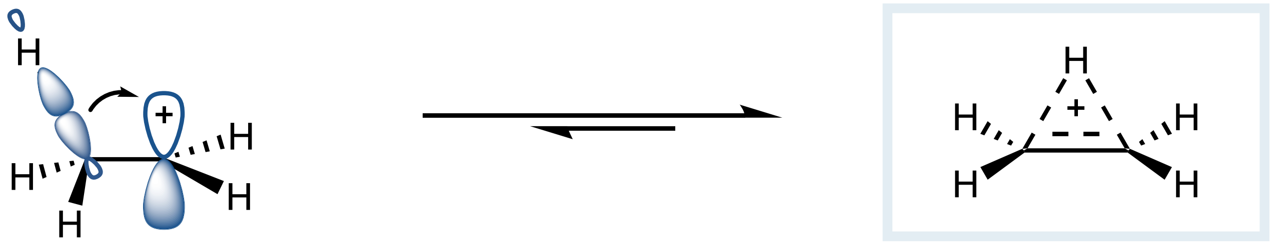

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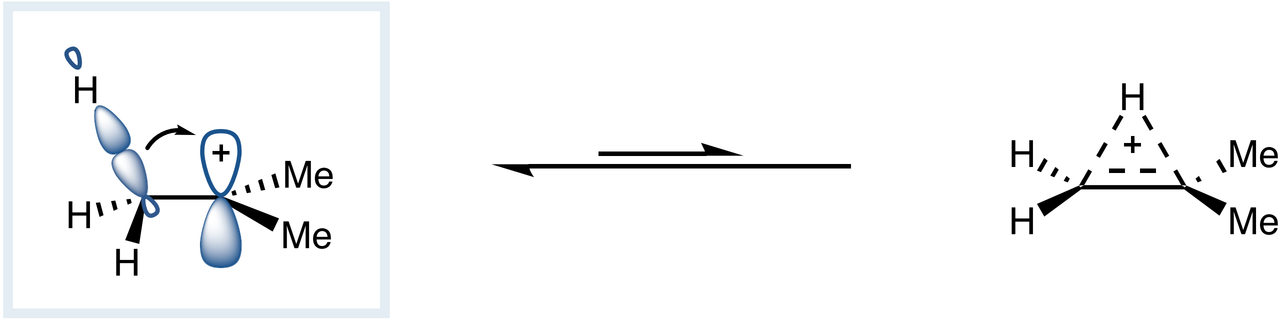

greater degree of substitution: higher interconversion barrier, carbenium favored

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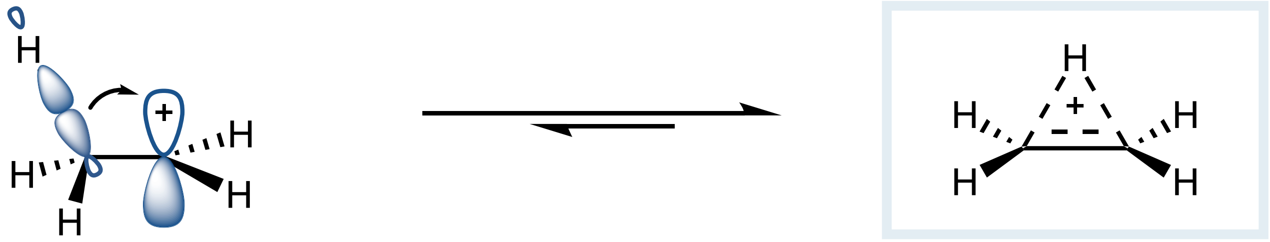
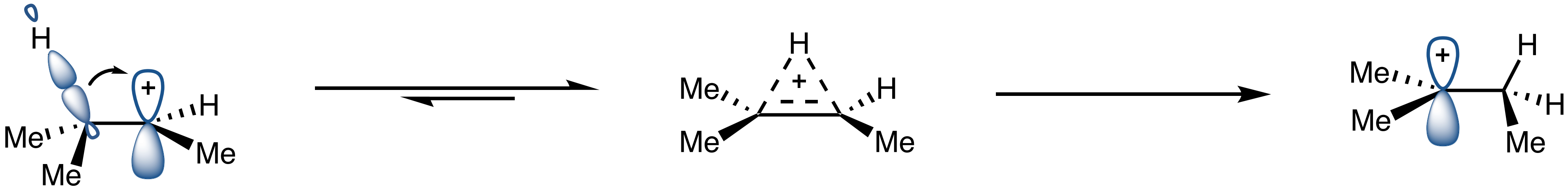


low barrier carbenium/carbonium interconversion

consistent with carbonium behavior observed in rearrangements and hydride shifts



2°, carbenium less stable

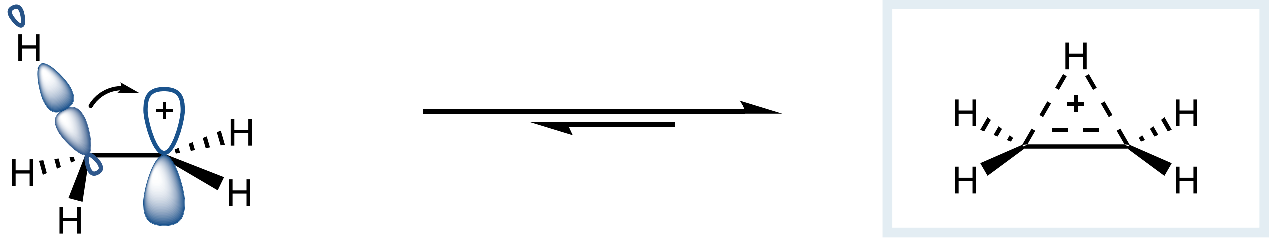
3°, thermodynamically favored

P. D. Bartlett. *Nonclassical Ions,* W.A. Benjamin, New York, 1965.

Carbenium vs. carbonium ions for simple systems

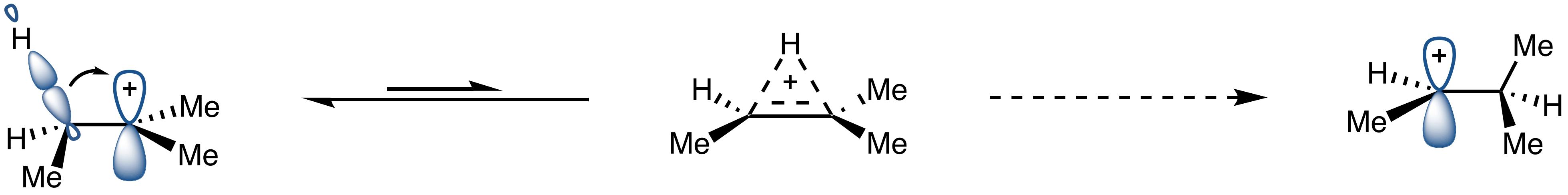
*3-center, 2-electron bonding description applies to numerous cases that **appear to be** carbenium ions*

isotopic scrambling consistent with hypervalence, delocalized intermediate



low barrier carbenium/carbonium interconversion

consistent with carbonium behavior observed in rearrangements and hydride shifts



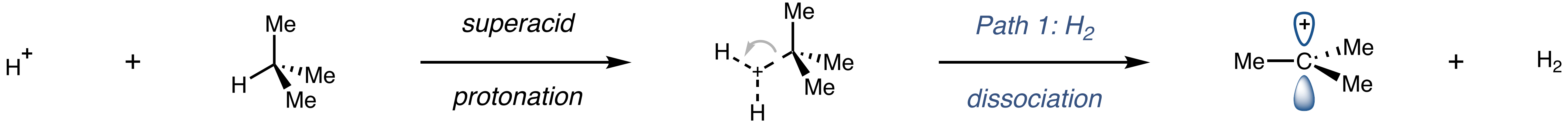
3°, carbenium already stable

2°, uphill rearrangement

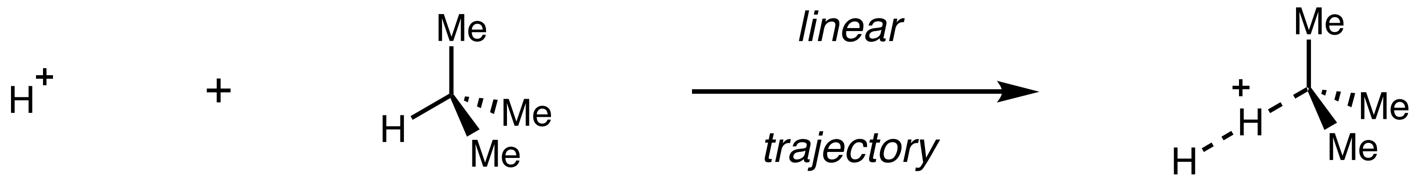
P. D. Bartlett. *Nonclassical Ions,* W.A. Benjamin, New York, 1965.

Carbonium ions via alkane protonation

Olah, Conroy, Lewis, Symons:



Hogeveen, Gaasbeek, Bickel:



- *no possibility to form methine-deuterated isobutane when using D-labeled acid (H–D gas in low [ ])*

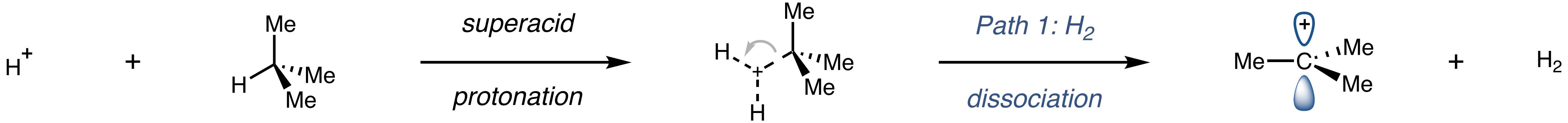
- *should not be capable of C–C bond protonation*

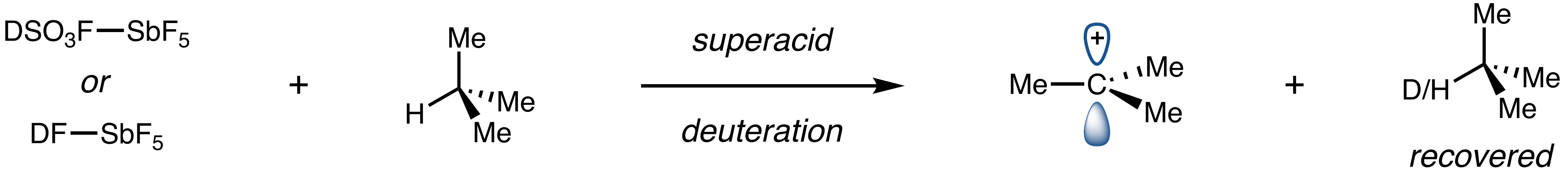
Hogeveen, H.; Gaasbeek, C. J.; Bickel, A. F. *Recl. Trav. Chim. Pays-Bas.* **1969**, *88*, 703.

Olah, G. A.; Halpern, Y.; Shen, J.; Mo, Y. K. *J. Am. Chem. Soc.* **1971**, *93*, 1251.

Carbonium ions via alkane protonation

Olah (1971):





- *D-incorporation only at methine of recovered isobutane, Me groups unlabeled*
- *tert-butyl carbocation stable under conditions, no evidence of olefin formation*

Olah, G. A.; Halpern, Y.; Shen, J.; Mo, Y. K. *J. Am. Chem. Soc.* **1971**, *93*, 1251.

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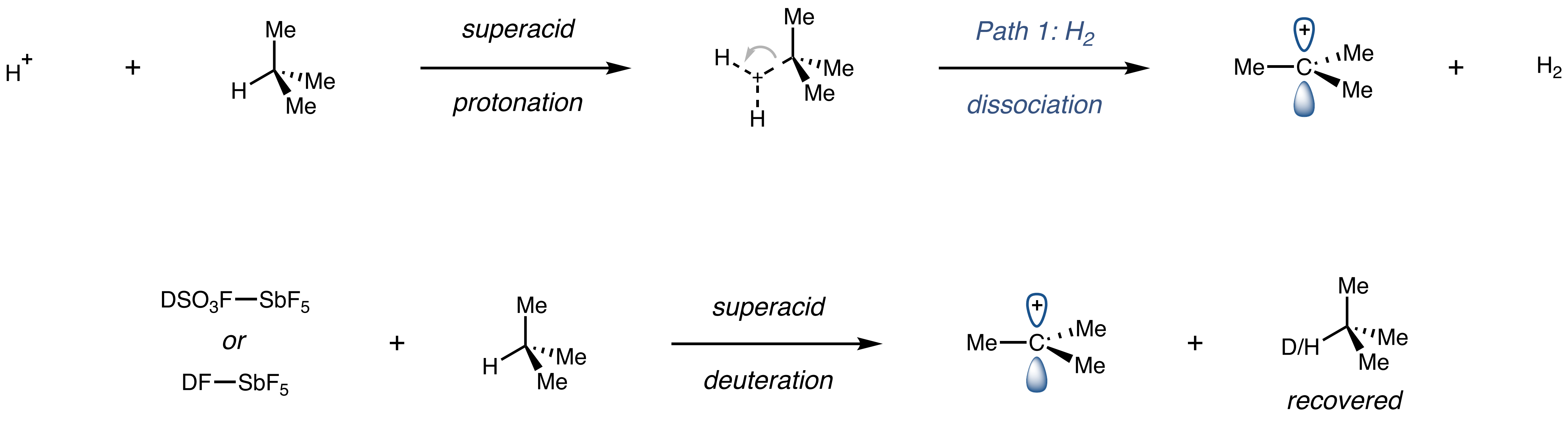

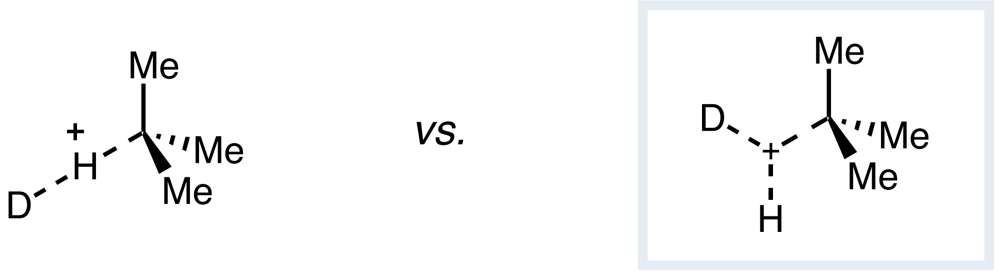

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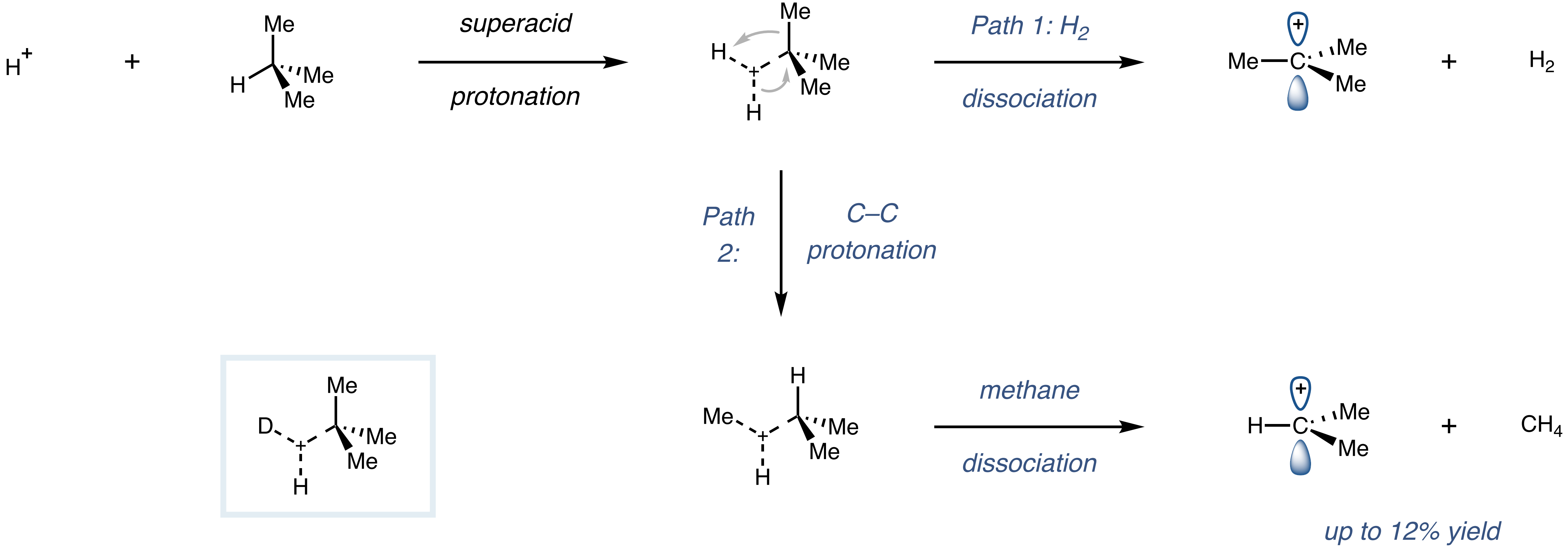
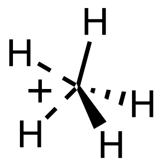


superacid protonation of C–H and C–C σ-bonds
showcases non-classical behavior in cations
derived from “simple” alkanes

Olah, G. A.; Halpern, Y.; Shen, J.; Mo, Y. K. *J. Am. Chem. Soc.* **1971**, *93*, 1251.

Typical examples of non-classical carbocations



methonium

parent non-classical cation

computed C_s symmetry

rapid exchange of protons, highly delocalized

Olah, G. A.; Halpern, Y.; Shen, J.; Mo, Y. K. *J. Am. Chem. Soc.* **1971**, *93*, 1251.
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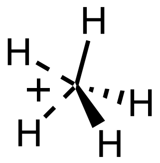
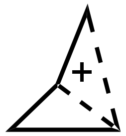
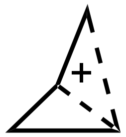


methonium

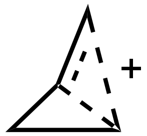


cyclopropyl carbinyl

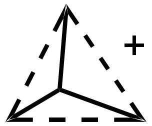
numerous variations have been proposed



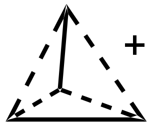
cyclopropyl carbinyl



bicyclobutonium

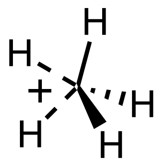


tricyclobutonium

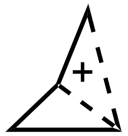


P. D. Bartlett. *Nonclassical Ions,* W.A. Benjamin, New York, 1965.

Typical examples of non-classical carbocations

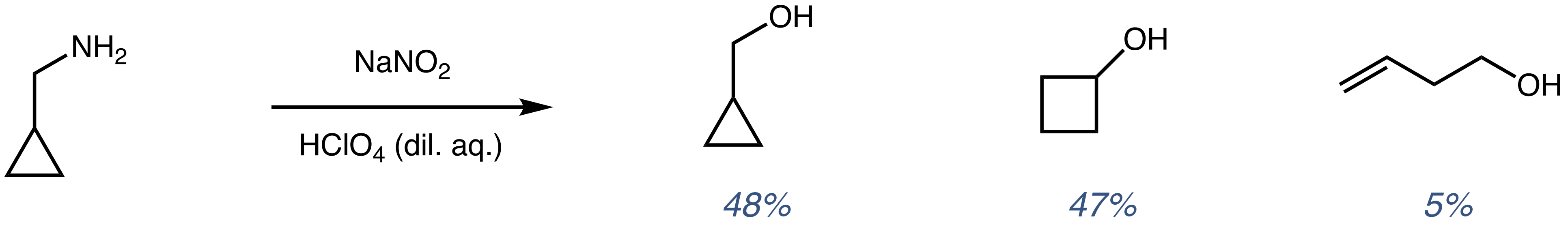


methonium

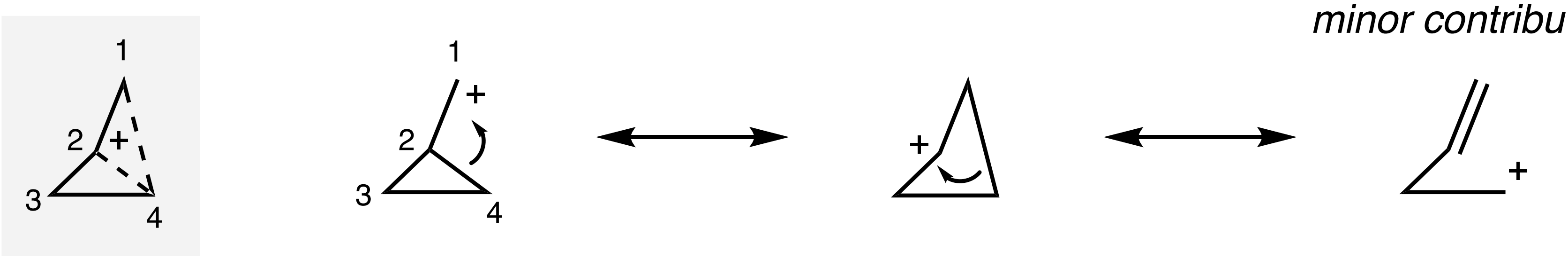


cyclopropyl carbinyl

Roberts, 1951:



minor contributor



Roberts, J. D.; Mazur, R. H. *J. Am. Chem. Soc.* **1951**, *73*, 3542.

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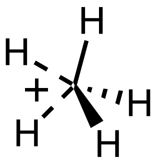
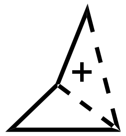
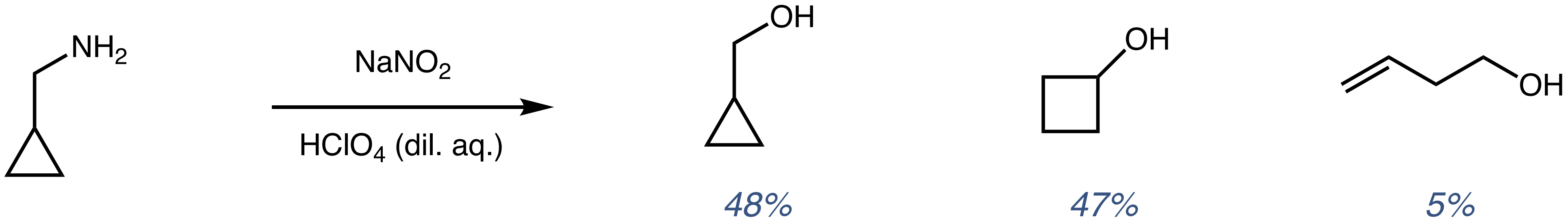


methonium

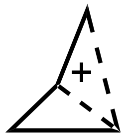


cyclopropyl carbinyl

Roberts, 1951:

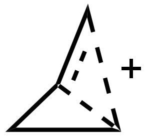


most consistent with:



cyclopropyl carbinyl

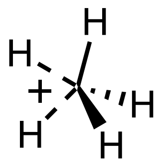
(ignore homoallyl contribution)



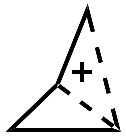
bicyclobutonium

Roberts, J. D.; Mazur, R. H. *J. Am. Chem. Soc.* **1951**, *73*, 3542.

Typical examples of non-classical carbocations



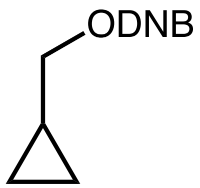
methonium



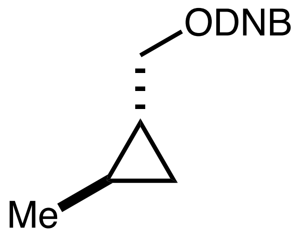
cyclopropyl carbinyl

Schleyer, 1966:

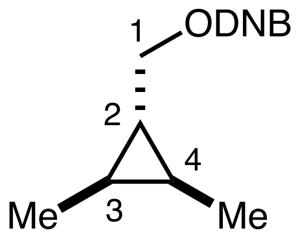
relative solvolysis rates in aq. acetone



$k_{rel} = 1$

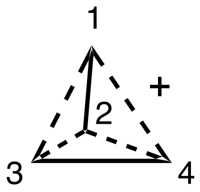


$k_{rel} = 11$



$k_{rel} = 124$

most consistent with:

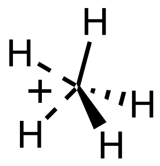


increased participation from distal ring

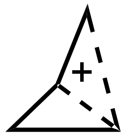
C atoms than previous structures

Schleyer, P. v. R.; Van Dine, G. W. *J. Am. Chem. Soc.* **1966**, *88*, 2321.

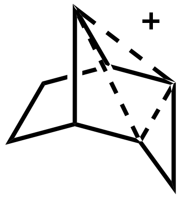
Typical examples of non-classical carbocations

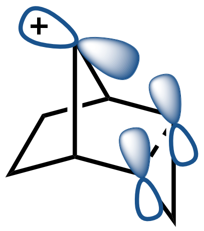


methonium



cyclopropyl carbinyl

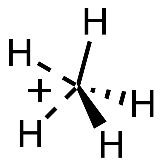




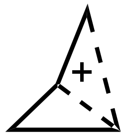
p-rich nature of cyclopropane C–C bonds leads to donation more similar to olefin π-systems

P. D. Bartlett. *Nonclassical Ions,* W.A. Benjamin, New York, 1965.

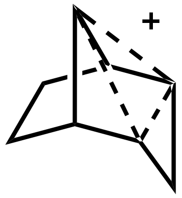
Typical examples of non-classical carbocations



methonium

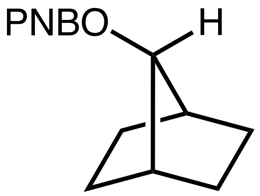


cyclopropyl carbinyl

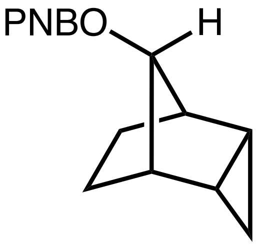


Tsuji, 1967:

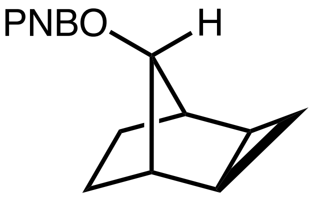
relative solvolysis rates in aq. acetone



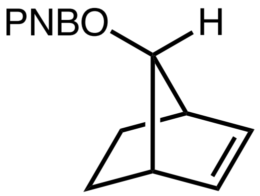
$k_{rel} = 1$



$k_{rel} = 10^{14}$

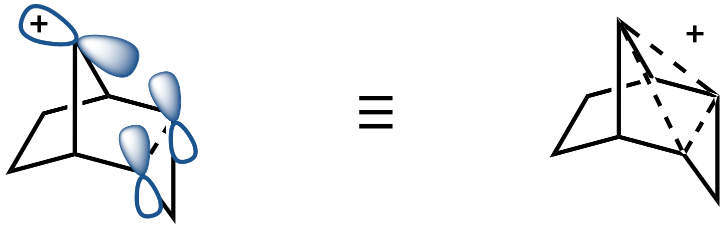


$k_{rel} = 0.4$



$k_{rel} = 10^{11}$

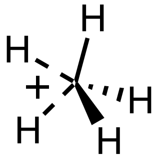
cyclopropane delocalization more effective than norbornene stabilization!



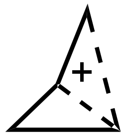
requires proper geometry for orbital overlap

Tanida, H.; Tsuji, T.; Irie, T. *J. Am. Chem. Soc.* **1967**, *89*, 1953.

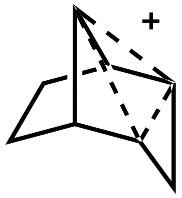
Typical examples of non-classical carbocations

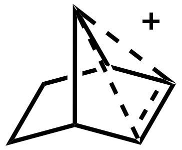


methonium



cyclopropyl carbinyl

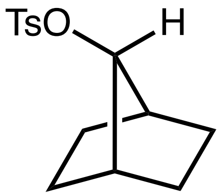




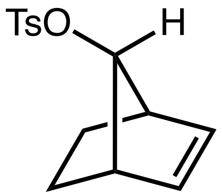
7-norbornenyl

Winstein, 1956:

relative solvolysis rates in HOAc

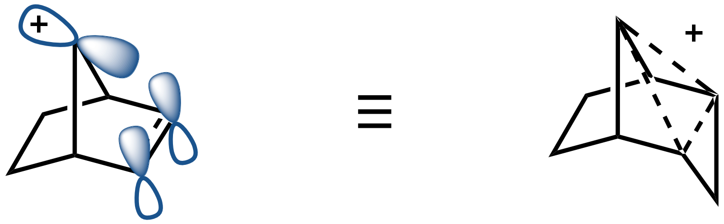


$k_{rel} = 1$



$k_{rel} = 10^{11}$

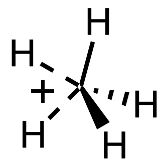
via:



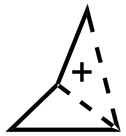
π-donation not formally "non-classical" but often included based on degree of rate enhancement

Winstein, S.; Shatavsky, M. *J. Am. Chem. Soc.* **1956**, *78*, 592.

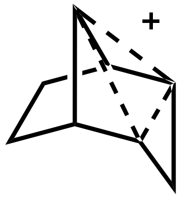
Typical examples of non-classical carbocations

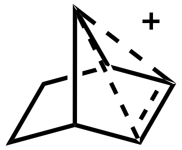


methonium

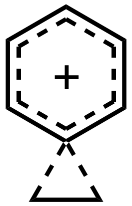


cyclopropyl carbinyl



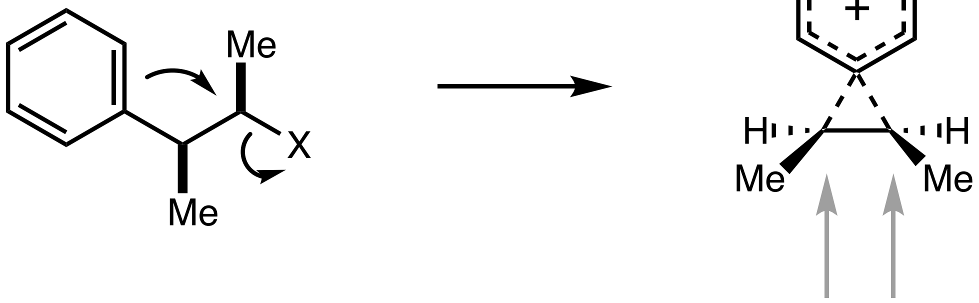


7-norbornenyl



phenonium

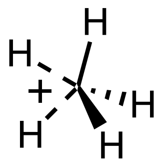
similar case to π-donation of olefins, not formally "non-classical" but uncommon homobenzylic delocalization



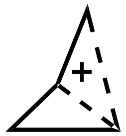
optically pure SM leads to two possible product enantiomers

Cram, D. J. *J. Am. Chem. Soc.* **1952**, *74*, 2129.

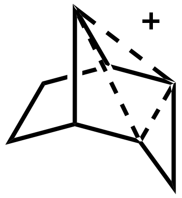
Typical examples of non-classical carbocations

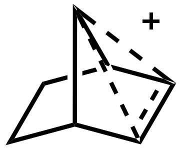


methonium

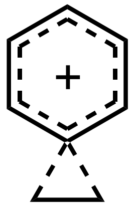


cyclopropyl carbinyl



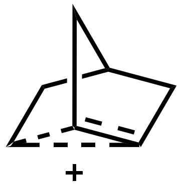


7-norbornenyl



phenonium

most iconic non-classical cation: the 2-norbornyl system

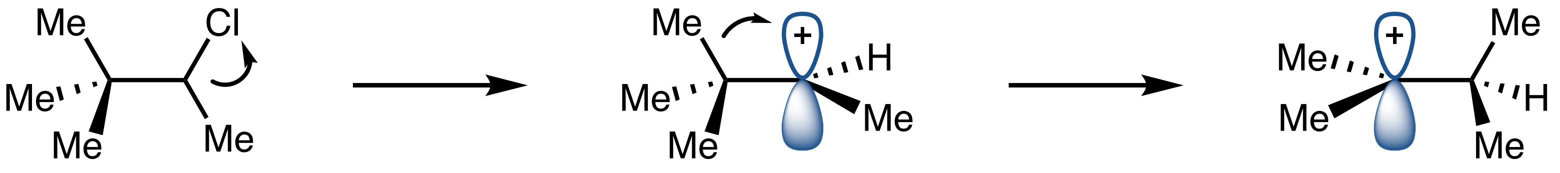


Outline

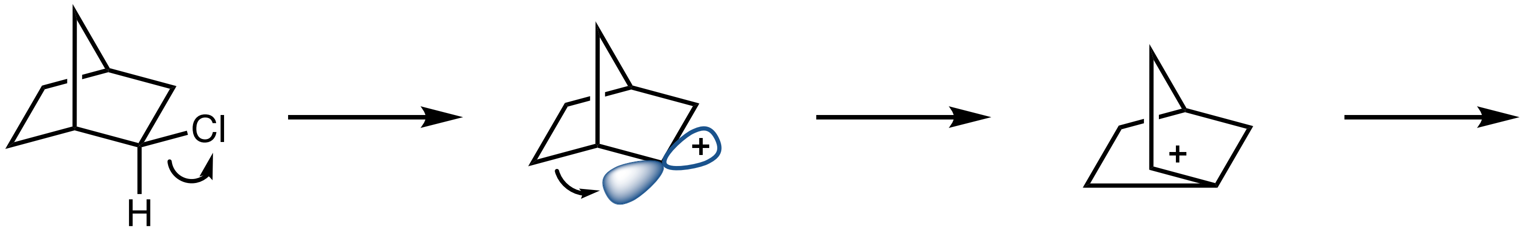
- *Fundamentals of non-classical carbocations: bonding, reactivity and common examples*
- *How it all began: the 2-norbornyl cation debate*
- *Non-classical reactivity in action: biosynthesis and reactions of complex molecules*
- *Modern developments in non-classical carbocation chemistry*
    - *enantioselective transformations (List/Schreiner)*
    - *intermolecular non-classical interactions in C–H activation (Nelson)*

Initial investigations of the 2-norbornyl cation

Wagner, turn of the 20th century:



Meerwein, 1922:



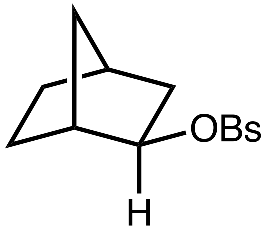
solvolysis, Cl^- trapping, etc.

2-norbornyl rearrangements were well-established but treated as classical Wagner-Meerwein processes

Meerwein, H.; van Emster, K. *Chem. Ber.* **1922**, *55B*, 2500.

Initial investigations of the 2-norbornyl cation

Winstein, 1949:

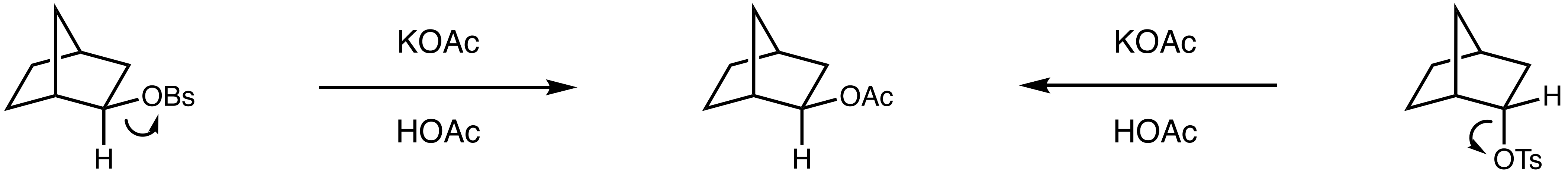


rates and selectivity of 2-norbornyl substitution reactions

Winstein, S.; Trifan, D. S. *J. Am. Chem. Soc.* **1949**, *71*, 2953.

Initial investigations of the 2-norbornyl cation

Winstein, 1949:

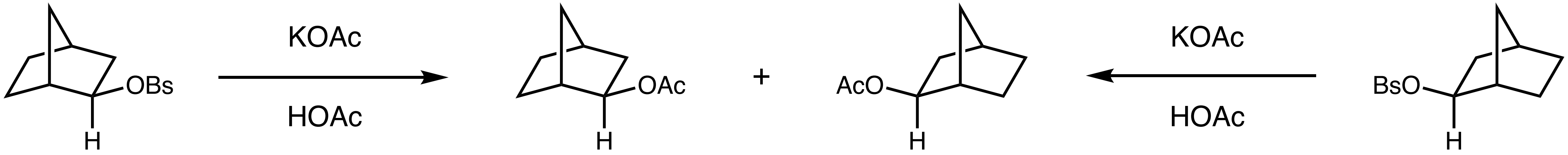


k_{rel} = 350

exclusive isomer

(<0.02% endo–OAc via GC)

k_{rel} = 1



enantiopure

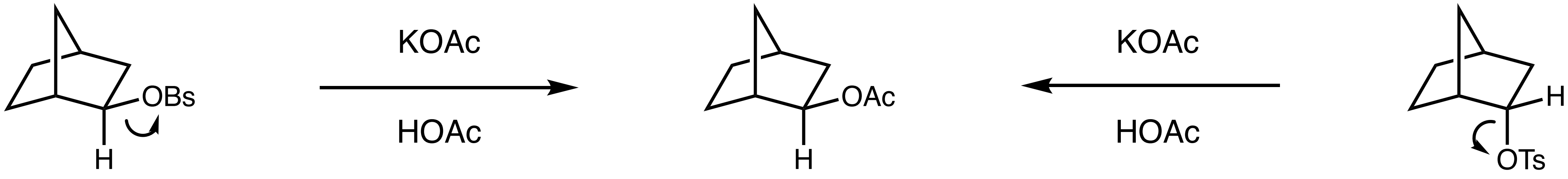
1:1 ratio

enantiopure

Winstein, S.; Trifan, D. S. *J. Am. Chem. Soc.* **1949**, *71*, 2953.

Initial investigations of the 2-norbornyl cation

Winstein, 1949:

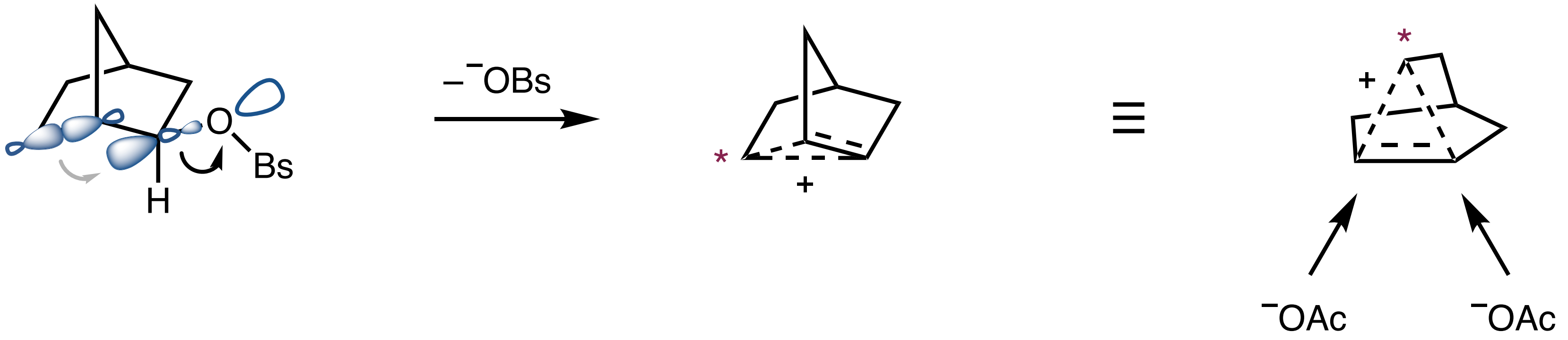


k_{rel} = 350

exclusive isomer
(<0.02% endo–OAc via GC)

k_{rel} = 1

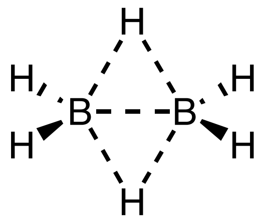
***proposal**: delocalized (“bridged”) carbonium intermediate;*
anchimeric assistance leading to faster generation from exo-brosylate



Winstein, S.; Trifan, D. S. *J. Am. Chem. Soc.* **1949**, *71*, 2953.

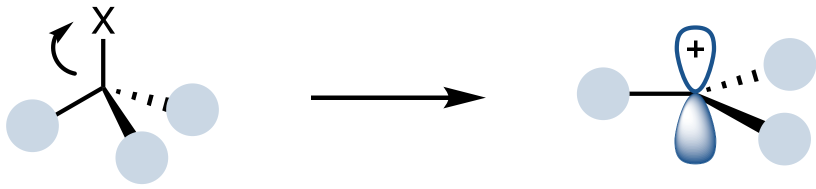
Classical vs. non-classical: the debate begins

H. C. Brown, 1960's:



most recognized for developments in boron-mediated transformations

However, Brown was also heavily invested in showcasing the role of sterics in substitution reactions:



as ● becomes larger, more steric strain
is relieved when rehybridizing from sp^3 to sp^2

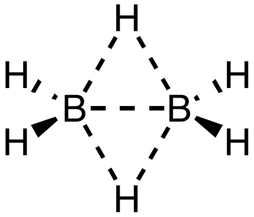
⬇

faster solvolysis and nucleophile trapping

Brown, H. C. *Science* **1946**, *103*, 385.

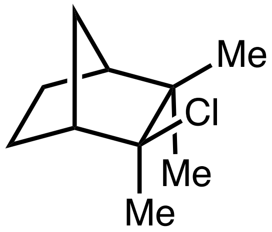
Classical vs. non-classical: the debate begins

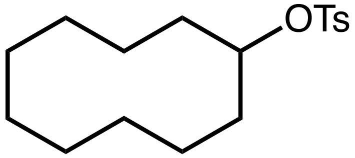
H. C. Brown, 1960's:



most recognized for developments in boron-mediated transformations

Winstein's report upends classical steric arguments for carbocation reactions





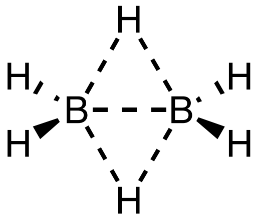
cations subsequently described via non-classical delocalization

reports retracted soon after

Brown, H. C. *Acc. Chem. Res.* **1983**, *16*, 432.

Classical vs. non-classical: the debate begins

H. C. Brown, 1960's:



most recognized for developments in boron-mediated transformations

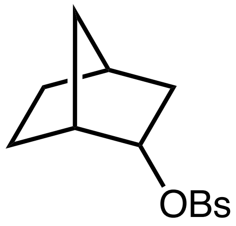
Brown enters debate to protect classical perspective as well as intellectual rigor of field

Brown, H. C. *Acc. Chem. Res.* **1983**, *16*, 432.

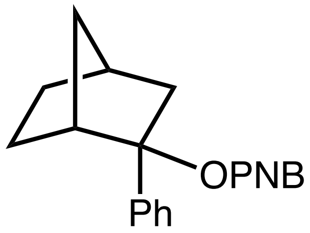
Classical rationales: sterics and thermochemistry

H. C. Brown, 1960's:

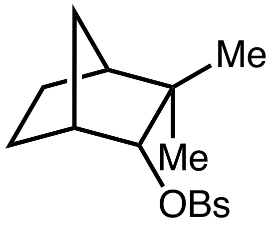
comparing exo/endo rates for acetate solvolysis:



$k_{exo}/k_{endo} = 350$



$k_{exo}/k_{endo} = 140$



$k_{exo}/k_{endo} = 1230$

3° cation better described as carbenium than carbonium;

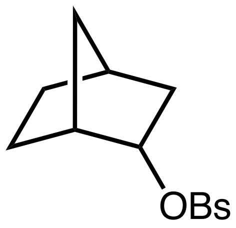
similar magnitudes of k_{exo}/k_{endo} rule out dominant non-classical effect

Brown, H. C.; Chloupek, F. J.; Rei, M.-H. *J. Am. Chem. Soc.* **1964**, *86*, 1248.

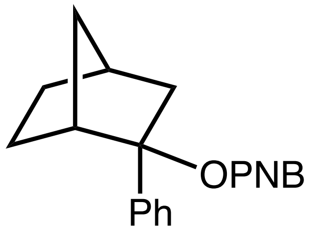
Classical rationales: sterics and thermochemistry

H. C. Brown, 1960's:

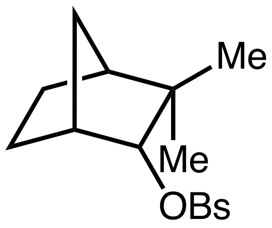
comparing exo/endo rates for acetate solvolysis:



$k_{exo}/k_{endo} = 350$

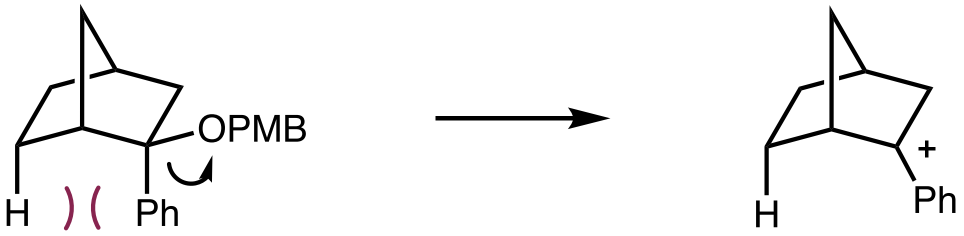


$k_{exo}/k_{endo} = 140$

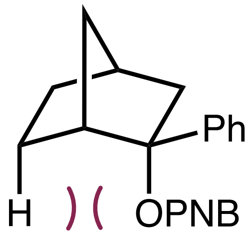


$k_{exo}/k_{endo} = 1230$

rationalized exo/endo ratios purely through steric effects and strain relief



exo: relief of diaxial strain in cation enhances rate



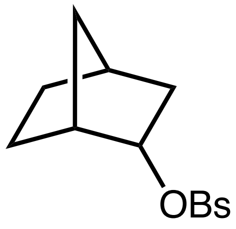
endo: leaving group trajectory obstructed by axial substituent

Brown, H. C.; Chloupek, F. J.; Rei, M.-H. *J. Am. Chem. Soc.* **1964**, *86*, 1248.

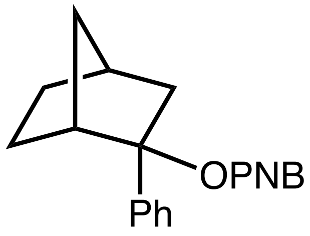
Classical rationales: sterics and thermochemistry

H. C. Brown, 1960's:

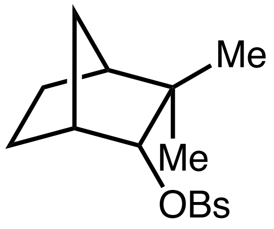
comparing exo/endo rates for acetate solvolysis:



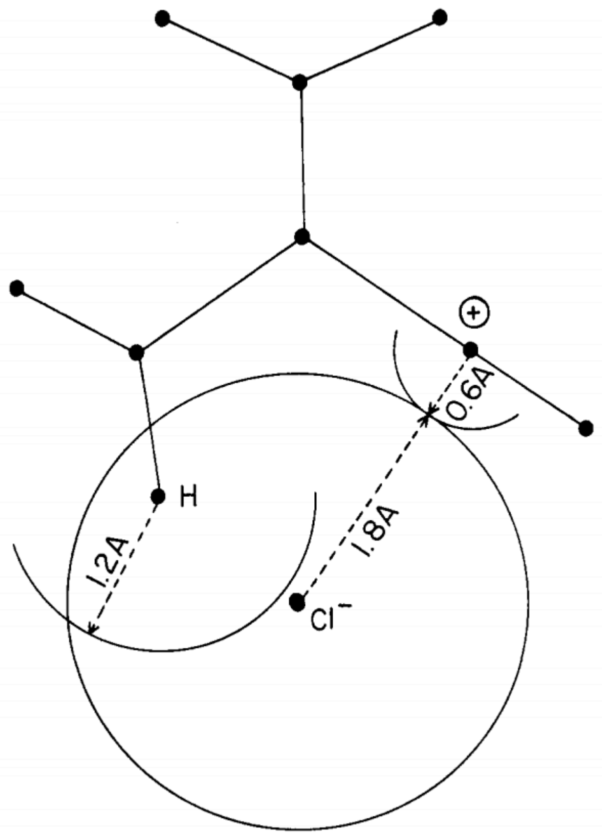
$k_{exo}/k_{endo} = 350$



$k_{exo}/k_{endo} = 140$



$k_{exo}/k_{endo} = 1230$

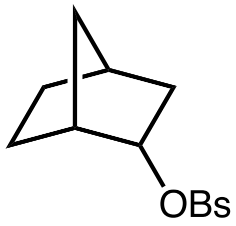


Brown, H. C.; Chloupek, F. J.; Rei, M.-H. *J. Am. Chem. Soc.* **1964**, *86*, 1248.

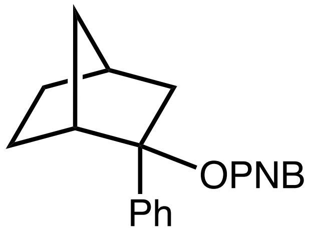
The 2-norbornyl cation: common ground and key energetic differences

H. C. Brown, 1960's:

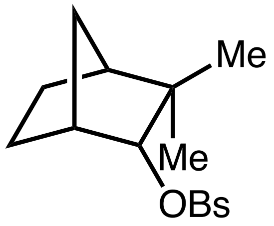
comparing exo/endo rates for acetate solvolysis:



$k_{exo}/k_{endo} = 350$

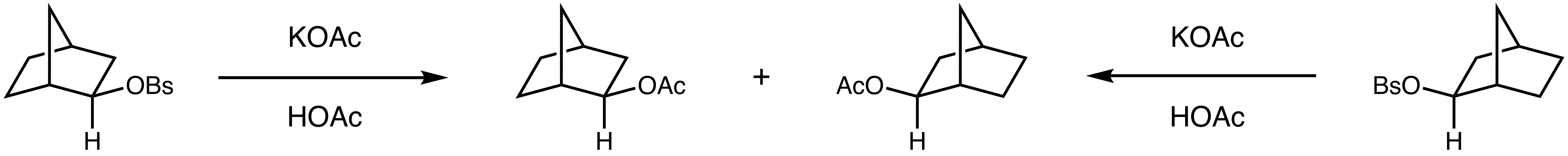


$k_{exo}/k_{endo} = 140$



$k_{exo}/k_{endo} = 1230$

beyond relative rate data, Winstein's "enantiopure to racemic" experiment indicates cation must be migrating



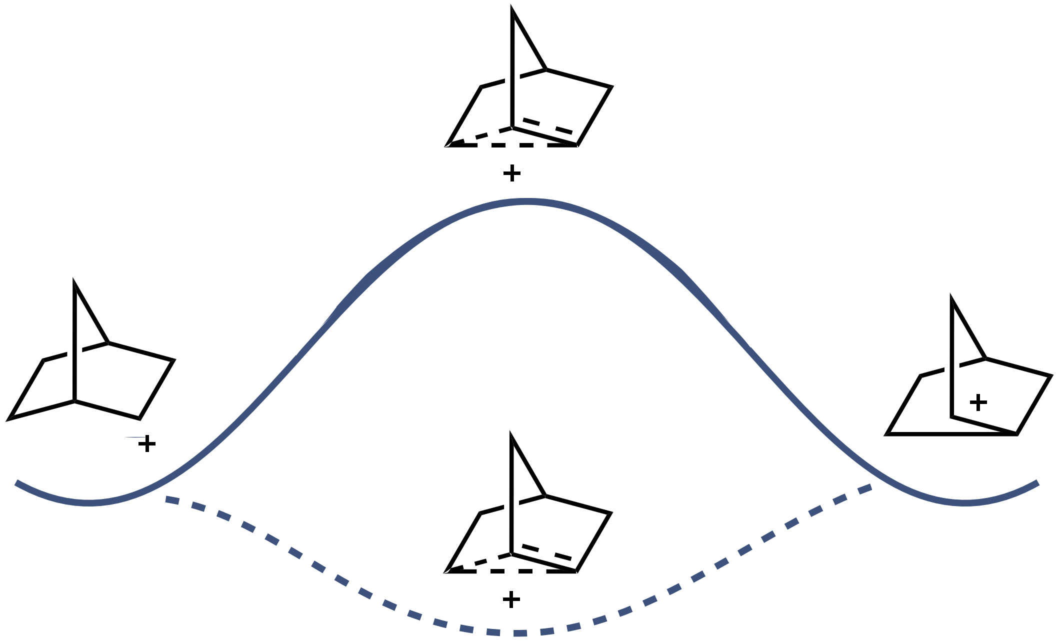
enantiopure

1:1 ratio

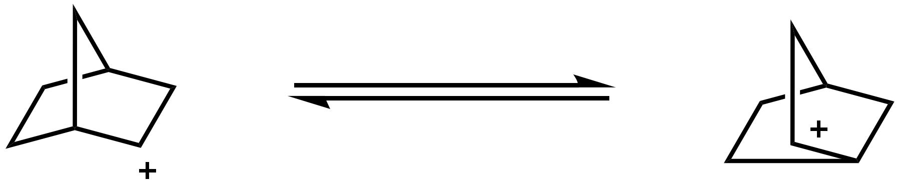
enantiopure

How would Brown interpret this result?

The 2-norbornyl cation: common ground and key energetic differences



Brown: non-classical cation is transition state between rapidly equilibrating classical intermediates



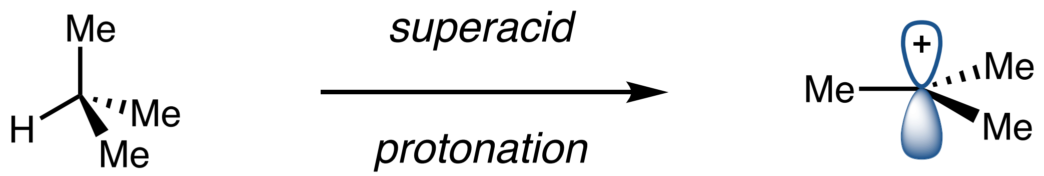
Winstein: non-classical cation is intermediate and local energetic minimum

Brown, H. C. *Acc. Chem. Res.* **1983**, *16*, 432.

Characterizing a non-classical intermediate

Olah, 1960's–1980's:

first expert in obtaining/characterizing stable carbocations

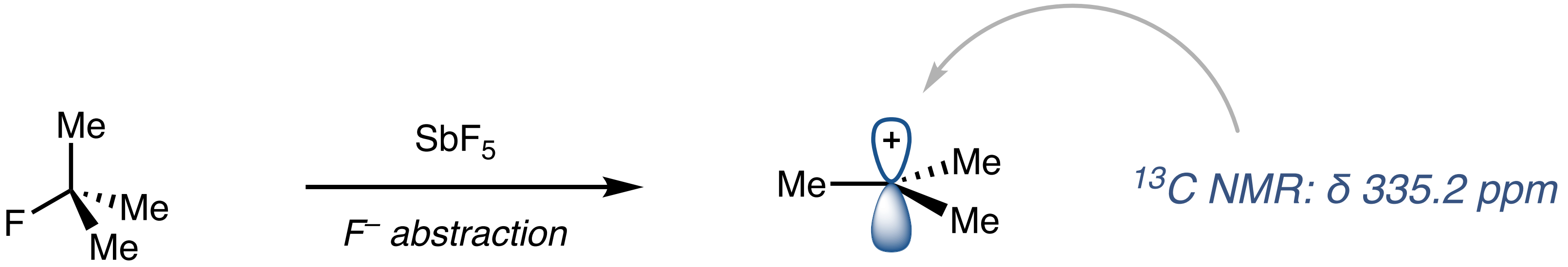


Sb-based superacids (e.g. "magic acid" - $FSO_3H{\bullet}SbF_5$) can reach pKa ~ –28

(10^{16} times more acidic than anhydrous H_2SO_4)

originally designed to prevent elimination of carbocations to olefins

Olah embraced early NMR techniques for probing reactive intermediates

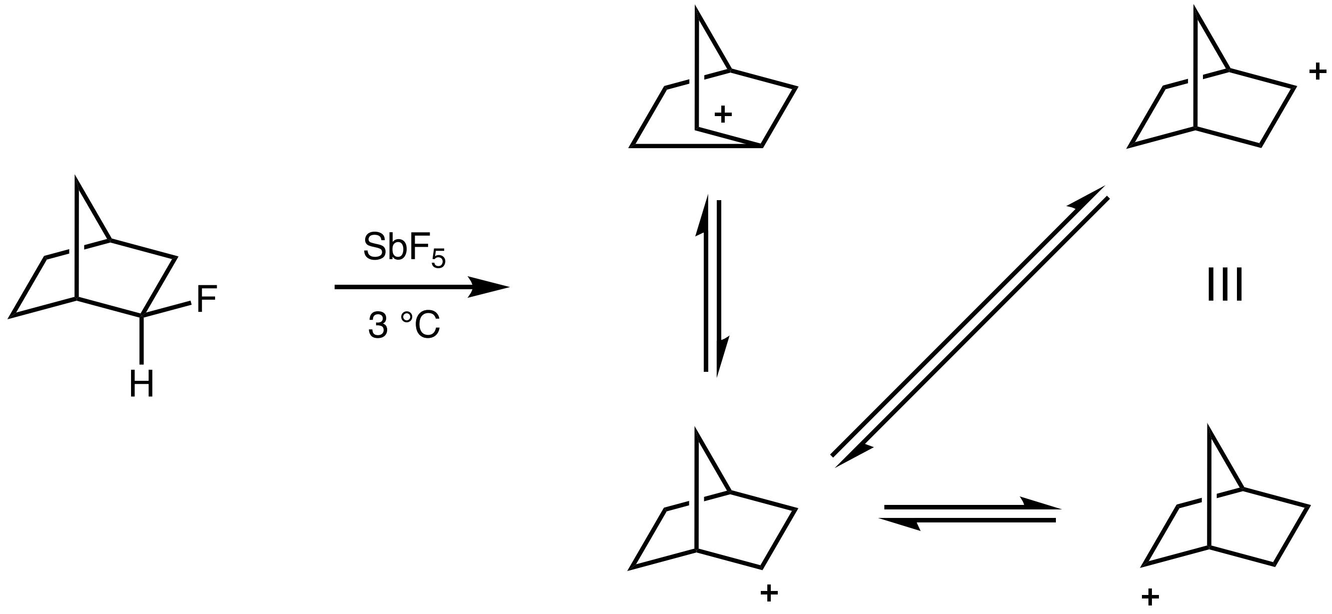


Olah, G. A.; Baker, E. B.; Evans, J. C.; Tolgyesi, W. S.; McIntyre, J. S.; Bastien, I. J. *J. Am. Chem. Soc.* **1964**, *86*, 1360.

Characterizing a non-classical intermediate

Olah, 1960's–1980's:
Saunders, Schleyer

convergence to singlet in ^{1}H NMR

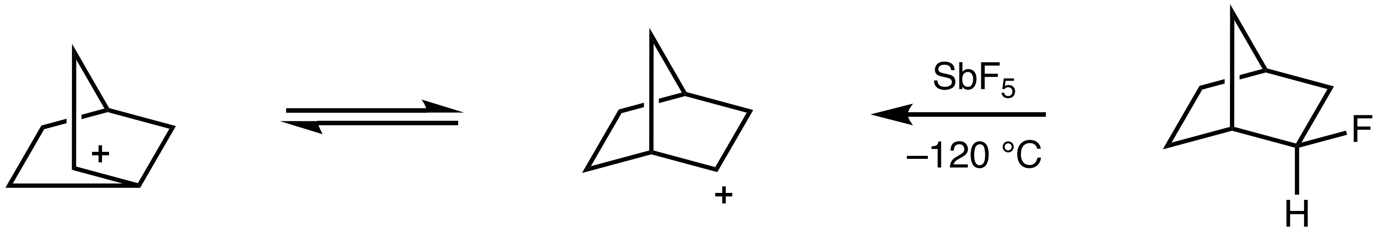


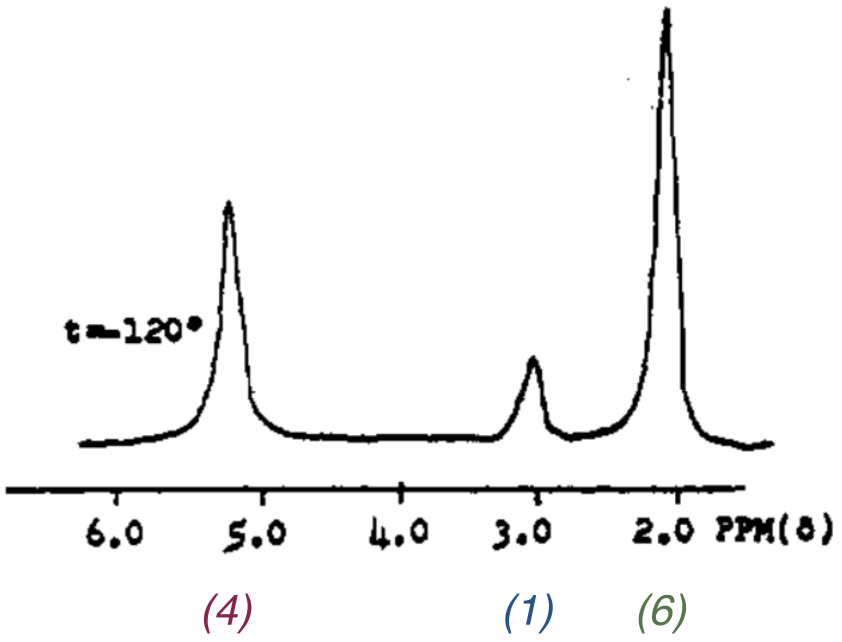
rapid Wagner-Meerwein and hydride shifts

Saunders, M.; Schleyer, P. v. R.; Olah, G. A. *J. Am. Chem. Soc.* **1964**, *86*, 5680.

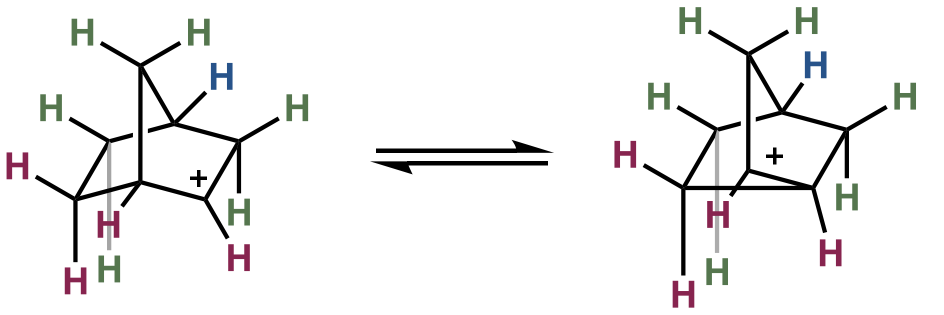
Characterizing a non-classical intermediate

Olah, 1960's–1980's:
Saunders, Schleyer





consistent with Wagner-Meerwein equilibration
of classical cations



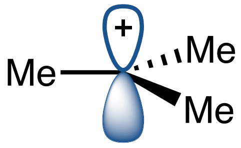
Saunders, M.; Schleyer, P. v. R.; Olah, G. A. *J. Am. Chem. Soc.* **1964**, *86*, 5680.

Characterizing a non-classical intermediate

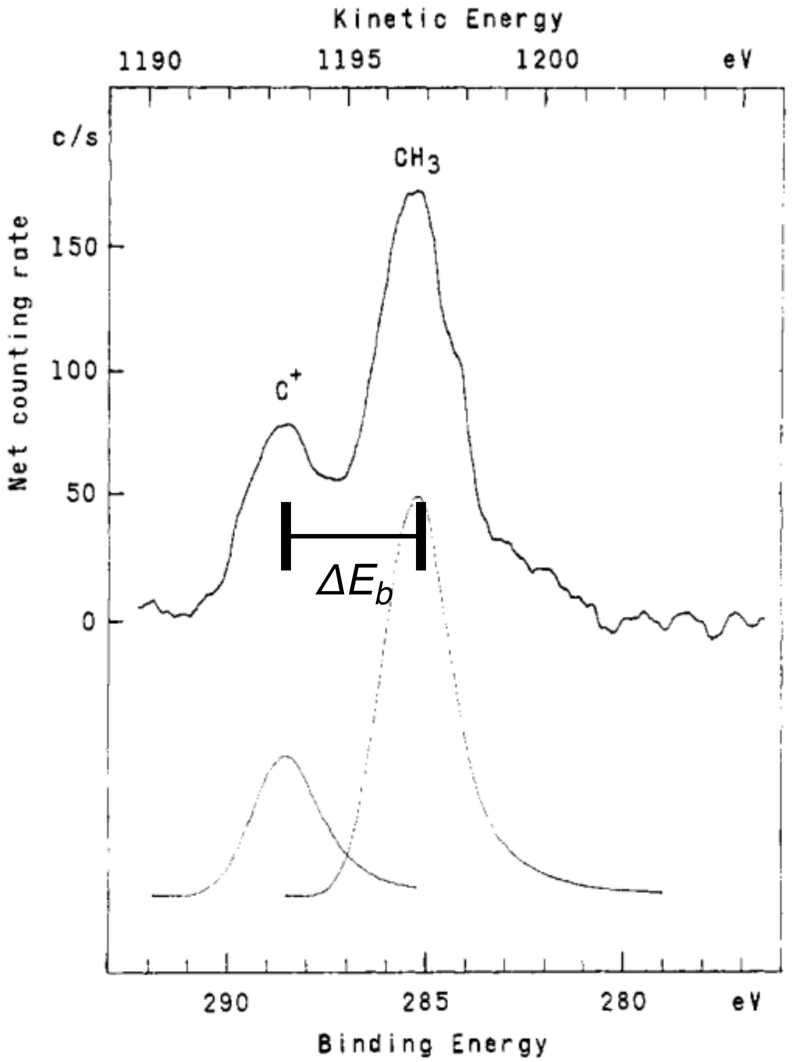
Olah, 1960's–1980's:

X-ray photoelectron spectroscopy: photo-emitted electrons can be trapped by cations as core electrons

highly localized charge leads to large increases (3–5 eV) in electron binding energy (ΔE_b) relative to standard tetravalent carbon



$\Delta E_b = 3.9$ eV →



Olah, G. A.; Mateescu, G. D.; Wilson, L. A.; Gross, M. H. *J. Am. Chem. Soc.* **1970**, *92*, 7231.

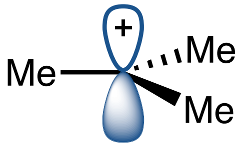
Olah, G. A.; Mateescu, G. D.; Reimenschneider, J. L. *J. Am. Chem. Soc.* **1972**, *94*, 2529.

Characterizing a non-classical intermediate

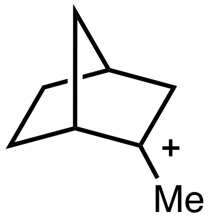
Olah, 1960's–1980's:

consistent with high degree of charge delocalization

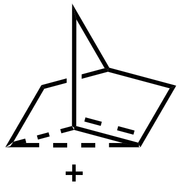
in 2-norbornyl cation



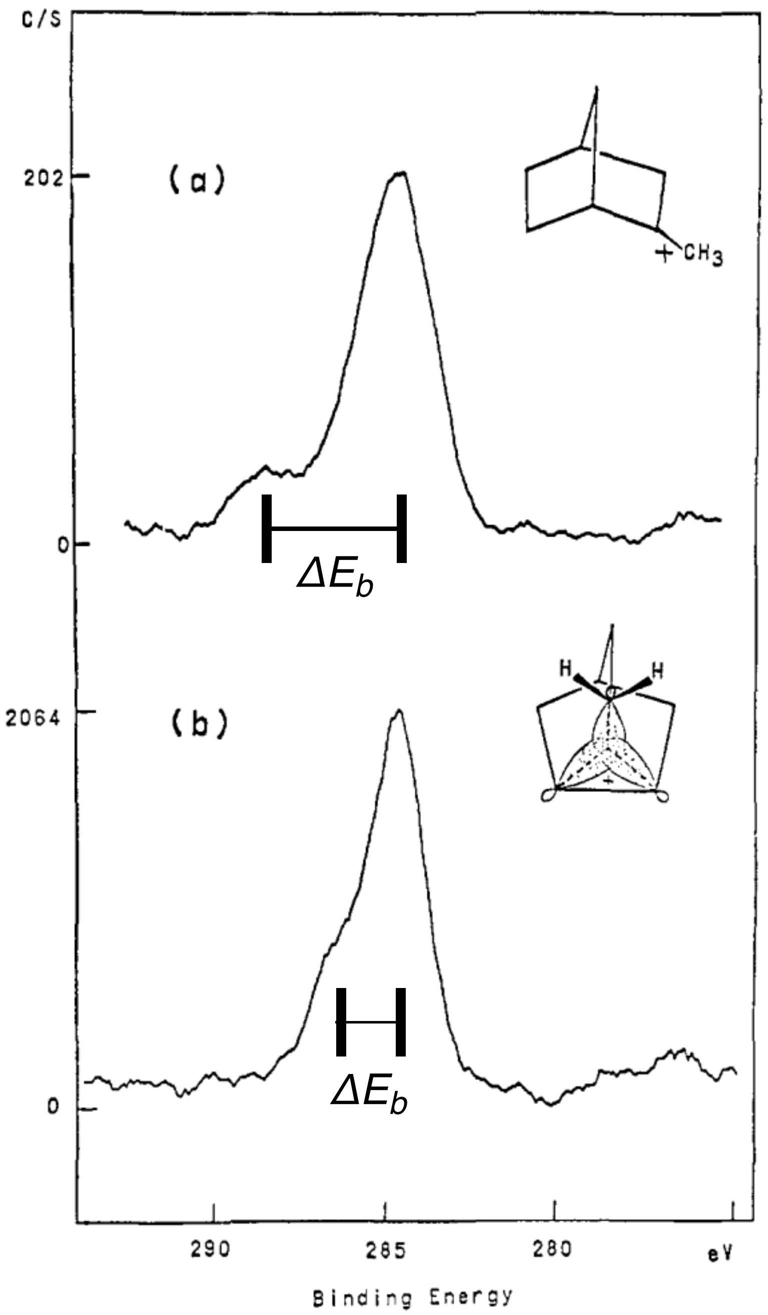
$\Delta E_b = 3.9$ eV



$\Delta E_b = 3.7$ eV →



$\Delta E_b = 1.7$ eV →

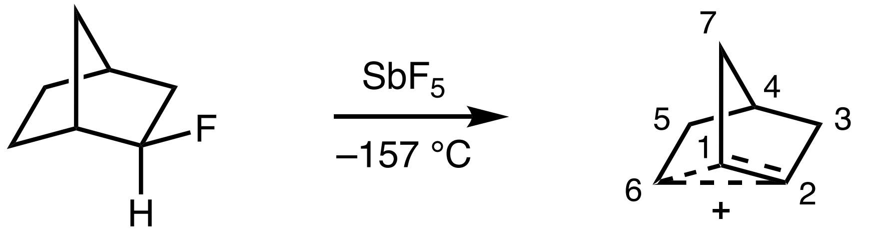


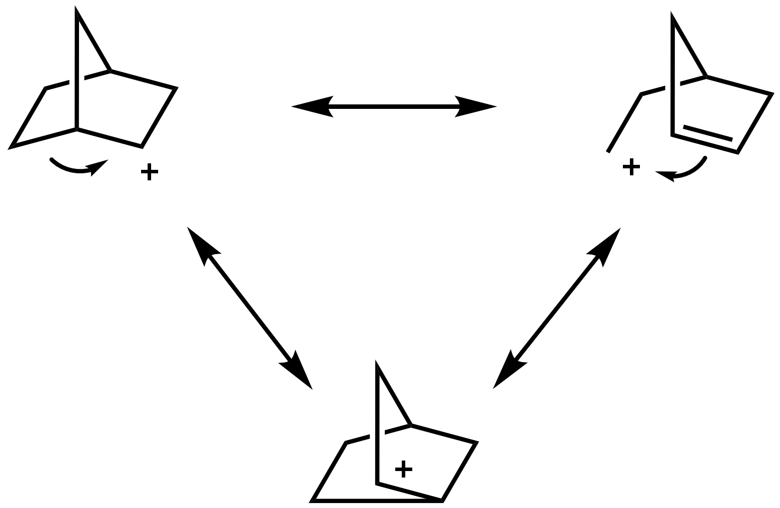
Olah, G. A.; Mateescu, G. D.; Wilson, L. A.; Gross, M. H. *J. Am. Chem. Soc.* **1970**, *92*, 7231.

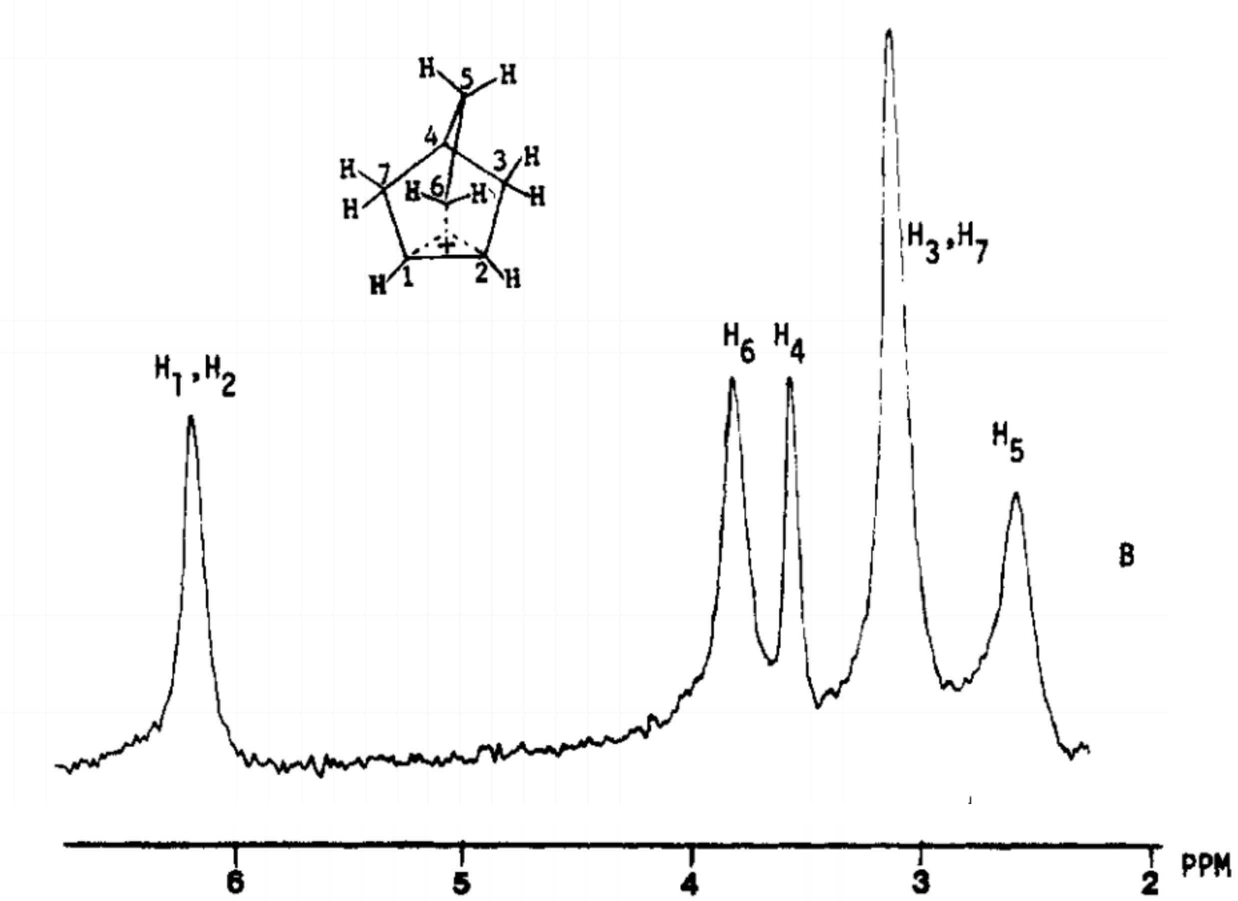
Olah, G. A.; Mateescu, G. D.; Reimenschneider, J. L. *J. Am. Chem. Soc.* **1972**, *94*, 2529.

Characterizing a non-classical intermediate

Olah, 1960's–1980's:
Saunders, Schleyer



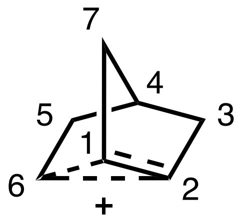




verification that delocalized 2-norbornyl cation can be long-lived and stable, suggests intermediacy

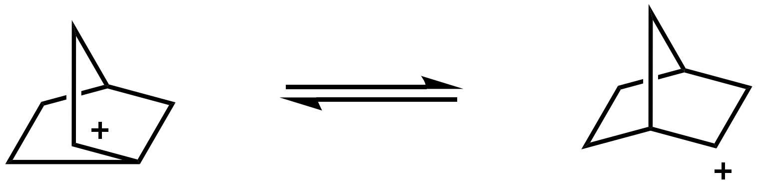
Olah, G. A.; Prakash, G. K. S.; Arvanaghi, M.; Anet, F. A. L. *J. Am. Chem. Soc.* **1982**, *104*, 7105.

Characterizing a non-classical intermediate

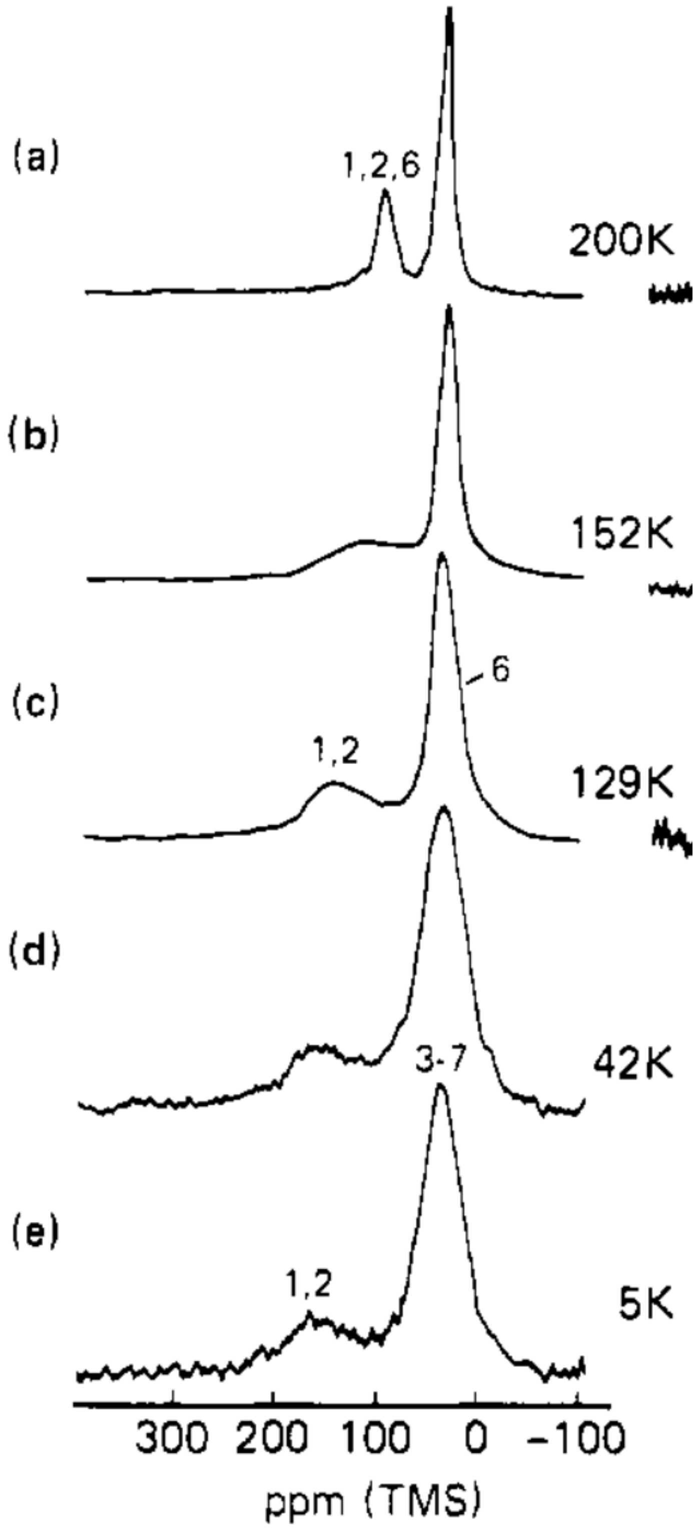


even at 5 K, ^{13}C NMR shows deshielding across multiple C atoms in 2-norbornyl cation

for classical ions related by Wagner-Meerwein shifts:



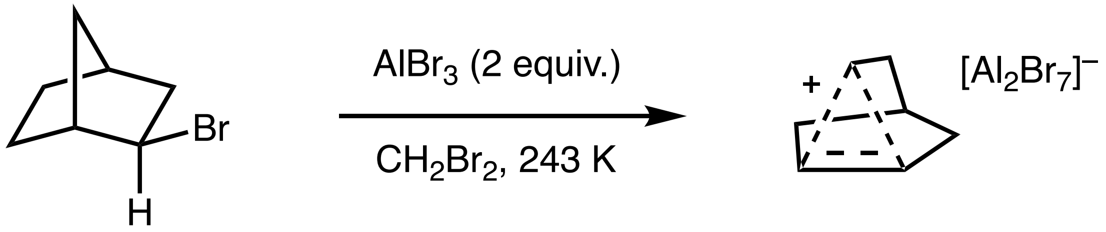
*calculated Wagner-Meerwein barrier to observe process at 5 K < 0.2 kcal/mol - **unreasonable!***



Yannoni, C. S.; Macho, V.; Myhre, P. C. *J. Am. Chem. Soc.* **1982**, *104*, 7380.

Unambiguous proof from a crystal structure

although numerous derivatives were crystallized over decades, the 2-norbornyl structure was only solved in 2013



stable below 213 K, but solid state too disordered above 86 K for XRD

(undesired rotations and 6,1,2-hydride shifts)

BUT

rapid cooling initiates phase transition, lattice change, cracks crystal

~10 careful annealing/cooling cycles, helium-cooled diffractometer required (final temp <50 K)

Karsten Meyer: "The crystallography was a tour de force… the procedure is insane – it put us through torture"

Scholz, F.; Himmel, D.; Heinemann, F. W.; Schleyer, P. v. R.; Meyer, K.; Krossing, I. *Science* **2013**, *341*, 62.

Unambiguous proof from a crystal structure

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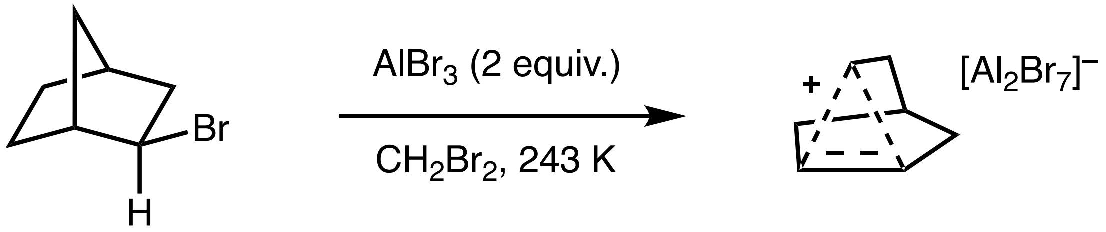

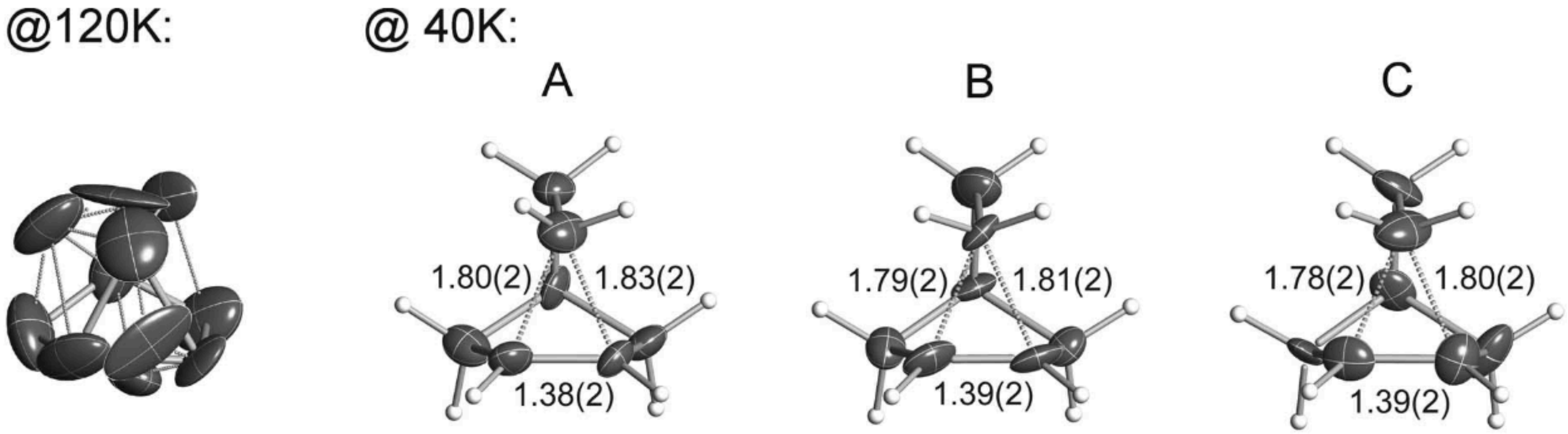

disordered

reproducible

highly symmetric, with two C–C bond orders <1 and one C–C bond with double-bond character

unambiguous confirmation of the non-classical nature of the 2-norbornyl cation

Scholz, F.; Himmel, D.; Heinemann, F. W.; Schleyer, P. v. R.; Meyer, K.; Krossing, I. *Science* **2013**, *341*, 62.

Looking back: who came out on top?

winners: *Winstein, Olah, Schleyer, Saunders, Roberts, etc.*

losers: *primarily Brown*

although these debates resulted in numerous experimental advances, the discourse was notoriously hostile

Olah, 1983 (Acc. Chem. Res.):

"It was hoped that [the non-classical evidence] would put an end to the prolonged 'nonclassical ion controversy'. The controversy, however, was kept alive by Brown… any further continuation of the classical-nonclassical ion controversy seems to be a futile exercise of semantics and not of relevant experimental facts."

Olah, G. A.; Prakash, G. K. S.; Saunders, M. *Acc. Chem. Res.* **1983**, *16*, 440.

Looking back: who came out on top?

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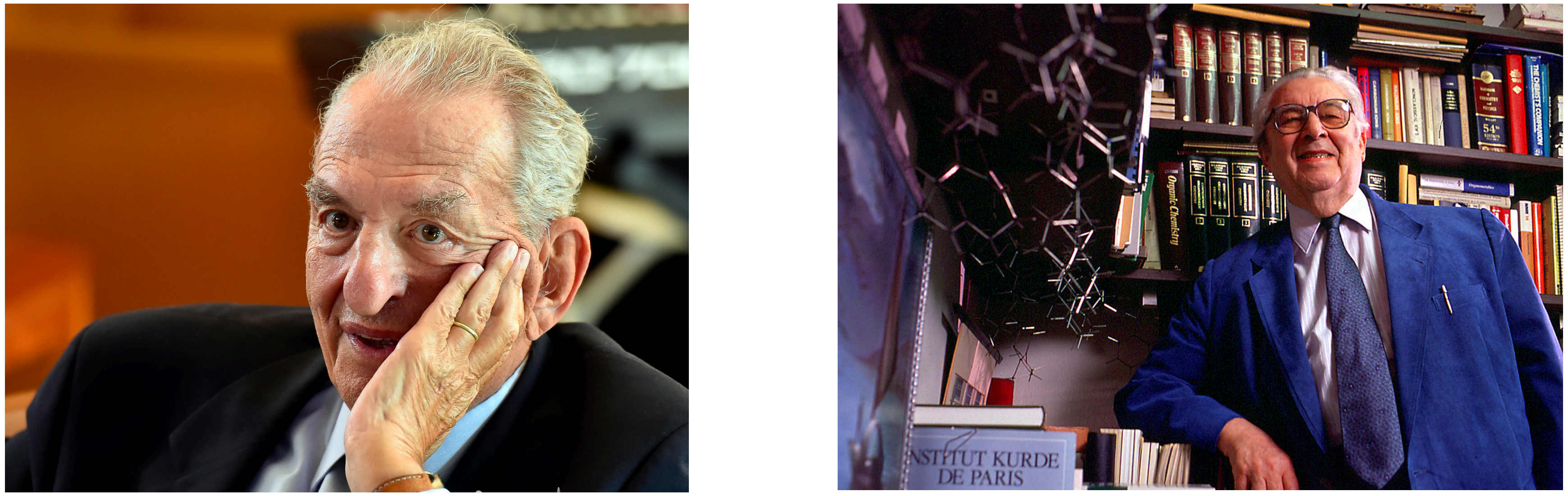

although these debates resulted in numerous experimental advances, the discourse was notoriously hostile

Brown, 1983 (Acc. Chem. Res., same issue):

“Invariably, the arguments and evidence [for non-classical behavior] have crumpled after careful study…[the 2-norbornyl cation] clearly does not have the non-classical stabilization energy that has been postulated for so long… it ill befits serious scientific workers in this area to ignore [our] data and results.”

Brown, H. C. *Acc. Chem. Res.* **1983**, *16*, 432.

Looking back: who came out on top?

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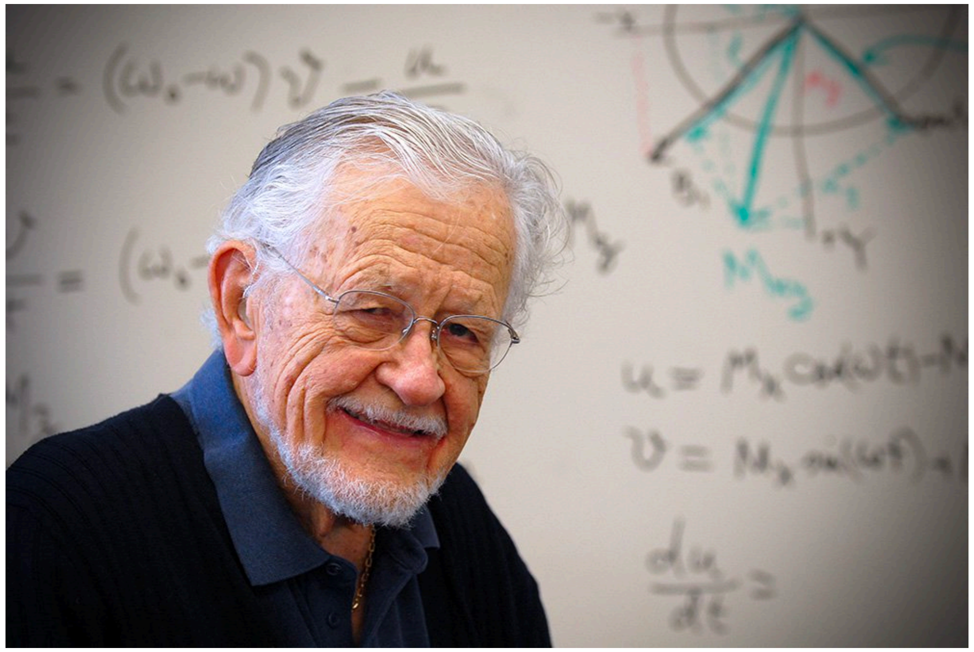


John D. Roberts, who coined the term "non-classical ion"

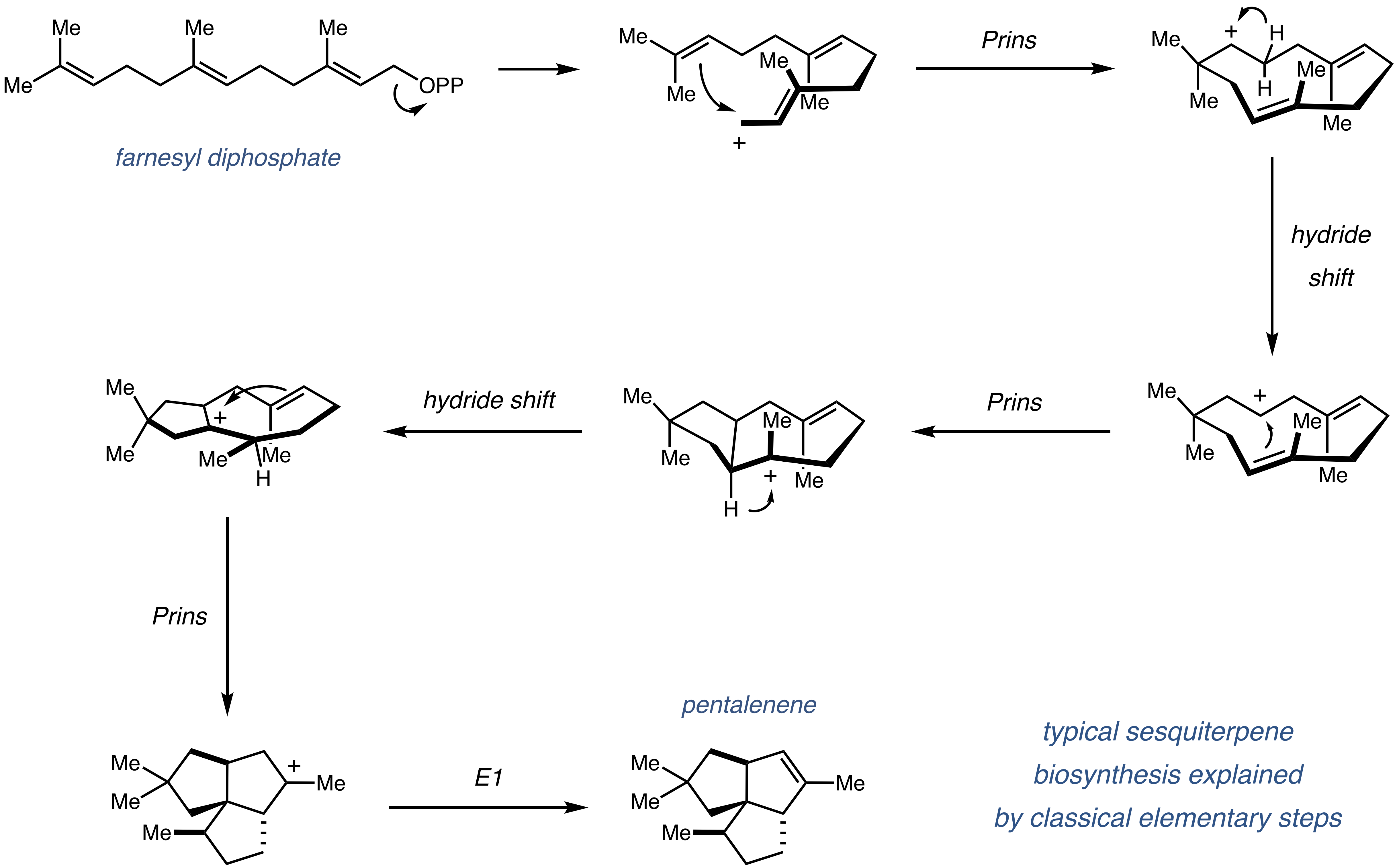
when asked at age 95 whether the 2013 crystal structure would have caused Brown to reconsider his position:

"Herb would be Herb no matter what happened."

Outline

- *Fundamentals of non-classical carbocations: bonding, reactivity and common examples*
- *How it all began: the 2-norbornyl cation debate*
- *Non-classical reactivity in action: biosynthesis and reactions of complex molecules*
- *Modern developments in non-classical carbocation chemistry*
  - *enantioselective transformations (List/Schreiner)*
  - *intermolecular non-classical interactions in C–H activation (Nelson)*

Non-classical biosynthetic pathways

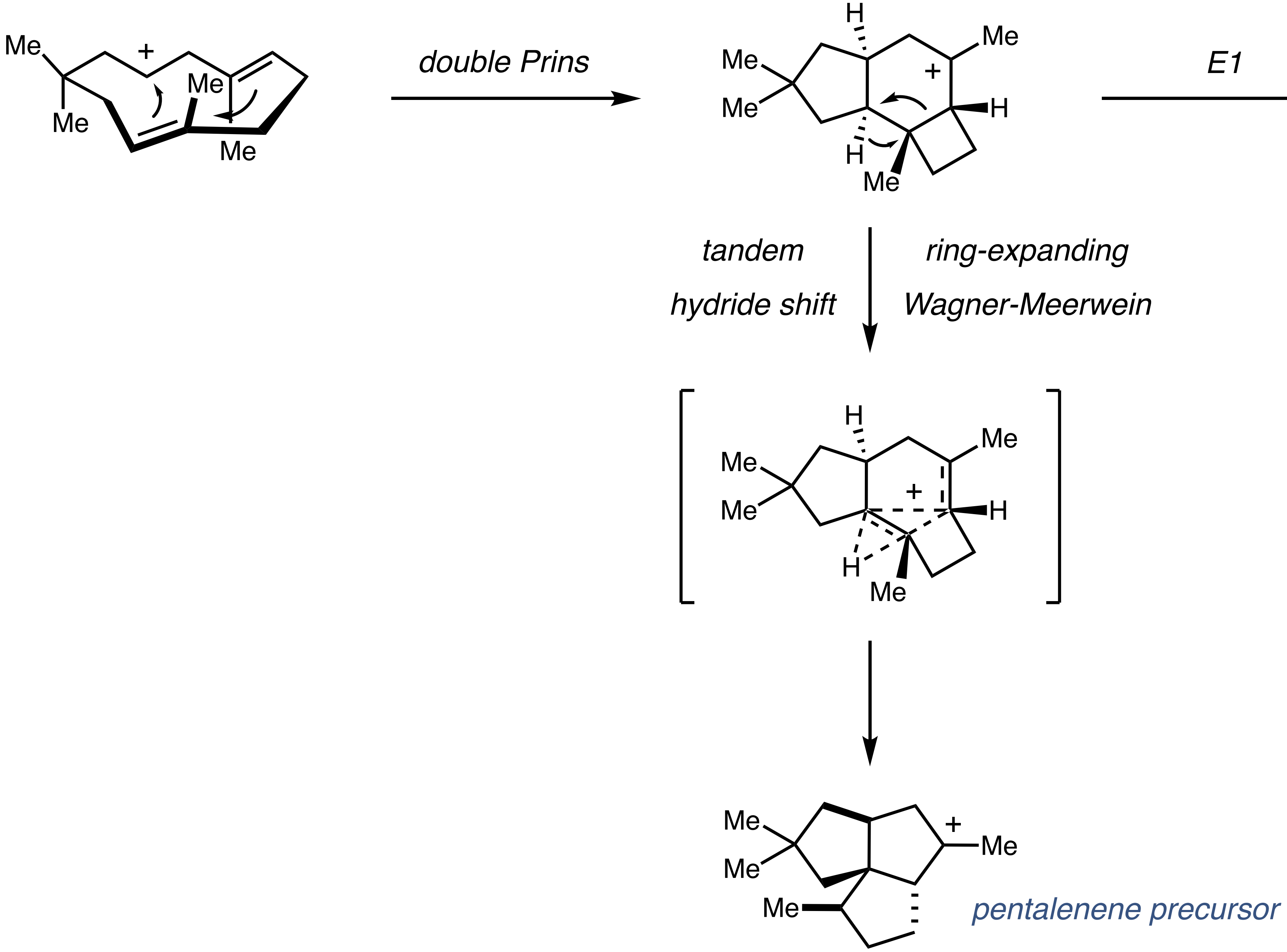


typical sesquiterpene
biosynthesis explained
by classical elementary steps

Gutta, P.; Tantillo, D. J. *J. Am. Chem. Soc.* **2006**, *128*, 6172.

Non-classical biosynthetic pathways

computational modeling identified competent non-classical transition states/intermediates that lead to additional products



Gutta, P.; Tantillo, D. J. *J. Am. Chem. Soc.* **2006**, *128*, 6172.

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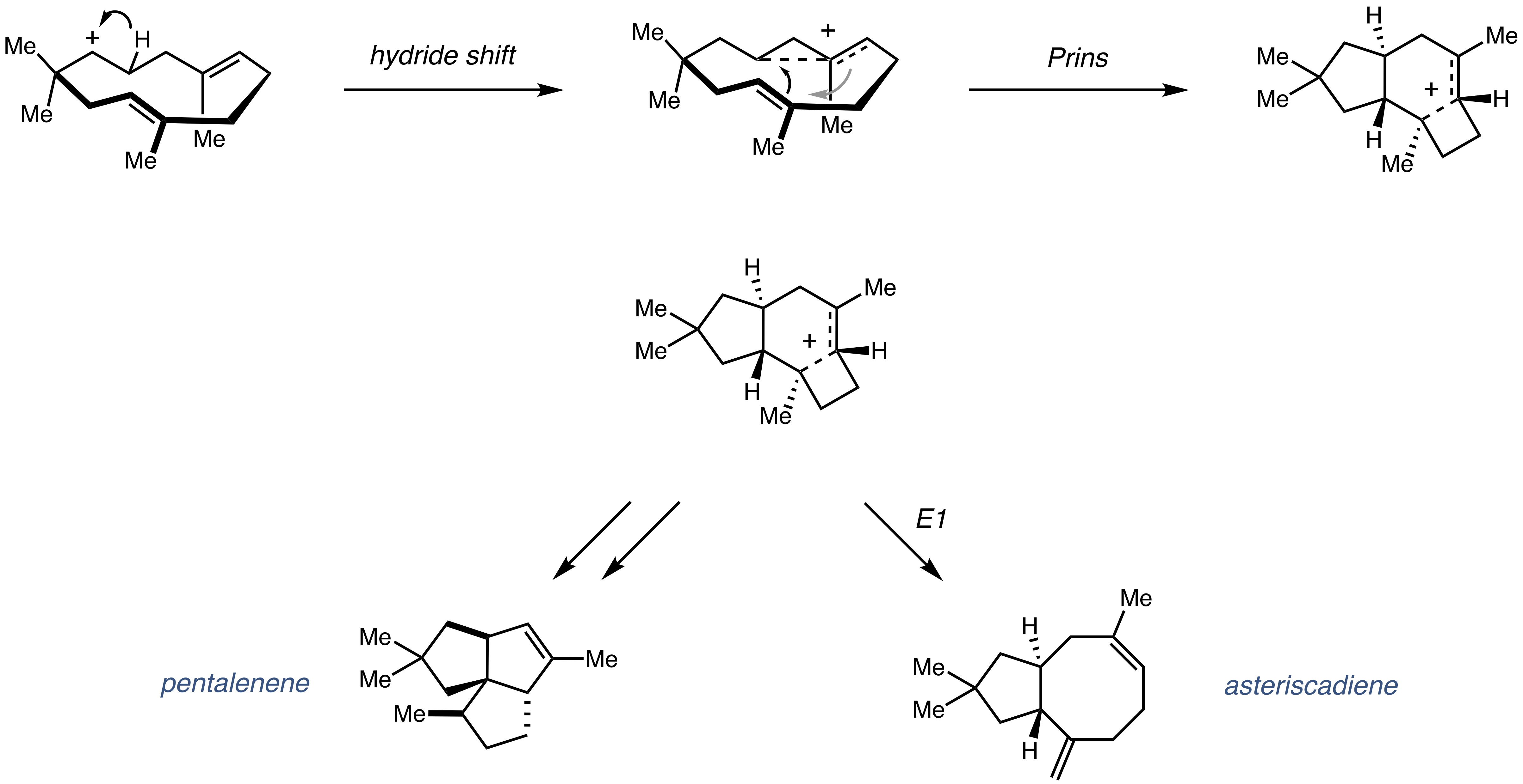
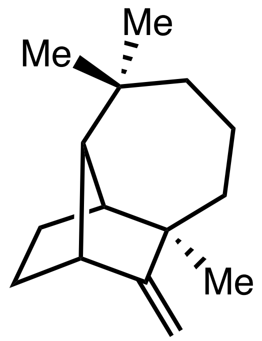


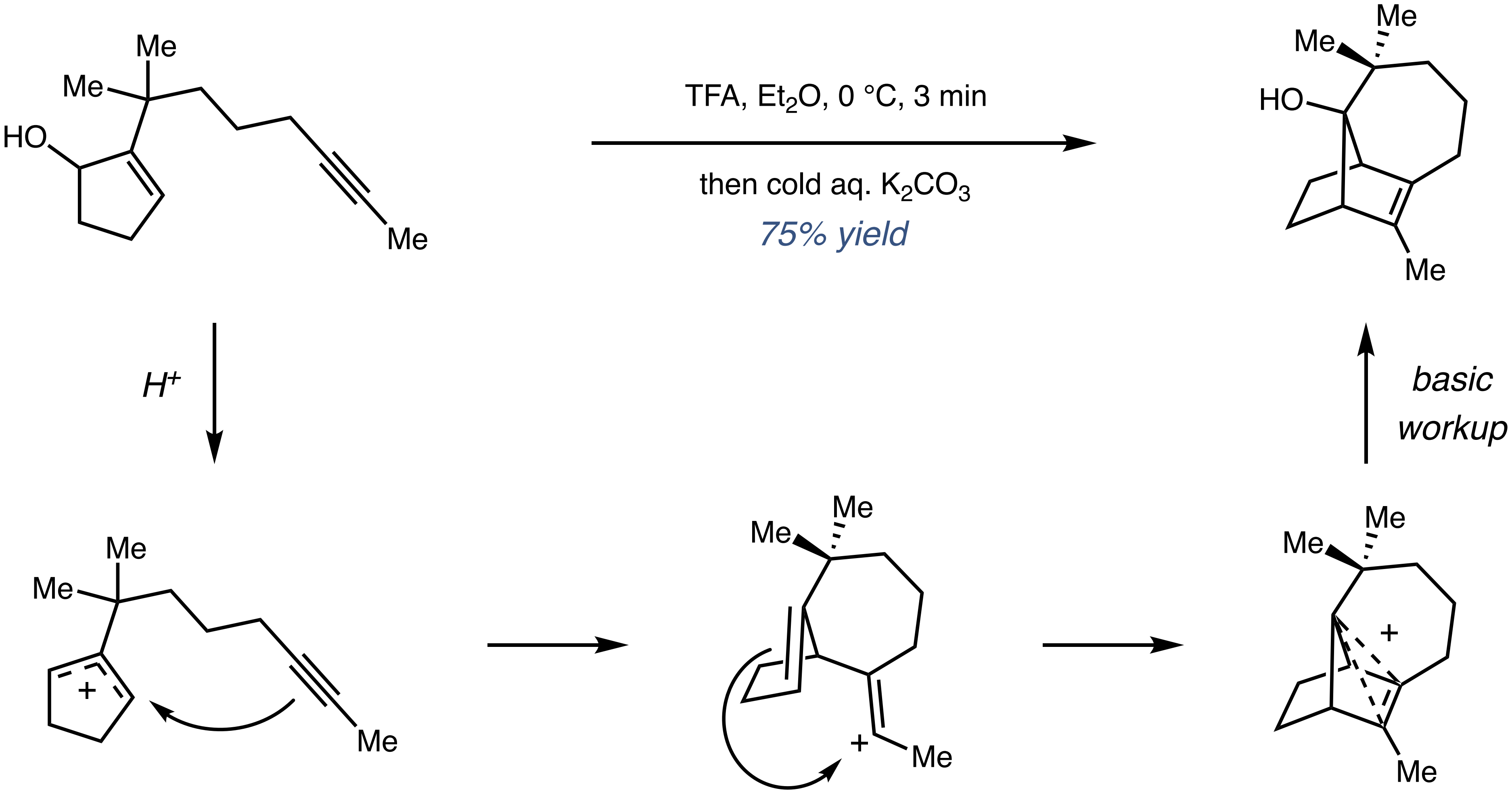
Gutta, P.; Tantillo, D. J. *J. Am. Chem. Soc.* **2006**, *128*, 6172.

Non-classical approaches in total synthesis



longifolene

Johnson, 1975:



TFA, Et_2O, 0 °C, 3 min

then cold aq. K_2CO_3

75% yield

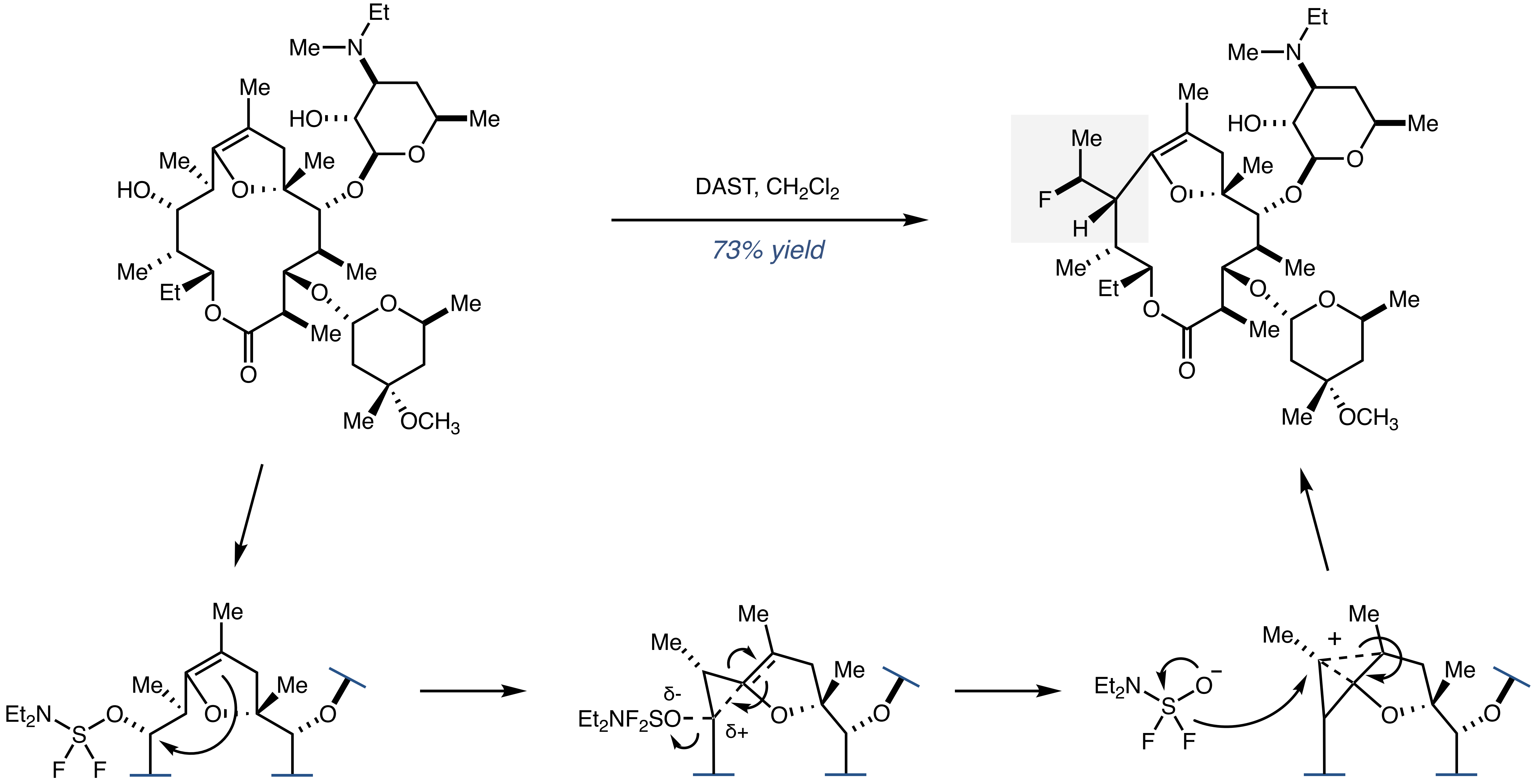
H^+

basic workup

Volkmann, R. A.; Andrews, G. C.; Johnson, W. S. *J. Am. Chem. Soc.* **1975**, *97*, 4777.

Uncommon rearrangements on complex substrates

macrolide ring contractions via deoxygenative fluorination



cyclopropyl carbinyl-type cation

Burnell-Curty, C.; Faghih, R.; Pagano, T.; Henry, R. F.; Lartey, P. A. *J. Org. Chem.* **1996**, *61*, 5153.

Outline

- *Fundamentals of non-classical carbocations: bonding, reactivity and common examples*

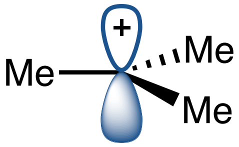
- *How it all began: the 2-norbornyl cation debate*

- *Non-classical reactivity in action: biosynthesis and reactions of complex molecules*

- *Modern developments in non-classical carbocation chemistry*
    - *enantioselective transformations (List/Schreiner)*
    - *intermolecular non-classical interactions in C–H activation (Nelson)*

Enantiocontrol in non-classical carbocation reactions

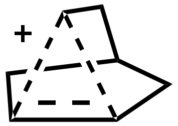
List and Schreiner, 2020:



numerous modern methods

for enantiocontrol

- *H-bond donor catalysis (i.e. squaramides)*
- *host-guest catalysis (supramolecular)*
- *Brønsted acid catalysis*



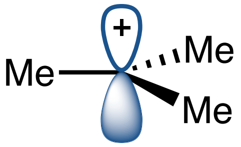
no known strategies for enantioinduction

with σ-delocalized cations

Propoerzi, R.; Kaib, P. S. J.; Leutzsch, M. *et al. Nat. Chem.* **2020**, *12*, 1174.

Enantiocontrol in non-classical carbocation reactions

List and Schreiner, 2020:



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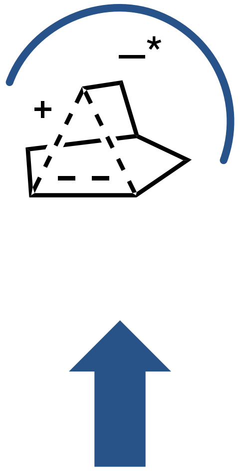
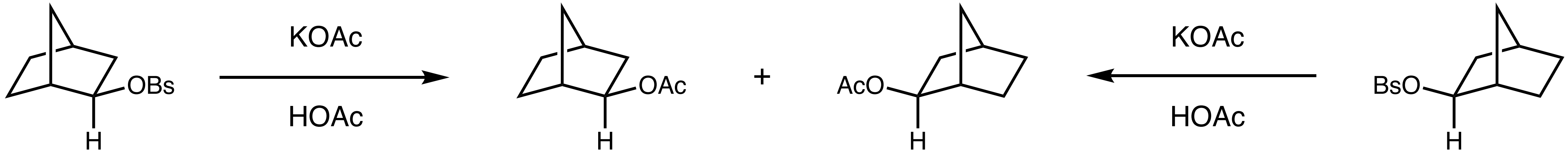


strategy: entrap intermediate in chiral ion pair "binding pocket"

Propoerzi, R.; Kaib, P. S. J.; Leutzsch, M. *et al. Nat. Chem.* **2020**, *12*, 1174.

“The reverse Winstein”

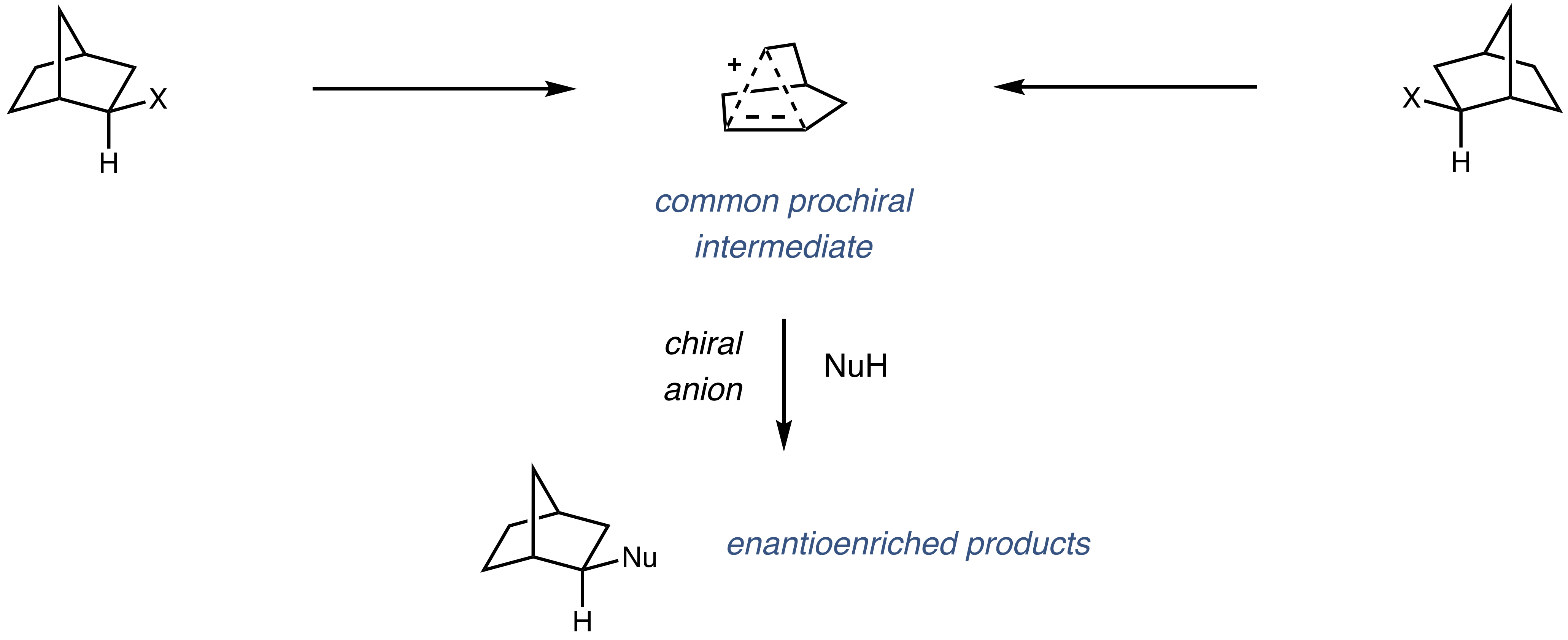
Winstein, 1949:



enantiopure

1:1 ratio

enantiopure

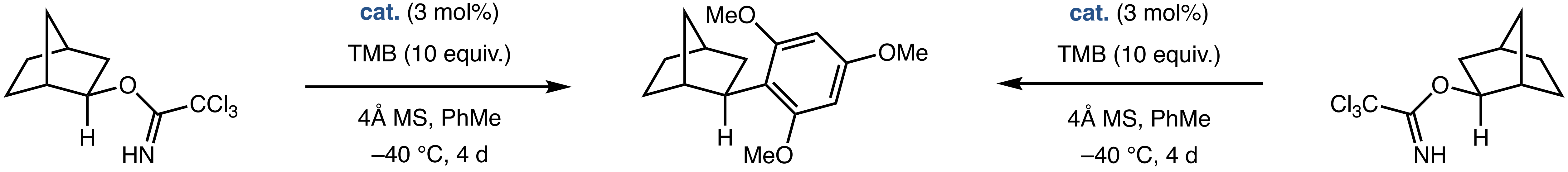


common prochiral intermediate

enantioenriched products

Propoerzi, R.; Kaib, P. S. J.; Leutzsch, M. *et al. Nat. Chem.* **2020**, *12*, 1174.

"The reverse Winstein"



cat. (3 mol%)
TMB (10 equiv.)
4Å MS, PhMe
−40 °C, 4 d

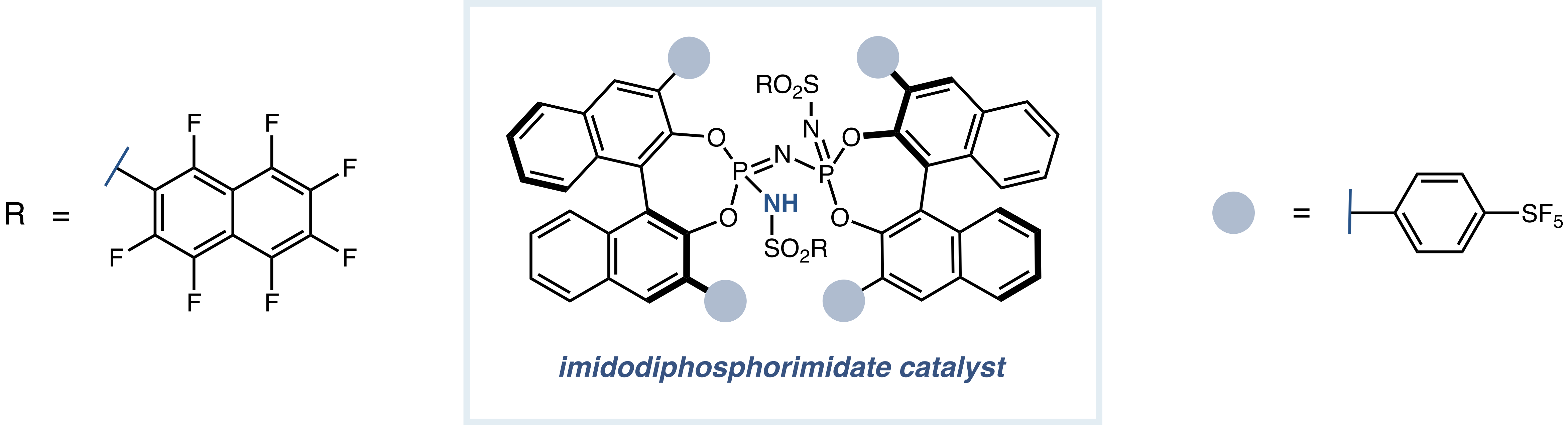
80% yield

97:3 er in both cases

cat. (3 mol%)
TMB (10 equiv.)
4Å MS, PhMe
−40 °C, 4 d

84% yield

using racemic substrate, same conditions: ***86% yield, 97:3 er***



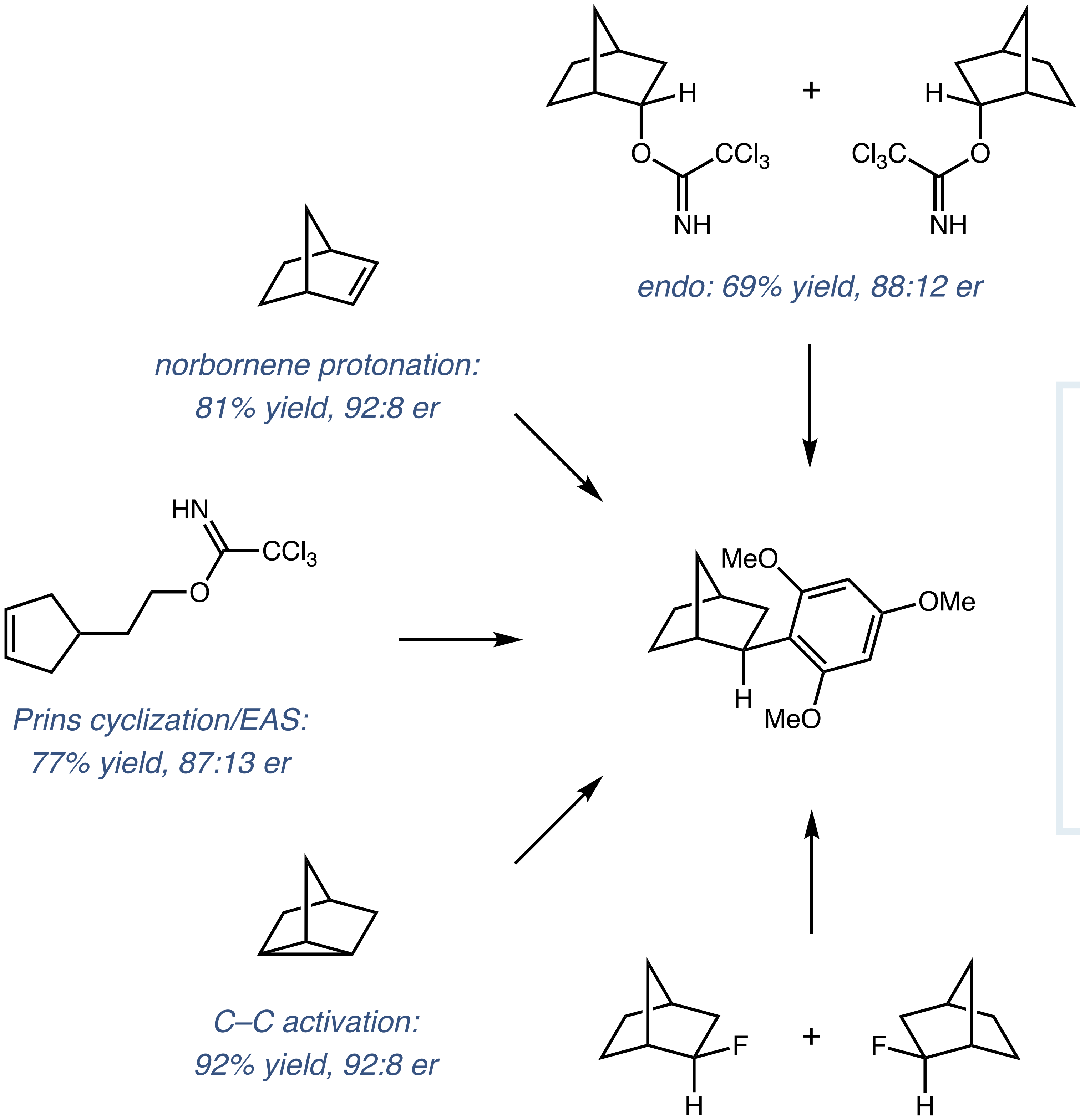
imidodiphosphorimidate catalyst

catalyst and leaving group optimization critical

other Brønsted acids produced conjugate bases capable of adding directly to 2-norbornyl cation

Propoerzi, R.; Kaib, P. S. J.; Leutzsch, M. *et al. Nat. Chem.* **2020**, *12*, 1174.

Enantiocontrol in non-classical carbocation reactions



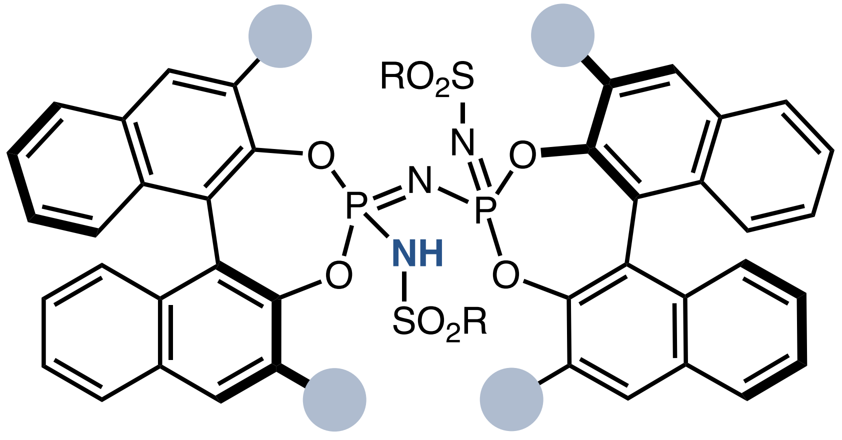
endo: 69% yield, 88:12 er

norbornene protonation:
81% yield, 92:8 er

Prins cyclization/EAS:
77% yield, 87:13 er

C–C activation:
92% yield, 92:8 er

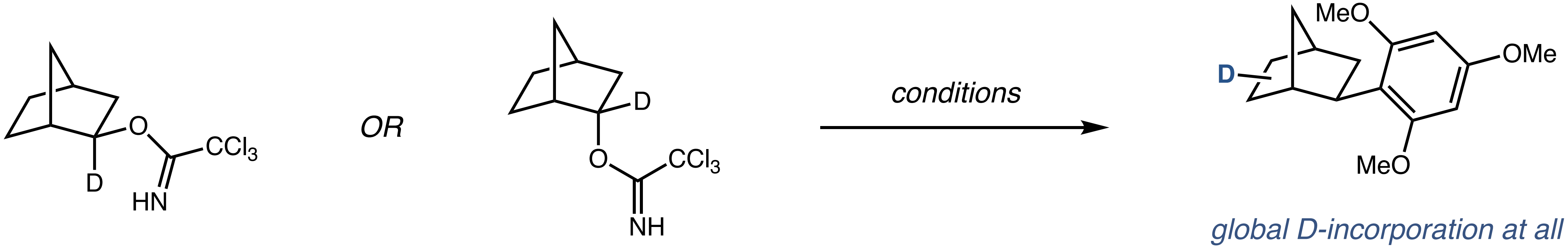
Si⁺ fluoride abstraction: 89% yield, 92:8 er



imidodiphosphorimidate catalyst

Propoerzi, R.; Kaib, P. S. J.; Leutzsch, M. *et al. Nat. Chem.* **2020**, *12*, 1174.

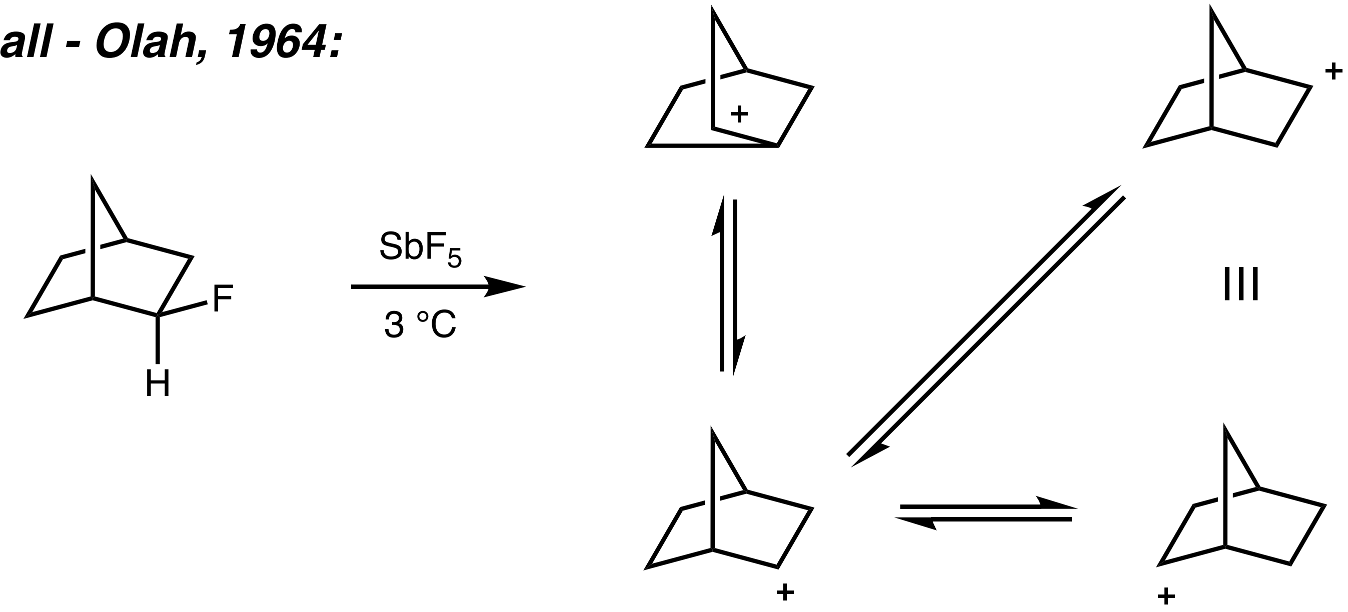
Enantiocontrol in non-classical carbocation reactions



isotopic labeling studies uninformative

global D-incorporation at all norbornane positions

Recall - Olah, 1964:

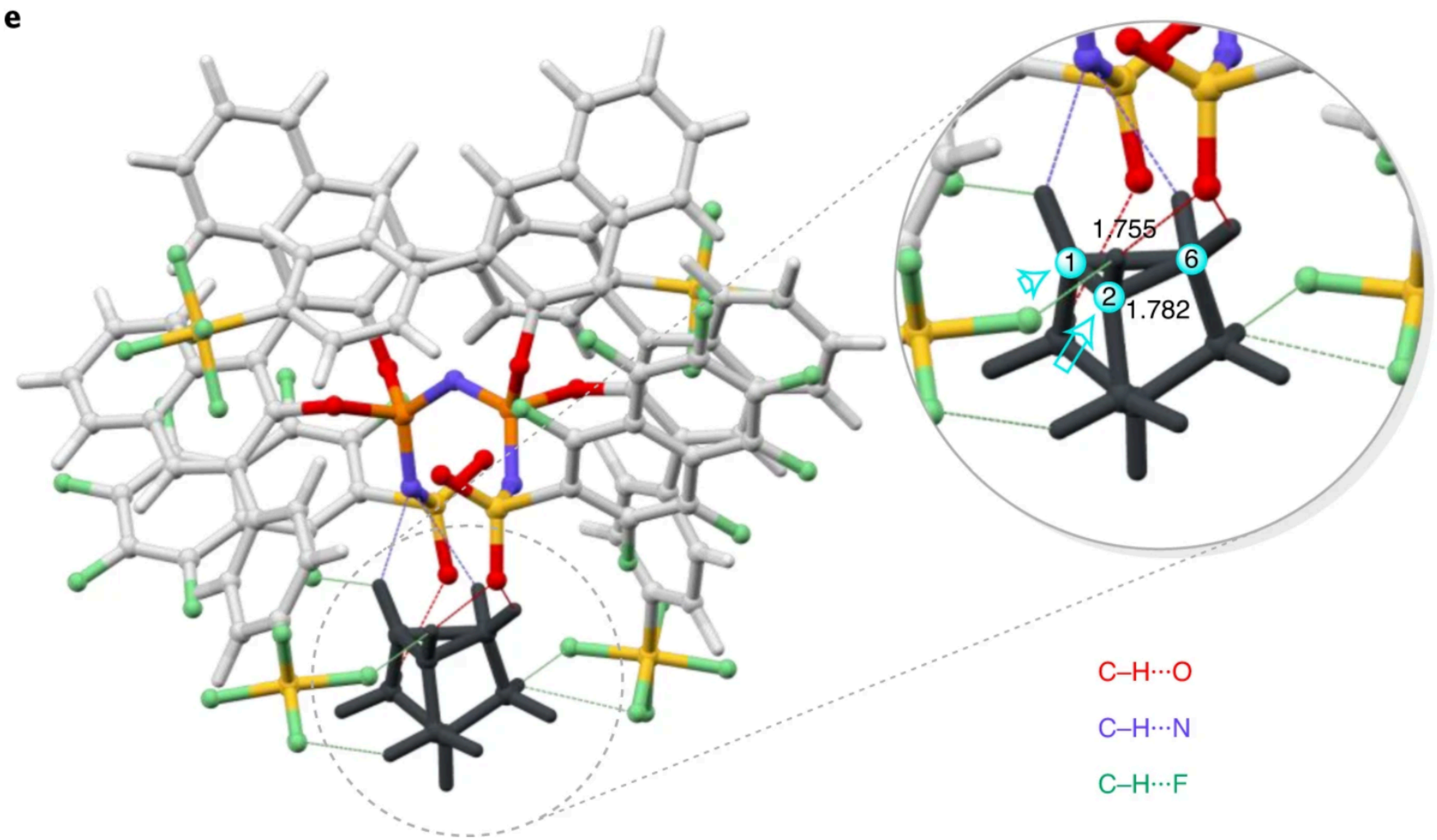


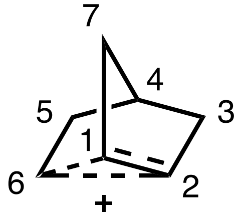
rapid Wagner-Meerwein and hydride shifts

similar scrambling consistent with non-classical intermediate

Propoerzi, R.; Kaib, P. S. J.; Leutzsch, M. *et al. Nat. Chem.* **2020**, *12*, 1174.

Enantiocontrol in non-classical carbocation reactions





DFT suggestive of anionic stabilization of three electrophilic positions in non-classical cation

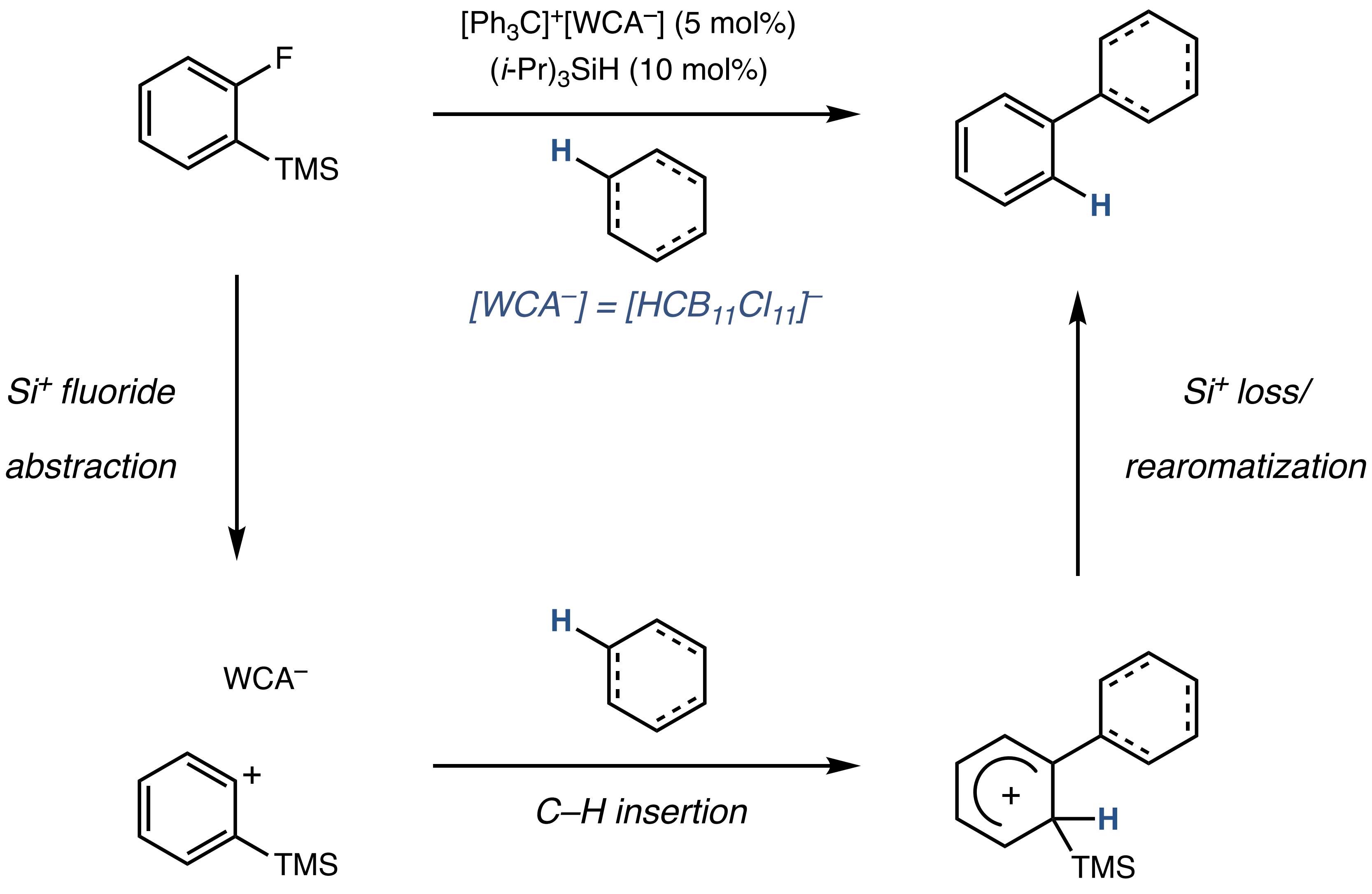
Propoerzi, R.; Kaib, P. S. J.; Leutzsch, M. *et al*. *Nat. Chem.* **2020**, *12*, 1174.

Outline

- *Fundamentals of non-classical carbocations: bonding, reactivity and common examples*
- *How it all began: the 2-norbornyl cation debate*
- *Non-classical reactivity in action: biosynthesis and reactions of complex molecules*
- *Modern developments in non-classical carbocation chemistry*
    - *enantioselective transformations (List/Schreiner)*
    - *intermolecular non-classical interactions in C–H activation (Nelson)*

C–H insertion by aryl cations

Nelson, 2017:



[Ph$_3$C]$^+$[WCA$^-$] (5 mol%)
(*i*-Pr)$_3$SiH (10 mol%)

[WCA$^-$] = [HCB$_{11}$Cl$_{11}$]$^-$

Si$^+$ fluoride abstraction

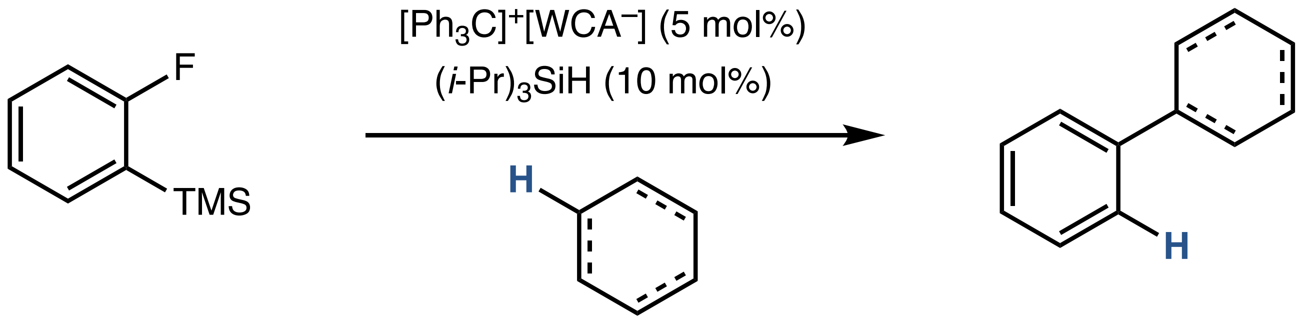
Si$^+$ loss/ rearomatization

C–H insertion

Shao, B.; Bagdasarian, A. L.; Popov, S.; Nelson, H. M. *Science* **2017**, *355*, 1403.

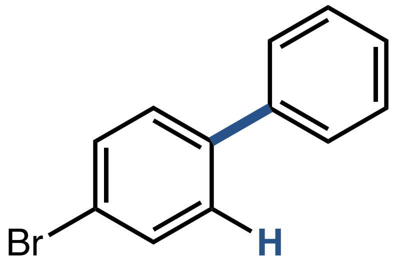
C–H insertion by aryl cations

Nelson, 2017:

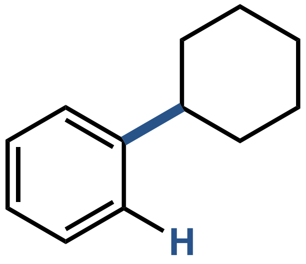


$[Ph_3C]^+[WCA^-]$ (5 mol%)
$(i\text{-}Pr)_3SiH$ (10 mol%)

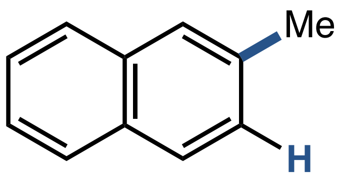
$[WCA^-] = [HCB_{11}Cl_{11}]^-$



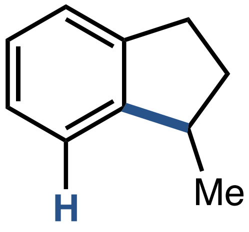
arylation



alkylation



methylation

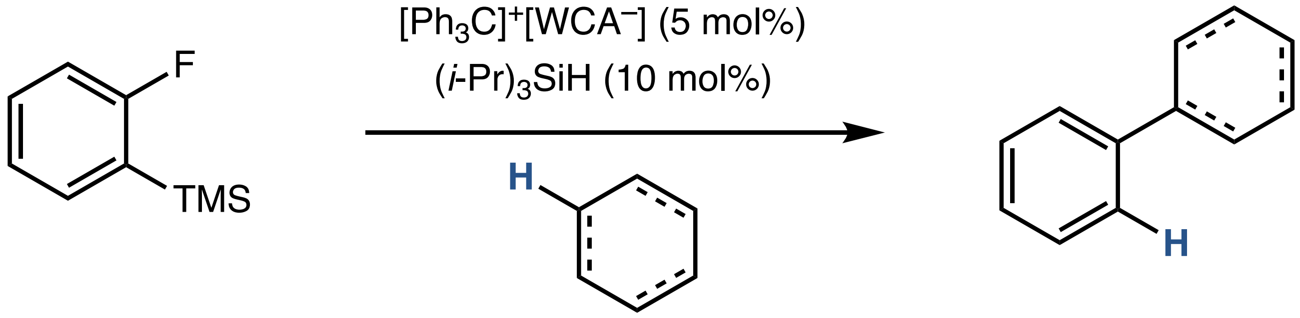


cyclization

Shao, B.; Bagdasarian, A. L.; Popov, S.; Nelson, H. M. *Science* **2017**, *355*, 1403.

C–H insertion by aryl cations

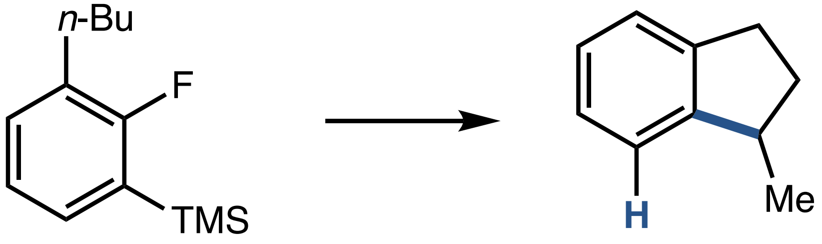
Nelson, 2017:



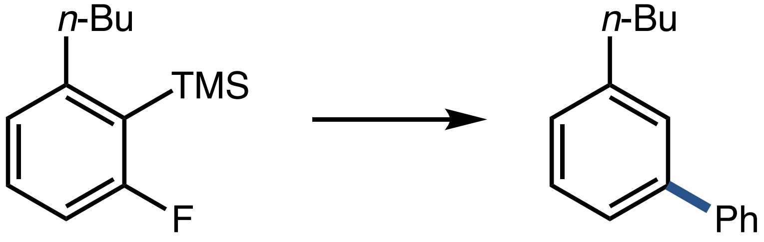
$[Ph_3C]^+[WCA^-]$ (5 mol%)
$(i\text{-}Pr)_3SiH$ (10 mol%)

$[WCA^-] = [HCB_{11}Cl_{11}]^-$

notable observations



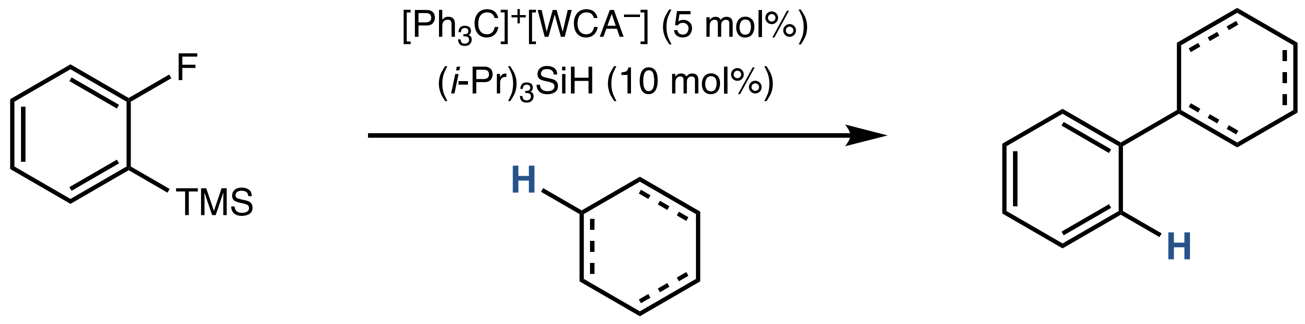
no evidence of aryne



Shao, B.; Bagdasarian, A. L.; Popov, S.; Nelson, H. M. *Science* **2017**, *355*, 1403.

C–H insertion by aryl cations

Nelson, 2017:



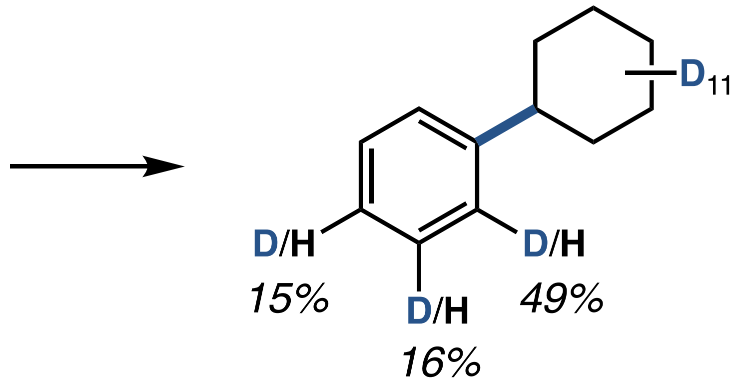
$[Ph_3C]^+[WCA^-]$ (5 mol%)

$(i\text{-Pr})_3SiH$ (10 mol%)

$[WCA^-] = [HCB_{11}Cl_{11}]^-$

notable observations

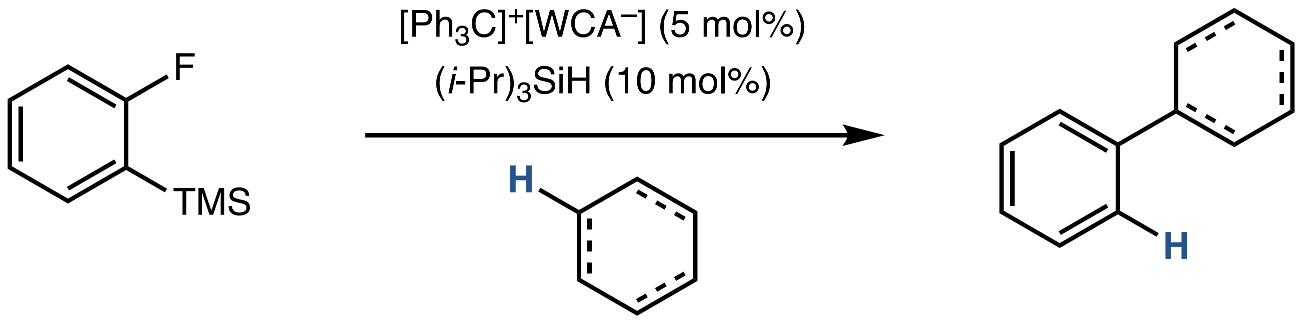
alkane = cyclohexane-d_{12}



Shao, B.; Bagdasarian, A. L.; Popov, S.; Nelson, H. M. *Science* **2017**, *355*, 1403.

C–H insertion by aryl cations

Nelson, 2017:



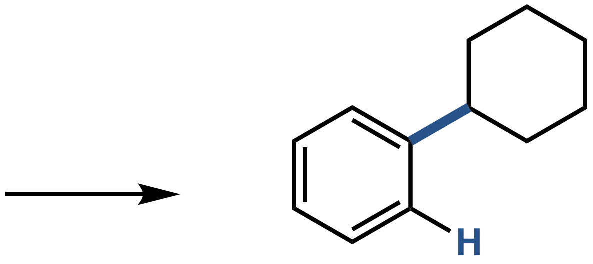
$[Ph_3C]^+[WCA^-]$ (5 mol%)

$(i\text{-}Pr)_3SiH$ (10 mol%)

$[WCA^-] = [HCB_{11}Cl_{11}]^-$

notable observations

alkane = cyclohexane-d_{12}
+ cyclohexane (1:1)



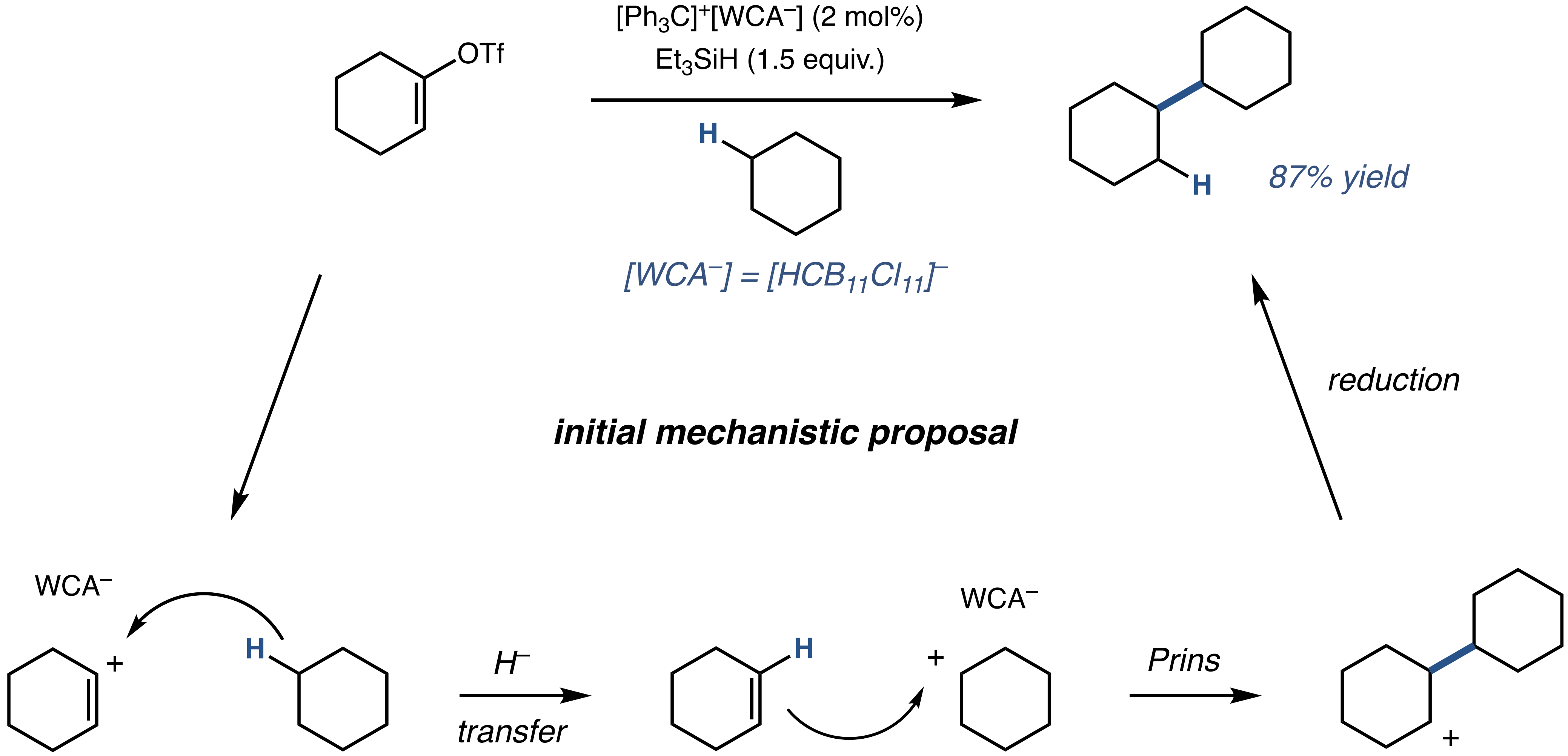
$k_H/k_D = 1.08$

non-rate-limiting C–H insertion?

Shao, B.; Bagdasarian, A. L.; Popov, S.; Nelson, H. M. *Science* **2017**, *355*, 1403.

C–H insertion by vinyl cations: evidence of a non-classical mechanism

Nelson, 2018:



$[Ph_3C]^+[WCA^-]$ (2 mol%)
Et_3SiH (1.5 equiv.)

87% yield

$[WCA^-] = [HCB_{11}Cl_{11}]^-$

initial mechanistic proposal

reduction

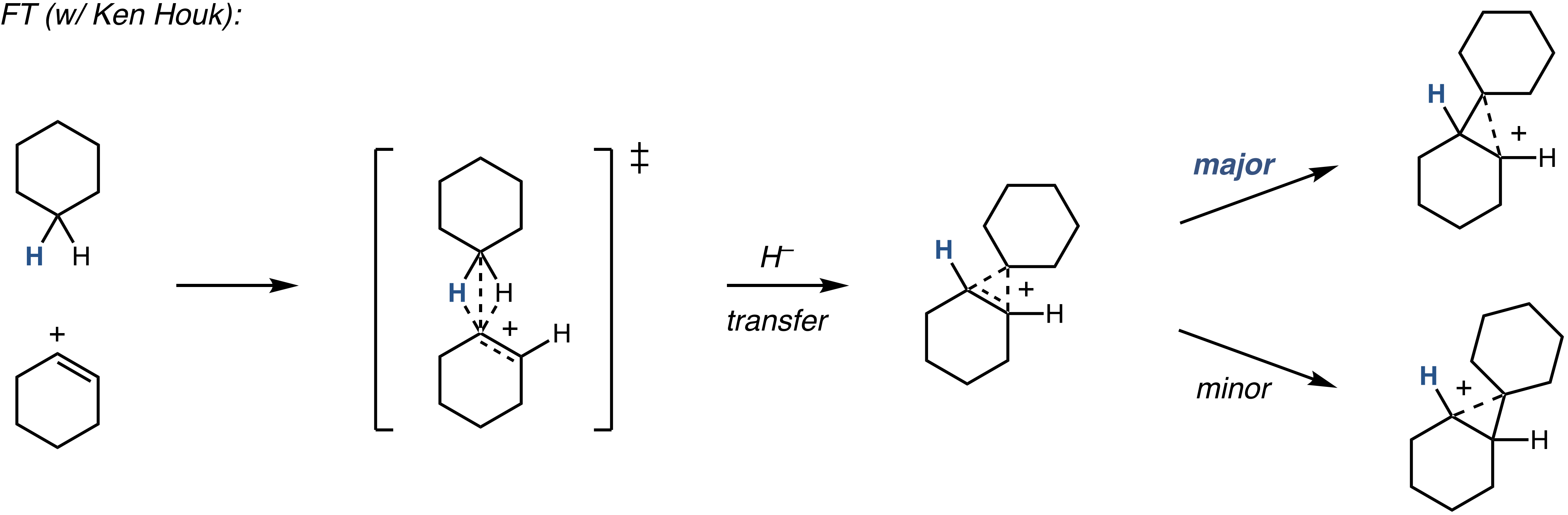
H^- transfer

Prins

Popov, S.; Shao, B.; Bagdasarian, A. L.; Benton, T. R.; Zuo, L.; Yang, Z.; Houk, K. N.; Nelson, H. M. *Science* **2018**, *361*, 381.

C–H insertion by vinyl cations: evidence of a non-classical mechanism

DFT (w/ Ken Houk):



unexpected finding that reaction depends on non-classical intermediates and favors geminal (1,1) insertion

hydride shifts still possible prior to reduction, resulting in scrambling of (1,1) arrangement

Popov, S.; Shao, B.; Bagdasarian, A. L.; Benton, T. R.; Zuo, L.; Yang, Z.; Houk, K. N.; Nelson, H. M. *Science* **2018**, *361*, 381.

C–H insertion by vinyl cations: evidence of a non-classical mechanism

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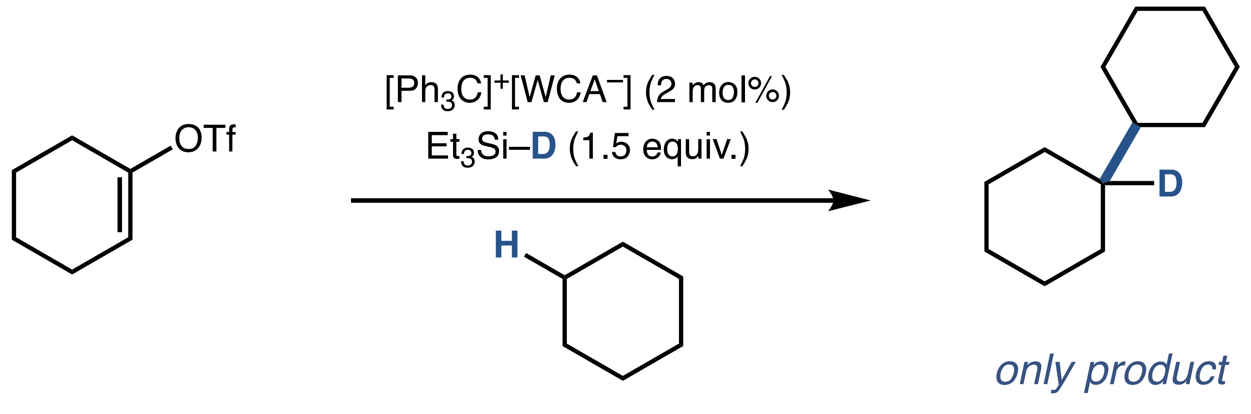
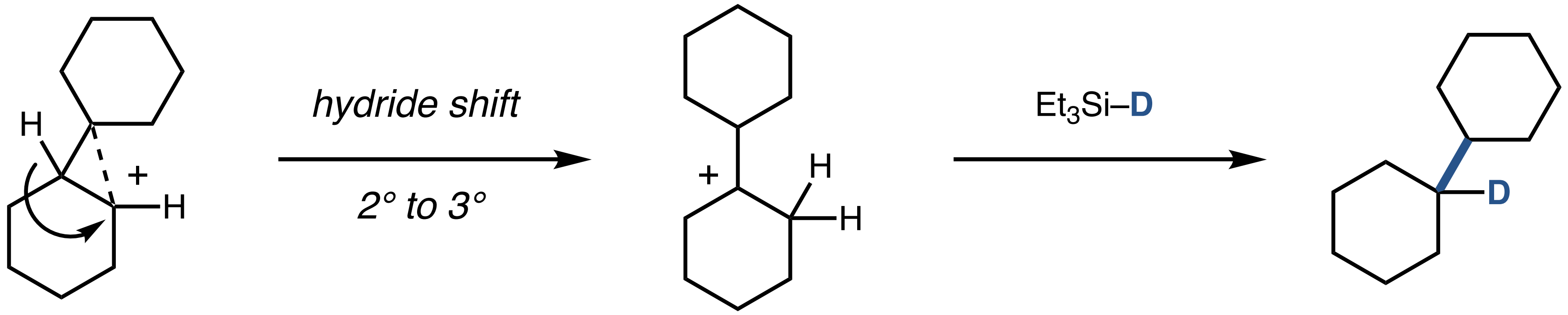


$[WCA^-] = [HCB_{11}Cl_{11}]^-$

only product



(1,1) intermediate

Popov, S.; Shao, B.; Bagdasarian, A. L.; Benton, T. R.; Zuo, L.; Yang, Z.; Houk, K. N.; Nelson, H. M. *Science* **2018**, *361*, 381.

C–H insertion by vinyl cations: evidence of a non-classical mechanism

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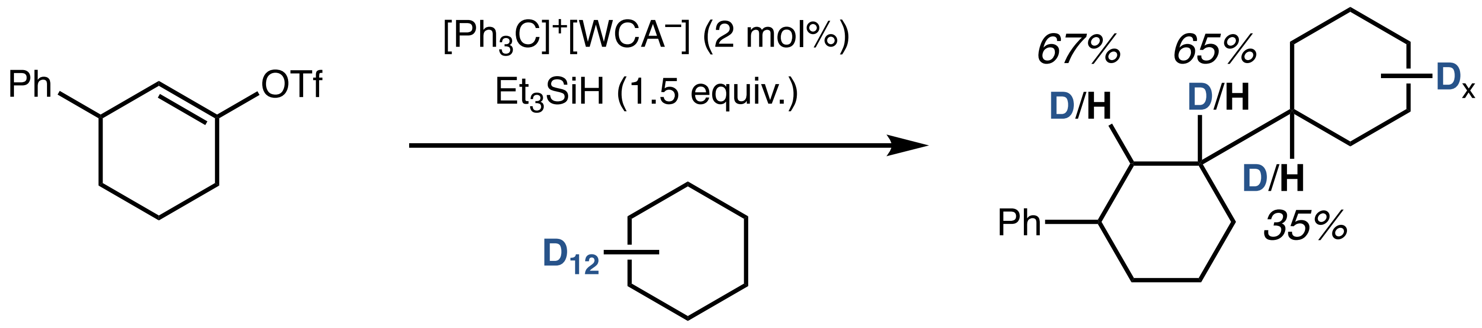
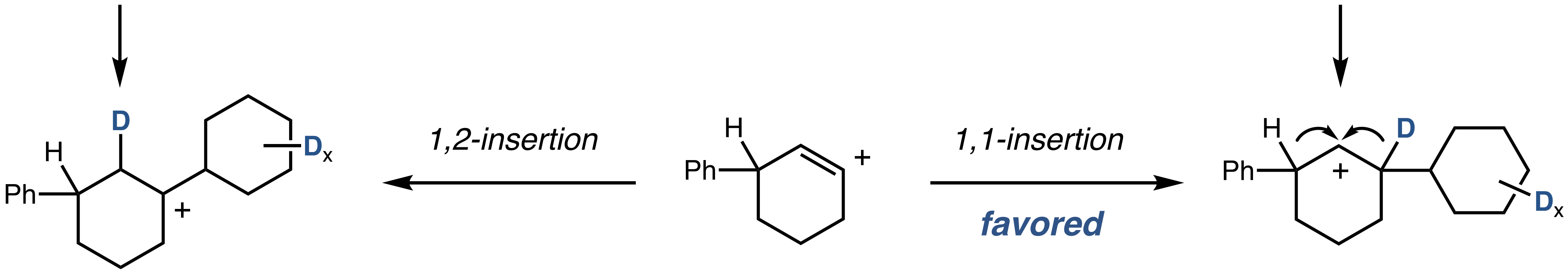


$[WCA^-] = [HCB_{11}Cl_{11}]^-$

will not shift (3° to 2°)
expect 100% D-incorporation

either H or D could shift (2° to 3° or benzylic)
expect H/D mixture



Popov, S.; Shao, B.; Bagdasarian, A. L.; Benton, T. R.; Zuo, L.; Yang, Z.; Houk, K. N.; Nelson, H. M. *Science* **2018**, *361*, 381.

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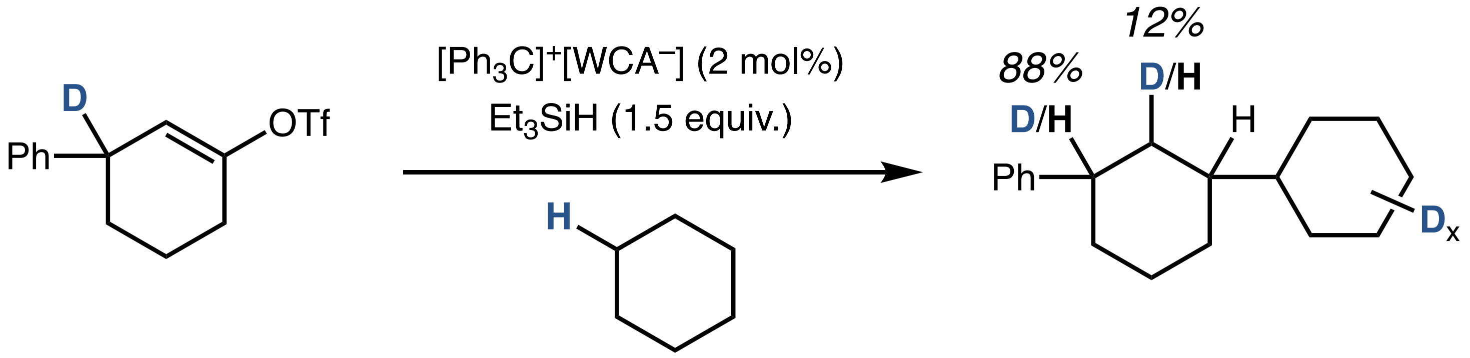
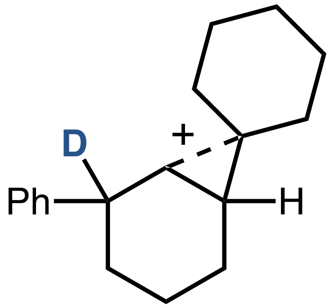


$[Ph_3C]^+[WCA^-]$ (2 mol%)
Et_3SiH (1.5 equiv.)

$[WCA^-] = [HCB_{11}Cl_{11}]^-$

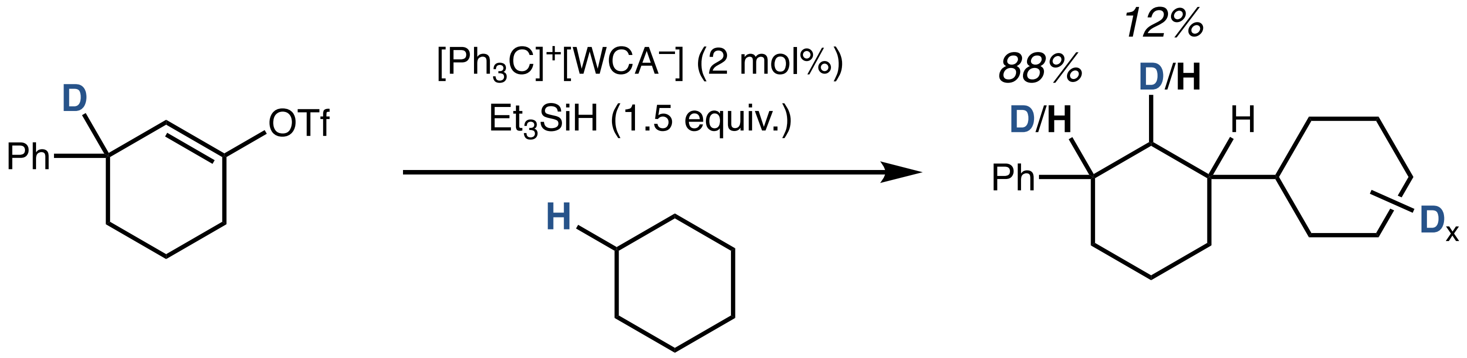


intermediate must be highly stabilized (i.e. non-classical) if formation of benzylic cation is slow

Popov, S.; Shao, B.; Bagdasarian, A. L.; Benton, T. R.; Zuo, L.; Yang, Z.; Houk, K. N.; Nelson, H. M. *Science* **2018**, *361*, 381.

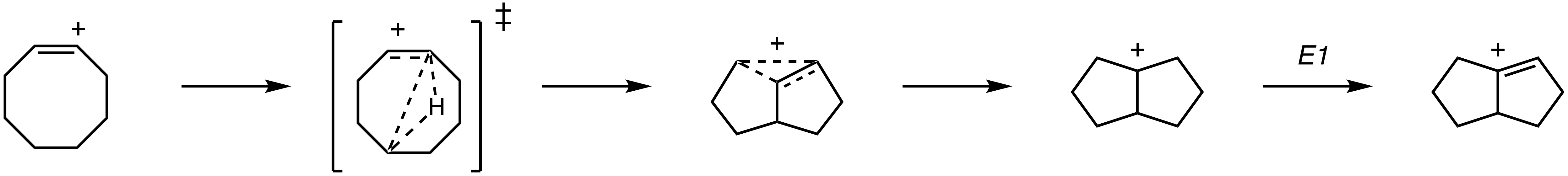
C–H insertion by vinyl cations: evidence of a non-classical mechanism

Nelson, 2018:



[WCA$^-$] = [HCB$_{11}$Cl$_{11}$]$^-$

trends hold for additional cases (i.e. intramolecular, transannular)



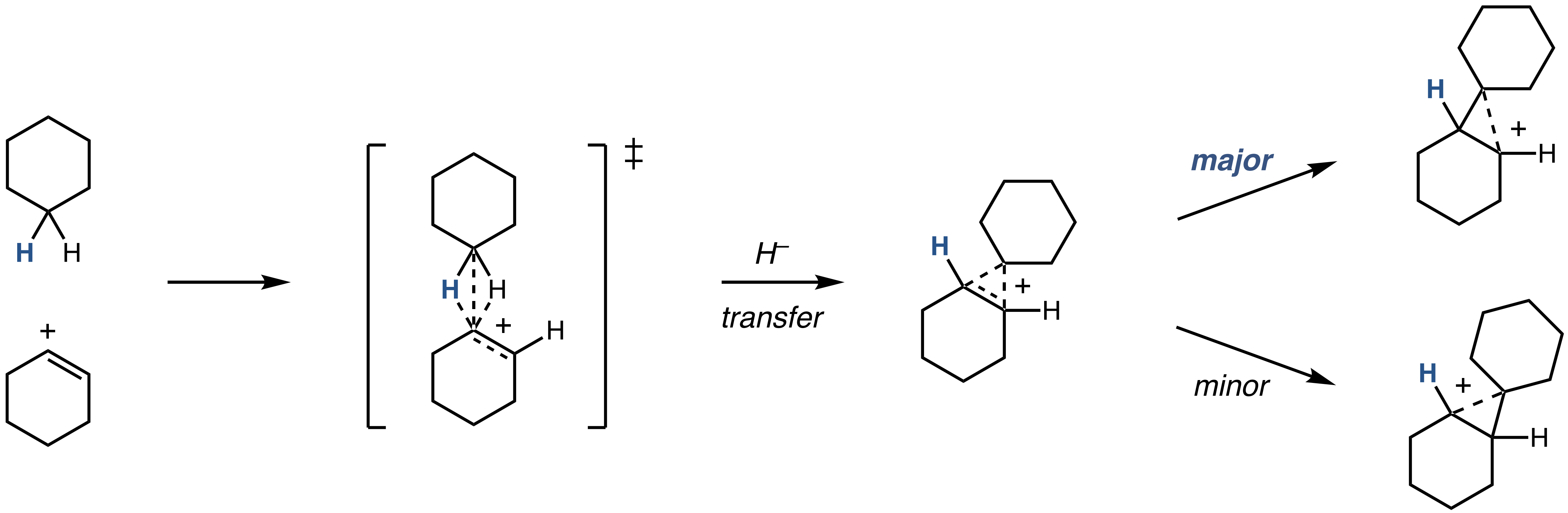
transannular C–H insertion

non-classical 2° to 3° transition

Wigman, B. *et al. J. Am. Chem. Soc.* **2019**, *141*, 9140.

Popov, S.; Shao, B.; Bagdasarian, A. L.; Benton, T. R.; Zuo, L.; Yang, Z.; Houk, K. N.; Nelson, H. M. *Science* **2018**, *361*, 381.

C–H insertion by vinyl cations: evidence of a non-classical mechanism



new intermolecular reactivity can be obtained via non-classical interactions of "naked" carbocations

Popov, S.; Shao, B.; Bagdasarian, A. L.; Benton, T. R.; Zuo, L.; Yang, Z.; Houk, K. N.; Nelson, H. M. *Science* **2018**, *361*, 381.