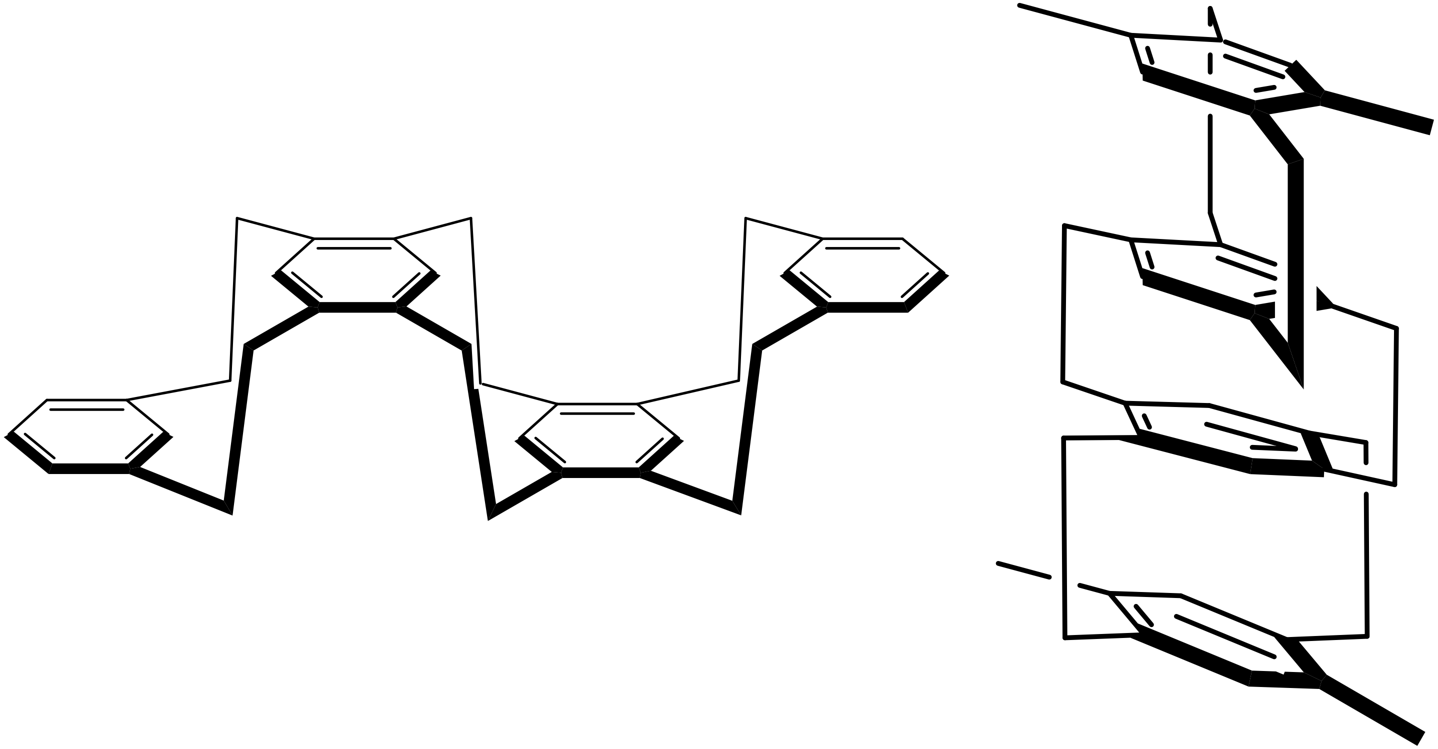
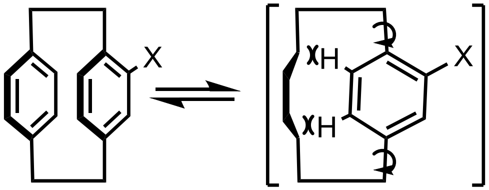
Cyclophanes: A Strained Overview

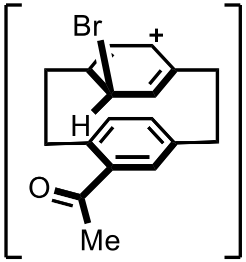


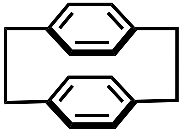
11/26/2019

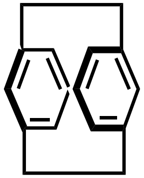
Brennan T. Rose

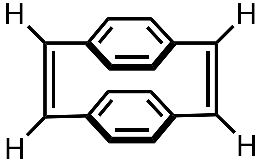
Overview

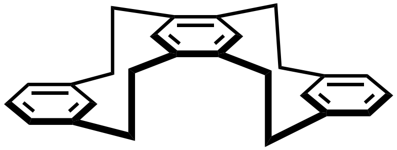


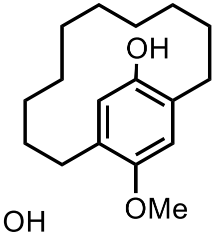


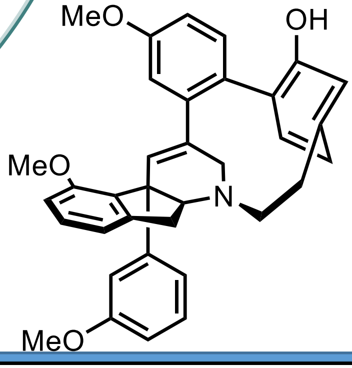






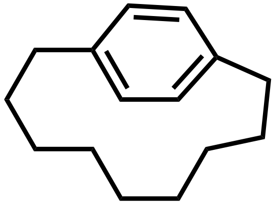


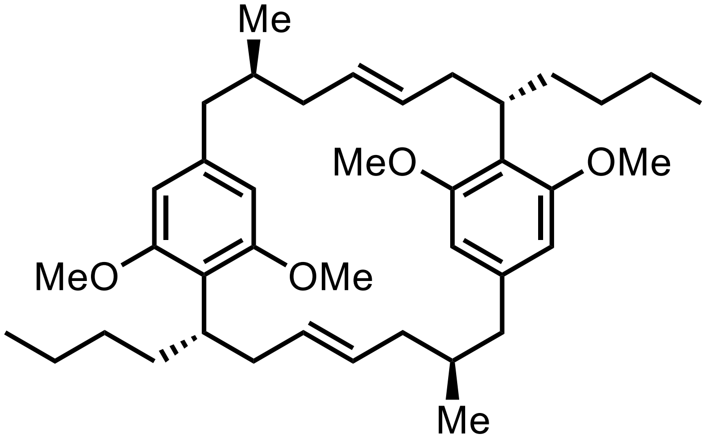




What is a Cyclophane?

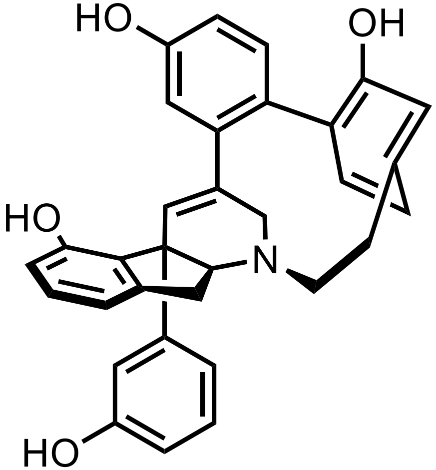
Traditional Definition: A hydrocarbon chain forming a bridge between two non adjacent positions on an aromatic ring

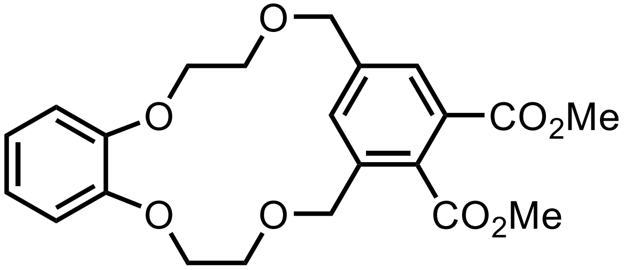




Modern Definition:

A cyclic system with or without heteroatoms and containing a non-adjacent fused aromatic ring

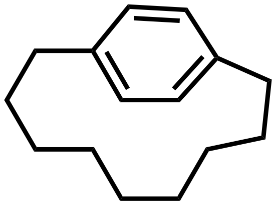




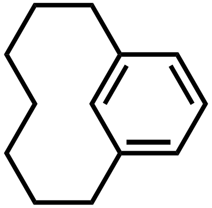
Baran, P. S. Nat. Prod. Rep. **2012**, 29, 899

Nomenclature of Simple Cyclophanes

Monoaromatic cyclophanes: formula [X]Ycyclophane
X = number of atoms in chain Y = substitution pattern of aromatic

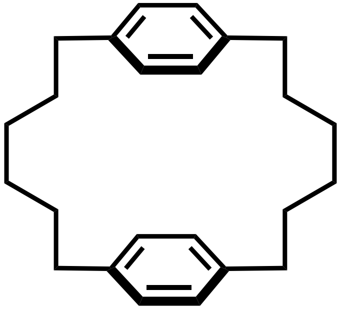


[9]Paracyclophane

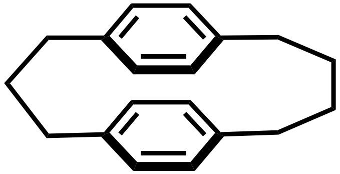


[7]metacyclophane

Bisaromatic cyclophanes: formula [X.X']Ycyclophane
X and X' = number of atoms in chain each chain between the atomatics Y = substitution pattern of aromatic



[6.6]Paracyclophane

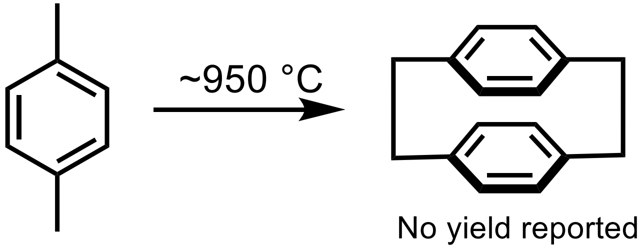


[3.4]Paracyclophane

Baran, P. S. Angew. Chem. Int. Ed. 2008, 47, 205

Discovery of [2.2]Paracyclophane

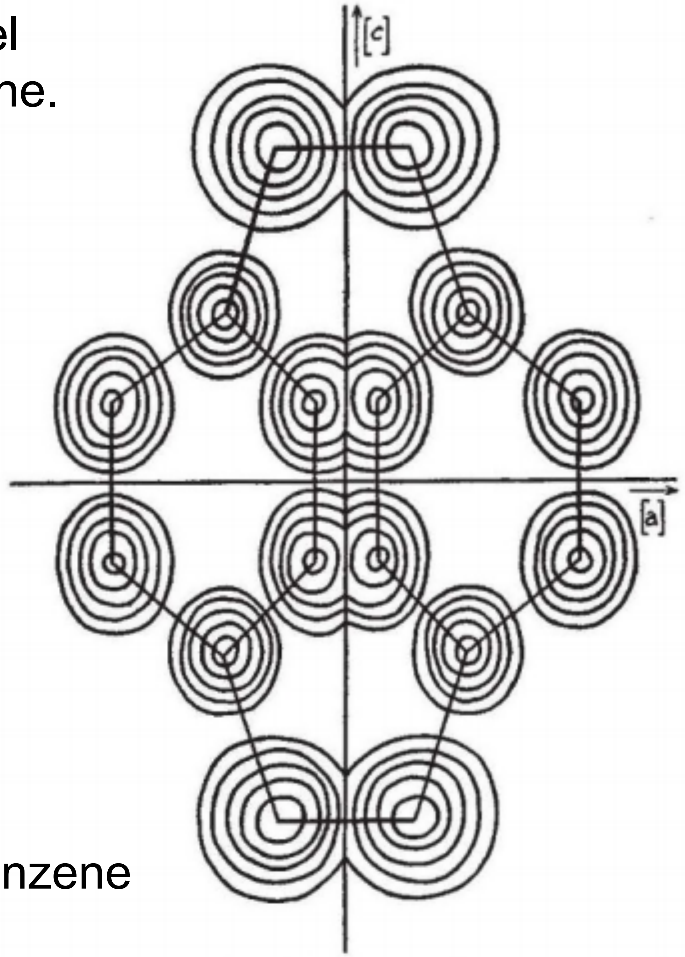
Serendipity: Brown and Farthing discovered a novel hydrocarbon during polymerization studies of *p*-xylene.



No yield reported

Proposed trivial name "di-*p*-xylene"

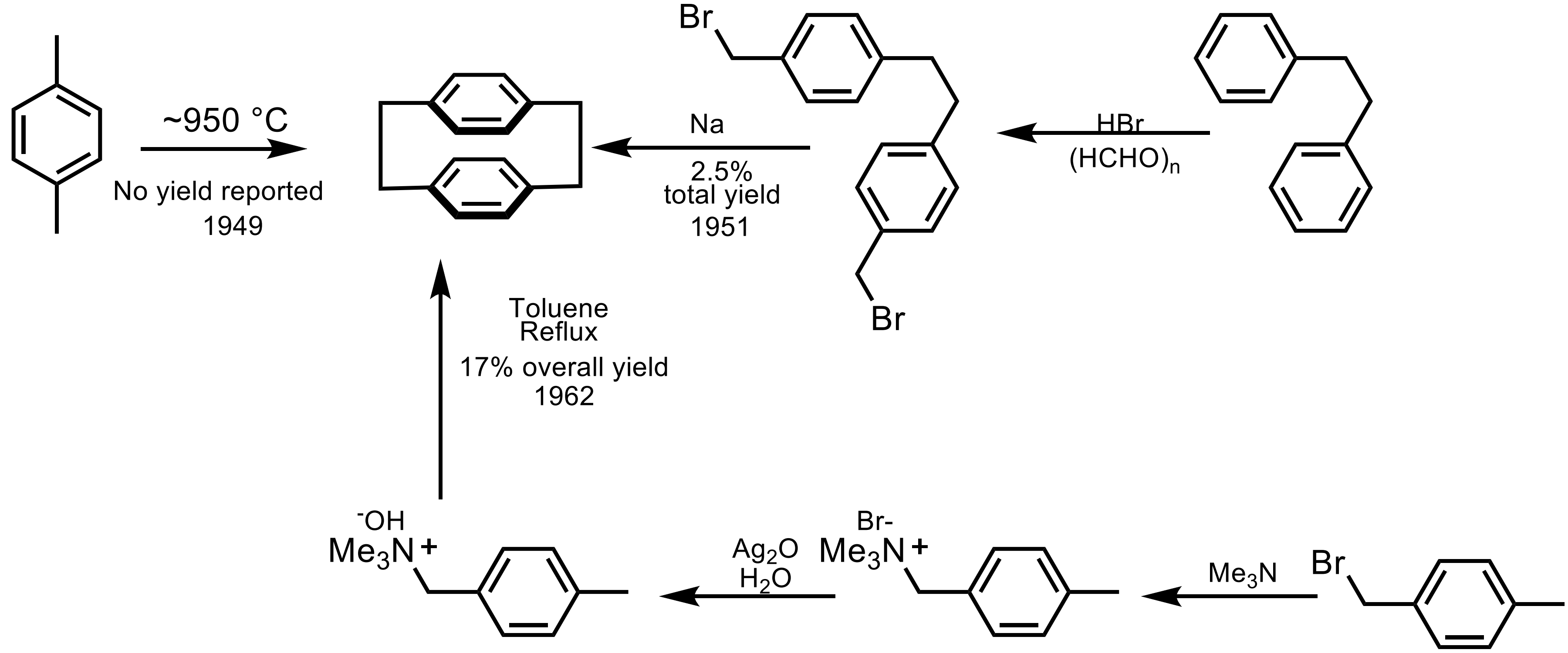
Bent benzene: The substituted carbons in each benzene ring are displaced from the plane by 0.13 **Å**



Composite three-dimensional electron density map of di-*p*-xylylene

Brown, C. J.; Farthing, A. C. *Nature,* ***1949***, 164, 915-916

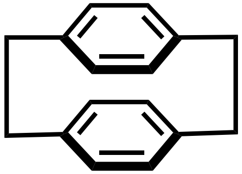
Synthesis of [2.2]Paracyclophane



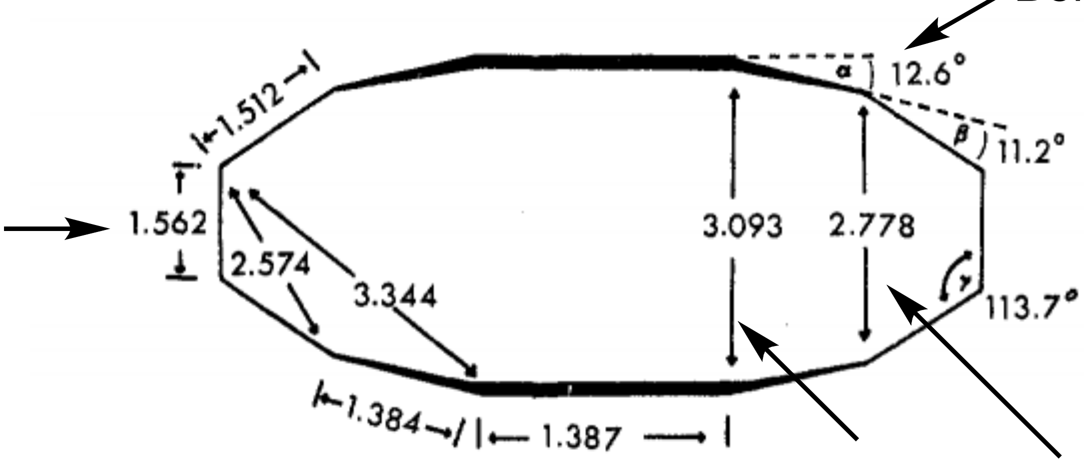
[2.2]paracyclophane: Commercially available $43.2/g

Brown, C. J.; Farthing, A. C. *Nature, **1949***, 164, 915-916
Cram, D. J.; Steinberg, H. *J. Am. Chem. Soc.* **1951**, 73, 5691 Winberg, H.W.; Fawcett, F.S. *Org. Synth.* **1962**, 42, 83

Unique Structural Properties



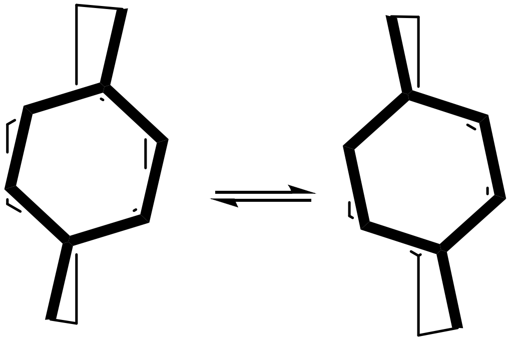
Elongated benzyl-benzyl bond



Bent benzene rings

Small distance between aromatic rings.
Typical intramolecular distance between stacked aromatic rings is 3.40 **Å**

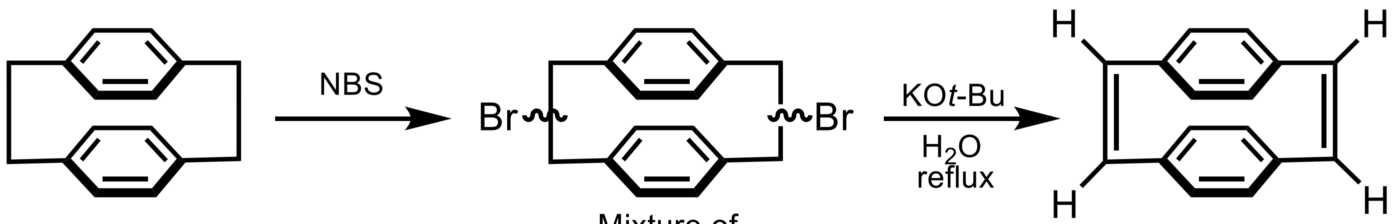
Molecular motion of [2.2]paracyclophane



Molecular motion: [2.2]paracyclophane demonstrates rotation of about 6° and causes difficulty obtaining a highly refined crystal structure

Cram, D. J.; Steinberg, H. *J. Am. Chem. Soc.* **1951**, 73, 569

Tetradehydro[2.2]paracyclophane

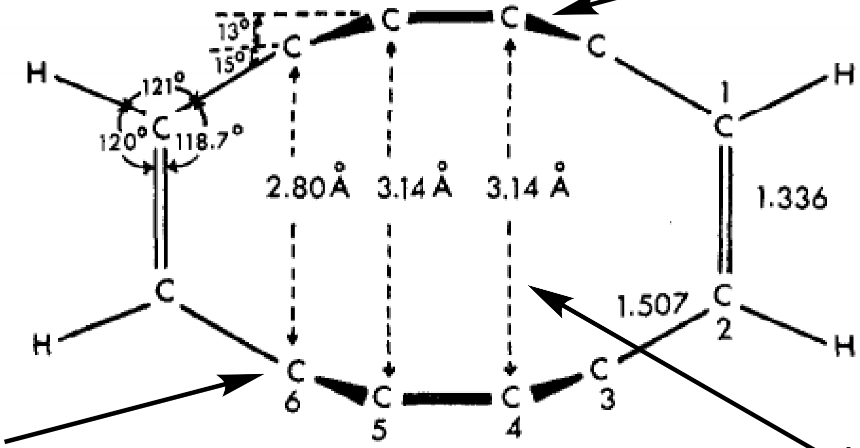


Mixture of constituional isomers
No geminal dibromide observed

No Molecular movement observed in crystal structure

Bent benzene ring

Chart II[a]



[a] Side profile of tetradehydro[2.2]paracyclophane (4).

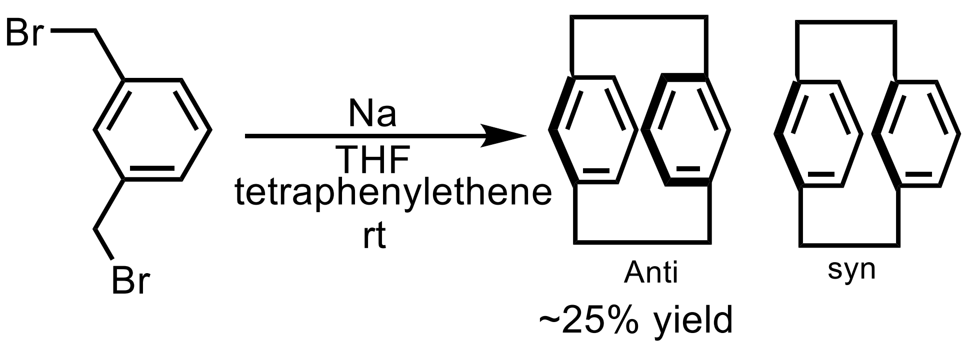
Hydrogen atoms on carbons 3,4,5,6 are bent inwards.

Due to π-π repulsion

Very short transannular distance

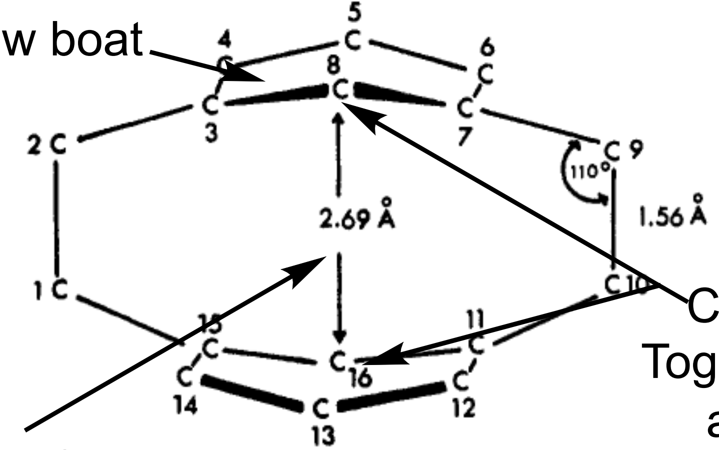
Dewhirst, K. C.; Cram, D.J. *J. Am. Chem. Soc.* **1958**, 80, 12, 3115-3125

[2.2]metacyclophane



~25% yield

- First cyclophane synthesized in 1899
- Left unexplored until 1949
- Unfunctionalized *syn* has never been made.
- Most highly cyclic molecules are rigid due to bonding interactions
- Small cyclophanes are rigid due to their nonbonding interactions



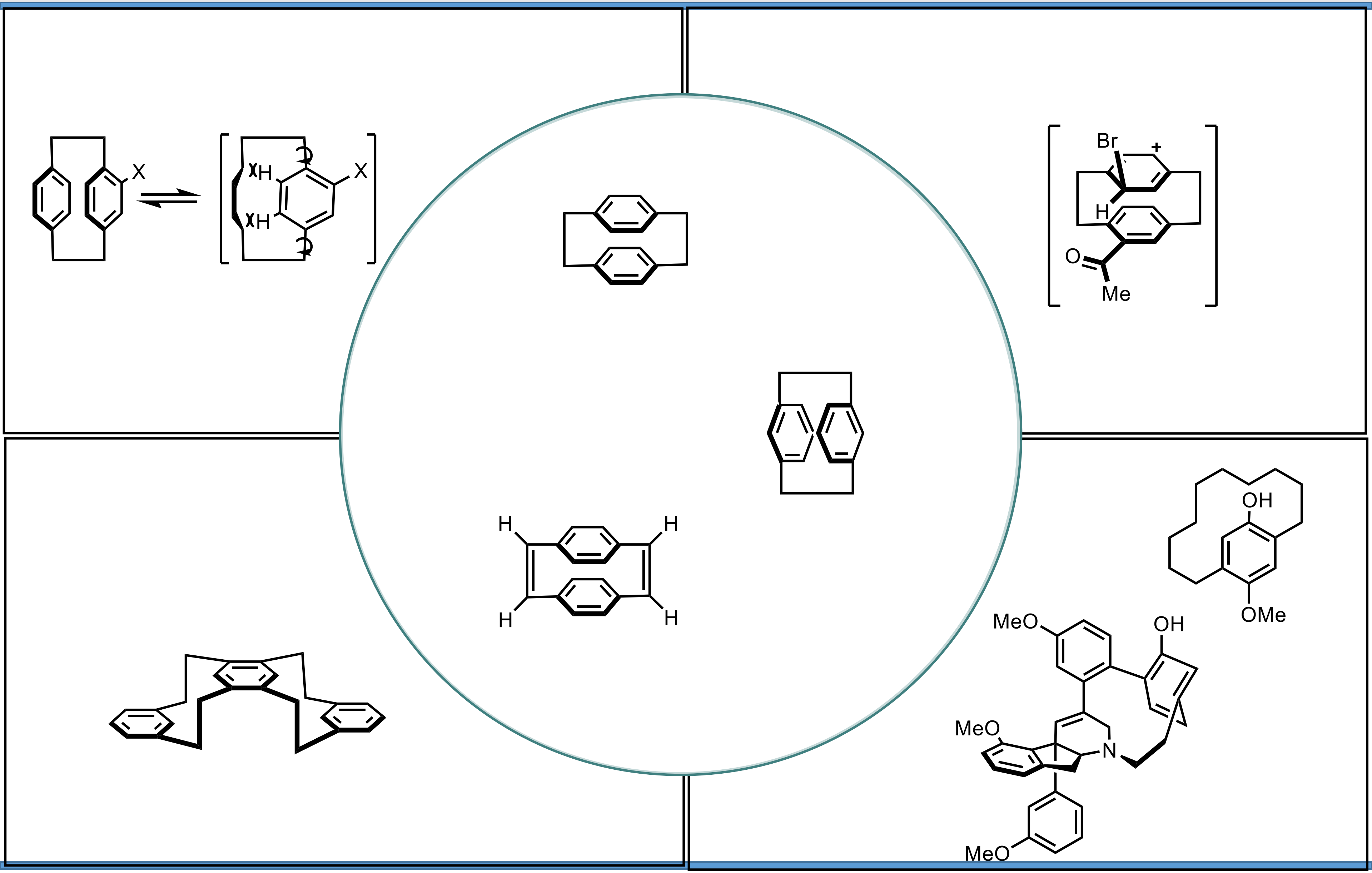
Benzene bent into a shallow boat

C8 and C16 are closest Together molecule forms an almost step like shape

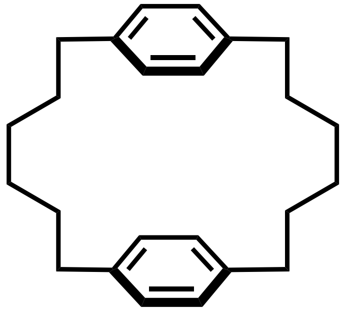
Shortest distance found in any cyclophane

Griffen Jr., R. W.; Boekelheide, V. J. Org. Chem. **1969**, 34, 6, 1960-1961.
Pellegrin, M.M Recl. Trab. Chim. Pays-Bas, **1899**, 18, 457

Overview

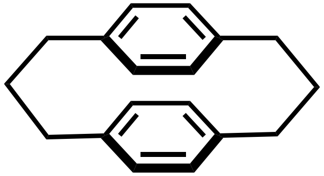


Ring Strain of Cyclophanes

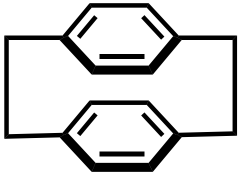


[6.6]Paracyclophane
2 kcal/mol

Essentially an open
chain compound

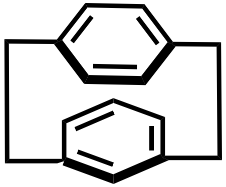


[3.3]Paracyclophane
12 kcal/mol

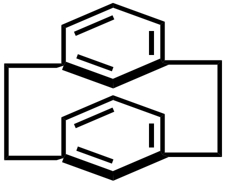


[2.2]Paracyclophane
31 kcal/mol

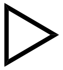
Under intense
ring strain



[2.2]metaparacyclophane
23 kcal/mol



[2.2]metacyclophane
13 kcal/mol

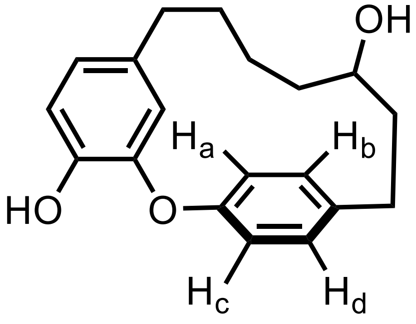


cyclopropane
27.5 kcal/mol

Cram, D. J.; Cram, J. M. *Acc. Chem. Res.* **1971**, 4, 6, 204-213

Restricted Rotation in Natural Products

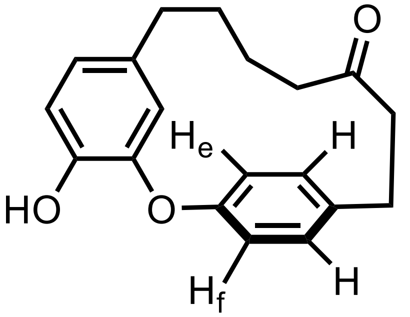
Acerogenin A and C have considerably different 1H NMR signals in the aromatic region.



Acerogenin A
Rotationally restricted

Protons A B C D all show up in the NMR as unique dd

Protons E and F form AB quartet in 1H NMR

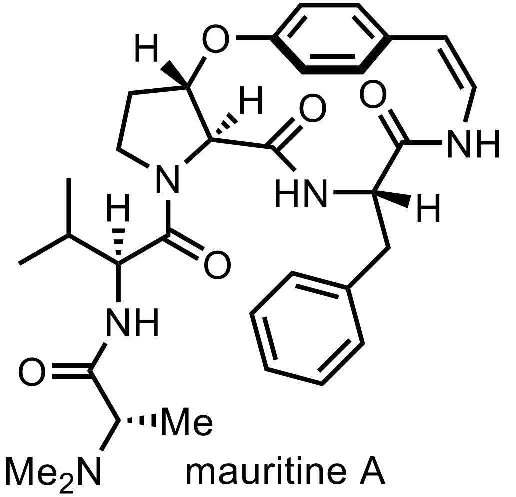


Acerogenin C
Rotationally flexible

Gonzalez, G. I.; Zhu, J. *J. Org. Chem.* 1997, 62, 22, 7544-7545

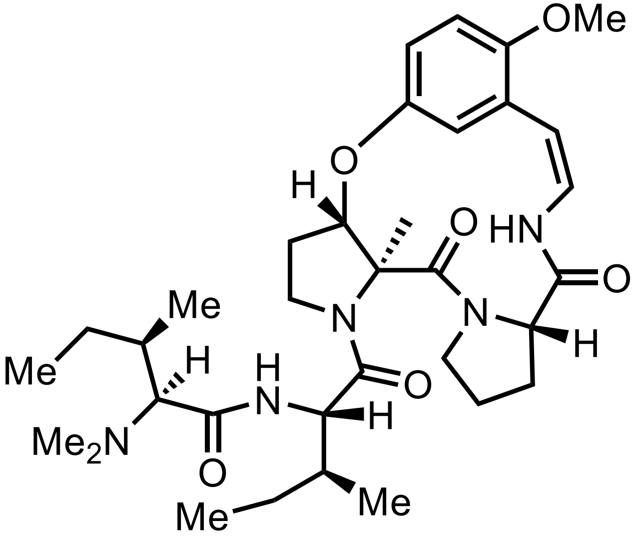
Restricted Rotation in Natural Products

Attachment point also matters for flexibility



mauritine A
Rotationally restricted

Mauritine A demonstrates distortion preventing conjugation of the π system and slight bending of the aromatic within the macrocycle

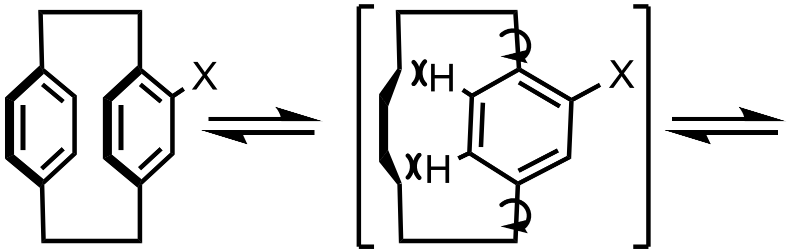


zizyphine A
Rotationally flexible

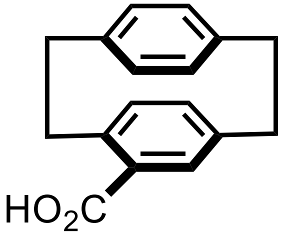
Zizyphine A demonstrates free rotation due to the meta substitution pattern of the cyclophane even though the ring system contains a second additional rigidifying proline and containing a smaller 13 membered cyclophane

Baran, P. S. Nat. Prod. Rep. **2012**, 29, 899

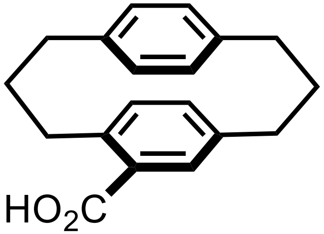
Ring Strain of Cyclophanes



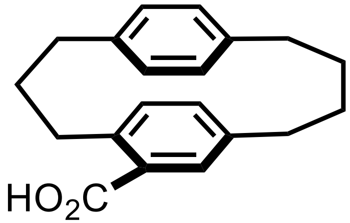
The unique rigidity and symmetry of cyclophanes provides the possibility for stable conformational isomers, high barriers for ring rotation, and planar chirality



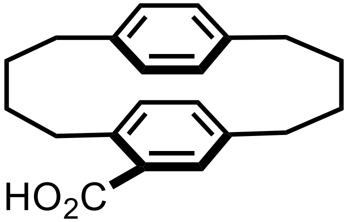
No racemization
Decomposition
200 °C



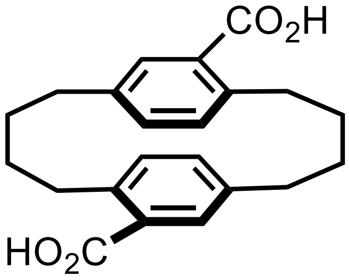
No racemization
240 °C



Slow Racemization at 160 °C
E.A. 33 kcal/mol



Not resolvable

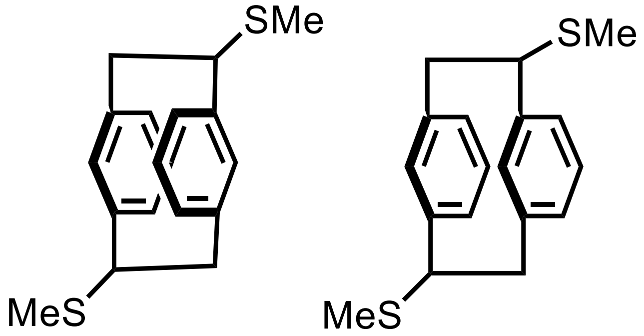


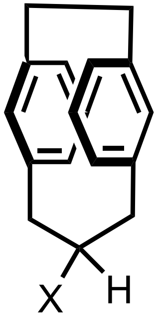
Racemization at 15 °C
E.A.. ~15 kcal/mol

Racemization occurs easily in rings with 16 or more atoms.

Cram, D. J.; Wechter, W. J.; Kierstead, R. W. J. *Am. Chem. Soc.* **1958**, 80, 12, 3126-3132

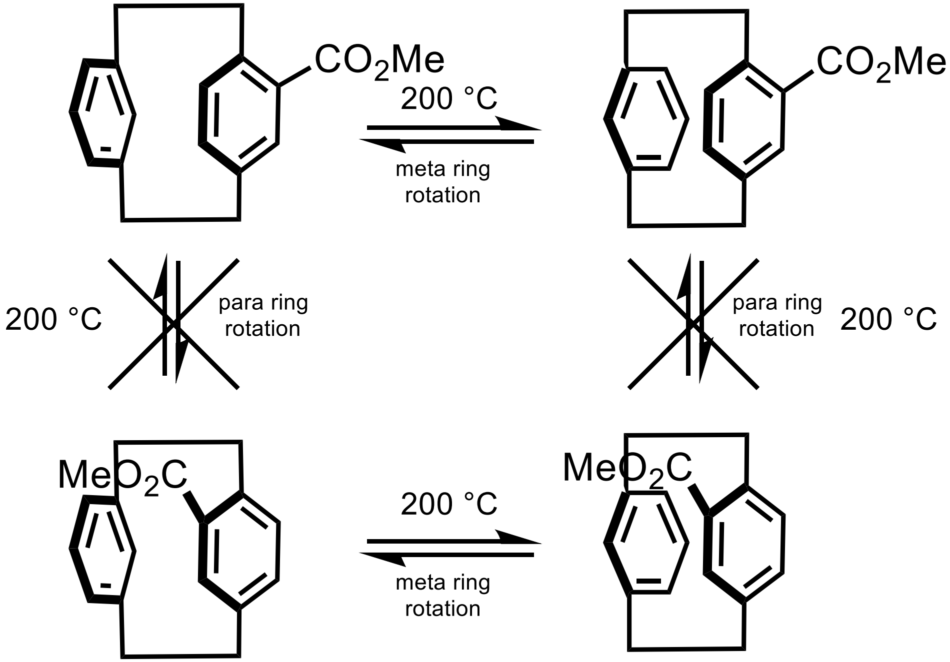
Rotational barriers



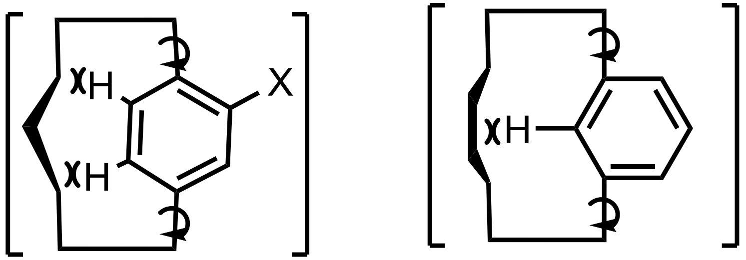


- [3.2]metacyclophane undergoes ring inversion between 60-120 °C depending on the substitutions
- E.A. 15.8-19.1 kcal/mol

- Mixture of constitutional isomers
- No ring inversion at 180 °C

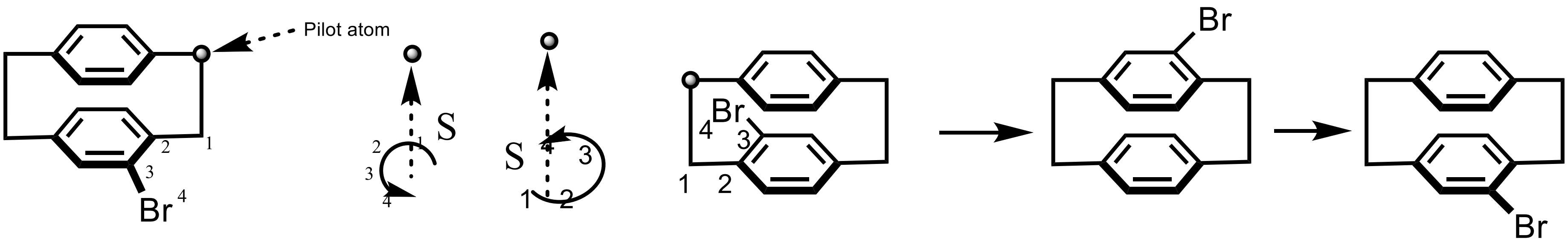


- Ring rotation in [2.2]metaparacyclophane has two possible rings that can undergo rotation
- Optically pure ester only inverts at the meta ring not the para ring

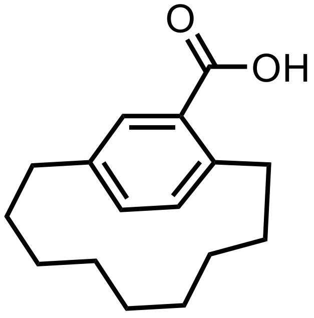


Cram, D. J.; Wechter, W. J.; Kierstead, R. W. J. *Am. Chem. Soc.* **1958**, 80, 12, 3126-3132

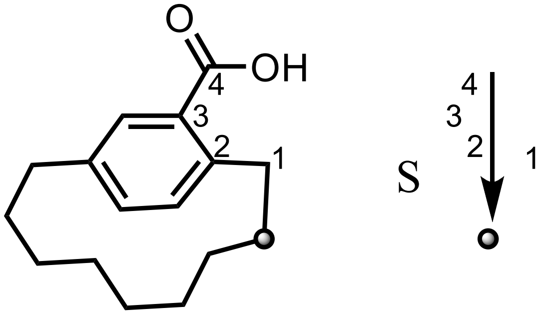
Assigning Absolute Configuration



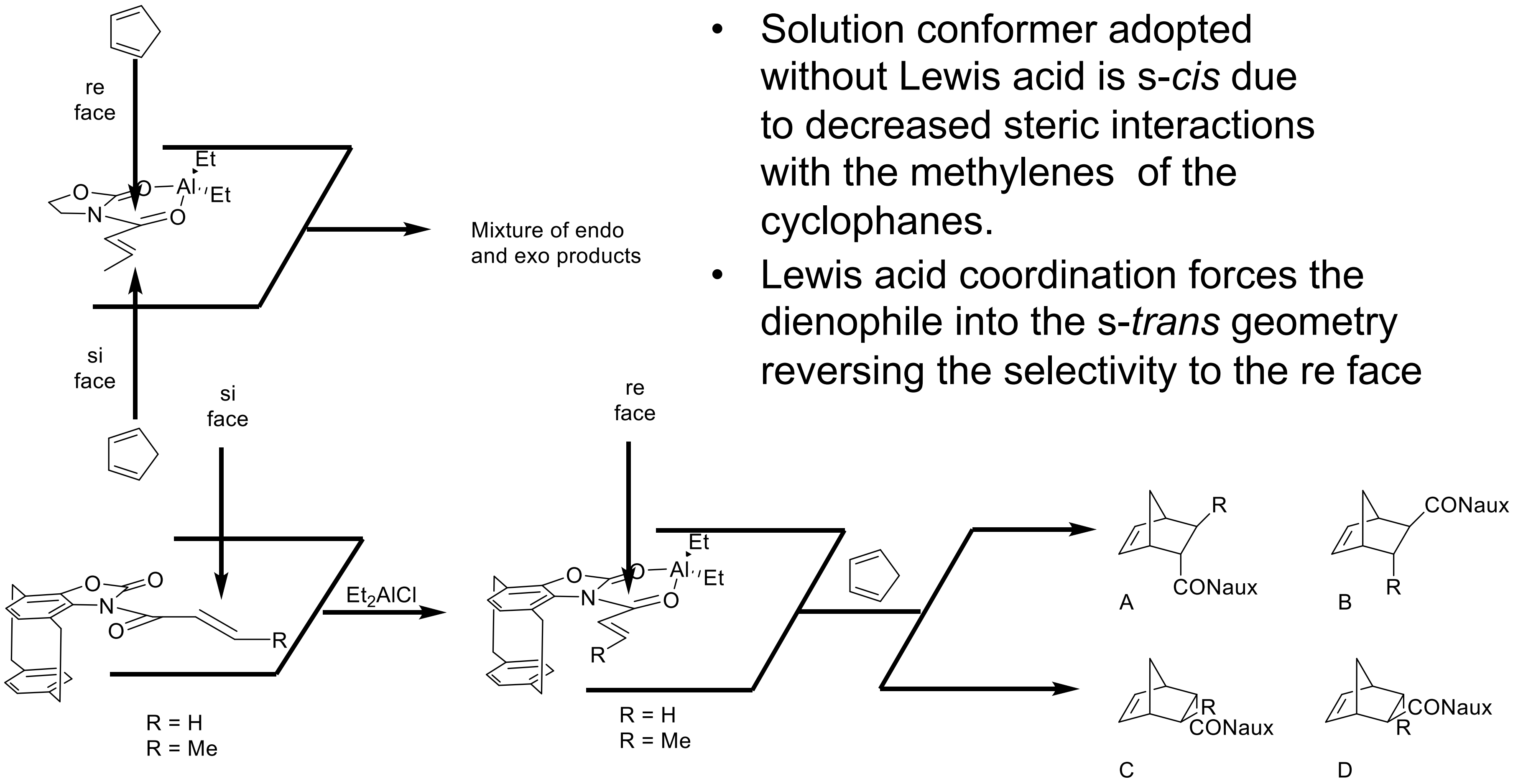
Practice problem



1. Arrange the cyclophane such that the arene and its substitution atoms all align in a plane.
2. Assign the pilot atom on the chain on the closest side to the highest Cahn Ingold Prelog priority non-chain substitution on the arene
3. Assign numbers to the atoms on route from the pilot atom to the substituent.
4. Look from the pilot atom into the numbered subs. R if numbers are clockwise or S if counter clockwise.



Cyclophanes Used as Auxiliaries



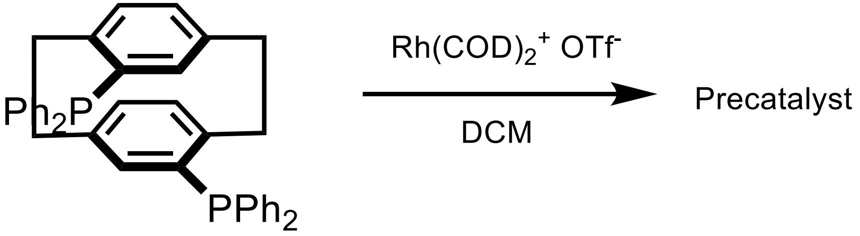
- Solution conformer adopted without Lewis acid is s-*cis* due to decreased steric interactions with the methylenes of the cyclophanes.
- Lewis acid coordination forces the dienophile into the s-*trans* geometry reversing the selectivity to the re face

Table 1. Diels–Alder Reactions of Dienophiles 8 and 9 with Cyclopentadiene

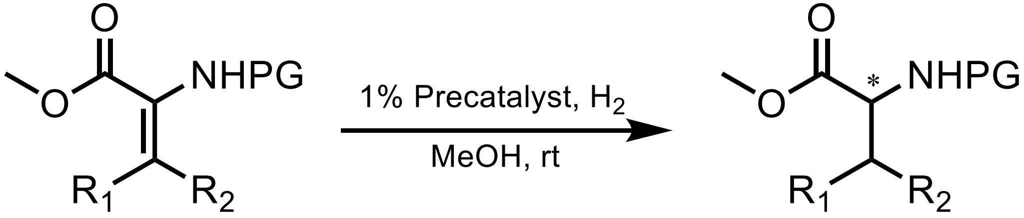
entry	dienophile	catalyst	solvent	T (°C)	**A** (%)[a]	**B** (%)[a]	**C** (%)[a]	**D** (%)[a]	yield (%)[a]
1	**R = H**	Et_2AlCl	CH_2Cl_2	−100	86		14		70[b]
2	**R = Me**	Et_2AlCl	CH_2Cl_2	−78	95.6	2.2	2.2		90[b]

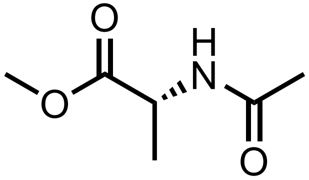
Cipiciani, A.; *et. Al. J. Org. Chem.* **2002**, 67, 8, 2665-2670

Cyclophanes Used as Ligands

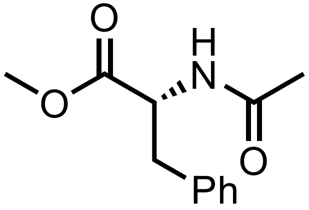


(R)-Phanephos

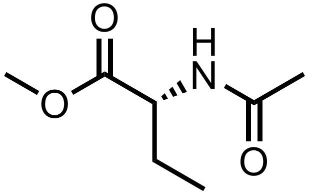




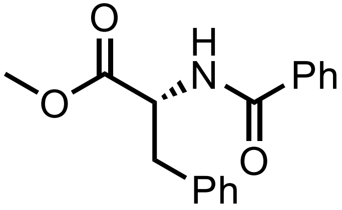
99.6 %ee



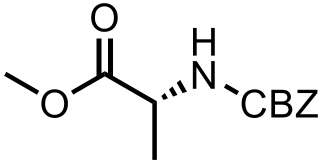
99 %ee



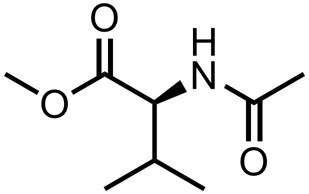
94 %ee



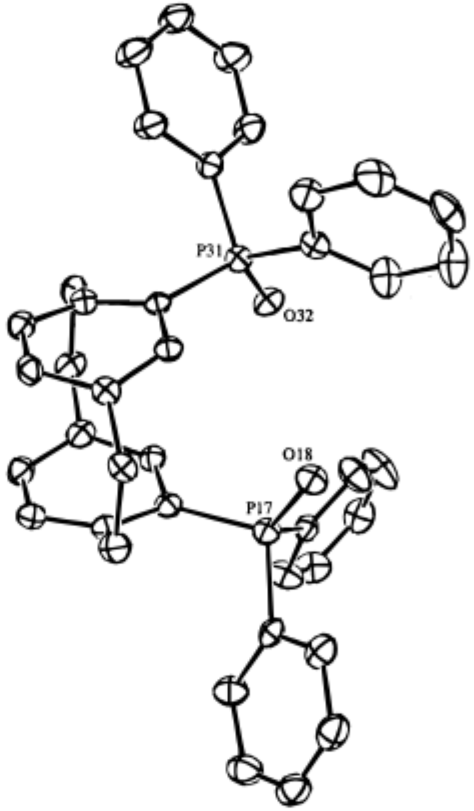
97 %ee



91 %ee

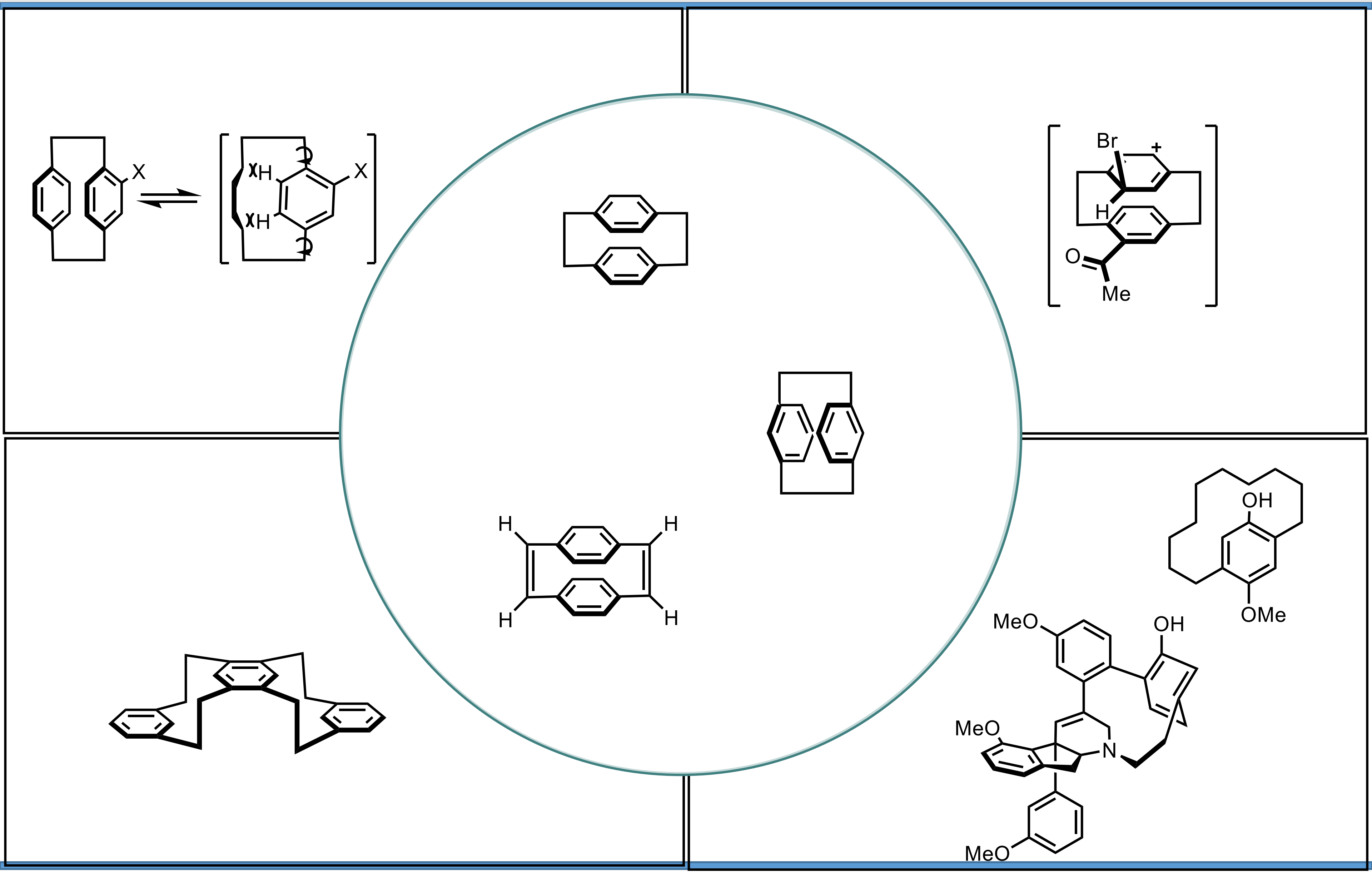


51 %ee

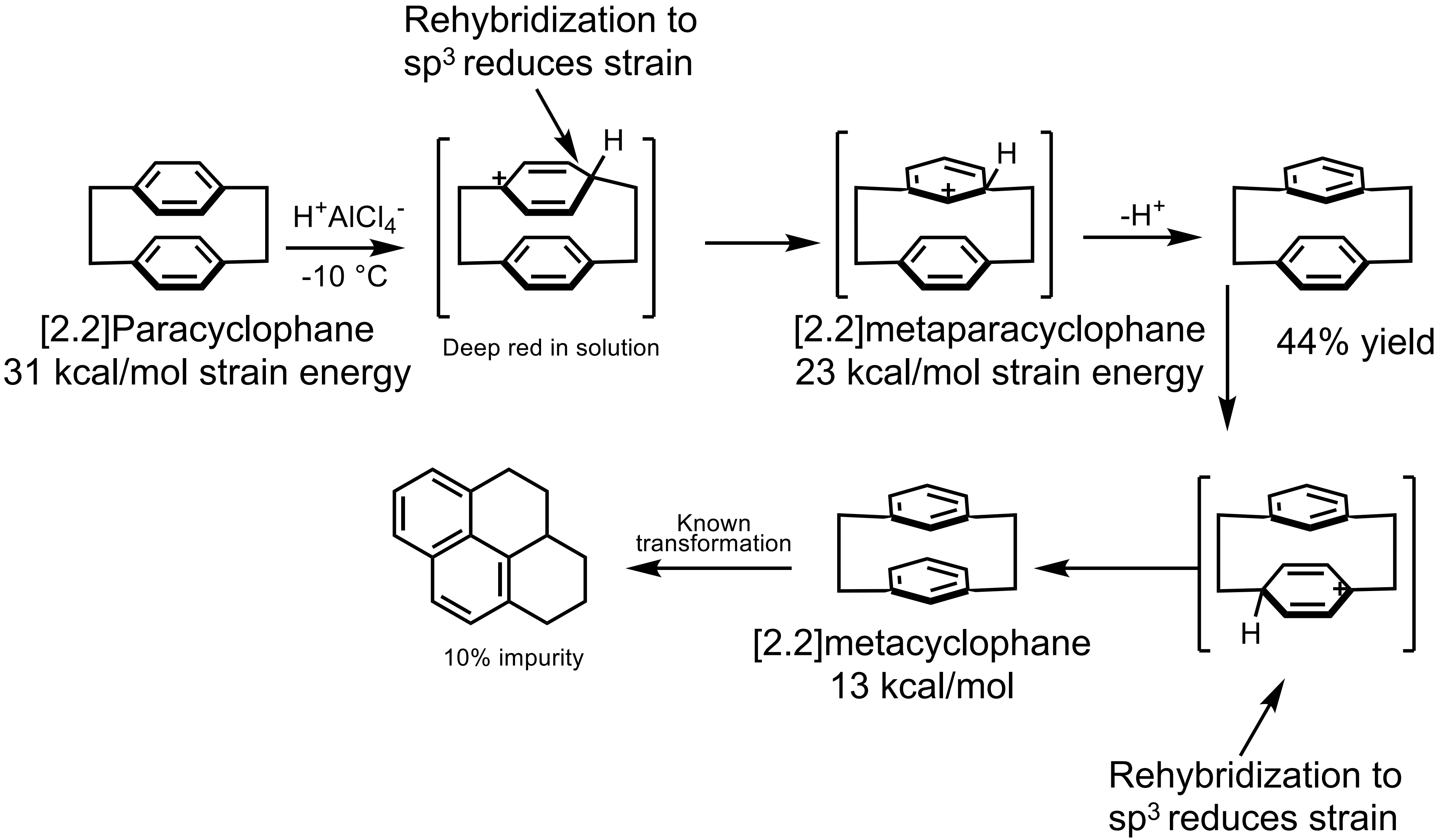


Pye, P. J; *et. Al. J. Am. Chem. Soc.* **1997**, 119, 6207-6208

Overview

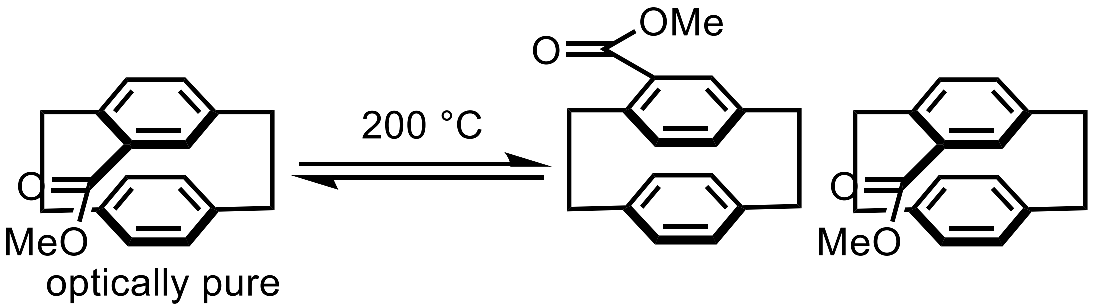


Synthesis of [2.2]metaparacyclophane



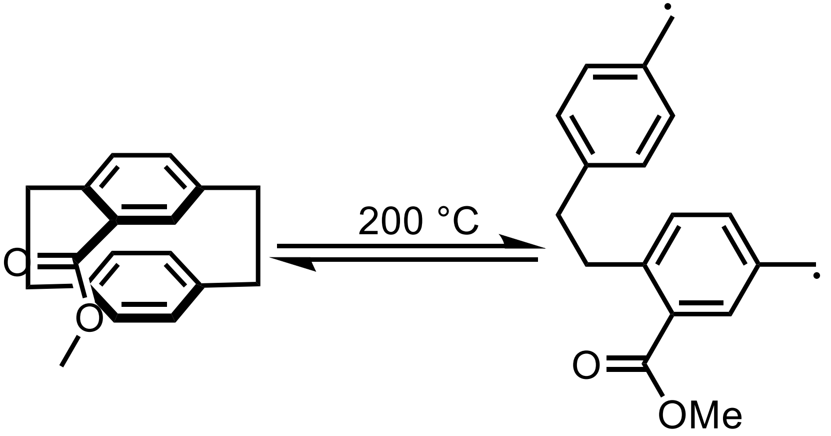
Pye, P. J; *et. Al. J. Am. Chem. Soc.* **1997**, 119, 6207-6208

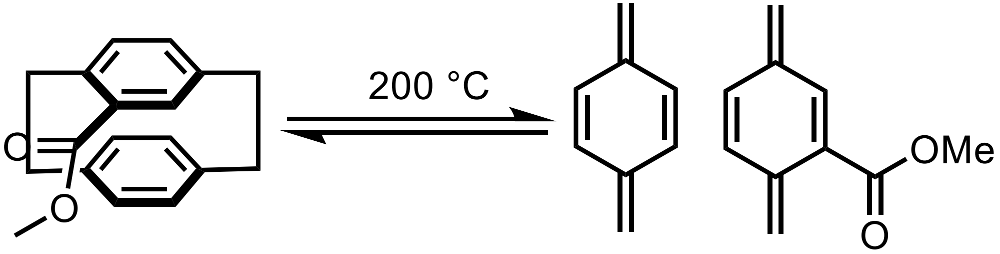
Racemization Mechanism

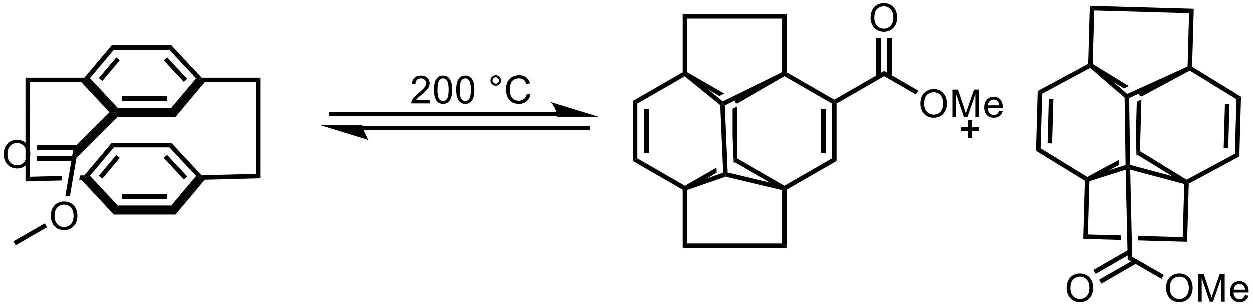


- 31 kcal/mol ring strain allows for unusual chemistry
- In [3.3]paracyclophane no racemization is observed at 240 °C something unusual must be occurring

3 Possible Mechanisms for racemization



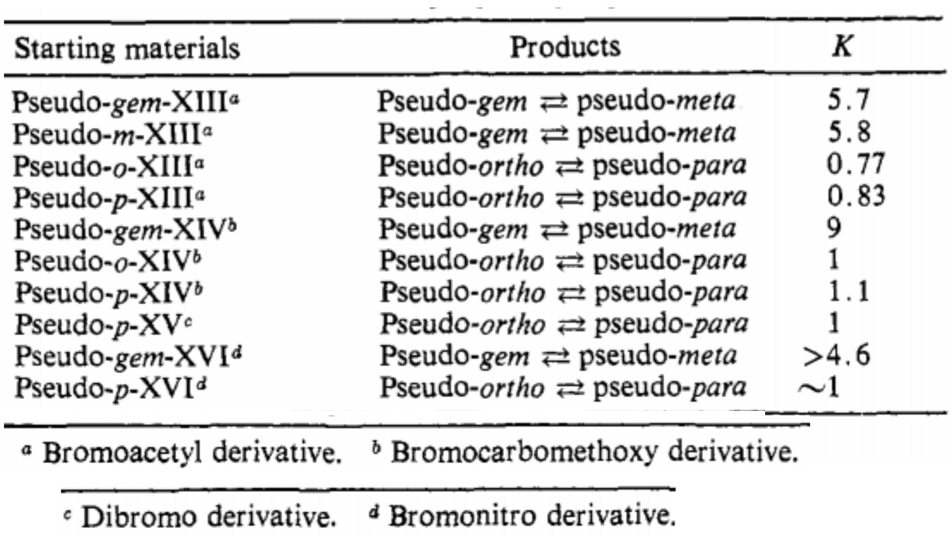




Cram, D. J.; Cram, J. M. *Acc. Chem. Res.* **1971**, 4, 6, 204-213

Crossover experiments

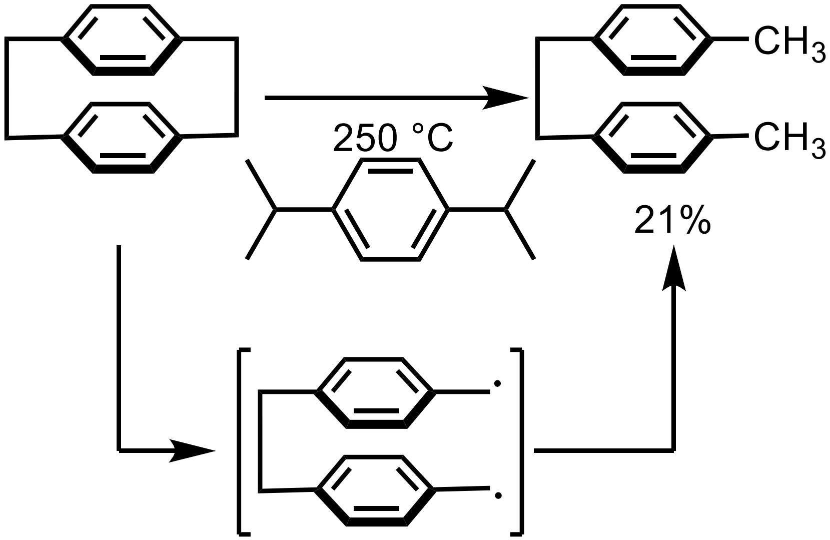
pseudo-*gem* pseudo-*meta* pseudo-*ortho* pseudo-*para*



Starting materials	Products	*K*
Pseudo-*gem*-XIII[a]	Pseudo-*gem* ⇄ pseudo-*meta*	5.7
Pseudo-*m*-XIII[a]	Pseudo-*gem* ⇄ pseudo-*meta*	5.8
Pseudo-*o*-XIII[a]	Pseudo-*ortho* ⇄ pseudo-*para*	0.77
Pseudo-*p*-XIII[a]	Pseudo-*ortho* ⇄ pseudo-*para*	0.83
Pseudo-*gem*-XIV[b]	Pseudo-*gem* ⇄ pseudo-*meta*	9
Pseudo-*o*-XIV[b]	Pseudo-*ortho* ⇄ pseudo-*para*	1
Pseudo-*p*-XIV[b]	Pseudo-*ortho* ⇄ pseudo-*para*	1.1
Pseudo-*p*-XV[c]	Pseudo-*ortho* ⇄ pseudo-*para*	1
Pseudo-*gem*-XVI[d]	Pseudo-*gem* ⇄ pseudo-*meta*	>4.6
Pseudo-*p*-XVI[d]	Pseudo-*ortho* ⇄ pseudo-*para*	~1

[a] Bromoacetyl derivative. [b] Bromocarbomethoxy derivative.

[c] Dibromo derivative. [d] Bromonitro derivative.

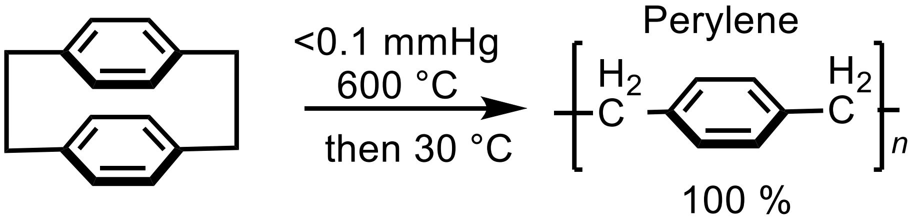


suggests diradical intermediate
rest of mass balance polymer

1. For the diradical mechanism only racemization would be observed
2. For *p*-xylylene mechanism that was at play 12 different compounds could theoretically be formed
3. The polycyclic mechanism is hard to distinguish from the diradical mechanism

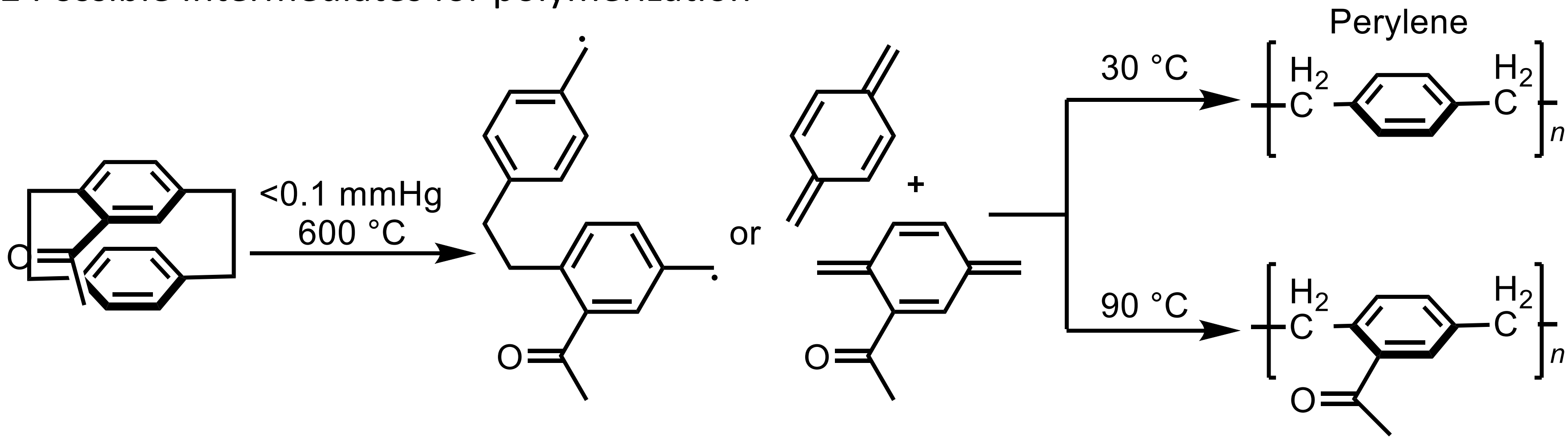
Reich, H, j.; Cram, D. J. *J. Am. Chem. Soc.* 1969, 91, 13, 3534-3543

Polymerization Perylene



- Thermally stable polymer of uniform thickness capable of coating objects at a 0.1 µm thickness
- Inhibits fungal and bacterial growth
- Dry lubrication properties
- Resists rust, corrosion, acids, bases
- Insulator

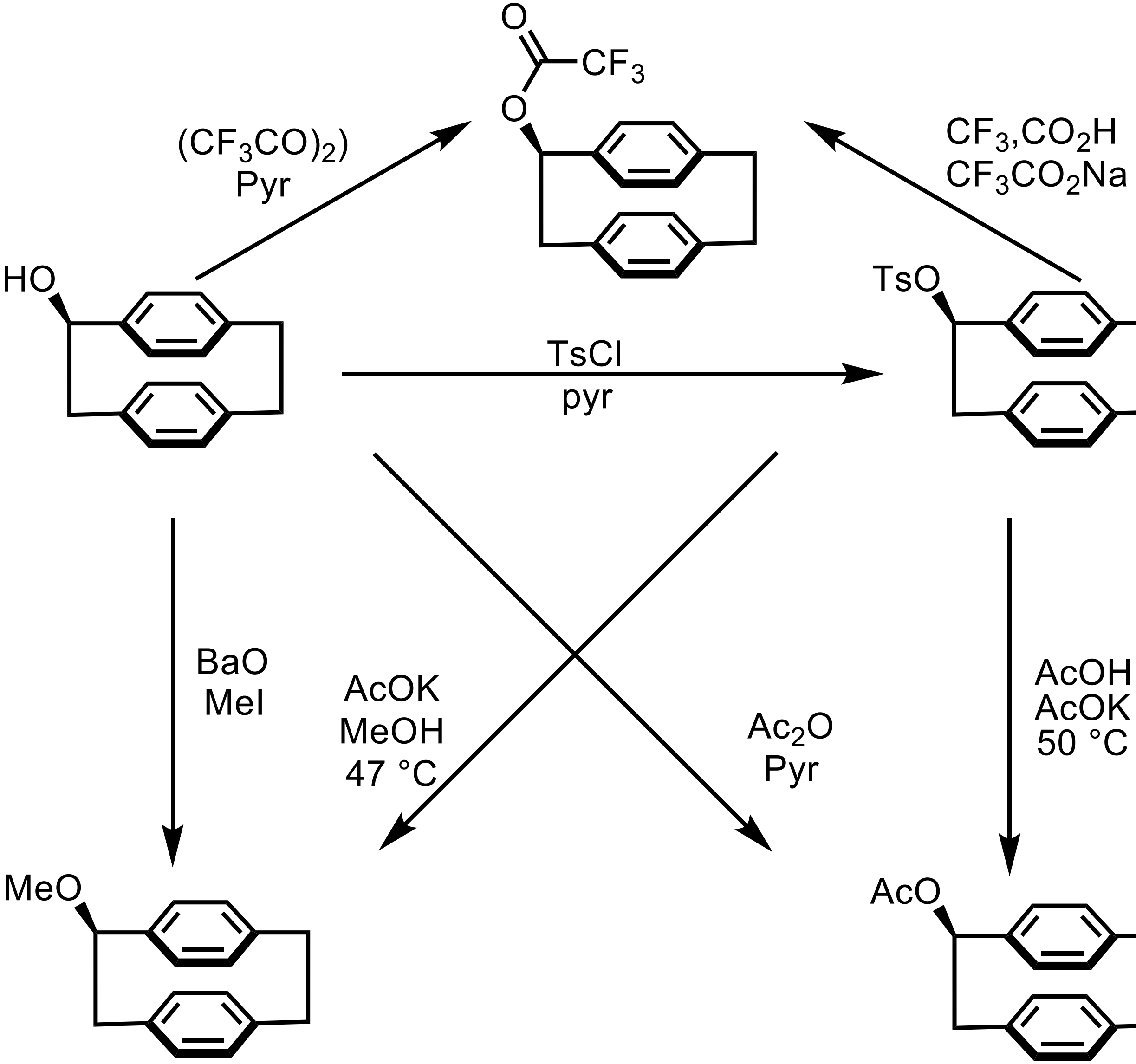
2 Possible Intermediates for polymerization



- Although this experiment does not prove that bond cleavage is stepwise or concerted.
- The formation of two distinct polymers suggests that the active polymerization reagent is the monomeric p-xylylene intermediates

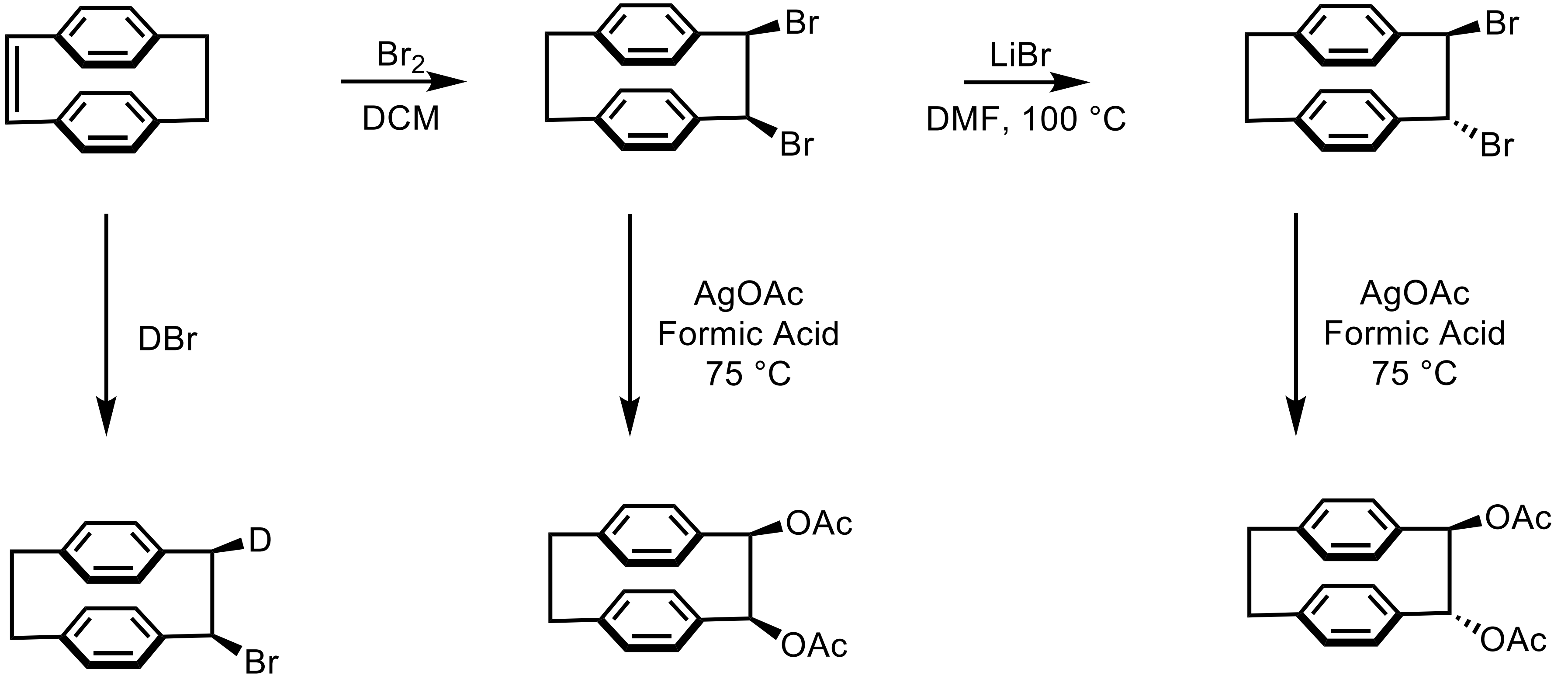
Hopf, H. *Angew. Chem. Int. Ed.* **2008**,47, 9808 – 9812
Gorham, W. F. *J. Poly. Sci*, **1966**, 3027-3029

Unusual Stereoretention



Cram, D. J.; Fischer, H. P. *J. Org. Chem.* **1965**, 30, 6, 1815-1819
Cram, D. J.; Cram, J. M. *Acc. Chem. Res.* **1971**, 4, 6, 204-213

Unusual Stereoretention



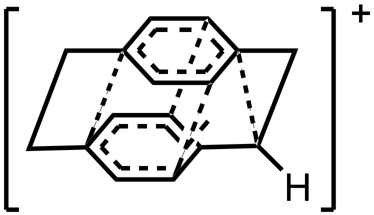
$\xrightarrow[\text{DCM}]{Br_2}$

$\xrightarrow[\text{DMF, 100 °C}]{\text{LiBr}}$

DBr

AgOAc
Formic Acid
75 °C

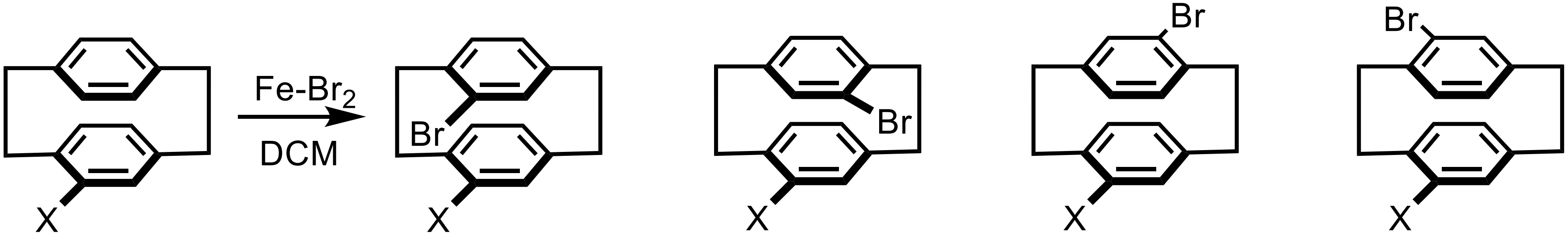
AgOAc
Formic Acid
75 °C

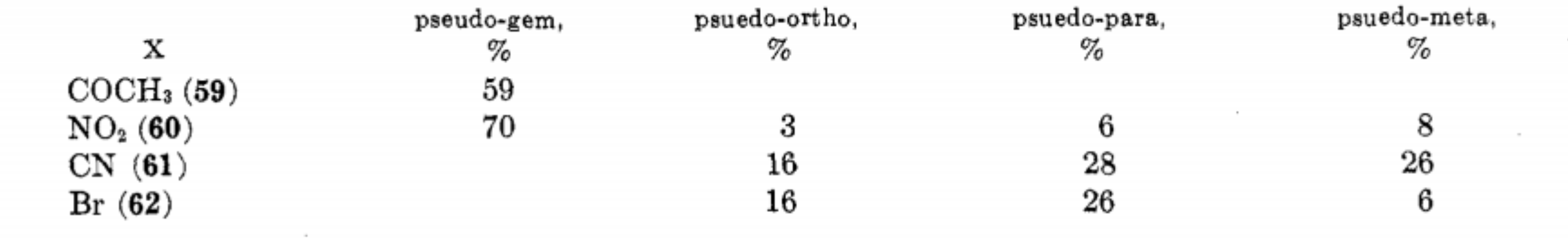


- Intermediate forms with participation of the proximal aromatic ring.
- This intermediate must be opened in a second step to provide net retention of configuration
- The intermediate releases angle strain and a decreases π-π repulsion

Cram, D. J.; Fischer, H. P. *J. Org. Chem.* **1965**, 30, 6, 1815-1819
Cram, D. J.; Cram, J. M. *Acc. Chem. Res.* **1971**, 4, 6, 204-213

The Gem Effect





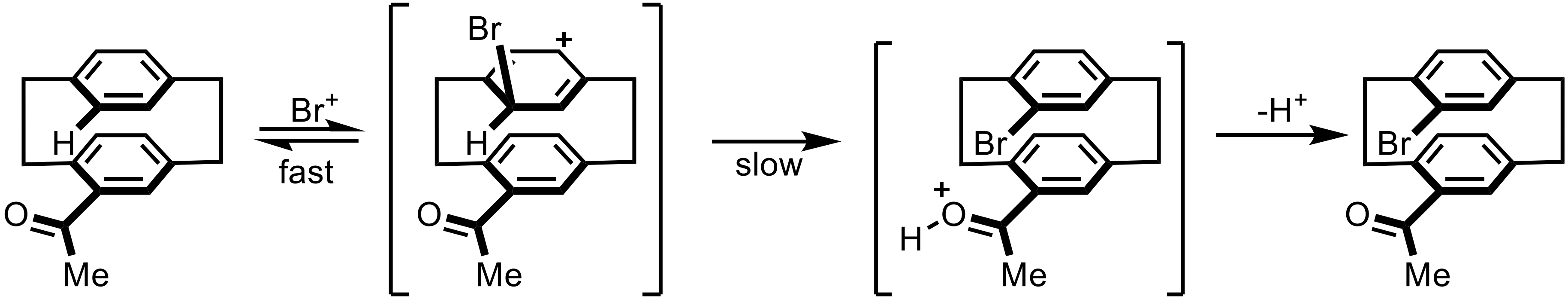
X	pseudo-gem, %	psuedo-ortho, %	psuedo-para, %	psuedo-meta, %
$COCH_3$ (**59**)	59			
NO_2 (**60**)	70	3	6	8
CN (**61**)		16	28	26
Br (**62**)		16	26	6

- Substitution occurs predominately geminal to basic groups

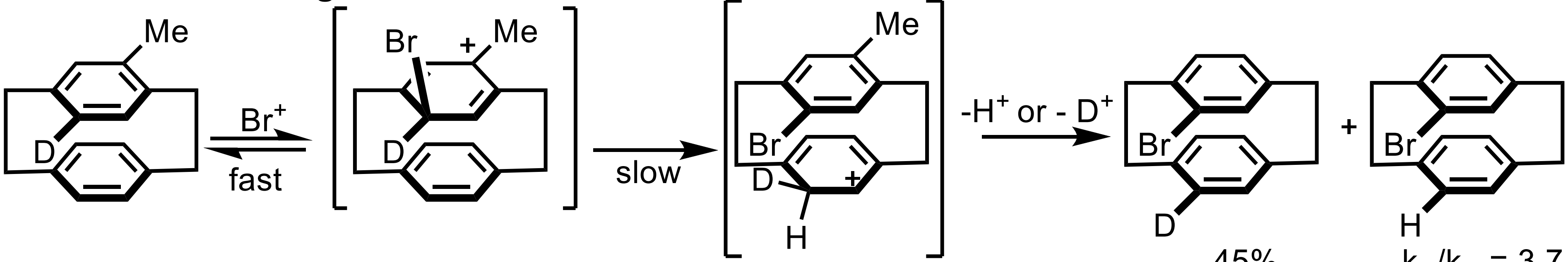
Cram, D. J.; Cram, J. M. *Acc. Chem. Res.* **1971**, 4, 6, 204-213

Mechanistic Rational

For Deactivated Rings



For Activated Rings

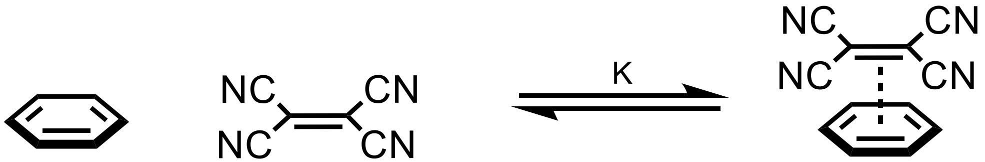


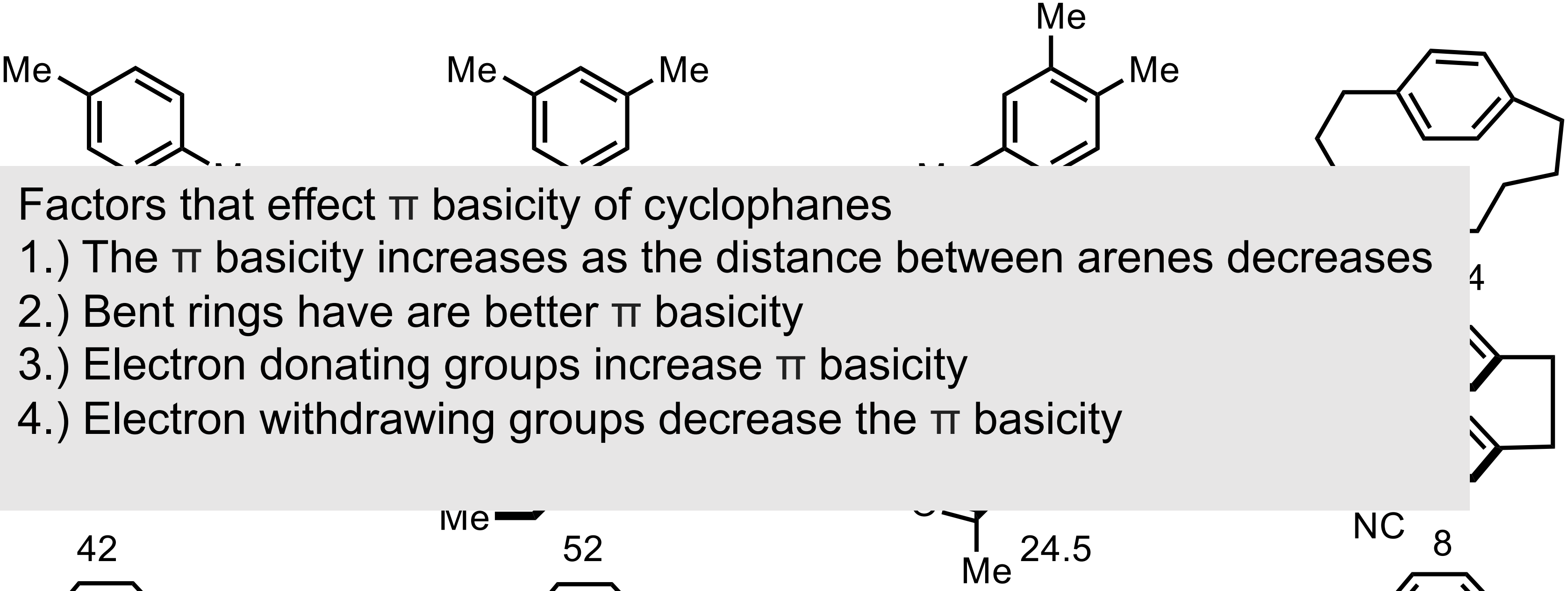
45% deuterium incorporation

$k_H/k_D = 3.7$

Cram, D. J.; Cram, J. M. *Acc. Chem. Res.* **1971**, 4, 6, 204-213

Transannular π basicity

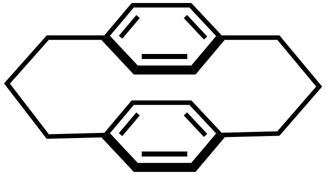
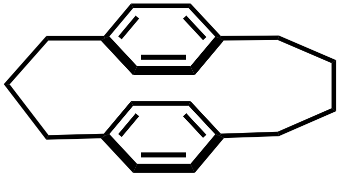
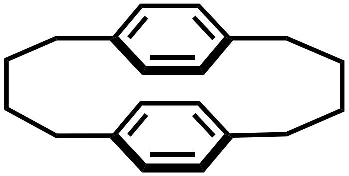
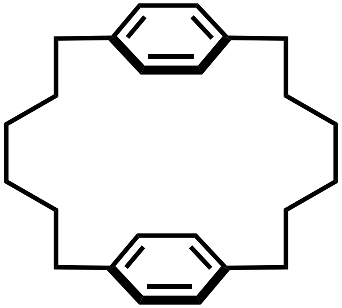




Factors that effect π basicity of cyclophanes
1.) The π basicity increases as the distance between arenes decreases
2.) Bent rings have are better π basicity
3.) Electron donating groups increase π basicity
4.) Electron withdrawing groups decrease the π basicity

K =

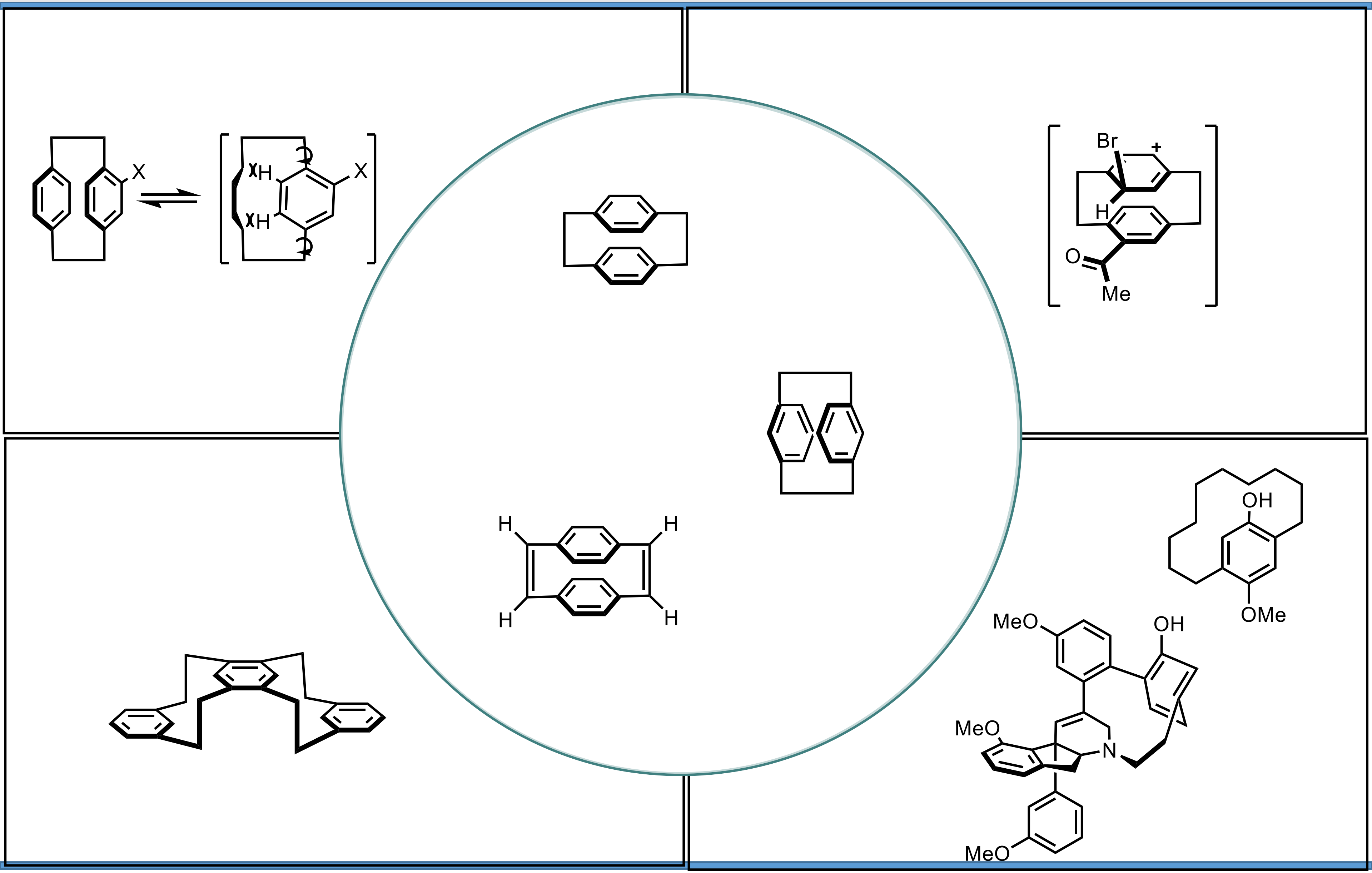
K = 42 52 24.5 8

K = 79 ± 12 52 ± 2 36 ± 2 13 ± 1

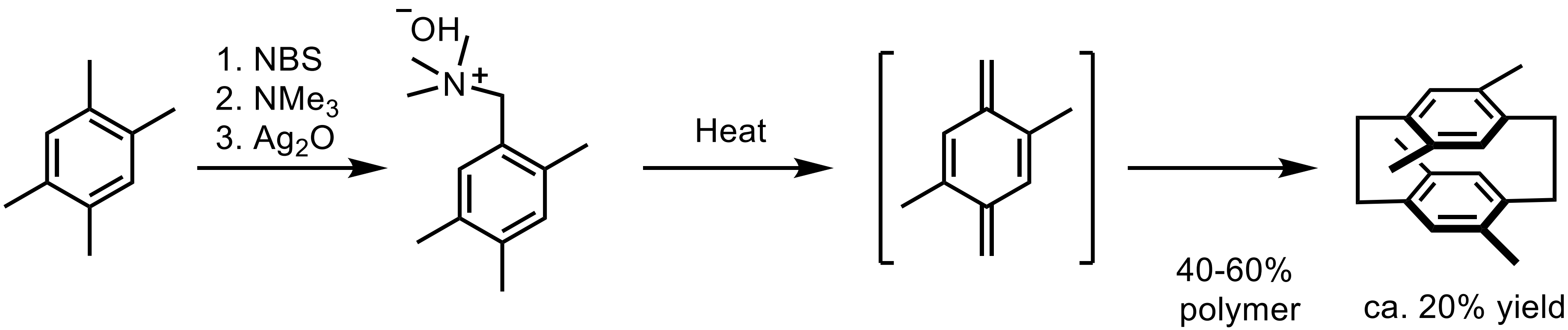
Sheehan, M.; Cram, D. J. *J. Am. Chem. Soc.* 1969, 91, 13, 3553-3558

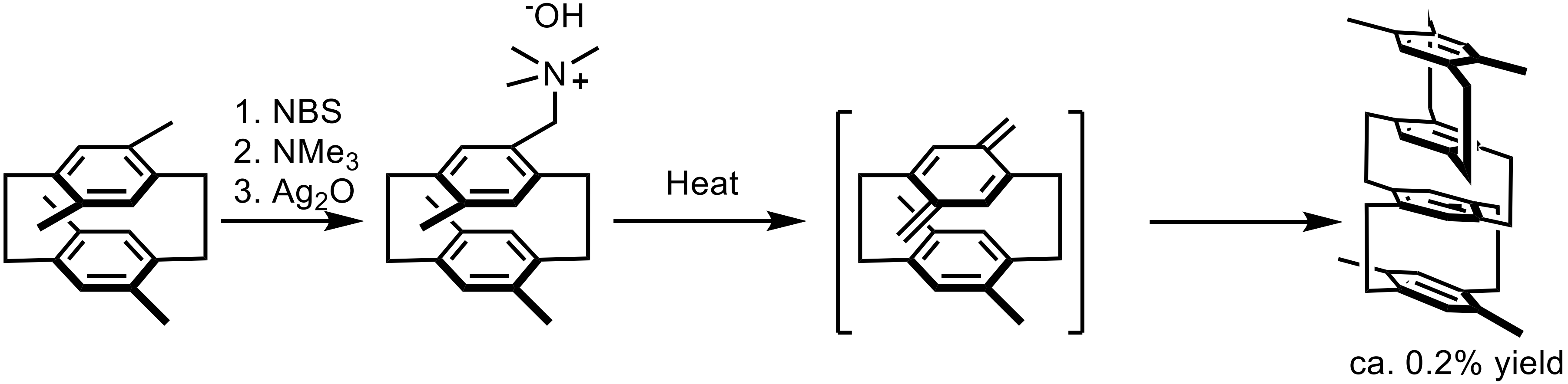
Overview



Layered cyclophanes

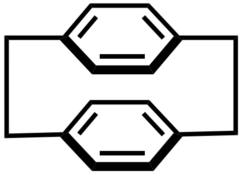
With the knowledge that rings in cyclophanes communicate electronically it was envisaged that electronic effects could be transmitted over long distances



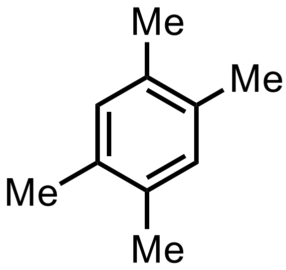


Longone, T. L.; Chow, H. S. J. Am. Chem. Soc. **1970**, 92, 4, 994-998

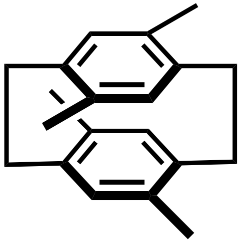
Transannular π basicity



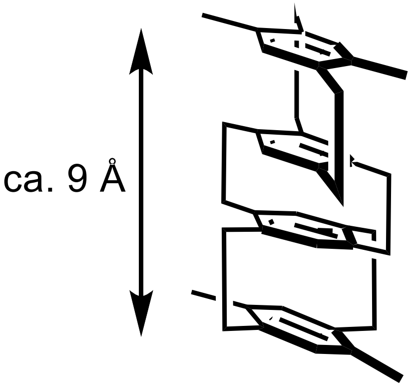
K = 42
λ_{max}= 521nm



K = 54.2
λ_{max}= 480 nm



K = 135
λ_{max}= 580 nm



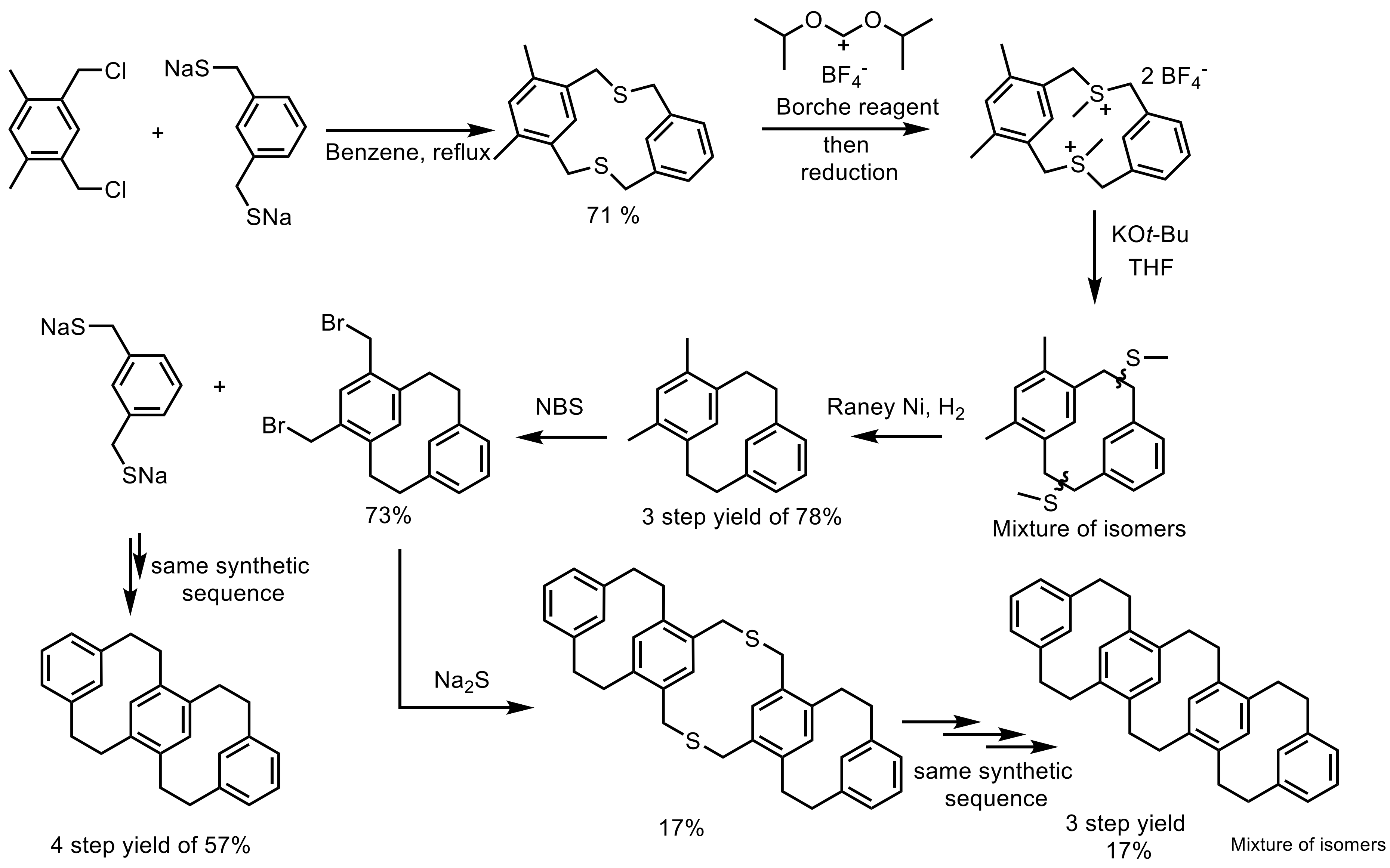
K = 630
$\lambda_{maxcalc}$= 690

Calculated
from K vs λν

The huge increase in binding clearly demonstrates that stacked cyclophanes can interact through multiple rings and some sort of additive effect is present

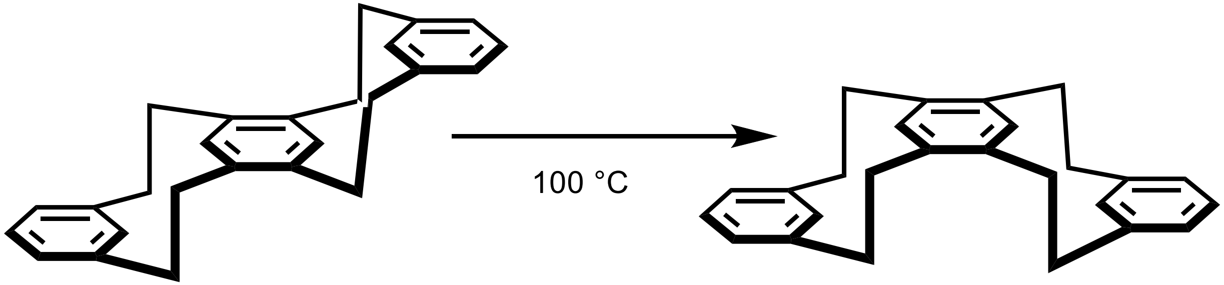
Longone, T. L.; Chow, H. S. J. Am. Chem. Soc. **1970**, 92, 4, 994-998

Molecular Ladder

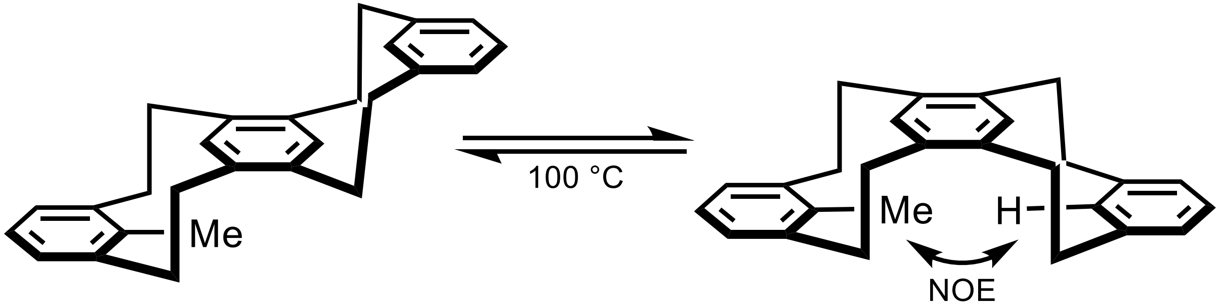


Umemoto, T.; Otsubuo, T.; Misumi, S. *Tetrahedron Letters* **1974**, 17, 1573 – 1576.

Molecular Ladder Becomes Staggared



1:1 after 4 minutes
0:1 after 16 minutes

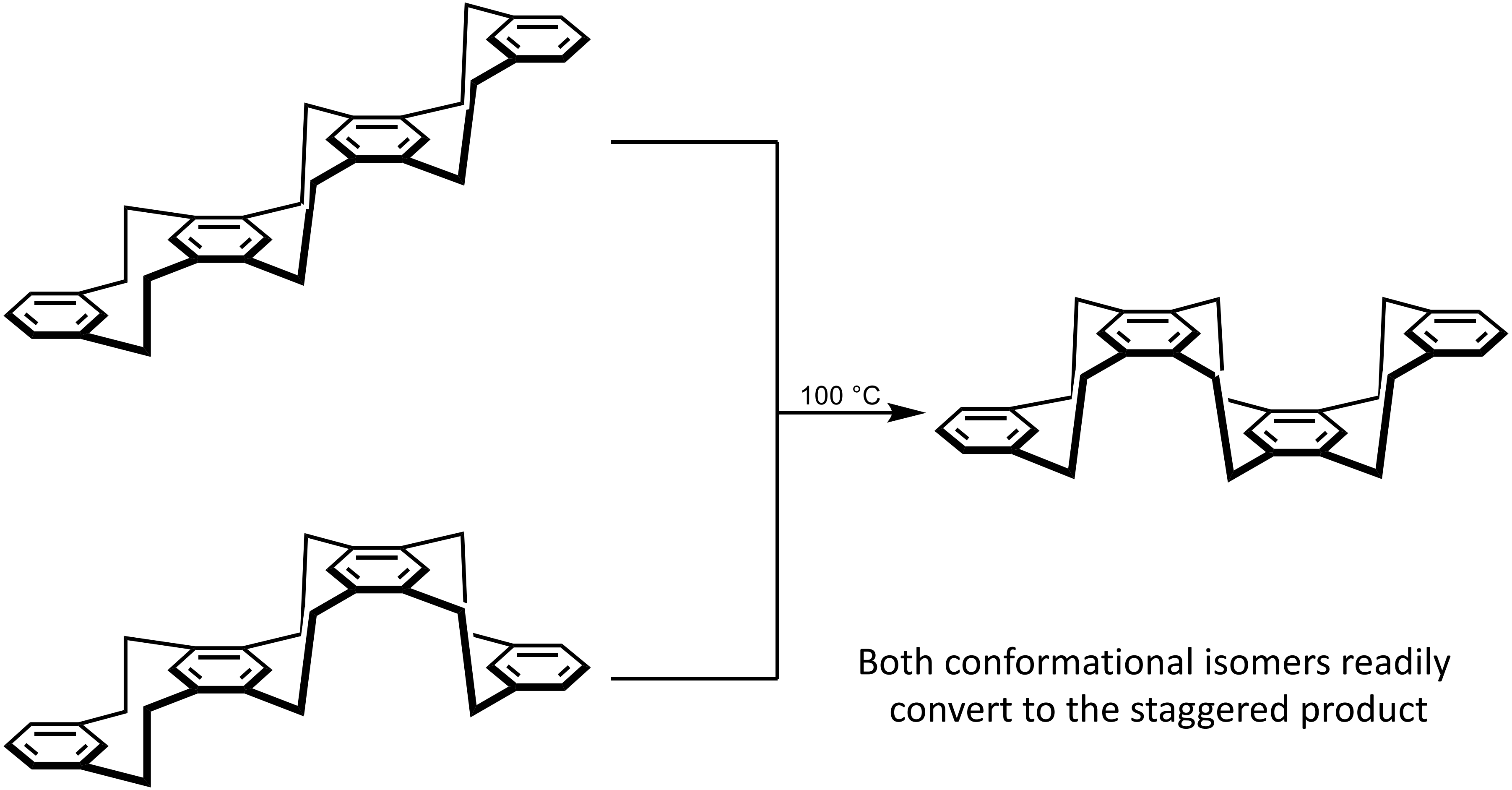


1:1 after 10 minutes
1:17 final equilibrium

Equilibrium caused by the steric repulsion of the methyl and aromatic proton

Umemoto, T.; Otsubuo, T.; Misumi, S. *Tetrahedron Letter*, **1973**, 593 – 596**.**

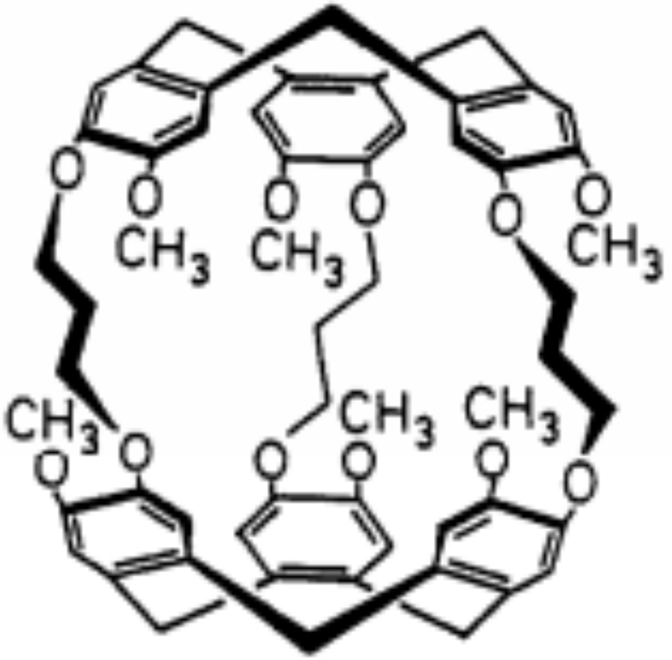
Molecular Ladder Becomes Staggered



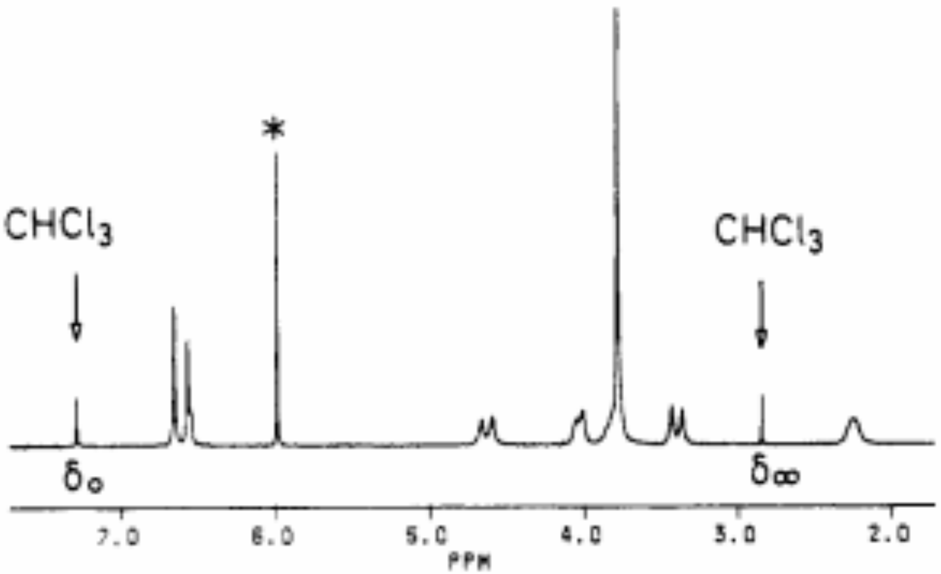
Both conformational isomers readily convert to the staggered product

Umemoto, T.; Otsubuo, T.; Misumi, S. *Tetrahedron Letters* **1974**, 17, 1573 – 1576.

Host Guest Chemistry

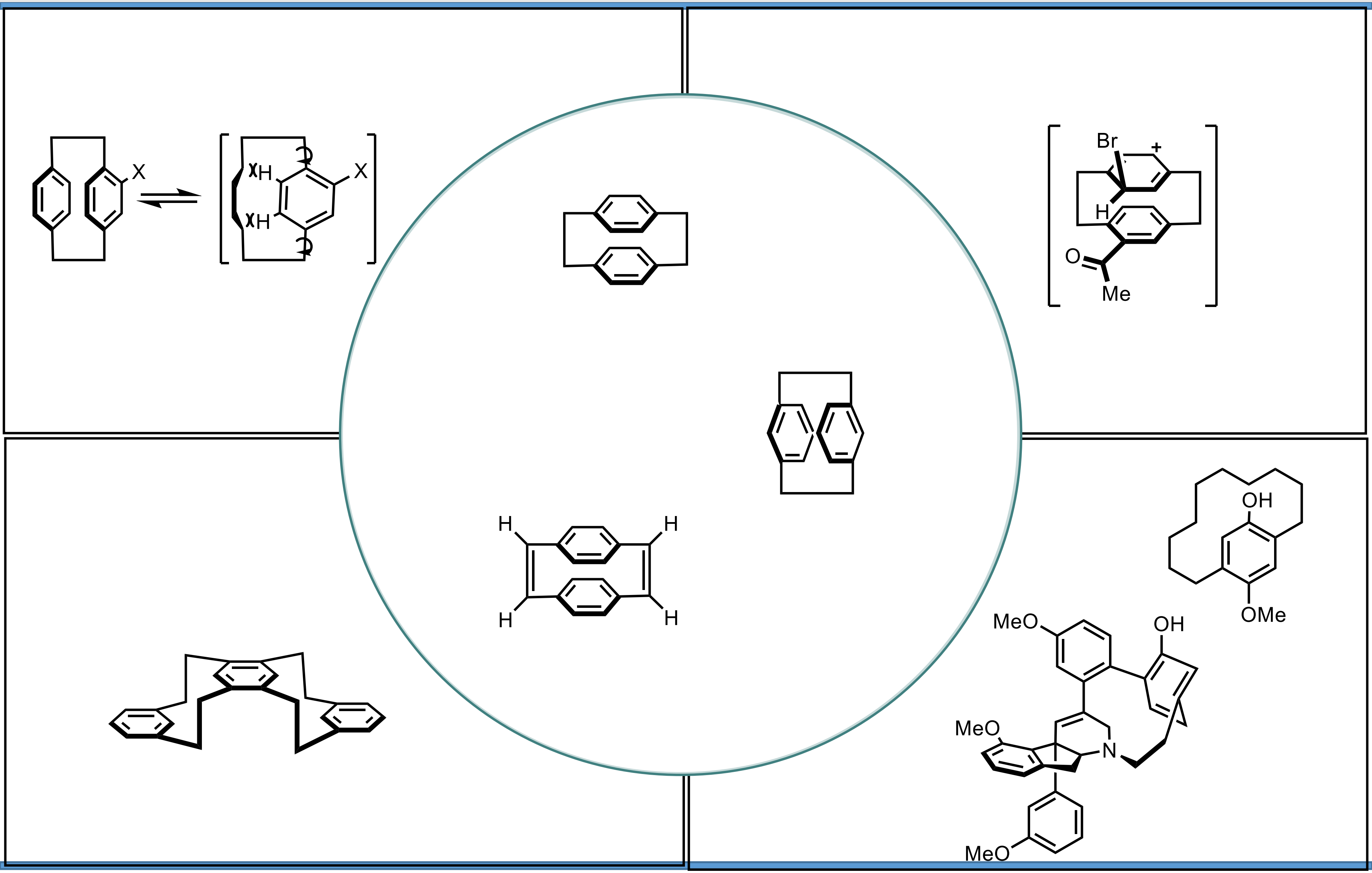


(+) 2



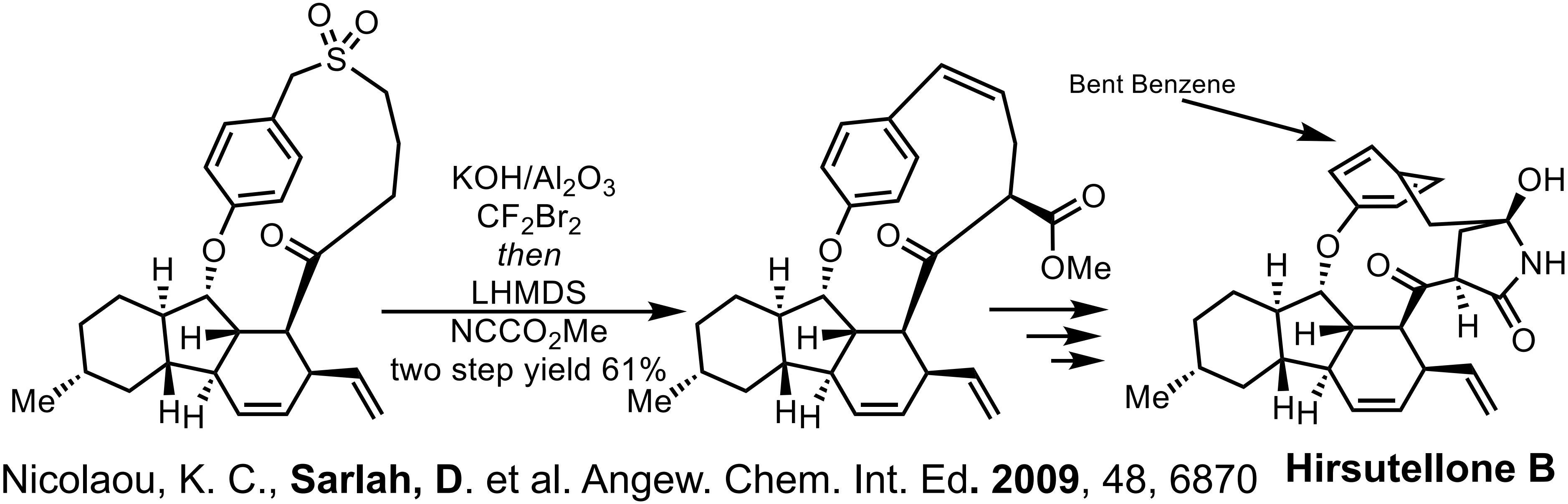
J. Am. Chem. Soc. 1986, 108, 14, 4230-4232.

Overview



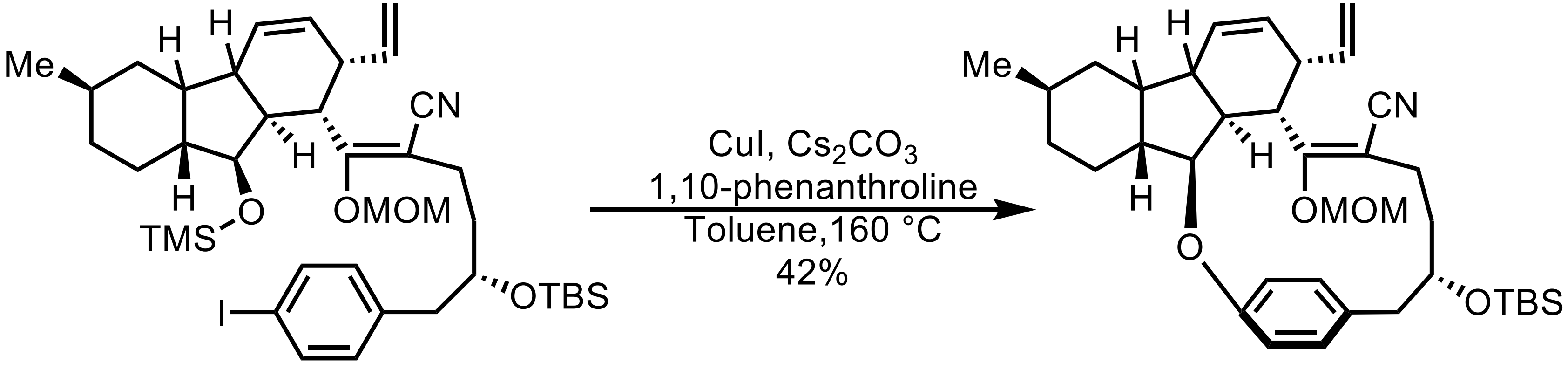
Cyclophane Synthesis

Hirsutellone B: Ramberg-Bäcklund olefination



Nicolaou, K. C., **Sarlah, D**. et al. Angew. Chem. Int. Ed**. 2009**, 48, 6870

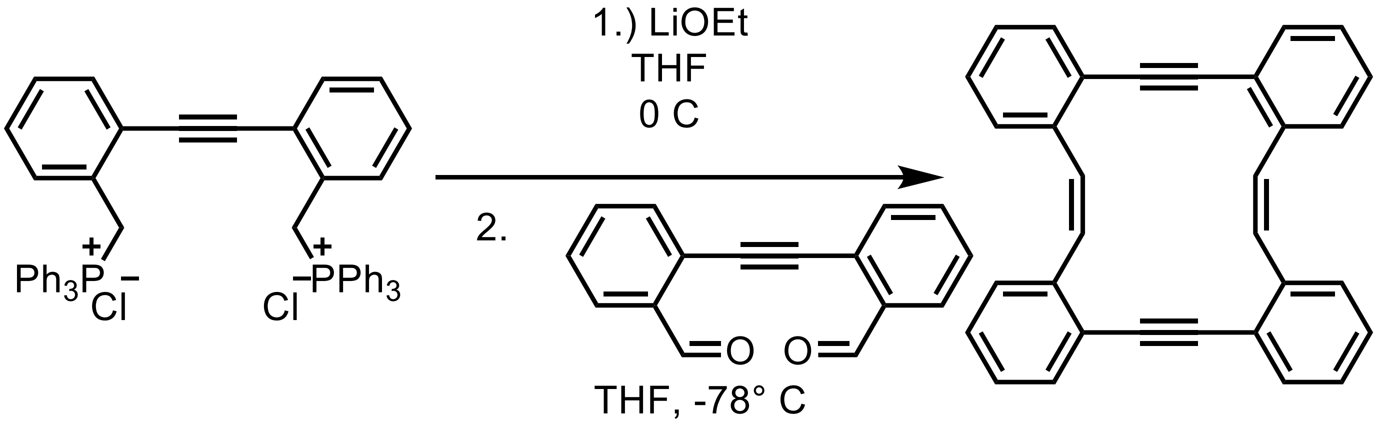
Hirsutellone B: Ullmann-type coupling



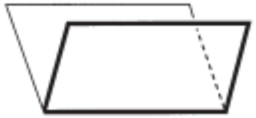
Uchiro, H. *et. al*. Org. Lett. 2011, 13, 6268-6271

Cyclophane Synthesis

Molecular Magazine Rack: Wittig Olefination

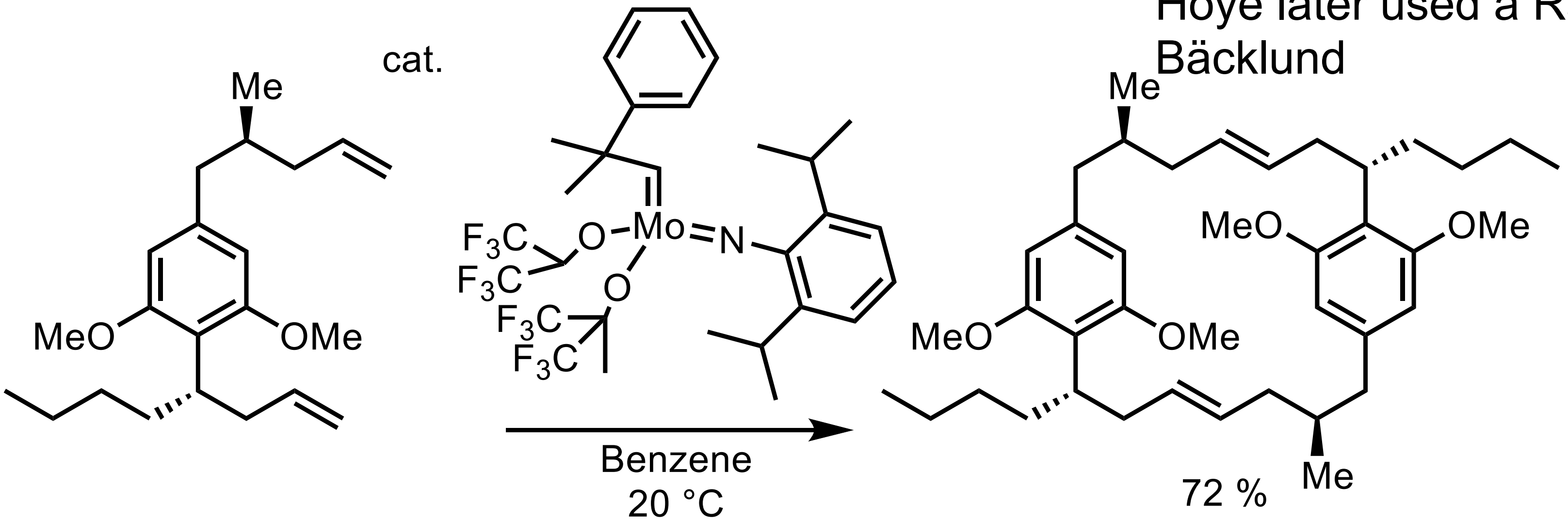


68% Z,Z/ E,E = 91:9



Orita, A.; *et. al. Chem. Lett.* **2002**, 136-137

(-)-Cylindrocyclophanes A and F: RCM



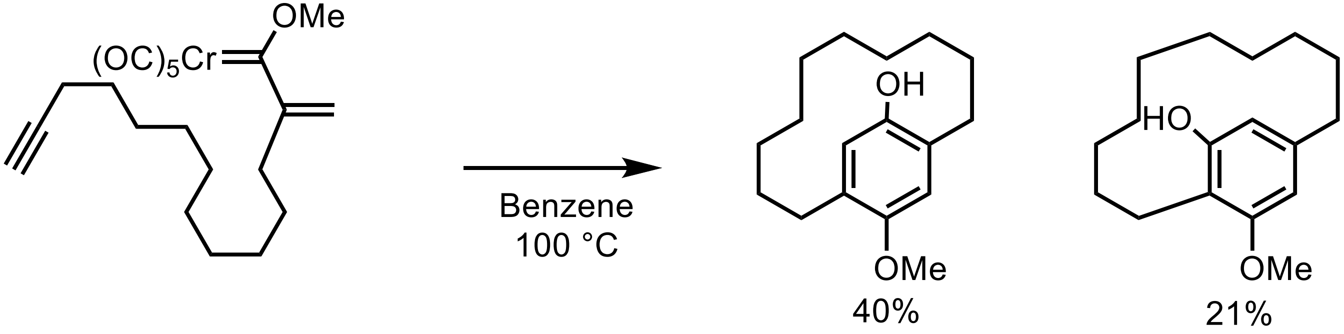
Stevens rearrangement and dimer cross coupling both failed.

Hoye later used a Ramberg-Bäcklund

Smith, A. B.; *et. al. J. Am. Chem. Soc.* **2001**, 123, 25, 5925-5937

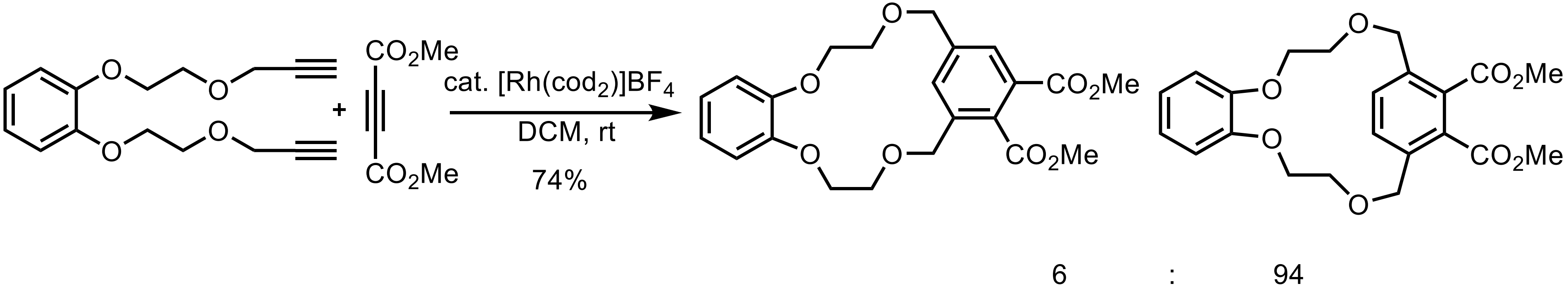
Cyclophane Synthesis

Para and meta cyclophanes: DOTZ Benzanulation



Wang, H.; *et. al. J. Am. Chem. Soc.* **2003**, 125, 8980-8981

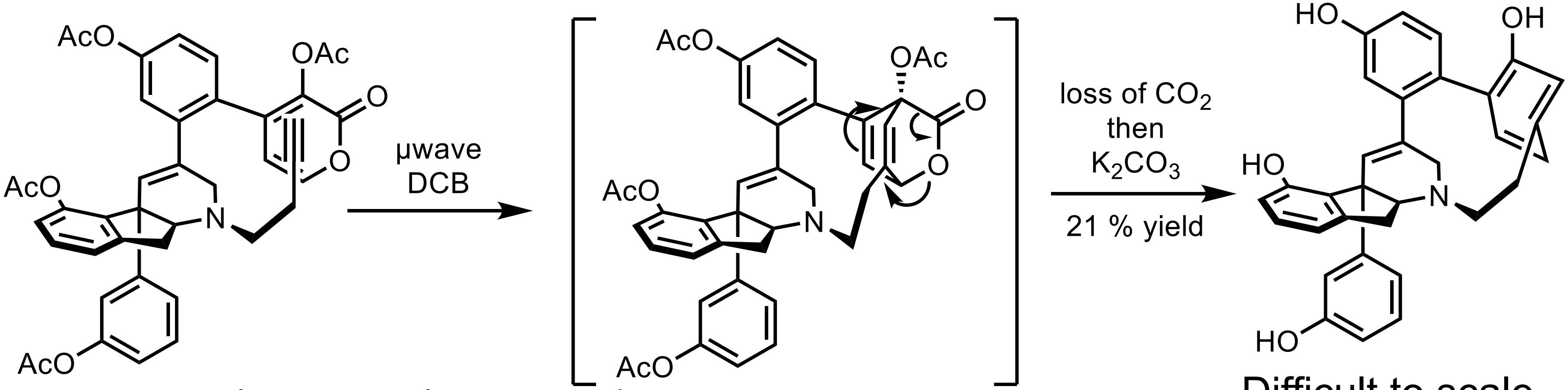
[15]polyether cyclophane: [2 +2 +2]



Tanaka, K.; *et. al. Eur. J. Org. Chem.* **2006**. 3575-3581

Cyclophane Synthesis

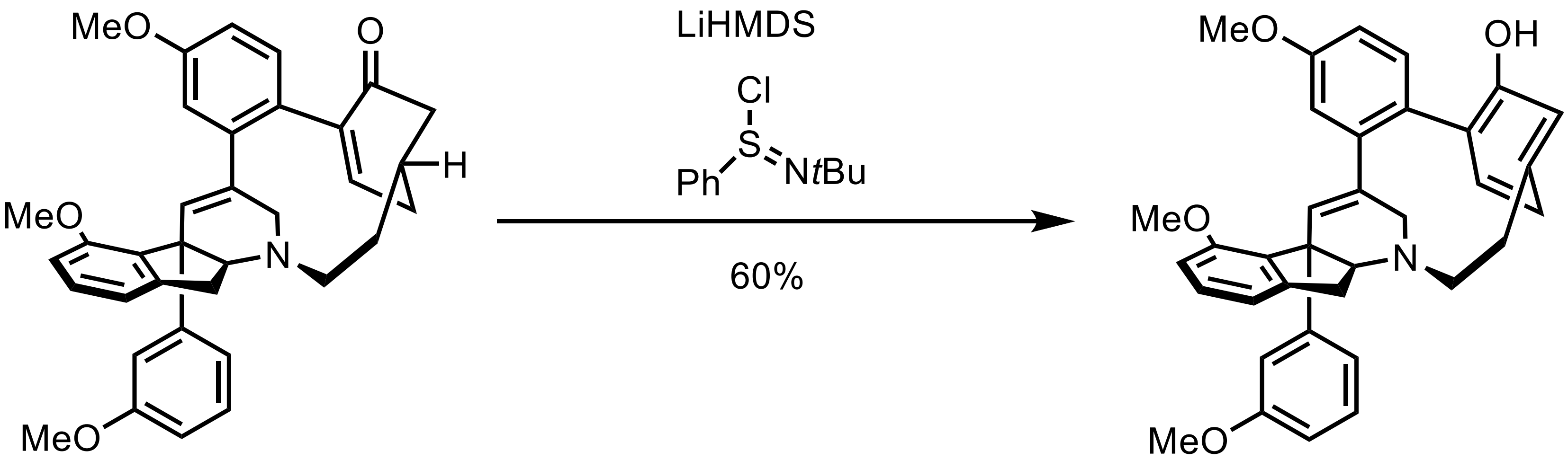
Haouamine A: Pyrone Diels-Alder



Difficult to scale

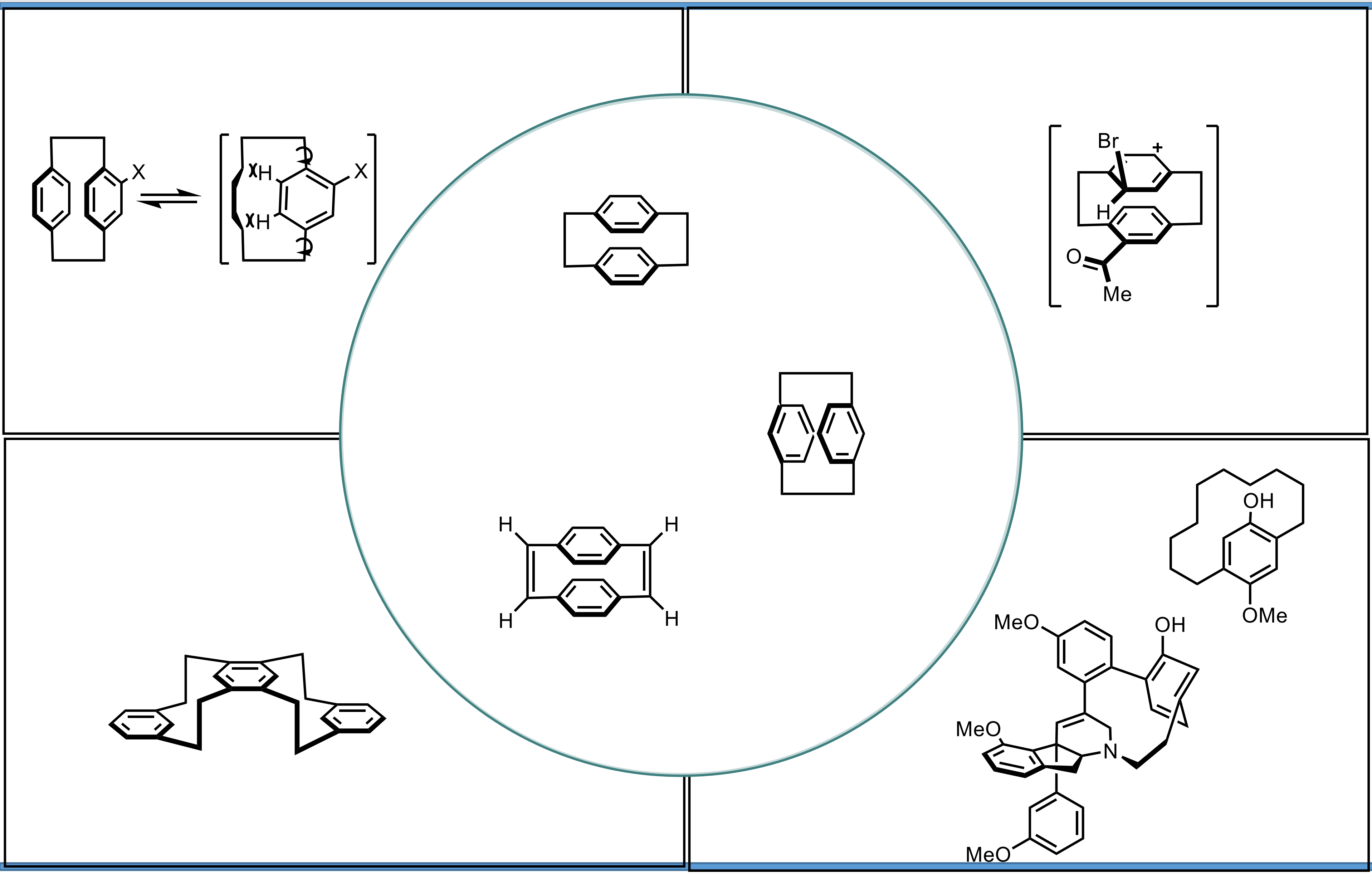
Baran, P. S. *et. al. Angew. Chem. Int. Ed.* **2008**, 47, 205

Haouamine A: Mukaiyama's reagent oxidation of eneone to phenol

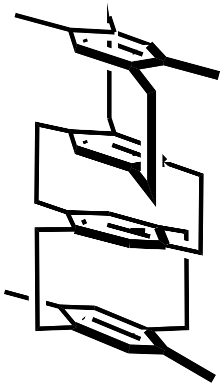


Baran, P. S.; *et. al. J. Am. Chem. Soc.* **2009**, 131, 9172

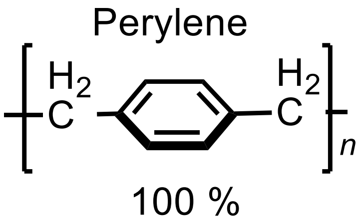
Conclusion



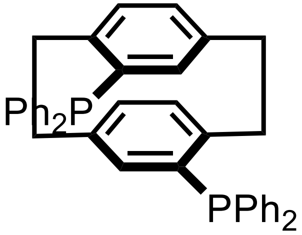
Future Directions



Materials



Polymers



Ligands

Thanks

Questions?

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