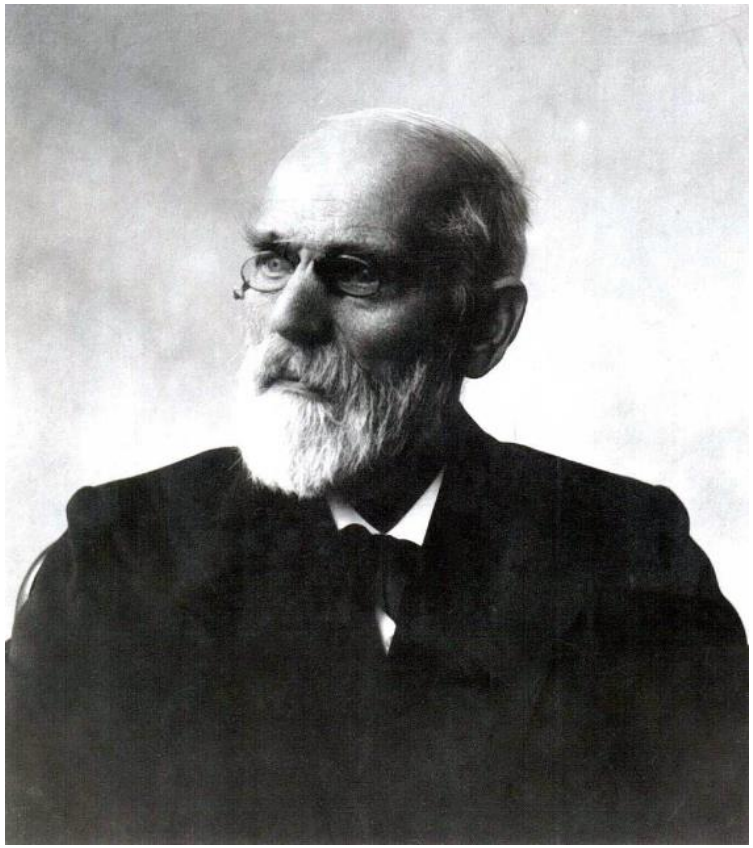
Dispersion – Reconsidering Steric Interactions

Andrew Zahrt

06/13/17

Johannes Diderik van der Waals

- Early Contributions by Johannes Diderik van der Waals (1873):
  - $(P + \frac{na^2}{V^2})(V - nb) = nRT$
  - Born: 1837
  - Did not go to secondary school – became an elementary school teacher
  - Took classes at Leiden University as an outside student
  - Allowed later to gain acceptance to Leiden
  - Won 1910 Nobel Prize



Fritz London

- Fritz London:
  - Born in Breslau, Germany (now Wroclaw, Poland)
  - First to use perturbation theory to describe weak, long range interactions (1930)
  - $E^{AB}{}_{disp} \approx -\frac{3I_A I_B}{2(I_A+I_B)}\alpha^0{}_A\alpha^0{}_B R^{-6} = -C_6{}^{AB}R^{-6}$
  - Forced to give up his position at University of Berlin in 1933
  - Worked as visiting professor at Oxford and College de France before starting at Duke University

Overview

- Theory
  - What are London Dispersion Forces?
  - Theoretical Limitations
- Factors Controlling the Strength of Dispersion Forces
  - Relative Magnitude
  - How do we modulate them?
- Attractive Steric Effects and Structure
- Attractive Steric Effects and Reactivity
- Future Directions

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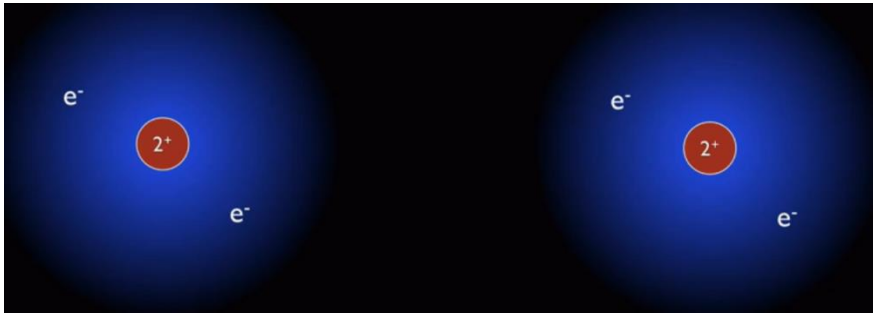
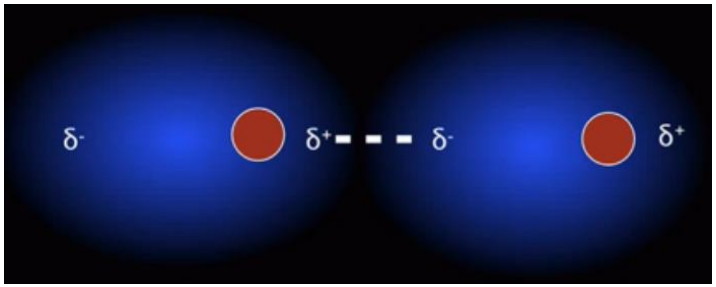
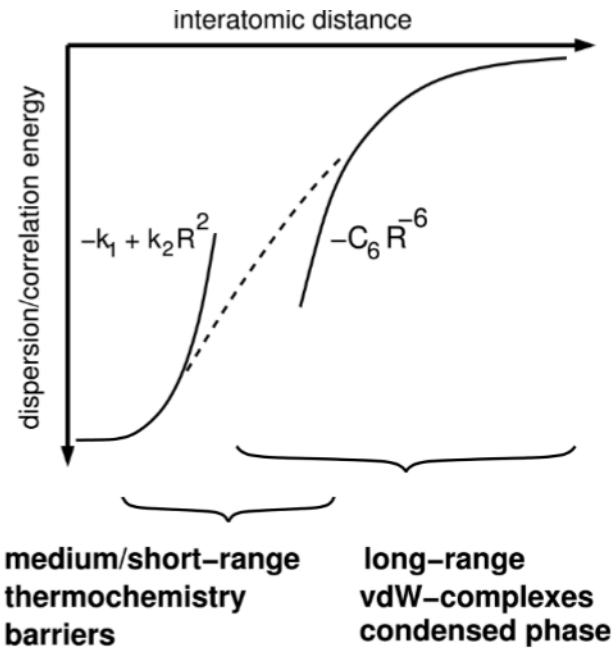
What are Dispersion Interactions?

- London Dispersion Forces: “Instantaneously Induced Dipoles”
  - Caused by Coulomb Correlation (electron correlation between spacial position).



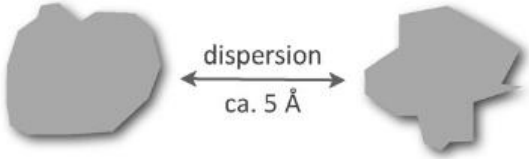




Two point charges:

$$E = -\frac{1}{10} E_h \approx 60\ kcal\ mol^{-1}$$

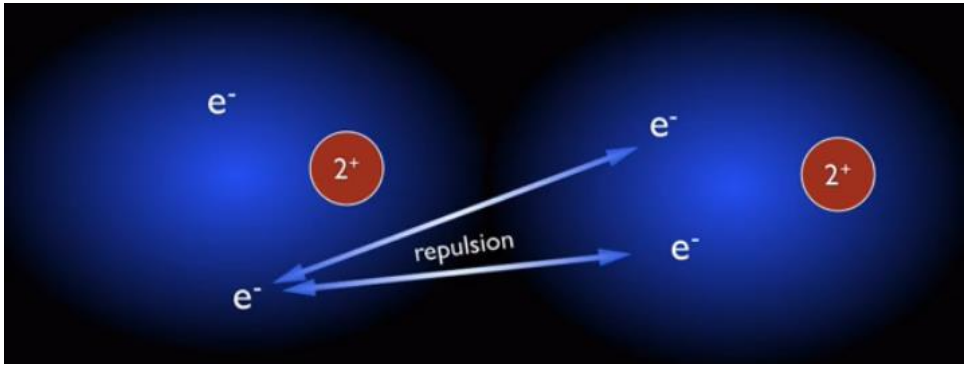
Two fragments or molecules (e.g. 100 HCNO atoms):

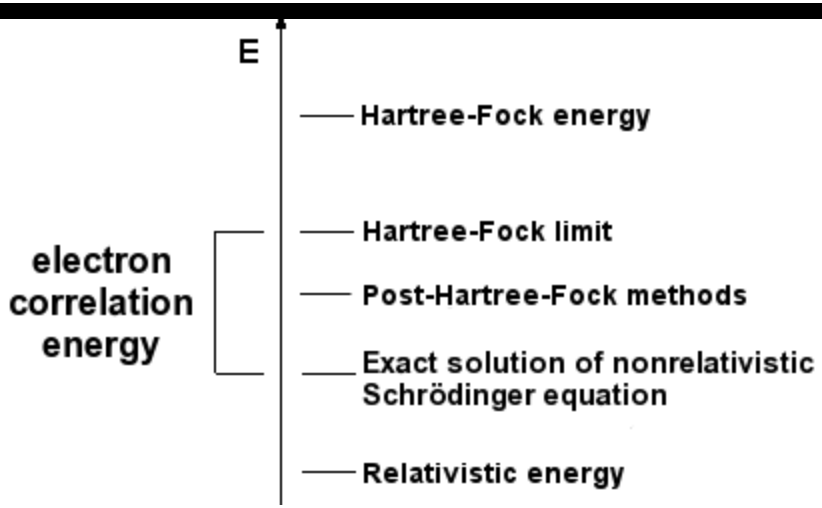


$$E = -\frac{10^2 \cdot 10^2 \cdot 10}{10^6} E_h \approx 60\ kcal\ mol^{-1}$$

Grimme *et al. Chem. Rev.* **2016**, *116*, 5105-5154

Electron Correlation





$$\widehat{H} = -\frac{1}{2}\sum_{i}^{N_e} \nabla_i^{\,2} - \sum_{i}^{N_e}\sum_{I}^{N_n} \frac{Z_I}{|r_i - R_I|} + \frac{1}{2}\sum_{i}^{N_e}\sum_{i\neq j}^{N_e} \frac{1}{|r_i - r_j|} + \frac{1}{2}\sum_{I}^{N_n}\sum_{I\neq J}^{N_n} \frac{Z_I Z_J}{|R_I - R_J|}$$

Hartree-Fock: Coulomb and Exchange operators

$$\sum_{j\neq i} \int \frac{e^2}{|r - r'|} \left|\varphi_j(r')\right|^2 d^3r'$$

$$\sum_{j\neq i} \varphi_j(r) \int \frac{e^2}{|r - r'|} \varphi *_j (r')\varphi_i(r')\, d^3r'$$

- Hartee-Fock fails to account for Coulomb Correlation.
- Post-HF methods:
  - MP2, MP3, MP4…
  - Configuration Interaction
  - Multi-configurational SCF

“Failures” of DFT

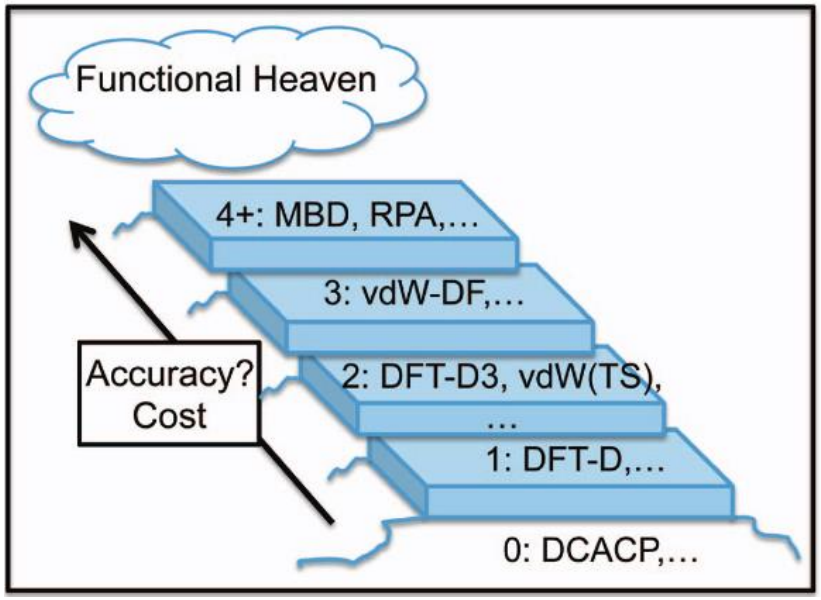
$$\left[-\frac{1}{2}\nabla_i^2 + \sum_A \frac{Z_A}{|\mathbf{R}_A - \mathbf{r}_1|} + \int \frac{\rho(\mathbf{r}_2)}{|\mathbf{r}_1 - \mathbf{r}_2|} + V_{\mathrm{XC}}[\rho]\right]\varphi_i(\mathbf{r}_1)$$

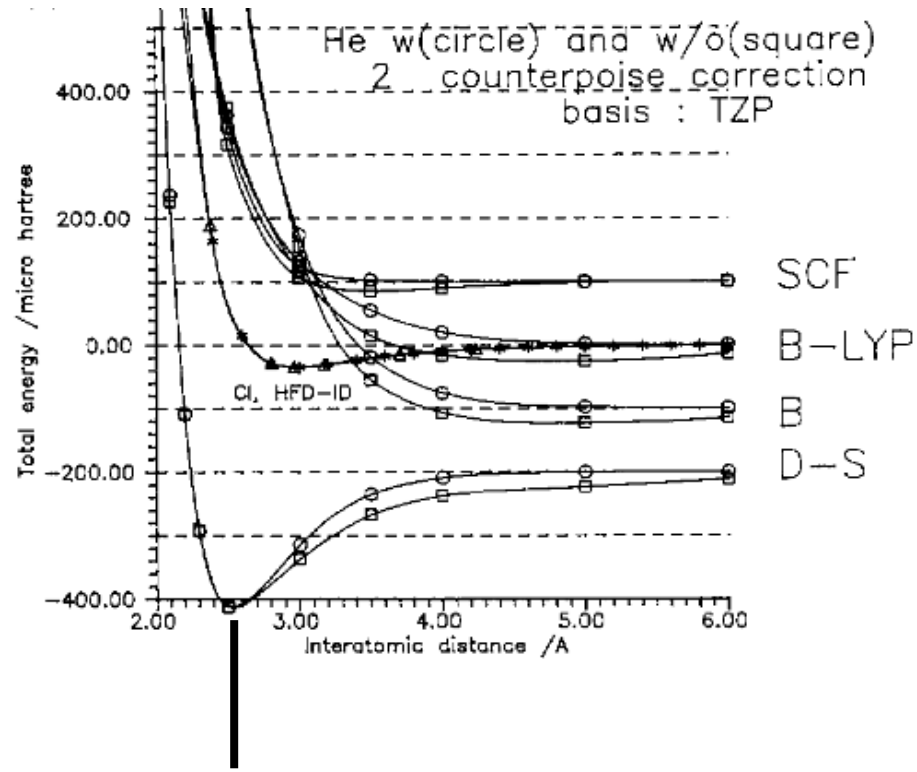
$$= h_{\mathrm{KS}}\varphi_i(\mathbf{r}_1) = \epsilon_i\varphi_i(\mathbf{r}_1)$$

$$V_{\mathrm{XC}}[\rho] = \delta E_{\mathrm{XC}}[\rho]/\delta\rho$$

$$E_{\mathrm{XC}} = (1 - a_x)E_X^{\mathrm{GGA}} + a_x E_X^{\mathrm{Fock}} + E_C^{\mathrm{GGA}}$$

Stairway to Heaven





Basis Set Superposition Error (BSSE)

Klimes, J.; Michaelides, A. *J. Chem. Phys*. **2012**, *137*, 120901
Kristyan, S.; Pulay, P. *Chem. Phys. Lett.* **1994**, *229*, 175-180
Grimme *et al. Chem. Rev.* **2016**, *116*, 5105-5154

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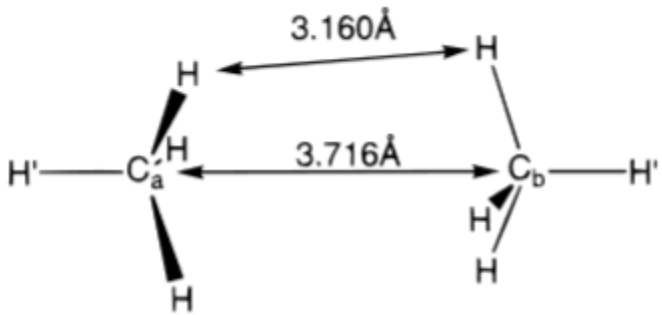
Strength of Dispersion Interactions

Methane Dimer:



Interaction Energies

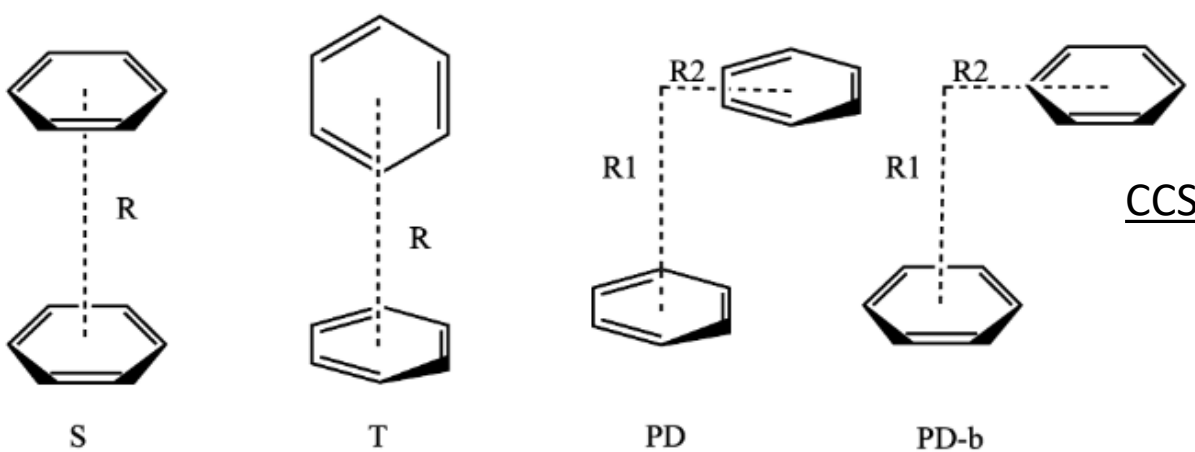
HF/cc-pV5Z = 0.365 kcal/mol

MP2/cc-pV5Z = -0.459 kcal/mol

CCSD(T)/CBS = -0.54 kcal/mol

Experiment: -0.33-0.46 kcal/mol

Benzene Dimer:



CCSD(T)/CBS Interaction Energy

S = -1.70 kcal/mol

T = -2.70 kcal/mol

PD = -2.71kcal/mol

Rappe, A.K.; Bernstein, E.R. J. Phys. Chem. A **2000**, *104*, 6117-6128

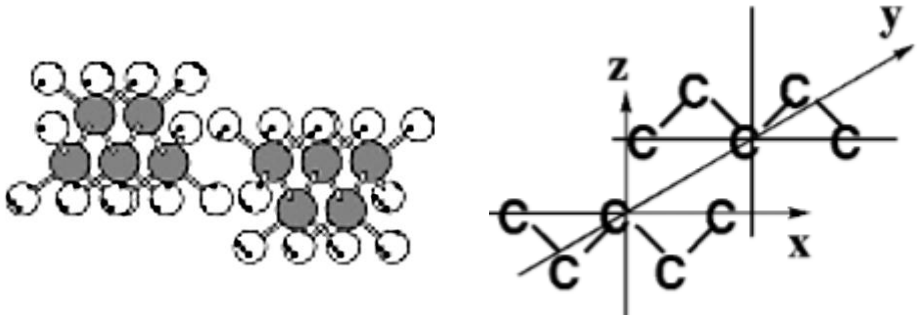
Reid *et al*. *J. Chem. Phys.* **1985**, 83, 5656-5662

Sherill *et al. J. Phys. Chem. A*. **2009**, *113*, 10146-10159

Saturated vs Unsaturated Interactions

Methane Dimer Interaction Energy:
-0.54 kcal/mol
Benzene Dimer Interaction Energy
S = -1.70 kcal/mol
T = -2.70 kcal/mol
PD = -2.71kcal/mol

Pentane Dimer:

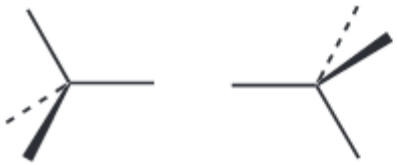


Dimer Interaction Energy: -3.75 kcal/mol

Group Question: Given the physical properties of benzene and pentane, do the dimerization energies make sense?

Tsuzuki *et al. J. Phys. Chem. A.* , **2004**, *108*, 10311-10316

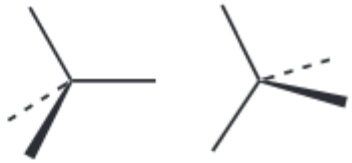
Interaction Classes



1:1

0.12 kcal/mol

n-Hexane:
0.37 kcal/mol

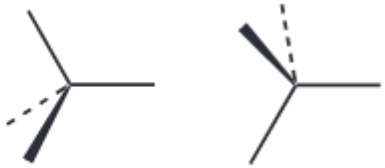


1:2

0.27 kcal/mol

1:3 eclipsed

0.37 kcal/mol



1:3 staggered

0.37 kcal/mol

2:2 eclipsed

0.25 kcal/mol

2:2 staggered

0.33 kcal/mol

3:3 eclipsed

0.38 kcal/mol

3:3 staggered

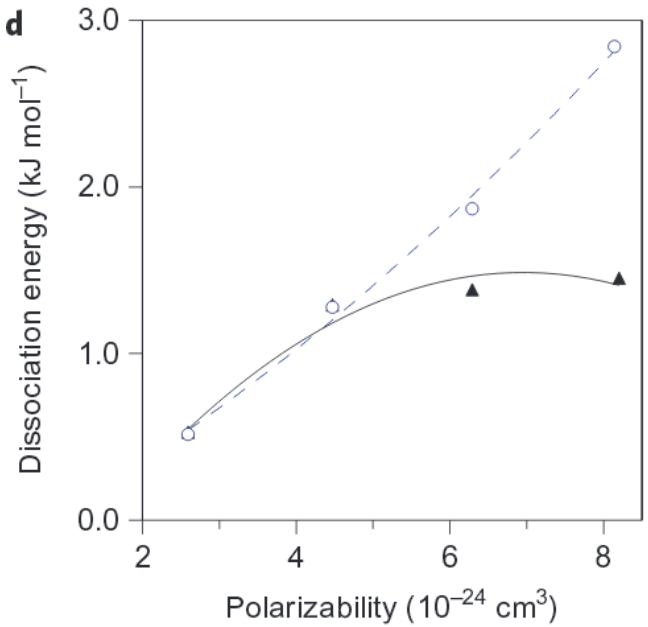
0.43 kcal/mol

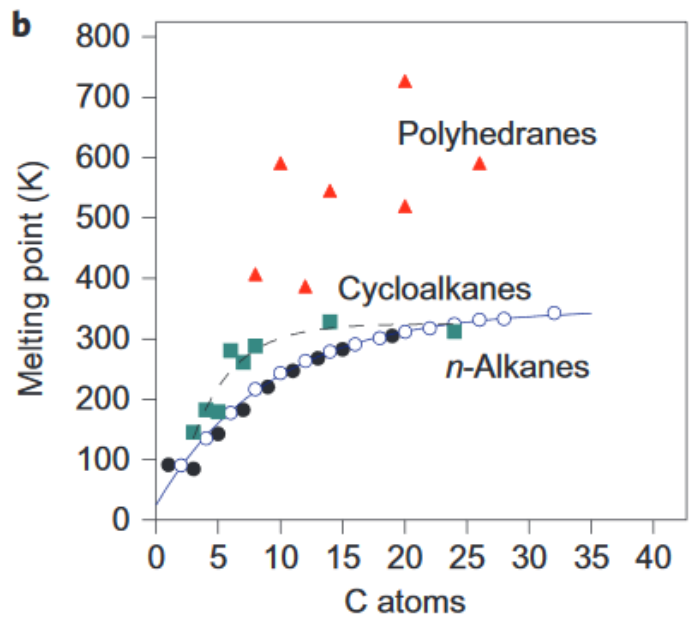
n-Hexane:
0.57 kcal/mol

Calculated at MP2/6-311++G(3df,3pd)
for Methane-Methane Interaction

Alvarez *et al.* *Nat. Chem.* **2011**, *3*, 323

Contributing Factors to Dispersion





Dashed: Branched Alkanes
Solid: Linear Alkanes

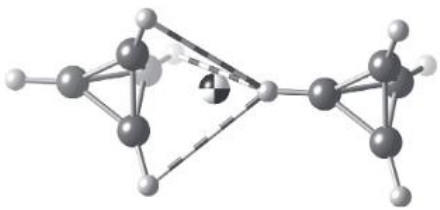
Important factors:

- Polarizablility (3 closest carbon atoms are most important)
- Surface Area
- Degrees of Freedom

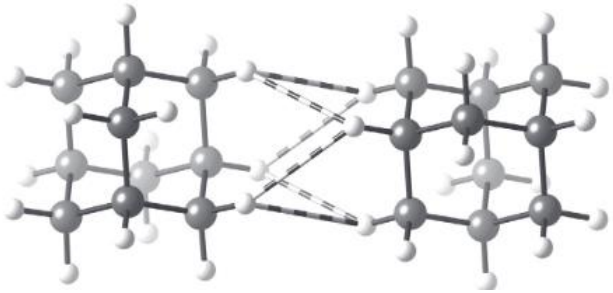
Alvarez *et al.* *Nat. Chem.* **2011**, *3*, 323

Polyhedranes

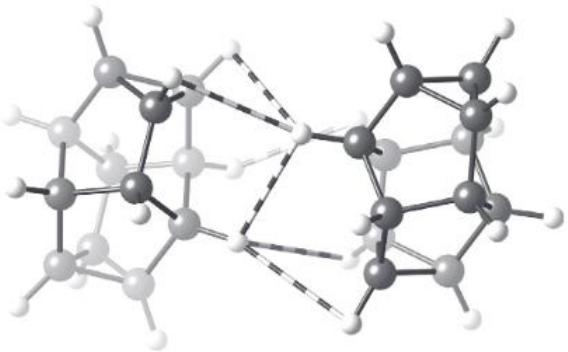
Tetrahedrane



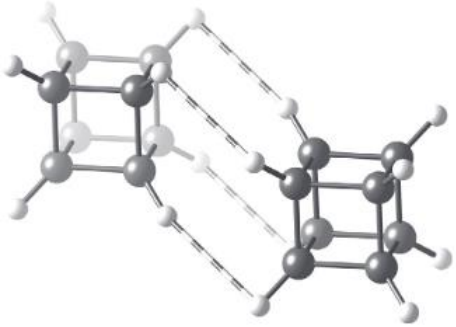
Adamantane



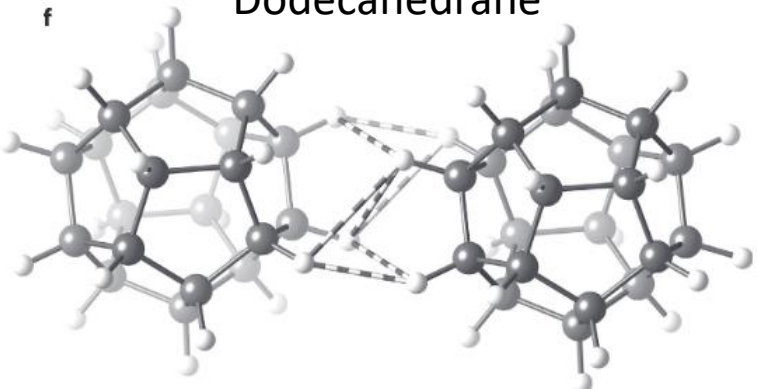
Octahedrane



Cubane



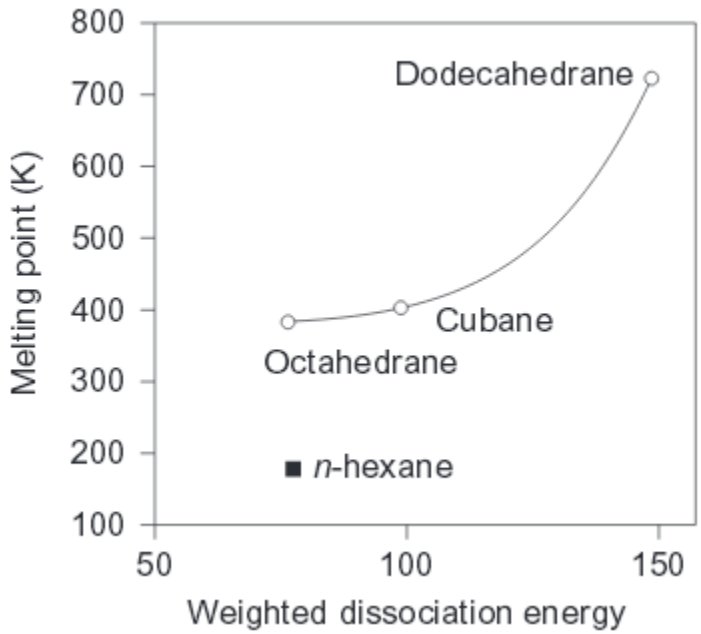
Dodecahedrane

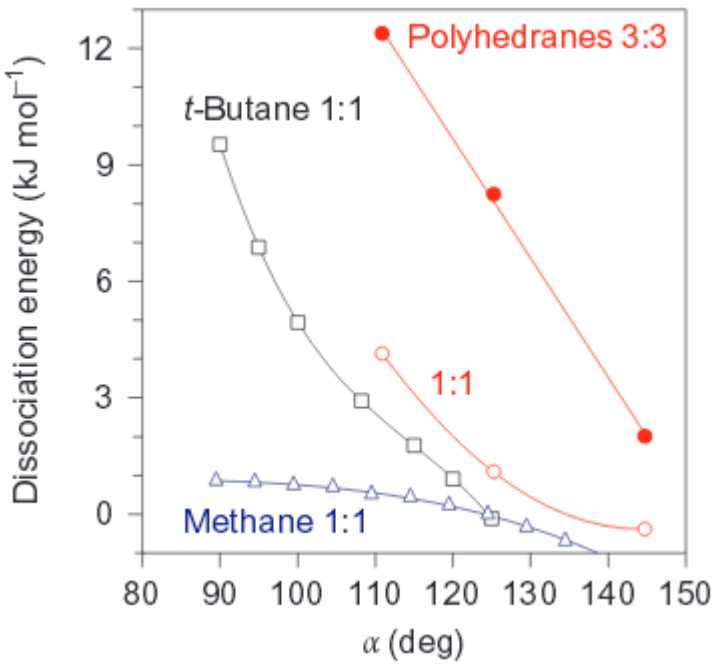


Polyhedrane	Topology	Interaction Energy (kcal/mol)	Nearest Neighbors
Tetrahedrane	3:1	0.86	-
	3:3	0.48	-
Adamantane	3:3	1.53	4
	4:4	1.44	8
Octahedrane	3:3 (trig)	1.53	2
	3:3 (pent)	2.53	6
Cubane	4:4	1.97	12
Dodecahedrane	3:3	2.96	12

Alvarez *et al.* *Nat. Chem.* **2011**, *3*, 323

Polyhedranes





Important Factors for alkane dimer interaction energy:

1) Electron-Donating groups at the C-H unit
2) Number of carbons at a two-bond distance
3) C-C-H pyramidality angle
4) Number of short H-H contacts
5) Entropy? $T_M = H_m/S_m$

Alvarez *et al.* *Nat. Chem.* **2011**, *3*, 323
Bond, A. *Nat. Chem.* **2015**, *7*, 89

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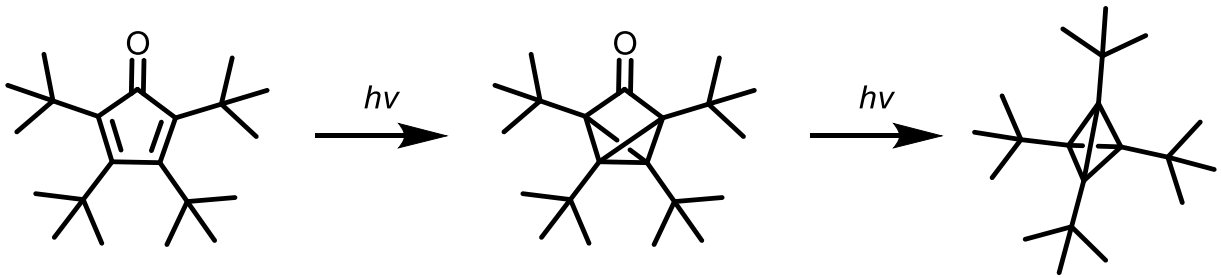
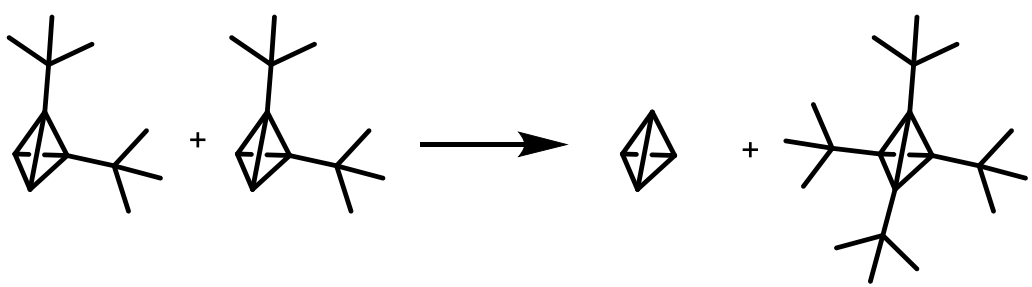
Case 1: Tetra-*tert*-butyltetrahedrane



(8): Tetra-*tert*-butylcyclopentadienone *(4)*[1] (313 mg, 1.03 mmol) in a Rigisolve matrix (35 ml) is irradiated with 254-nm light[13] for 77 h at the temperature of liquid nitrogen in thin quartz tubes. After removal of the solvent and chromatography of the crude orange product on SiO_2 [−5°C; 85 × 1 cm, pentane/ether (50:1)] the following fractions are successively eluted: tetrahedrane *(8)* (100 mg, 35%), ketene *(6)* (37 mg), and a mixture (65 mg) of starting dienone *(4)* and tricyclopentanone *(5)*. Tetra-*tert*-butyltetrahedrane crystal-

Corset Effect: Other large groups prevent *t*-butyl groups from repelling each other – prevents homolytic bond cleavage.

"New" Corset Effect: Large groups contribute disersion energy to stabilize strained structure



ΔH_f

B3LYP = +5.7kcal/mol

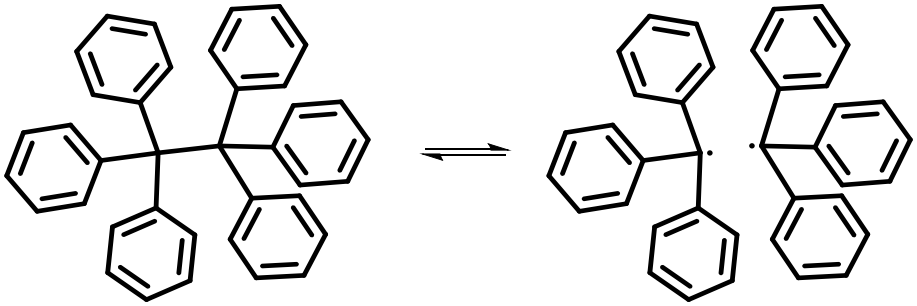
B3LYP-D = -3.1kcal/mol

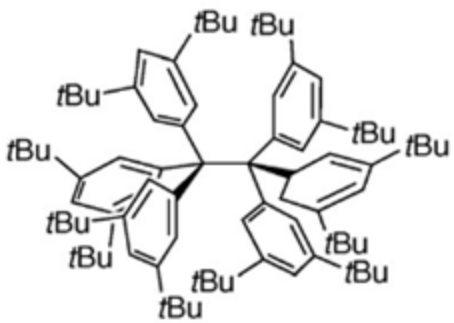
Mayer *et al*, ACIE **1978**, *90*, 552

Schreiner *et al*, *Nature,* **2011**, *477*, 308

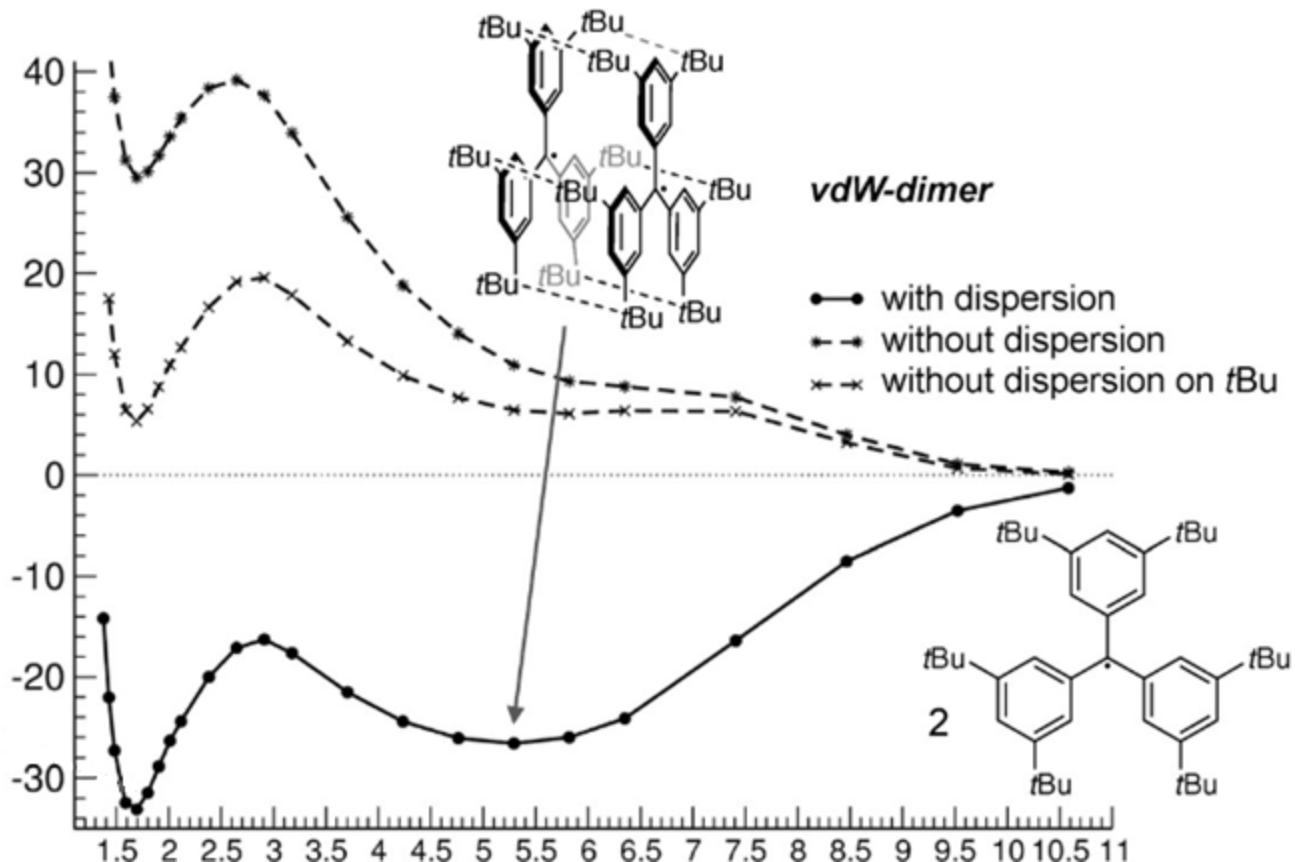
Case 2: The riddle of hexaphenyl ethane

"Too sterically encumbered to be synthetically accessible"

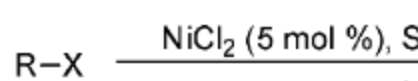


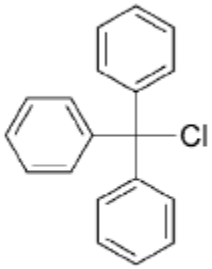
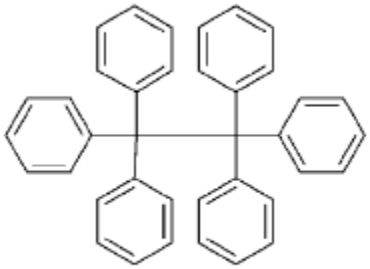
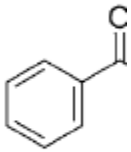


Crystal Structure Obtained!

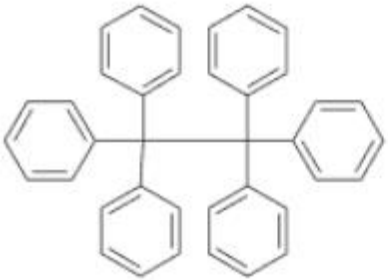


Reported Synthesis



Entry[a]	R–X	R–R	t [h]	Yield[b] [%]	Entry[a]	R-
	1o	2m				
16			16	43	39	
	1p	2n				

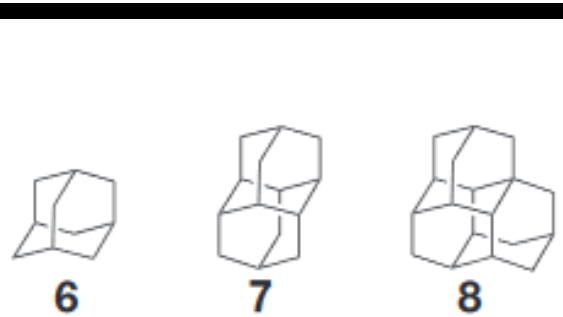
Hexaphenylethane (2n)

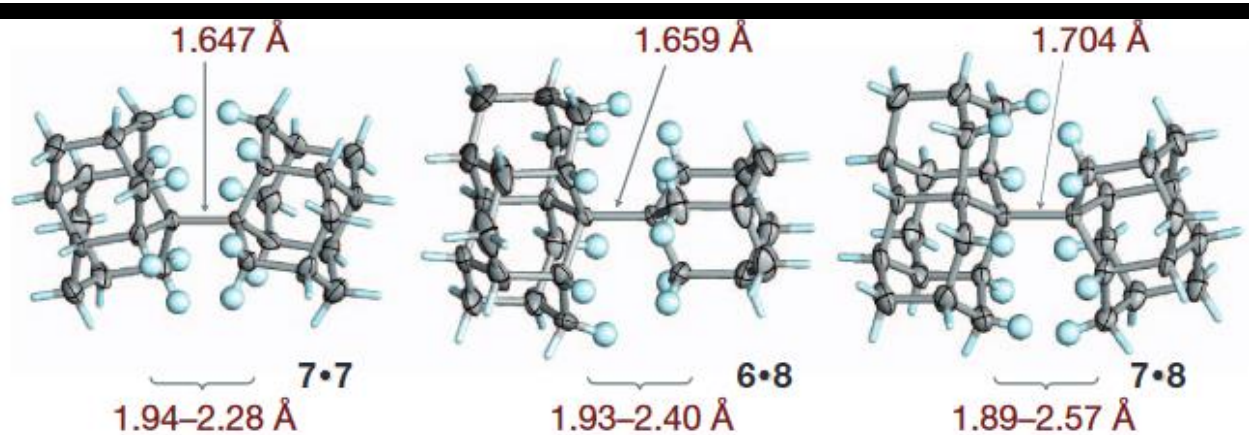


CAS Number: 17854-07-8; white solid; m.p. 230-233 °C (lit. 2227-230 °C);[10] ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.97-7.30 (m, 30H); ^{13}C NMR (125 MHz, $CDCl_3$) δ131.2, 129.4, 128.4, 128.2, 127.3, 126.2, 125.8, 56.4.

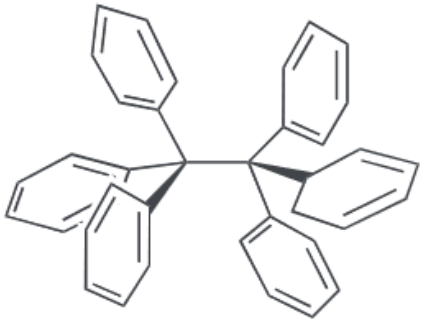
Chemistry - An Asian Journal, **2017,** 12, 673-678

Case 3: Diamonoid Structures

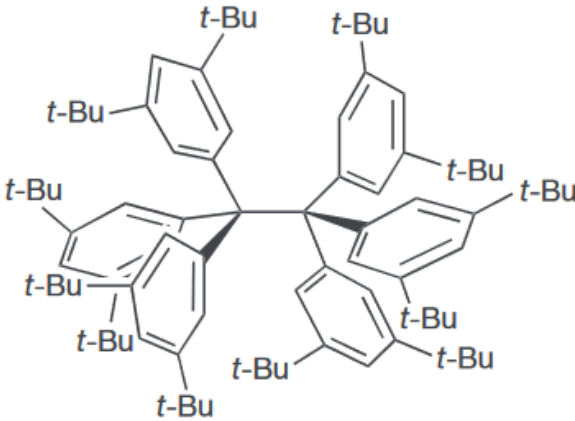




7•7



5 (R = H)

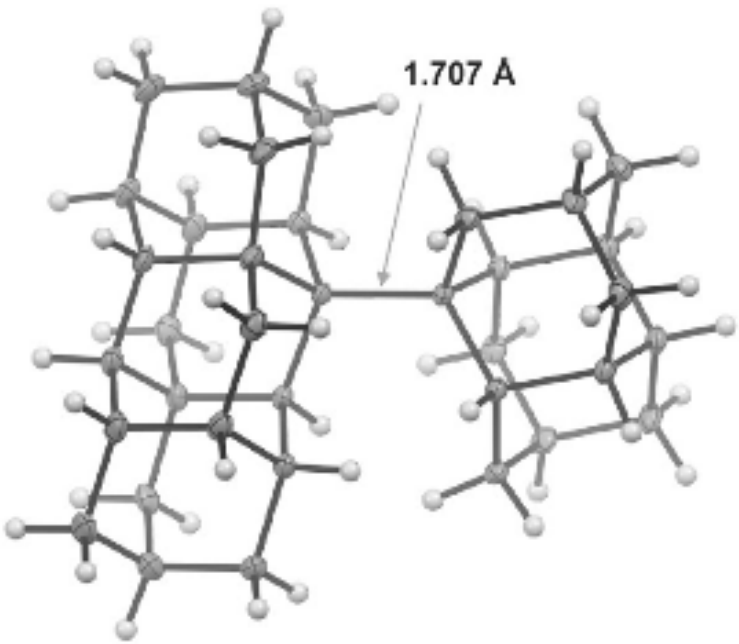


5 (R = *t*-Bu)

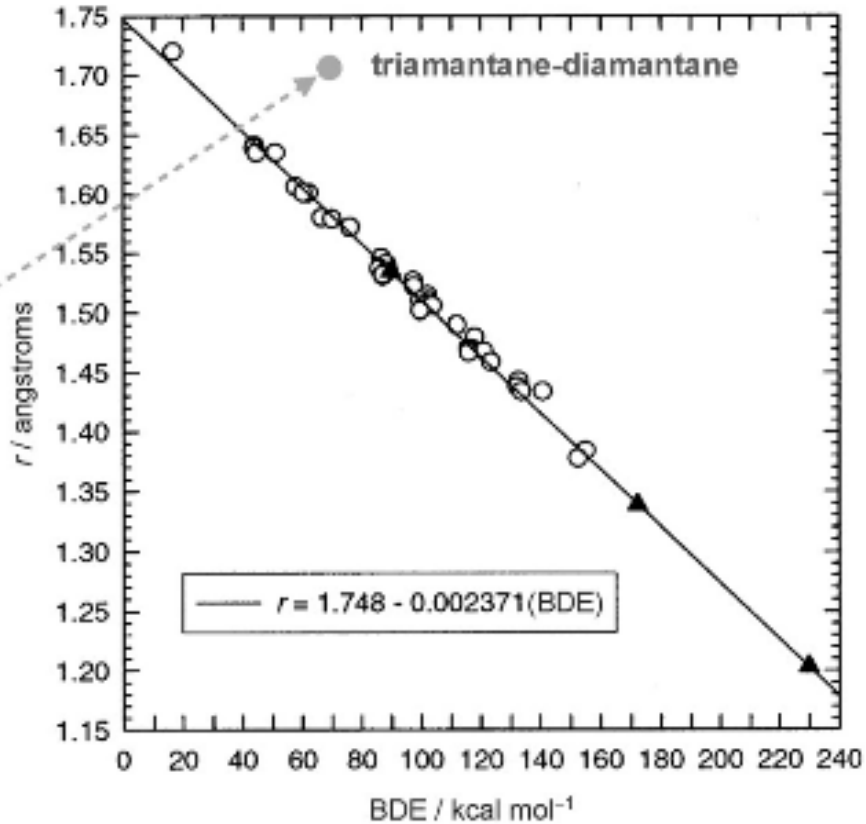
Method/quantity	BDE (kcal mol^{-1})	C–C (Å)	BDE (kcal mol^{-1})	C–C (Å)	BDE (kcal mol^{-1})	C–C (Å)
B3LYP/6-31G(d,p)	43.9	1.674	−20.9	1.730	−26.1	1.709
B3LYP-D/6-31G(d,p)	70.7	1.653	10.3	1.735	44.5	1.674
B97D/6-31G(d,p)	64.5	1.668	6.5	1.791	38.8	1.698
M06-2X/6-31G(d,p)	65.8	1.648	12.3	1.702	33.0	1.669
Experiment	—	1.647	—	—	—	1.670(3)

Schreiner *et al*, *Nature*, **2011**, *477*, 308

Dispersion Stabilized Long C-C bond



Tetramantane-diamantane dimer (currently the longest C–C bond in a pure alkane: **stable** at least up to m.p. of 247 °C (dec.).



Zavitas, A. *J. Phys. Chem. A.* **2003**, *107*, 897
Schreiner *et al*, *Nature,* **2011**, *477*, 308
Wagner, J.; Schreiner, P. *Angew. Chem. Int. Ed.* **2015**, *54*, 12274

Overview

- Theory
  - What are London Dispersion Forces?
  - Theoretical Limitations
- Factors Controlling the Strength of Dispersion Forces
  - Relative Magnitude
  - How do we modulate them?
- Attractive Steric Effects and Structure
- Attractive Steric Effects and Reactivity
- Future Directions

Intermission

Overview

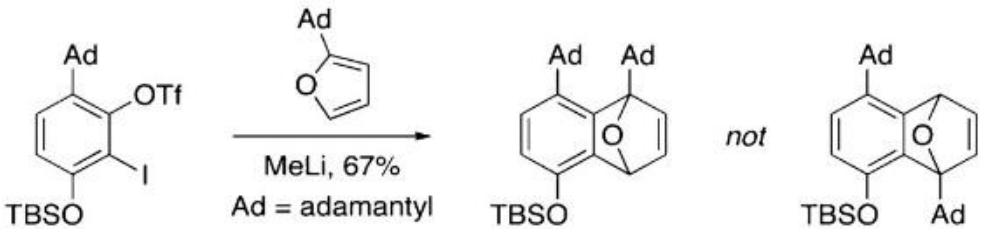
- Theory
  - What are London Dispersion Forces?
  - Theoretical Limitations
- Factors Controlling the Strength of Dispersion Forces
  - Relative Magnitude
  - How do we modulate them?
- Attractive Steric Effects and Structure
- Attractive Steric Effects and Reactivity
- Future Directions

Dispersion Energy Donors

The installation of groups with favorable dispersive interactions allows the synthesis of molecules that would otherwise be "sterically forbidden."

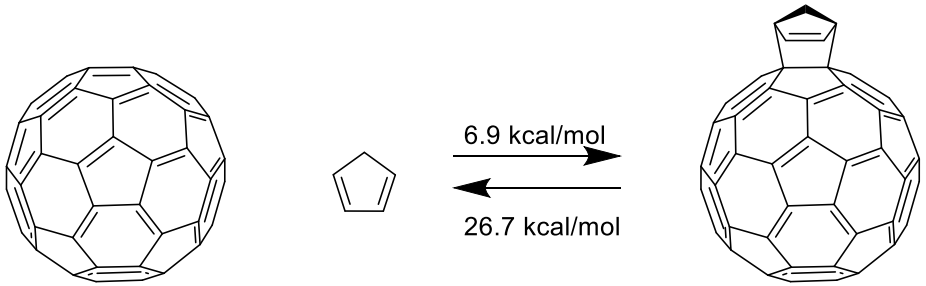
Can we use these motifs to influence the reactivity of molecules?

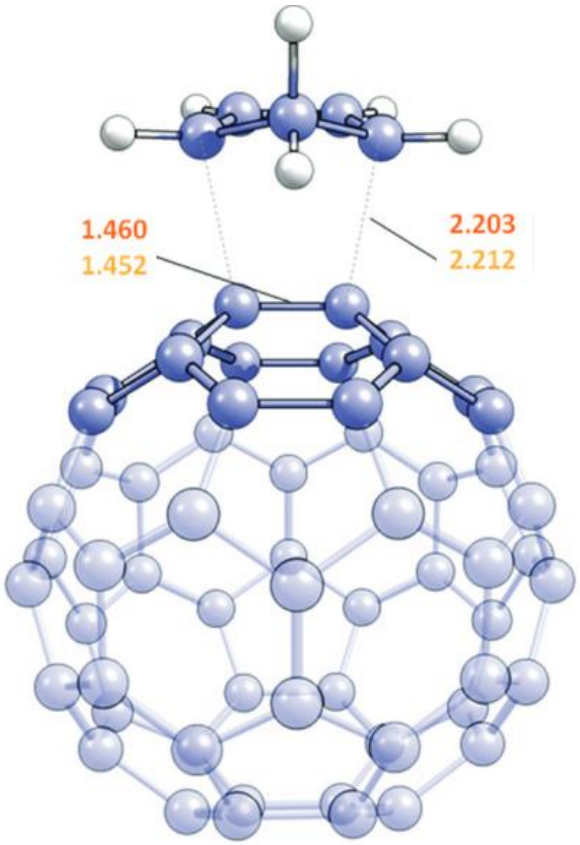
Yes - Dispersion energy donors

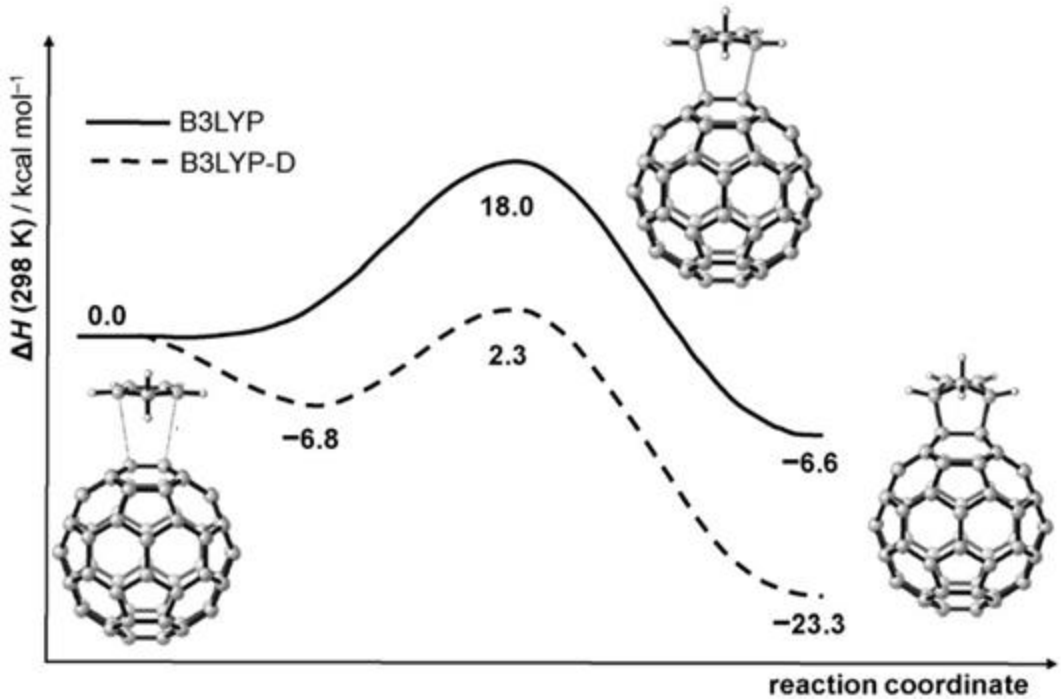


H. Aikawa, Y. Takahira, M. Yamaguchi, **Chem.Commun**. **2011**, *47*, 1479

Kinetic Barriers

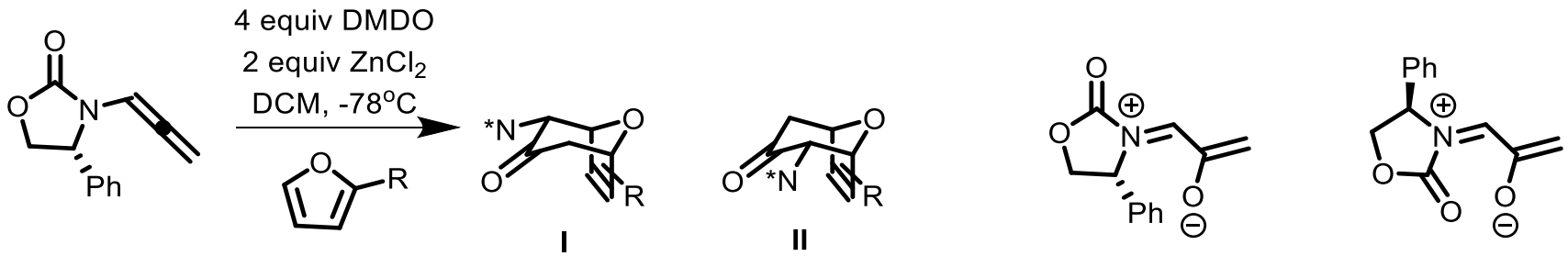




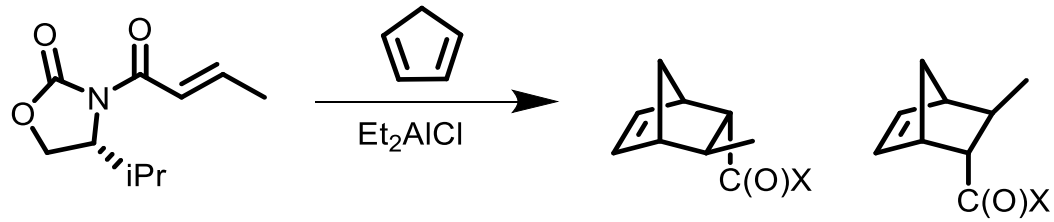


S. L. Osuna, M. Swart, M. Solà *J. Phys. Chem. A* **2011**, *115*, 3491

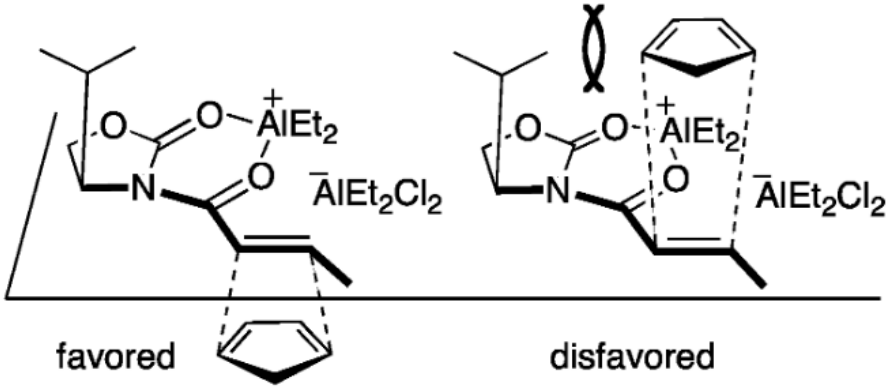
Selectivity in (4+3) cycloadditions



R	dr *I*:*II*	
	uncat.	$ZnCl_2$-cat.
H	82:18	≥96:4
Me	90:10	100:0
CO_2Me	0:100	30:70

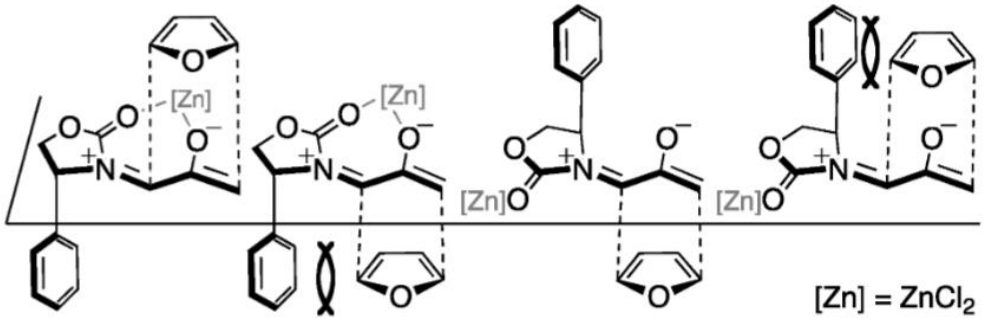


Why the Inversion of Selectivity?



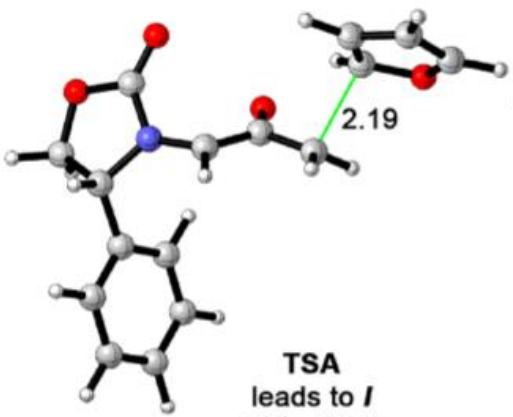
Hsung *et al.* J. *Am. Chem. Soc.* **2001**, *123*, 7174
Hsung *et al.* J. *Synlett* **2008**, 739

A Stereochemical Model for Unsubstituted Furan

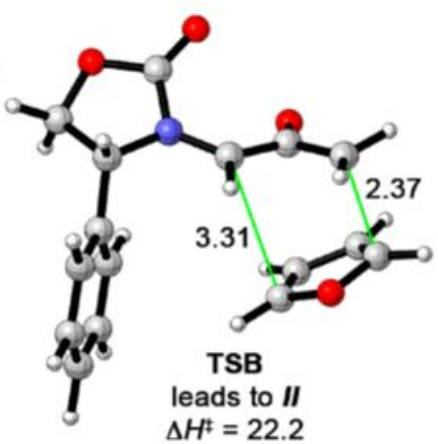


TSA leads to ***I*** | **TSB** leads to ***II*** | **TSC** leads to ***II*** | **TSD** leads to ***I***

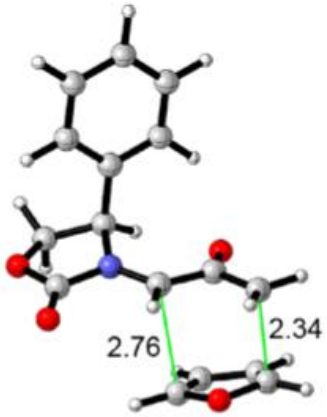
	$\Delta E^{\ddagger}_{rel}$	
	TSC	**TSD**
B3LYP	0	–0.3
B3LYP[a]	0	–0.5
B3LYP-D	0	–1.8
B3LYP-D3	0	–2.0
B97-D	0	–2.0
M06-2X	0	–1.4
M06-2X[a]	0	–2.0



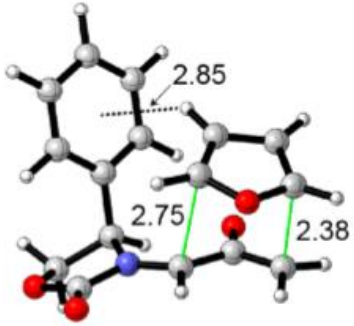
TSA
leads to ***I***
$\Delta H^{\ddagger}$ = 24.4
$\Delta G^{\ddagger}$ = 35.6



TSB
leads to ***II***
$\Delta H^{\ddagger}$ = 22.2
$\Delta G^{\ddagger}$ = 34.7



TSC
leads to ***II***
$\Delta H^{\ddagger}$ = 6.8
$\Delta G^{\ddagger}$ = 20.3



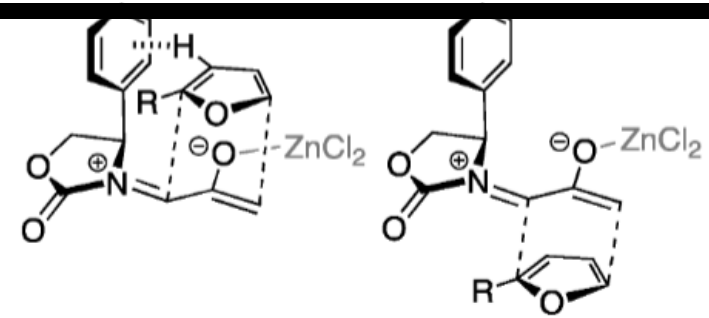
TSD
leads to ***I***
$\Delta H^{\ddagger}$ = 6.6
$\Delta G^{\ddagger}$ = 20.0

Houk, K.N., Sung, R. *et al J. Am. Chem. Soc*. **2011**, *133*, 14443

The Effect of 2-Substituents on Selectivity

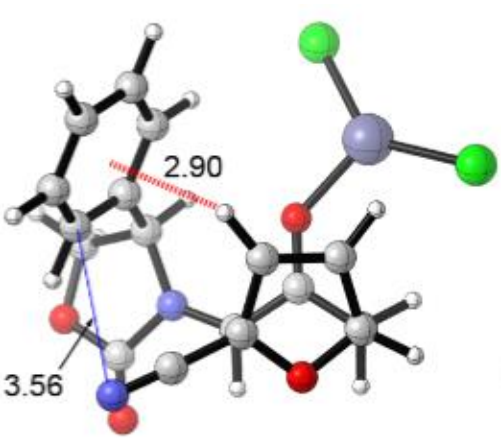
System	TS-syn-1*	TS-anti-1*	TS-syn-2*	TS-anti-2*	Exp. Ratio
2-Methylfuran (with Zinc)	11.7	13.6	11.7	13.4	80:20:0:0
Methyl-2-furoate (with Zinc)	14.1	18.5	13.9	18.4	30:0:70:0
2-cyanofuran (with Zinc)	17	20.9	17.7	21.4	83:0:17:0

*ΔΔG in kcal/mol

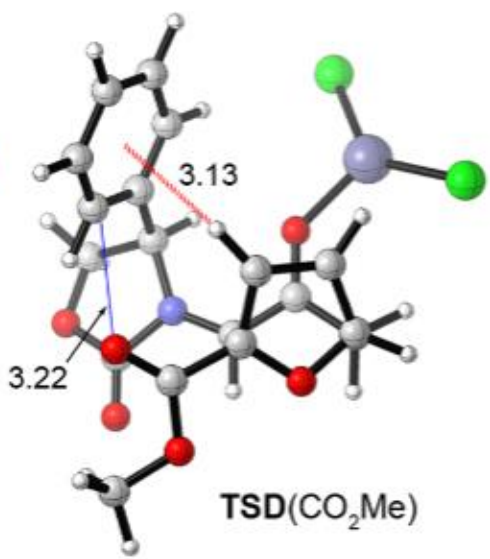


TS-*syn-I* TS-*syn-II*

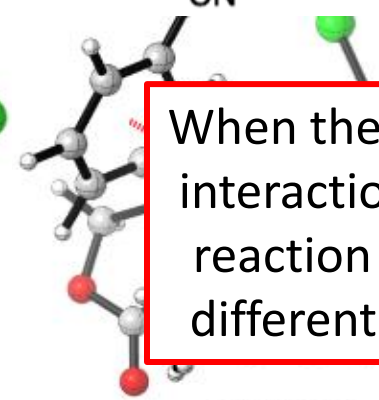
R	E_{disp} TS-*syn-I*	E_{disp} TS-*syn-II*
$ZnCl_2$-catalyzed		
Me	−46.3	−43.4
CO_2Me	−50.0	−50.0
CN	−45.2	−44.3



TSD(CN)



TSD(CO_2Me)

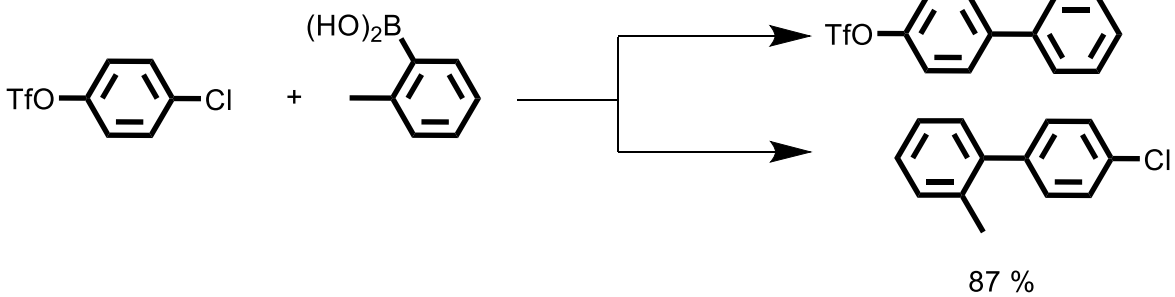


TSD(Me)

When the favorable dispersion interaction is interrupted, the reaction proceeds through a different transition structure

Houk, K.N., Sung, R. *et al J. Am. Chem. Soc.* **2011**, *133*, 14443

Regioselectivity of Oxidative Addition

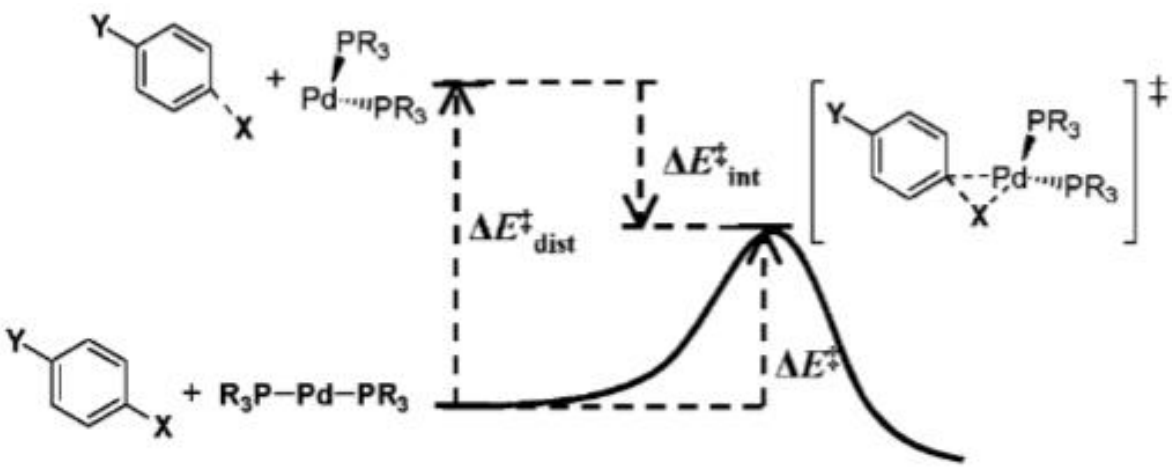


Conditions

1.5 % $Pd(dba)_3$
3 mol% P(*t*-Bu)$_3$
3 equiv KF
THF, r.t.

3 mol % $Pd(OAc)_2$
6 mol% $P(Cy)_3$
3 equiv KF
THF, r.t.

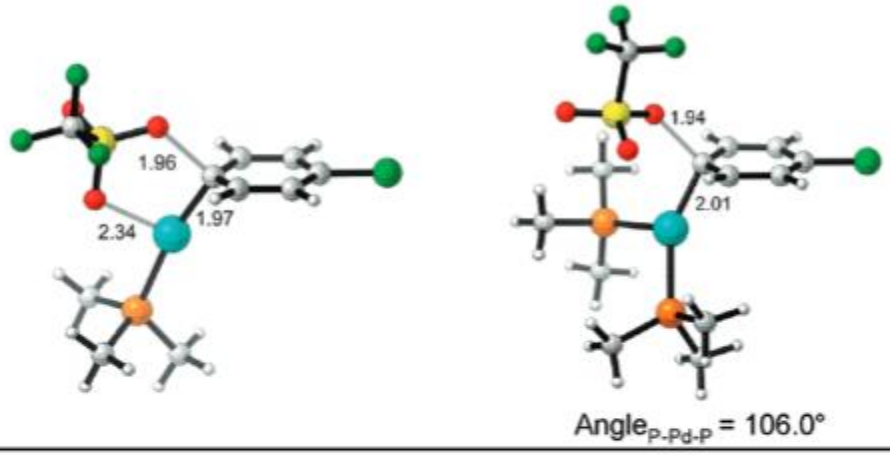
insertion position	Pd Species	$\Delta E^{\ddagger}$
C−Cl	$PdPMe_3$	14.4
C−OTf	$PdPMe_3$	19.9
C−Cl	$Pd(PMe_3)_2$	*21.5*
C−OTf	$Pd(PMe_3)_2$	*16.9*

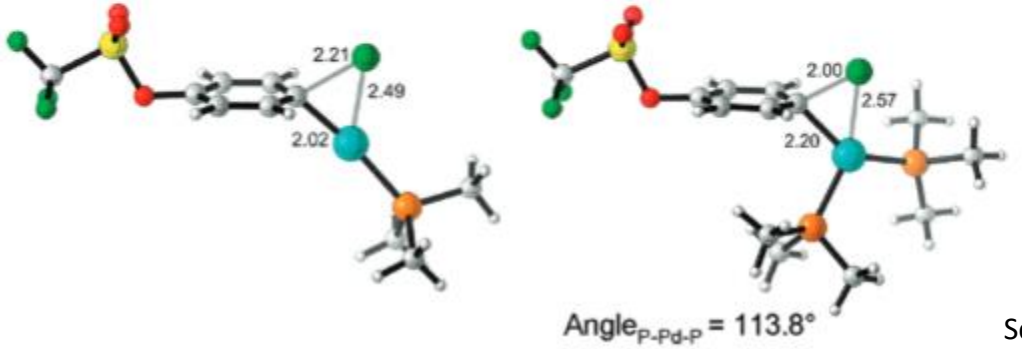


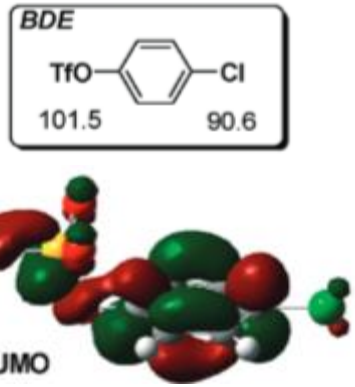
Fu *et al. J. Am. Chem. Soc.* **2000**, *122*, 4020-4028
Schonebeck, F.; Houk, K.N. J. Am. Chem. Soc. 2010, 132, 2496

Regioselectivity of OA– D/I analysis

insertion position	Pd Species	$\Delta E^{\ddagger}$	ΔE_{dist} (Pd)	ΔE_{dist} (substrate)	ΔE_{int}	$\Delta G^{\ddagger}$
C−Cl	$PdPMe_3$	14.4	3.2	32.1	−20.9	13.7
C−OTf	$PdPMe_3$	19.9	4.3	52.6	−37.0	20.1





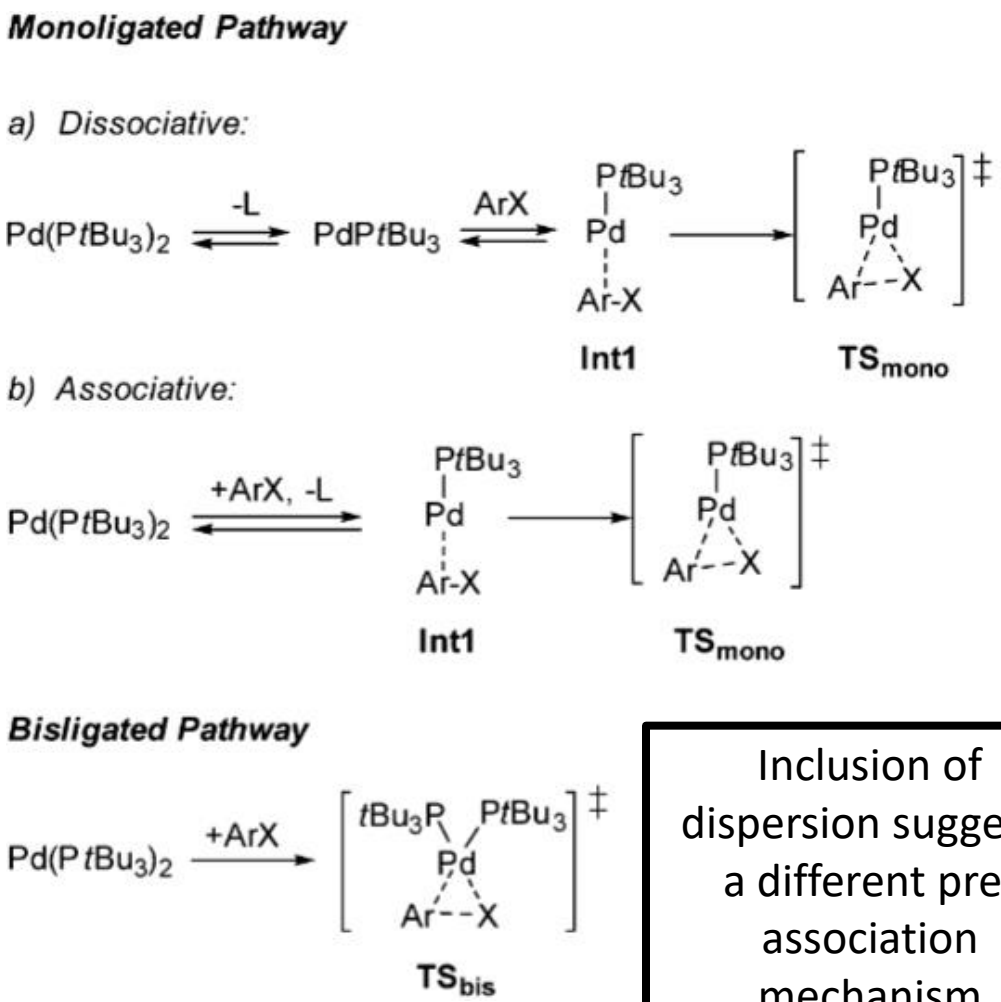


Monoligated =
Distortion Controlled

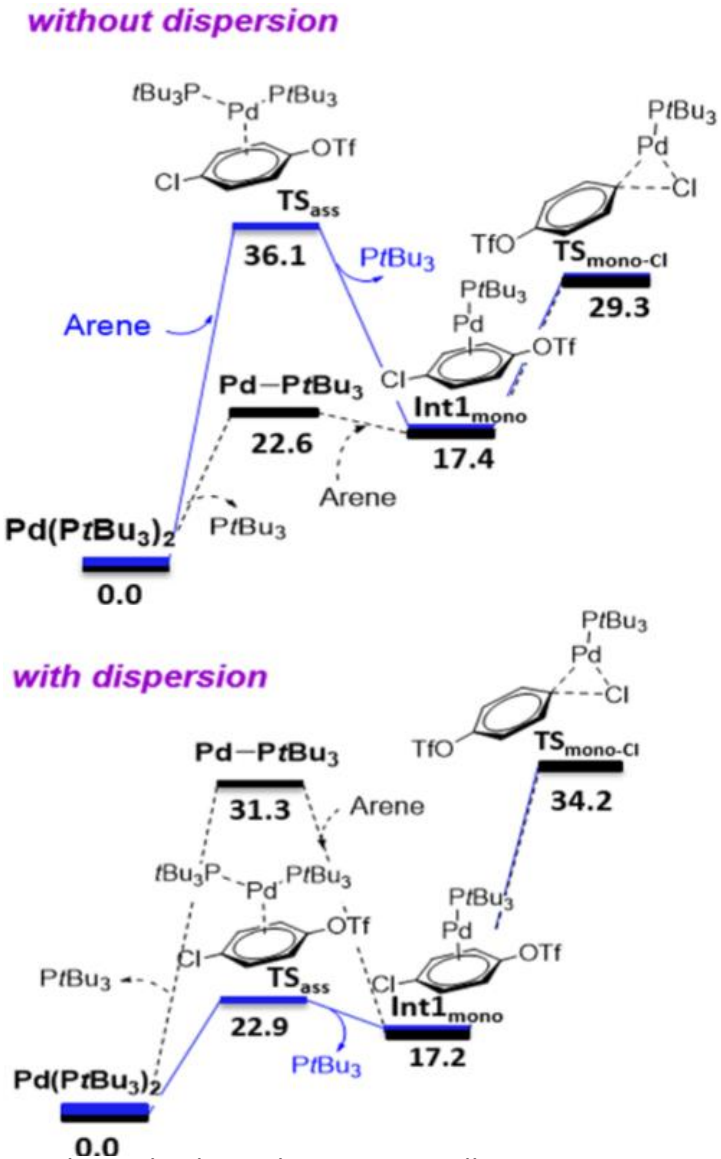
Bisligated =
Interaction Controlled

Schonebeck, F.; Houk, K.N. J. Am. Chem. Soc. 2010, 132, 2496

Pre-Oxidative Addition Intermediates

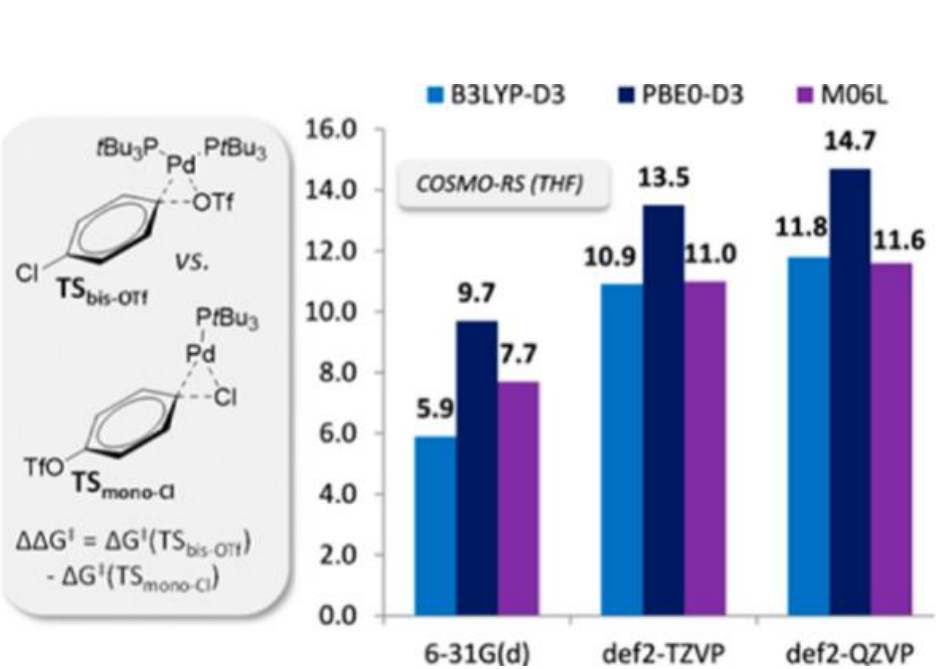


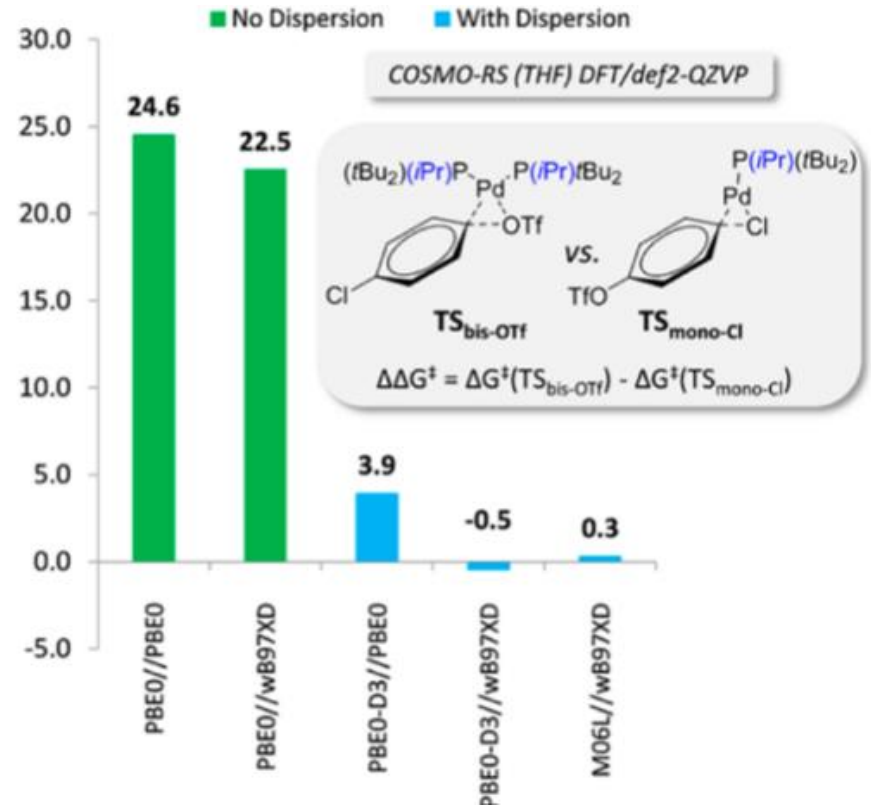
Inclusion of dispersion suggests a different pre-association mechanism



Schoenebeck *et al. Organometallics* **2015**, *34*, 805

Dispersion's Effect of Barrier Heights

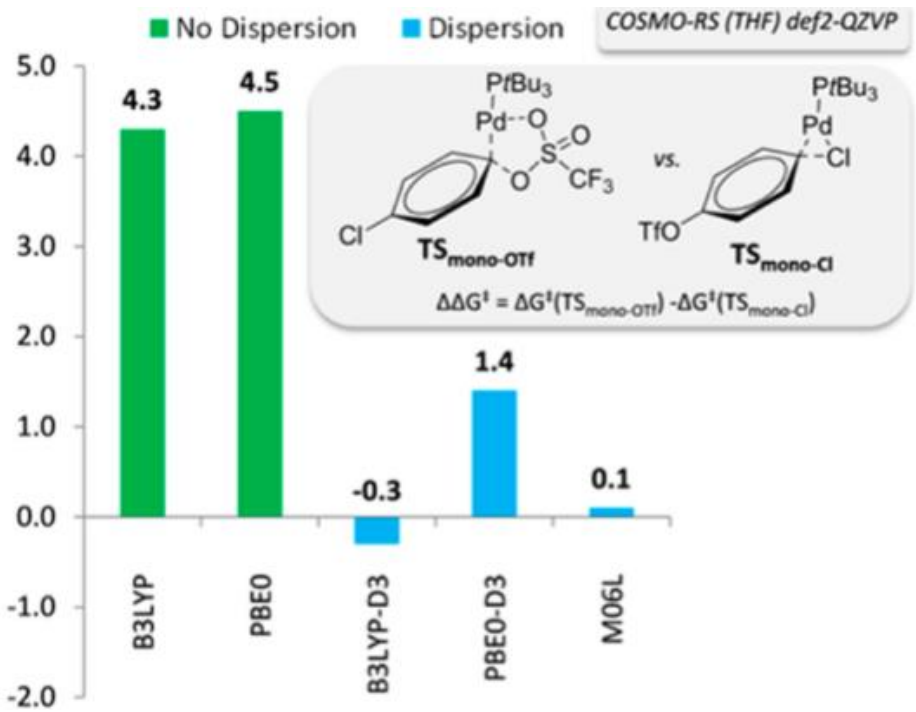


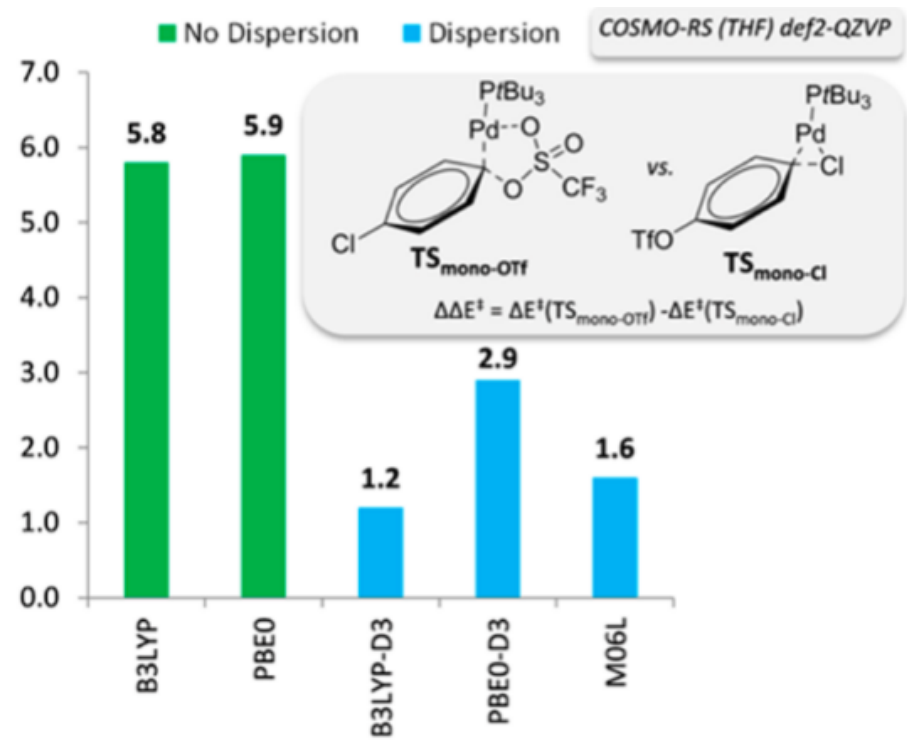


Only by including dispersion interactions can the appropriate switch in selectivity be achieved

Fu *et al. J. Am. Chem. Soc.* **2000**, *122*, 4020-4028

Regioselectivity of Oxidative Addition





Schoenebeck *et al. Organometallics* **2015**, *34*, 805

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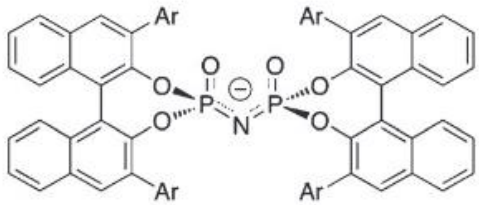
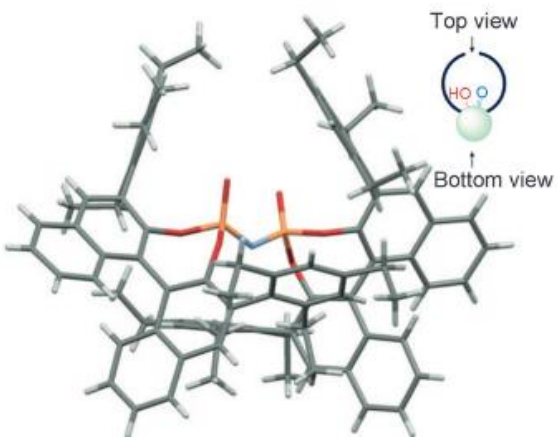
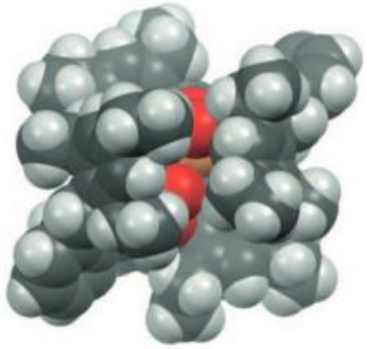
Future Directions

Catalyst design in asymmetric synthesis generally includes steric interactions to disfavor an undersired transition state over a desired transition state

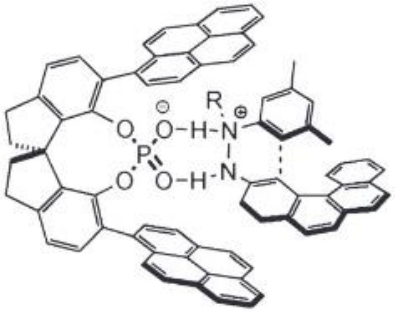


Ar = 2,4,6-triethylbenzene

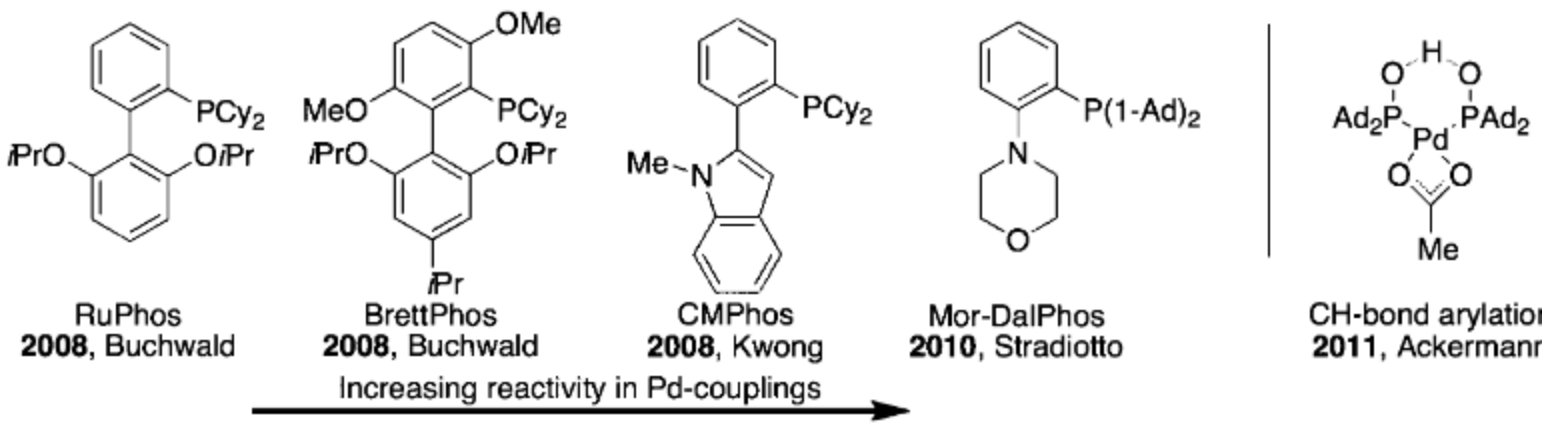




top view



Future Directions



"… it would be very useful to have available a quantitatively accurate scale of dispersion energy donors (DEDs) that could then be utilized as design elements for chemical synthesis, the construction of new materials, and to fine-tune organic reactivity as well as catalysis."