Dyotropic Rearrangements

Presented by Matthew Burk
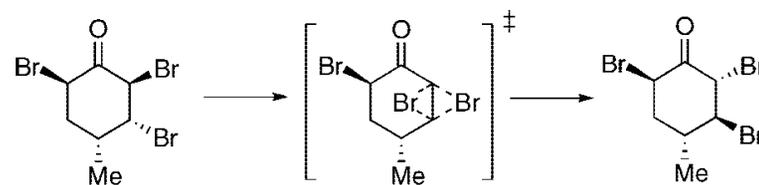
5-11-2010

What is a Dyotropic Rearrangement?

A process in which two σ-bonds simultaneously migrate intramolecularly

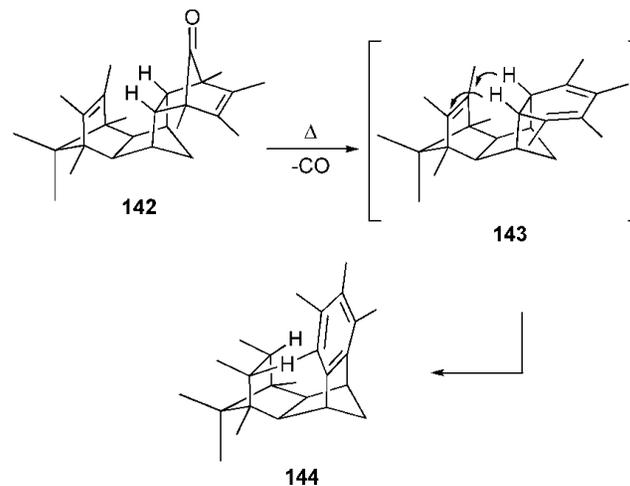**Type 1**

2 σ bonds exchange their positions


Type 2

No direct positional interchange occurs

(1)   Reetz, M. T. *ACIE*. **1972**, *11*, 129-130.
(2)   Reetz, M. T. *ACIE*. **1972**, *11*, 130-131.

Orbital Symmetry Requirements for Type I Dyotropic Rearrangements

Formally $[\sigma_s 2 + \sigma_s 2]$ pericyclic reactions

Permitted suprafacially only with inversion at the migrating group and/or participation of a lone pair, d orbital, extended π system, or element of π symmetry
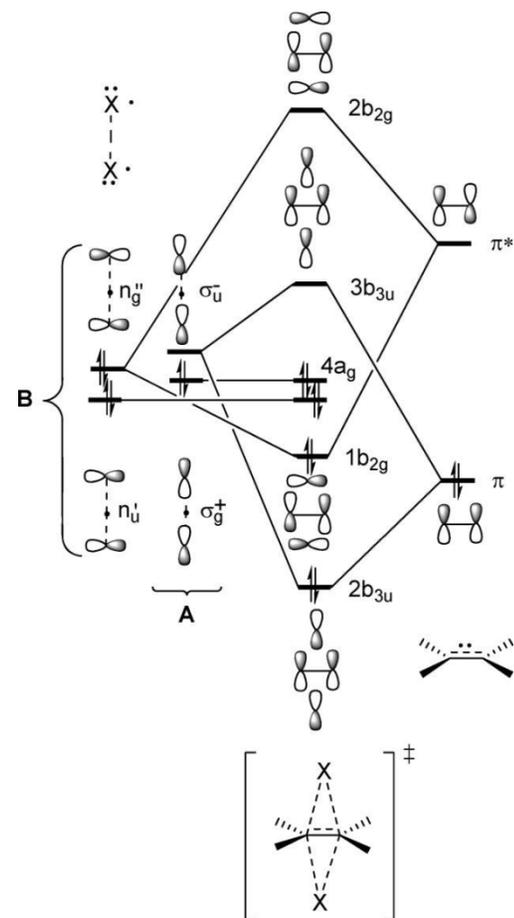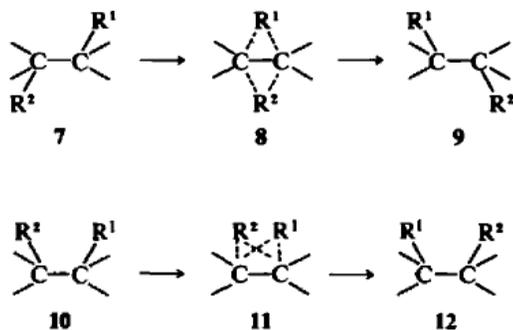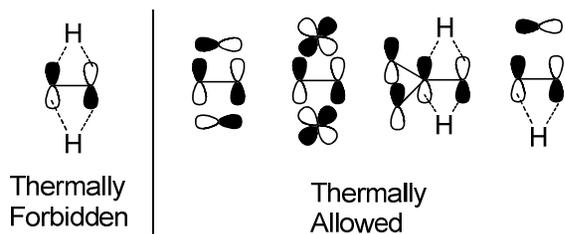
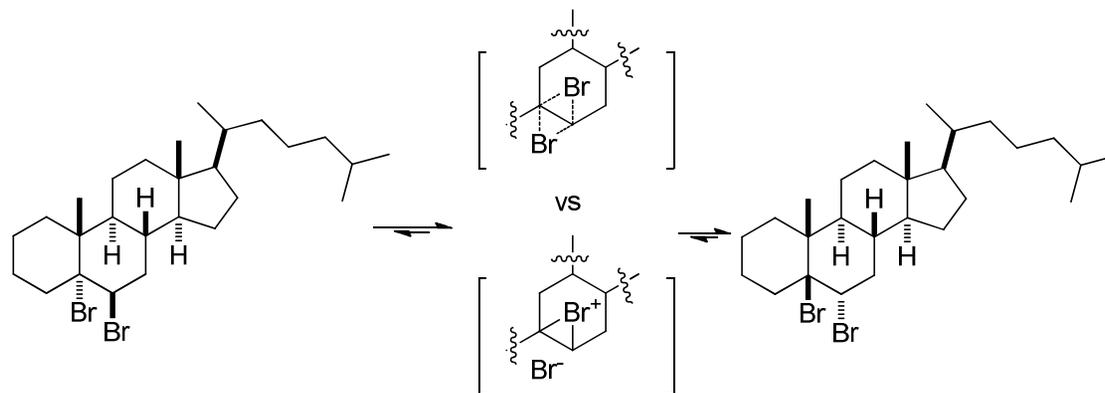Non-concerted processes are also possible, bypassing orbital symmetry requirements

Reetz, M. T. *ACIE*. **1972**, *11*, 129-130.
Reetz, M. T. *ACIE*. **1972**, *11*, 130-131.
Reetz, M. *Tetrahedron*. **1973**, *29*, 2189-2194.
Fernández, I.; Cossío, F. P.; Sierra, M. A. *Chem. Rev.* **2009**, *109*, 6687-711.

Mutarotation of Dihalogens

Solvent	heptane	CCl_4	C_6H_6	$C_6H_5NO_2$	$CHCl_3$	$CHCl_3$-/AcOH 1:1	$CHCl_3$-/EtOH 1:1
K_{rel}	1	2.7	5.3	28	86	115	284

(at 40 C)

In more polar solvents, solvolysis and elimination are also observed
The proportion of solvolysis and elimination are insensitive to added Br- and OAc-
The rate is insensitive to added HBr and catechol and benzoyl peroxide

Conclusion
"It is considered probable that the nature of the intermediate changes gradually as the ionizing power of the solvent decreases until, in the poorest ionizing solvents, an
intermediate or transition state is involved with negligible charge separation, both bromine atoms being essentially equivalent"
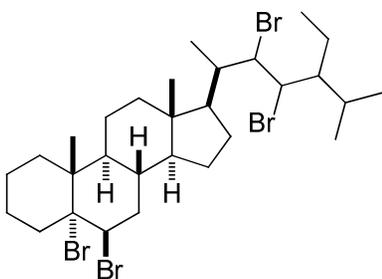
Grob, C. A.; Winstein, S. *Helv. Chim. Acta*. **1952**, *35*, 782-802.

Activation Parameters
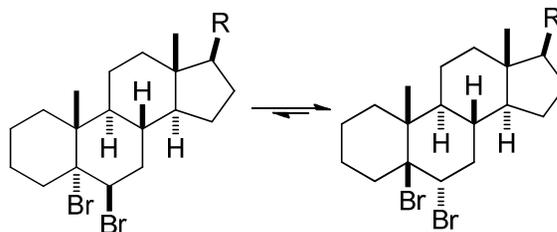
(in CHCl$_3$)
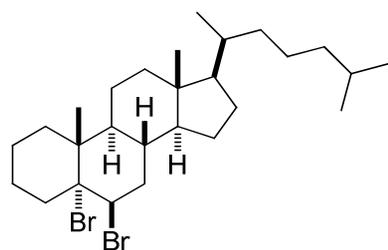
$$k = 10^{10.1} e^{\frac{-20.4 \left(\frac{kcal}{mol}\right)}{RT}} sec^{-1}$$

$\Delta H^{\ddagger}$= 20.1 kcal/mol
$\Delta S^{\ddagger}$=-13.2 cal/(mol*K)
$\Delta G^{\ddagger}$= +24.0 kcal/mol (@298 K)

$$k = 10^{10.0} e^{\frac{-20.4 \left(\frac{kcal}{mol}\right)}{RT}} sec^{-1}$$

$\Delta H^{\ddagger}$= 20.1 kcal/mol
$\Delta S^{\ddagger}$=-14.2 cal/(mol*K)
$\Delta G^{\ddagger}$= +24.3 kcal/mol (@298 K)
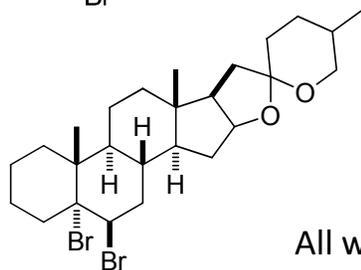
$$k = 10^{10.0} e^{\frac{-20.4 \left(\frac{kcal}{mol}\right)}{RT}} sec^{-1}$$

$\Delta H^{\ddagger}$= 19.9 kcal/mol
$\Delta S^{\ddagger}$=-14.3 cal/(mol*K)
$\Delta G^{\ddagger}$= +24.2 kcal/mol (@298 K)

y = -1.014E+04x + 1.710E+01
R^2 = 9.998E-01

ln(k/T)

1/T (K)
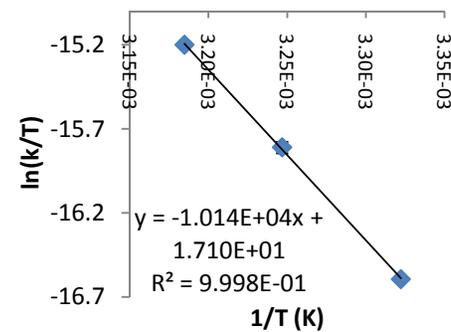
All were first order in dibromide
$\Delta S^{\ddagger}$<0 shows that the transition states have fewer degrees of freedom than the ground states
This is consistent with a concerted dyotropic shift
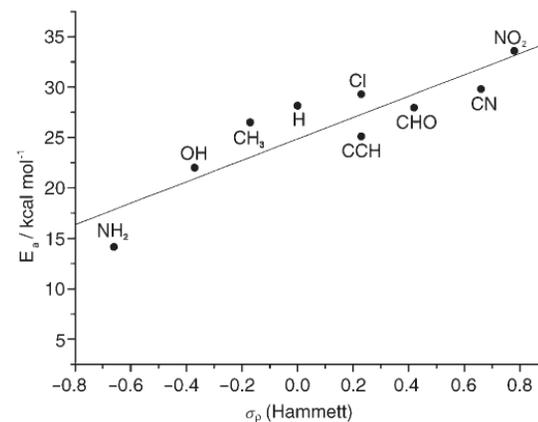An ionization/internal return mechanism would show $\Delta S^{\ddagger}$>0

Barton, D. H.; Head, A. J. *J. Chem. Soc*. **1954**, 932.

Computational Investigations

1 $\xrightarrow{\Delta E_a}$ **2** ‡

2a (D_{2h})

E_a / kcal mol^{-1} vs σ_p (Hammett)
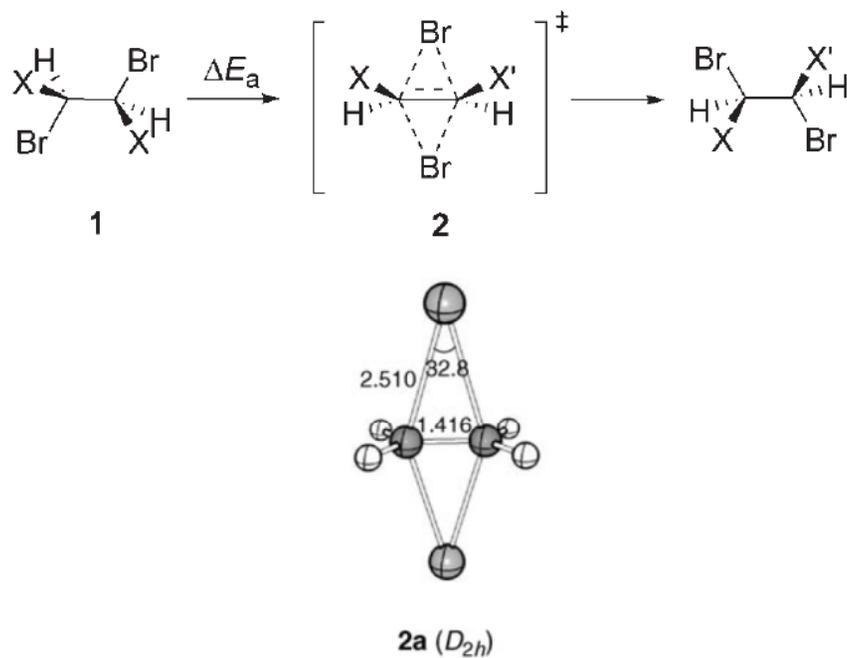
Figure 4. Plot of the activation energies (E_a) versus the σ_p Hammett substituent constants of monosubstituted 1,2-dibromoethanes.

[**10**]‡

Concerted and highly synchronous mechanism
Activation energy is reduced by electron-donating substituents
Calculated activation energy is low for cholestane analog

Fernández, I.; Sierra, M. A.; Cossío, F. P. *Chem. Eur. J.* **2006**, *12*, 6323-30.

Lactone Ring Expansion

10

$R_1 = H, Ph$
$R_2 = H, Ph, tBu, OPh, SPh$

94-98%

Stereospecific

H migrates somewhat faster than Me

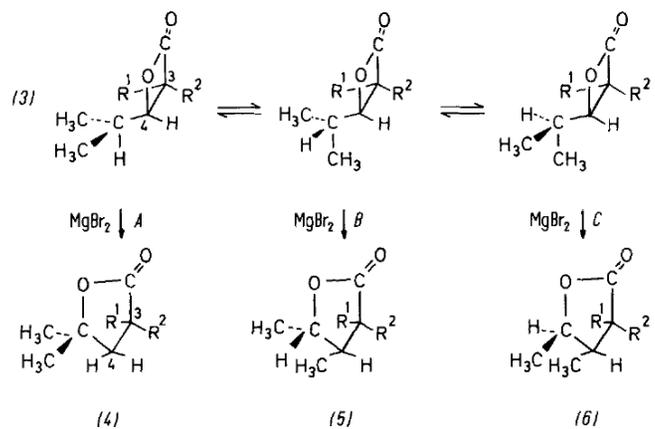Stereospecificity implies concerted mechanism

(3)

MgBr₂ | A   MgBr₂ | B   MgBr₂ | C

(4)   (5)   (6)
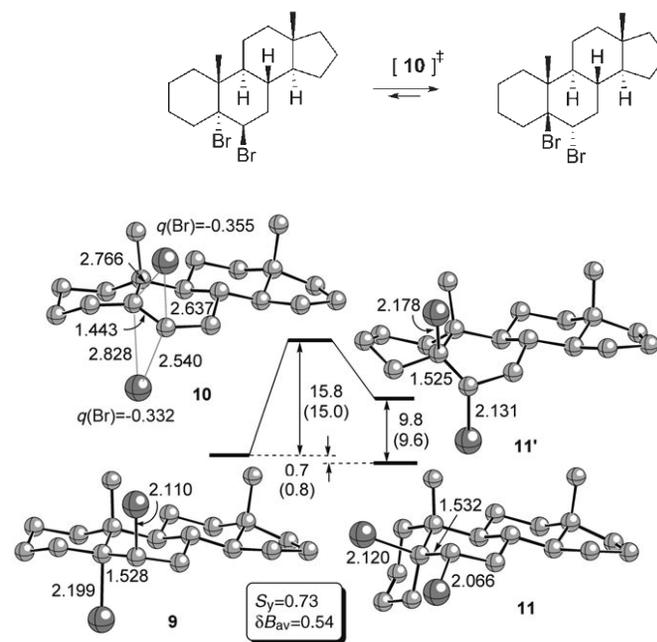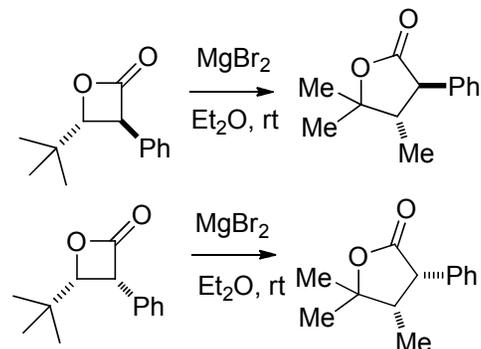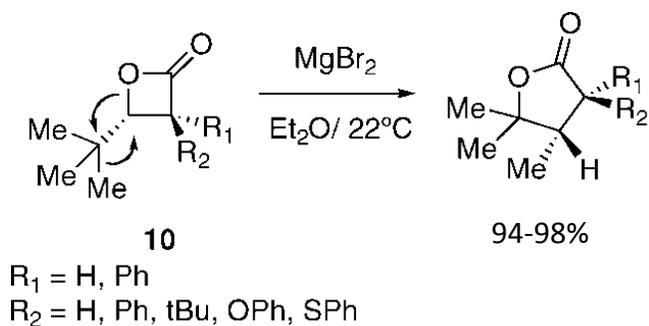
R^1=H, R^2=Ph 78:7:15 **4:5:6**
R^1=Ph, R^2=H >98% **6**

Mulzer, J.; Br trup, G. *ACIE Int. Ed Engl.* **1979**, *18*, 793-794.

Caged Lactone Ring Expansion

(1) a : n = 1

b : n = 2

(2) (3) $(2')$

Table I   Kinetic data for the thermal reactions of (2)
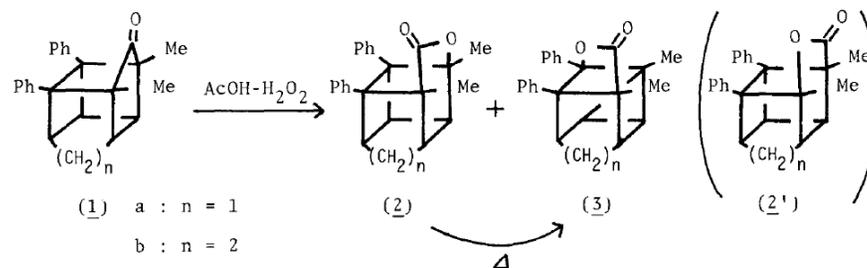
compd.	Temp. (°C)	$10^5 \times k$ (sec^{-1})	E_a (kcal/mol)*	$\Delta S^{\ddagger}$ (eu)*
$(2a)$	230	8.54	36.5±2.8	-5.6±5.6
$(2b)$	230	13.2	29.5±1.9	-20.4±3.8

* temperature range 210-240 °C, in o-dichlorobenzene

Quantitative by FVP @ 350 °C

Authors also note that 2 rearranges to 3 "readily" in the presence of BF$_3$

$\Delta S^{\ddagger}$ is consistent with a concerted dyotropic reaction

(2) → ... (7) a : n = 1

b : n = 2

30-40%

(8) ← (3)

(4) (5) (6)

(1) Sato, K.; Yamashita, Y.; Mukai, T. *Tetrahedron Lett.* **1981**, *22*, 5303-5306.
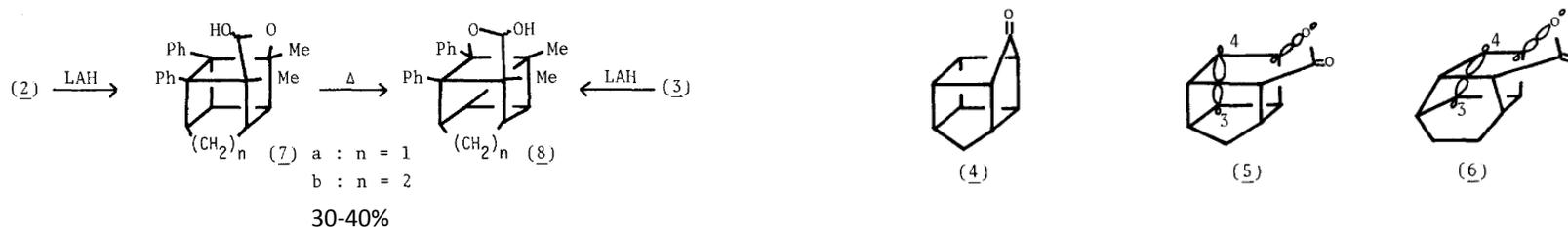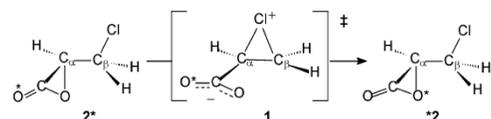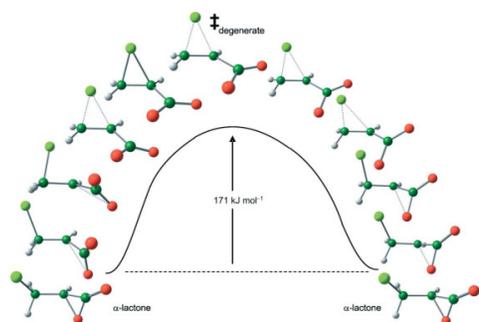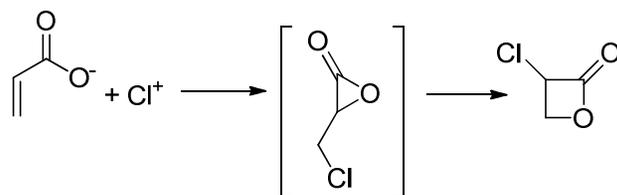
Small Ring Chlorolactonization

$\Delta E^{\ddagger}$ = 40.8 kcal/mol (in vacuo)
16.9 kcal/mol (PCM H_2O)
23.5 kcal/mol (in explicit DFT/MM H_2O)

3-exo-tet ?

4-exo-tet ?

spiro

fused

1 (R = H)
8 (R = Me)

2 (R = H)
5 (R = Me)

3 (R = H)
7 (R = Me)

4 (R = H)
6 (R = Me)
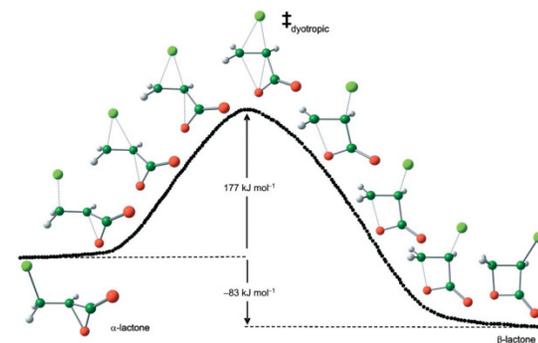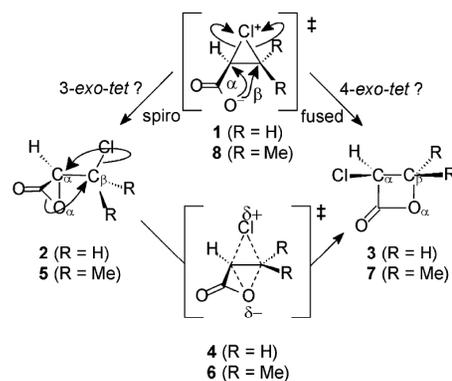
$\Delta E^{\ddagger}$ = 42.3 kcal/mol (in vacuo)
32.7 kcal/mol (PCM H_2O)
36.0 kcal/mol (in explicit DFT/MM H_2O)
ΔE_{rxn} = -20 kcal/mol in vacuo
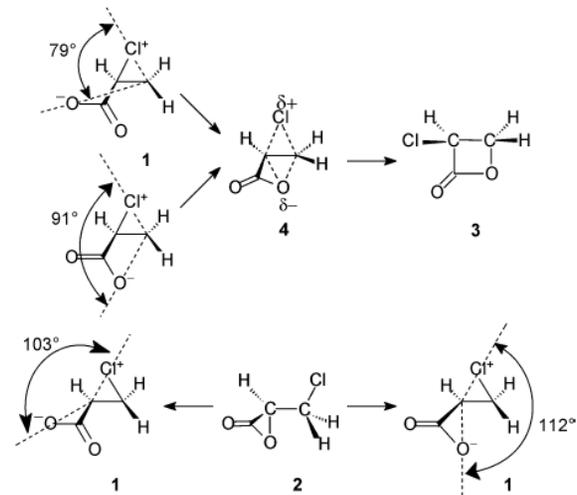
Chloronium carboxylate is a transition state for a degenerate rearrangement
No barrier to α-lactone formation could be located
α-lactone undergoes a dyotropic rearrangement to β-lactone

Ruggiero, G. D.; Williams, I. H. *Chemical Commun.* **2002**, 732-3.
Buchanan, J. G.; Ruggiero, G. D.; Williams, I. H. *Organic & Biomolecular Chemistry*. **2008**, *6*, 66-72.

Cuprate Rearrangements
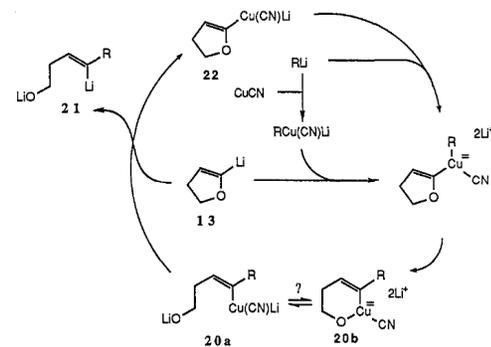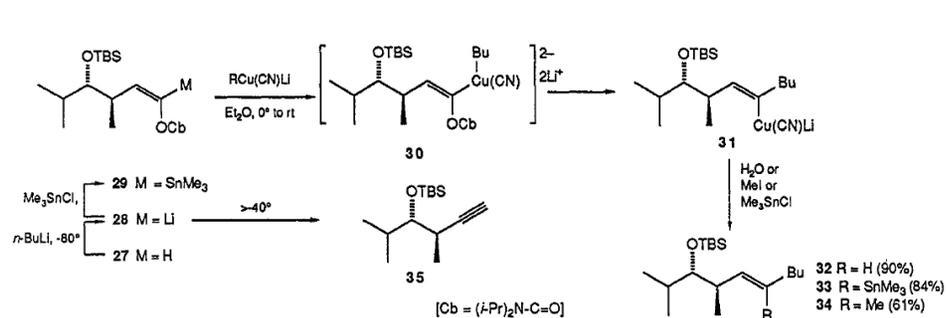
Excellent method for obtaining stereodefined trisubstituted alkenes and organometallic reagents
Can be used in three component coupling reactions

Kocien'ski, P.; Barber, C. *Pure Appl. Chem.* **1990**, *62*, 1933-1940.

Other Metallate Rearrangements

Bu—≡—I →(R$_2$BH)→ **48** →(NaOMe)→ **49** →(HOAc)→ **50 : 82%**

→(RMgX)→ →(BuONa)→ →(-NaBr)→

51 →(Bu$_3$ZnLi$_2$ / THF, -85°C, 3 h)→ **52** →(AcOH / THF, 0°C)→ **53 : 64%**

59 →(C$_8$H$_{17}$, Cp$_2$Zr—Cl)→ **60** →(dyotropic rearrangement)→ **61** →(H$_2$O)→ **62**

Kocien'ski, P.; Barber, C. *Pure Appl. Chem.* **1990**, *62*, 1933-1940.
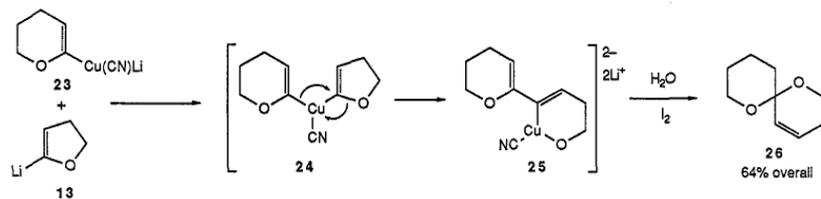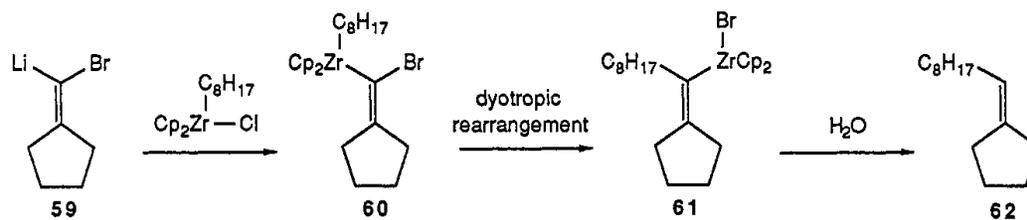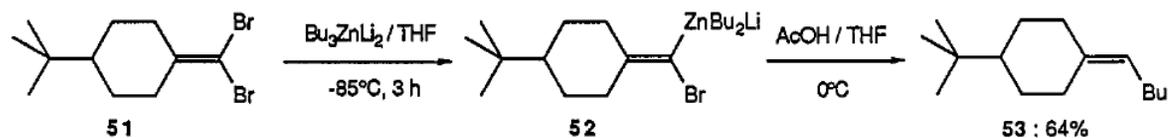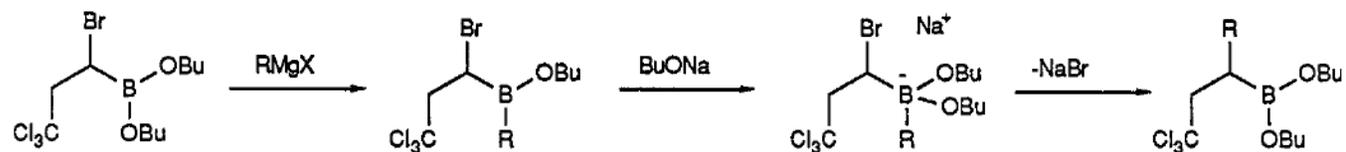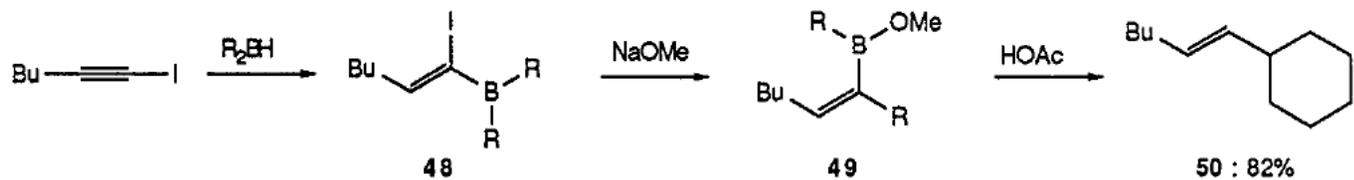
Syn Dyotropic Rearrangements of Organoboranes
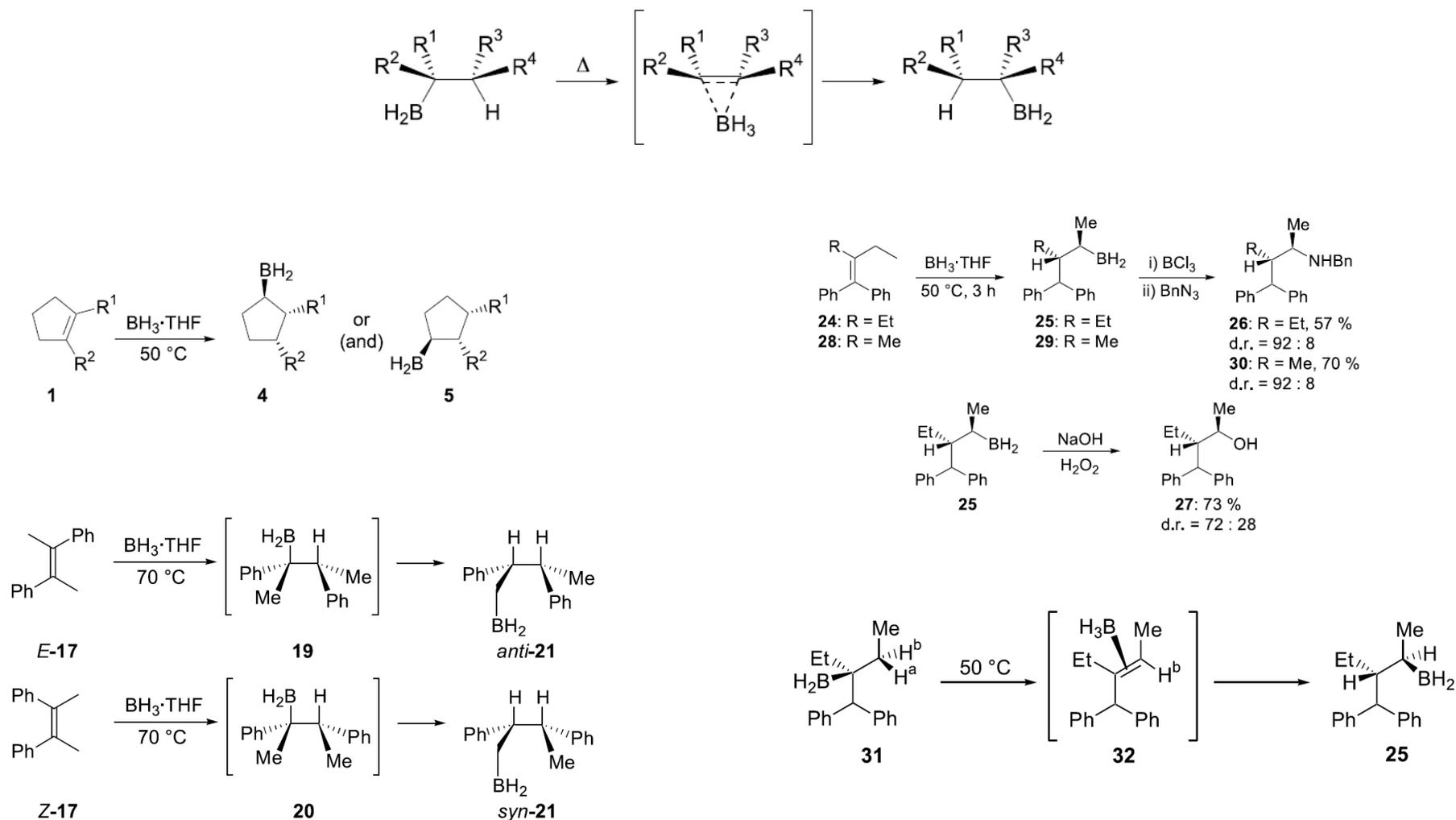
One of only 2 examples of *syn* type 1 dyotropic rearrangements

Hupe, E.; Denisenko, D.; Knochel, P. *Tetrahedron*. **2003**, *59*, 9187-9198.

Syn Silane Migration
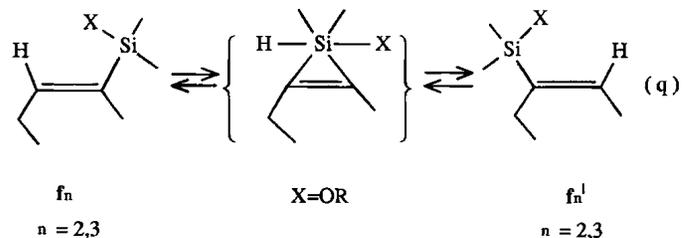
The 2nd of two reported *syn* type I dyotropic reactions
Has not been investigated in detail, the mechanism depicted is the authors hypothesis
Only observed during protodeboronation of *Z*-bora-sila-alkenes

Köster, R.; Seidel, G.; Boese, R.; Wrackmeyer, B. *Chem. Ber.* **1990**, *123*, 1013-1028.
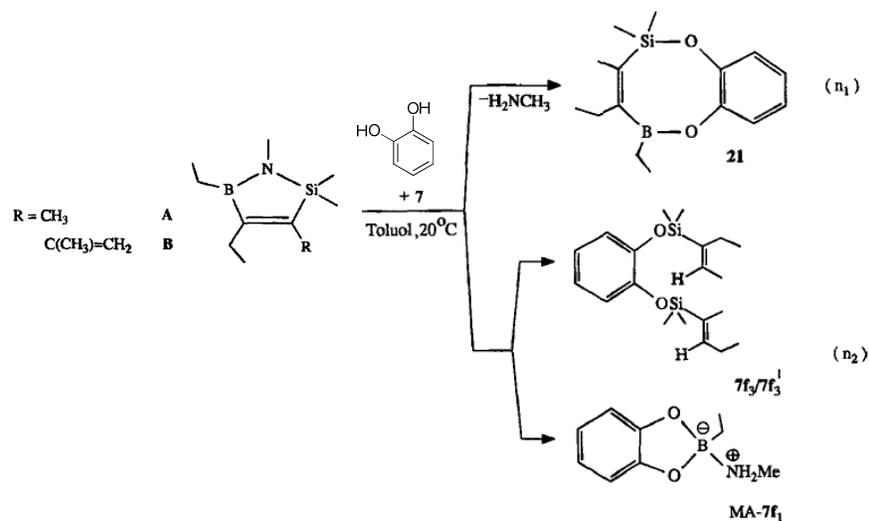
Type II Dyotropic Rearrangements
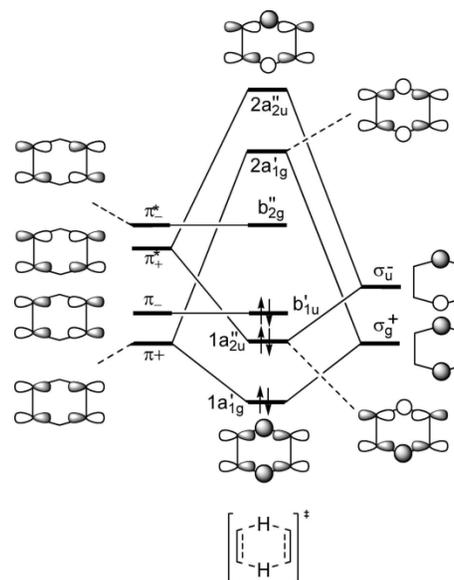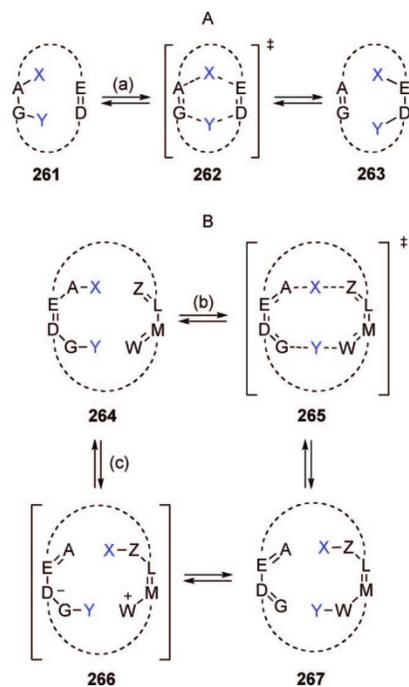
Many possible scaffolds
Most common is type A, a thermally allowed 6-π e⁻ process

Reetz, M. T. *ACIE*. **1972**, *11*, 129-130.
 Reetz, M. T. *ACIE*. **1972**, *11*, 130-131.
Reetz, M. *Tetrahedron*. **1973**, *29*, 2189-2194.
Fernández, I.; Cossío, F. P.; Sierra, M. A. *Chem. Rev.* **2009**, *109*, 6687-711.

Type II Dyotropic Reactions: Double Hydrogen Migrations

12   **13**
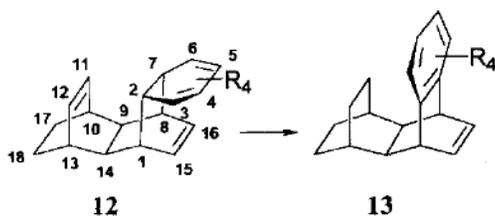
For R=H
$\Delta H^{\ddagger}$= +18.3 kcal/mol
$\Delta S^{\ddagger}$=-17.0 cal/(mol*K)
$\Delta G^{\ddagger}$= +23.4 kcal/mol (@298 K)

6-d_2   **7-d_2**   **6'-d_2**
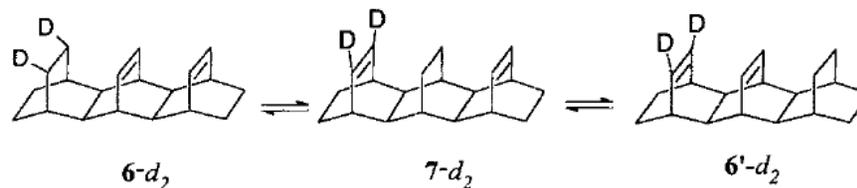
For 6 -> 7
$\Delta H^{\ddagger}$= +35.8 kcal/mol
$\Delta S^{\ddagger}$=-10.0 cal/(mol*K)
$\Delta G^{\ddagger}$= +38.7 kcal/mol (@298 K)

For 7 -> 6
$\Delta H^{\ddagger}$= +36.9 kcal/mol
$\Delta S^{\ddagger}$=-6.9 cal/(mol*K)
$\Delta G^{\ddagger}$= +40.0 kcal/mol (@298 K)

Most extensively studied form of type II dyotropic rearrangement
Components must be held in close proximity

Thermoneutral reactions have large barriers,
despite being symmetry allowed processes

$\Delta S^{\ddagger} < 0$

Grimme, W.; Pohl, K.; Wortmann, J.; Frowein, D. *Liebigs Annalen*. **1996**, 1905-1916.

Double Hydrogen Migrations: Isotope Effects

k_{2H}/k_{2D} = 7.6@ 100 ^{o}C
(extrapolated to 13.8 @ 25 ^{o}C)

Ar= 4-ClC$_6$H$_4$

5

38

k_{2H}/k_{2D} = 4.6@ 207 ^{o}C
(extrapolated to 10.8 @ 100 ^{o}C)
(extrapolated to 28.2 @ 25 ^{o}C)

Table 8 Activation parameters for dyotropy, ^{1}H- and ^{2}H-trienes **5** and -pyrazolines **38**

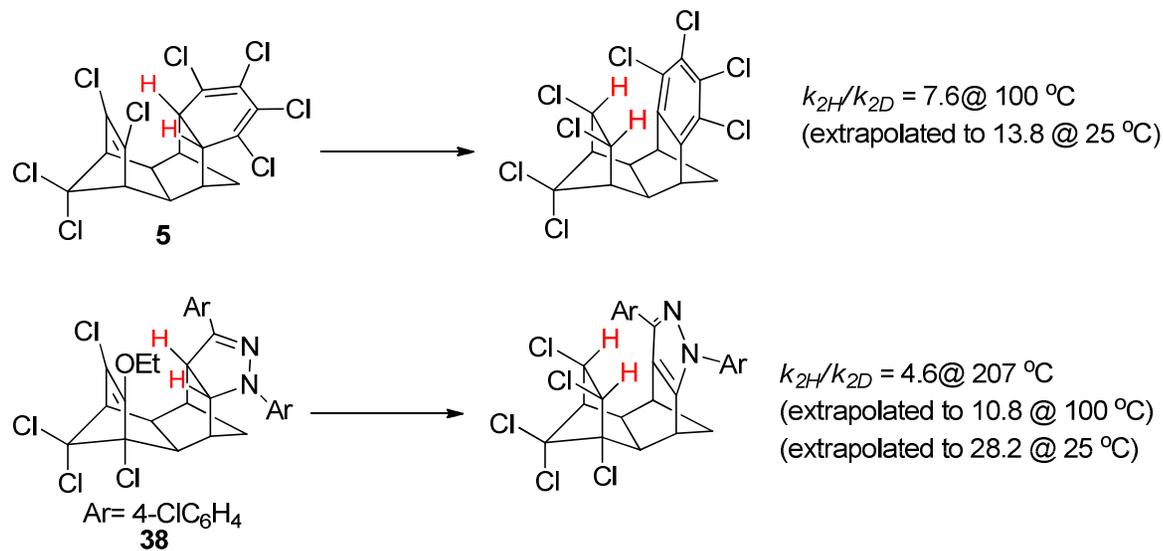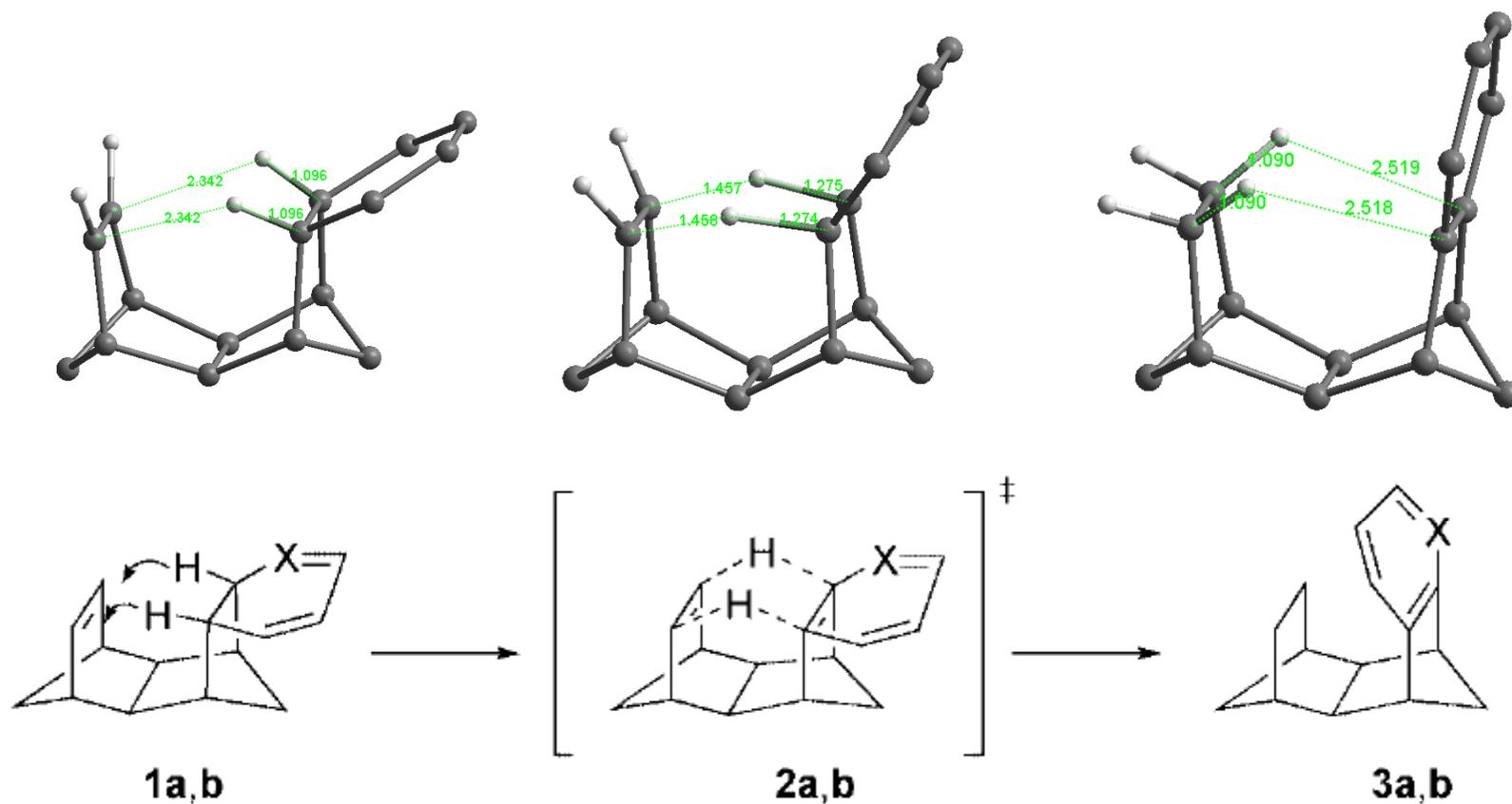|	$\Delta E_a{}^a$	$\Delta H^{\ddagger a}$	$\Delta S^{\ddagger b}$	$\Delta G^{\ddagger a}$	log A
[^{1}H]-**5**	25.07 ± 0.07	24.47 ± 0.09	−9.87 ± 0.05	27.39	11.09 ± 0.06
[^{2}H]-**5**^{c}	26.77 ± 0.09	26.18 ± 0.09	−9.27 ± 0.04(5)	28.95	11.20 ± 0.05
[^{1}H]-**38**	31.43 ± 0.21	30.83 ± 0.20	−13.33 ± 0.12	34.81	10.32 ± 0.10
[^{2}H]-**38**^{c}	34.23 ± 0.30	33.63 ± 0.29(6)	−10.49 ± 0.13	36.76	10.93 ± 0.14

^{a} kcal mol^{-1}. ^{b} cals mol^{-1} K^{-1} converted from data in kJ, (1 cal = 4.18 J). ^{c} To simplify expressions used in describing and discussing data ^{2}H ≡ D.

Mackenzie, K.; Howard, J. A.; Mason, S.; Gravett, E. C.; Astin, K. B.; Shi-xiong, L.; Batsanov, A. S.; Vlaovic, D.; Maher, J. P.; Murray, M.; Wilson, C.; Johnson, R. E.; Preil, T.; Gregory, R. J. *J. Chem. Soc., Perkin Trans. II*. **1993**, 1211.
Howard, J.; Mackenzie, K.; Johnson, K.; Robert, E. *J. Chem. Soc., Perkin Trans. II*. **1996**, 1749.

Computational Study of Double Hydrogen Migrations

For X=CH Ea=19.9 kcal/mol (B3LYP/6-31+G(d))
Sy (a measure of synchronicity) = 0.89 (for a perfectly synchronous reaction Sy=1.0)

Frenking, G.; Cossío, F. P.; Sierra, M. A.; Fernández, I. *Eur J. Org Chem*. **2007**, 5410-5415.

Correlation with Aromatic Stabilization Energy

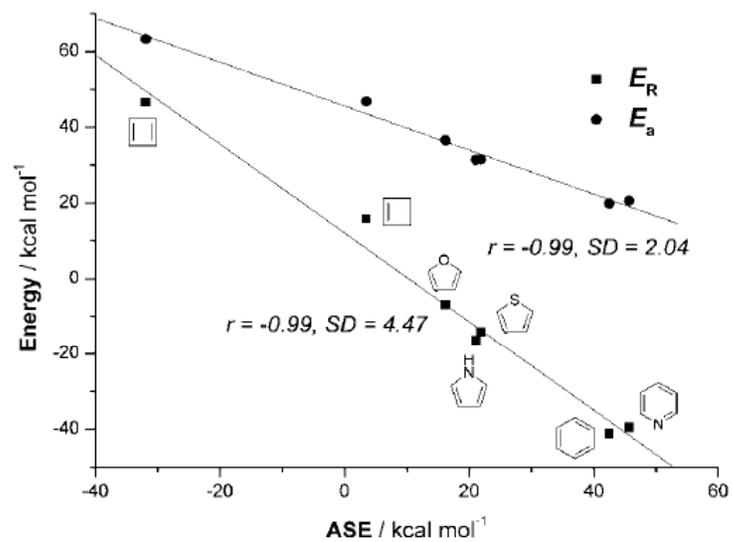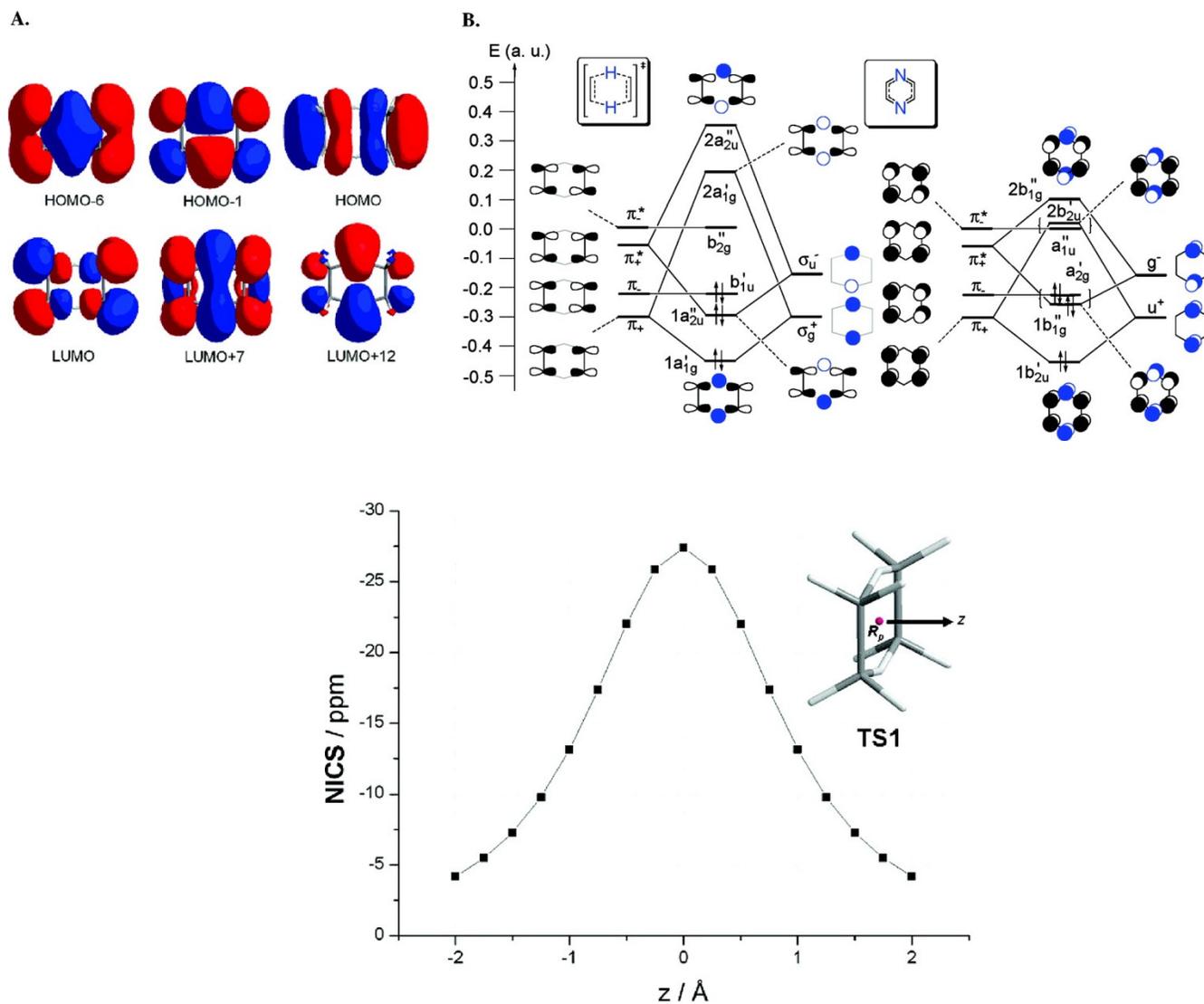
Figure 2. Plot of the ASE values vs. the activation (circles) and reaction (squares) energies for the dyotropic process $1 \rightarrow 3$.
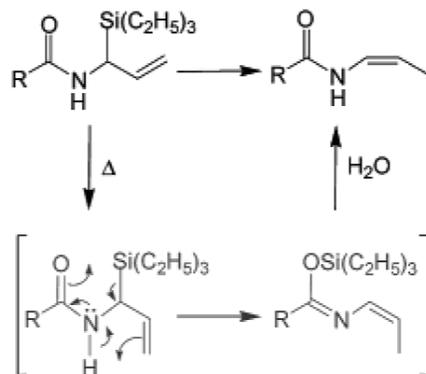
Table 2. Activation energies (E_a, kcal/mol),[a] reaction energies (E_R, kcal/mol),[a] synchronicities (S_y, in a.u.), NICS(0), and NICS(1) values (in ppm), associated with the $1 \rightarrow 3$ double hydrogen atom transfers.

Entry	X	E_a[b]	E_R[c]	S_y	NICS(0)[d]	NICS(1)[e]
1	CH	19.9	−41.1	0.89	−26.03	−12.14
2	N	20.6	−39.5	0.88	−26.59	−12.57
3	O	36.6	−6.8	0.84	−24.57	−12.11
4	S	31.5	−14.0	0.84	−24.85	−11.84
5	NH	31.4	−16.4	0.84	−24.62	−12.19
6	CH	63.3	+46.6	0.93	−16.06	−6.49
7	CH_2	46.9	+15.9	0.92	−24.44	−11.53

Frenking, G.; Cossío, F. P.; Sierra, M. A.; Fernández, I. *Eur J. Org Chem*. **2007**, 5410-5415.

Type 2 Dyotropic Reactions: Planar Aromaticity

A.

HOMO-6 HOMO-1 HOMO

LUMO LUMO+7 LUMO+12

B.

TS1

Fernández, I.; Sierra, M. a.; Cossío, F. P. *J. Org. Chem*. **2007**, *72*, 1488-91.

Dyotropic Rearrangement of α-Silyl Amides

cis-Enamide Formation
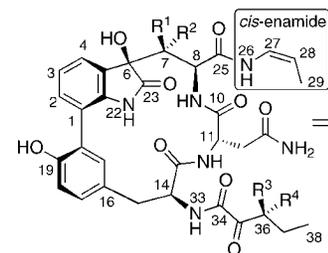
TMC-95

TMC-95	R¹	R²	R³	R⁴
A (1a)	H	OH	CH₃	H
B (1b)	H	OH	H	CH₃
C (1c)	OH	H	CH₃	H
D (1d)	OH	H	H	CH₃

Table 1. Rearrangement–hydrolysis of α-silylallyl amides **3**.[a]

Entry	R =	Conditions	Yield [%]
1	a	a) toluene, 110 °C, 10 h; b) H₂O	81
2	b	a) toluene, 110 °C, 20 h; b) H₂O	73
3	c	a) toluene, 110 °C, 27 h; b) H₂O	67
4	d	a) toluene, 110 °C, 3 d; b) H₂O	72
5	e	a) o-xylene, 135 °C, 4 d; b) H₂O	52

[a] TES = triethylsilyl, Boc = tert-butoxycarbonyl, EDC = 1-[3-(dimethyla-mino)propyl]-3-ethylcarbodiimide hydrochloride, HOAT = 1-hydroxy-7-azabenzotriazole.

26a,b R = TES
27a,b R = H

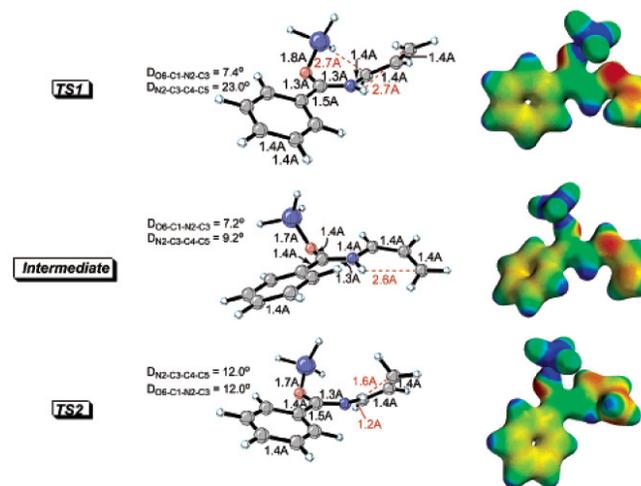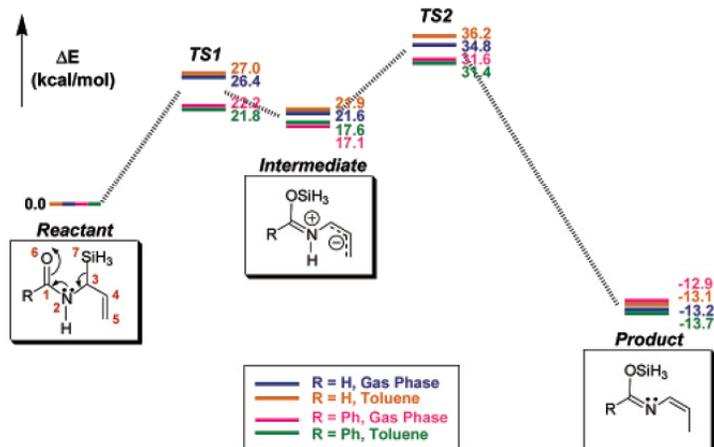**28a,b** R¹ = R² = TES
29a,b R¹ = TES, R² = H
1a,b R¹ = R² = H
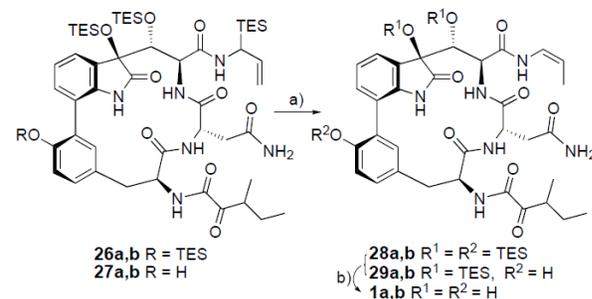
Scheme 6. Synthesis of TMC-95A (**1a**) and TMC-95B (**1b**). a) 1) o-xylene, 140 °C, 3 d; 2) H₂O; b) HF/Py, THF/Py; then Me₃SiOMe; 49 % (two steps).

Lin, S.; Danishefsky, S. J. *ACIE* **2002**, *41*, 512-5.

Dyotropic Rearrangement of α-Silyl Amides : Mechanism
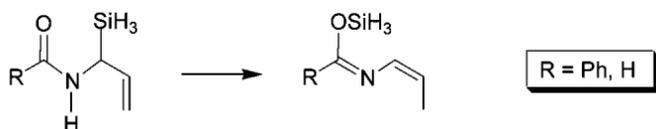
Scheme 3. Energetics Computed for the Reactions When R = Ph and R = H

ΔE (kcal/mol)

R = Ph, H

	reactant	TS1	intermediate	TS2	product

Legend:
— R = H, Gas Phase
— R = H, Toluene
— R = Ph, Gas Phase
— R = Ph, Toluene
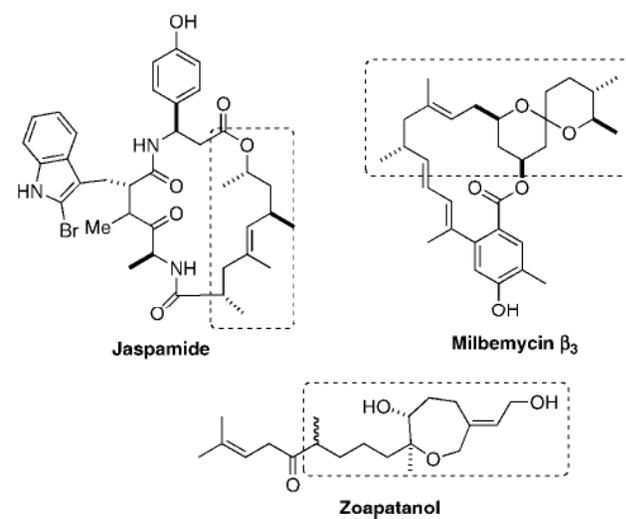
Table 1. Dipole Moments with B3LYP/6-311++G(3d,3p)//B3LYP/6-31G(d) Calculations (Gas Phase)

	reactant	TS1	intermediate	TS2	product
R = Ph	4.2	3.1	1.7	1.5	0.9
R = H	3.7	2.3	2.2	3.2	1.8

Calculations support a stepwise mechanism via an intermediate azomethine ylide
A transition structure corresponding to a concerted reaction could not be located, despite being formally a 10 e- process

Zhang, X.; Houk, K. N.; Lin, S.; Danishefsky, S. J. *J. Am. Chem. Soc*. **2003**, *125*, 5111-4.

Metallate Rearrangements in Synthesis

Jaspamide

Milbemycin β₃

Zoapatanol
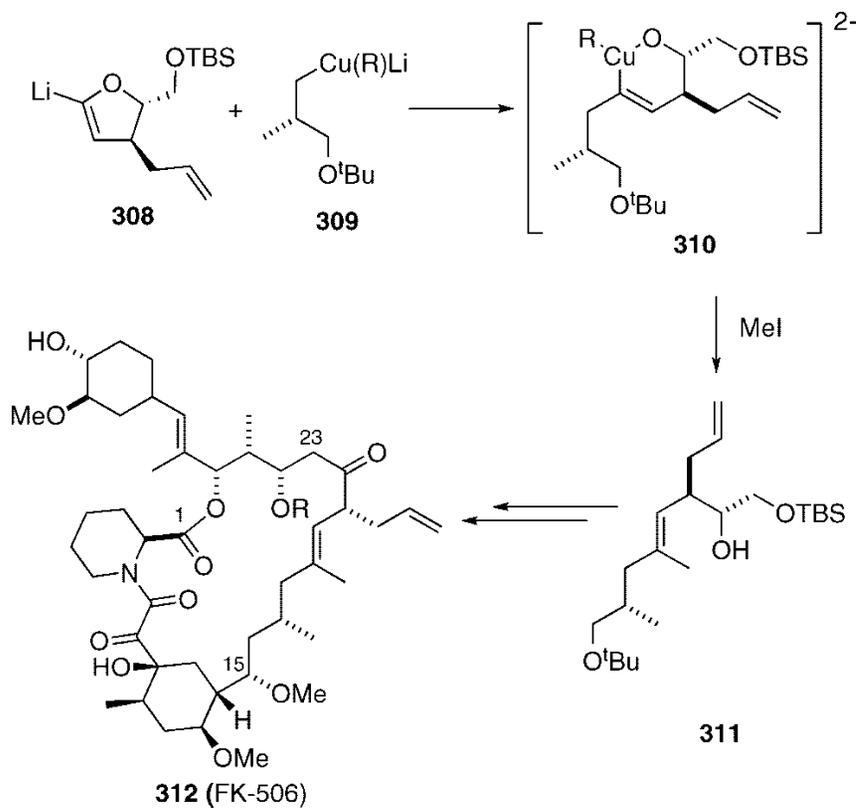
[a] The dotted box indicates the fragment of the molecule which has been constructed by a 1,2-dyotropic rearrangement.

Kocien'ski, P.; Barber, C. *Pure Appl. Chem*. **1990**, *62*, 1933-1940.

Synthetic Applications Of Type 1 Dyotropic Rearrangements: Synthesis of Cephalostatins
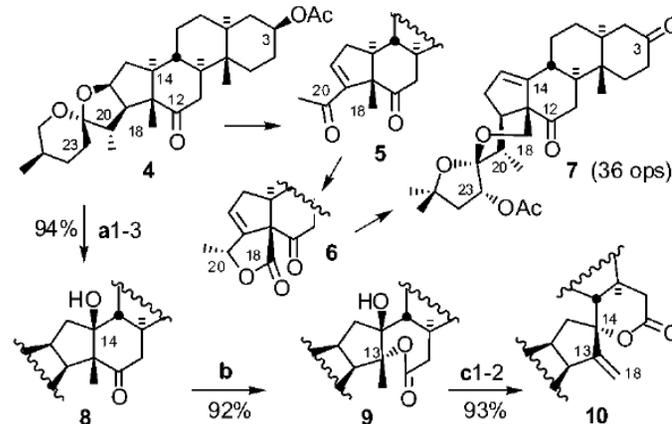

285 → **286** → dyotropic → **287**

36 steps

14 steps

288

289 (23-dehydroxy-Cephalostatin 1)
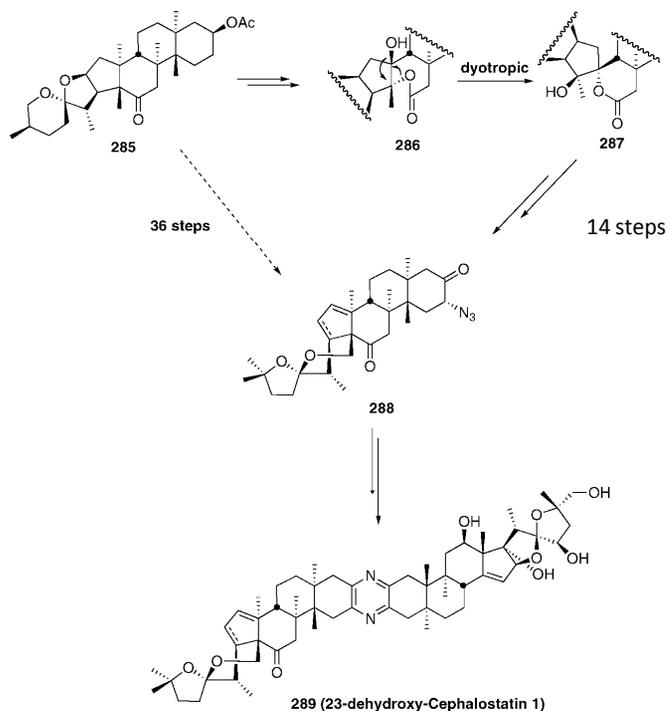
New synthesis: 16 steps, 9% overall
(not counting other fragment, ca 25 steps by previous method)

4 → **5** → **7** (36 ops)

6

94% | **a1-3**

8 → **9** → **10**

92%   b   93%   c1-2

^{a} **a**1. $h\nu$, CH$_2$Cl$_2$; **a**2. evap; add 3:1 HOAc/H$_2$O; **a**3. add H$_2$CrO$_4$; **b**. 2 equiv mCPBA, 4 equiv Na$_2$HPO$_4$, CH$_2$Cl$_2$, 11 d; **c**1. 2% TMSOTf, PhMe, 3 h; **c**2. add 5 equiv pyridine, 1.5 equiv SOCl$_2$, 50−55 °C, 50 min.

Scheme 2

9 → **11a** (X-ray) + **11b** (X-ray)   ~ 1 : 2

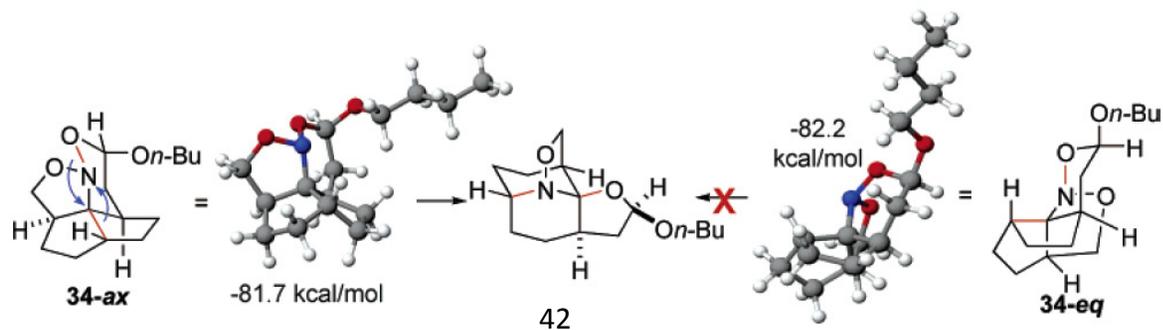Li, W.; LaCour, T. G.; Fuchs, P. L. *J. Am. Chem. Soc.* **2002**, *124*, 4548-9.
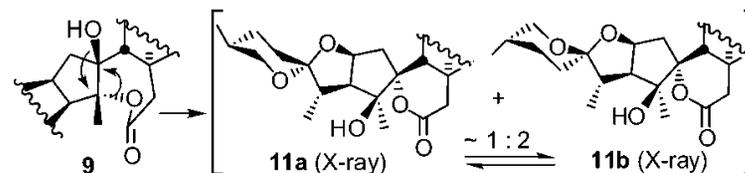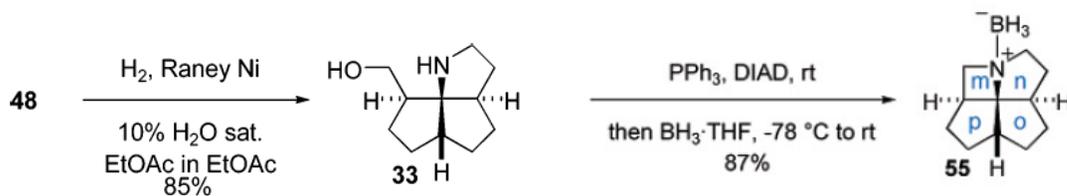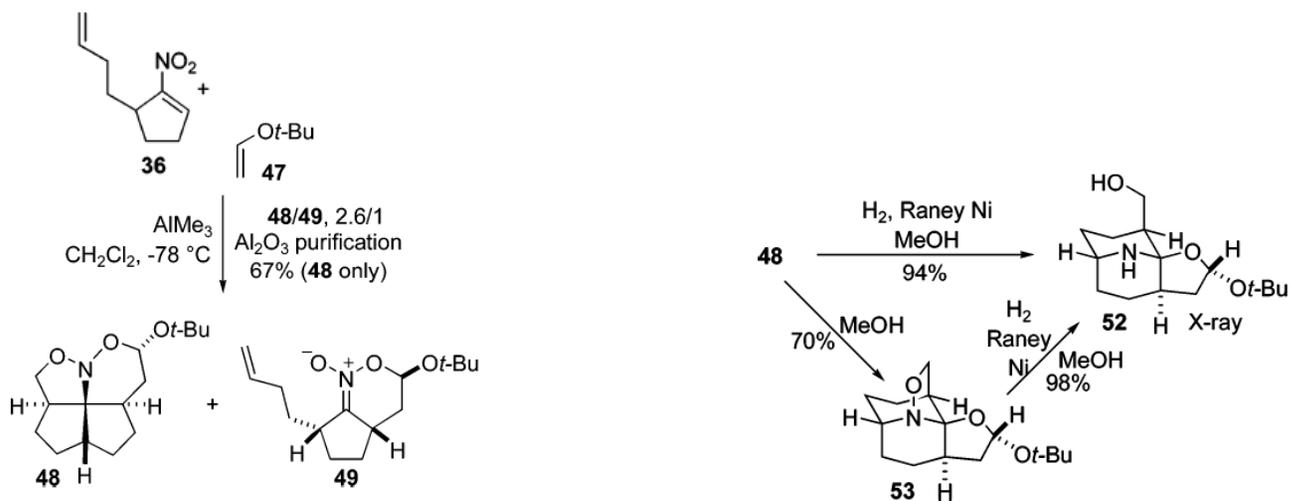
Group History: Dyotropic Rearrangements in Azafenestrane Synthesis
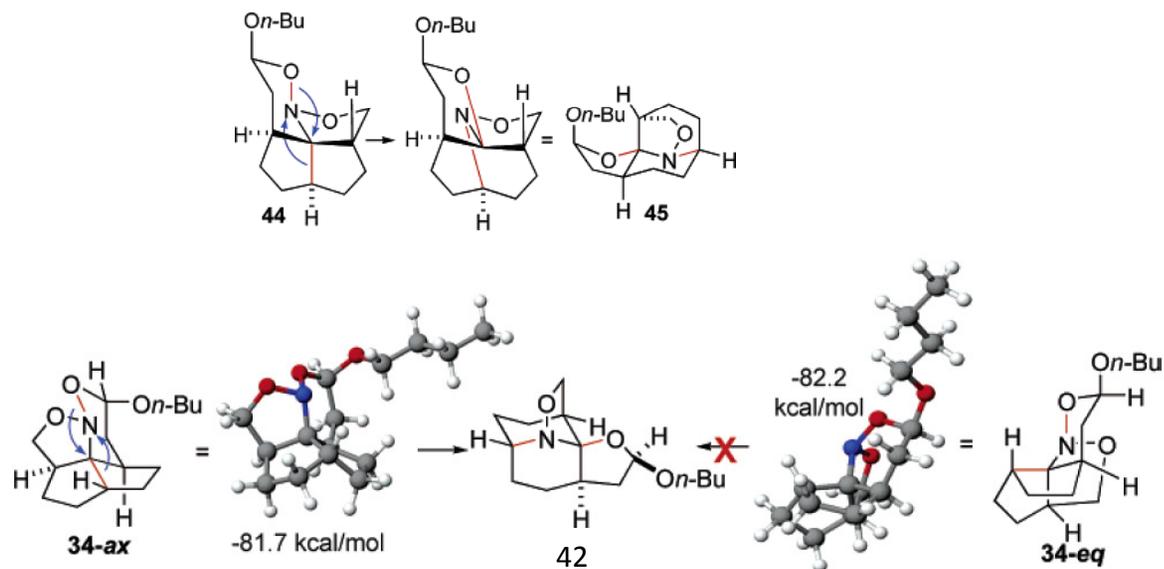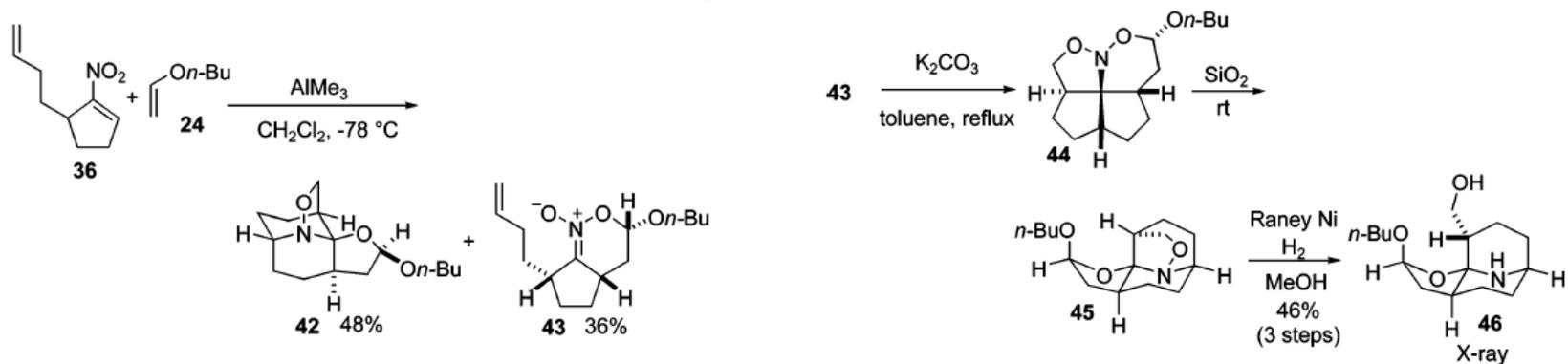
Nitroso acetal **34** conformers and PM3 minimized energy structures with heats of formation.

Denmark, S. E.; Montgomery, J. I. *ACIE,* **2005**, *44*, 3732-6.
Denmark, S. E.; Montgomery, J. I.; Kramps, L. A. *J. Am. Chem. Soc*. **2006**, *128*, 11620-30.

34-ax −81.7 kcal/mol

−82.2 kcal/mol

34-eq

42

Nitroso acetal **34** conformers and PM3 minimized energy structures with heats of formation.

36 + **47** (Ot-Bu)

AlMe₃
CH₂Cl₂, −78 °C

48/49, 2.6/1
Al₂O₃ purification
67% (**48** only)

48 + **49**

H₂, Raney Ni
MeOH
94%

48 → **52** H X-ray

70% MeOH

H₂
Raney
Ni MeOH
98%

53 H

48

H₂, Raney Ni

10% H₂O sat.
EtOAc in EtOAc
85%

33 H

PPh₃, DIAD, rt

then BH₃·THF, −78 °C to rt
87%

55 H

Denmark, S. E.; Montgomery, J. I. *ACIE,* **2005**, *44*, 3732-6.
Denmark, S. E.; Montgomery, J. I.; Kramps, L. A. *J. Am. Chem. Soc*. **2006**, *128*, 11620-30.

Conclusions

Dyotropic reactions are mechanistically interesting processes with practical applications

Despite nearly 60 years of investigation, new applications and insights are still being developed.

Dyotropic reactions can occur by concerted or stepwise processes

Above all, dyotropic reactions are not limited to esoteric contrived substrates