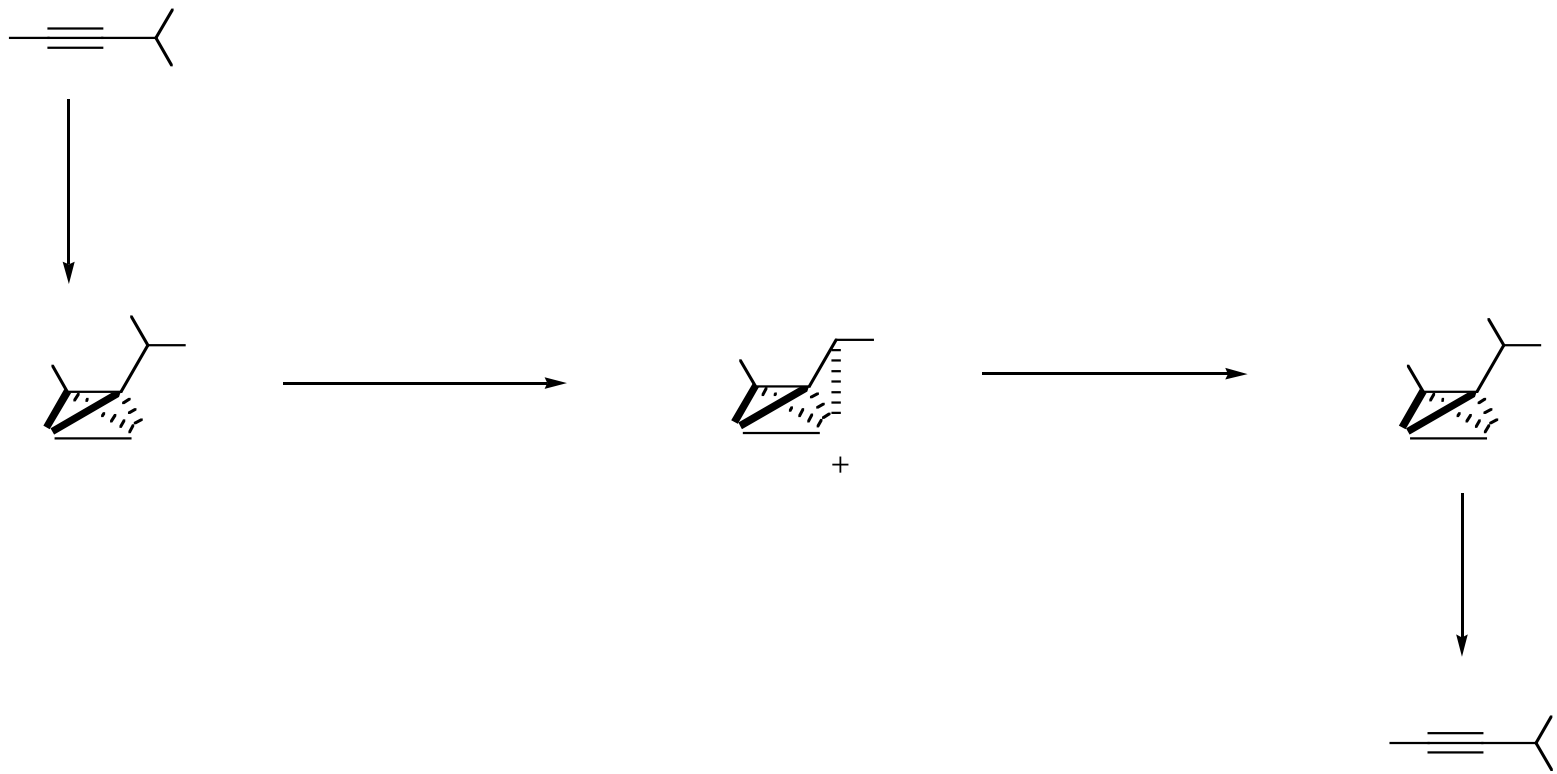
# Chemistry of Propargyldicobalt Cations: The Nicholas Reaction

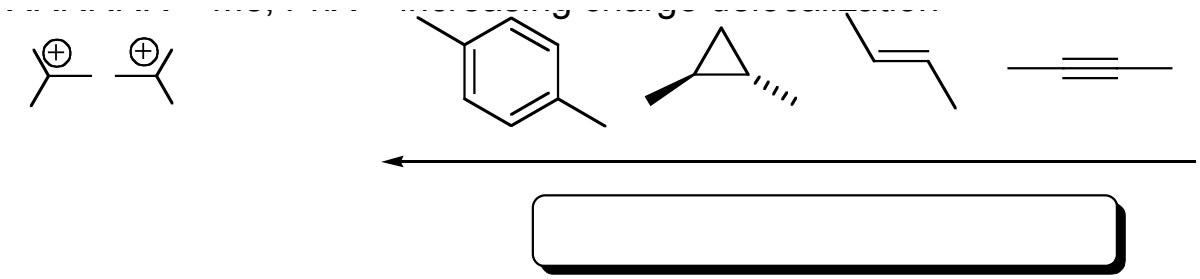


William Collins

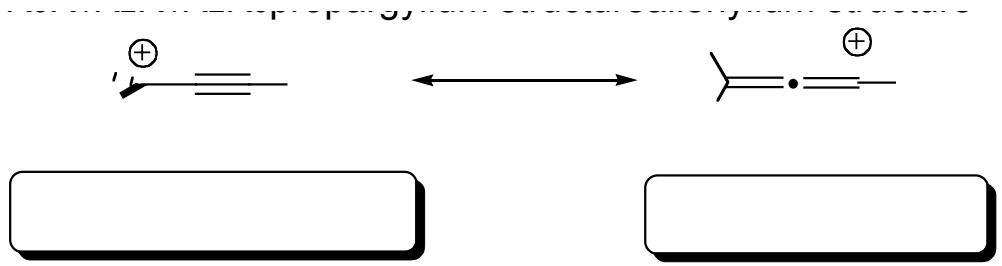
Group Meeting, September 28th 2004

# Why do we care?

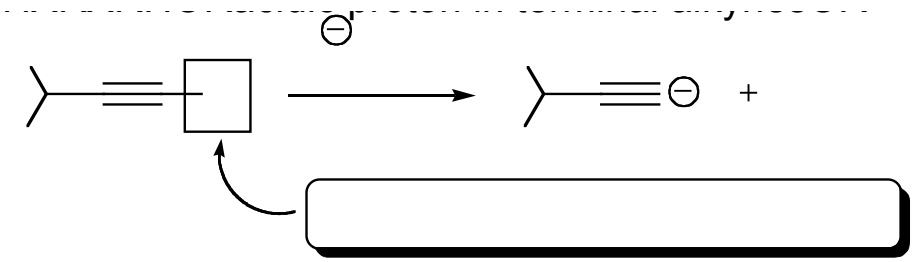
- The problem with substitution at propargylic positions:
  - Alkynes, unlike alkenes, have a poor stabilizing ability for adjacent positive charge.

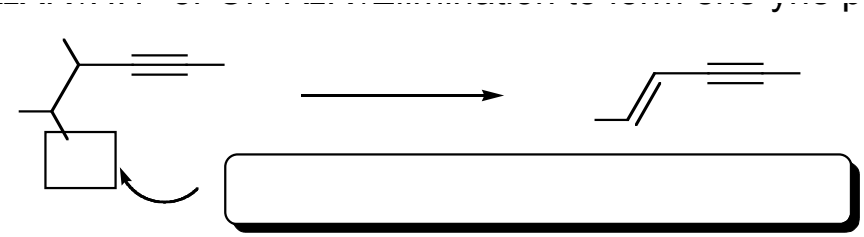


  - The electronic ground state of the propargylic cation



  - Other problems:

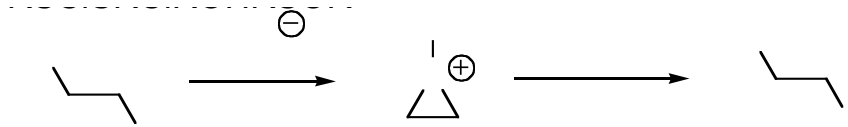




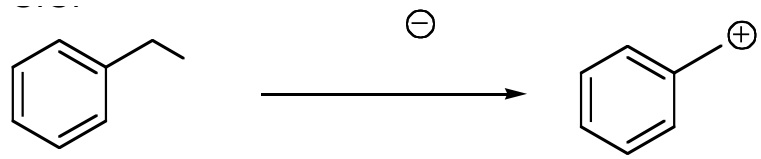
Olah, G., *et. al. J. Amer. Chem. Soc.* **1976**, *98*, 2501.
Drenth, W., *et. al. J. Org. Chem.* **1978**, *43*, 763.

# Definition of Anchimeric Assistance

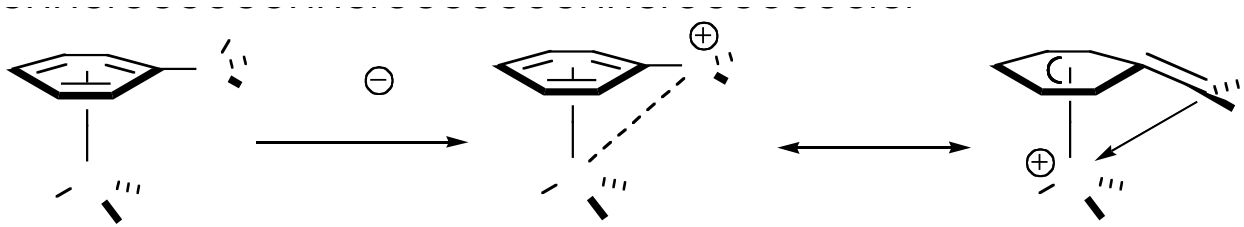
- "When neighboring-group participation leads to an enhanced reaction rate, the group is said to provide *anchimeric assistance*." -McManus, S. P.



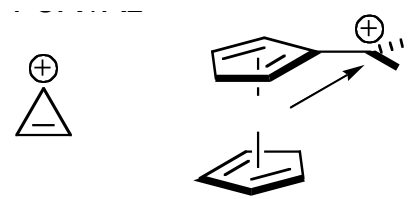
- <u>Organometallic:</u>



100,000-fold rate increase in hydrolysis. attributed to stabilization of intermediate cation



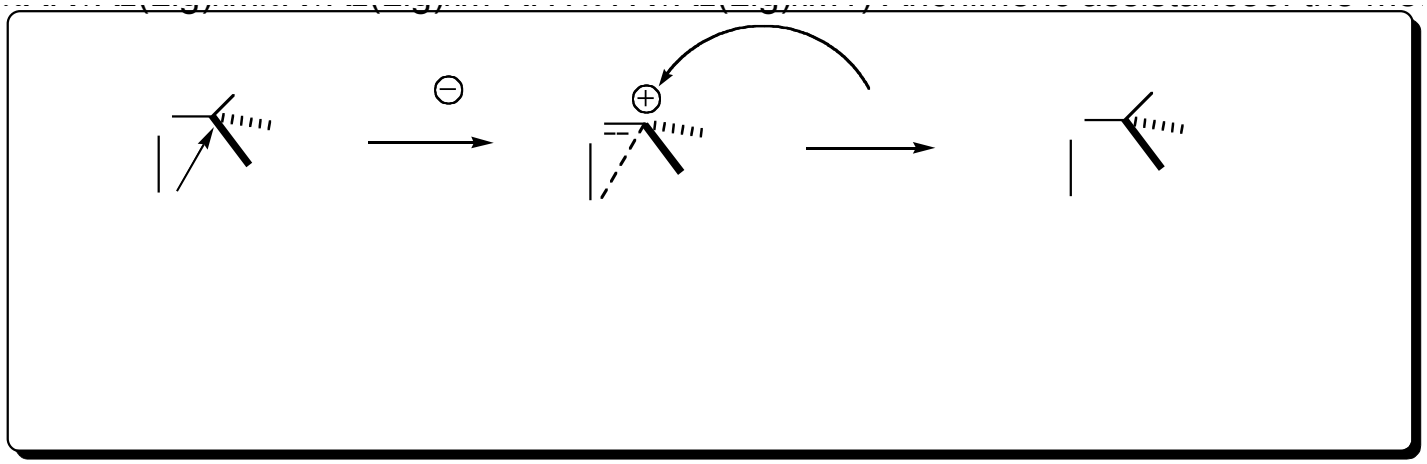
The thermodynamic stabilities of $\alpha$-ferrocenyl carbocations are similar to cyclopropenium ions.



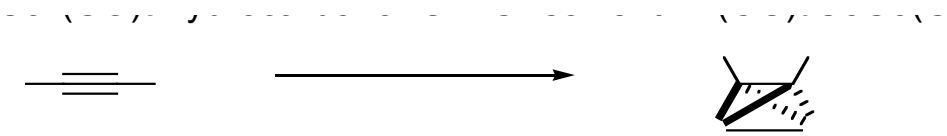

McManus, S. P., *et al.* "Neighboring Group Participation"; Plenum: New York, 1976.
McGlinchey, M., *et. al. Coord. Chem. Rev.* **1995**, *143*, 331.

# Application to Propargylic Alkylations:

- Model:



- Metal clusters with highly polarizable electron clouds can alleviate the positive charge on proximally attached atoms.
- 1956, Sternberg and coworkers found that dicobalt octacarbonyl reacts readily with high selectively for alkynes to form the dicobalt hexacarbonyl cluster:




Mingos, D. *Acc. Chem. Res.* **1984**, *17*, 311.
Sternberg, H., *et. al. J. Am. Chem. Soc.* **1956**, *78*, 120.

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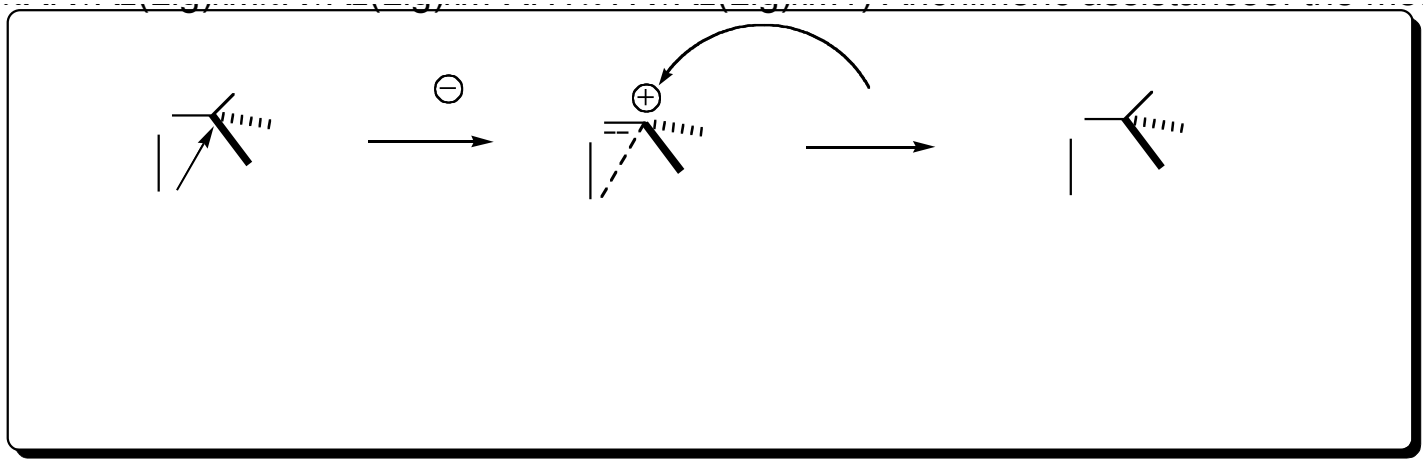
- Model:



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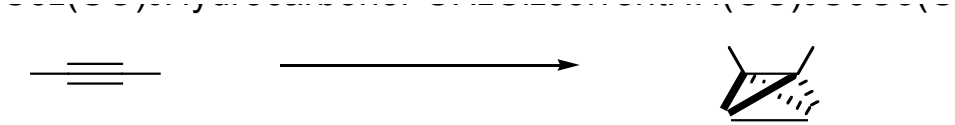
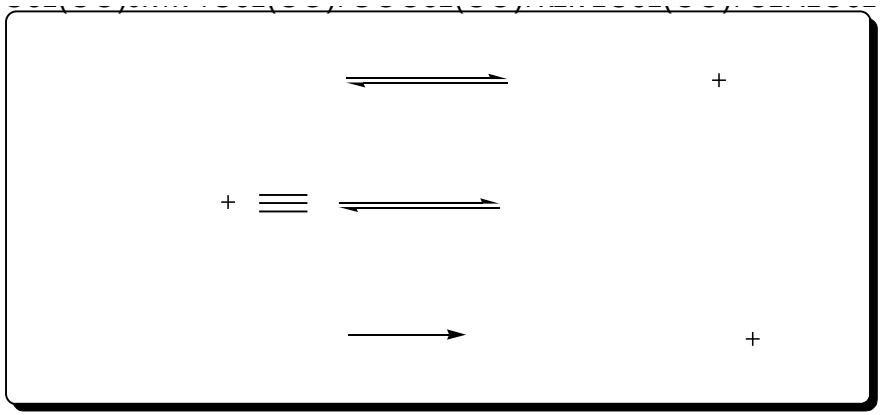
Mingos, D. *Acc. Chem. Res.* **1984**, *17*, 311.
Sternberg, H., *et. al. J. Am. Chem. Soc.* **1956**, *78*, 120.

# $Co_2(CO)_8$ as a Protecting Group:



- Proposed Mech:



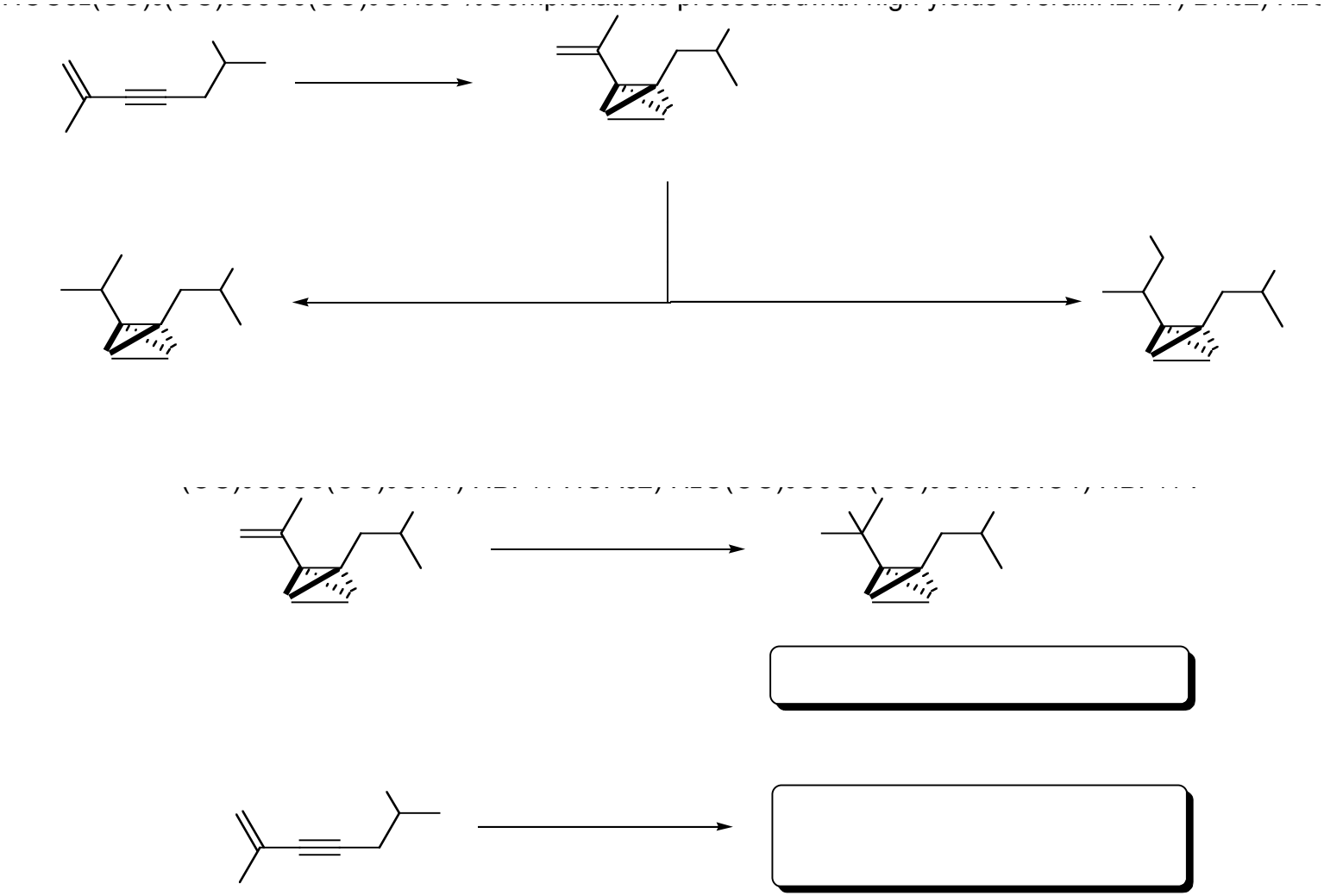
Reactive species is proposed to be the dicobalt heptacarbonyl species.

- Methods of removal:
  - **Oxidative methods to give decomplexed alkynes**
    - Ferric nitrate, ceric ammonium nitrate, N-methylmorpholine N-oxide, DMSO
  - **Reductive methods to give decomplexed alkenes**
    - Lithium in liq. Ammonia, hydrogenation over Rh-charcoal, hydrogenation over Wilkinson's cat., tributyltin hydride, tributyltin hydride and N-bromosuccinimide in 1,4-cyclohexadiene, triethylsilane (to give vinylsilane)

Ellgen, P., *et. al. Inorg. Chem.* **1972**, *4*, 691.
Teobald, B. *Tetrahedron* **2003**, *58*, 4133.

# Application to Propargylic Alkylations:

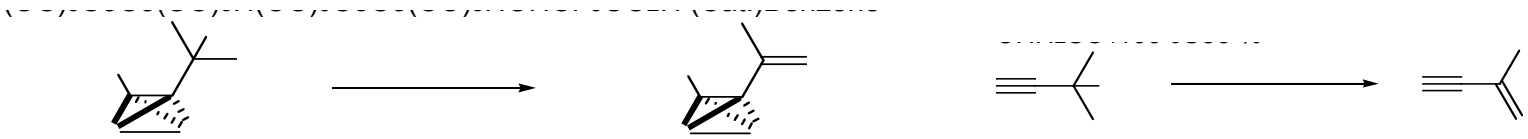
- Nicholas and coworkers studied complexation with ene-ynes:

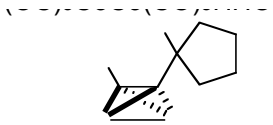
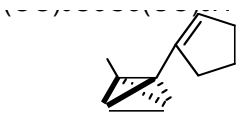
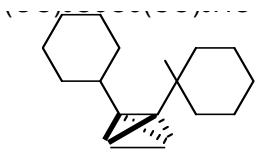
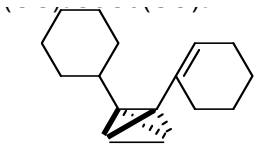
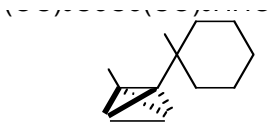
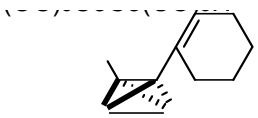
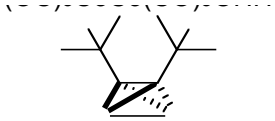
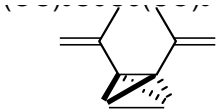


Nicholas, K. *et.al. Tett. Lett.* **1971**, *37*, 3475.

# Dehydration of Propargyl Alcohol Complexes:

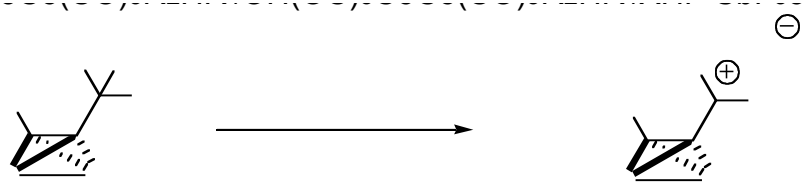
- Nicholas and coworkers began to evaluate the stability of α-(alkynyl)dicobalt hexacarbonyl cations:



| *Alcohol complex* | *Product* | *Yield (%)* |
|---|---|---|
|  |  | *81* |
|  |  | *76* |
|  |  | *65* |
|  |  | *79* |

Nicholas, K., *et. al. J. Organomet. Chem.* **1972**, *44*, C21.

# Isolation of α-[(ethynyl)dicobalt hexacarbonyl] salts



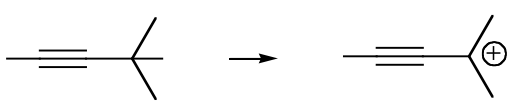
**Carbonyl Absorptions:**

| IR DATA: | Alcohol (cm-1) | Cation (cm-1) |
|---|---|---|
| $R^1 = R^2 = CH3$ | 2025 | 2085 |
| $R^1 = R^2 = Ph$ | 2050 | 2105 |
| $R^1 = R^2 = H$ | 2090 | 2130 |

Shift ($\Delta\nu$ +40-60 cm-1) indicates increased C-O bonding from decreased d(Co)-π*(CO) donation in electron deficient cations.

| NMR DATA: | | Alcohol (ppm) | Cation (ppm) | Δδ (ppm) |
|---|---|---|---|---|
| $R^1 = R^2 = CH3$ | $R^1$ | 1.5 | 2.2 | -0.7 |
| | H | 6.2 | 7.6 | -1.4 |
| $R^1 = R^2 = Ph$ | $R^1$ | 7.4 | 7.6 | -0.2 |
| | H | 6.7 | 8.2 | -1.5 |
| $R^1 = CH3$; | $R^1$ | 1.5 | 2.2 | -0.7 |
| $R^2 = H$ | $R^2$ | 5.0 | 6.6 | -1.6 |
| | H | 6.2 | 7.7 | -1.5 |
| $R^1 = R^2 = H$ | $R^1$ | 4.7 | 5.3 | -0.7 |
| | H | 6.2 | 7.9 | -1.7 |

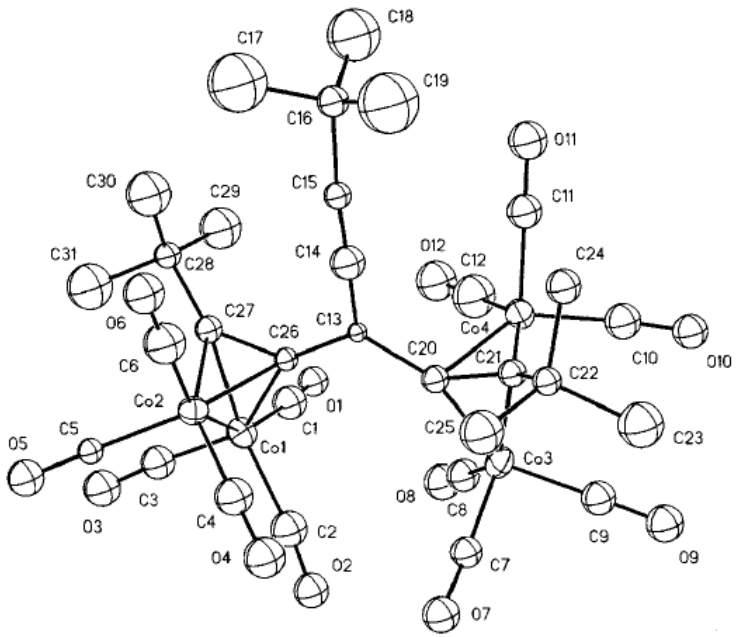
| Cation | $pK_R^+$ |
|---|---|
| $R^1 = R^2 = CH3$ | -7.2 |
| $R^1 = R^2 = Ph$ | -7.4 |
| $R^1 = R^2 = H$ | -6.8 |
| α-Ferrocenylmethyl | -1.5 |
| Triphenylmethyl | -6.6 |
| α–[(Benzene)chromium tricarbonyl]methyl | -11.8 |



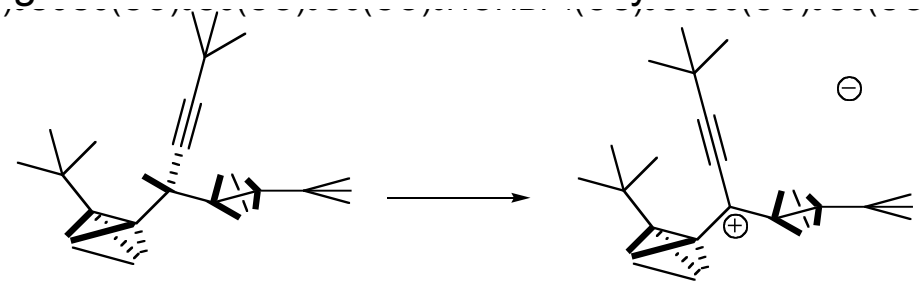
Nicholas, K. *et. al. J. Organomet. Chem* ***1977****, 125*, C45.

# X-Ray Structure of $[Co_2(CO)_6]$-Propargyl Cation:

- Thermal lability and low crystallinity of organometallic cations makes X-ray characterization very difficult.
- 1998, Melikyan and coworkers:




- Coordination of cation to metal atoms affects non-bonding distances. Before ionization C13 is equidistant from all four cobalt atoms. In contrast, the cationic C13 is shifted 0.26 A closer to Co2 and 0.38 A towards Co4.



- Central carbon (C13) nearly flat (out of plane <0.5°) with almost ideal trigonal planar arrangement (119-121°).

- C13-C14 bond is more sensitive to rehybridization (1.43 A to 1.34 A) than to the complexed alkynes (C13-C20 1.49 A vs. 1.45 A; C13-C26 1.53 A vs. 1.51 A).

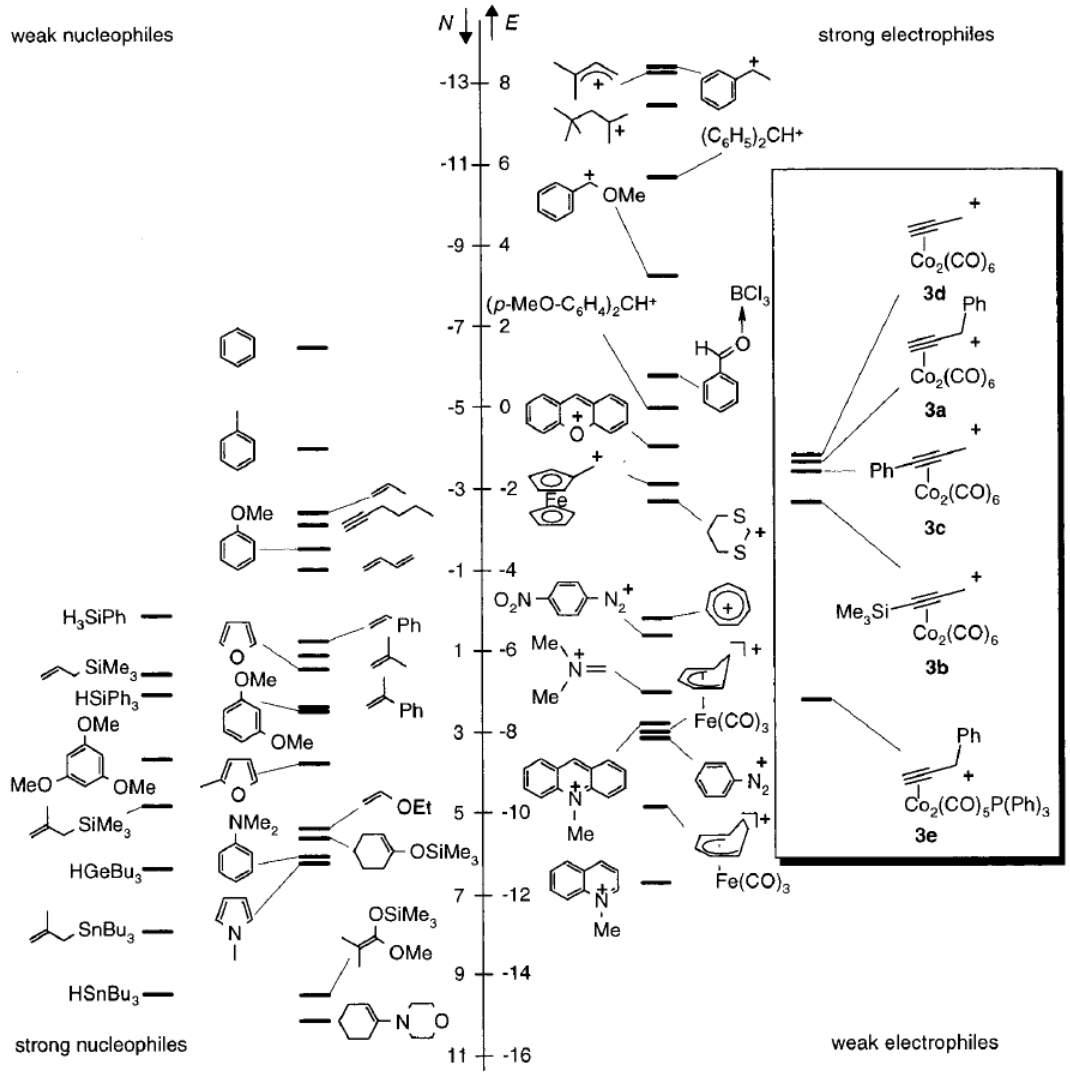
- Geometry of the alkyne complex (C27-C26-C13, C21-C20-C13) proved indifferent to charge/rehybridization (134-135° vs. 136°).

- Metal clusters are non-equivalent (angle between C26-C27 and Co1-Co2 is 82.3° , C20-C21 and Co3-Co4 is 89.7°) with one adopting a skew from perpendicular by 7.7°.

Melikyan, G., *et. al. Angew. Chem. Int. Ed.* **1998**, *37*, 161.

# How Electrophilic are the Complexed Cations?

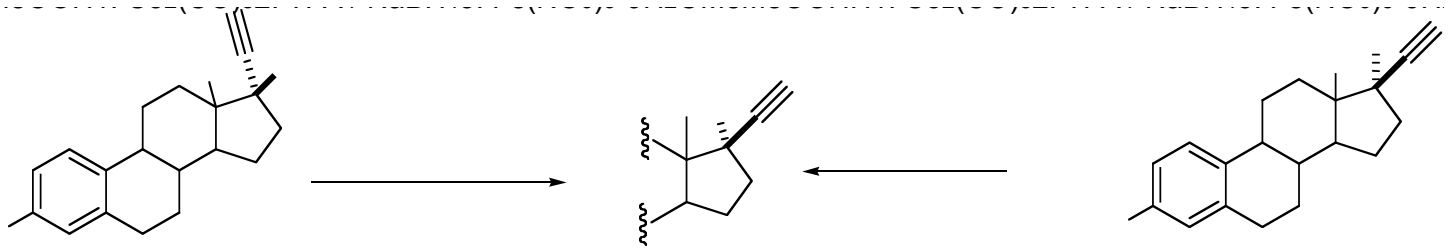
- Mayr's nucleophilicity / electrophiliciy scale:



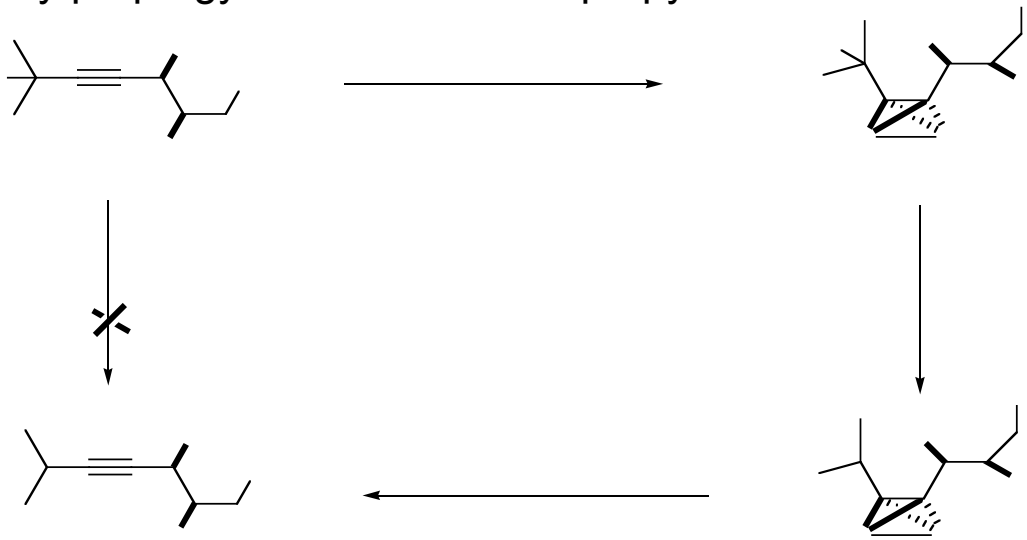

Mayr, H., *et. al. J. Amer. Chem. Soc.* **1998**, *120*, 900.

# Hydride as a Nucleophile:

- Due to competitive elimination reactions for standard acetylene coupling methods, Nicholas and Siegel developed the reduction method for the formation of 2$^{o}$ alkylacetylenes.



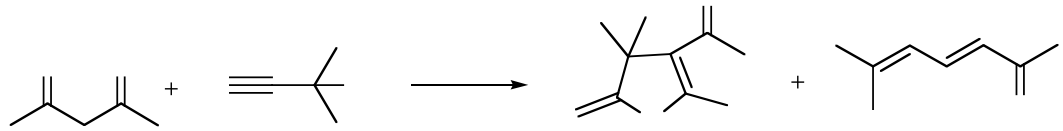
- In their synthesis of (+)-bengamide E, Hanaoka et. al. described the deoxygenation of the tertiary propargyl alcohol to the isopropyl derrivative **A**.

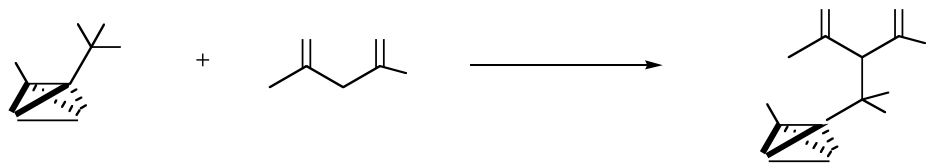



Nicholas, K., Siegel, J. *J. Amer. Chem. Soc.* **1985**, *107*, 4999.
Hanaoka, M., *et. al. J. Chem. Soc. Perkin 1* **1995**, 2849.

# Enol Derivatives as a Nucleophile:

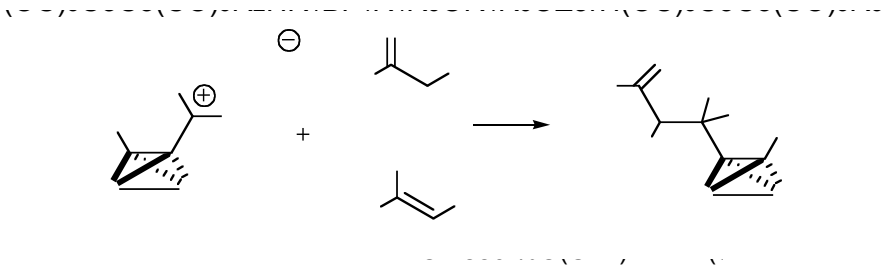
- Problem with direct substitution with enols:

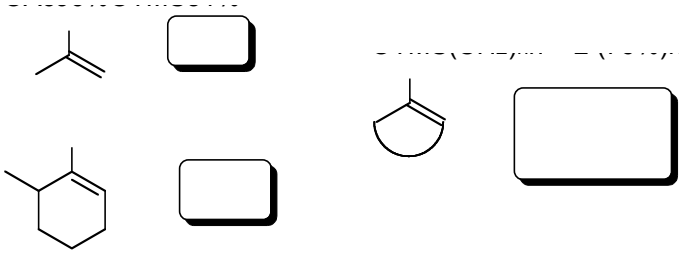


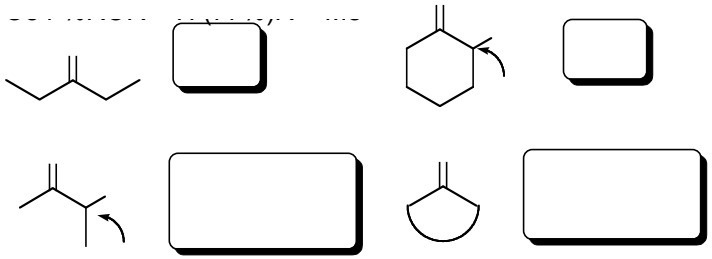


| $R^1$ | $R^2$ | $R^3$ | Yield (%) |
|---|---|---|---|
| H | H | $CH_3$ | 95 |
| H | $CH_3$ | $CH_3$ | 65 |
| H | Ph | $CH_3$ | 91 |
| H | H | Ph | 90 |
| H | $CH_3$ | Ph | 65 |
| H | Ph | Ph | 95 |

- Cationic complexes can react with ketones/enolates:



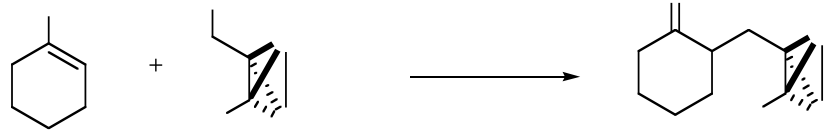




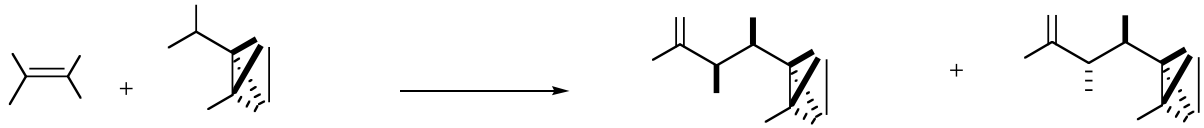

Nicholas, K. *et. al. Tett. Lett.* **1978**, *45*, 4349.
Nicholas, K. *et. al. J. Amer. Chem. Soc.* **1980**, 102, 2508.

# Lewis Acid Mediated Nicholas Reaction

- Schreiber and coworkers found that cobalt-complexed propargylic ethers can undergo the same reaction as Nicholas but with Lewis acids instead of bronsted.



- The results of stereochemical studies that employed both E and Z trimethylsilyl enol ethers of propiophenone:

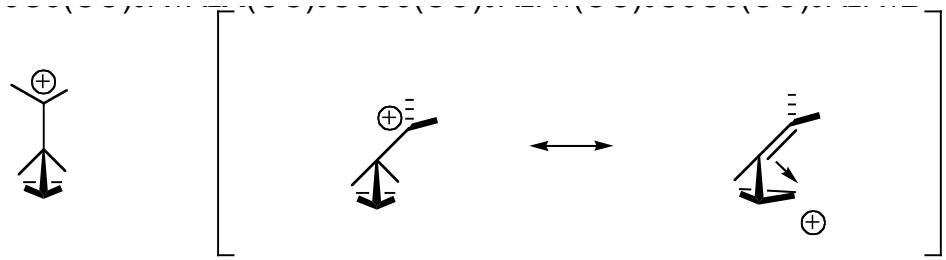


| R | $R^1$ | $R^2$ | Lewis acid | syn/anti |
|---|---|---|---|---|
| $Me_3Si$ | Me | H | $BF_3$-$OEt_2$ | 15:1 |
| Ph | Me | H | $EtAlCl_2$ | 18:1 |
| Ph | H | Me | $EtAlCl_2$ | 9:1 |
| Me | Me | H | $BF_3$-$OEt_2$ | 6.8:1 |
| Me | H | Me | $BF_3$-$OEt_2$ | 3.5:1 |
| H | Me | H | $EtAlCl_2$ | 1.6:1 |

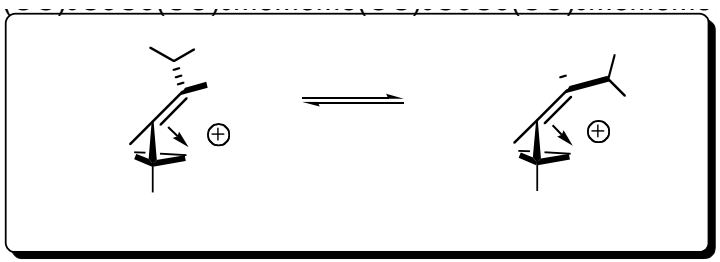
Schreiber, S., *et. al. J. Amer. Chem. Soc.* **1986**, *108*, 3130.

# Stereochemical Model for Nicholas Rxn:

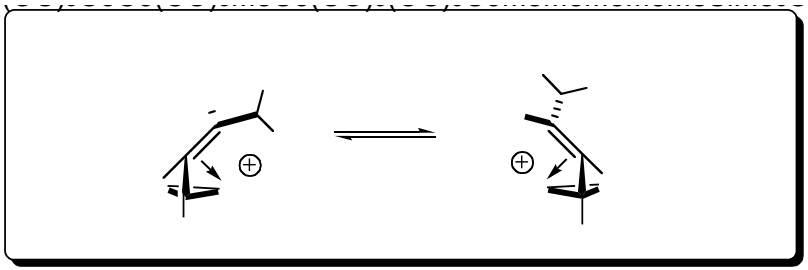
- Model <u>must</u> take into account the fact that the cobalt complex to the alkyne is **dynamic not static**!
- Hoffman has predicted that bending of the cationic carbon toward one of the cobalt atoms would result in hyperconjugative stabilization, and that the upright structure **A** is 17.5 kcal / mol higher in energy than **B**.



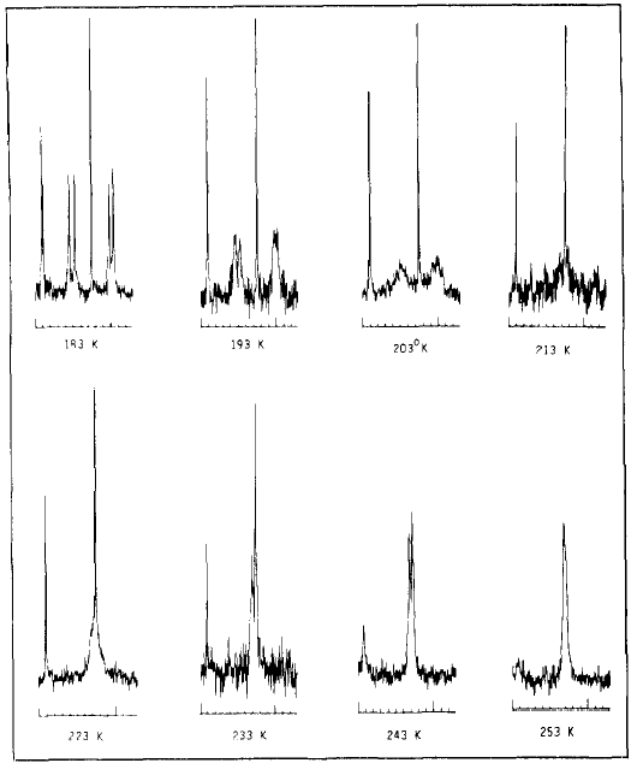
- Schreiber's variable temp. NMR experiments



Fluxional process of enantiomerization had $\Delta G^{\ddagger}$ = 10.1 kcal/mol



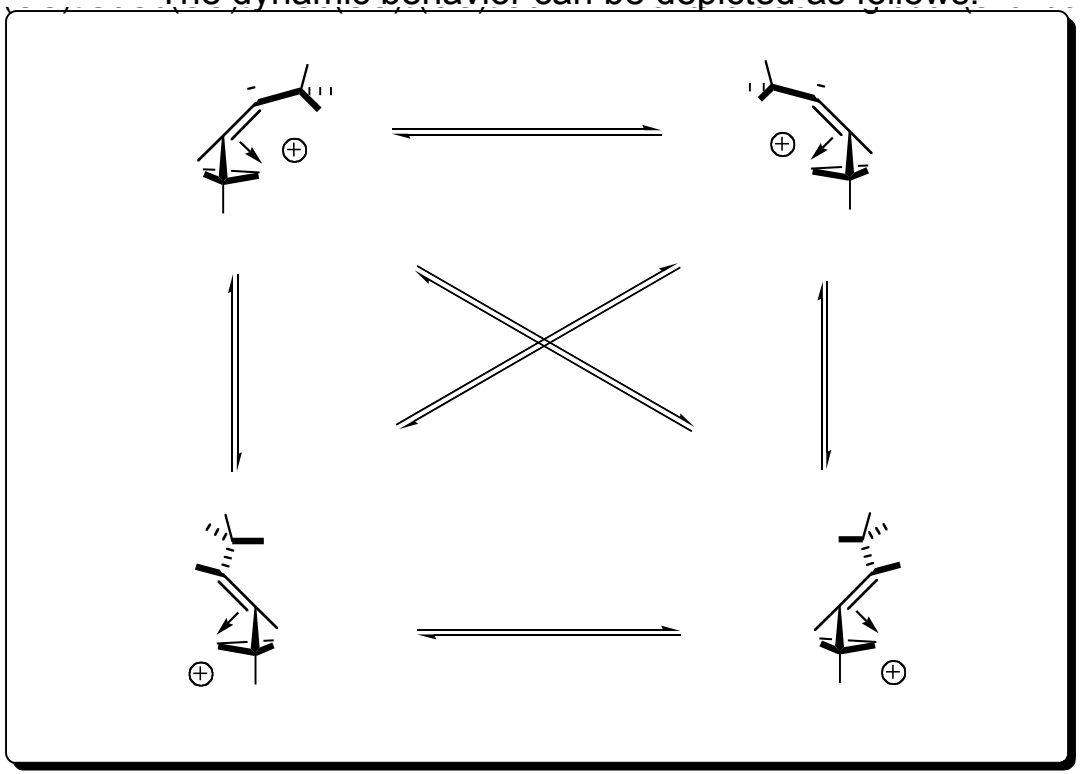
2nd fluxional process that results in syn/anti isomerization was detected at higher temps ($\Delta G^{\ddagger}$ = 12.6 kcal /mol)



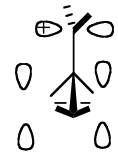

Schreiber, S., *et. al. J. Amer. Chem. Soc.* **1987**, *109*, 5749.

# Stereochemical Model for Nicholas Rxn:

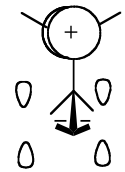
- The dynamic behavior can be depicted as follows:



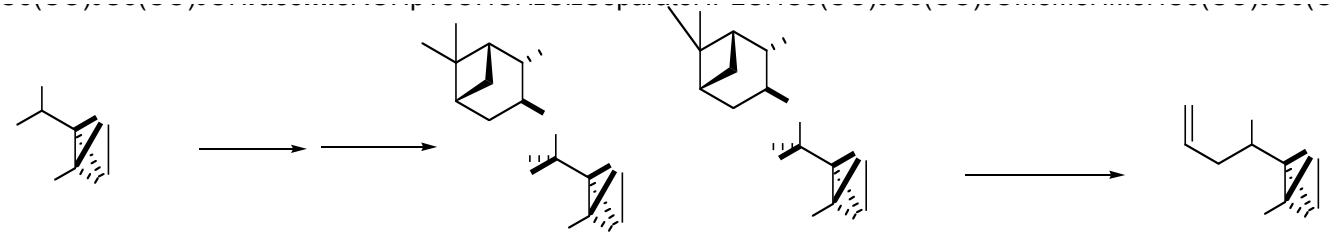
stabilized TS



w.o. stabilization



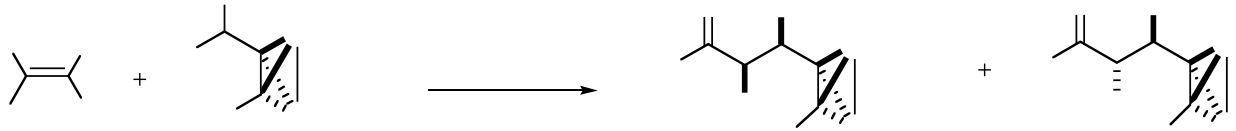
-Antarafacial migration and rotation processes result in exposure of the opposite enantiotopic face for attack by a nucleophile.
-Only suprafacial migration preserves exposure of the kinetically formed face.



**<u>Racemization occurs at a rate that is fast relative to alkylation!</u>**

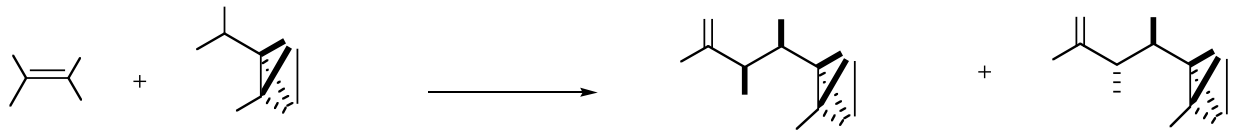
Schreiber, S., *et. al. J. Amer. Chem. Soc.* **1987**, *109*, 5749.

# Stereochemical Model for Nicholas Rxn:



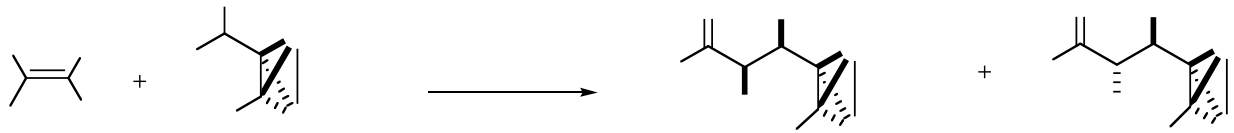
Schreiber, S., *et. al. J. Amer. Chem. Soc.* **1986**, *108*, 3130.
Schreiber, S., *et. al. J. Amer. Chem. Soc.* **1987**, *109*, 5749.

# Stereochemical Model for Nicholas Rxn:

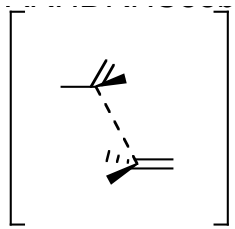


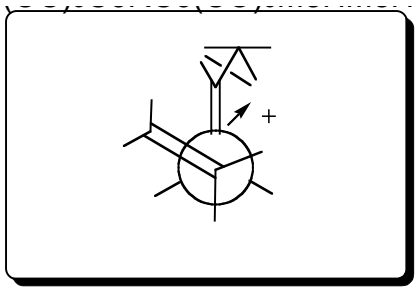
Schreiber, S., *et. al. J. Amer. Chem. Soc.* **1986**, *108*, 3130.
Schreiber, S., *et. al. J. Amer. Chem. Soc.* **1987**, *109*, 5749.

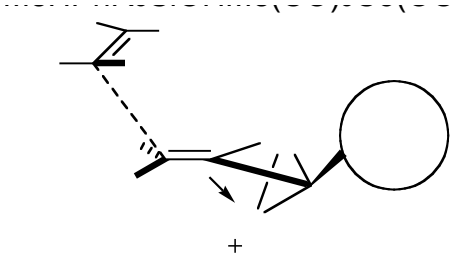
# Stereochemical Model for Nicholas Rxn:

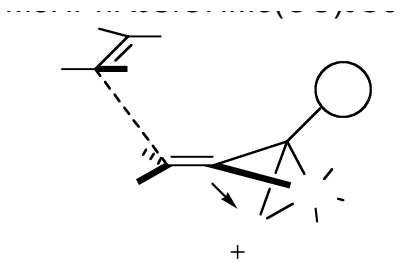


- The model most successful in providing a rationale for the observed stereochemistry is a synclinal relationship of the donar and acceptor Π systems.







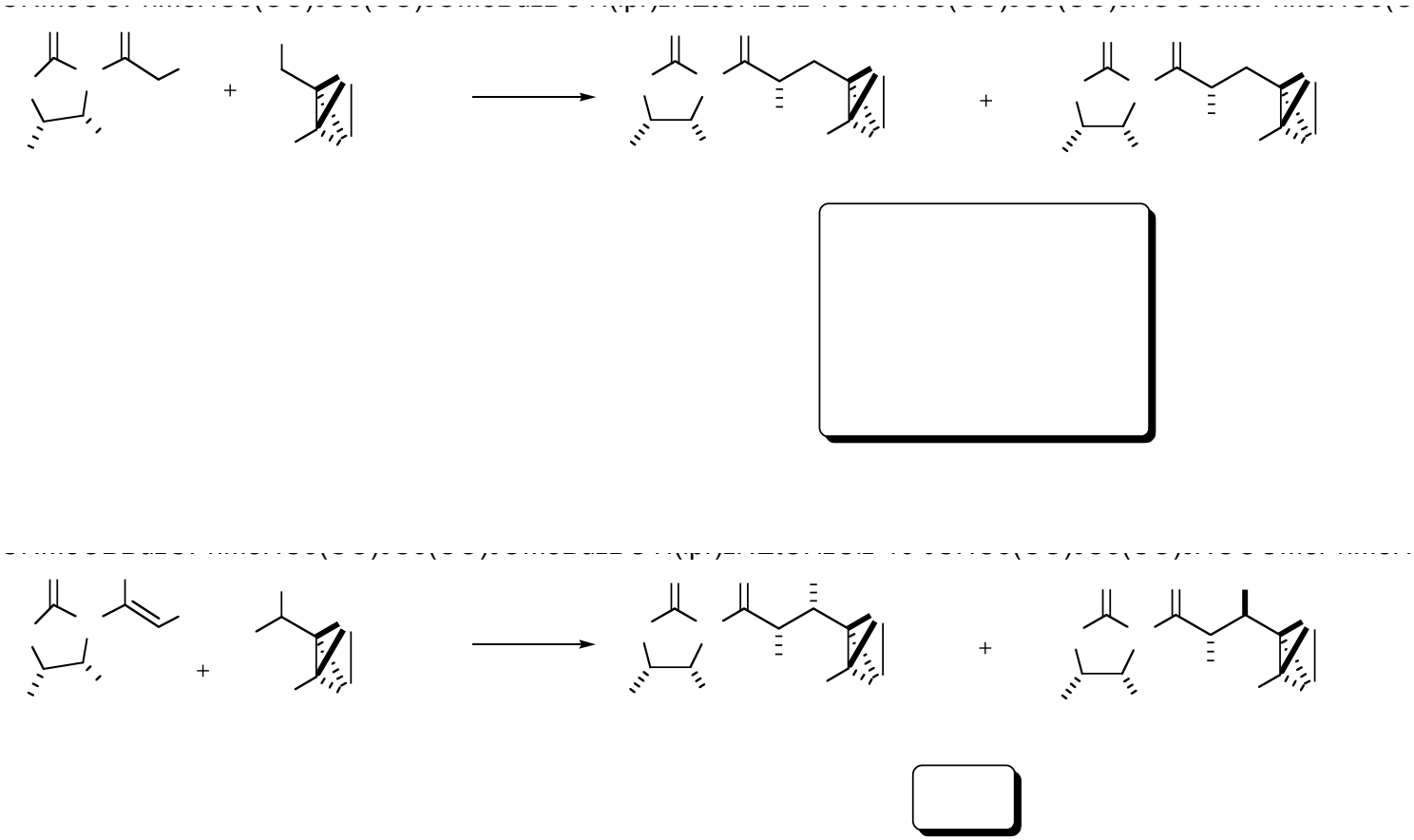


The relative face selectivity of this rxn as compared to Seebach's model is a result of "unusual topographical features of the cobalt cation".


Schreiber, S., *et. al. J. Amer. Chem. Soc.* **1986**, *108*,3130.
Schreiber, S., *et. al. J. Amer. Chem. Soc.* **1987**, *109*,5749.

# Kinetic Resolution of Racemizing Cobalt Cation

- The ability of the cobalt cation to enantiomerize during the alkylation reaction, combined with the intrinsic relative facial selectivity of the reaction “suggests that a double stereodifferentiating process may be achieved *with kinetic resolution of a racemizing cation* if a suitable chiral, nonracemic nucleophile can be found” (5754).



Schreiber, S., *et. al. J. Amer. Chem. Soc.* **1987**, *109*,5749.

# Kinetic Resolution of Racemizing Cobalt Cation

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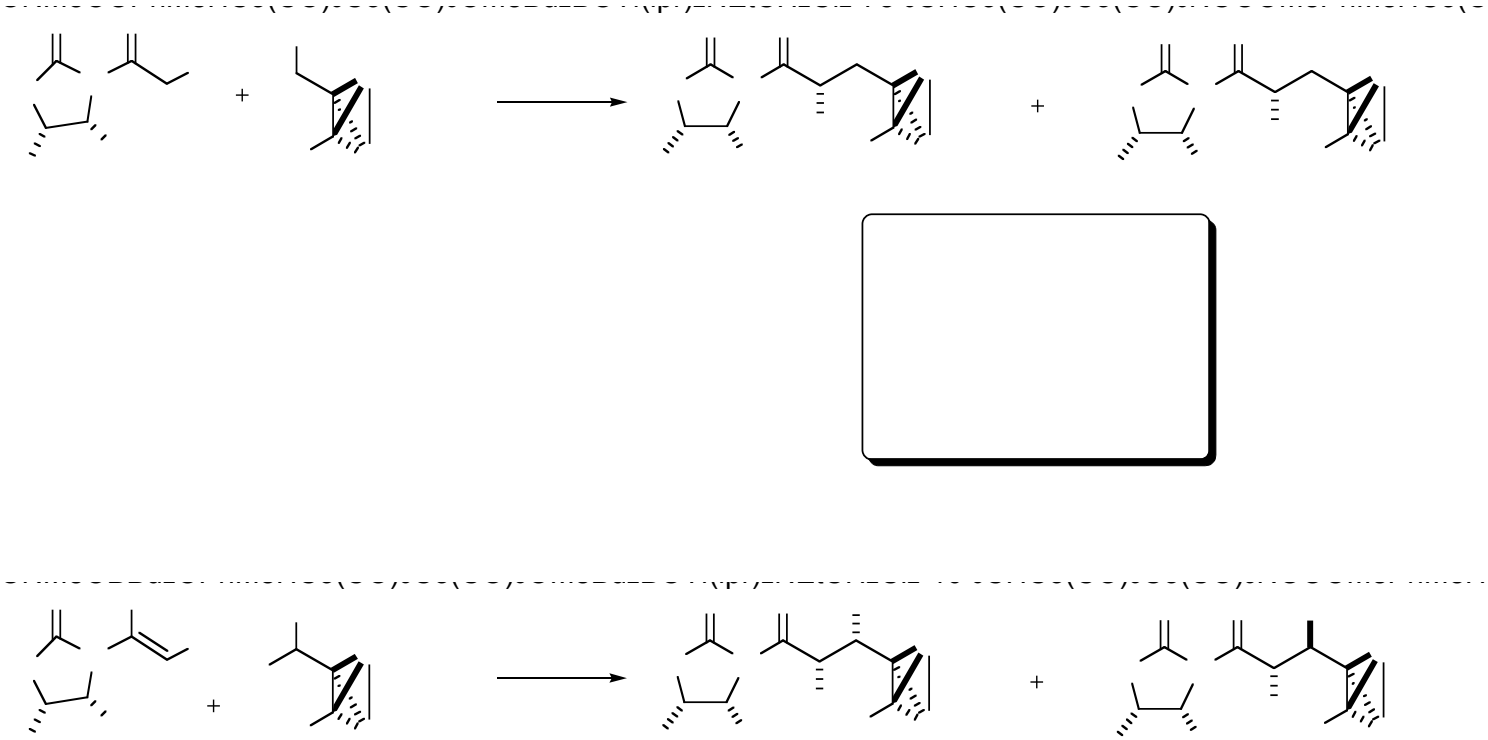
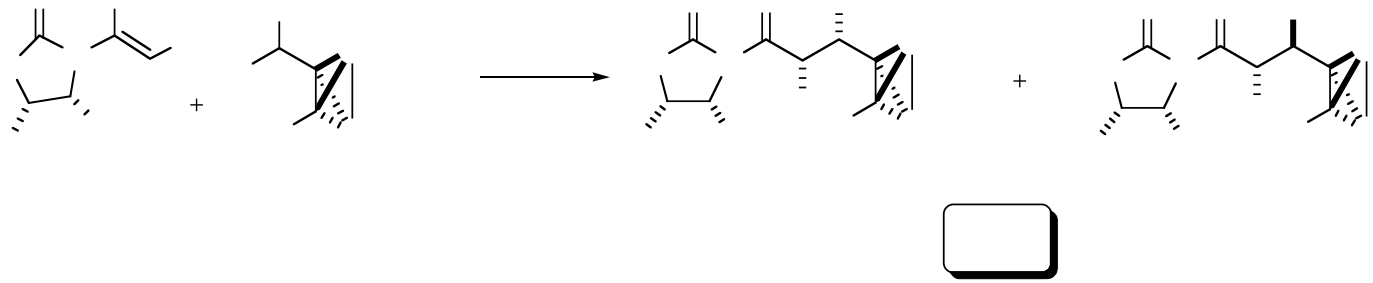
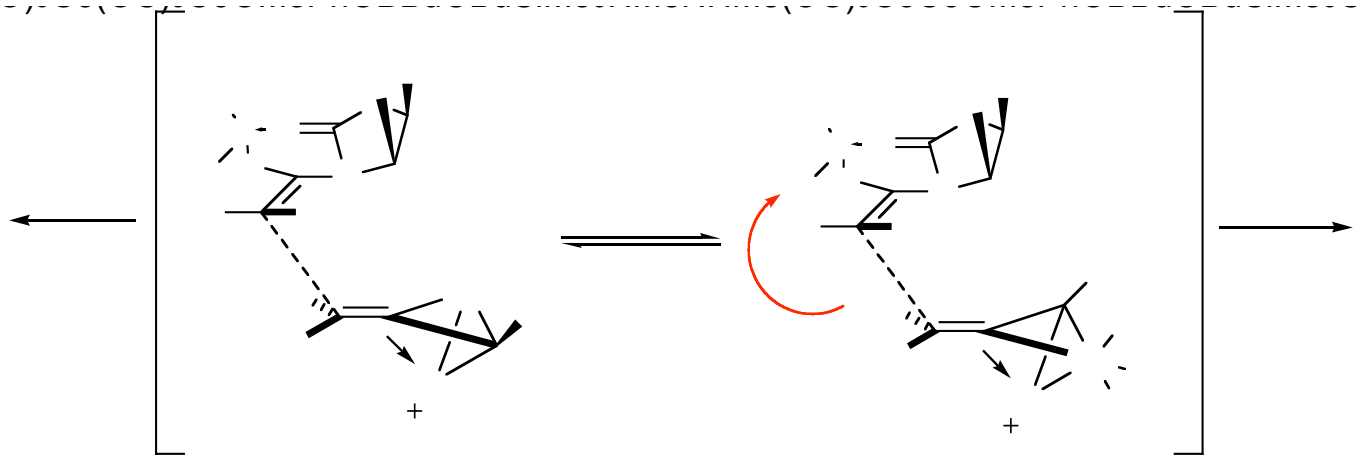


Schreiber, S., *et. al. J. Amer. Chem. Soc.* **1987**, *109*,5749.

# Kinetic Resolution of Racemizing Cobalt Cation



- Utilizing synclinal transition states:

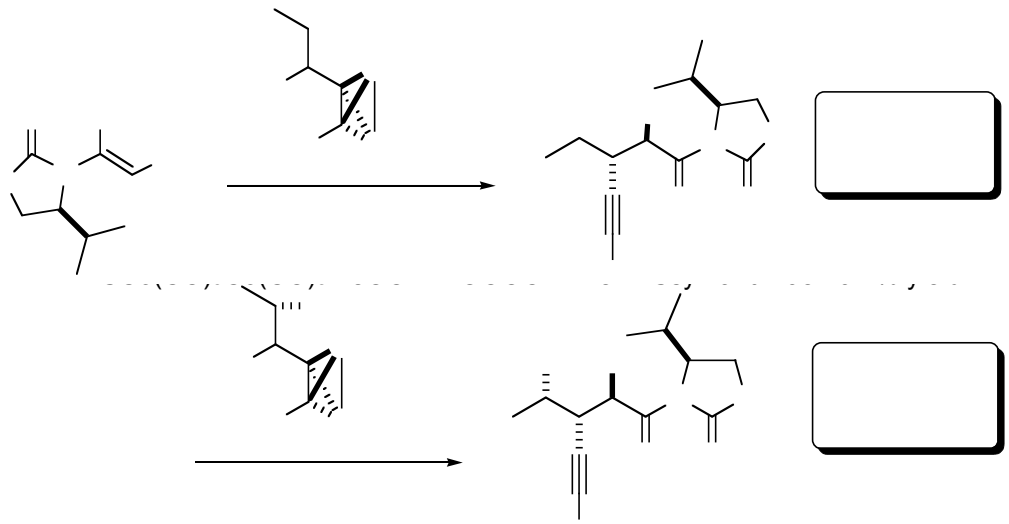


Because the two enantiomeric cations undergo interconversion under the reaction conditions and react at different rates, the racemic pair of ethers can be converted to 12:1 mix of diastereomers.

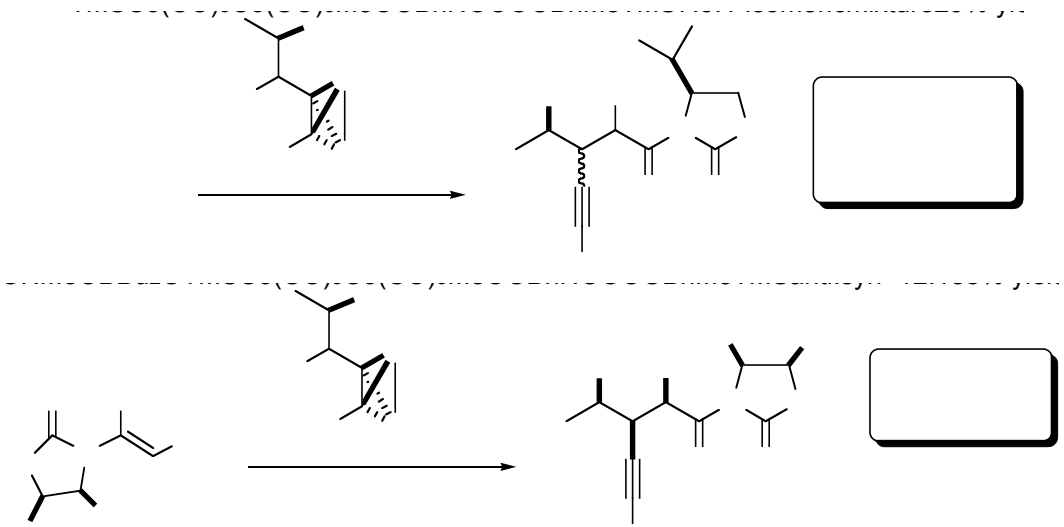
Schreiber, S., *et. al. J. Amer. Chem. Soc.* **1987**, *109*,5749.

# Chiral Enolate Additions to Cobalt Complexes:

- Matched:



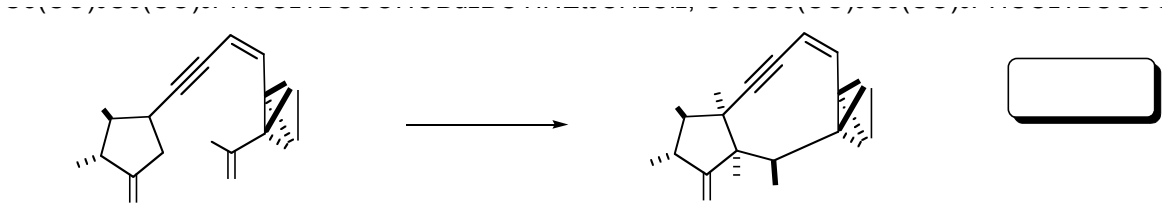
- Mis-matched:



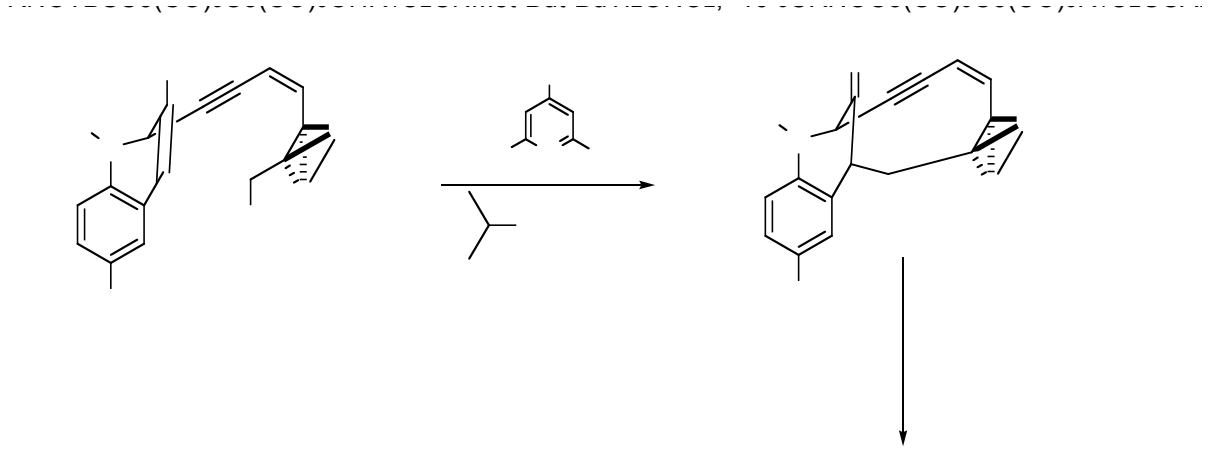
Jacobi, P., *et.al. Tett. Lett.* **1992**, *33*, 6231.

# Enolates as Nucleophiles:

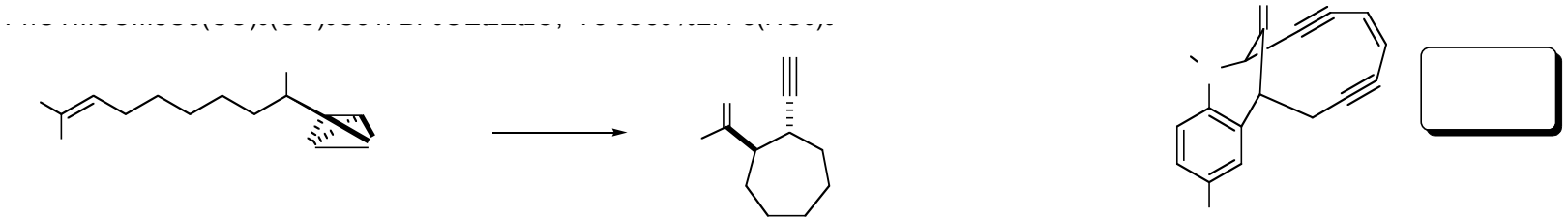
- Caddick's kedarcidin synthesis:



- Magnus' dynemicin synthesis:



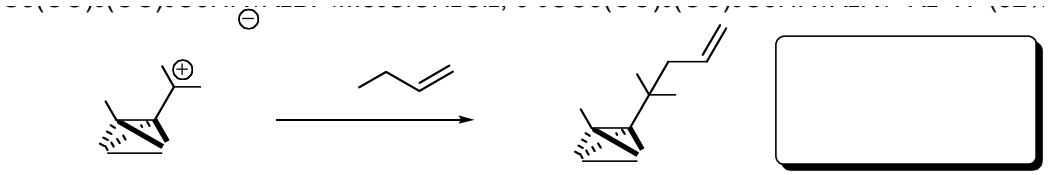
∀ β-alkynl ketones:



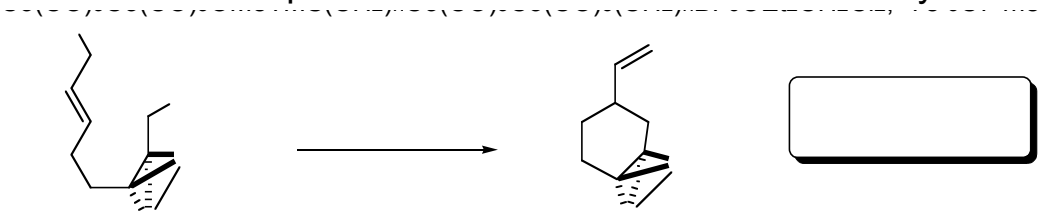

Caddick, S., *et. al. Tett. Lett.* **1997**, *38*, 2355.
Magnus, P., *et. al. J. Chem. Soc., Chem. Commun.* **1994**, 1543.
Tyrrell, E., *et. al. Synlett* **1993**, 769.

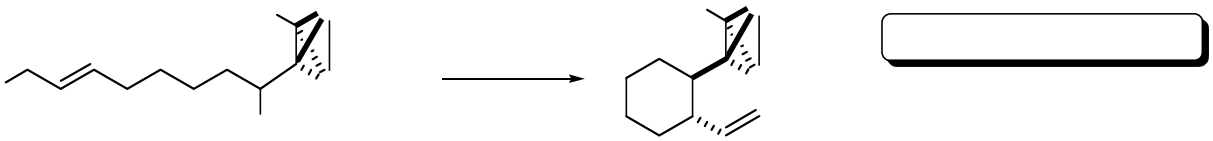
# Carbon as a Nucleophile: Allylations

- Nicholas and coworkers pioneered the first coupling of allylsilanes and propargyl cobalt complexes:

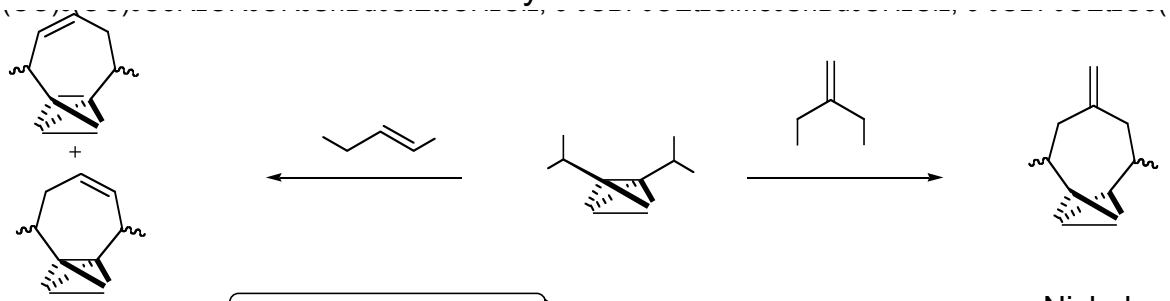


- Schreiber and coworkers developed an intramolecular variant of the allylation reaction





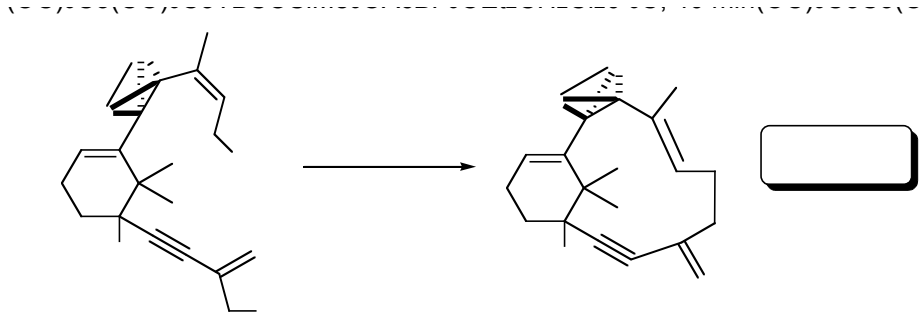
- Green and coworker's double Nicholas allylation:



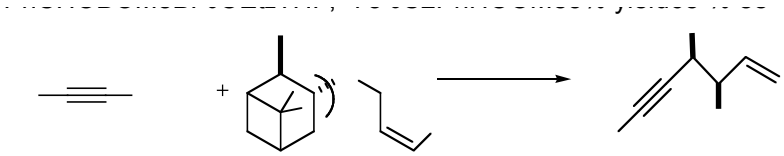

Nicholas, K.,*et. al. Tett. Lett.* **1980,** *21*, 1595.
Schreiber, S., *et. al. JACS.* **1986**, *108*, 3130.
Green, J., *et.al. Chem. Comm.* **1999**, 509.

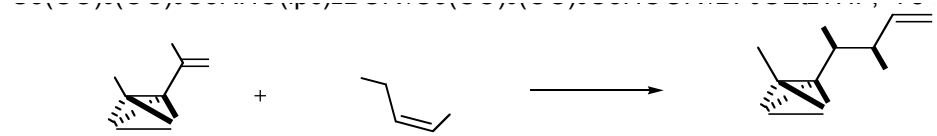
# Carbon as a Nucleophile: Allylations

- Isobe and coworker's synthesis of a taxoid diterpenoid skeleton:



- Asymmetric allylations:



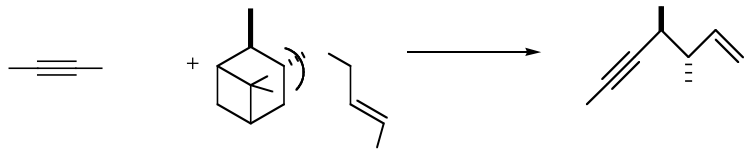


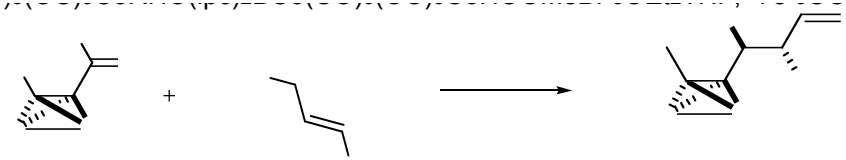
Without complexation, allylation mainly produces polymerization product.

| aldehyde | borane | yield(%) | de (%) | ee(%) |
|---|---|---|---|---|
| R = Ph | $R^1$ = Me | 75 | >95 | >98 |
| R = Ph | $R^1$ = $CH_2OMe$ | 62 | >95 | >96 |
| R = Me | $R^1$ = Me | 73 | >95 | >96 |
| R = Me | $R^1$ = $CH_2OMe$ | 65 | >95 | >96 |
| R = H | $R^1$ = Me | 76 | 88 | >96 |


Isobe, M., *et. al. Synlett* **1998**, 373.
Nicholas, K., *et. al. J. Org. Chem.* **1993**, *58,* 5587.

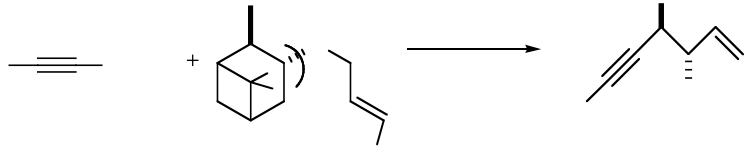
# Carbon as a Nucleophile: Allylations

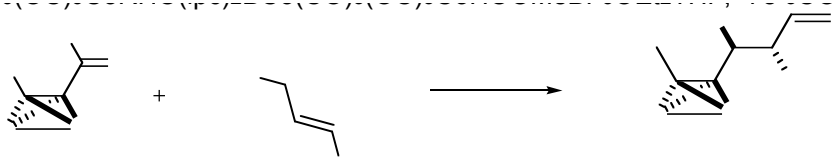




| aldehyde | yield(%) | de(%) | ee(%) |
|---|---|---|---|
| R = Ph | 50 | >95 | >95 |
| R = Me | 44 | >95 | >95 |
| R = H | 20 | >95 | >95 |

# Carbon as a Nucleophile: Allylations





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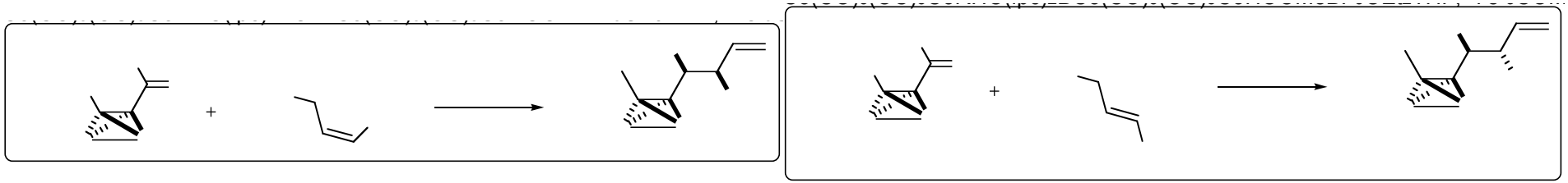
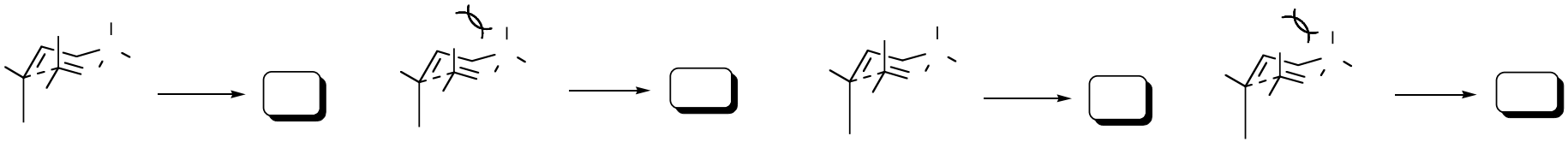
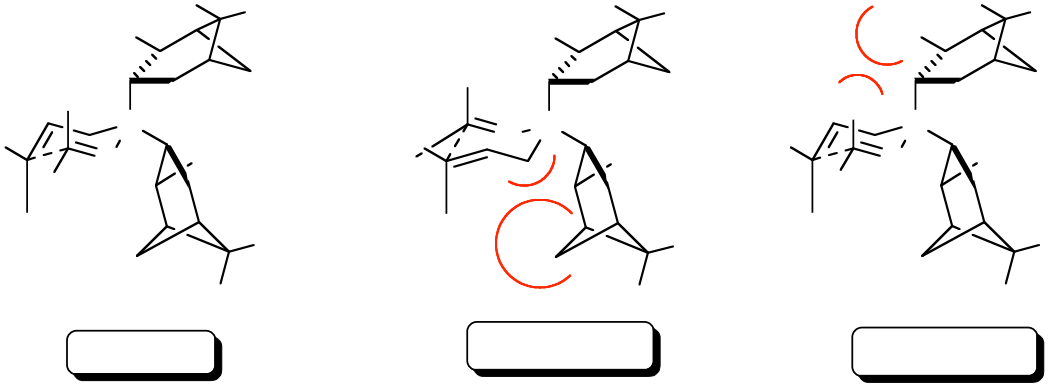
# Carbon as a Nucleophile: Allylations



Diastereoselectivity:



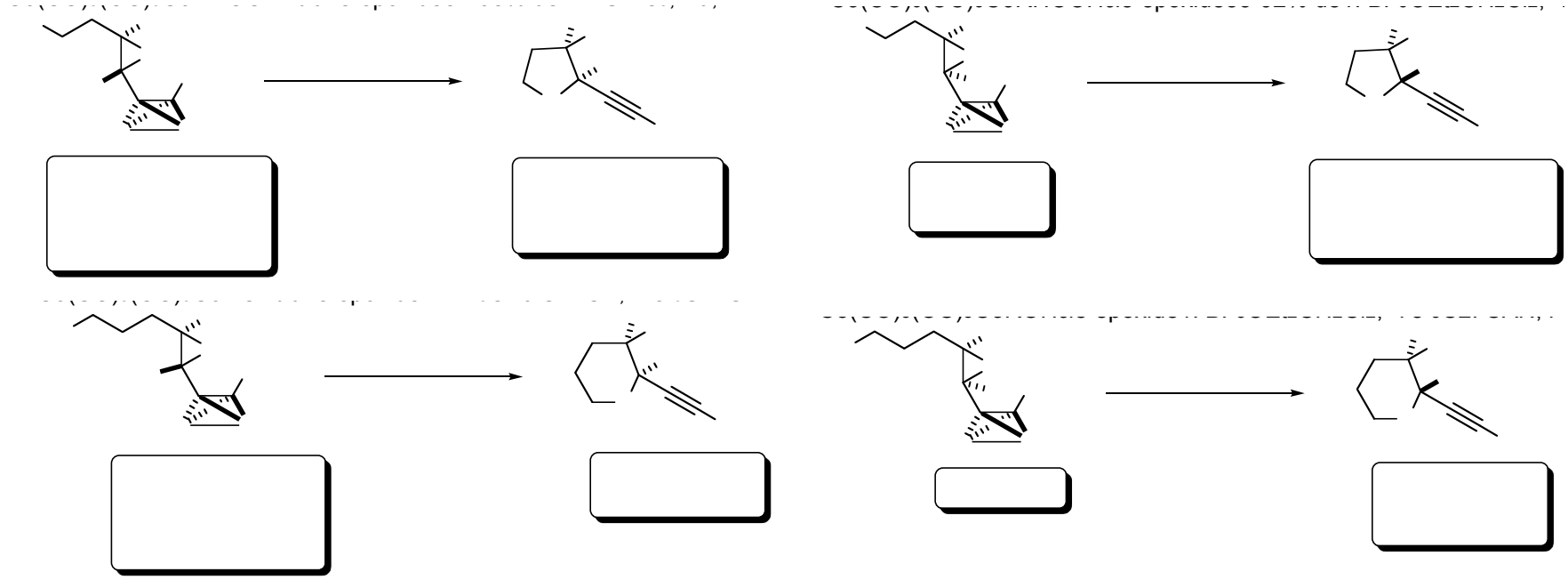
Enantioselectivity:



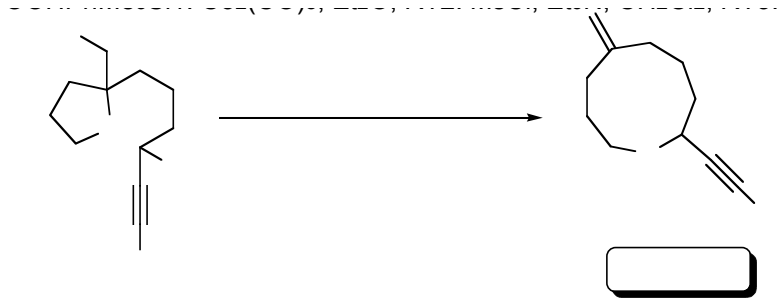
Nicholas, K., *et. al. J. Org. Chem.* **1997**, *62*, 1737.

# Oxygen as a Nucleophile

∀ α-epoxides:



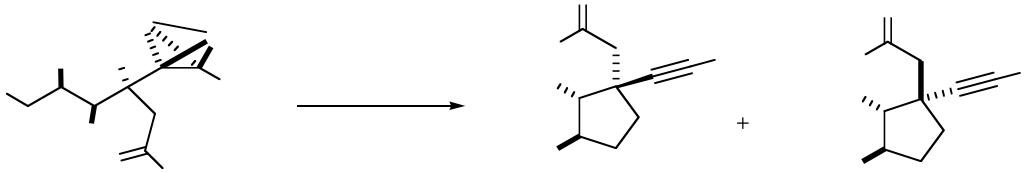
Highly stereoselective endo-mode ring closure (cobalt assisted double inversion process).
The intermolecular oxygen addition to α-epoxides has little to no stereoselectivity.



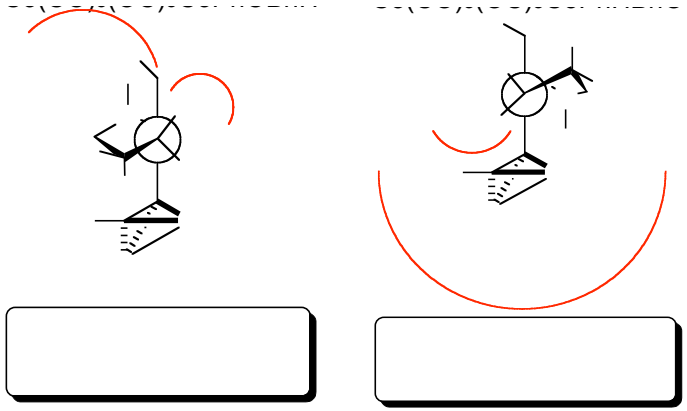

Mukai, C., Hanaoka, M., *et. al. Tetrahedron* **1998**, *54*, 823.
Mukai, C., Hanaoka, M., *et. al. Tetrahedron* **2000**, *56*, 2203.

# Oxygen as a Nucleophile:

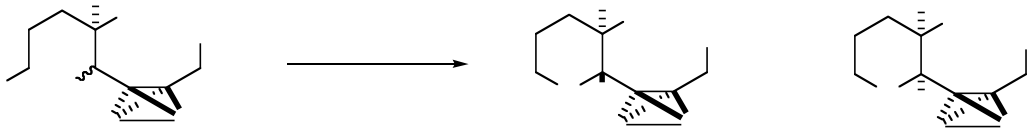
- Mukai and Hanaoka's synthesis of (+)-secosyrins:

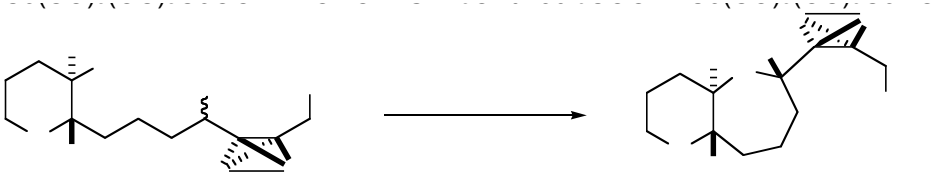


Origin of diastereoselectivity:



- Medium sized rings and fused bicyclic rings:

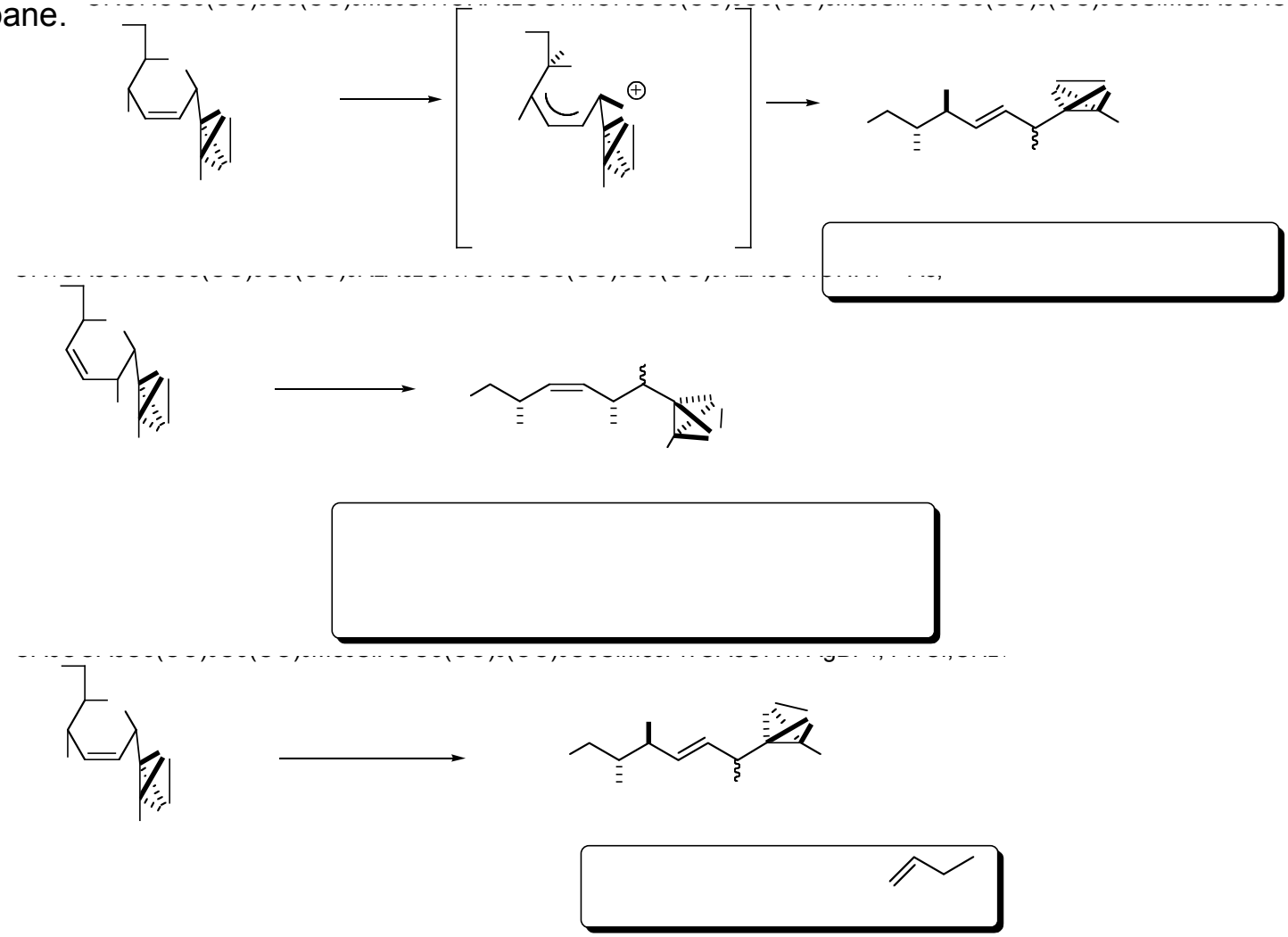





Mukai, C., Hanaoka, M., *et. al. J. Org. Chem.* **1997**, *62*, 8095.
Martin, V., *et. al. Tett. Lett.* **1995**, *36*, 3549.

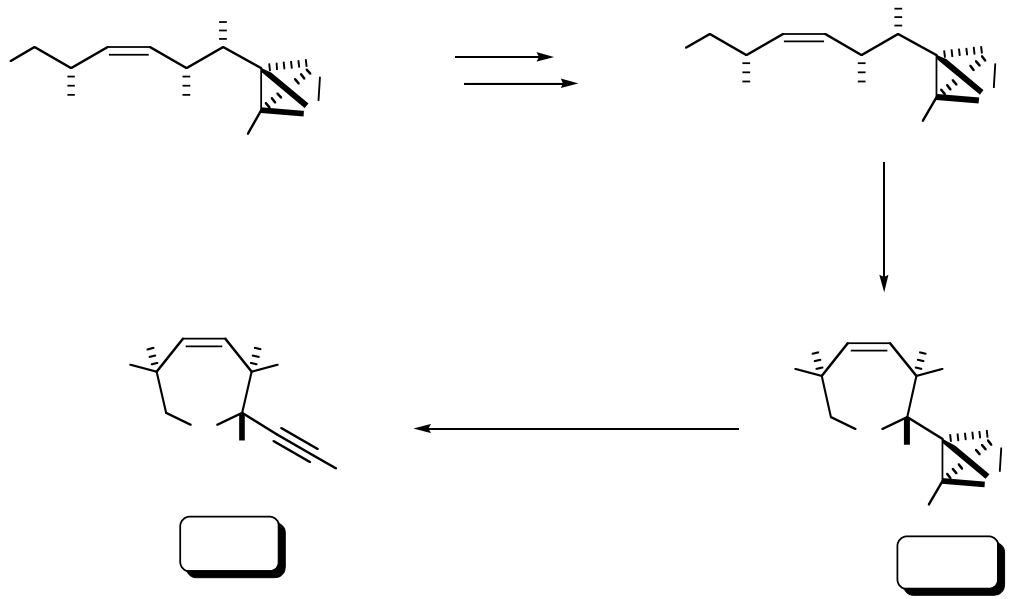
# Pyranose Ring Opening:

- During Isobe and coworkers' studied whether $\alpha$-substituted pyranoses could undergo a cobalt-assisted ring opening, and whether the intermediates could be manipulated and re-cycled to form another oxepane.

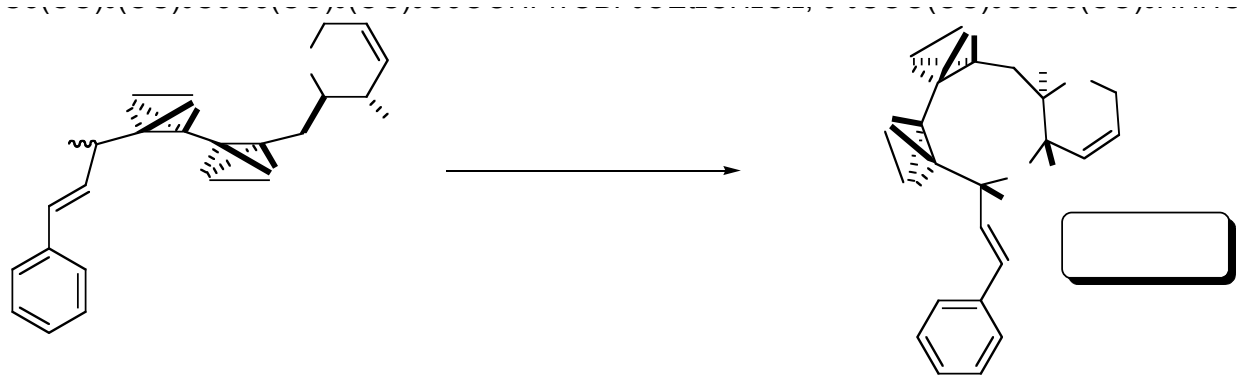


Isobe, M., *et. al. Tett. Lett.* **1994**, *35*, 7801.

# Oxepane Formation:



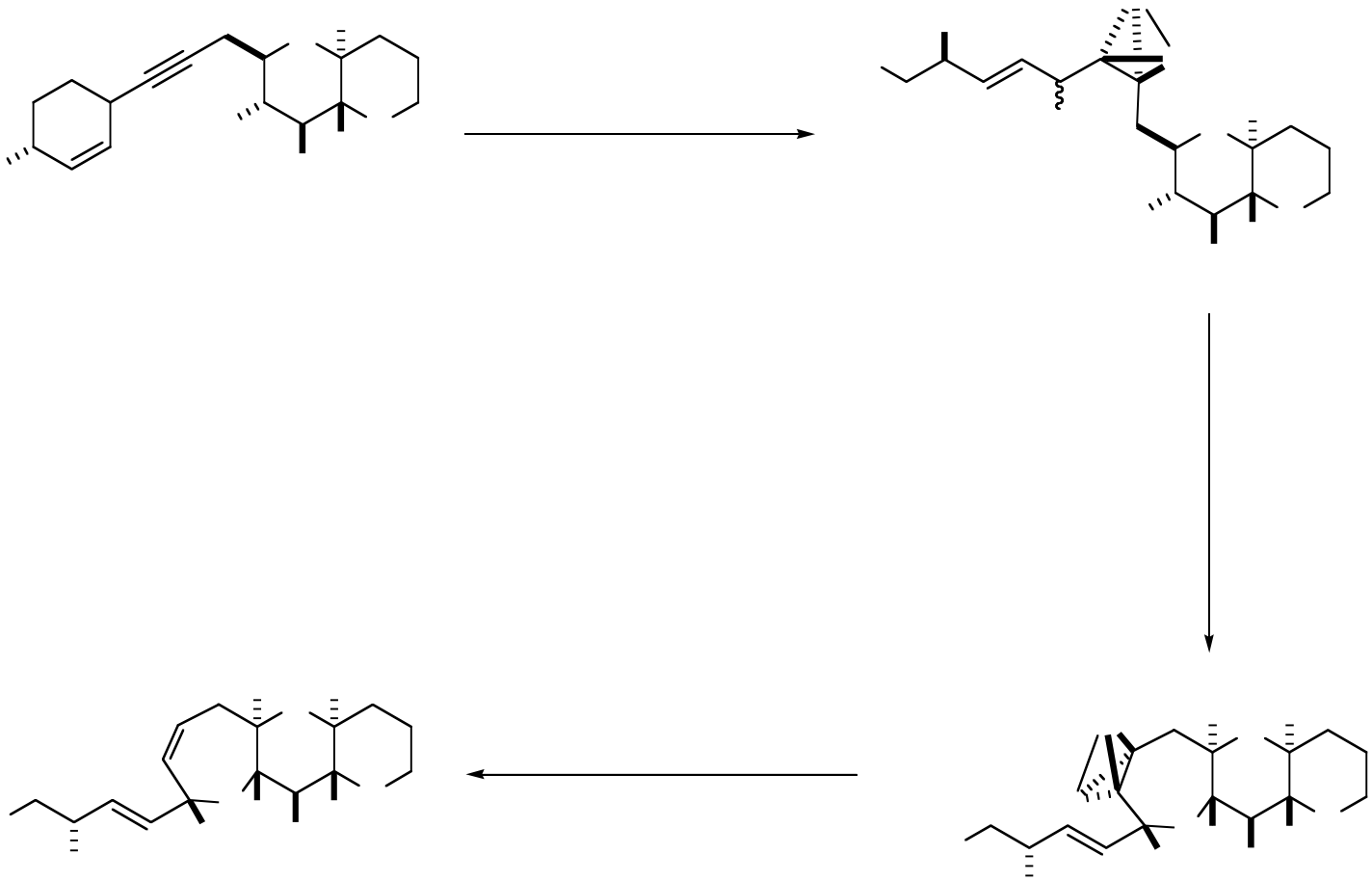
Exclusive formation of syn stereoisomer:



Isobe, M., *et. al. Tetrahedron* **1994**, 50, 12883.
Isobe, M., *et. al. Synlett* **1995**, 1179.

# Oxepane Formation:

- Isobe and coworkers' synthesis of ciguatoxin (ABC):



Isobe, M., *et. al. Tett. Lett.* **1999**, *40*, 1911.

# Conclusions:

- Through cobalt directed anchimeric assistance a wide variety of nucleophiles can undergo Sn1 – type reactions at the propargylic position
- Using chiral auxillaries a moderate degree of stereocontrol can be achieved.
- A catalytic enantioselective variant of the Nicholas reaction has not been discovered.

  – Topics not discussed in this talk:
    - Alkenes as nucleophiles
    - Aromatic as nucleophiles
    - Glycosylation chemistry
    - Nitrogen as a nucleophile (azides, amines)
    - Sulphur as a nucleophile
    - Nicholas promoted carbonyl-ene reactions
    - Nicholas promoted rearrangements
    - Radical reactions
    - Nicholas promoted ene-yne additions