

Pauson-Khand Reaction

Regio-, Diastereo- and Enantioselectivity

Zesheng Li

College of Chemistry and Molecular Engineering

Peking University

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Outline

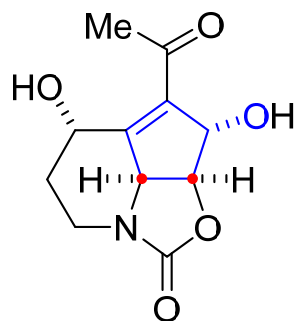
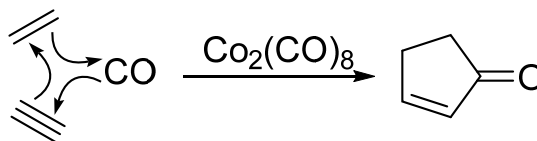
- Introduction
 - History
 - General Mechanism
- Regioselectivity
 - Trans Effect Proposal
 - Curtin-Hammett Proposal
 - Regioselectivity for Alkene
- Diastereoselectivity
- Enantioselectivity
- Summary

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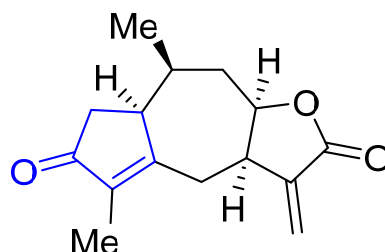
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Introduction

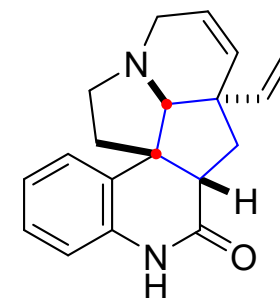
- PKR is a useful methodology for constructing cyclopentenone skeletons.



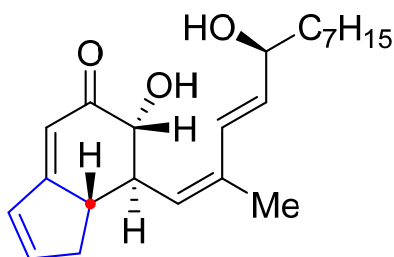
(±)-8α-hydroxystreptazolone
Org. Lett. **2002**, 4, 4301–4304.



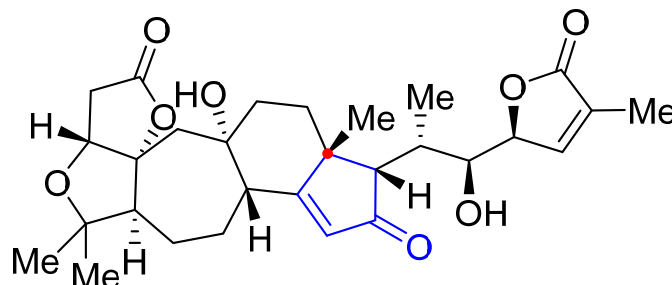
(+)-achalensolide
J. Org. Chem. **2008**, 73, 1061-1066.



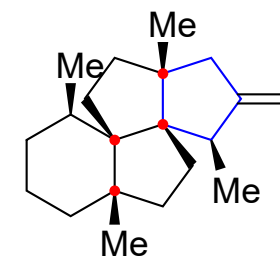
(±)-meloscine
Org. Lett. **2011**, 13, 1778-1780.



(+)-penostatin E
J. Org. Chem. **2014**, 79, 7512-7519.

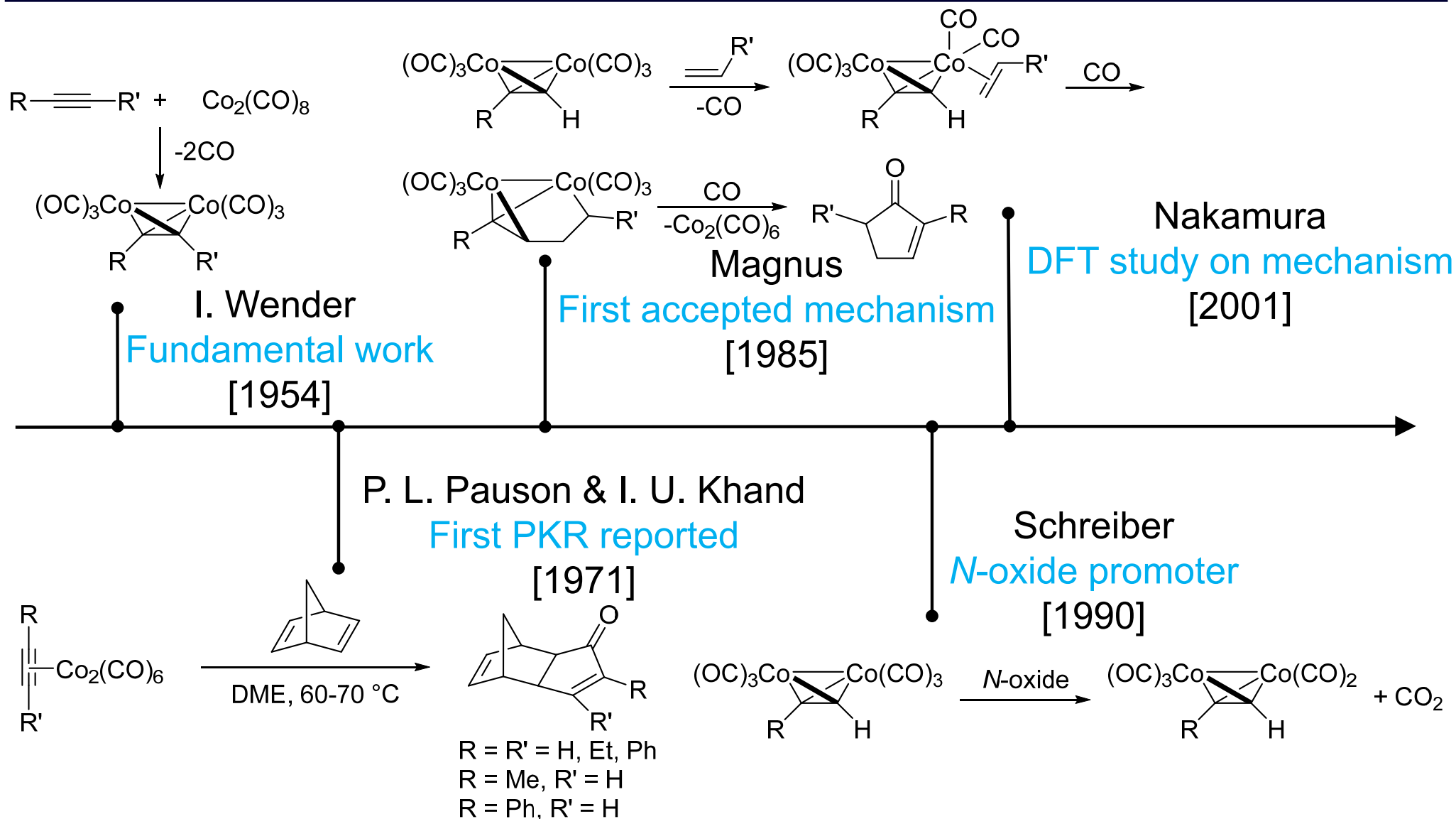


(+)-propindilactone G
J. Am. Chem. Soc. **2015**, 137, 10120-10123.



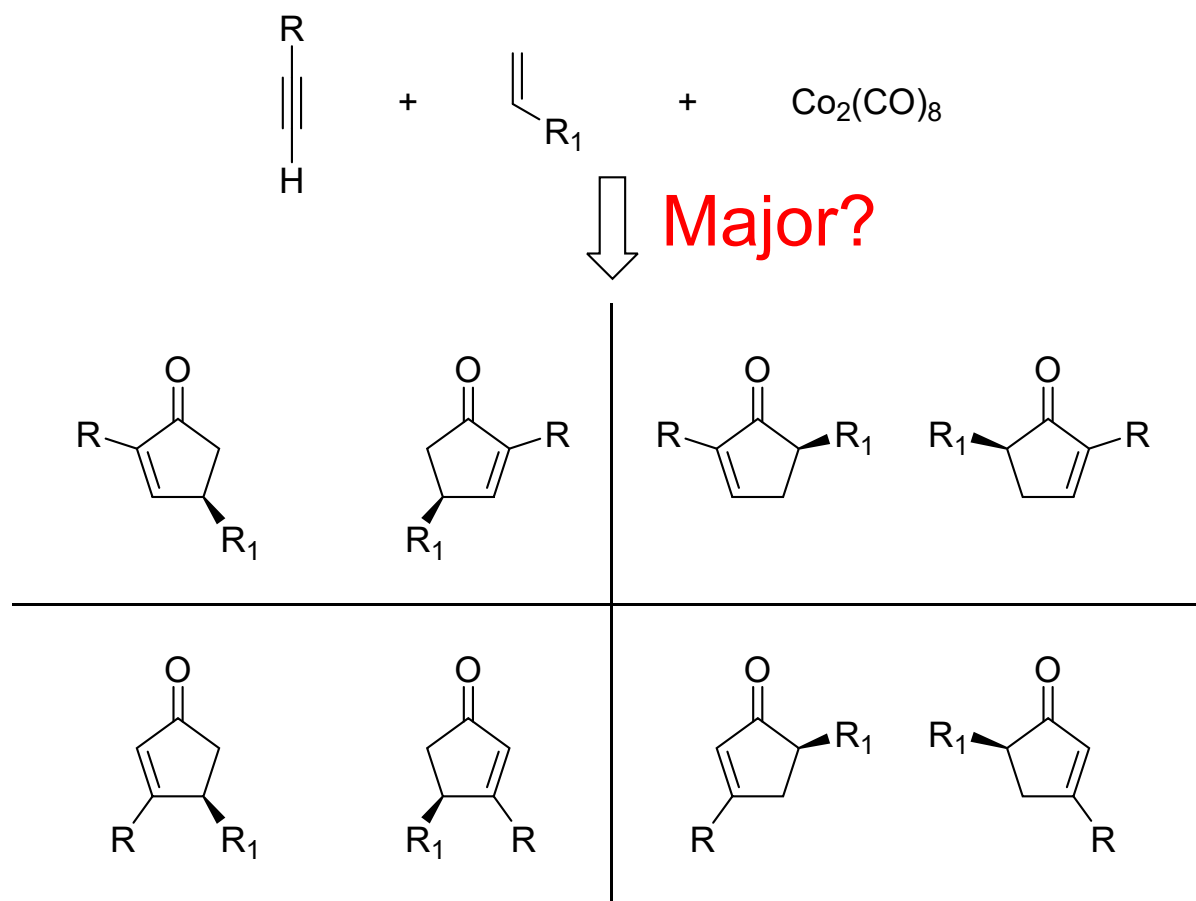
(+)-waihoensene
J. Am. Chem. Soc.
2020, 142, 6511-6515.

History

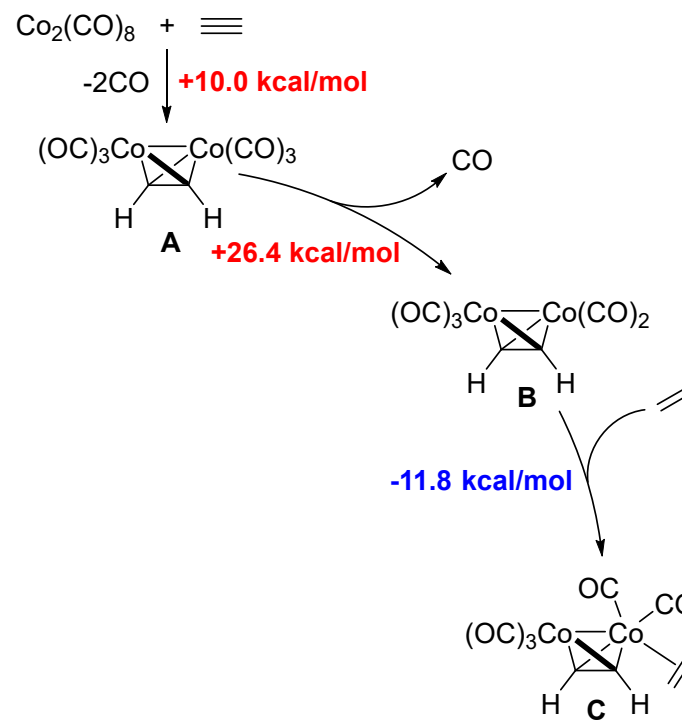


Selectivity Issue

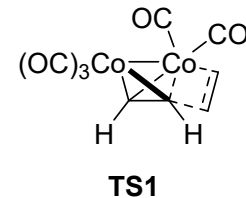
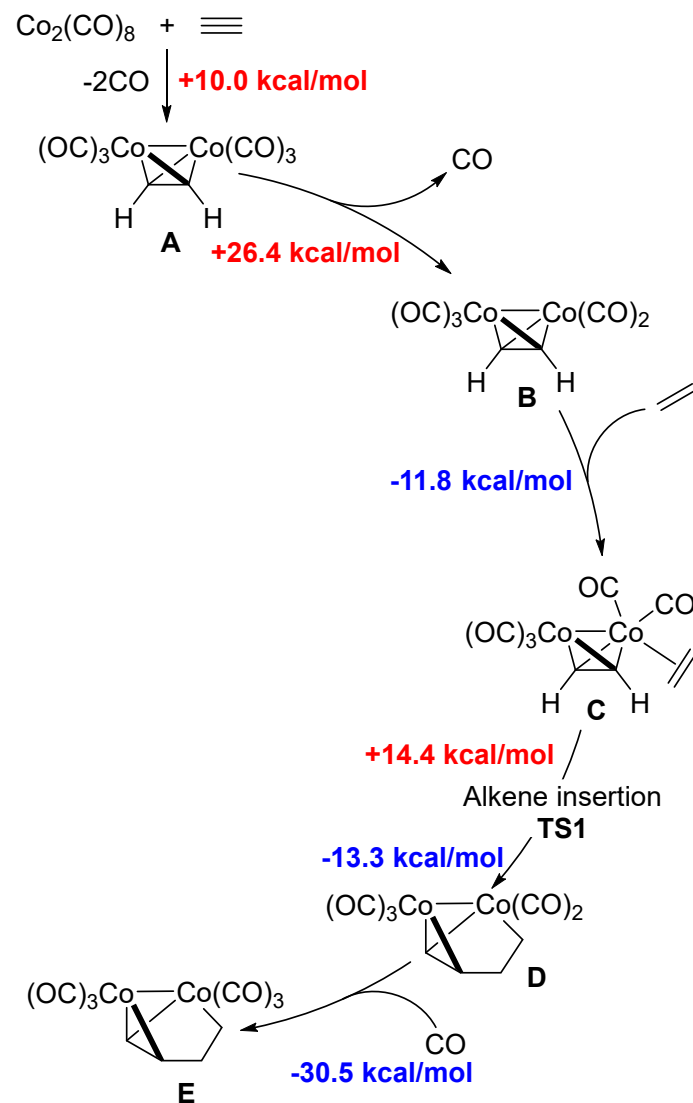
- 8 possible products for asymmetric alkene and alkyne substrates



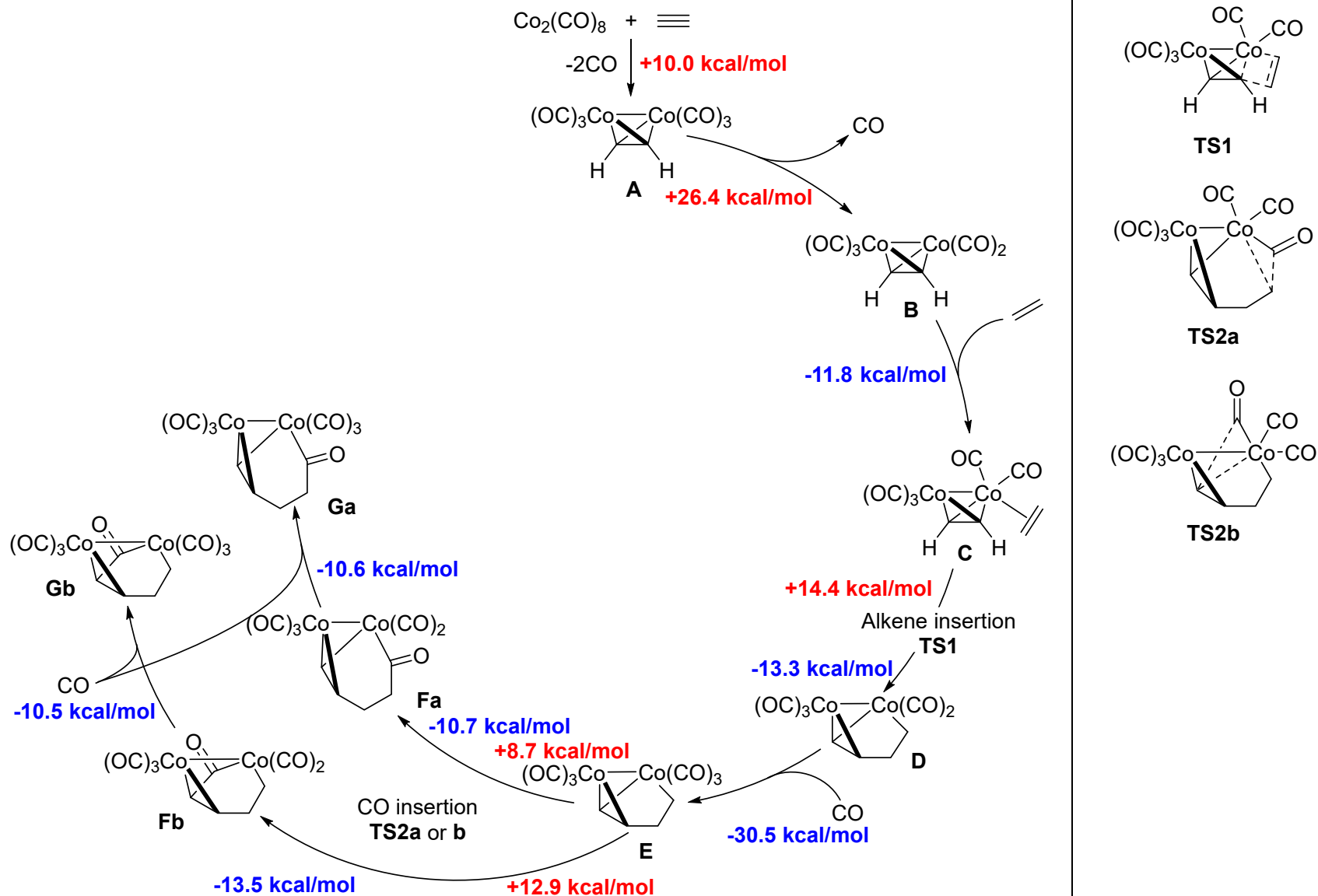
General Mechanism



General Mechanism

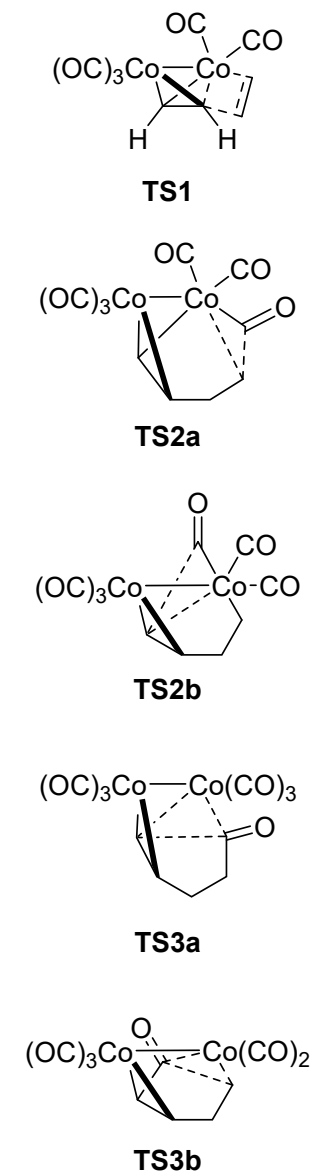
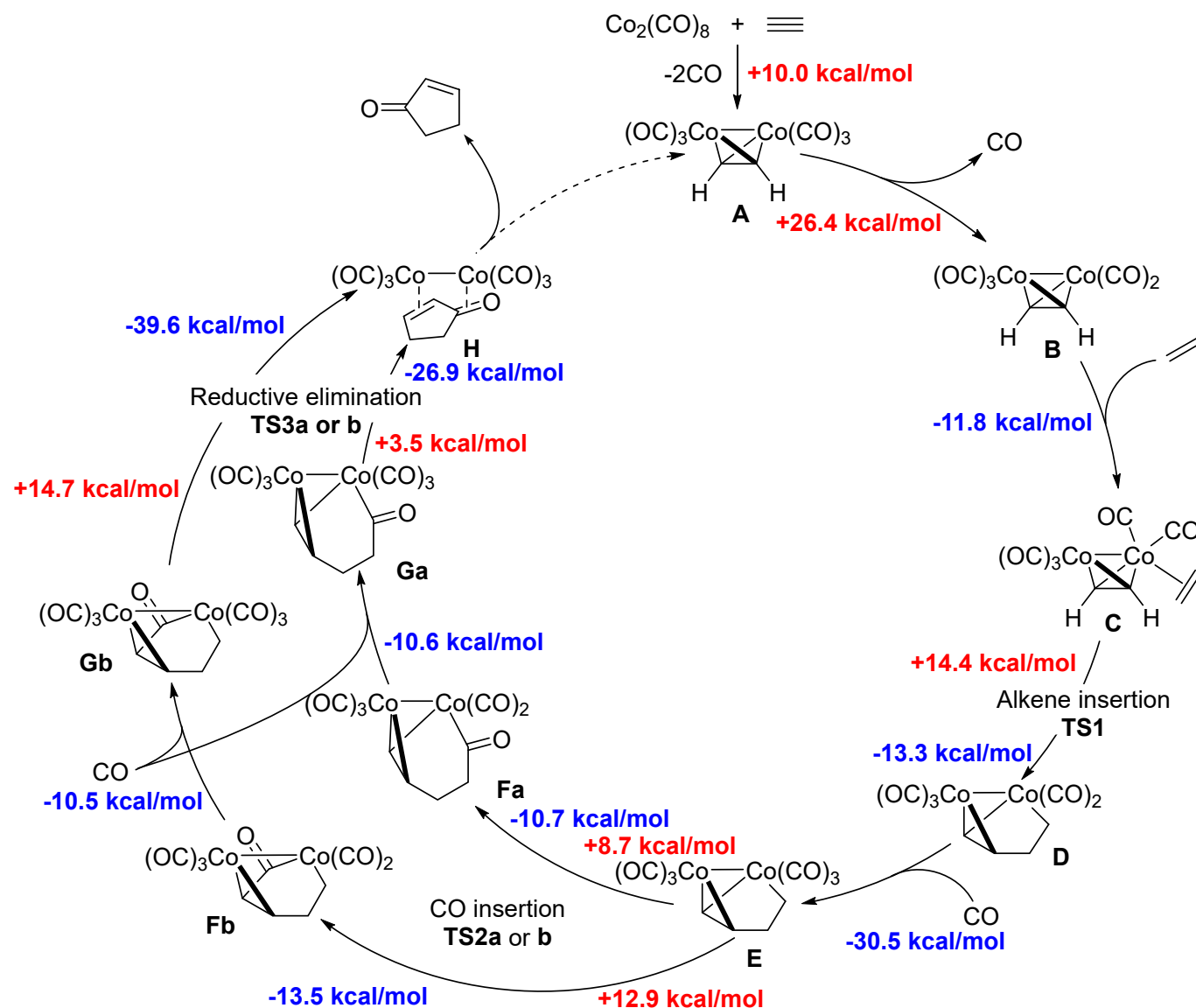


General Mechanism



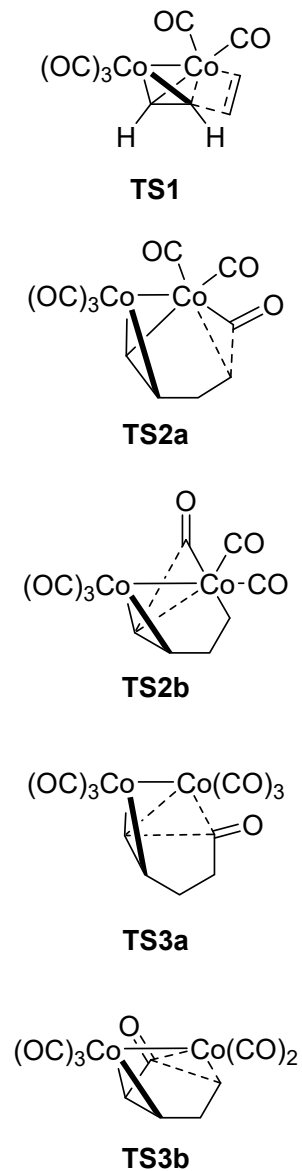
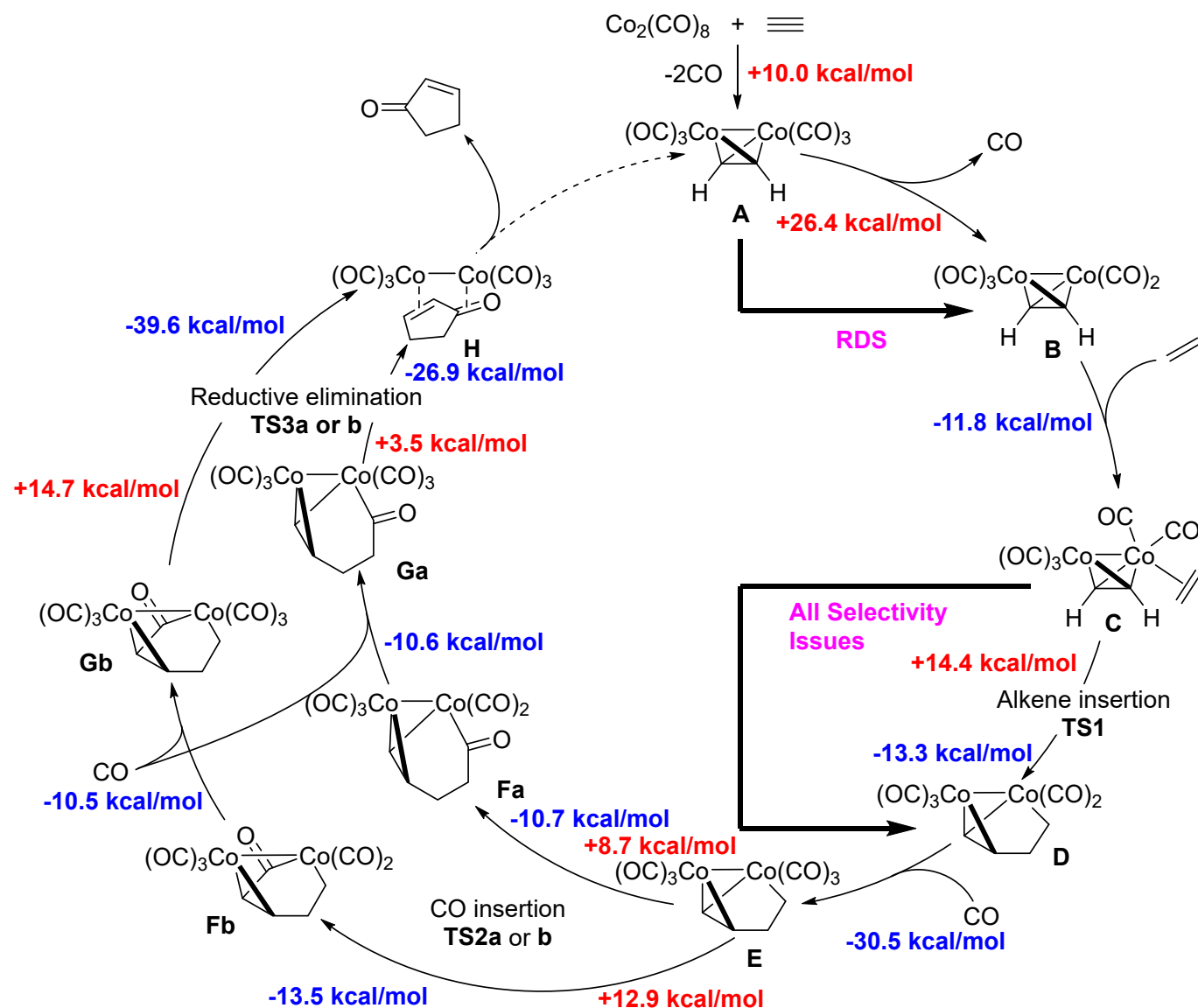
J. Am. Chem. Soc. **2001**, *123*, 1703-1708.

General Mechanism



J. Am. Chem. Soc. **2001**, *123*, 1703-1708.

General Mechanism



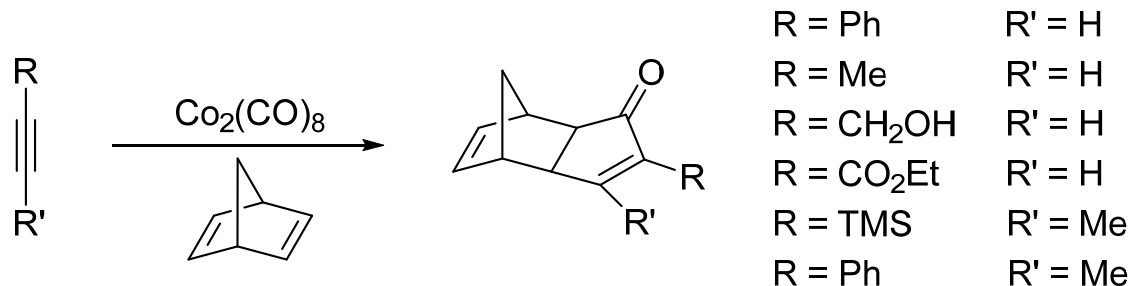
J. Am. Chem. Soc. **2001**, *123*, 1703-1708.

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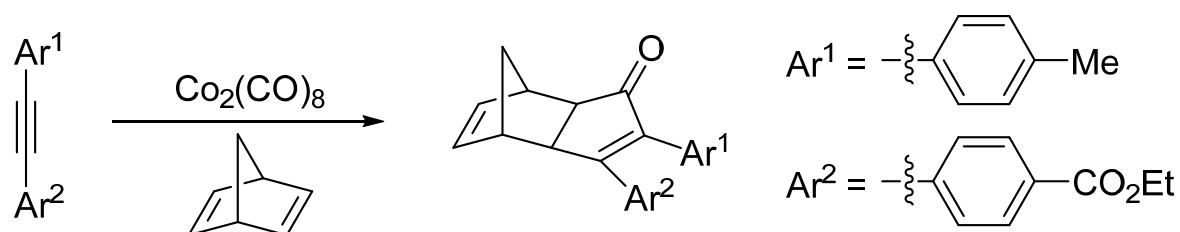
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Experimental Researches

- For sterically uneven alkyne: steric effect

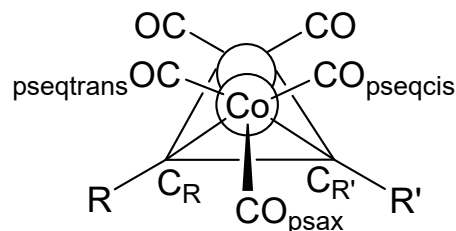


- For polarized alkyne: electronic effect



- Trans effect proposal: alkyne carbons have uneven trans effects on pseudoequatorial CO ligand and thus affect the regioselectivity.

Nature of (alkyne)Co₂(CO)₆: Structure



- 1a** R = H R' = Me
1b R = H R' = CO₂Me
1c R = Me R' = CO₂Me

• Lability

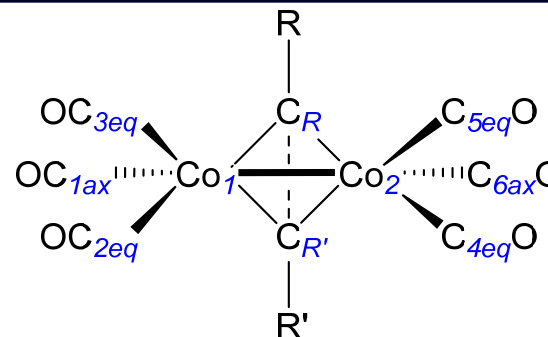


Why?

• Co-C_R bond type

Covalent?

Coordinate?



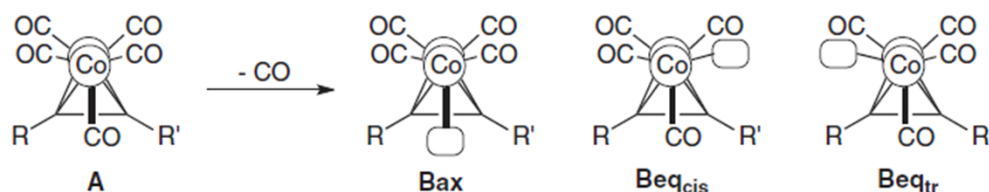
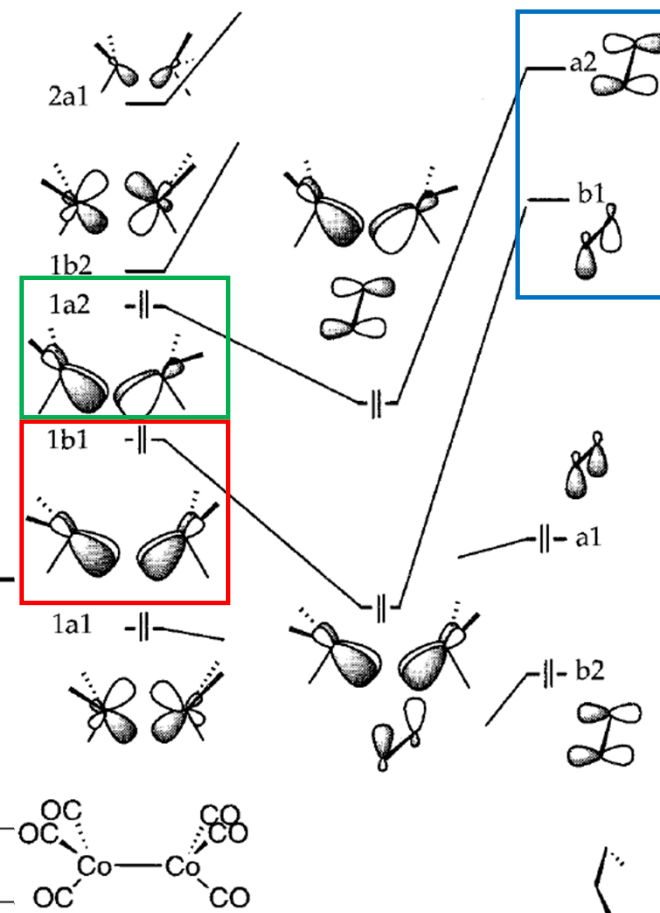
entry	X-Y	1a	1b	1c	X-ray ^{22b}
1	Co1-Co2	2.468	2.470	2.465	2.463(1)
2	Co1-C1ax	1.780	1.796	1.792	1.786(5)
3	Co1-C2eq	1.818	1.828	1.832	1.816(4)
4	Co1-C3eq	1.827	1.823	1.815	1.815(5)
5	Co2-C6ax	1.780	1.790	1.783	1.786(5)
6	Co2-C4eq	1.818	1.827	1.833	1.803(5)
7	Co2-C5eq	1.827	1.824	1.821	1.823(5)
8	C _R -C _{R'}	1.342	1.355	1.352	1.335(6)
9	Co1-C _R	1.965	1.944	1.962	1.994(4)
10	Co1-C _{R'}	1.979	1.956	1.966	2.003(4)
11	Co2-C _R	1.965	1.955	1.976	1.992(4)
12	Co2-C _{R'}	1.979	1.949	1.943	1.995(4)
13	R-C _R -C _{R'}	142.6	140.0	141.6	144.8(4)
14	R'-C _{R'} -C _{R'}	143.8	138.8	138.6	144.5(4)

[1] *J. Am. Chem. Soc.* **2001**, *123*, 5396-5400.

[2] *J. Am. Chem. Soc.* **1976**, *98*, 1774-1779.

Nature of (alkyne)Co₂(CO)₆: Bonding

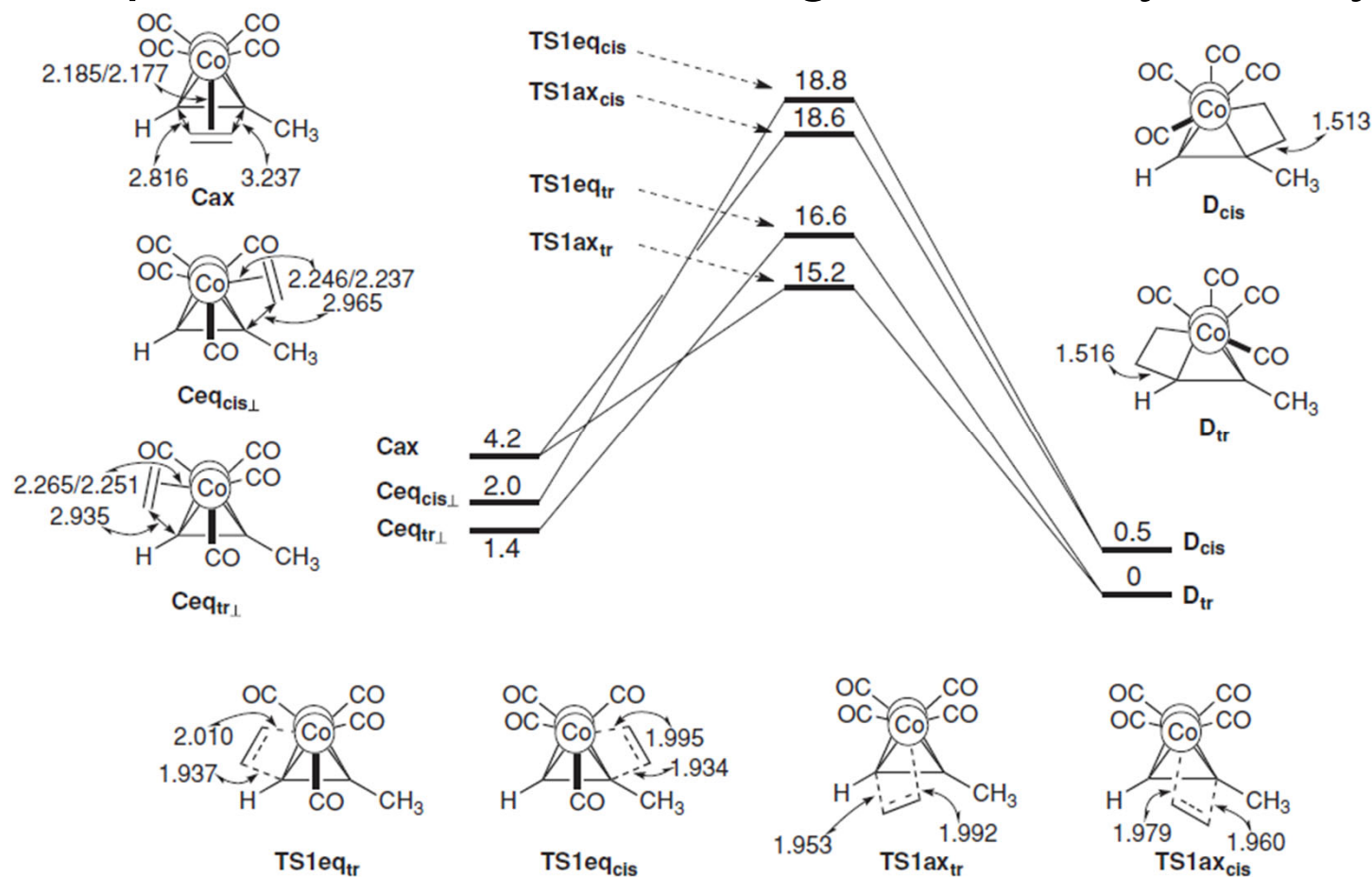
- Main orbital interaction:
From **bonding** & **nonbonding**
combinations of $d_{x^2-y^2}$ to π^* of alkyne
- CO lability difference:
Trans effect



Starting complex	R	R'	q(C _R)	q(C _{R'})	Δq	ΔE _{A→B}		
						Bax	Beq _{cis}	Beq _{tr}
A ₁	H	CH ₃	-0.31	-0.18	-0.13	- ^a	- ^b	24.2
A ₂	H	CO ₂ CH ₃	-0.36	-0.33	-0.03	37.1	26.4	26.7
A ₃	CH ₃	CO ₂ CH ₃	-0.14	-0.34	+0.20	37.9	24.5	- ^c

Trans Effect Proposal

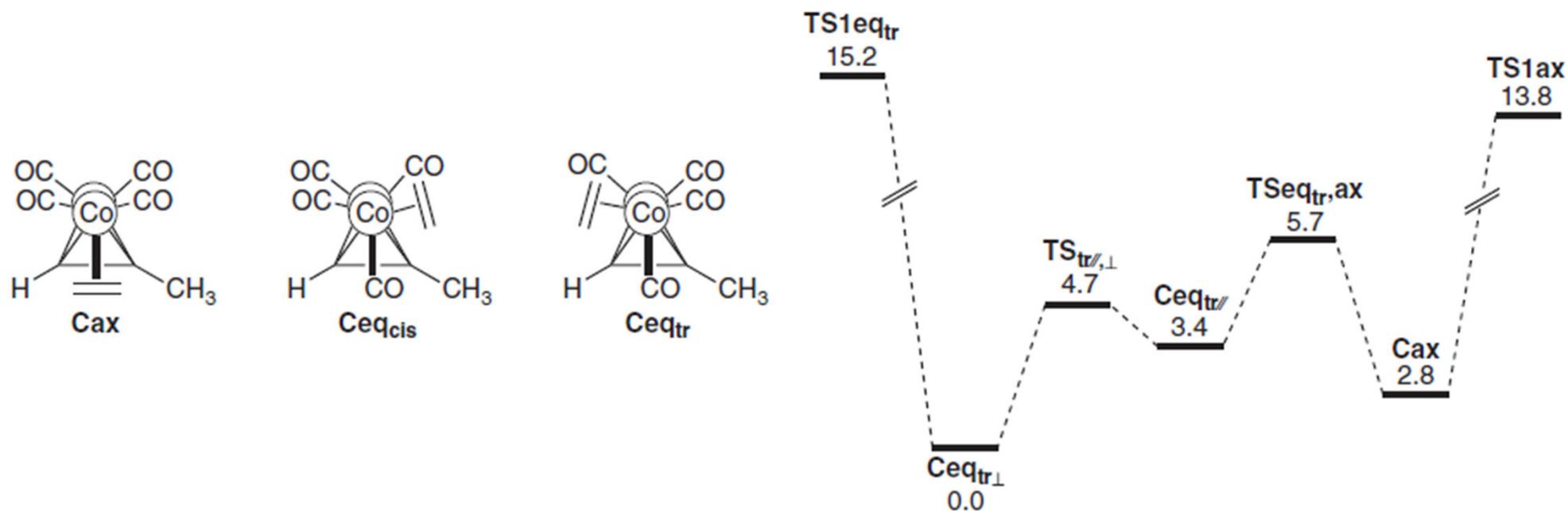
- CO vacant position controls the regiochemistry of alkyne.



- But what if (alkyne)(alkene) $\text{Co}_2(\text{CO})_5$ undergoes **isomerization** faster than alkene insertion?

Mechanism Containing Isomerization

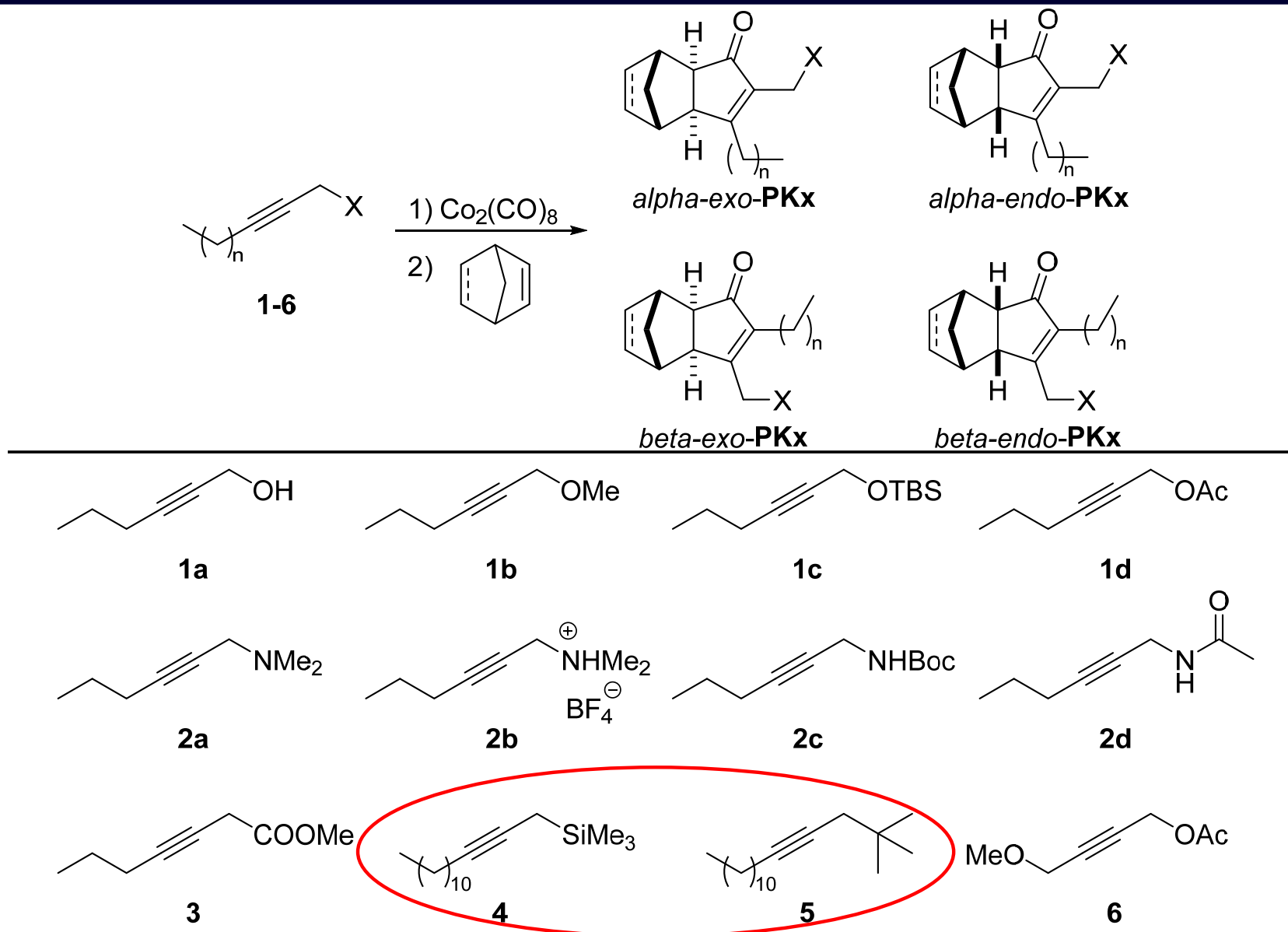
- Curtin-Hammett principal is fit for the system.



Factors that affect the absolute energy of TS:

- Steric
- Electronic (How?)

Electronic Effect



Electronic Effect

- The computed NBO charge differences (C2–C3) and (C1–C4) both correlate well with the results.

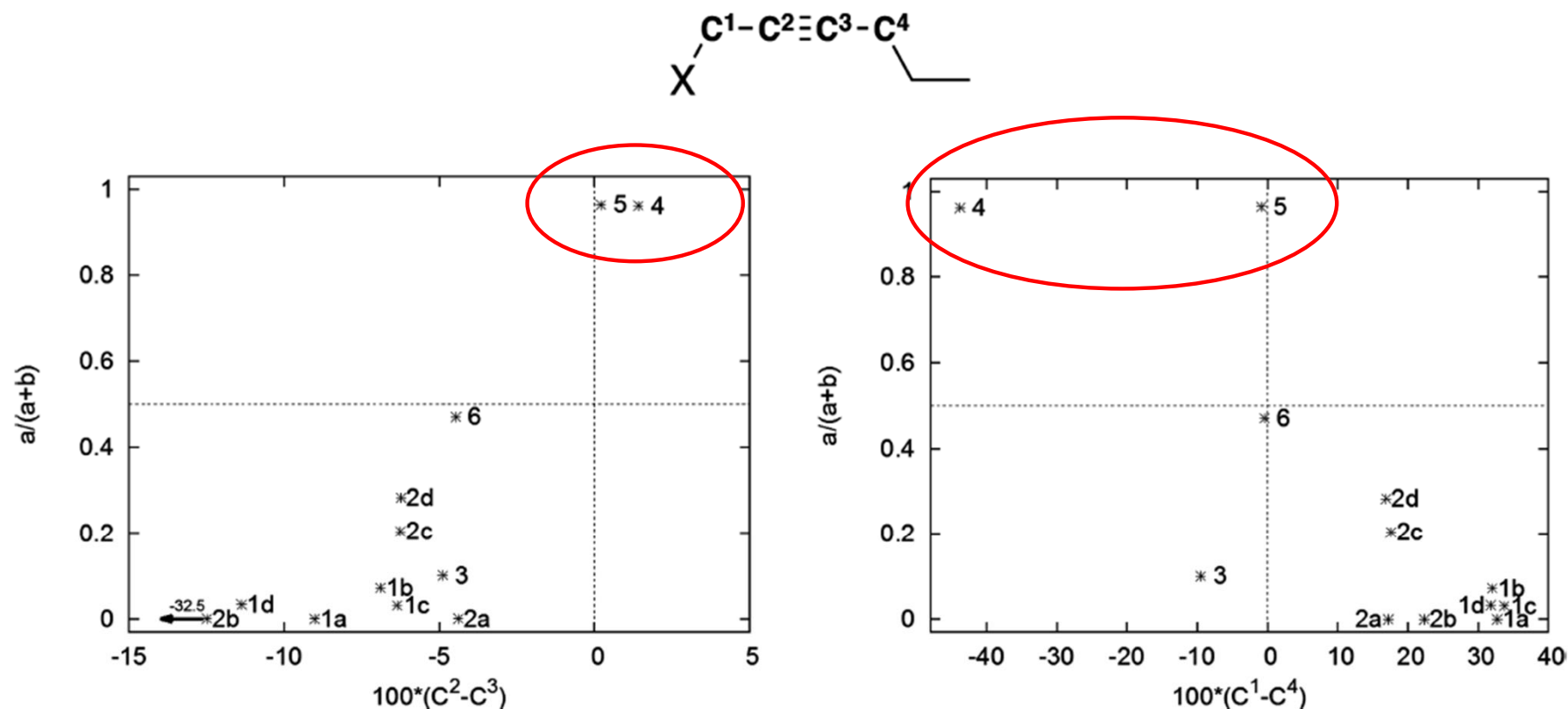
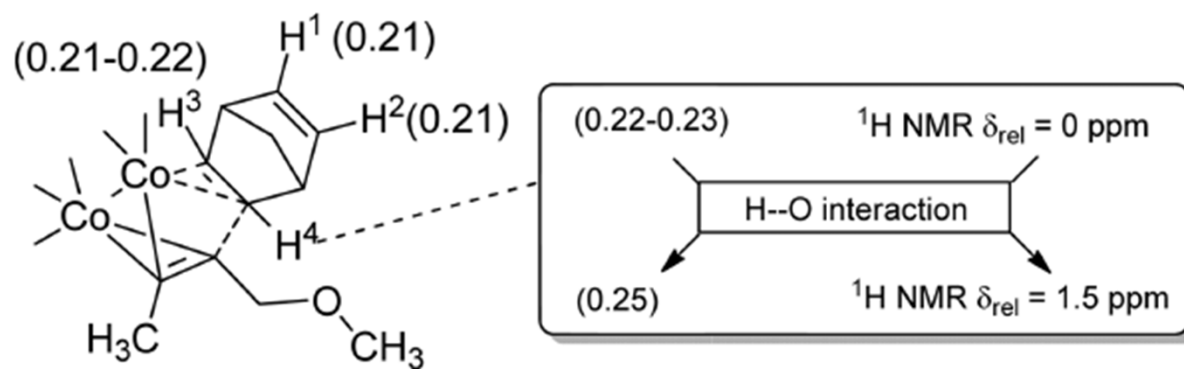
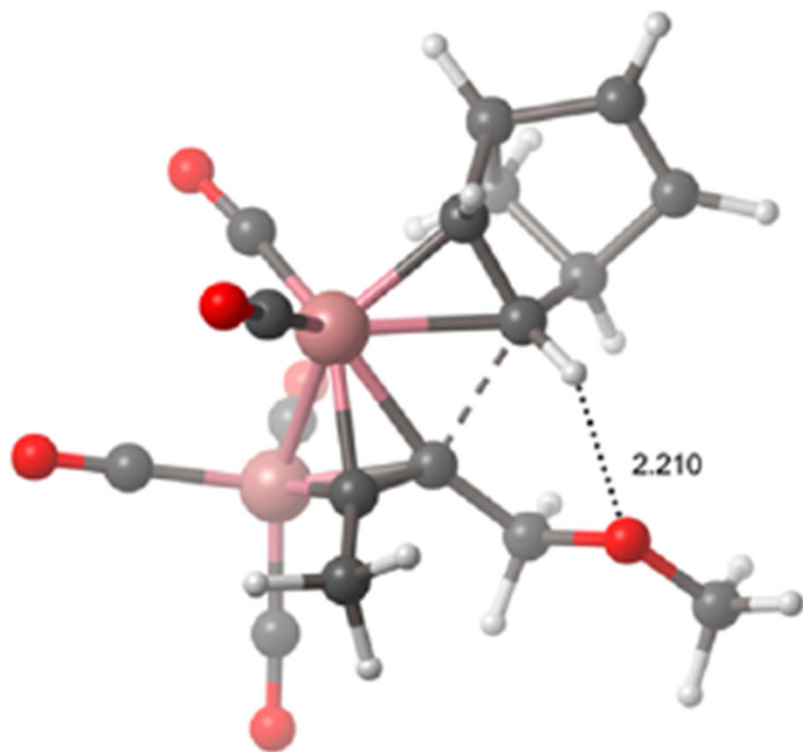
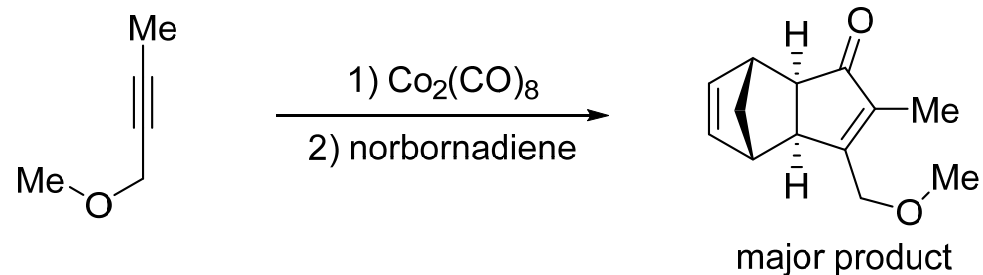
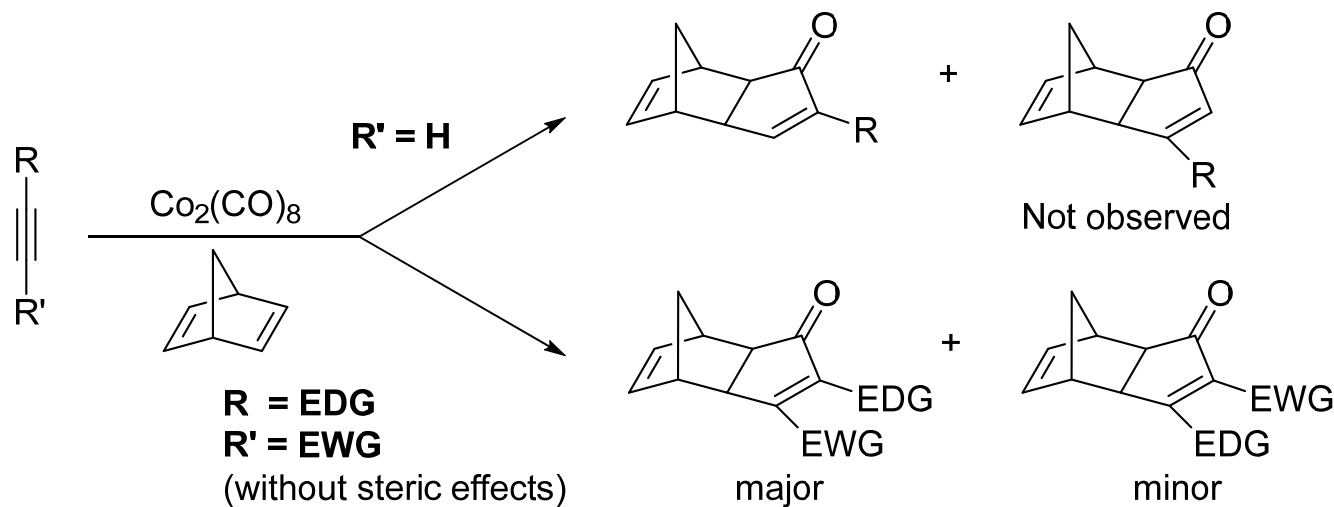


Figure 6. Plot of the NBO charge differences (C^2-C^3/C^1-C^4) of alkynyl carbons (TPSS-D3/def2-TZVPP) versus the regiochemical outcome of the PKR ($\alpha/\alpha+\beta$). Both *endo* and *exo* contribution are taken into account for α/β ratio.

Weak Interactions



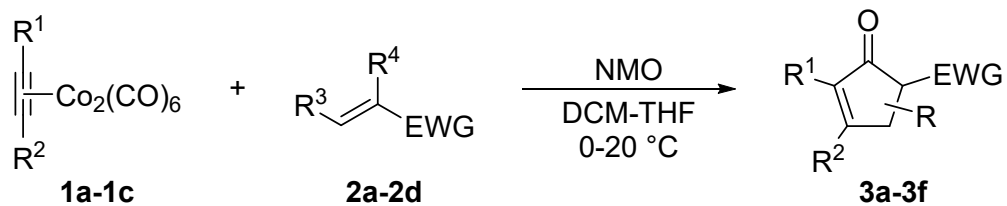
Conclusion



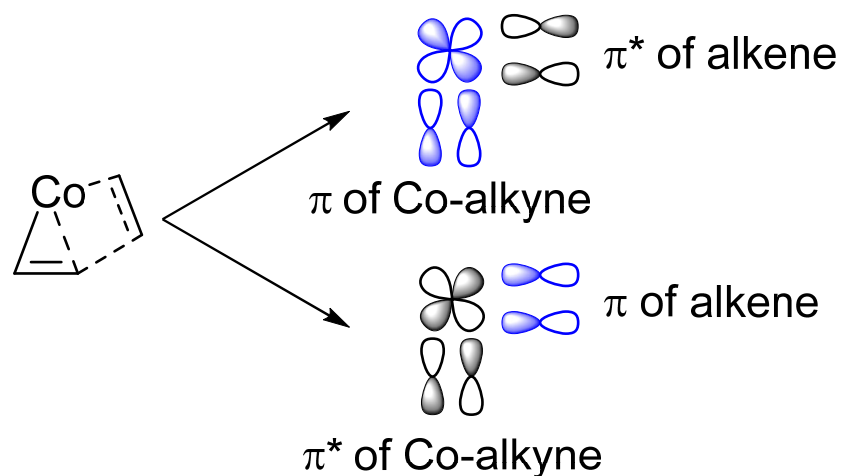
The energy differences between different TSs are usually no more than 3 kcal/mol.

Therefore, any small changes might alter the regioselectivity.

Regioselectivity for Alkene



- Polarized alkene:
- Electronic effect dominant
- Steric effect

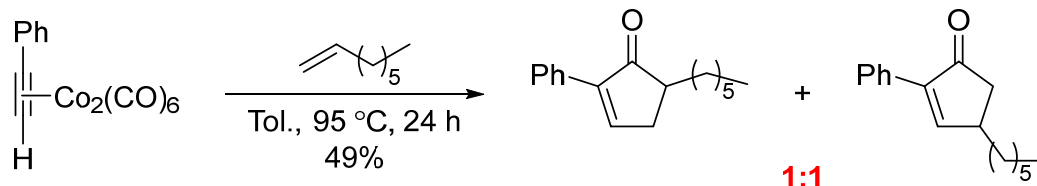


Tetrahedron Lett. **1999**, *40*, 5503-5506.

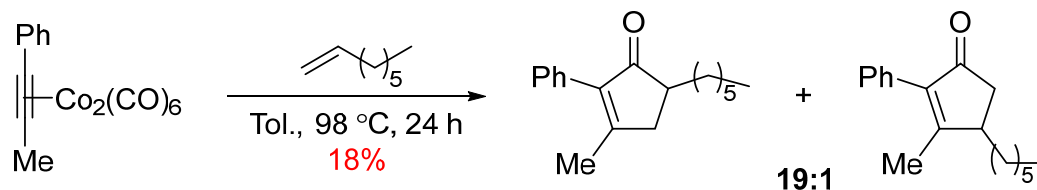
Entry	Alkyne	Alkene	Product	Yield(%)
1		 2a	 3a	59
2	 1a	 2b	NR	
3		 2d	 3b	71
4		 2a	 3c	47
5	 1b	 2c	 3d	8
6		 2d	 3e	49
7	 1c	 2a	 3f	41

Steric Control: Two Extremes

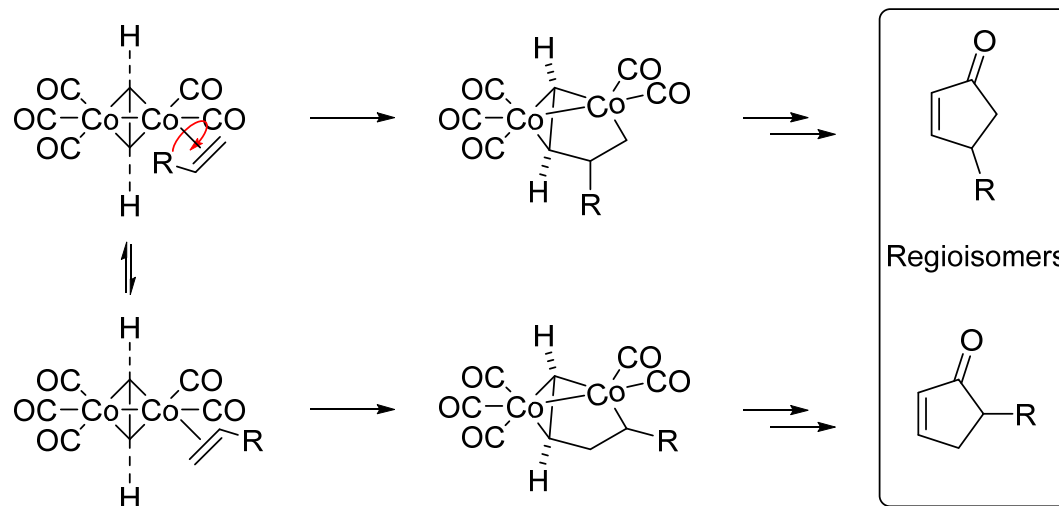
- Weak steric effect: poor selectivity



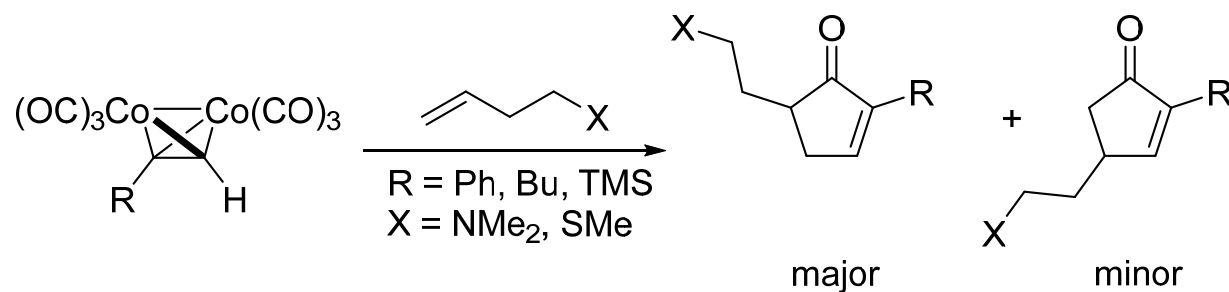
- Strong steric effect: poor yield



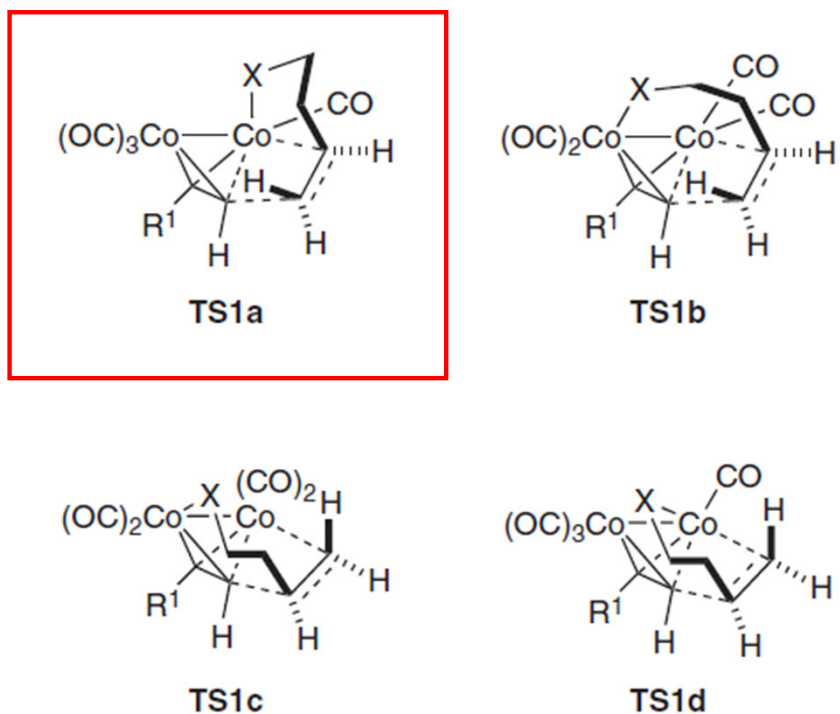
Extremely low barrier of **alkene rotation** makes it hard to control the regioselectivity of nonpolar alkene.



Chelating Group Strategy



Most favored



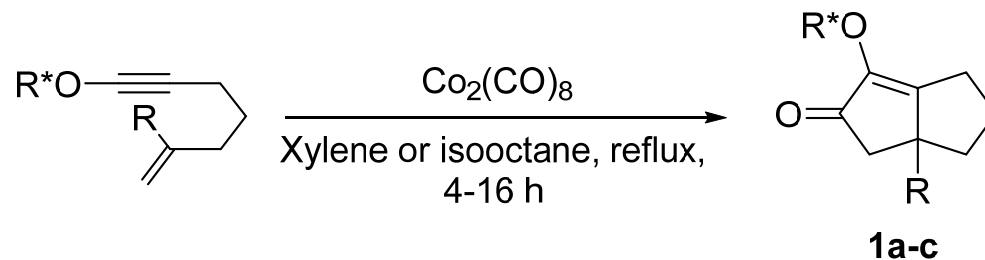
[1] *J. Am. Chem. Soc.* **1988**, *110*, 968-970.

[2] *J. Org. Chem.* **1992**, *57*, 5106-5115.

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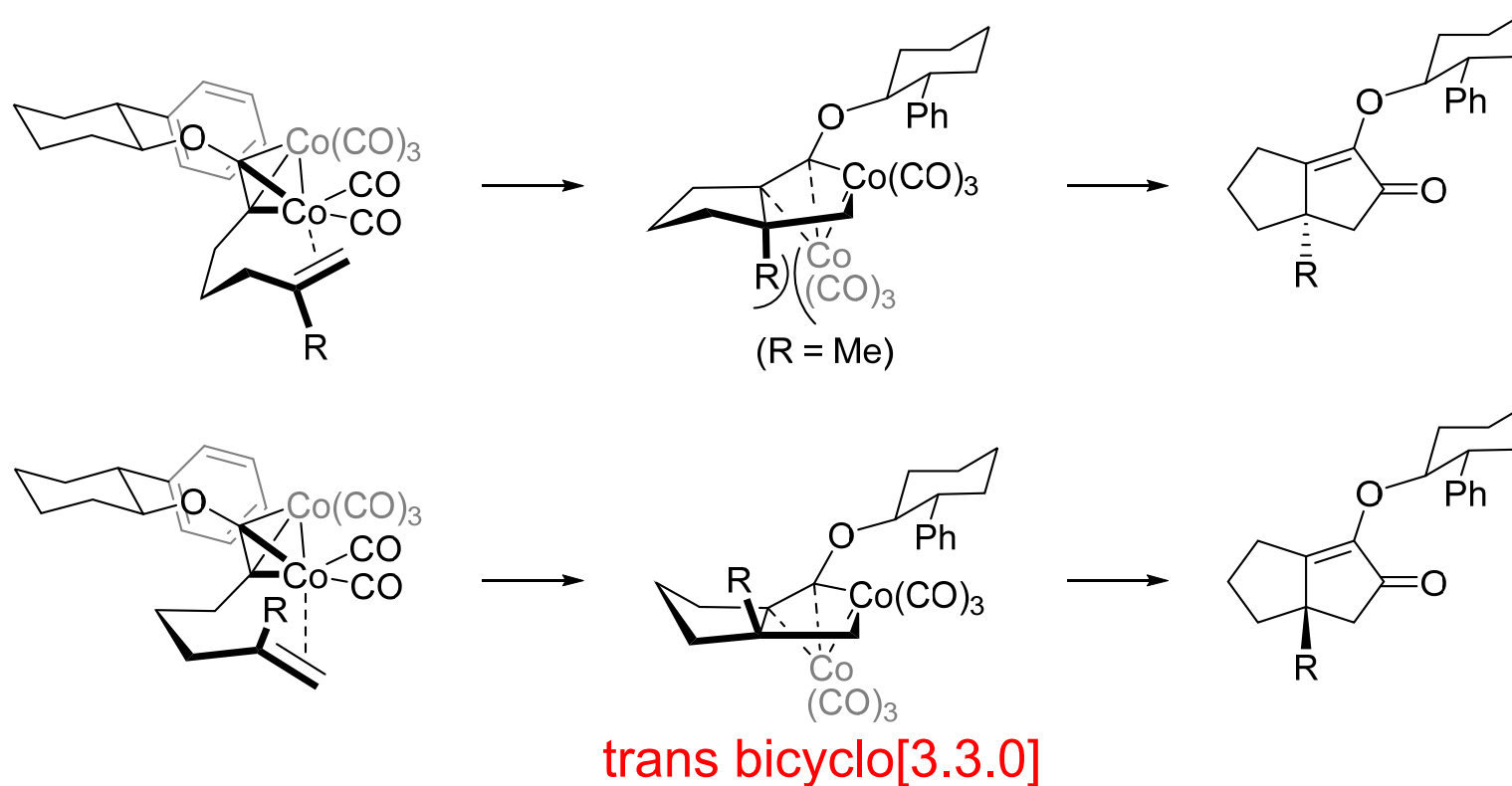
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Chiral Auxiliaries on Alkyne



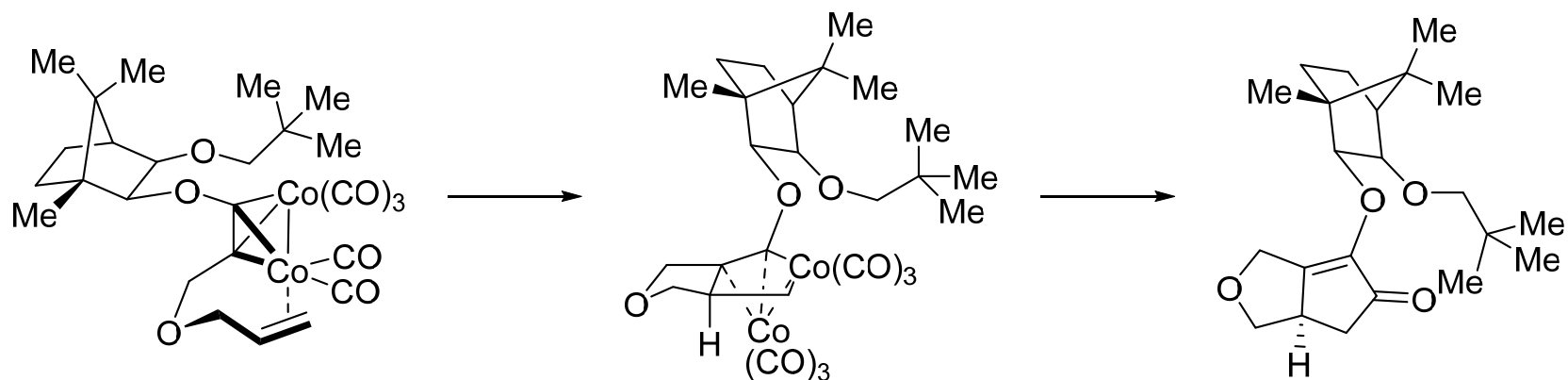
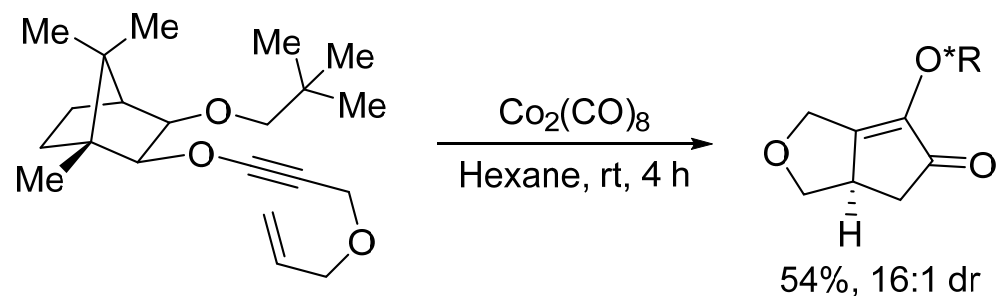
Product	R*O-	R	Yield(%)	Dr
1a		H	30	1.1:1
1b		H	38	3.2:1
1c		Me	28	1.2:1

Conformational Control



What if phenyl is replaced with a larger substituent?

Improvement

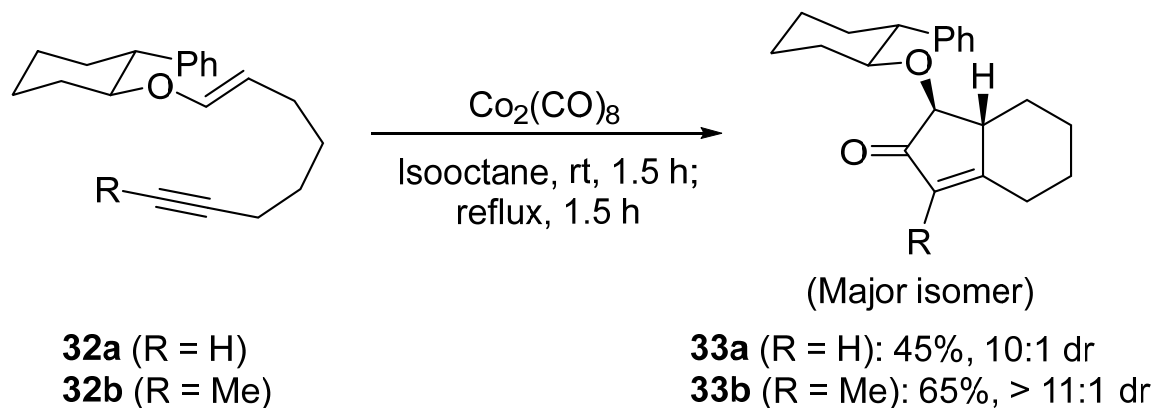


- More rigid bicyclo [2.2.1] skeleton
- Tert-butyl group closer to Co

[1] *J. Org. Chem.* **1987**, 52, 2919-2922.

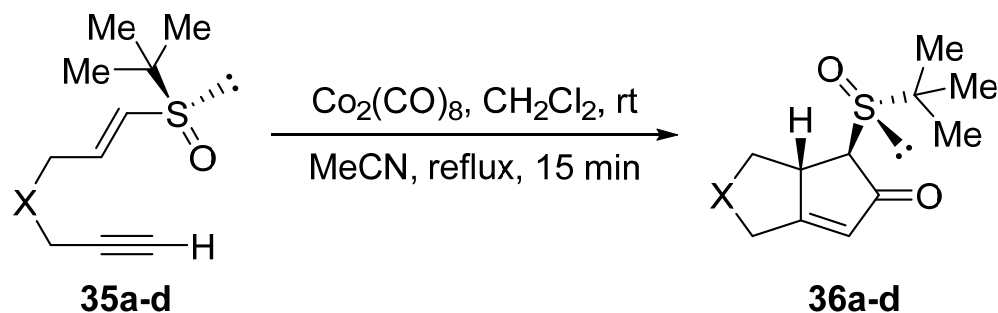
[2] *Tetrahedron Lett.* **1990**, 31, 7505-7508.

Chiral Auxiliaries on Alkene



- A better dr value was obtained because more direct effect on alkene from phenyl .

Chiral Auxiliaries on Alkene

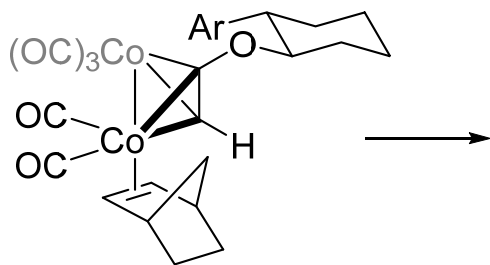
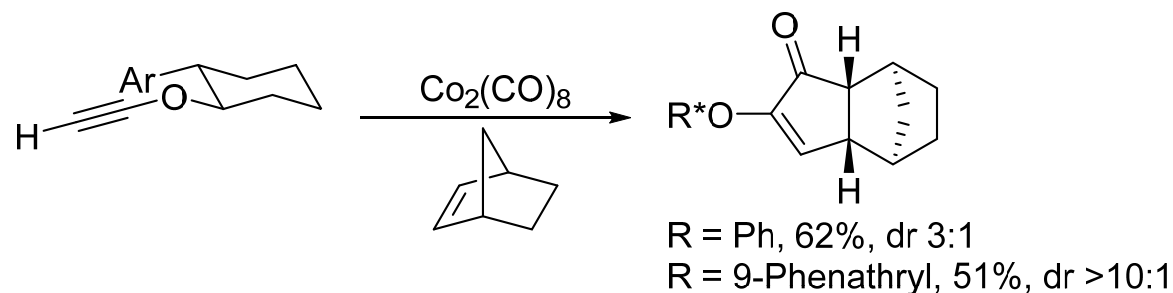


Enyne	X	Product	Yield(%)	Dr
35a	CH_2	36a	50	>44:1
35b	CMe_2	36b	65	>44:1
35c	$\text{C}(\text{CO}_2\text{Et})_2$	36c	60	>44:1
35d	$\text{N}(\text{CO}_2^t\text{Bu})$	36d	60	>44:1

- A dihedral angle $\text{C}=\text{C}-\text{S}-\text{O}$ of *ca.* 0° in the most stable conformation.

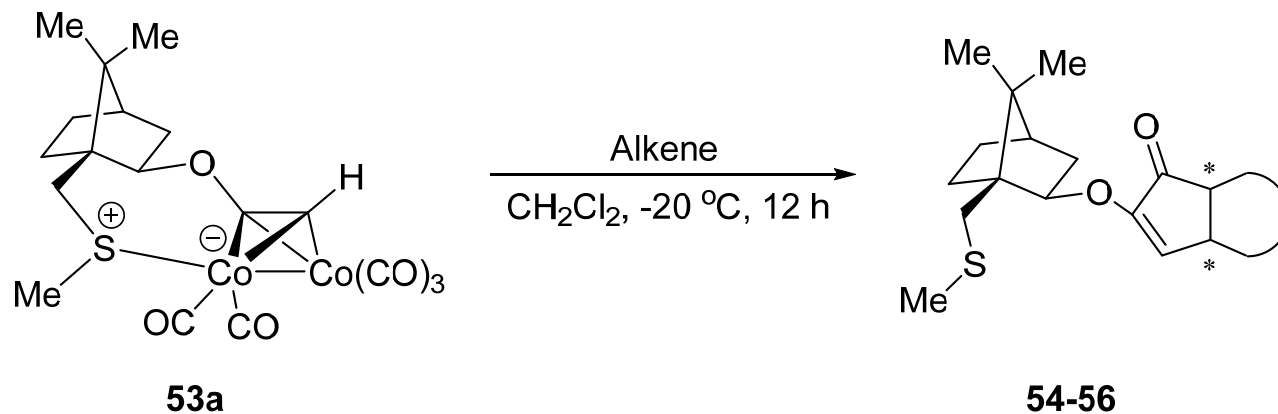
Intermolecular Diastereoselective PKR

- Chiral auxiliaries strategy can still be adopted.



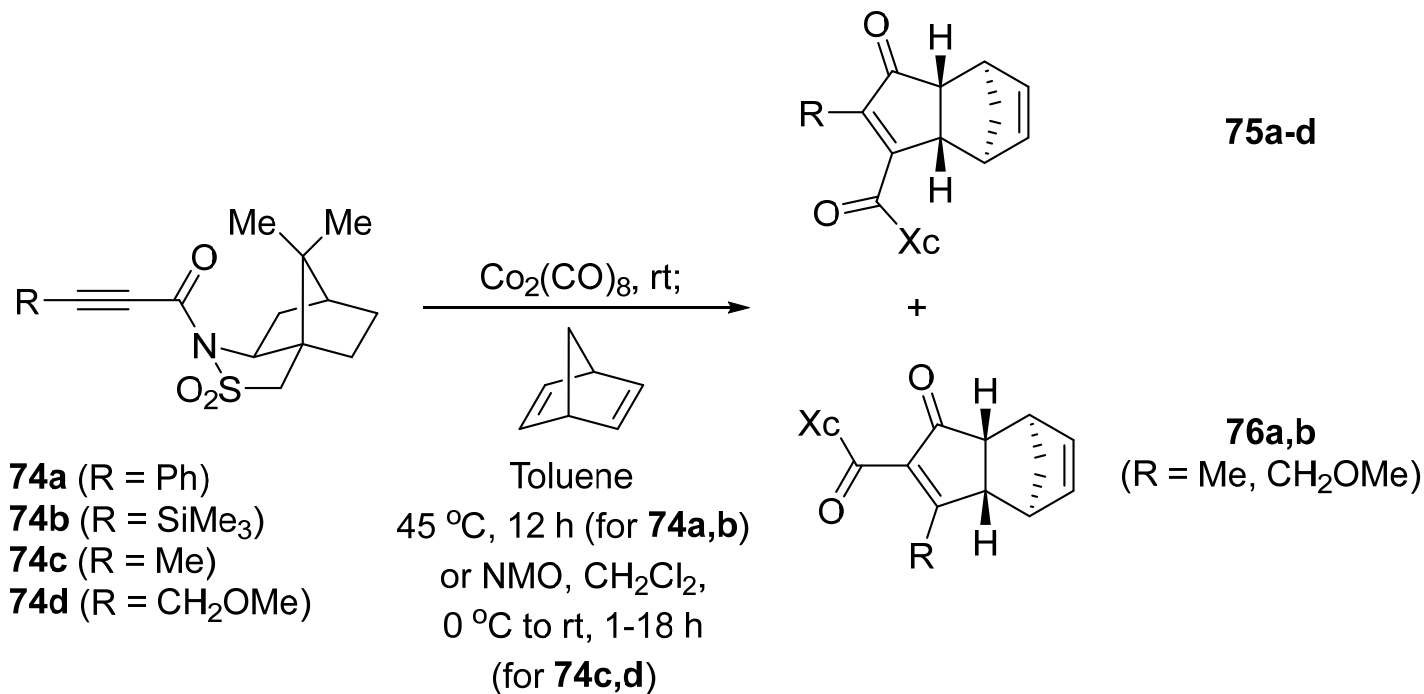
Tetrahedron Lett. **1994**, 35, 575-578.

Chelating Group Strategy



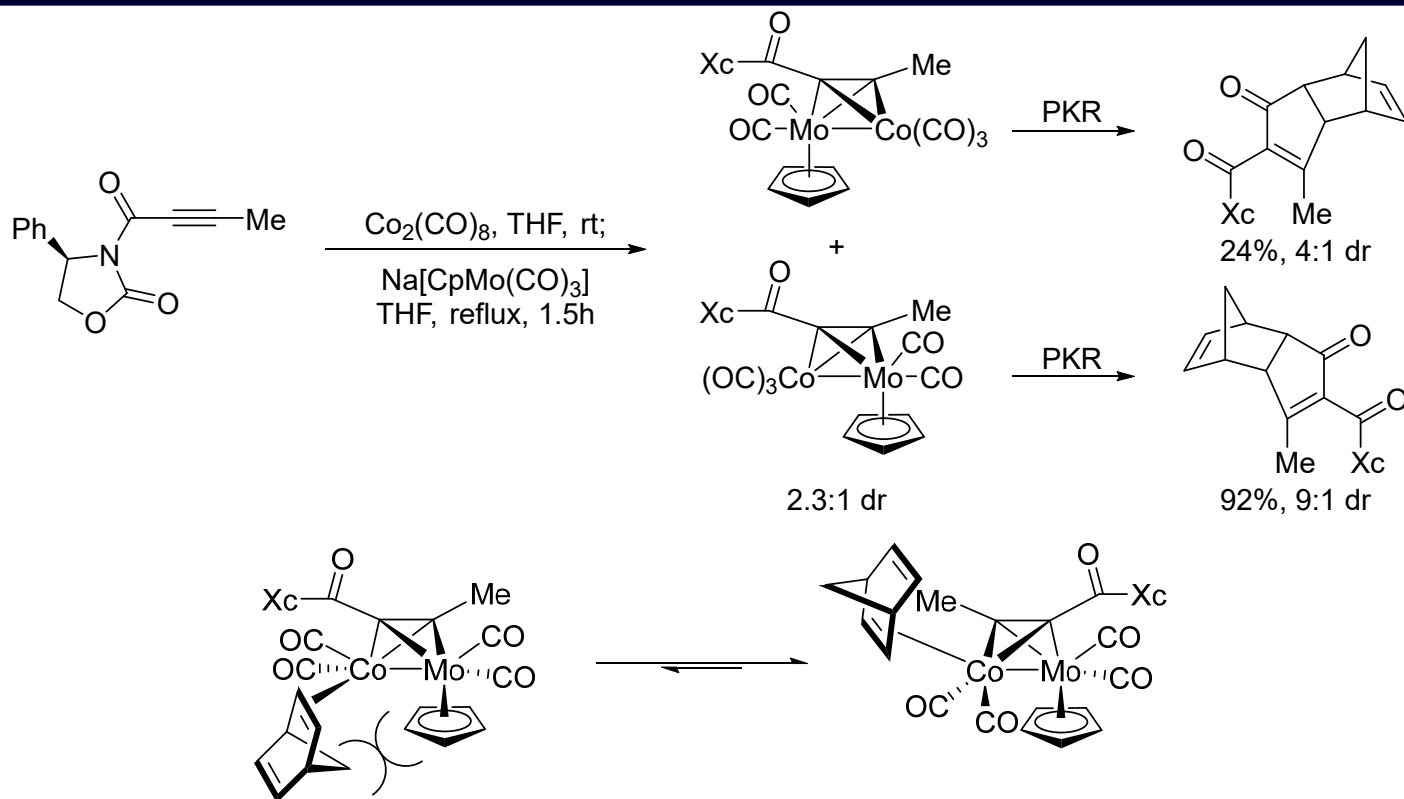
Alkene	Product	Yield(%)	Dr
	54	77	12:1
	55	82	24:1
	56	91	13:1

Chelating Group Strategy



Alkyne	R	Product	Yield(%)	Dr
74a	Ph	75a	93	>800:1
74b	TMS	75b	78	>800:1
74c	Me	75c	55	318:1
		76a	24	1.7:1
74d	CH ₂ OMe	75d	52	>800:1
		76b	23	1.1:1

Heterobimetallic Strategy



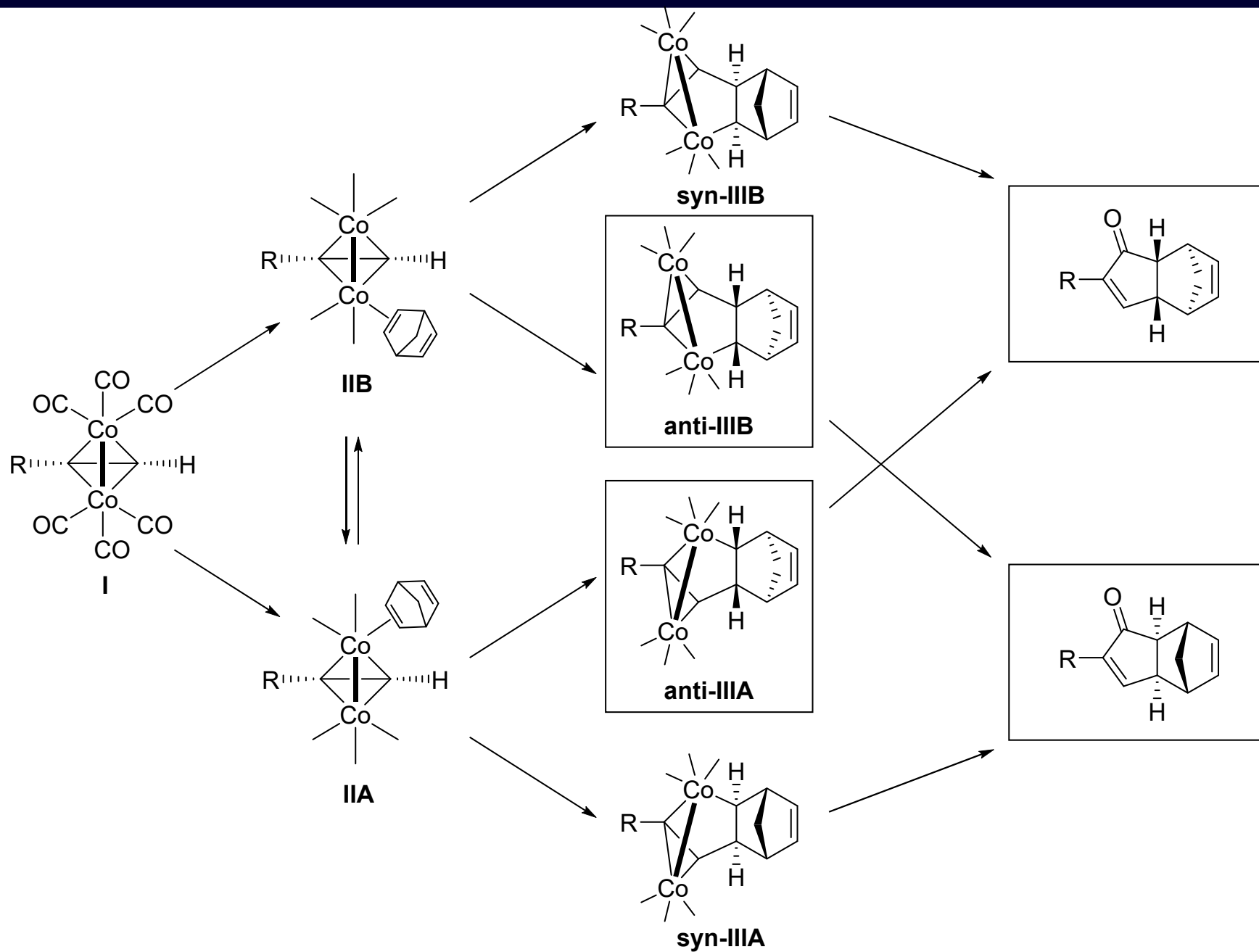
Conclusion

- Make two cobalt atoms different.
- Avoid alkene rotation.

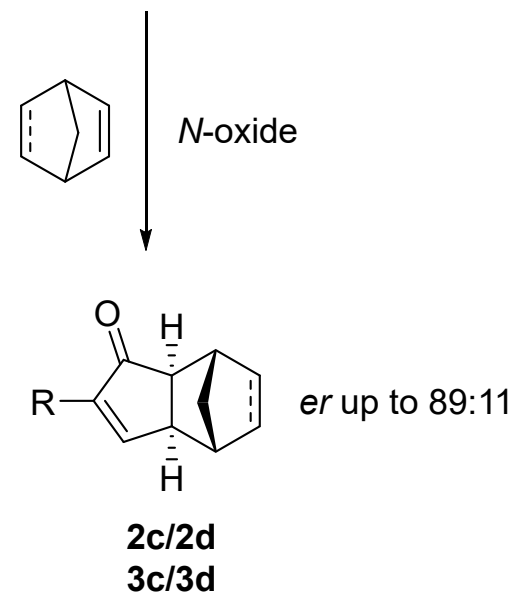
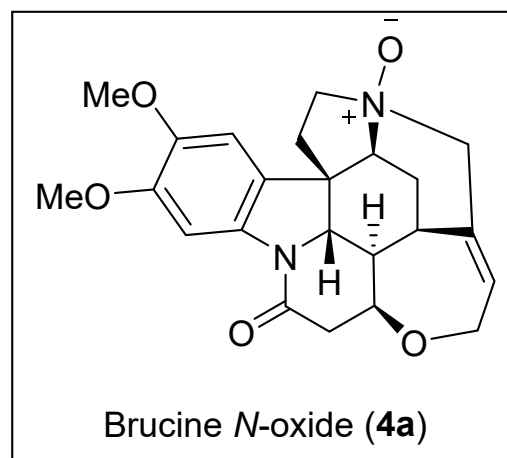
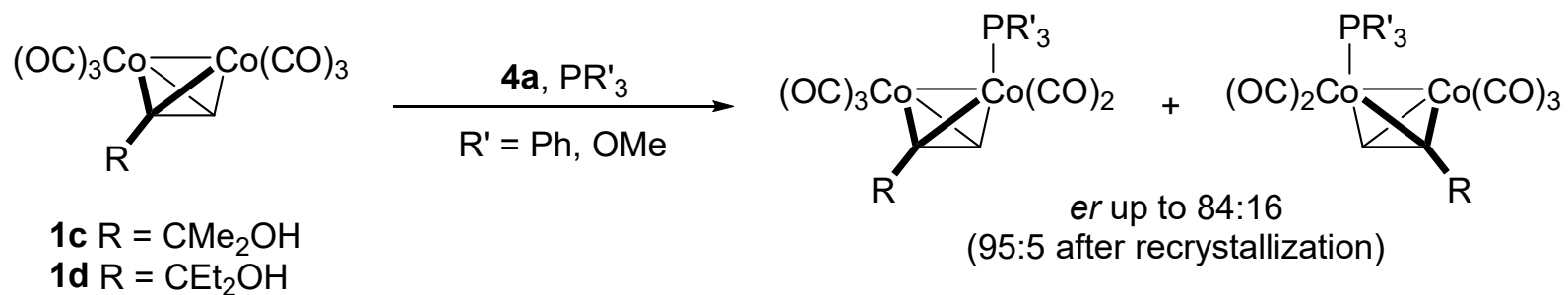
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From Nonchiral to Chiral

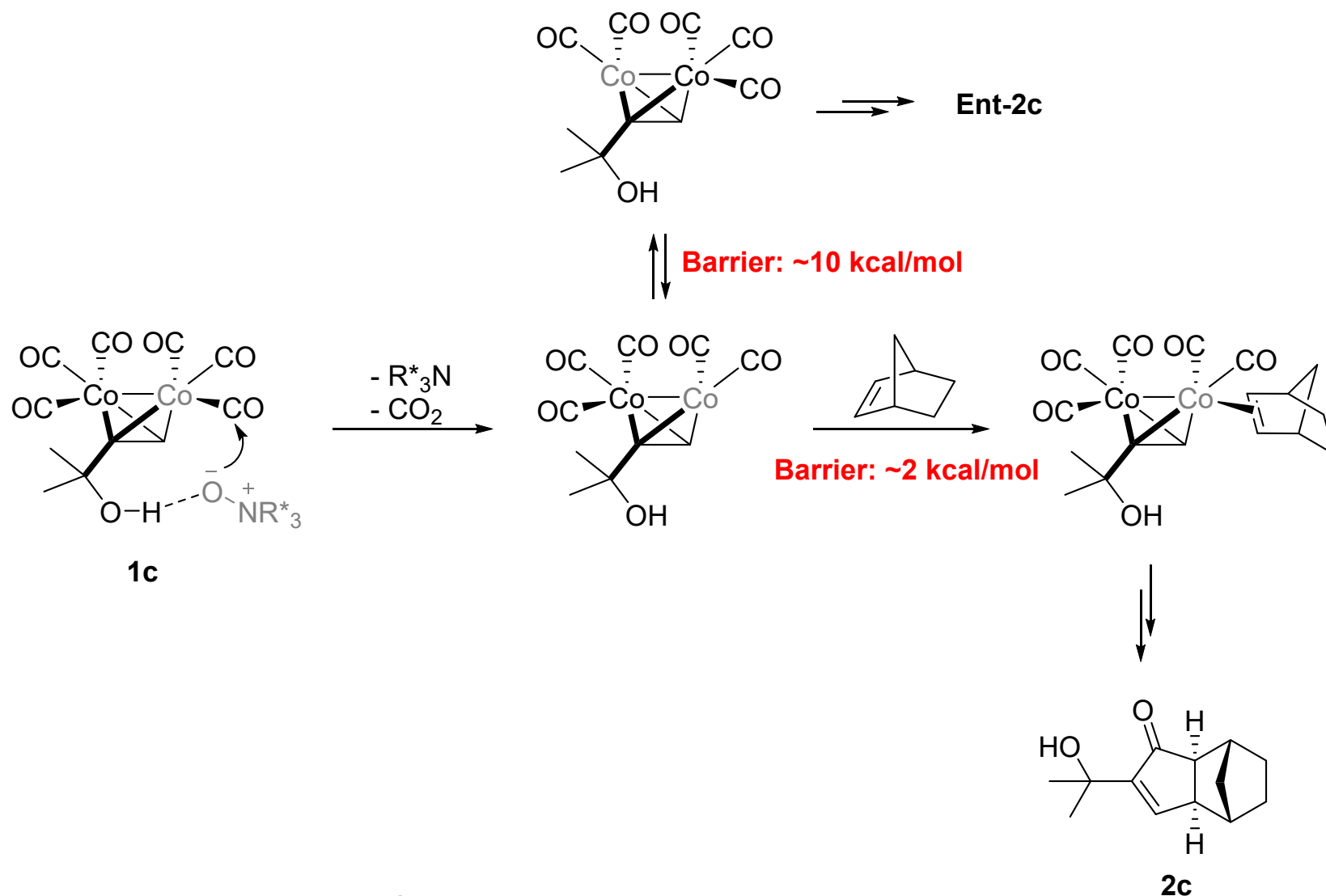


Chiral *N*-Oxide Strategy

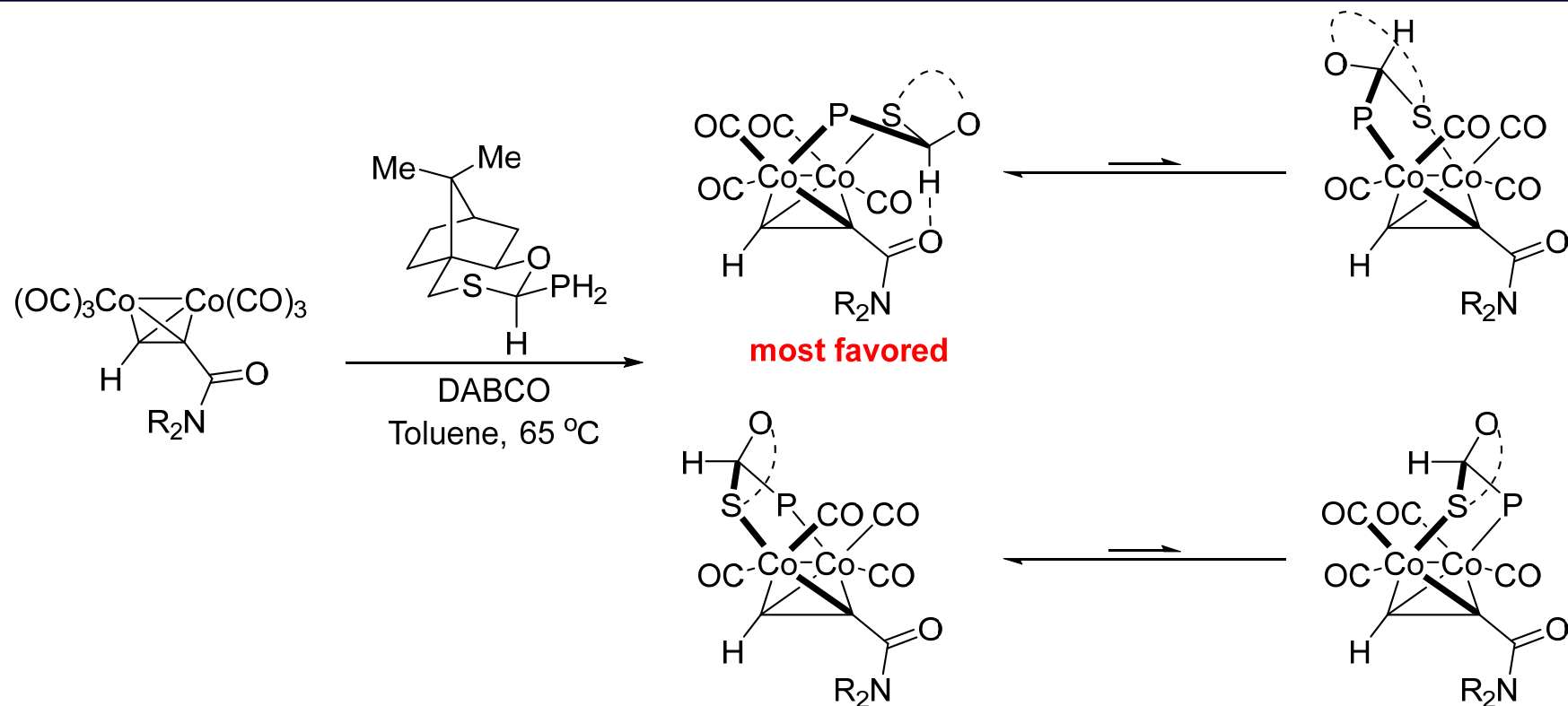


Chiral *N*-Oxide Strategy

- Hydroxyl as directing group is essential.



Chiral Bidentate (P, S) Ligand



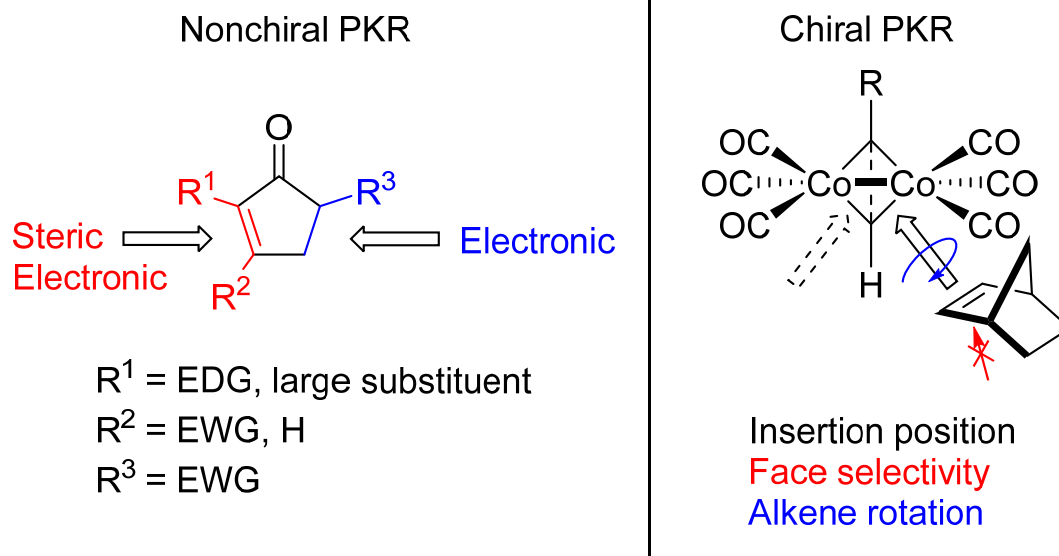
- S-Co bond cleavage directs alkene to certain place.
- Alkene insertion is restricted to particular position.

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Summary

- All selectivity issues are determined in early steps in PKR.



- Conformational analysis is key to selectivity prediction!