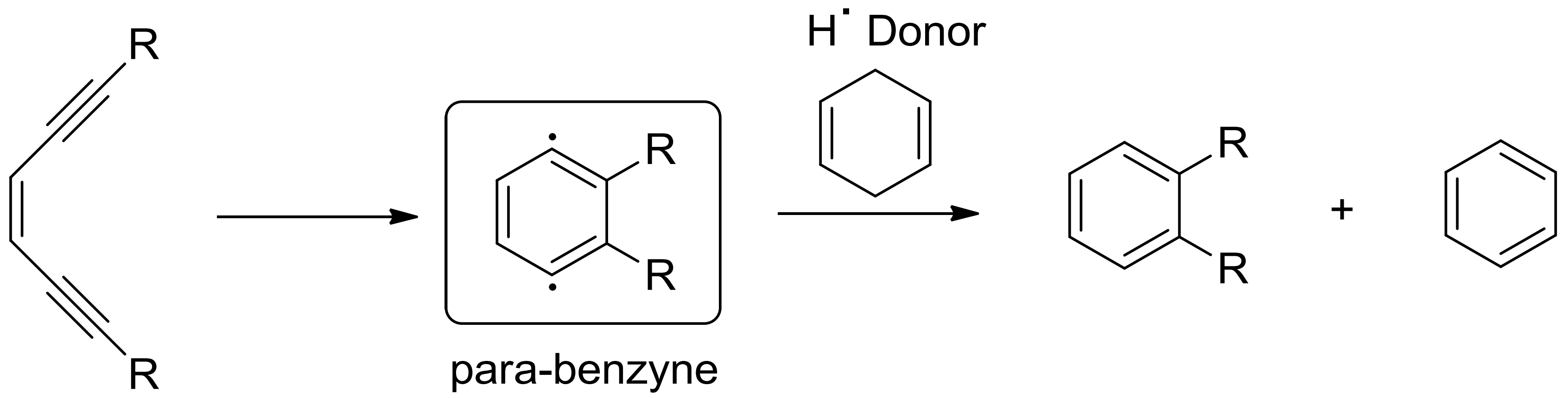
Enediyne Chemistry

Wed. Night Group Meeting
12/5/2012
Chris Johnson

Overview

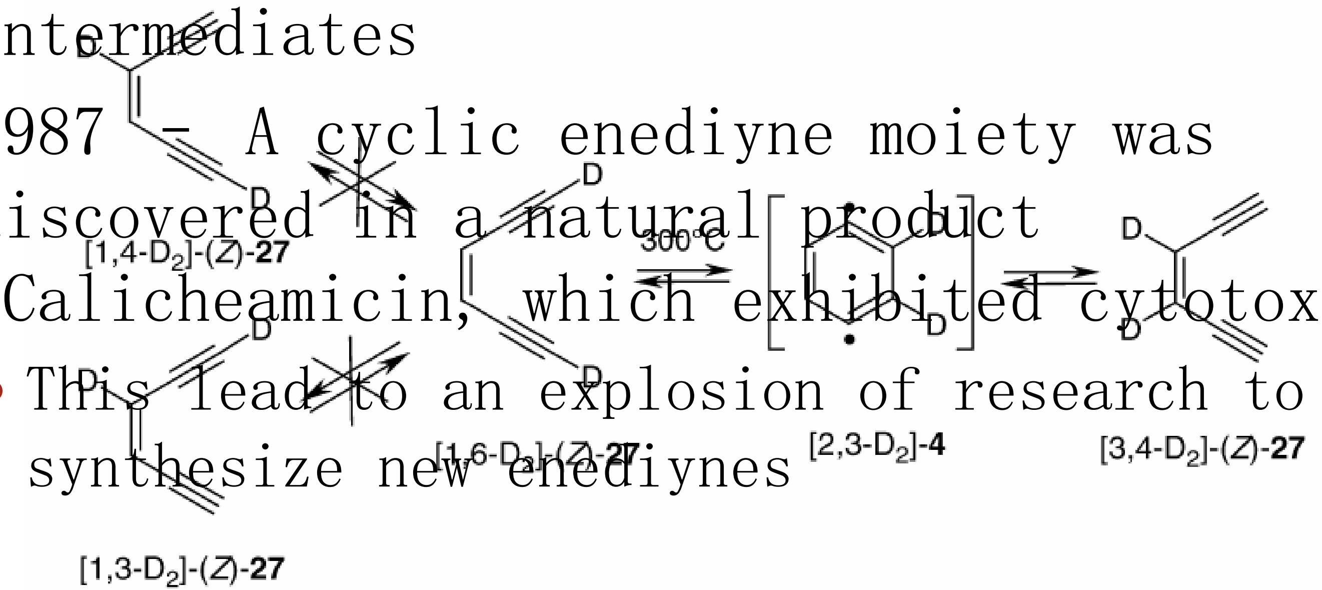
1. Bergman Cyclization (BC)
   - History
   - Thermal BC
   - Natural Products
   - Transition Metal Mediated BC
   - Photochemical BC
   - BC in materials
2. Cascade Reactions
   - Au
   - Ru
   - Pt
   - Pd

Bergman Cyclization



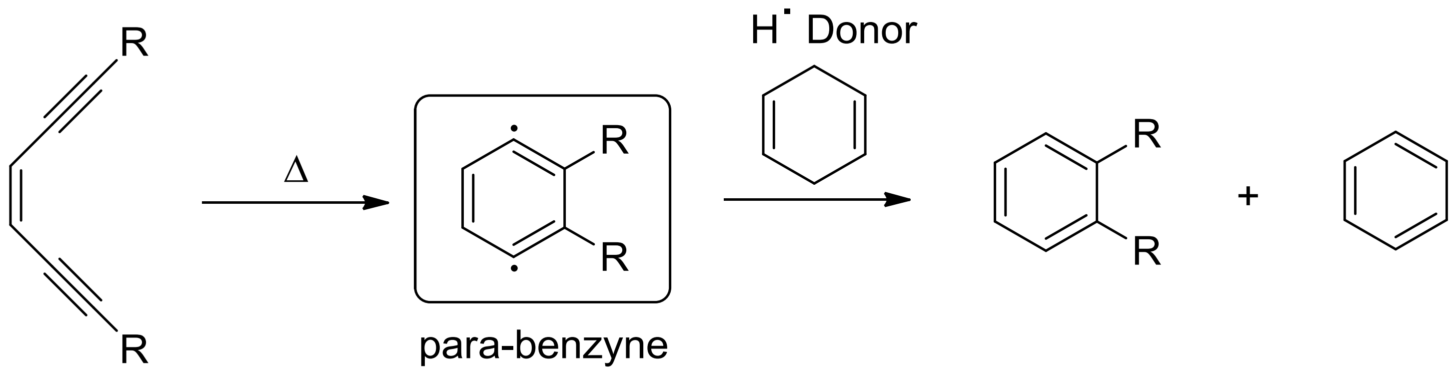
History

- 1971 – Masamune showed conversion of a benzannulated enediyne to anthracene
- 1972 – Bergman provided the first evidence of a 1,4-didehydrobenzene diradical intermediates
- 1987 – A cyclic enediyne moiety was discovered in a natural product ,Calicheamicin, which exhibited cytotoxicity
  - This lead to an explosion of research to synthesize new enediynes



Masamune, S. *Chem. Commun.* **1971**, 1516.; Bergman, R. G. *J. Am. Chem. Soc.* **1972**, 94, 660.;
D. B. Borders, *J. Am. Chem. Soc.* **1987**, 109, 3466.

Thermal BC



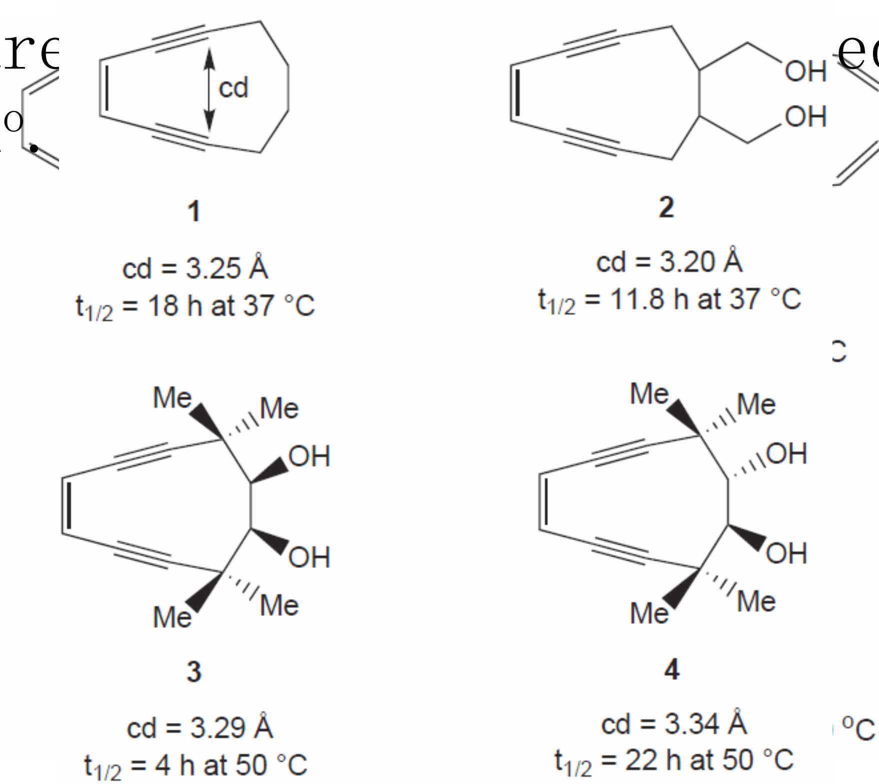
- BCwas first observed only at very high temp. (R = H; $t_{1/2}$ = 30sec @ 200 °C)
- Once natural products were discovered which cycloaromatized at physiological temperatures people began investigating geometic factors which affect BC.

Zaleski, Z. M. *Synlett* **2004**, 3, 393.

Geometric Control

- Nicolaou proposed that BC temperature was directly related to the distance between the alkyne carbon termini for simple enediynes.

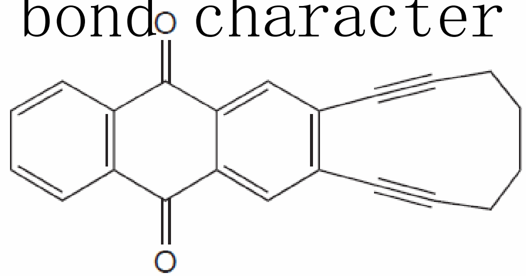
  This lead to the idea of a "critical distance" (cd) of 3.2-3.31 A° at which alkynes would undergo BC at ambient temperature ... ed this to 2.9-3.4 A°.



Nicolaou, K. C. *J. Am. Chem. Soc.* **1992**, 114, 7360.; Cremer, D. *J. Am. Chem. Soc.* **1994**, 116, 4929.

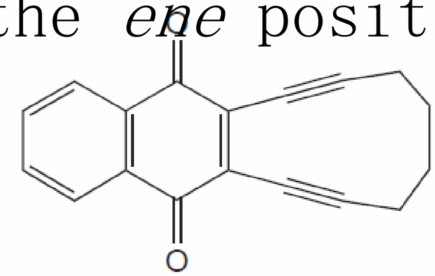
Electronic Control

- Semmelhack showed that the activation barrier to BC is affected by the degree of double bond character at the *ene* position.



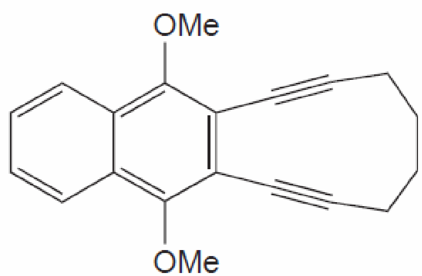
17

$t_{1/2}$ = 15 h, 84 °C



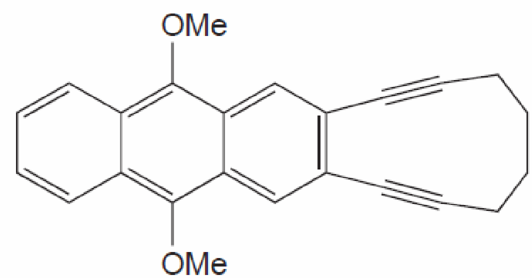
18

$t_{1/2}$ = 3 h, 84 °C; 88 h, 40 °C



19

$t_{1/2}$ > 7 d, 120 °C



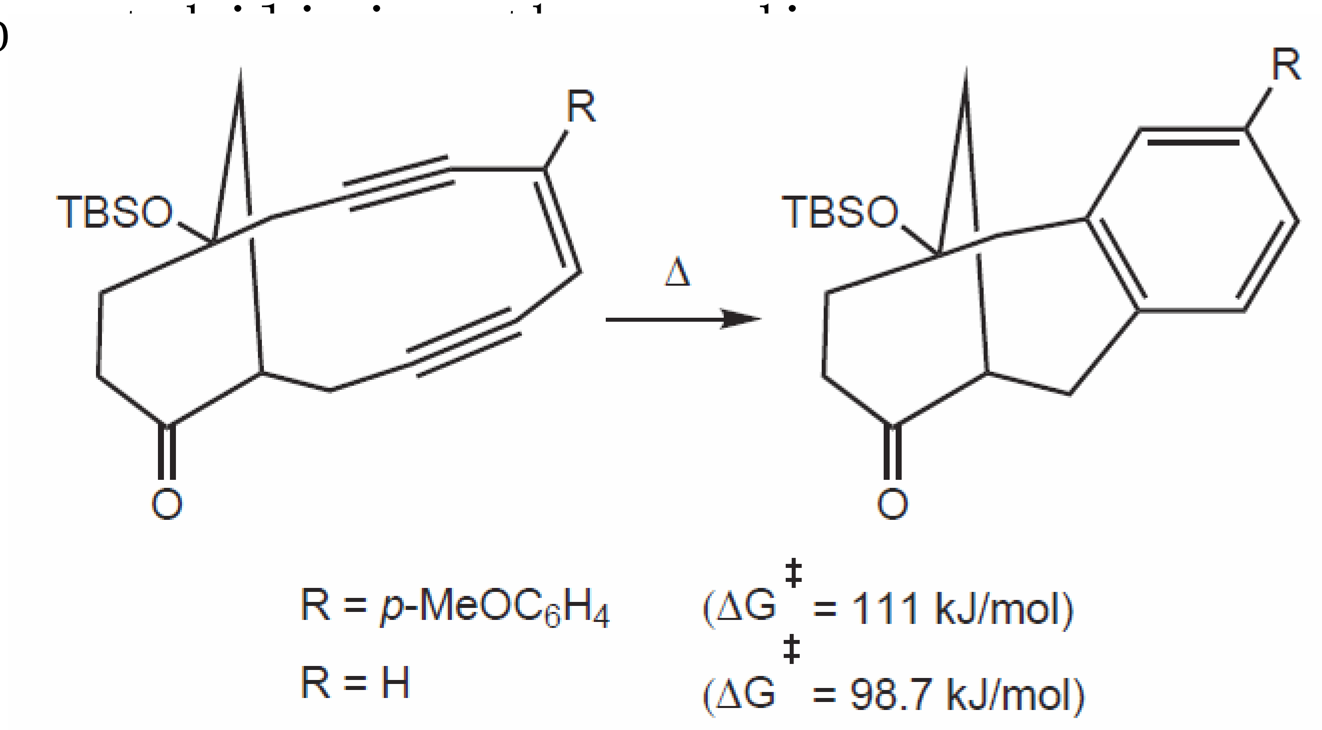
20

$t_{1/2}$ > 1 d, 120 °C

Semmelhack, M. F. *J. Org. Chem.* **1994**, 59, 5038.

Electronic Control

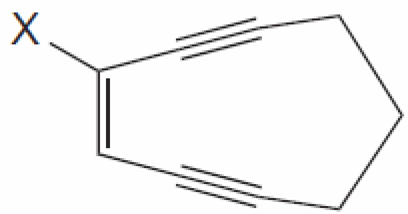
- Maier showed that EDG's on the vinyl substituent increase the activation energy b



Maier, M. E. *Liebigs Ann.* **1992**, 855.

Electronic control

- Jones showed, via *ab-initio* studies, that sigma-electron withdrawing vinyl substituents increase the barrier to cyclization while sigma donating decrease it, uents hav



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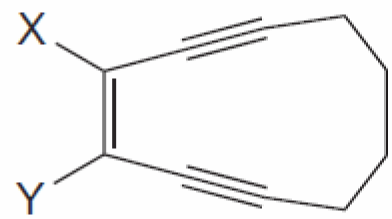
$X = Cl$, $t_{1/2} = 8$ h at 0 °C

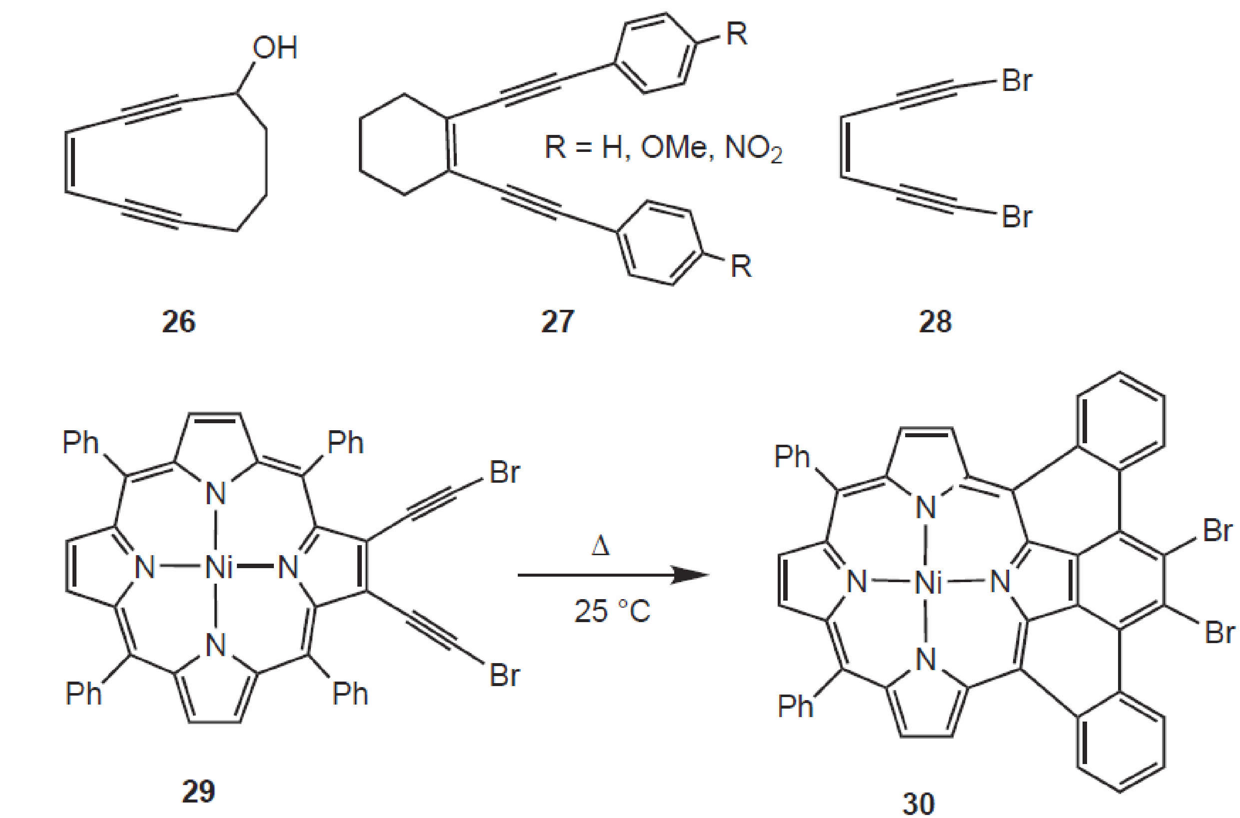


25

$X = Cl$, $Y = H$, $t_{1/2} = 5$ h at 60 °C
$X = Cl$, $Y = Cl$, $t_{1/2} = 24$ h at 170 °C

Jones, G. B. *Org. Lett.* **2000**, 2, 1757.
Jones, G. B. *J. Am. Chem. Soc.* **2001**, 123, 2134.

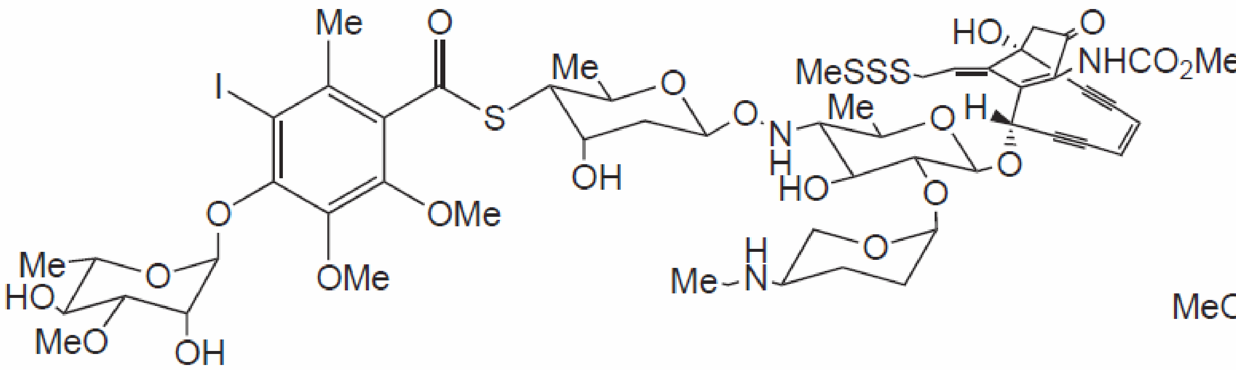
Electronic Control



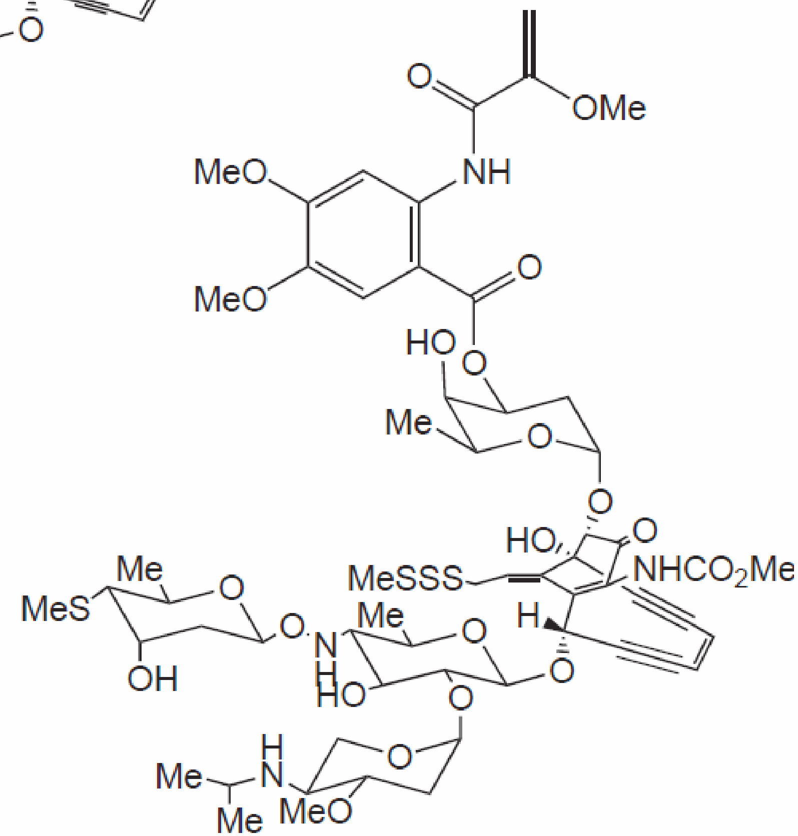
- Substitution at alkyne termini also affects BC

Zaleski, Z. M. *Synlett* **2004**, 3, 393.

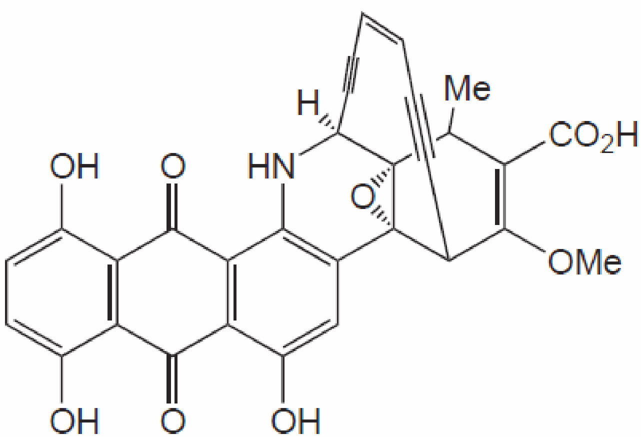
Natural Products



calicheamicin γ_1^{I}



esperamicin A_1

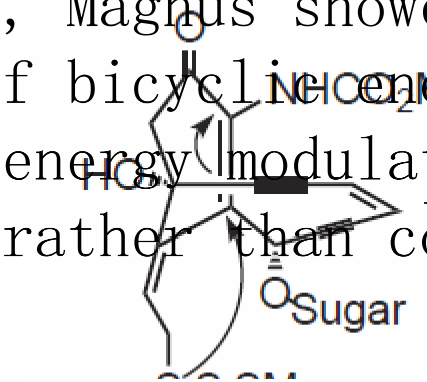


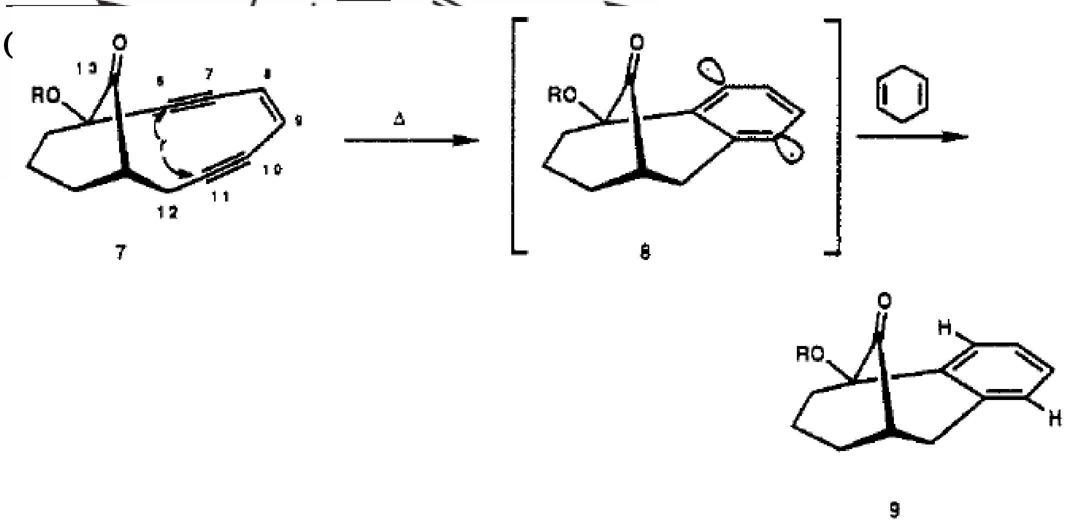
dynemicin A

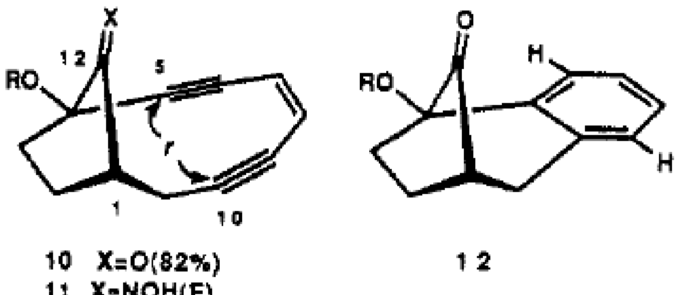
Zaleski, Z. M. *Synlett* **2004**, 3, 393.

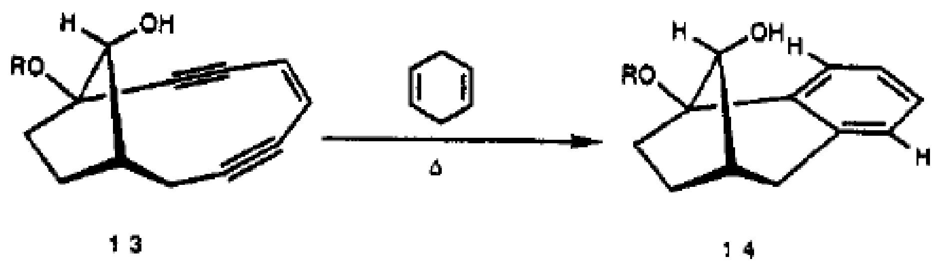
Calicheamicin and Esperamicin

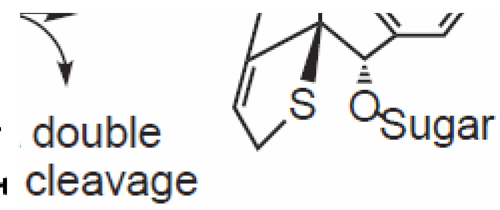
In 1990, Magnus showed that the cylization rates of bicyclic enediynes are governed by strain-energy modulation in the transition state, rather than c





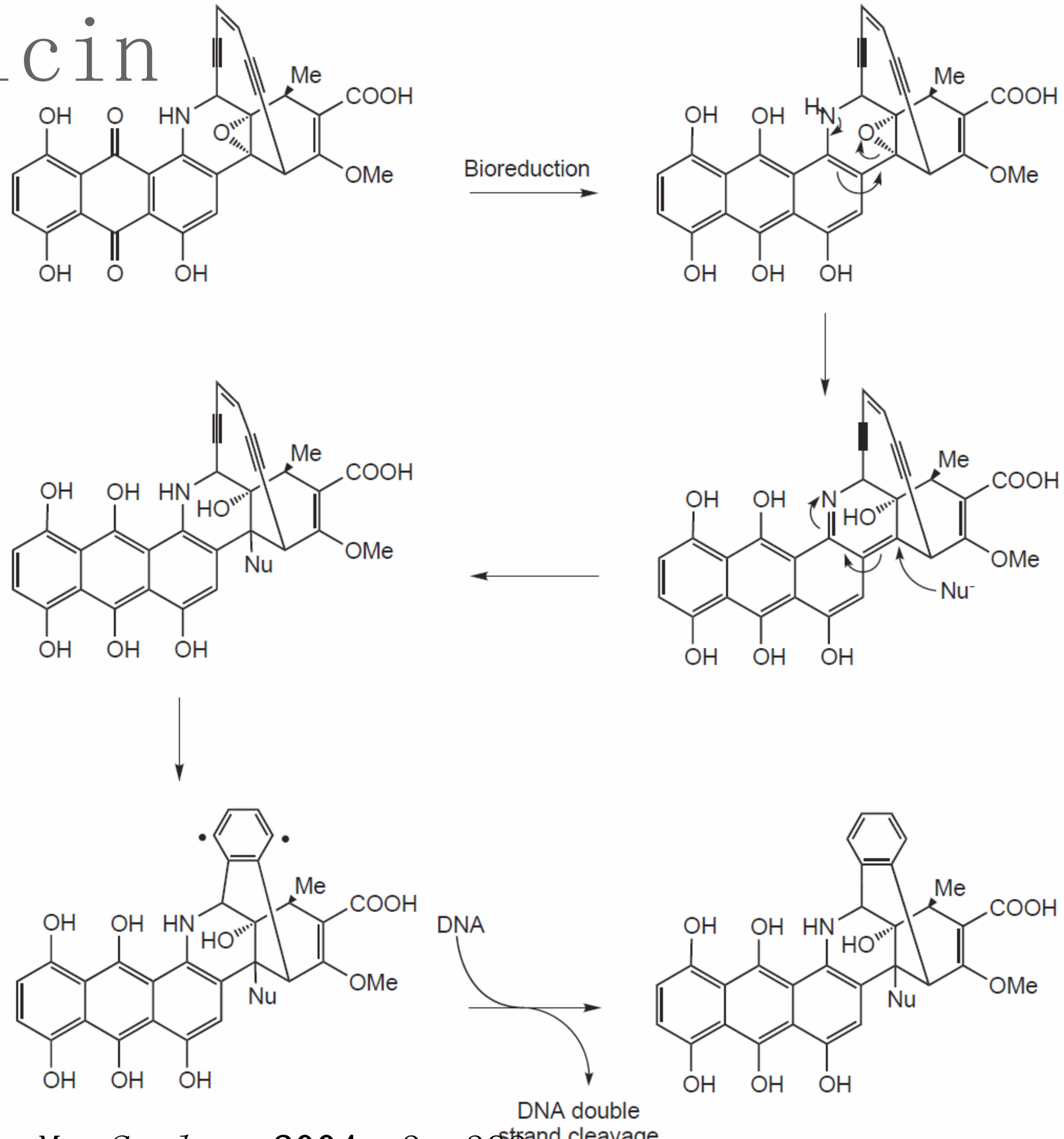






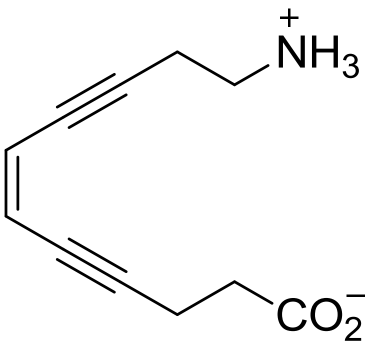
Magnus, P. *J. Am. Chem. Soc.* **1990**, 112, 4986.
Sander, W. *Angew. Chem. Int. Ed.* **2003**, 42, 502.

Dynemicin

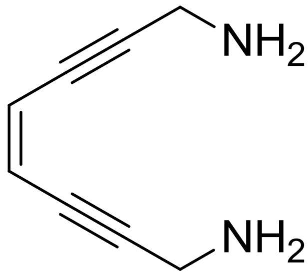


Zaleski, Z. M. *Synlett* **2004**, 3, 393.

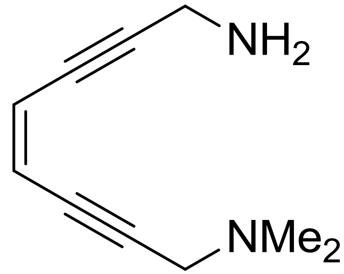
Acyclic Enediynes



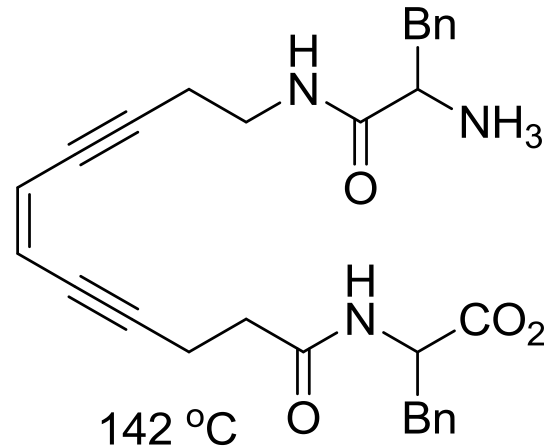
99 °C



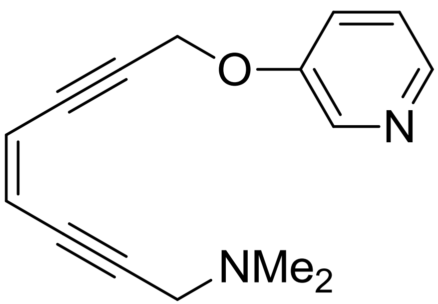
106 °C



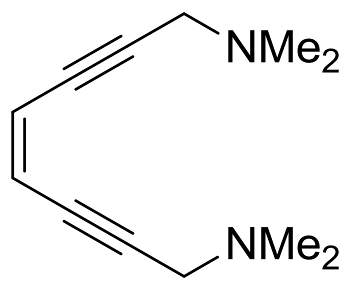
139 °C



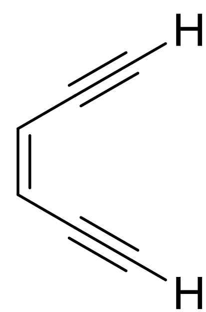
142 °C



149 °C



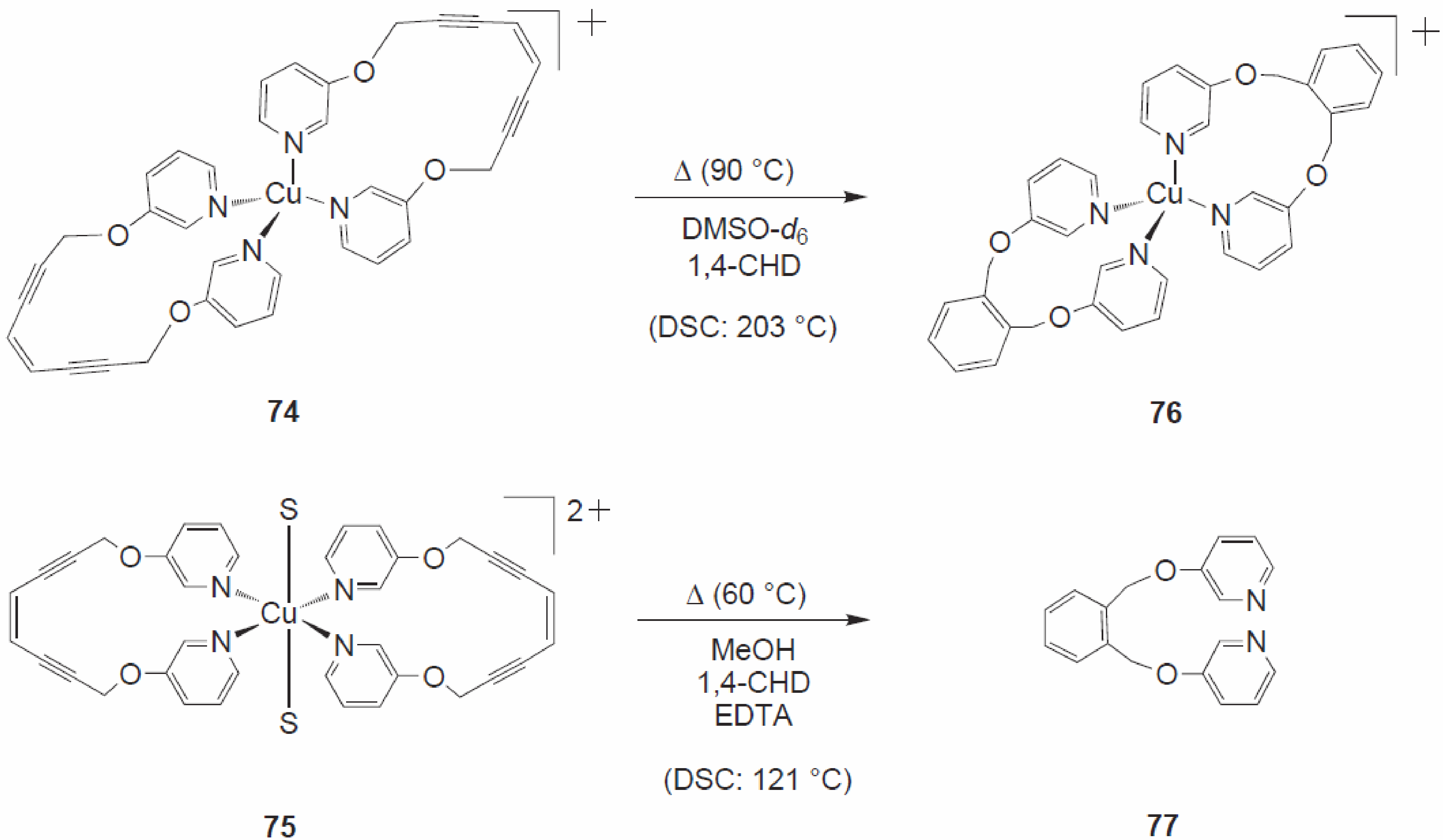
186 °C



200 °C

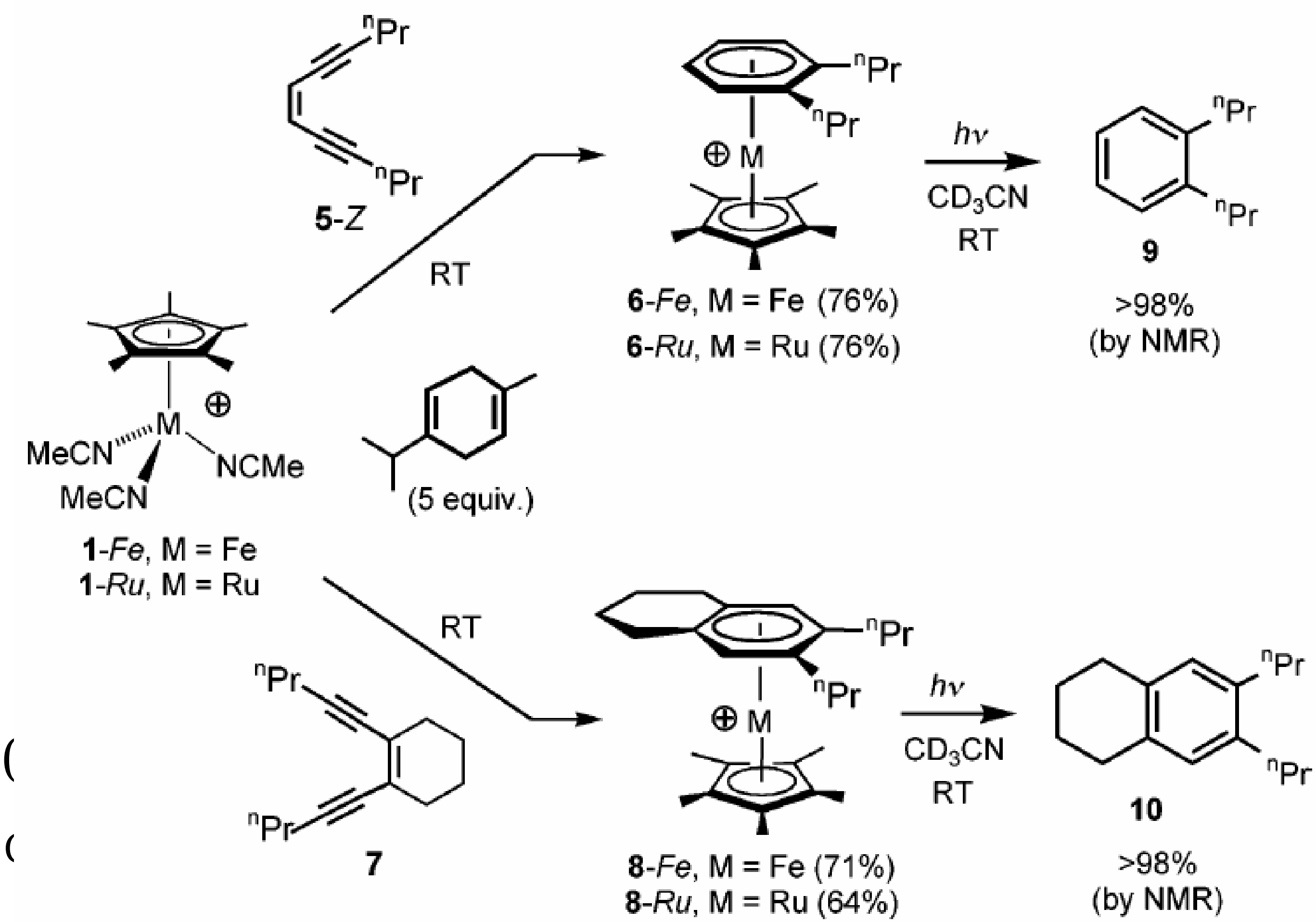
Zaleski, J. M. *J. Am. Chem. Soc.* **2000**, 2493.

Metallocyclic Enediynes



Zaleski, J. M. *J. Am. Chem. Soc.* **2000**, 122, 7208.

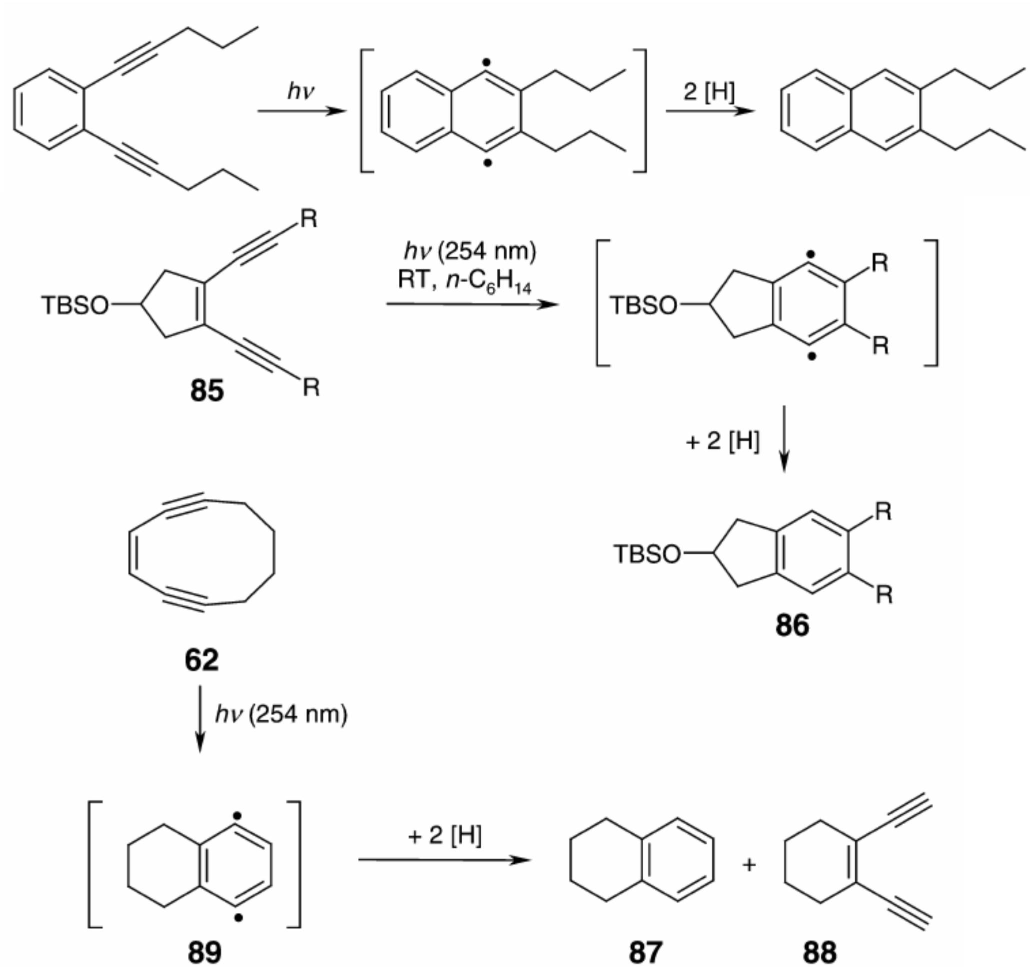
Transition Metal Mediated BC



- (… 3C is
  (…

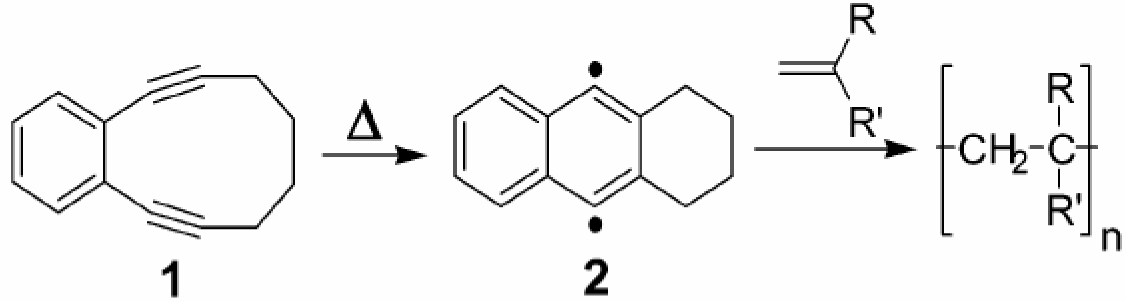
O' Connor, J. M. *J. Am. Chem. Soc.* **2000**, 122, 12057.
O' Connor, J. M. *J. Am. Chem. Soc.* **2005**, 127, 16342.

Photochemical BC



Eglington, G. *J. Chem. Soc. C* 1968, 2120.
Turro, N. J. *J. Am. Chem. Soc.* 1998, 120, 1835.
Hirama, M. *Angew. Chem. Int. Ed.* 1999, 38, 1267.

BC Polymerization



entry	monomer	$T_{50\%}$[h,i]	color[j]
1	1	472	brown
2	1	>900	tan
3	1	>900	tan
4	1	791	tan
5	1	898	brown
6	1	>900	tan
7	1	>900	orange[m]
8	1	375	green
9	1	490	black
10	3	>900	brown
11	3	617	tan
12	3	>900	black
13	3	>900	black

Table 1. Thermal F

[a] Dashes signify th ... eactions were carried out in a thick-walled ... . The reaction times were generally 24–4 ... F versus polystyrene standards. [e] Number ... curred. [h] Determined by thermogravimetric ... weight loss occurred. [j] Color of neat polym ... ble portion and TGA data obtained on the ... omer. [o] The reaction was run without solvent.

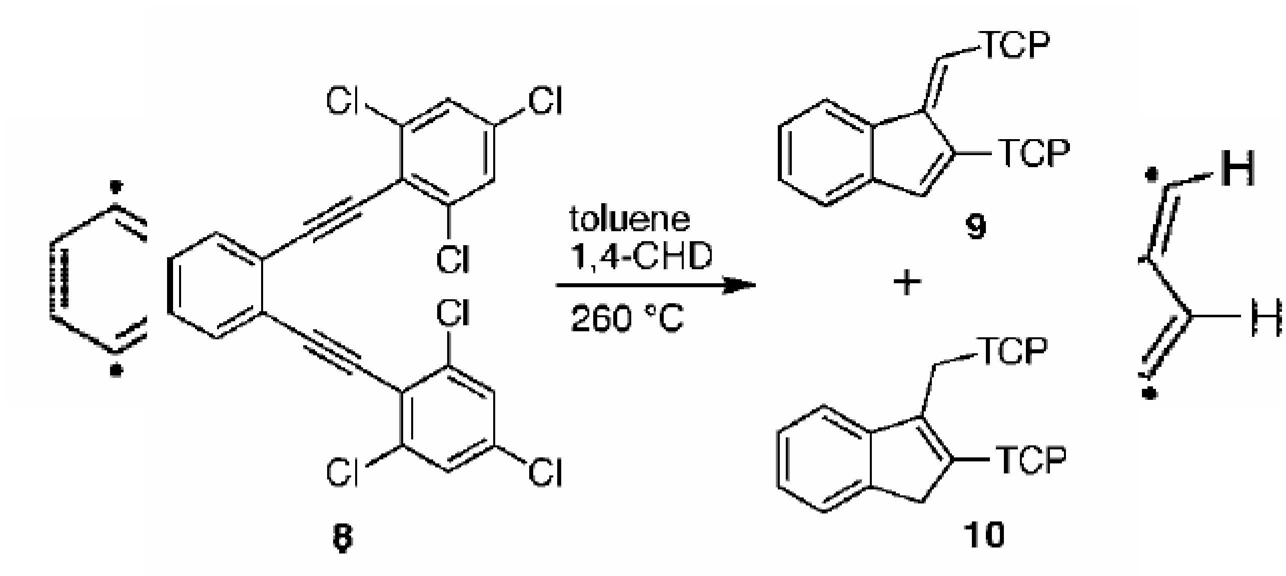
Table 1. Polymerization Initiated by Enediyne **1**[a]

monomer	[1] (mM)	yield (%)[b]	M_n[c]	PDI
butyl methacrylate	22	93	714 000	1.38
methyl methacrylate	27	87	482 000	2.52
methyl acrylate	21	29	626 000	1.89
styrene	24	12	265 000	1.84
methacrylonitrile	31	7		
acrylonitrile	30	3		
vinylidene chloride	26	1		

[a] Reactions ran for 2.5 h at 100 °C. [b] Yield of isolated polymer. [c] GPC data based on refractive index, viscometry, and light scattering.

Tour, J. M. *J. Am. Chem. Soc.* **1994**, 116, 5011.
Moore, J. S. *J. Am. Chem. Soc.* **2003**, 125, 12992.

C^1–C^5 Cyclization



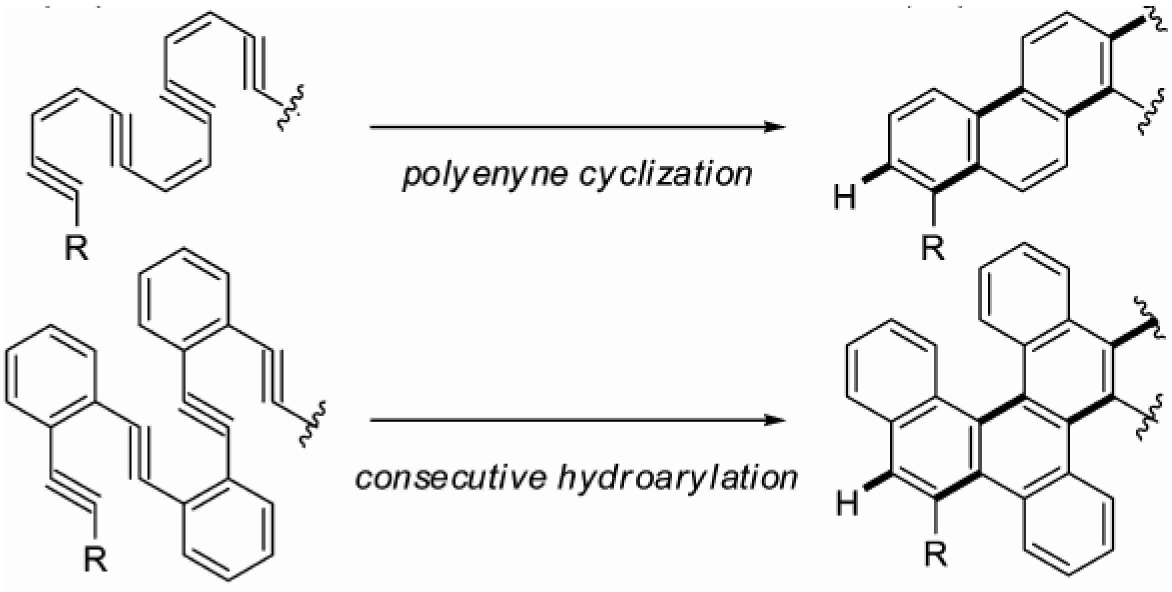
- In 2001 Schreiner calculated that the barrier for C1-C5 cyclization was 41 kcal/mol while C1-C6 was only 25 kcal/mol
- In 2008 Pascal calculated that the C1-C5 pathway was possible and then accomplished it with certain arene substituted enediynes

Schreiner, P. R. *J. Phys. Chem.* **2001**, 105, 9265.
Pascal, R. A. *J. Am. Chem. Soc.* **2008**, 130, 13549.

BC Summary

- Many natural enediynes are in clinical trials for use as antitumor, antimicrobial, and cytotoxic drugs.
- The multitude of synthetic enediynes have been used to probe the geometic and electronic contributions of BC
  - Many of these have shown cytotoxic properties of there own, but none have made it into clinical trials.
- BC has found use in material science to form polyphenylene/polynaphthalenes and as a radical initiator in alkene polymerization

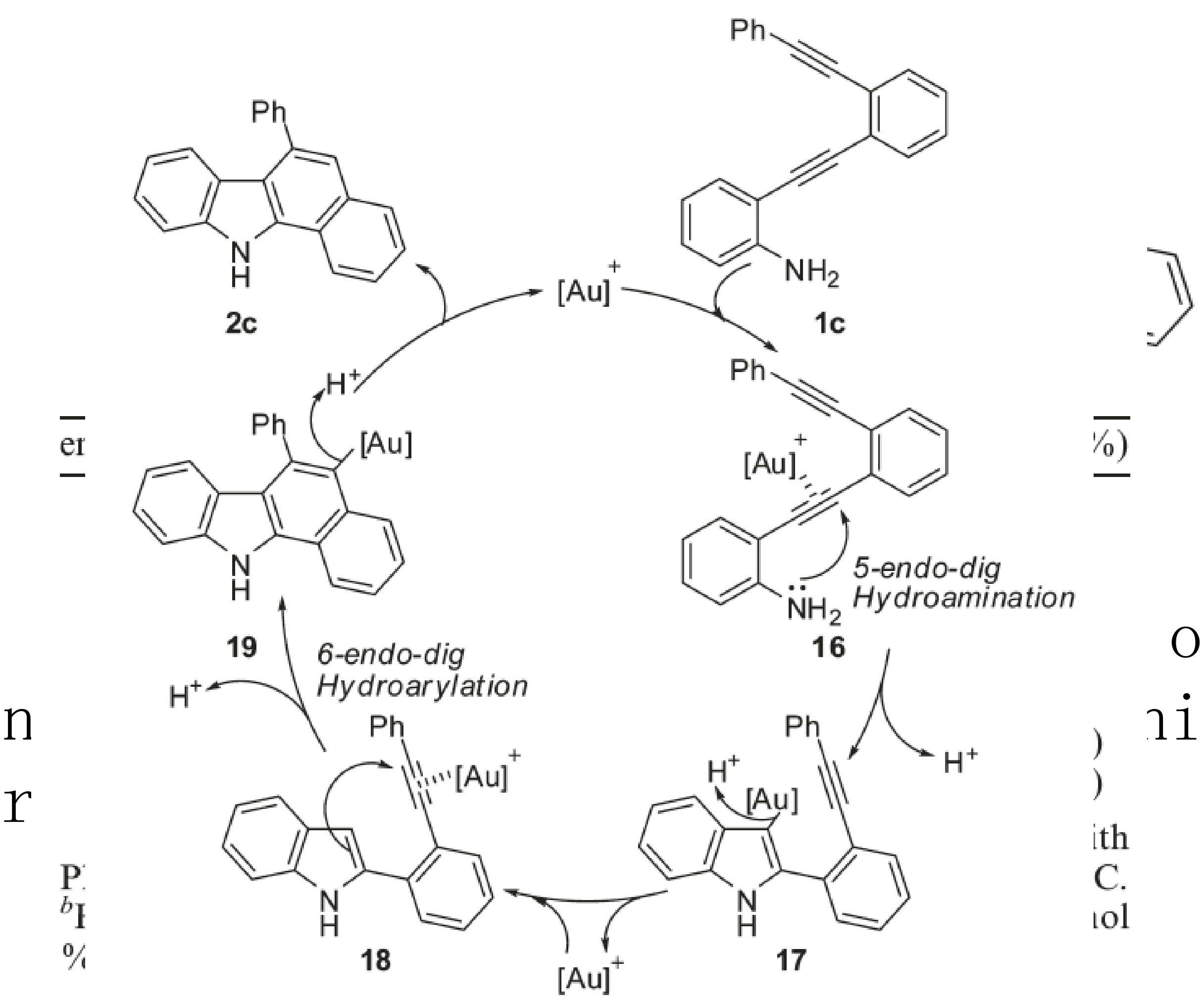
Metal Catalyzed Cyclization of Eneynes



- Cascade reactions of enediynes resulting in fused benezene or naphthyl rings has been accomplished via Au, Ru, Pd, and Pt catalysts with either internal or external nucleophiles.

Ohno, H. *J. Org. Chem.* **2011**, 76, 9068.

Au Catalyzed Cyclizations



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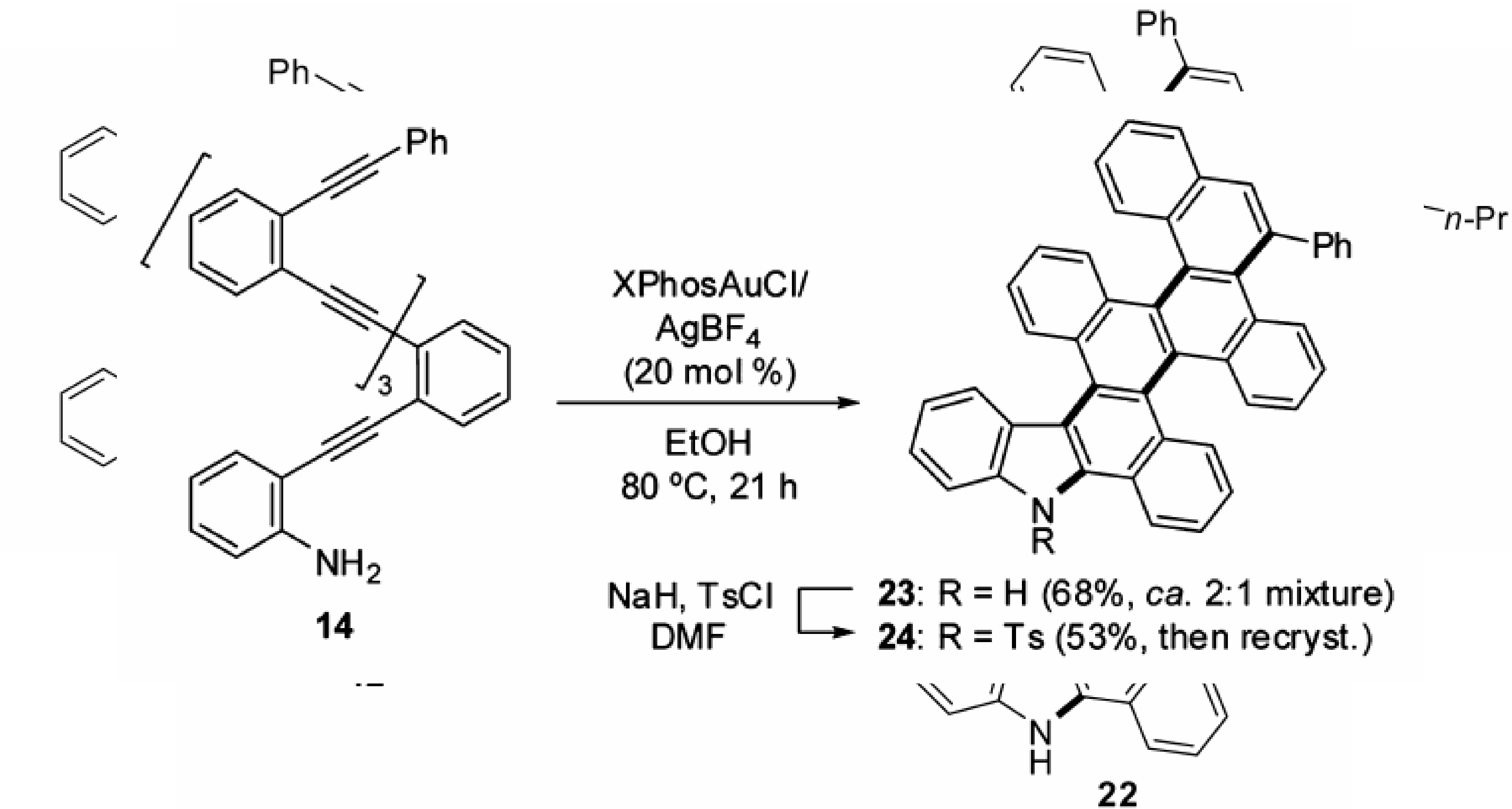
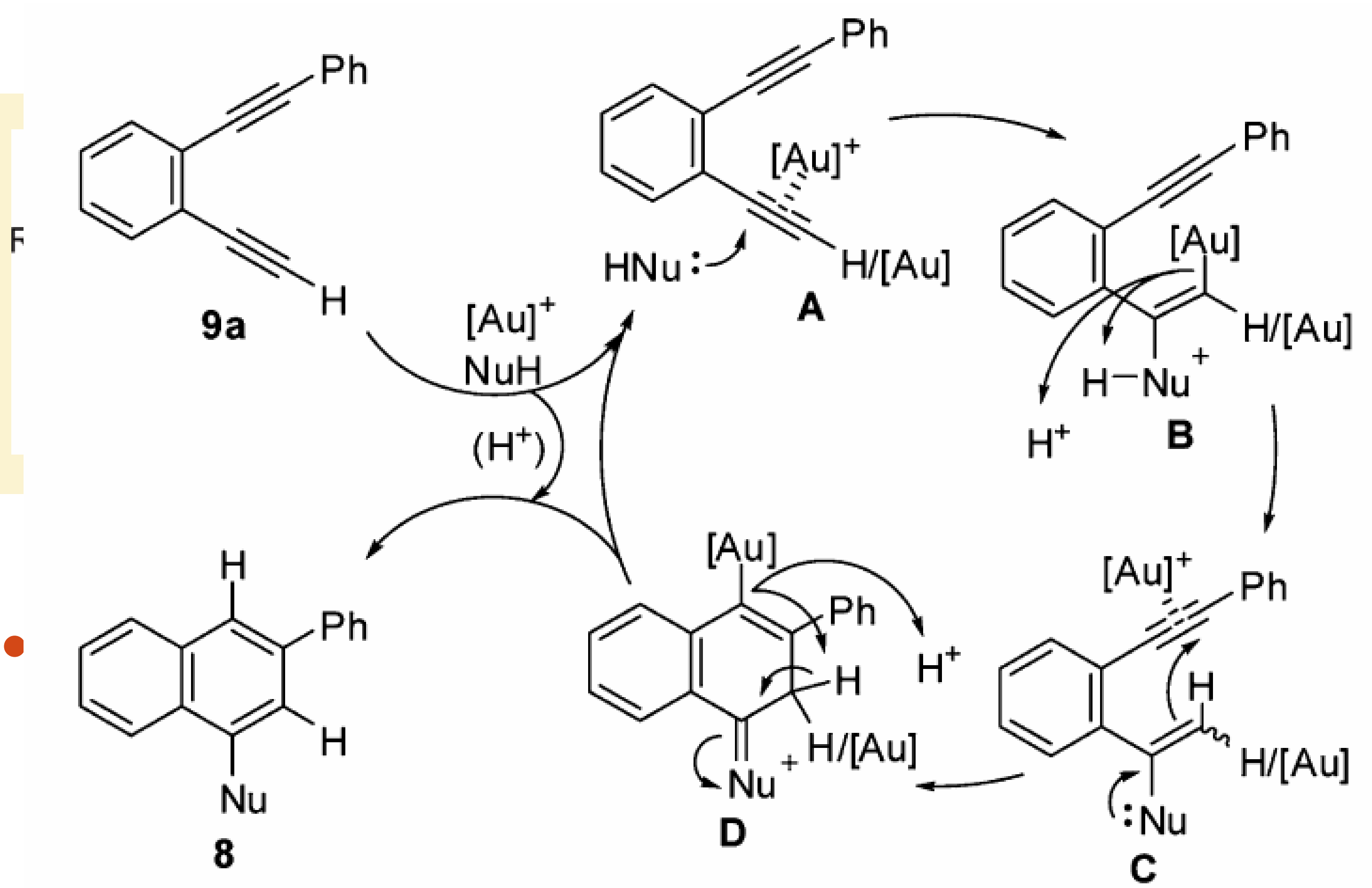
Ohno, H. *J. Org. Chem.* **2011**, 76, 1212.

Au Catalyzed Cyclizations



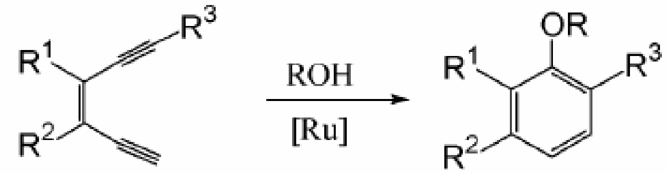
Ohno, H. *J. Org. Chem.* **2011**, 76, 9068.

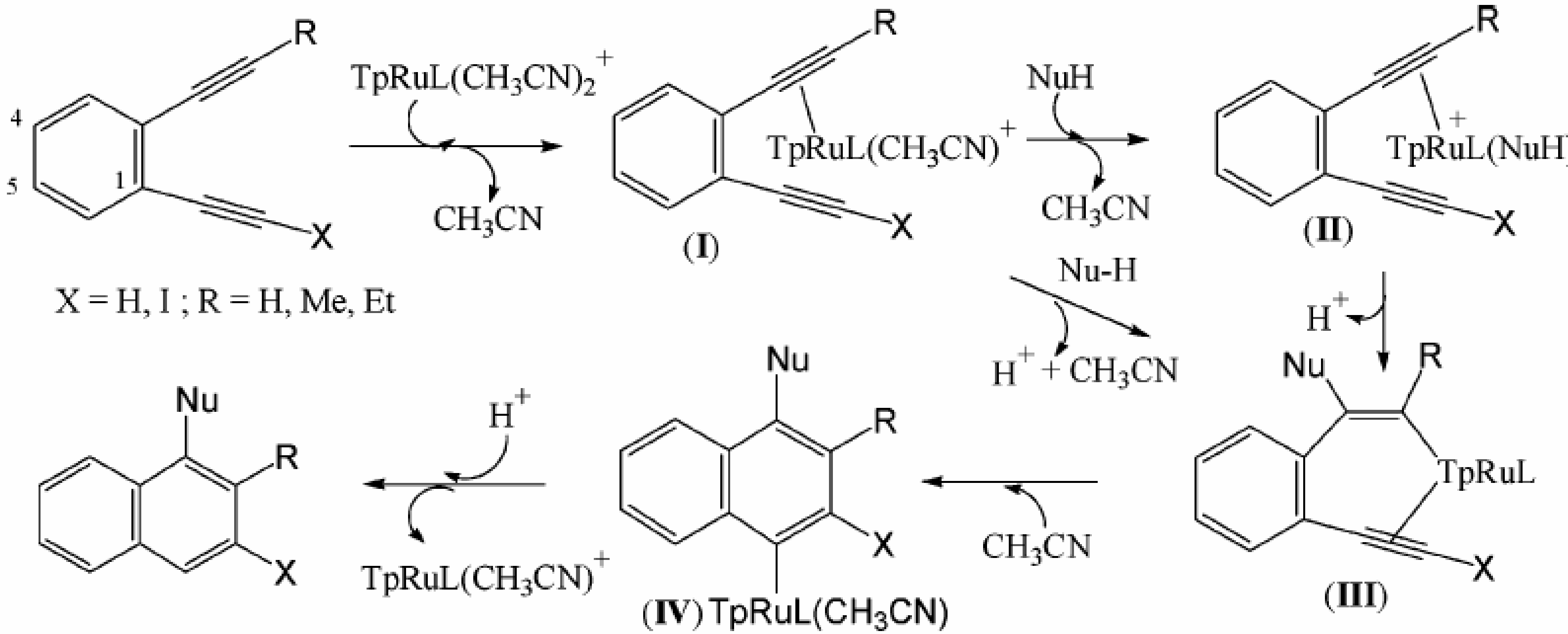
Au Catalyzed Cyclizations



Ohno, H. *J. Org. Chem.* **2012**, 77, 4907.

Ru Catalyzed Cyclizations





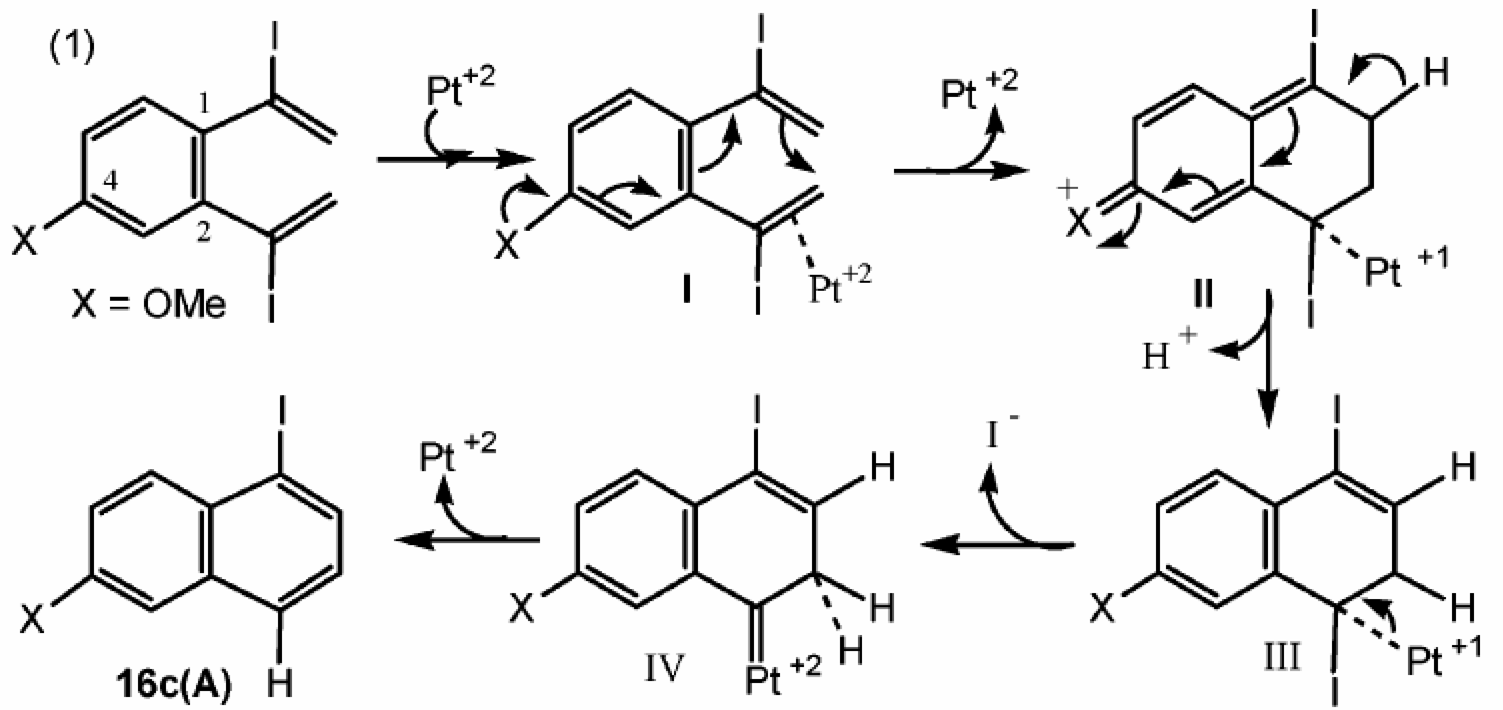
(6) R^3 = H (**1d**)	R = H	**2**i (77%)	(12)	**1h**	R = ^{i}Bu	**2o** (70%)

[a] 10 mol % catalyst, 100 °C, 12 h for alcohols (6.0 equiv) and 24 h for water. [b] Water and 3-pentanone (vol. 1:1) were used as a mixing solvent. [c] Yields were reported after separation from a silica column.

Lui, R. *J. Am. Chem. Soc.* **2005**, 127, 3406.

Pt

TABLE 2. Regioselectivity in the Hydrohalogenation of 4-Substituted 1,2-Bis(ethynyl)benzenes



substrates	HX[a]	time[b]	products (yields)[c]
(11) 14	HBr	3 h	85% (18-Br, A)
(12) 14	HI	1 h	80% (18-I, B)

[a] 2.1 equiv of HX (X = Cl, 37 wt %; Br, 48 wt %; I, 52 wt %).
[b] $PtCl_2$ (10 mol %), 3-pentanone, 100 °C, [substrate] = 0.40 M.
[c] Yields shown are after separation from a silica column.

10 %)
11)
12 , 2-I (26%)
13

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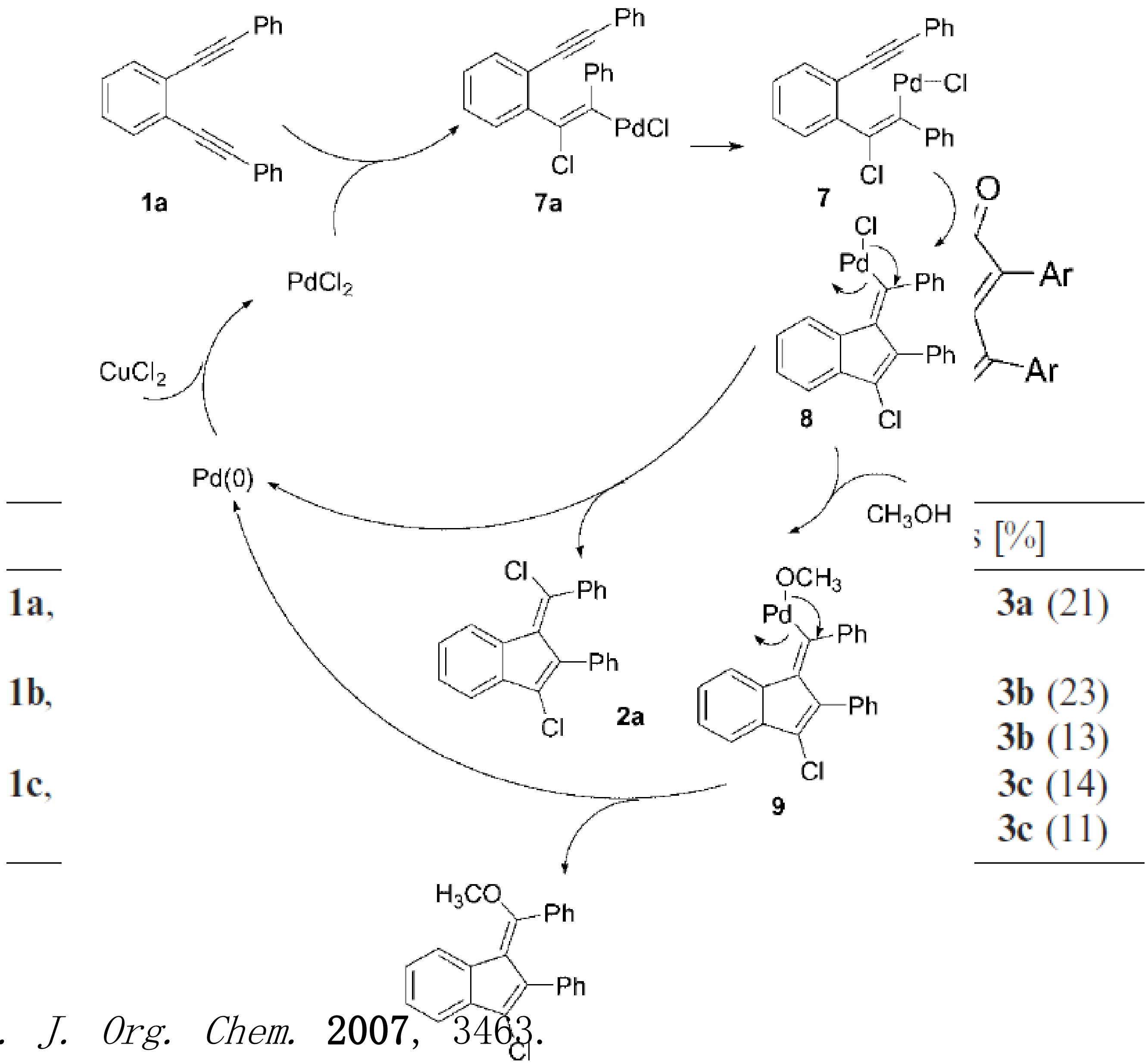
Lui, R. *J. Org. Chem.* **2005**, 70, 10482.

Pd Catalyzed Cyclizations

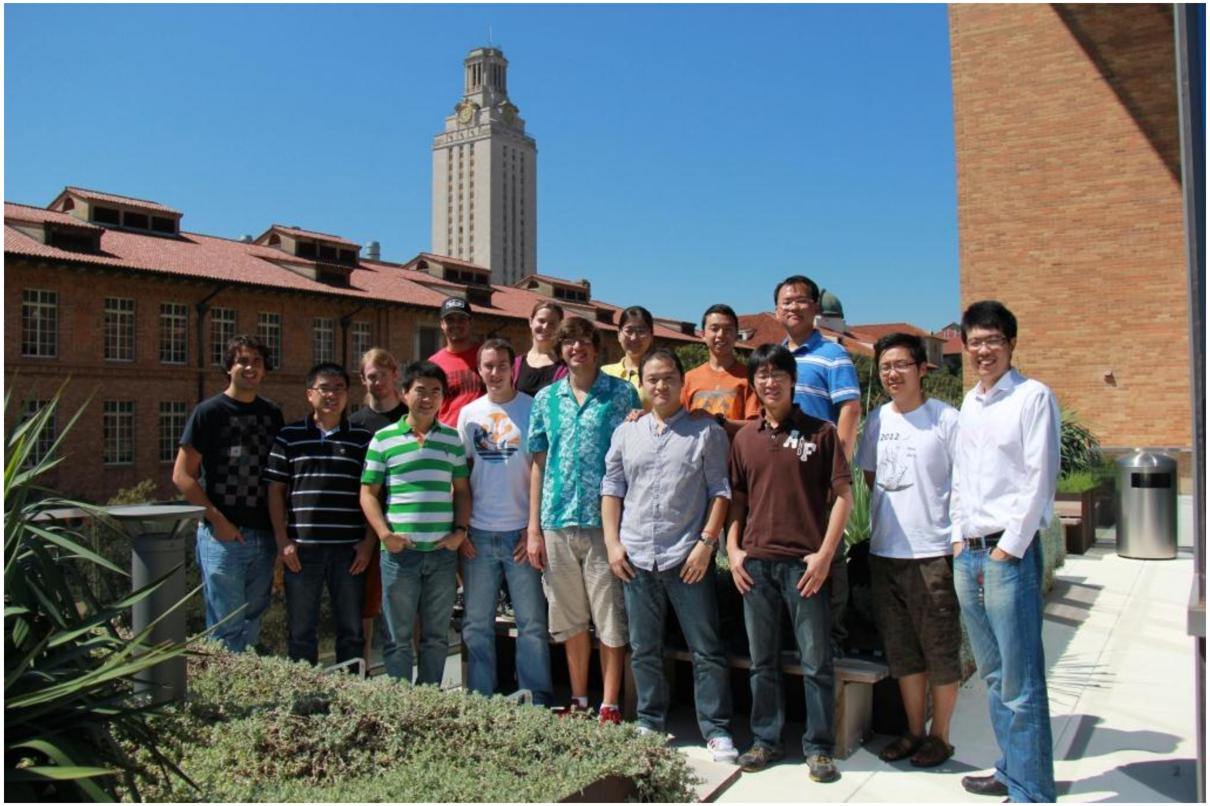


Wu, M. *Eur. J. Org. Chem.* **2007**, 3463.

Summary

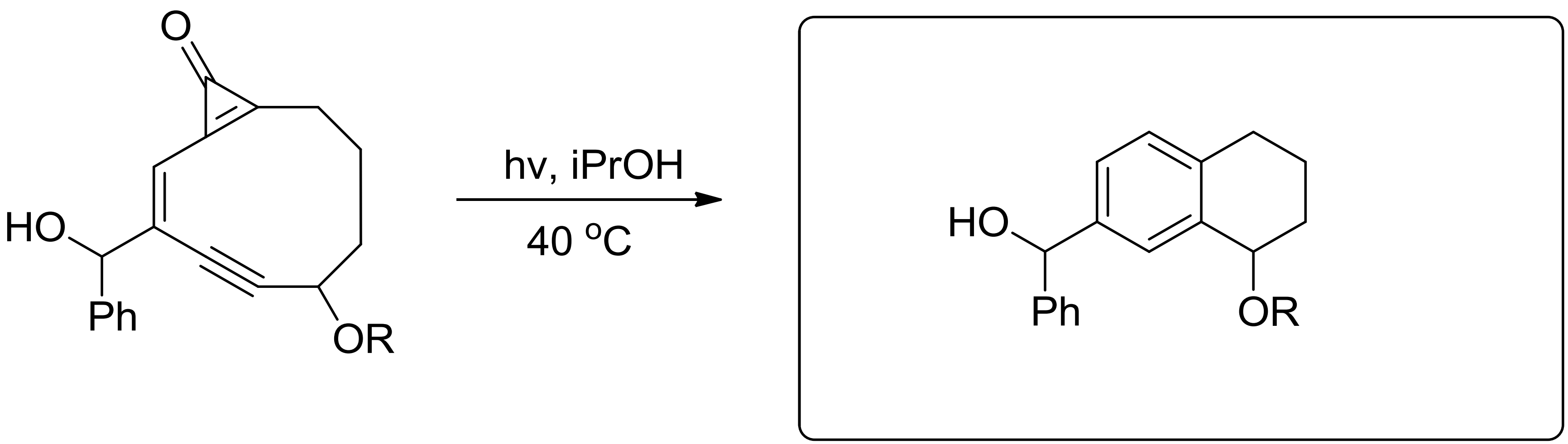
- The majority of metal catalyzed enediyne cyclizations utilize Au catalysts
- Ru, Pd, and Pt catalysts enable the use of nucleophiles and formation of different regioisomers than Au catalysis

THANKS!!!!!



QUESTIONS?????

Question 1



Question 2

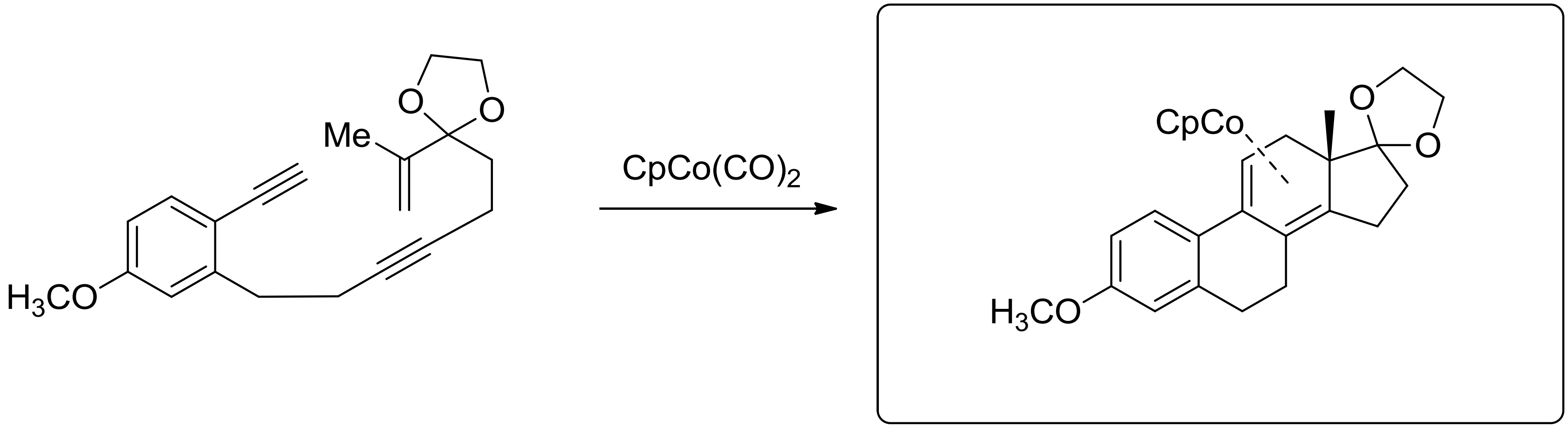
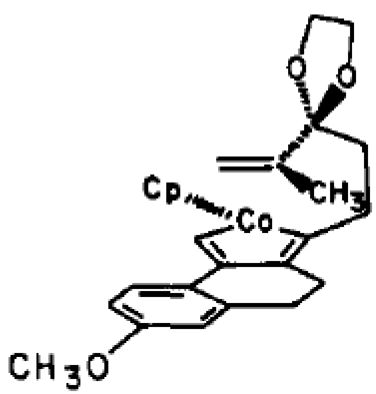


Chart I



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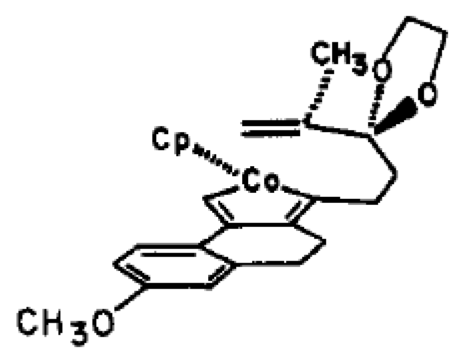

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Question 3