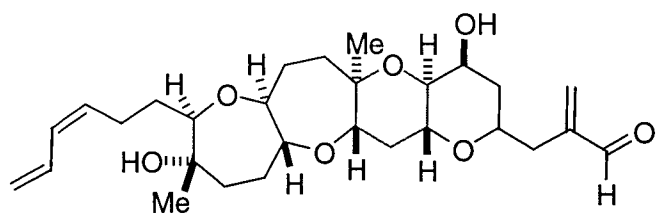
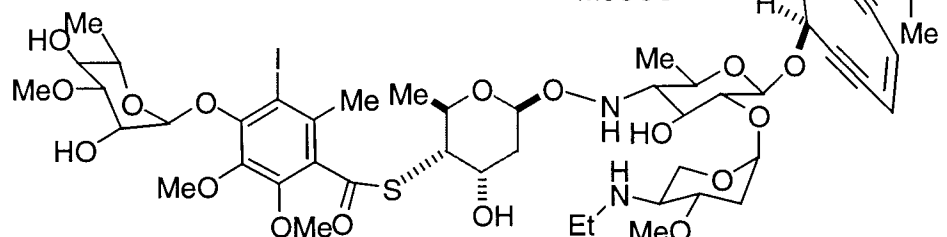
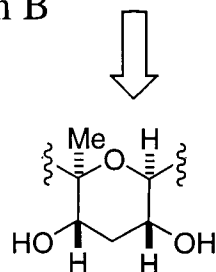


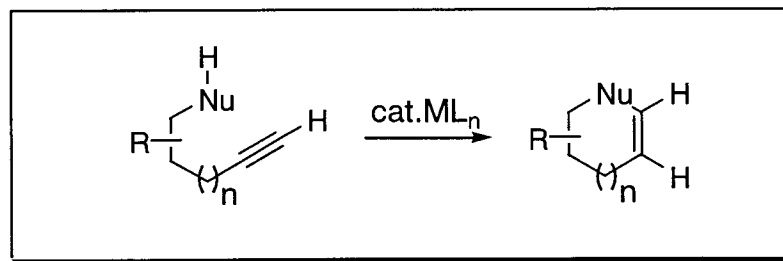
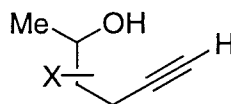
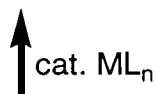
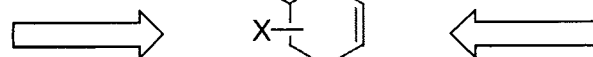
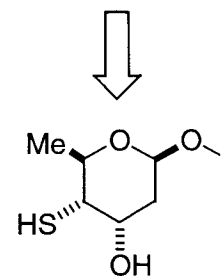
# Transition Metal-Catalyzed Cycloisomerization of Terminal Alkynes



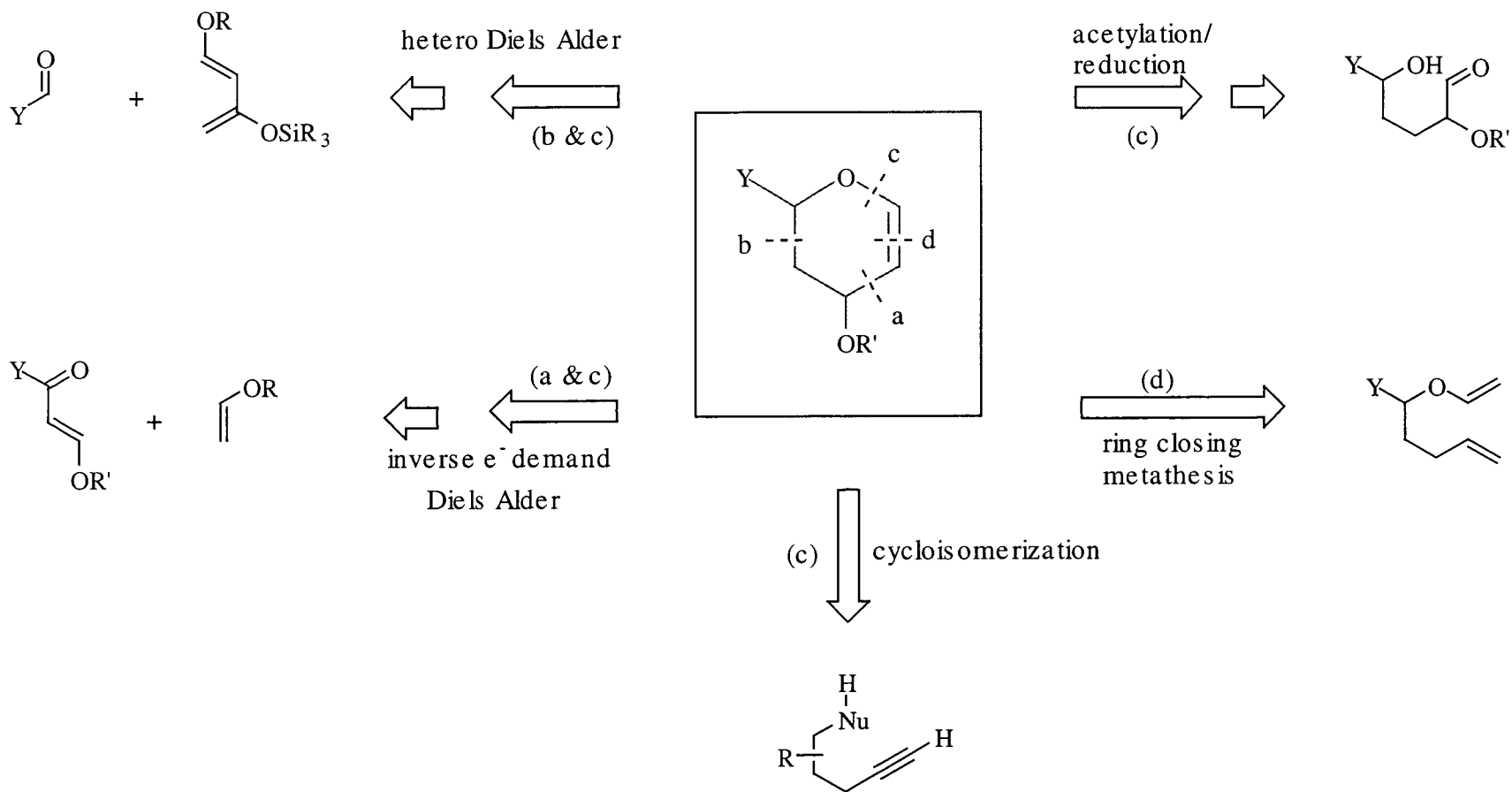
Hemibrevetoxin B



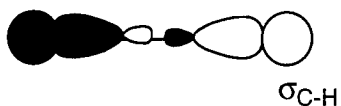
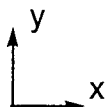
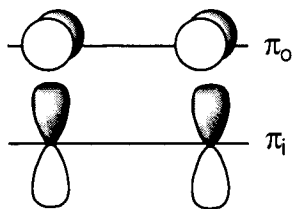
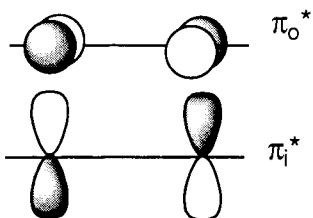
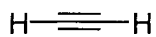
Calicheamicin



# Dihydropyran Derivatives: Strategic Bond Disconnection



# Nature of Metal-Acetylene Interaction

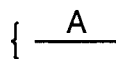
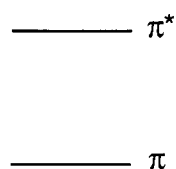


Acetylene

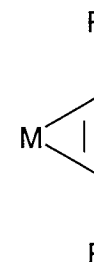
Metal valence  
shell electrons

Two limiting scenarios

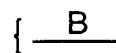
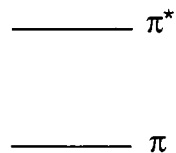
case 1



case 1

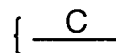
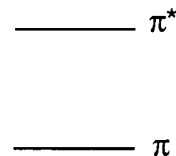


case 2

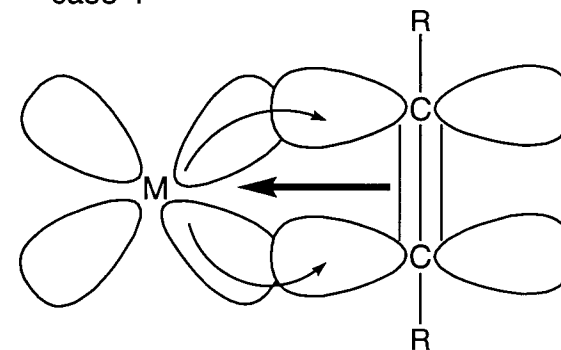


two metal-carbon  $\sigma$  bonds  
with complete rehybridization  
of the carbon atoms

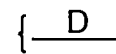
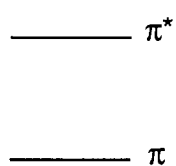
case 3



case 4



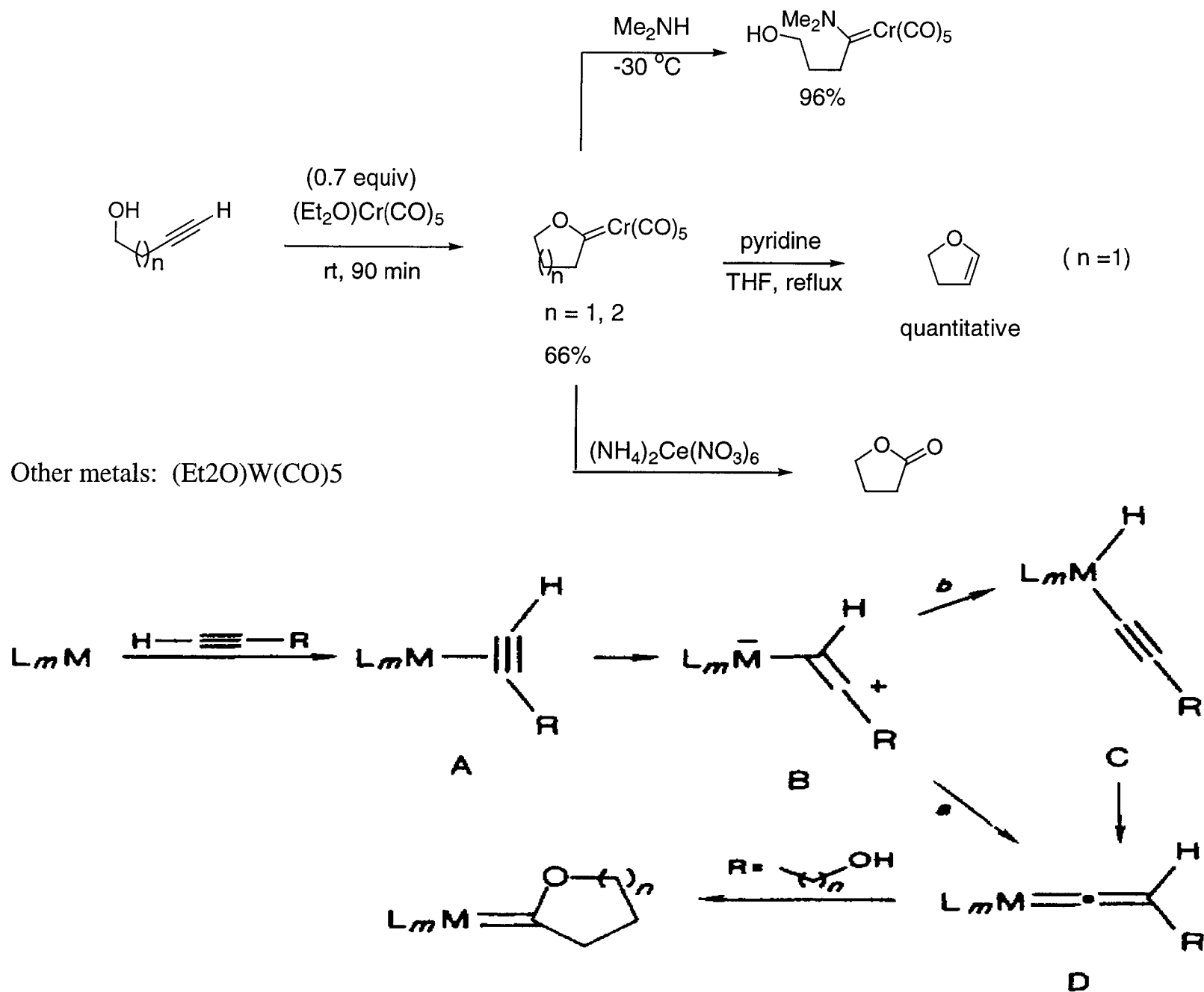
case 4



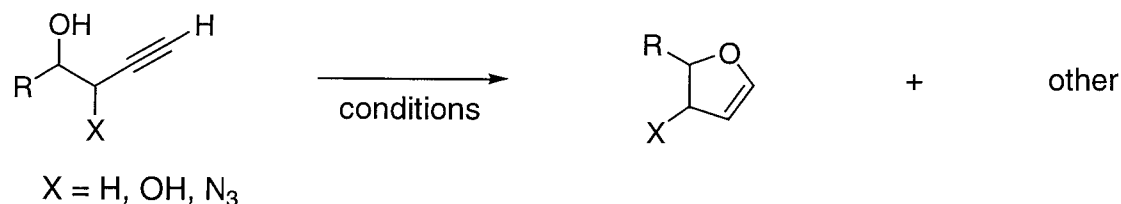
the bonding orbital has mostly metal  
character while the antibonding orbital  
has acetylene character.

Maitlis, P.M. *Can. J. Chem.* 1968, 46, 3880.  
Hoffmann, R. *Helv. Chim. Acta.* 1985, 68, 1461.  
Chatt, J. *J. Chem. Soc.* 1953, 2939.

# Initial Finding on Metal-Assisted Cyclization of Alkynols



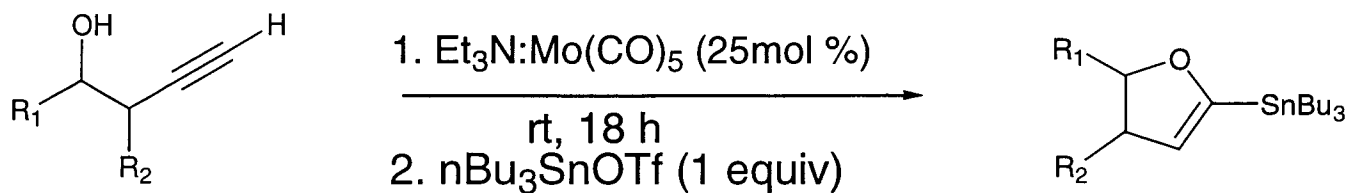
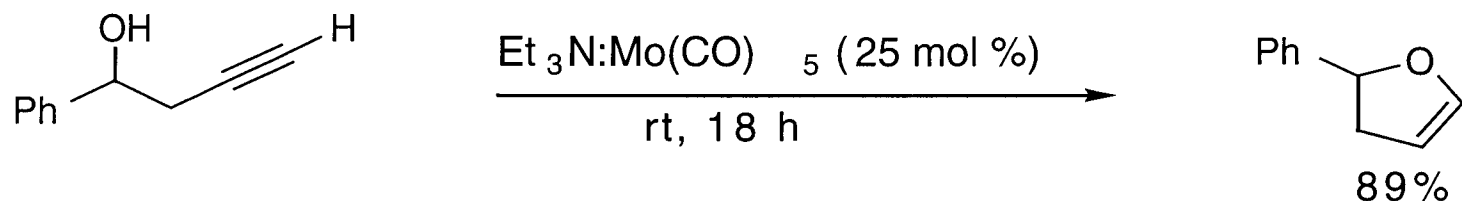
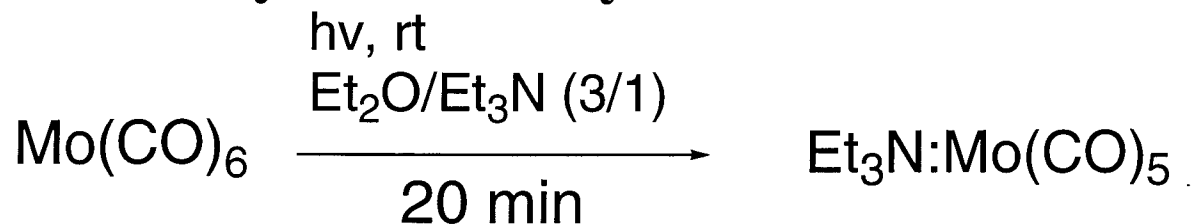
# Molybdenum-Promoted Cycloisomerization



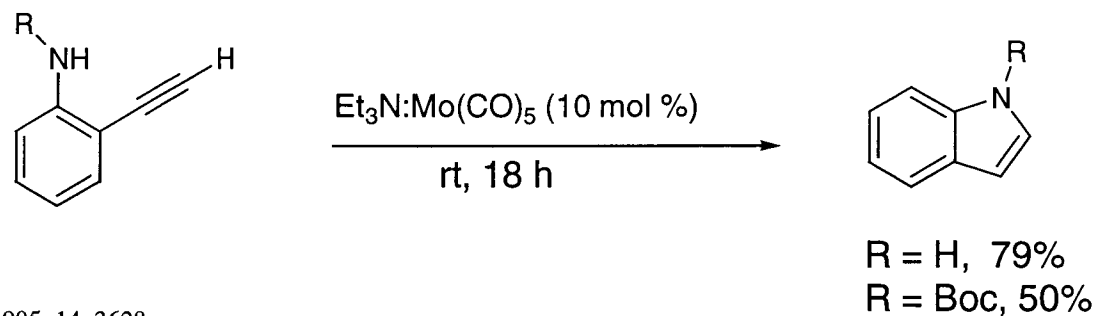
entry	substrate <sup>a</sup>	conditions <sup>c</sup>	product (yield, %)
1		Me <sub>3</sub> N-Cr(CO) <sub>6</sub> <sup>b</sup> (1 equiv), Et <sub>2</sub> O, 120 h	 2 (59)
2	1	W(CO) <sub>6</sub> (1 equiv), TMNO (1 equiv), Et <sub>2</sub> O, 120 h	 3 (24)
3	1	Mo(CO) <sub>6</sub> (0.5 equiv), TMNO (0.5 equiv), Et <sub>3</sub> N, Et <sub>2</sub> O, 60 h	 4 (71)
4		Mo(CO) <sub>6</sub> (0.5 equiv), TMNO (0.5 equiv), Et <sub>3</sub> N, Et <sub>2</sub> O, 92 h	 6 + 7 (ca. 9:1, combined yield 59%)
5		Mo(CO) <sub>6</sub> (0.5 equiv), TMNO (0.5 equiv), Et <sub>3</sub> N, Et <sub>2</sub> O, 72 h	 9 (52)
6		Mo(CO) <sub>6</sub> (1 equiv), TMNO (1 equiv), Et <sub>3</sub> N, Et <sub>2</sub> O, 19 h	 11 (58)
7		Mo(CO) <sub>6</sub> (0.5 equiv), TMNO (0.5 equiv), Et <sub>3</sub> N, Et <sub>2</sub> O, 12 h	 13 (60)

<sup>a</sup> M(CO)<sub>6</sub> and TMNO were dissolved in Et<sub>2</sub>O (0.1 M) and Et<sub>3</sub>N (0.03 M) under N<sub>2</sub> at 20 °C. The solution rapidly turned green (M = Cr), brown (M = Mo), or yellow (M = W), and after 30–60 min the alkynyl alcohol was added and stirred at 20 °C for the time indicated. Dihydrofuran products were isolated by evaporation of solvent followed by silica gel chromatography (pentane/Et<sub>2</sub>O/1% diethylamine); carbene products were purified by silica gel chromatography (pentane/Et<sub>2</sub>O) and recrystallized (pentane, -78 °C). <sup>b</sup> Preformed Me<sub>3</sub>N-Cr(CO)<sub>6</sub> gave better yields than those obtained from *in situ* generation from Cr(CO)<sub>6</sub> and TMNO (1 → 2, 34% yield). <sup>c</sup> Isolated yields.

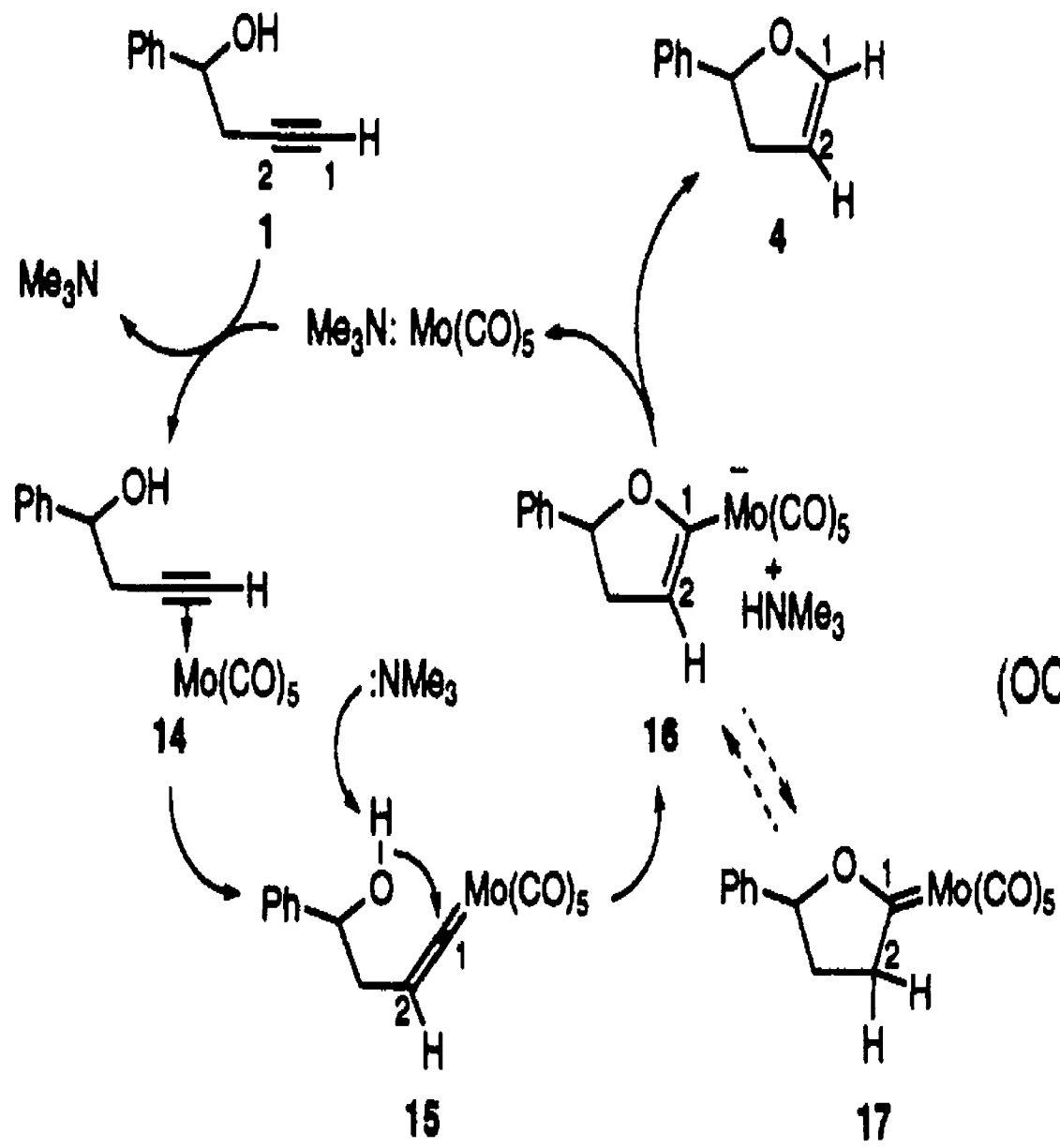
# Generation of Triethylamine-Molybdenum Pentacarbonyl Complex



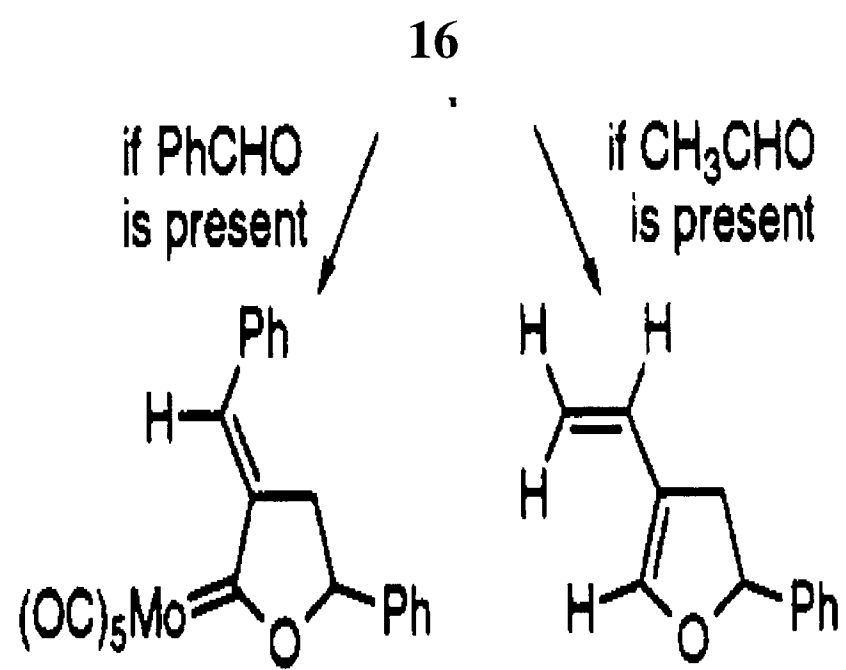
substrate	yield
R <sub>1</sub> = Ph R <sub>2</sub> = H	65%
R <sub>1</sub> = H R <sub>2</sub> = H	64%
R <sub>1</sub> = H R <sub>2</sub> = Me	45%



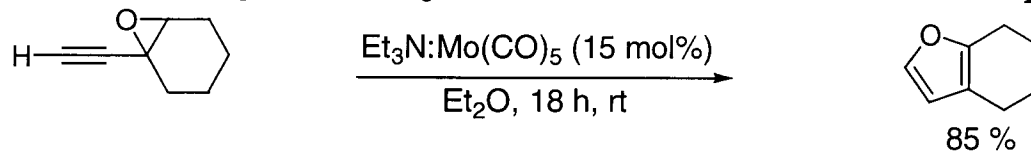
# Proposed Mechanism



Trapping of intermediate 16

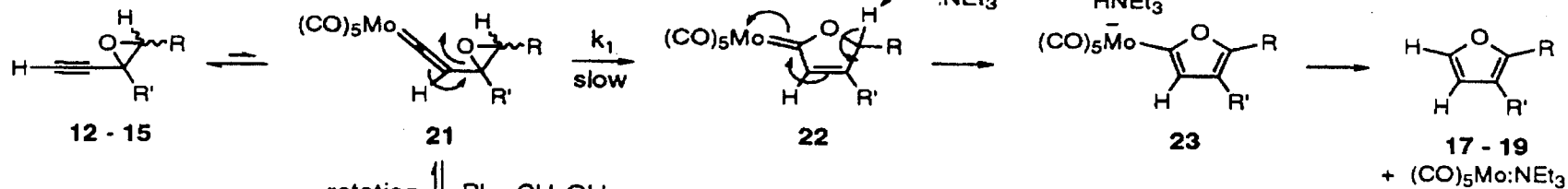


# Molybdenum-Catalyzed Cycloisomerization of Epoxyalkynes

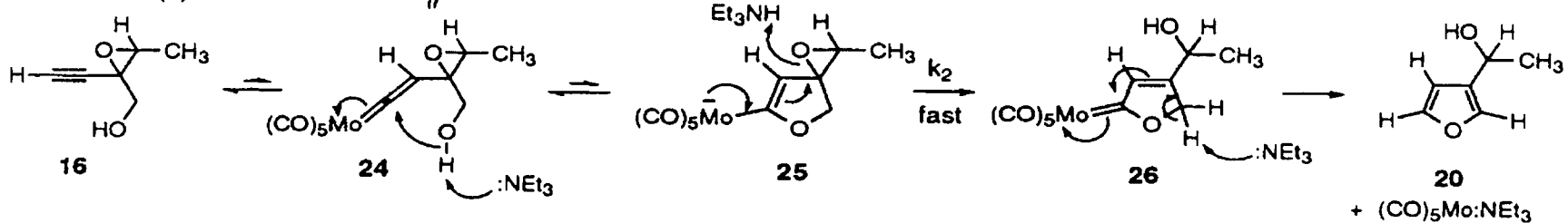


entry	enynne	epoxyalkyne	furan	furan yield
1				85%
2				76%
3				83%
4				85%
5				63%

mechanism (a):

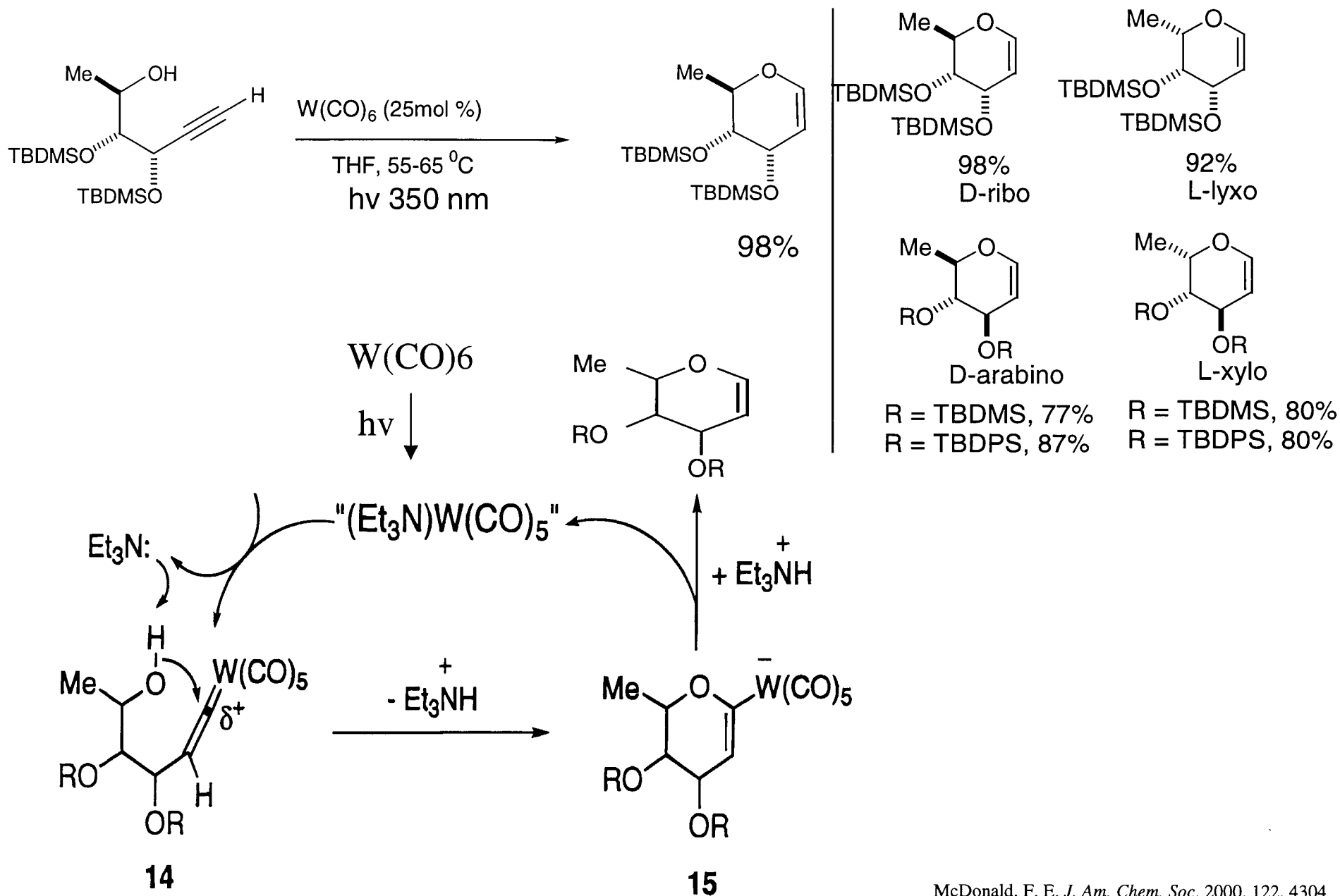


mechanism (b):

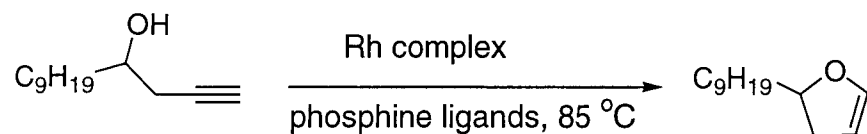




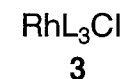
# Tungsten-Catalyzed Cycloisomerization of Terminal Alkynes



# Rhodium-Catalyzed Cycloisomerization of Terminal Alkynes



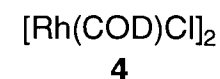
Rh complex



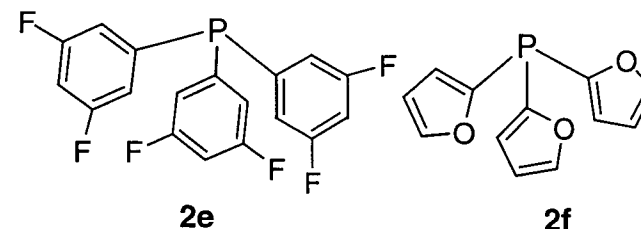
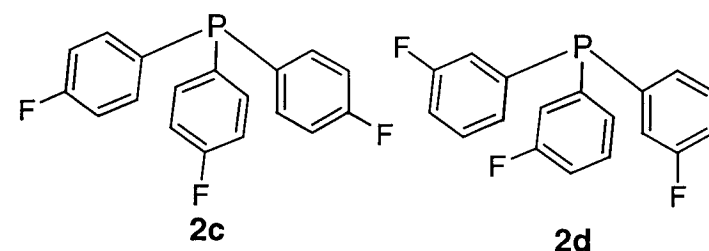
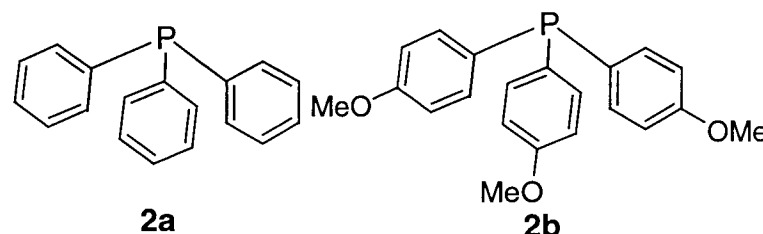
a) L = 2a      c) L = 2d

b) L = 2c      d) L = 2e

entry	Rh complex	ligand	time (h)	conv	yield <sup>a</sup>
1	<b>3a</b> (10%)		2	100%	25%
2	<b>3a</b> (10%)	<b>2a</b> (40%)	2	100%	46%
3	<b>3a</b> (10%)	<b>2a</b> (60%)	2	100%	53%
4	<b>3a</b> (10%)	<b>2a</b> (80%)	2	100%	51%
5	<b>4</b> (2.5%)	<b>2a</b> (55%)	2	100%	55%
6	<b>4</b> (2.5%)	<b>2b</b> (55%)	2	100%	42%
7	<b>4</b> (2.5%)	<b>2c</b> (55%)	2	100%	61%
8	<b>4</b> (2.5%)	<b>2d</b> (55%)	2	100%	69%
9	<b>4</b> (2.5%)	<b>2e</b> (55%)	2	100%	75% (69%) <sup>b</sup>
10	<b>4</b> (2.5%)	<b>2f</b> (55%)	4	40%	29%
11	<b>3d</b> (5%)	<b>2e</b> (30%)	1	100%	73% (68%) <sup>b</sup>
12	<b>3d</b> (3%)	<b>2e</b> (20%)	2	83%	55%

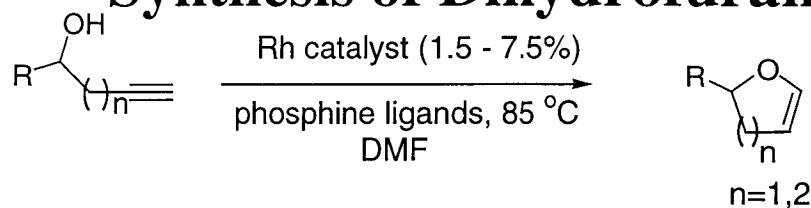


Ligands



<sup>a</sup> GC yield. <sup>b</sup> Isolated yield.

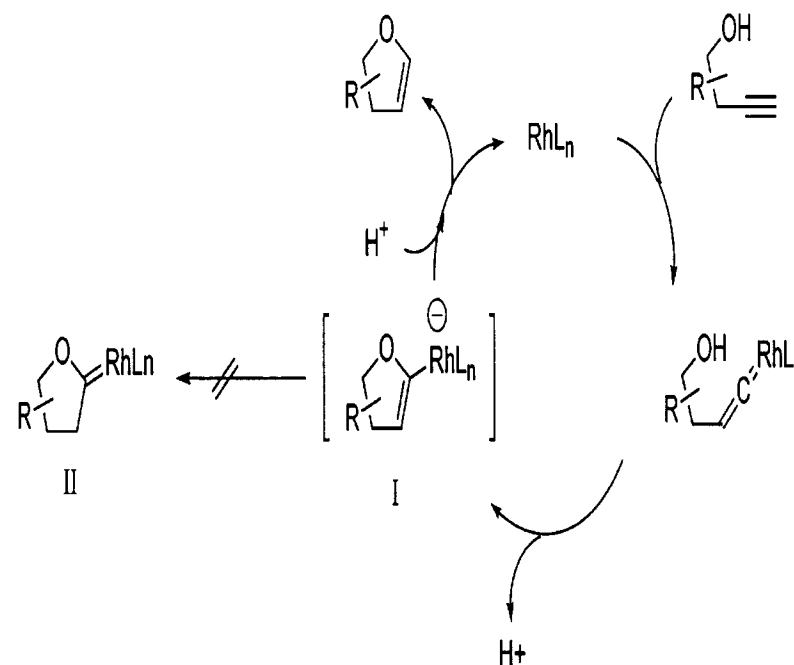
# Synthesis of Dihydrofurans and Dihhydropyrans



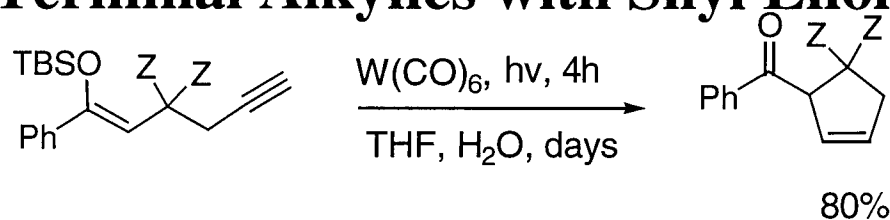
Entry	Substrate	Product	Method <sup>a</sup>	Conv	Yield <sup>b</sup>
1			A	100%	69%
			B	85%	52%
			C	100%	68%
2			A	90%	62%
3			A	100%	71%
			C	100%	68%
4			A	100%	74%
			B	>98%	67%
5			A	100%	61%
6			C	100%	61%
7			C	100%	58%
			D	>98%	70%
8			C	>95%	54%
			D	>95%	67%
9			A	94%	52%

<sup>a</sup> Method A: catalyst **4** (2.5%), ligand **2e** (55%) were used. Method B: catalyst **4** (1.5%), ligand **2e** (33%) were used. Method C: catalyst **3d** (5%), ligand **2e** (30%) were used. Method D: catalyst **3c** (7.5%), ligand **2d** (45%) were used. <sup>b</sup> Isolated yield.

## Mechanism:

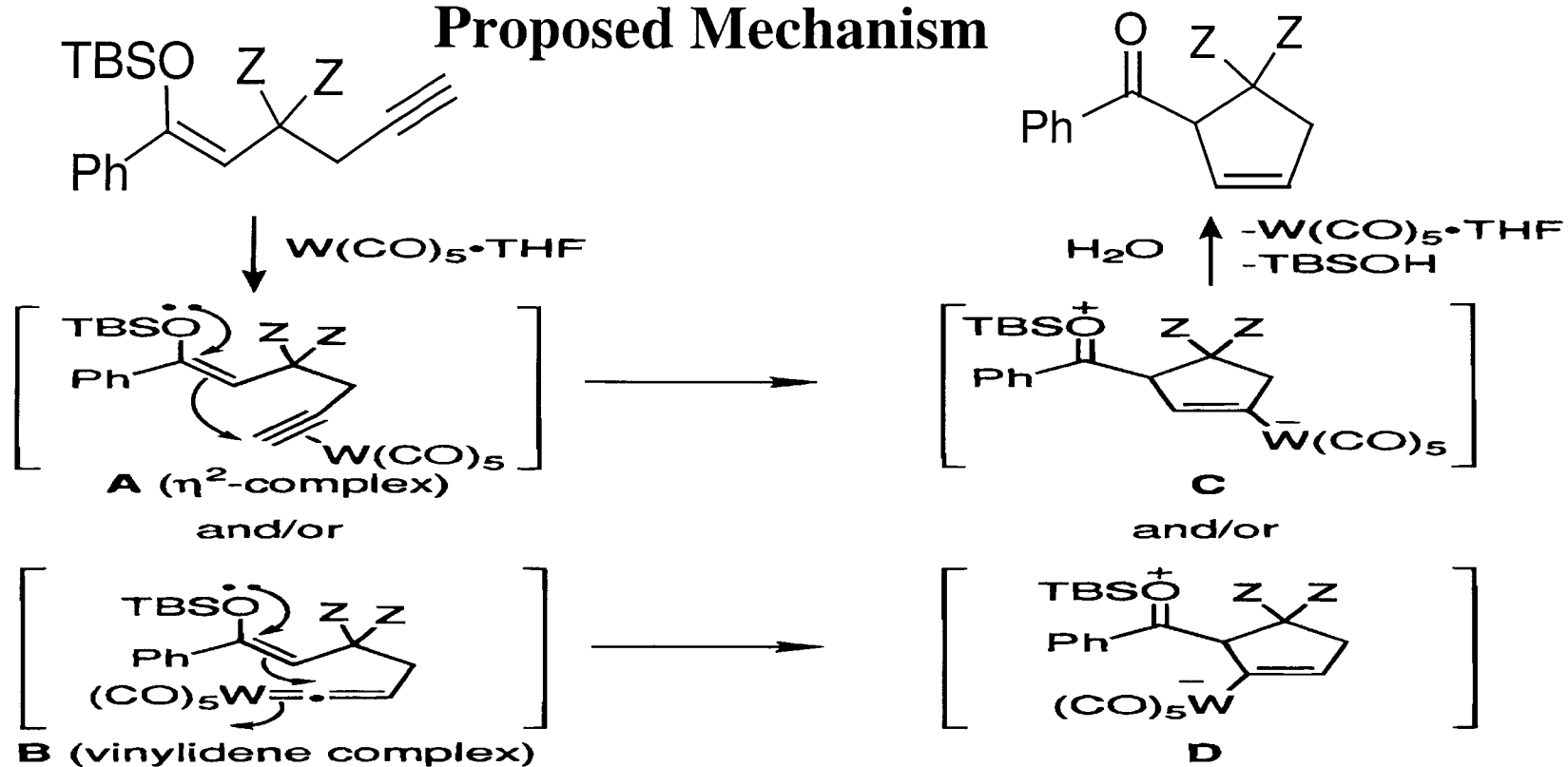


# Terminal Alkynes with Silyl Enol Ether Tether

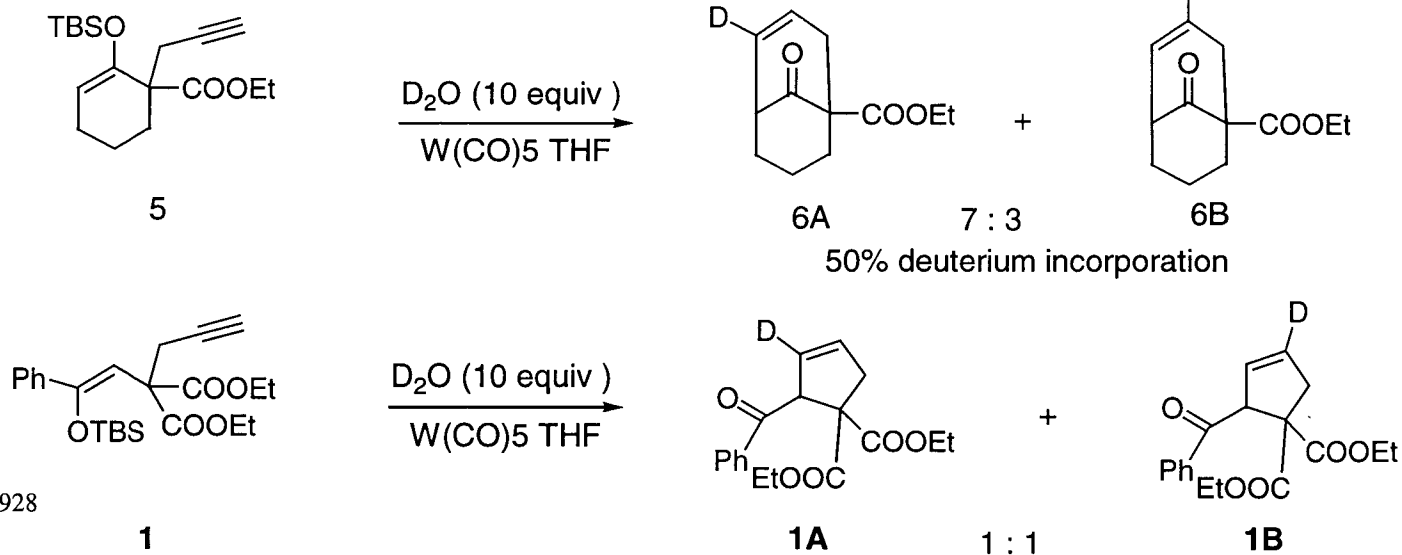


Starting Material	Product	Yield(%)		
		Amount of W(CO) <sub>5</sub> ·THF 1.2-1.5 eq	0.3 eq	0.1 eq
<p><b>1</b> (Z=COOEt)</p>	<p><b>2</b></p>	80	73	56 <sup>b</sup>
<p><b>3a</b></p>	<p><b>4</b></p>	93	93	96
<p><b>3b</b> <i>n</i>-Bu</p>		No Reaction		
<p><b>5</b></p>	<p><b>6</b></p>	88	90	90
<p><b>7</b></p>	<p><b>8</b></p>	90	93	97
<p><b>9</b></p>	<p><b>10</b></p>	74	77	64 <sup>c</sup>
<p><b>11</b></p>	<p><b>12</b></p>	80	82	83

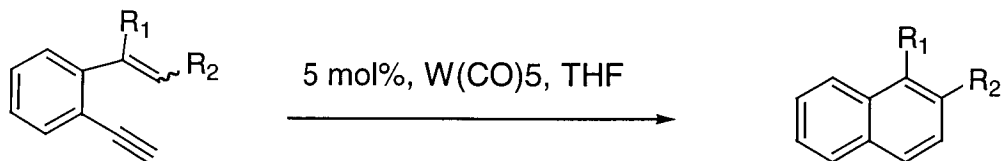
# Proposed Mechanism



Deuterium labeling  
Experiments:



# Alkene Tethers



Naphthelene derivatives

R<sub>2</sub> = COOMe

R<sub>1</sub> = Me 100% (Z)

R<sub>1</sub> = Me 88% (E)

R<sub>1</sub> = OTBS 90%

R<sub>1</sub> = R<sub>2</sub> = Me 16%

R<sub>2</sub> = H

R<sub>1</sub> = Me 80%

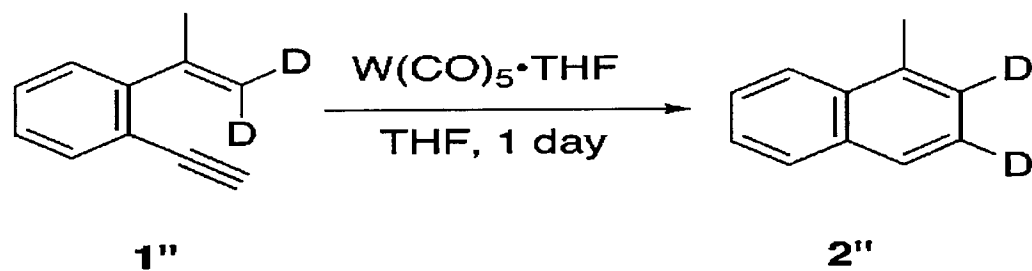
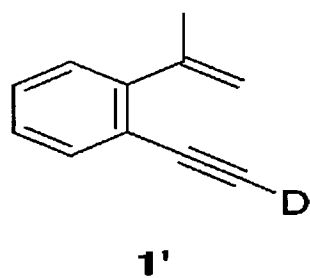
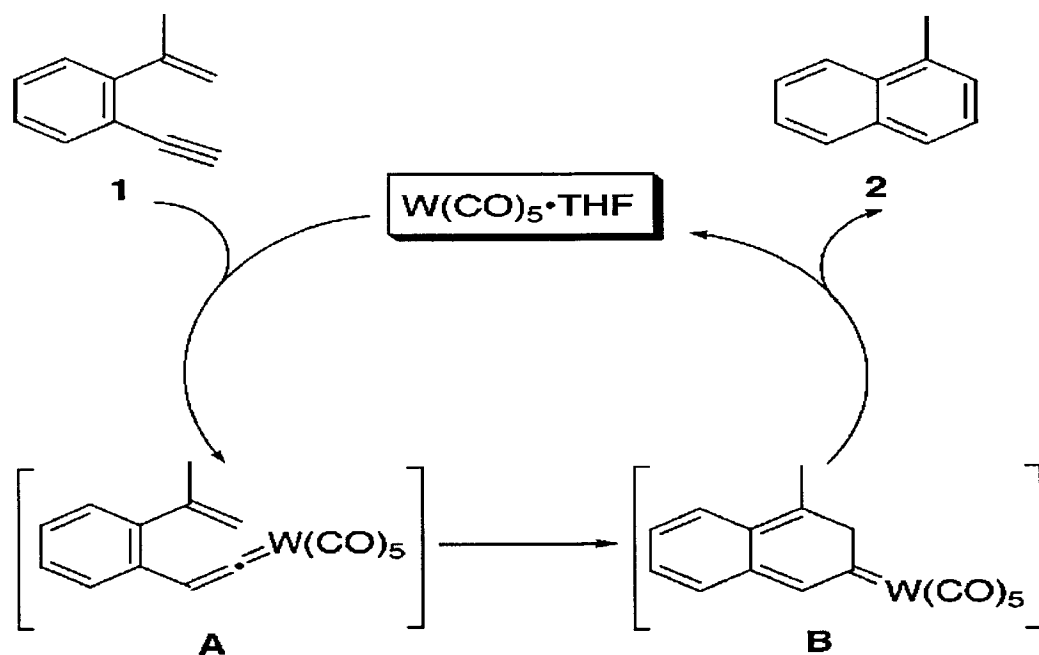
R<sub>1</sub> = COOMe 84%

R<sub>1</sub> = OTBS 100%

Substrates	Product(%)
<p><b>17</b></p>	<p><b>18</b> 82%<sup>a)</sup></p>
<p><b>19</b></p>	<p><b>20</b> 82%</p>
<p><b>21</b></p>	<p><b>22</b> 99%</p>
<p><b>23</b></p>	<p><b>24</b> 89%</p>

Procedure: The reaction was carried out in the same manner as shown in Table 1. a) 100 mol% amount of W(CO)<sub>5</sub>·THF was used.

# Proposed Mechanism for Electrocyclization



# Ruthenium-Catalyzed Cyclization of Dienylalkynes



entry	catalyst <sup>a</sup>	time (h)	yield (%)
1	1% RuClCp(PPh <sub>3</sub> ) <sub>2</sub>	24 <sup>b</sup>	9 <sup>c</sup>
2	none	24 <sup>b</sup>	0
3	10% RuClCp(PPh <sub>3</sub> ) <sub>2</sub>	22	51
4	5% RuClCp(PPh <sub>3</sub> ) <sub>2</sub>	30	44 <sup>c</sup>
5	5% RuClCp(dppe)	24	56
6	5% RuClCp(dppm)	~24	19 <sup>c</sup>
7	6% RuClCp[P(OEt) <sub>3</sub> ] <sub>2</sub>	40	66 <sup>c</sup>
8	4% [RuCl <sub>2</sub> (CO) <sub>3</sub> ] <sub>2</sub> /CO	48 <sup>b</sup>	58
9	5% RuCl <sub>2</sub> (C <sub>6</sub> H <sub>6</sub> )AsPh <sub>3</sub>	43	42
10	7% RuCl <sub>2</sub> (C <sub>6</sub> H <sub>6</sub> )PPh <sub>3</sub>	24	80 <sup>c</sup>
11	5% RuCl <sub>2</sub> (C <sub>6</sub> H <sub>6</sub> )[P(OEt) <sub>3</sub> ]	45	79 <sup>c</sup>
12	4% RuCl <sub>2</sub> (p-cymene)PPh <sub>3</sub>	10	89

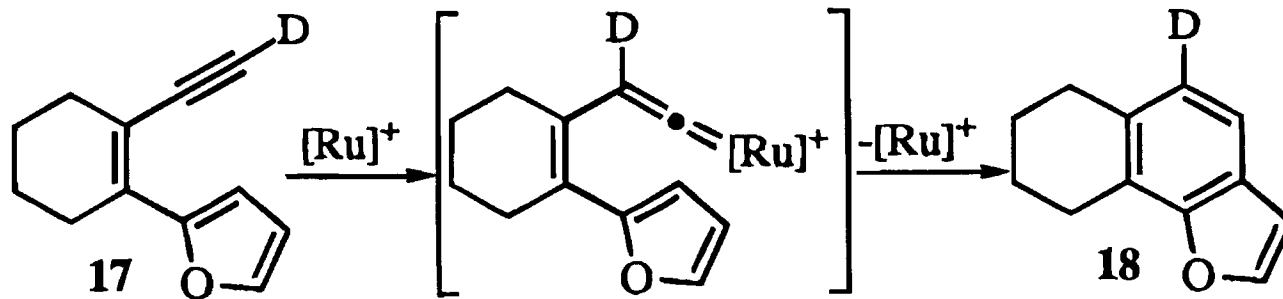
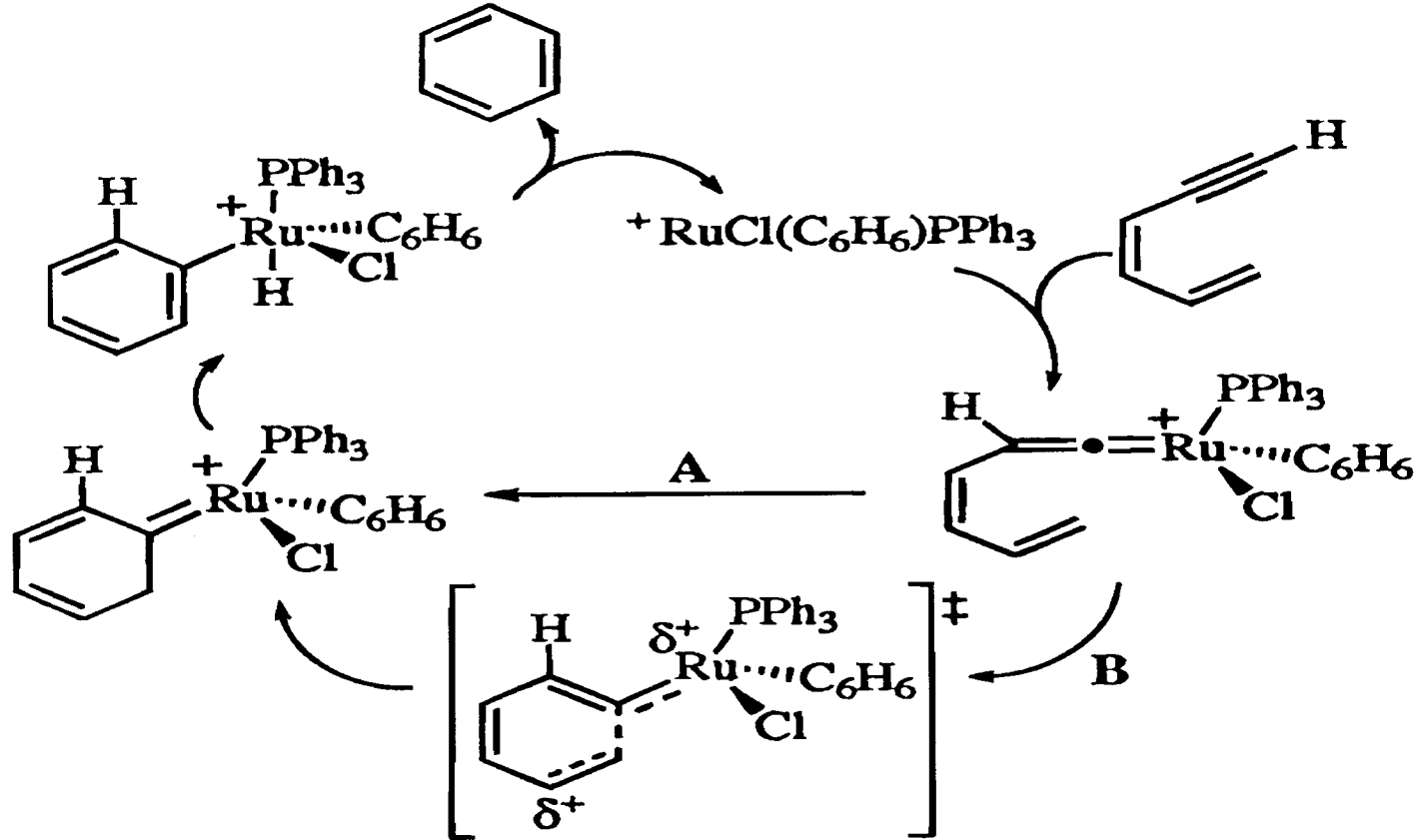
<sup>a</sup> Reaction performed in the presence of 5–14% NH<sub>4</sub>PF<sub>6</sub> in refluxing CH<sub>2</sub>Cl<sub>2</sub> unless otherwise noted. <sup>b</sup> THF solvent. <sup>c</sup> Yield calculated from <sup>1</sup>H NMR integration.

entry	substrate	product	cond. <sup>a</sup>	yield (%)
1			A	89
2			A	74
3			B	18 <sup>b</sup>
4			A	86
5			B	57
6			C	0
7			A	12 <sup>b</sup>
8			A	23 <sup>b</sup>

<sup>a</sup> Conditions: refluxing CH<sub>2</sub>Cl<sub>2</sub> or C<sub>2</sub>H<sub>4</sub>Cl<sub>2</sub>; (A) 5–15% NH<sub>4</sub>PF<sub>6</sub>, ~5% RuCl<sub>2</sub>(p-cymene)PPh<sub>3</sub>; (B) 6% NH<sub>4</sub>PF<sub>6</sub>, ~5% RuCl<sub>2</sub>(C<sub>6</sub>H<sub>6</sub>)PPh<sub>3</sub>; (C) attempted several catalysts. <sup>b</sup> Yield calculated from <sup>1</sup>H NMR integration.

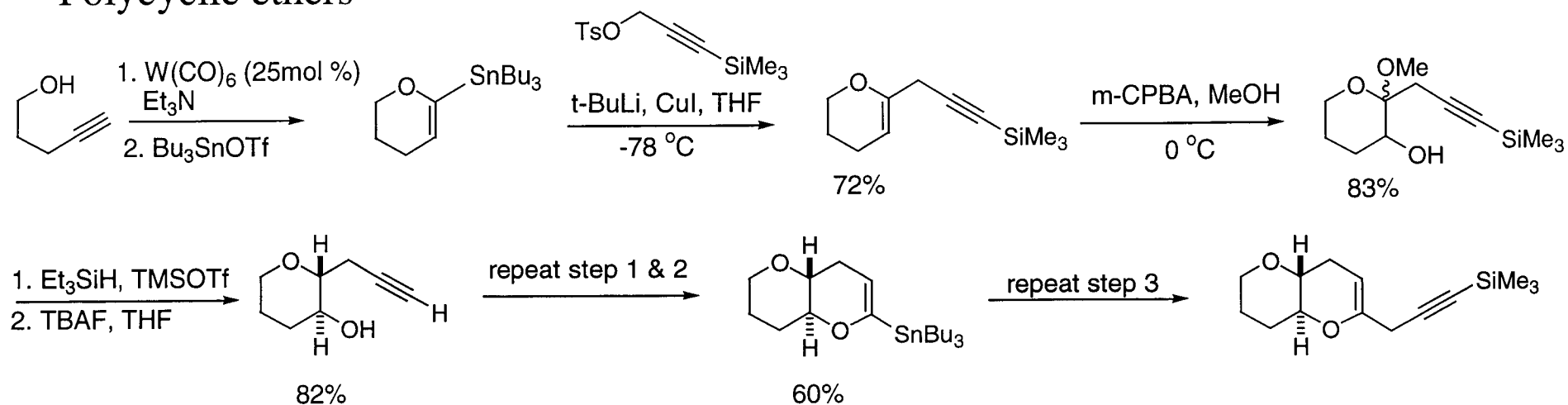


# Proposed Mechanism

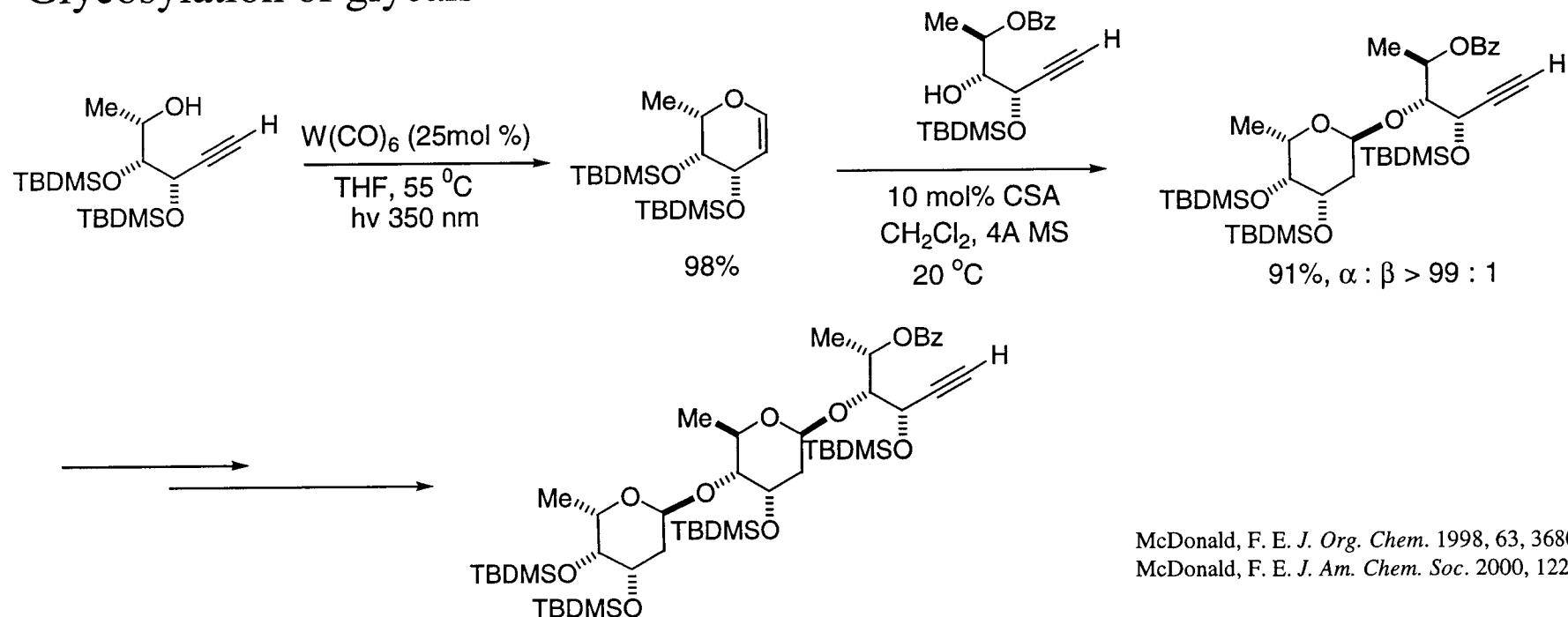


# Application in Synthesis

## Polycyclic ethers



## Glycosylation of glycals



## Conclusions

- Cycloisomerization provides a mild and efficient method for the synthesis of dihydrofuran and dihydropyran derivatives.
- There is still room for improvement on the generality of the reaction: catalysts and substrate scope (nitrogen nucleophiles).
- The metal vinylidene intermediate has been proven to be synthetically useful.