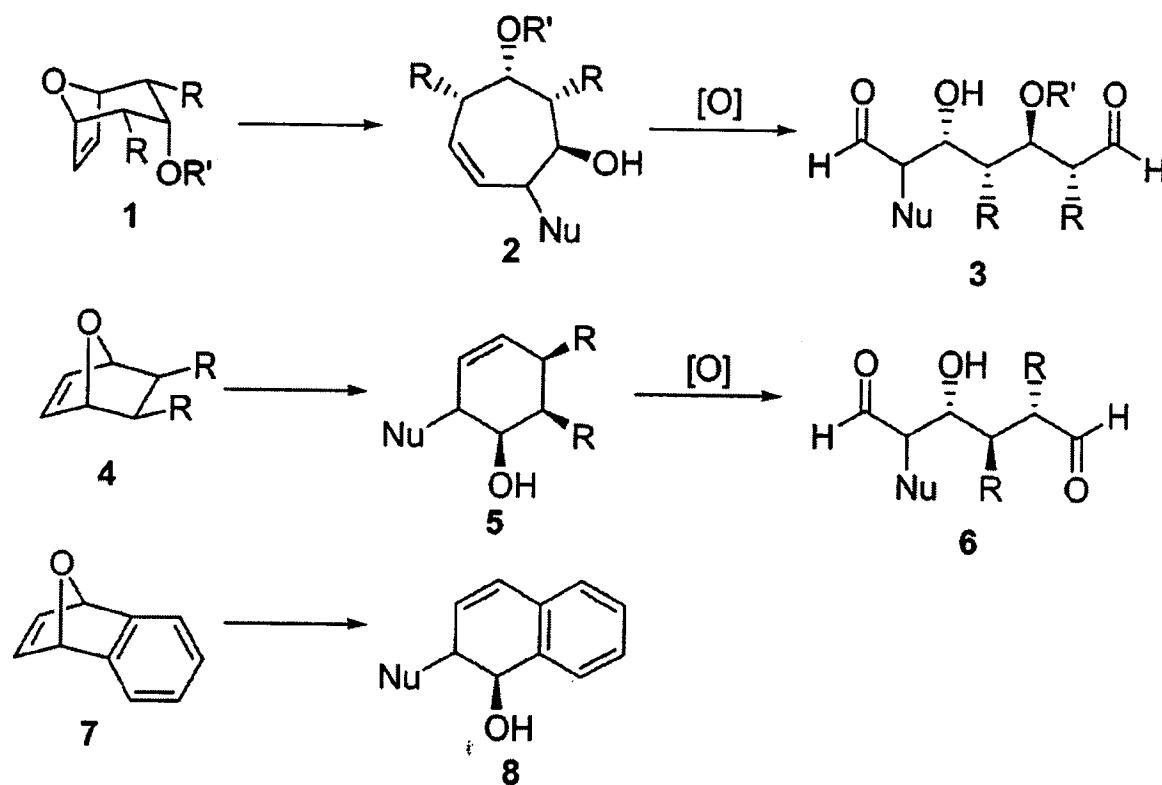
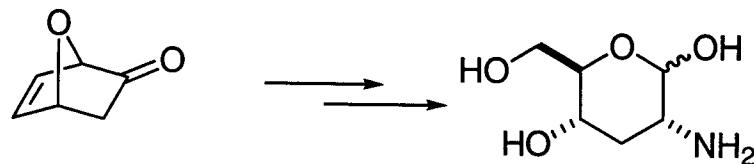


# Stereoselective Ring Opening Reactions of *meso*-Oxabicyclic Alkenes



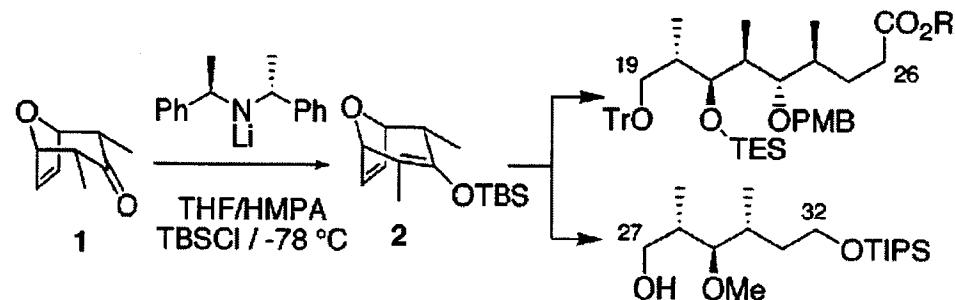
Denmark Group Meeting  
4/29/03  
Shinji Fujimori

# Oxabicyclic Alkenes in Enantioselective Synthesis



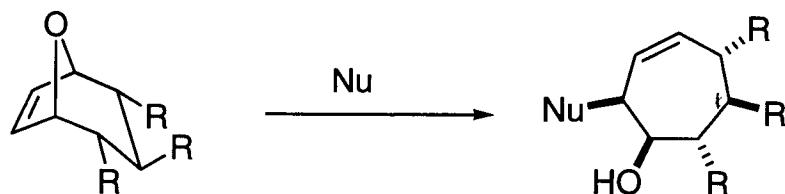
Use of optically active oxabicyclic compounds

Warm, A.; Vogel, P. *J. Org. Chem.* **1986**, *51*, 5348.



Desymmetrization of *meso*-oxabicyclic/ subsequent opening reaction

Hunt, K. W.; Grieco, P. A. *Org. Lett.* **2002**, *4*, 245.

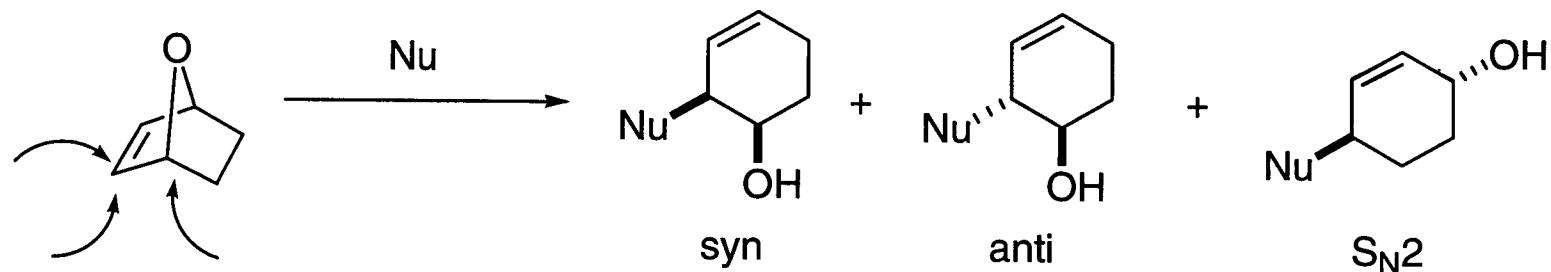


Desymmetrization reaction as the ring-opening event?

Lautens, M. *Synlett* **1993**, 177.  
Woo, S.; Keay, B. A. *Synthesis* **1996**, 669.  
Lautens, M. *Top. Curr. Chem.* **1997**, *190*, 1.

# Ring Opening Reactions with Nucleophiles: Overview

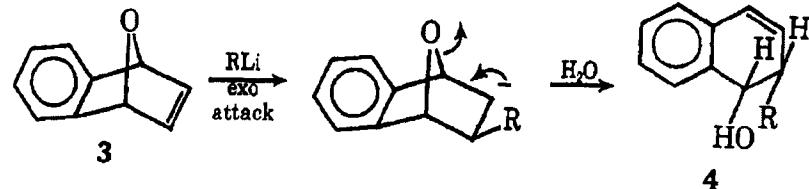
- Type of nucleophiles: hydride, carbon nucleophiles, heteroatom nucleophiles
- Selectivity: chemoselectivity, regioselectivity, enantioselectivity



- Catalysis by transition metal (Ni, Pd, Rh, Fe, etc.)
- Chiral ligands for asymmetric ring opening reactions

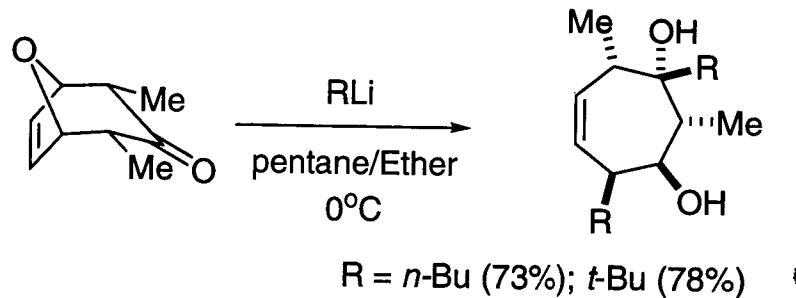
# Ring Opening Reactions Using Alkyl Lithium

Caples (1971):



Conditions: 1.1 – 3 eq. of RLi in Et<sub>2</sub>O  
rt for 15 min. – 1 hr

Lautens (1990):



R = *t*-Bu; quant.

R = *n*-Bu; 85 – 90% w/ formation of double addition

- *cis* relationship established by NMR coupling constant (*J* = ~5 Hz)

- Prior coordination of Li to oxygen proposed

**Table I. Organolithium Opening of Oxabicyclo[3.2.1]-octenes**

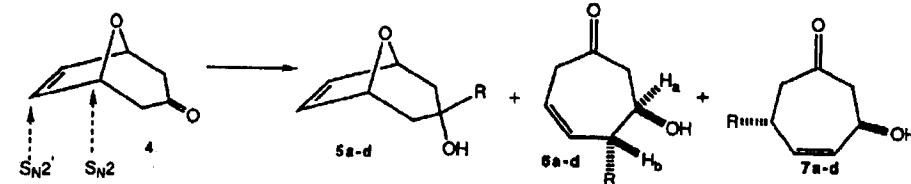
| entry | oxabicyclo[3.2.1]-octenes | product                | yield, <sup>a</sup> % |
|-------|---------------------------|------------------------|-----------------------|
| 1     |                           |                        | 85                    |
| 2     | (a)                       | 7; R = H, R' = Bu      | 92                    |
|       | (b)                       | 8; R = H, R' = Me      | 72 <sup>b</sup>       |
|       | (c)                       | 10; R = TBDMS, R' = Bu | 79                    |
|       |                           |                        |                       |
| 3     | (a)                       | 12; R = <i>t</i> -Bu   | 82                    |
|       | (b)                       | 13; R = <i>n</i> -Bu   | 88                    |
| 4     |                           |                        | 74                    |

<sup>a</sup> Isolated yields of analytically pure material. <sup>b</sup> 1:1 ether/TMEDA were required as solvent before reaction occurred.

Caples, R.; Chen, G. M. S.; Nelson, J. D. *J. Org. Chem.* 1971, 36, 2874.  
Lautens, M. et. al. *J. Org. Chem.* 1990, 55, 5305.

# Ring Opening Reactions Using Alkyl Cuprate

- [3,2,1]-system gives anti product.



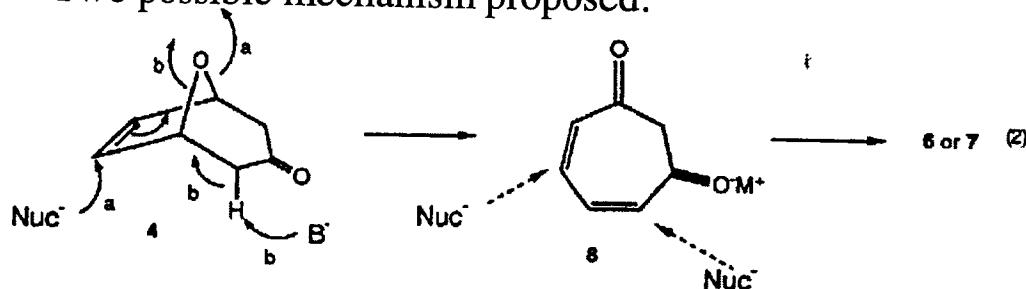
-[2,2,1]-system gives syn product.



| Entry | RLi           | Copper Source          | Conditions                                   | Product(s)       | Yield <sup>1</sup> |
|-------|---------------|------------------------|--|------------------|--------------------|
| 1     | MeLi          | CuCN                   | Et <sub>2</sub> O, -23°C                     | 10:1:0 5a:6a:7a  | 55% <sup>2</sup>   |
| 2     | MeLi          | CuCN                   | Et <sub>2</sub> O, -78°C                     | 1:0:0 " "        | 20% <sup>3</sup>   |
| 3     | MeLi          | CuCN                   | Et <sub>2</sub> O, 0 °C to r.t.              | 1:15:0 " "       | 66%                |
| 4     | BuLi          | CuCN                   | Et <sub>2</sub> O, 0 °C to r.t.              | 1:19:10 5b:6b:7b | 60%                |
| 5     | BuLi          | CuCN                   | THF, 0 °C to r.t.                            | 1:15:0 " "       | 59%                |
| 6     | BuLi          | CuCN                   | THF : Et <sub>2</sub> O (1:1), 0 °C to r.t.  | 1:3:0 " "        | 70%                |
| 7     | BuLi          | CuCN                   | Me <sub>2</sub> S, 0 °C to r.t.              | 1:1.6:5.8 " "    | 57%                |
| 8     | BuLi          | CuI                    | THF, 0 °C to r.t.                            | " "              |                    |
| 9     | BuLi          | CuBr-Me <sub>2</sub> S | THF, 0 °C to r.t.                            | 0:13:1 " "       | 77%                |
| 10    | s-BuLi        | CuCN                   | THF, 0 °C to r.t.                            | 0:8:1 5c:6c:7c   | 85%                |
| 11    | t-BuLi        | CuCN                   | THF, 0 °C to r.t.                            | 0:1:0 5d:6d:7d   | 37% <sup>4</sup>   |
| 12    | vinyl lithium | CuCN                   | THF : Et <sub>2</sub> O (2:1), 0 °C to r.t.. | 1:2:2.5 5e:6e:7e | 76%                |

1. Combined yield of all isomers. 2. 33% recovered starting material. 3. 60% recovered starting material. 4. Unoptimized yield.

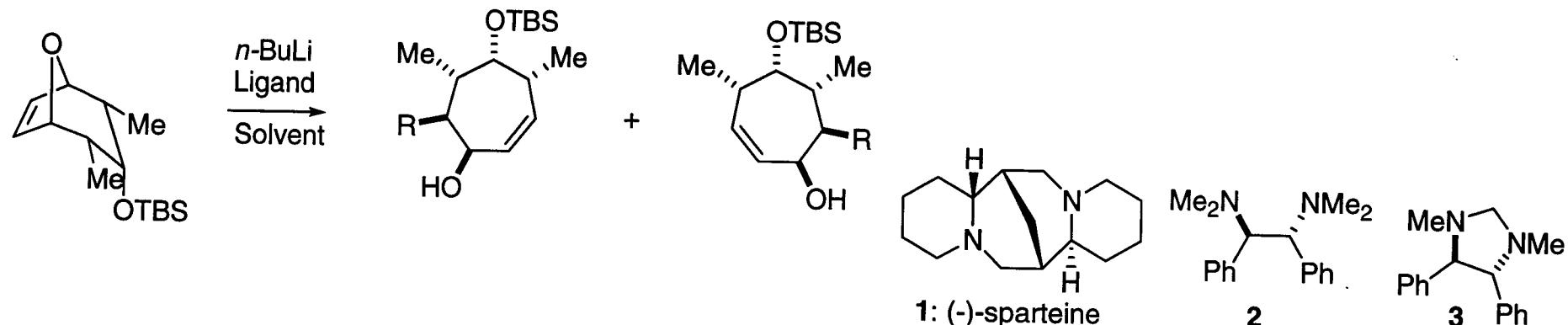
- Two possible mechanism proposed:



- Addition to C=O minimized with cuprate
- S<sub>N</sub>2' selectivity dependent on: temperature, solvent and size of alkyl
- [2,2,1] system is less reactive
- change in selectivity may be explained by coordination of Cu

# First Asymmetric Ring Opening Reaction

Lautens (1993): Alkyl lithium/Sparteine



- reaction in ether (\*) is fast, but unselective
- reaction in pentane, 24 – 48 hrs
- Ligands **2** (4%ee) and **3** (20%ee) are not selective
- Sparteine loading can be lowered to 15 mol %  
result: 52%ee, 60% yield
- Precomplexation of RLi and Ligand necessary

| entry | temp. | Lig./RLi/Subst. | ee% | yield |
|-------|-------|-----------------|-----|-------|
| 1     | Rt    | 5/5/1           | 26  | 77    |
| 2     | 0     | 5/5/1           | 35  | 79    |
| 3     | -40   | 5/5/1           | 40  | 52    |
| 4*    | -78   | 5/5/1           | 20  | 36    |
| 5     | -78   | 25/5/1          | 52  | 69    |
| 6     | -78   | 0.15/5/1        | 52  | 60    |
| 7     | -78   | 0.03/5/1        | 30  | 60    |

# Transition Metal Catalyzed Ring Opening Reactions-Ni/RMgX

Table 1.  $(PPh_3)_2NiCl_2$ -Catalyzed Ring Opening of 1

| Entry | RMgX                   | Catalyst<br>( mol%) | Product | Temperature | Time | Yield <sup>a</sup><br>(%) |
|-------|------------------------|---------------------|---------|-------------|------|---------------------------|
|       |                        |                     |         |             |      |                           |
| 1     | MeMgBr                 | 2.6                 | 2       | r.t.        | 23 h | 70                        |
| 2     | MeMgBr                 | 0                   | 2       | reflux      | 48 h | <5                        |
| 3     | PhMgBr                 | 2.5                 | 3       | r.t.        | 5 h  | 67                        |
| 4     | PhCH <sub>2</sub> MgCl | 6.0                 | 4       | reflux      | 9 h  | 18                        |

<sup>a</sup> Isolated yield of analytically pure material.

- Previously unreactive substrate reacted w/ Ni-cat.
- Clean  $S_N2'$  can be achieved w/ syn selectivity
- Solvent effect: significantly change product ratio
- *anti*-product can be obtained but low selectivity ( $5/6 = 1.4/1 \sim 1/2.8$ )
- intermediacy of  $\pi$ -allyl nickel:

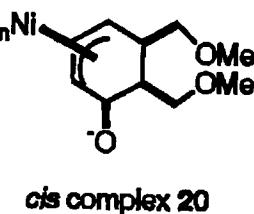
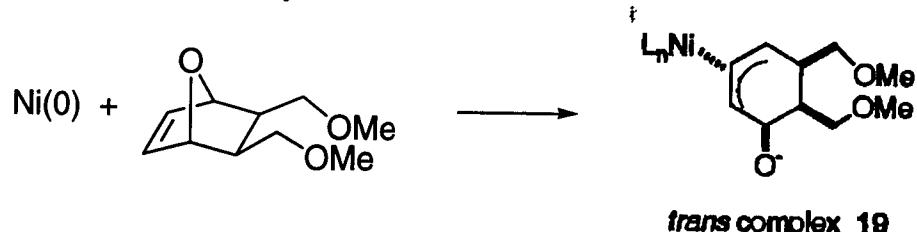
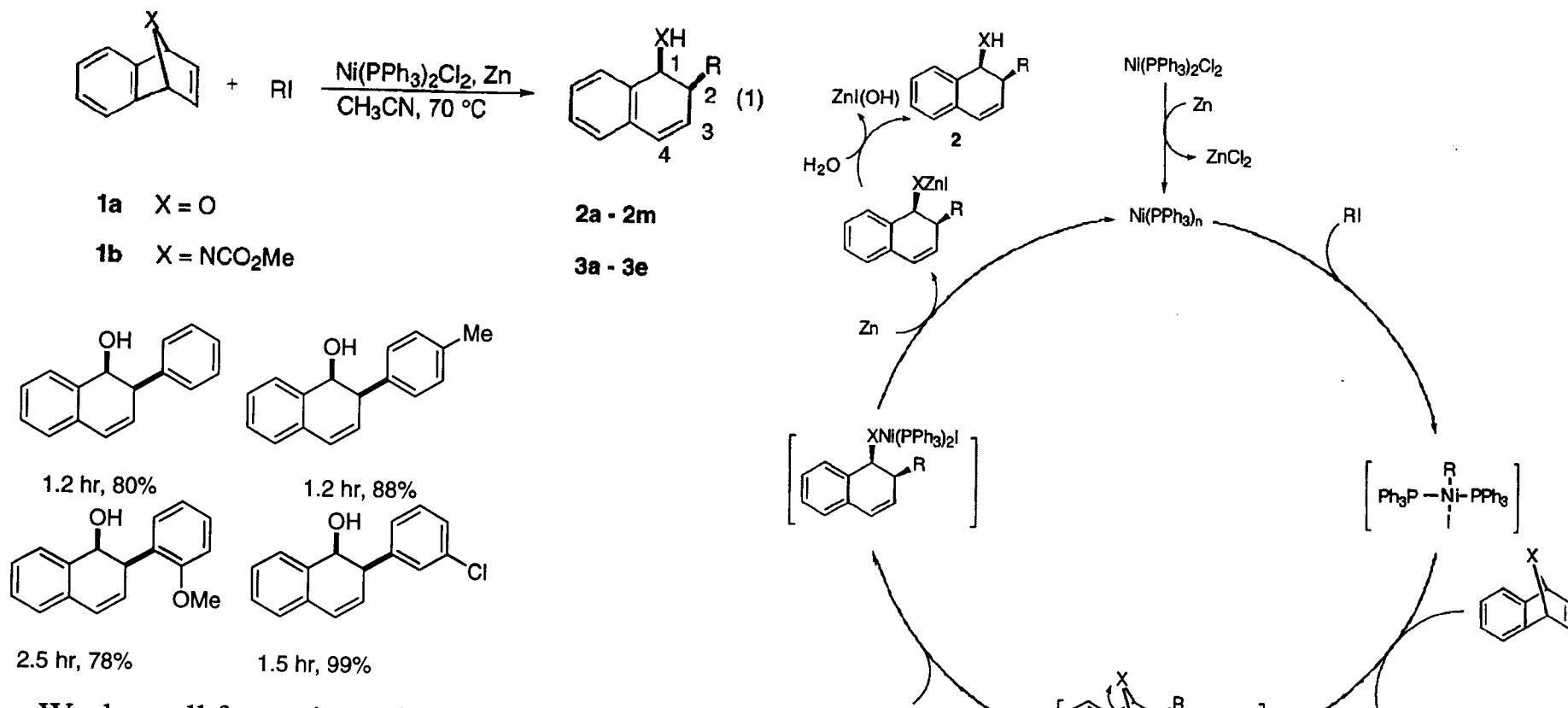


Table 2. Catalyst and Solvent Effect in the Reaction of MeMgBr with 1

| Entry | Catalyst <sup>a</sup> | Solvent                              | Yield of 2 <sup>b</sup> | Yield of 5+6 <sup>b,c</sup> |
|-------|-----------------------|--------------------------------------|-------------------------|-----------------------------|
|       |                       |                                      | Yield of 5 <sup>d</sup> |                             |
| 1     |                       | THF                                  | 70%                     |                             |
| 2     | $Ni(COD)_2$           | $Et_2O$                              | 48% <sup>d</sup>        |                             |
| 3     |                       | $Et_2O/HMPA^e$                       | 30% <sup>f</sup>        |                             |
| 4     |                       | THF                                  | 70%                     |                             |
| 5     | $(PPh_3)_2NiCl_2$     | THF/HMPA <sup>e</sup>                | 68%                     |                             |
| 6     |                       | $Et_2O/HMPA^e$                       |                         | 5% <sup>f</sup>             |
| 7     |                       | THF                                  | 64%                     |                             |
| 8     | $(dppp)NiCl_2$        | $Et_2O/HMPA^e$                       |                         | 95%                         |
| 9     |                       | $t\text{-butyl methyl ether}/HMPA^e$ |                         | 84%                         |
| 10    |                       | toluene/HMPA <sup>e</sup>            |                         | 80%                         |

<sup>a</sup> Conditions: 2 mol % to 10 mol % catalyst, 5.0 equiv of MeMgBr, 22 °C. <sup>b</sup> Isolated yield. <sup>c</sup> Ratio of 5:6, see ref 6a. <sup>d</sup> 28 mol %  $Ni(COD)_2$ , at reflux temperature. <sup>e</sup> Solvent/HMPA is 15:1. <sup>f</sup> Starting material recovered.

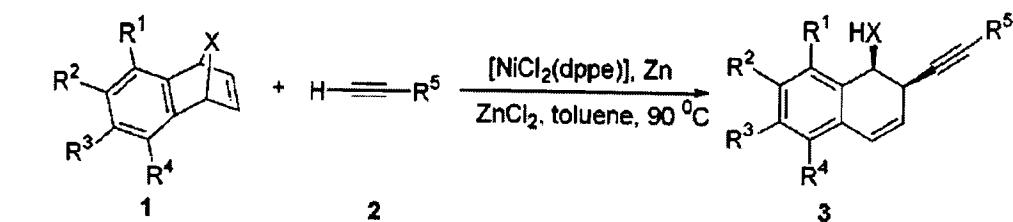
# Transition Metal Catalyzed Ring Opening Reactions-Ni/RX/Zn



- Works well for variety of aryl iodides except for OH, NH<sub>2</sub>, NO<sub>2</sub>, Ac substituted
- Ar-Br (poor); Ar-Cl (no rxn)
- Solvent: MeCN optimal  
THF, MeOH, DMF, DMSO, PhMe,  $\text{CH}_2\text{Cl}_2$  not suitable
- excess  $\text{PPh}_3$  inhibits catalytic cycle

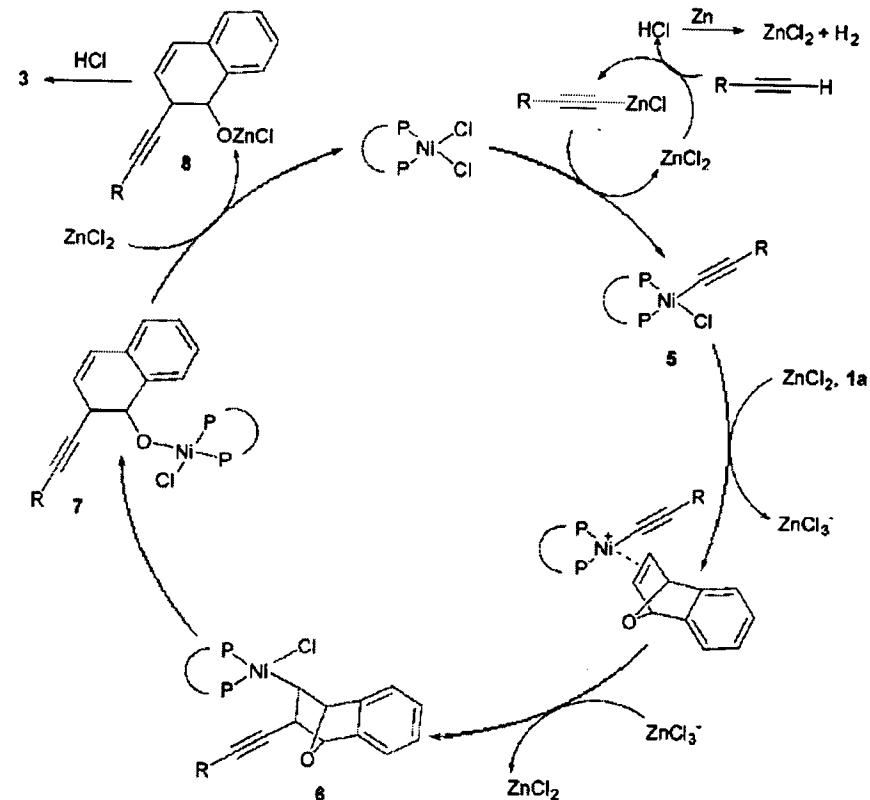
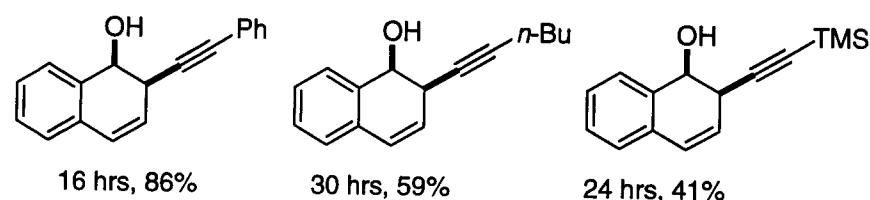
Feng, C.-C.; Nandi, M.; Sambaiah, T.; Cheng, C.-H. *J. Org. Chem.* **1999**, *64*, 3538.

# Transition Metal Catalyzed Ring Opening Reactions-Ni/Alkyne/Zn



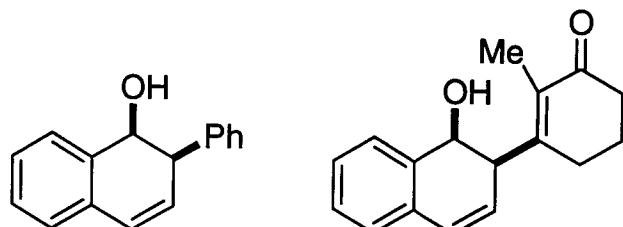
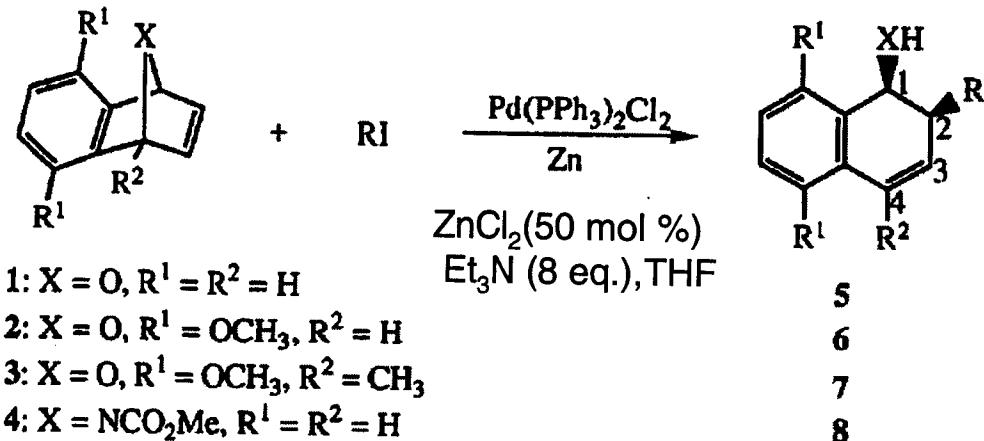
Proposed catalytic cycle:

Scheme 4



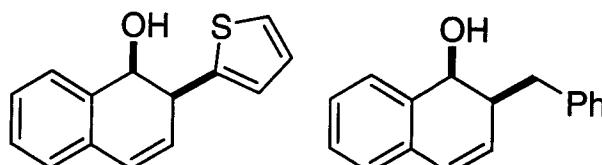
- Variety of reaction pathways envisioned under these conditions. ([2+2+2], [2+2])
- Extensive condition optimization carried out.
- chelating phosphine ligand minimizes the side processes
- Polar solvents promote [2+2+2] process
- Broad substrate scope, but long reaction time.

# Transition Metal Catalyzed Ring Opening Reactions-Pd/RX/Zn



4 hr, 86%

9 hr, 83%

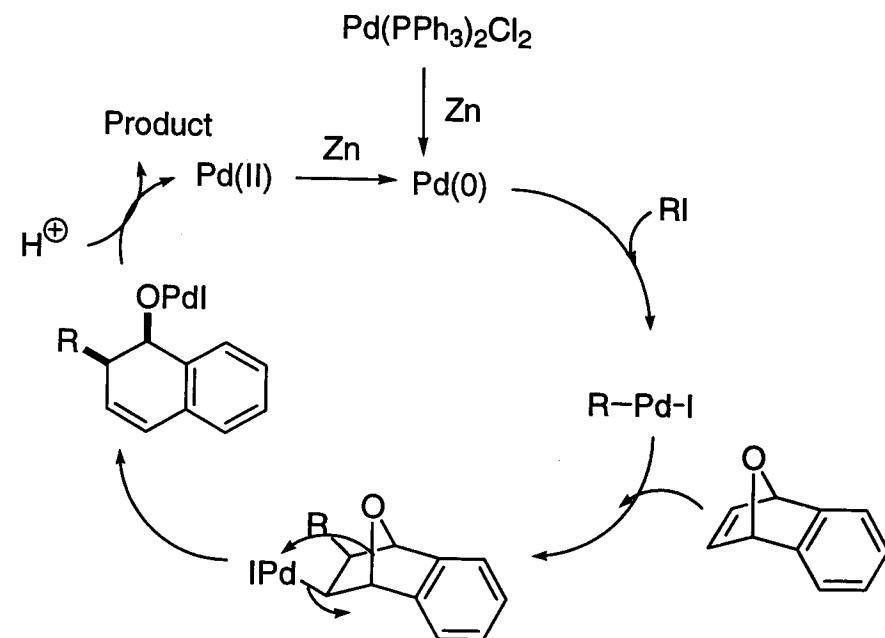


37 hr, 71%  
w/o Et<sub>3</sub>N

11 hr, 99%  
w/o Et<sub>3</sub>N

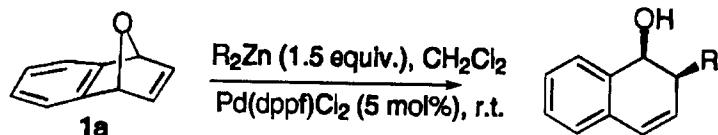
- Clean S<sub>N</sub>2' product, syn addition
- (I) - No reaction without Zn(0)
- Without ZnCl<sub>2</sub>, Et<sub>3</sub>N, low yields

Proposed mechanism:



Cheng, C.-H.; Duan, J.-P. *Tetrahedron Lett.* **1993**, *34*, 4019.  
 Cheng, C.-H.; Duan, J.-P. *Organometallics* **1995**, *14*, 1608.

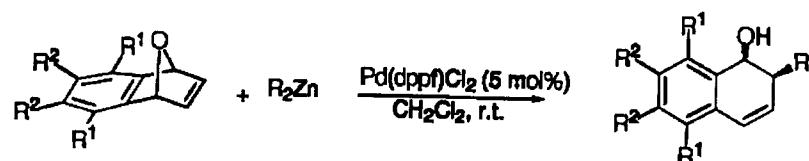
# Transition Metal Catalyzed Ring Opening Reactions-Pd/R<sub>2</sub>Zn



| R                  | yield <sup>a</sup> (%) | de <sup>b</sup> (%) |
|--------------------|------------------------|---------------------|
| Me                 | 80                     | >98                 |
| Et                 | 92                     | >98                 |
| t-Bu               | 72                     | >98                 |
| vinyl              | 55                     | >98                 |
| TMSCH <sub>2</sub> | 67                     | >98                 |

<sup>a</sup> Isolated yield. <sup>b</sup> Determined by <sup>1</sup>H NMR

Table 2. Addition to Other Oxabicycles



| entry | R  | substrate | R <sup>1</sup> | R <sup>2</sup>       | yield <sup>a</sup> (%) |
|-------|----|-----------|----------------|----------------------|------------------------|
| 1     | Me | <b>1b</b> | H              | F                    | 73                     |
| 2     | Me | <b>1c</b> | Me             | Br                   | 71                     |
| 3     | Me | <b>1d</b> | Me             | H                    | 65                     |
| 4     | Me | <b>1e</b> | H              | O(CH <sub>2</sub> )O | quant.                 |
| 5     | Et | <b>1b</b> | H              | F                    | 89                     |
| 6     | Et | <b>1e</b> | H              | O(CH <sub>2</sub> )O | 83                     |

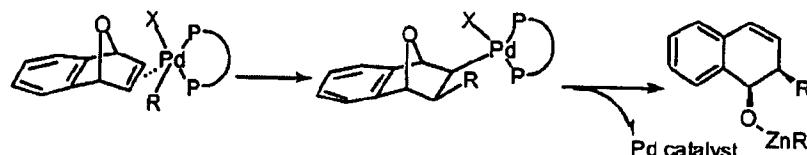
<sup>a</sup> Isolated yield.

- Exclusive syn selectivity for various organozinc reagents
- R<sub>2</sub>Zn reacts slowly with **1a** to form mixture of products
- Chelating ligand provide better results than (PPh<sub>3</sub>)<sub>2</sub>PdCl<sub>2</sub>  
P-Pd-P, Cl-Pd-Cl angles

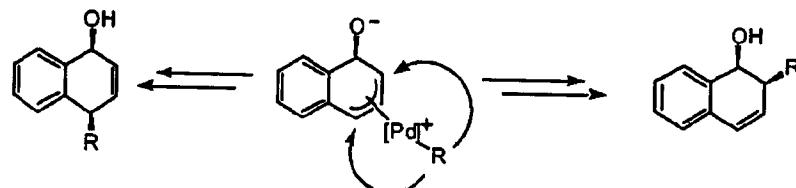
- Ni(II) catalyst was not effective

# Mechanistic Study on Pd-catalyzed Ring Opening Reaction

carbopalladation pathway

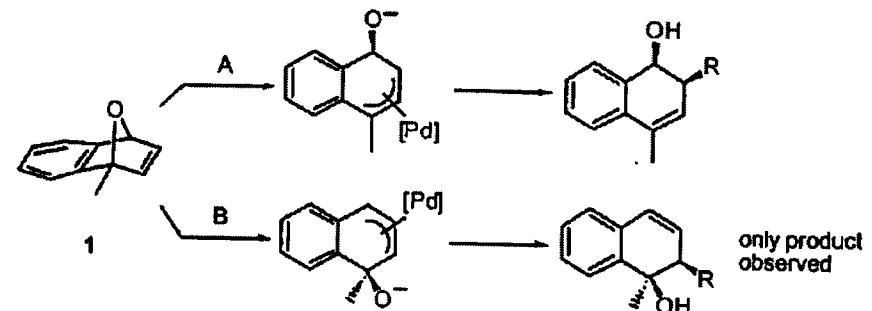


$\pi$ -allyl pathway



- Two proposed pathways
- Evidence against  $\pi$ -allyl intermediate
- Pd(0) is not catalytically active

Scheme 3

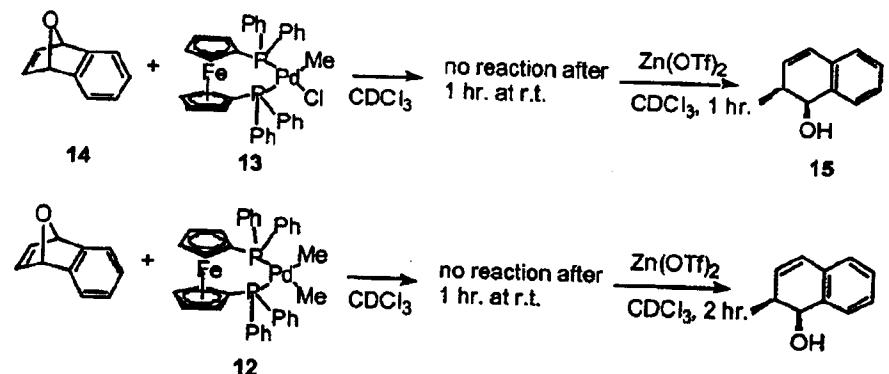
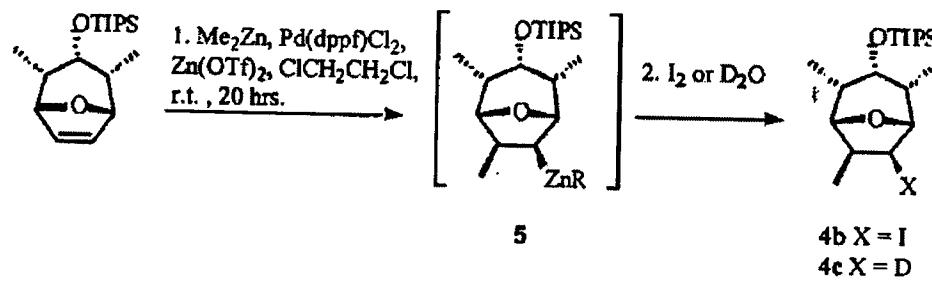


Evidence for the carbopalladation pathway:

- trapping the intermediate with electrophiles

- reaction with Pd-alkyl species

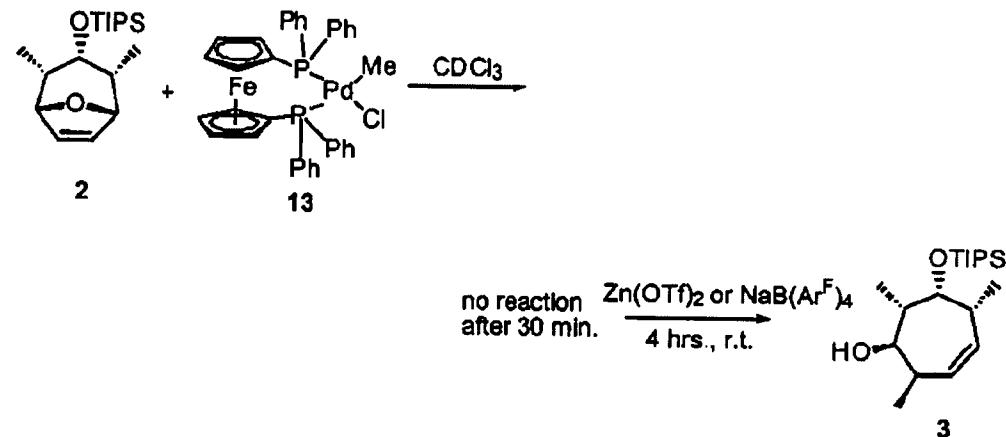
Scheme 8



# Mechanistic Study on Pd-catalyzed Ring Opening Reaction

Effect of Zinc Salt: Formation of cationic palladium species

Scheme 11



Mechanism:

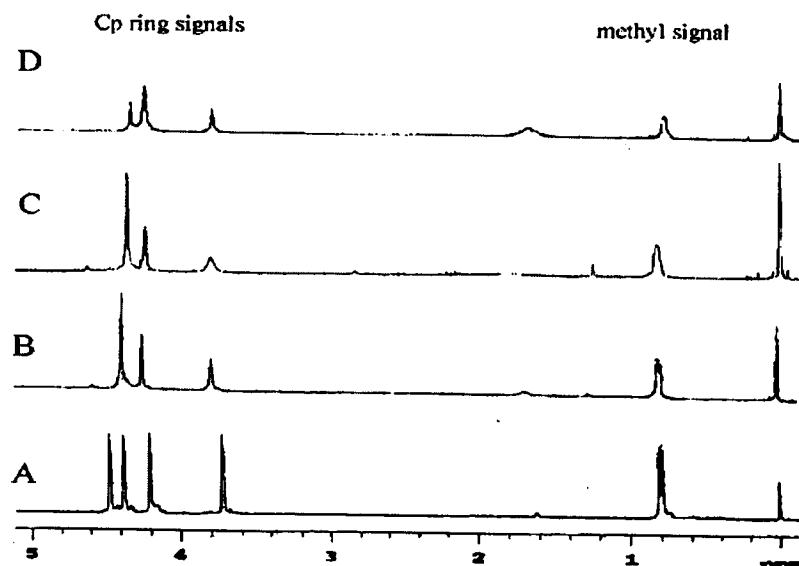
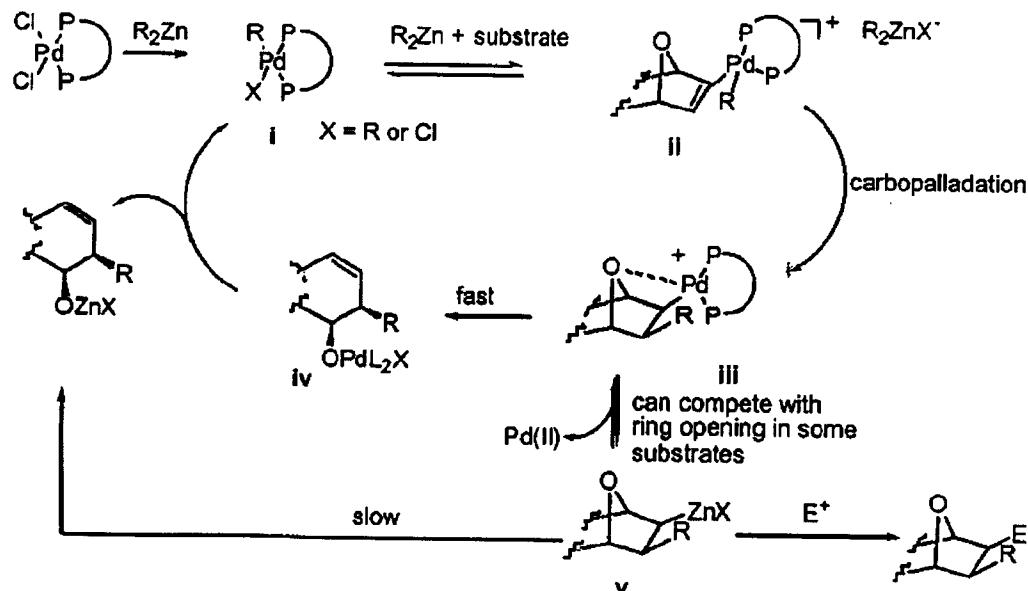
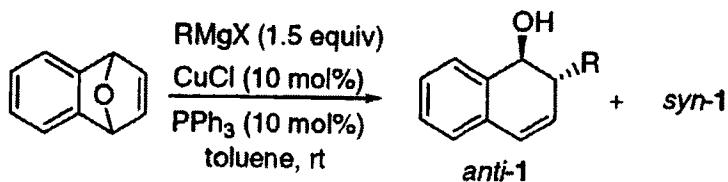


Figure 1.  $^1\text{H}$  NMR of  $\text{Pd}(\text{dppf})\text{MeCl}$  (A),  $\text{Pd}(\text{dppf})\text{MeCl} + \text{Zn}(\text{OTf})_2$  (B),  $\text{Pd}(\text{dppf})\text{MeCl} + \text{AgOTf}$  (C), and  $\text{Pd}(\text{dppf})\text{MeCl} + \text{NaB}(\text{ArF})_4$  (D).

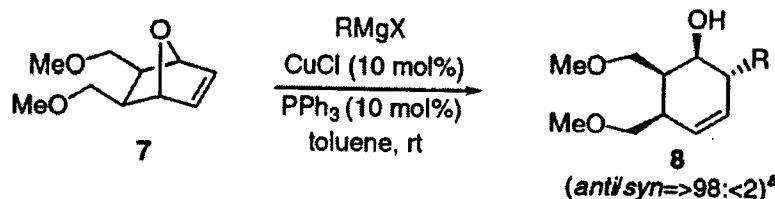
- Coalescence of Cp signals upon addition of metal salts indicative of removal of chloride from Pd-alkyl complex

# Ring Opening Reaction with Catalytic Amount of Cu/RMgX



| entry           | X  | R   | product   | t (h) | anti/syn <sup>a</sup> | yield <sup>b</sup> |
|-----------------|----|---|-----------|-------|-----------------------|--------------------|
| 1               | Br | Me  | <b>1a</b> | 6     | >98:<2                | 92                 |
| 2 <sup>c</sup>  | Br | Et  | <b>1b</b> | 0.3   | 97:3                  | 76                 |
| 3               | Br | Et  | <b>1b</b> | 0.3   | 95:5                  | 83                 |
| 4               | Br | <i>i</i> -Bu                                  | <b>1c</b> | 3     | >98:<2                | 89                 |
| 5               | Cl | decyl   | <b>1d</b> | 4     | 90:10                 | 66                 |
| 6               | Cl | Cy  | <b>1e</b> | 2     | >98:<2                | 51                 |
| 7 <sup>c</sup>  | Cl | Cy  | <b>1e</b> | 1     | >98:<2                | 64                 |
| 8               | Br | Bn  | <b>1f</b> | 12    | >98:<2                | 47 <sup>d</sup>    |
| 9               | Br | Ph  | <b>1g</b> | 2     | >98:<2                | 90                 |
| 10 <sup>c</sup> | Br | Ph  | <b>1g</b> | 4     | >98:<2                | 84                 |
| 11 <sup>c</sup> | Br | ( <i>p</i> -OMe)C <sub>6</sub> H <sub>4</sub> | <b>1h</b> | 12    | >98:<2                | 92 <sup>e</sup>    |
| 12              | Br | ( <i>p</i> -F)C <sub>6</sub> H <sub>4</sub>   | <b>1i</b> | 1.5   | >98:<2                | 94                 |

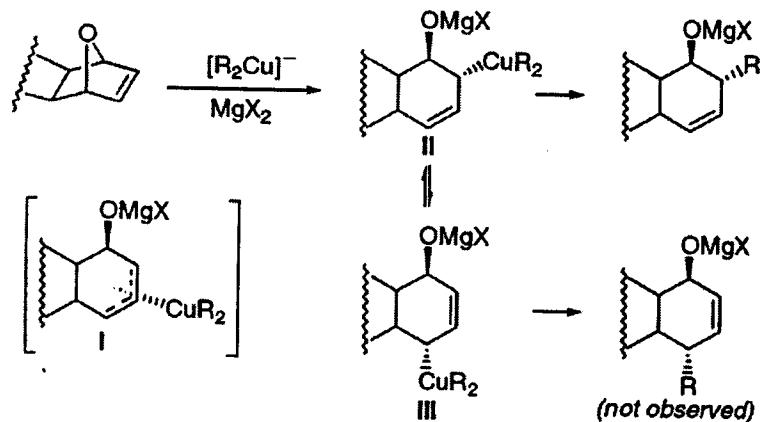
<sup>a</sup> Determined by <sup>1</sup>H NMR. <sup>b</sup> Yield (%) of anti product after chromatography. <sup>c</sup> 10 mol % of CuTC (copper thiophene-2-carboxylate) was used instead of CuCl. <sup>d</sup> Yield in converted product (10% of starting material was recovered); 35% of naphthalene was also obtained. <sup>e</sup> Yield of converted product (15% of starting material was recovered).



| entry          | X  | R            | product   | time (h) | yield <sup>b</sup> (%) |
|----------------|----|--------------|-----------|----------|------------------------|
| 1              | Br | Me           | <b>8a</b> | 72       | 69                     |
| 2 <sup>c</sup> | Br | Me           | <b>8a</b> | 12       | 74                     |
| 3              | Br | Et           | <b>8b</b> | 0.5      | 61 <sup>d</sup>        |
| 4              | Br | <i>i</i> -Bu | <b>8c</b> | 24       | 77 <sup>e</sup>        |
| 5              | Br | decyl        | <b>8d</b> | 24       | 78                     |
| 6 <sup>c</sup> | Cl | Cy           | <b>8e</b> | 12       | 42 <sup>d</sup>        |
| 7 <sup>c</sup> | Br | Ph           | <b>8g</b> | 12       | 79                     |

<sup>a</sup> The syn diastereomer was not detected by <sup>1</sup>H NMR in the crude reaction mixture. <sup>b</sup> Yield after chromatographic purification. <sup>c</sup> Reaction carried out at 60 °C. <sup>d</sup> Diene **9** (see ref 25) was also isolated. <sup>e</sup> Yield in converted product (13% of starting **7** was recovered).

**Scheme 1.** Mechanistic Proposal for the Cu-Catalyzed Ring-Opening of Oxabicyclic Alkenes with Grignard Reagents.



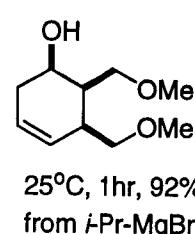
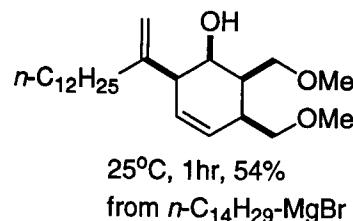
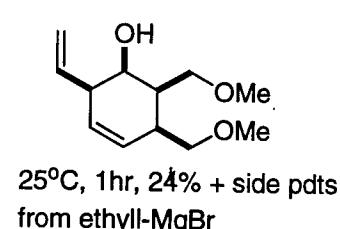
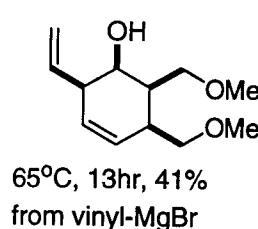
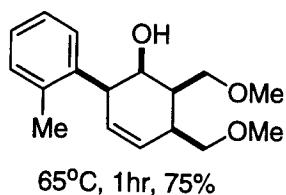
- exclusive anti selectivity
- π-allyl Copper intermediate to rationalize the observed stereochemistry

# Transition Metal Catalyzed Ring Opening Reactions-Fe/RMgX

**Table 1.** Effect of TMEDA on the Iron-Catalyzed Ring-Opening Reaction of **1**<sup>a</sup>

| entry | catalyst                   | TMEDA     | temp  | time | yield <sup>b</sup> |
|-------|----------------------------|-----------|-------|------|--------------------|
| 1     | FeCl <sub>3</sub> (5 mol%) | none      | 25 °C | 8 h  | 65%                |
| 2     | FeCl <sub>3</sub> (5 mol%) | 3.0 equiv | 25 °C | 3 h  | 74%                |
| 3     | none                       | 3.0 equiv | 25 °C | 10 h | 0%                 |

<sup>a</sup> Reaction was performed by the addition of a THF solution of FeCl<sub>3</sub> (5 mol %) to a mixture of the oxabicyclic alkene **1** and phenylmagnesium bromide (2.0 equiv) in THF in the presence or absence of TMEDA (3.0 equiv). <sup>b</sup> Isolated yield.



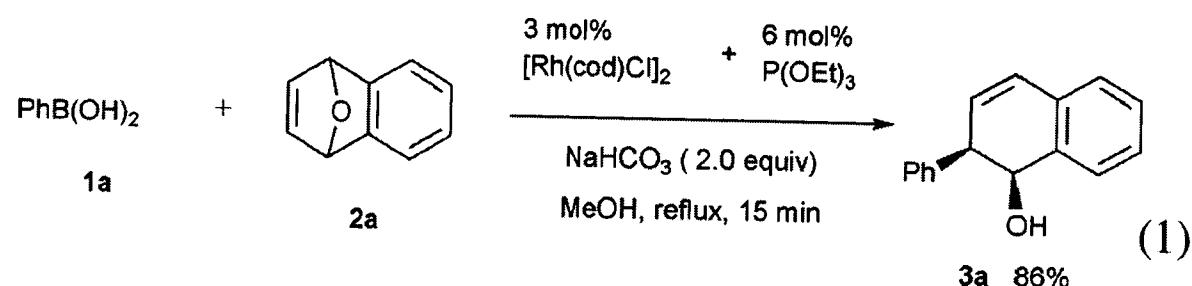
**Table 3.** Reaction of Various Oxabicyclic Alkenes with Phenylmagnesium Bromide<sup>a</sup>

| entry | substrate | temp. | time             | product (yield) <sup>b</sup> |
|-------|-----------|-------|------------------|------------------------------|
| 1     |           | 25 °C | 3 h              | <br>11 (80%)                 |
| 2     |           | 65 °C | 9 h              | <br>13 (67%) <sup>c</sup>    |
| 3     |           | 25 °C | 2 h <sup>d</sup> | <br>15 (54%) <sup>e</sup>    |

<sup>a</sup> Reaction was performed with FeCl<sub>3</sub> (5 mol %), PhMgBr (2.0 equiv), and TMEDA (3.0 equiv) in THF. <sup>b</sup> Isolated yield. <sup>c</sup> Starting alkene **12** was obtained in 9% yield. <sup>d</sup> Reaction was performed at 0 °C for 1 h and at 25 °C for 2 h. <sup>e</sup> Naphthalene was obtained in 28% yield as a side product.

- Mechanism of the reaction not clear:  
carbometallation or π-allyl Fe (?)

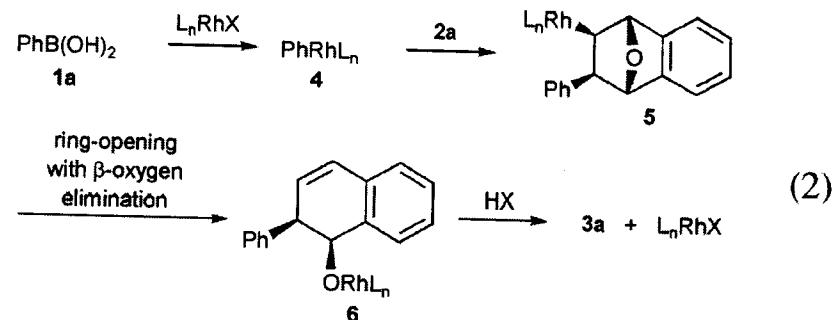
# Transition Metal Catalyzed Ring Opening Reactions-Rh/RB(OH)<sub>2</sub>



| Entry | ArB(OH) <sub>2</sub> | 2               | 3 Yield (%)                     |
|-------|----------------------|-----------------|---------------------------------|
| 1     | <chem>1b</chem>      | <chem>2a</chem> | <chem>3b</chem> 86              |
| 2     | <chem>1c</chem>      | <chem>2a</chem> | <chem>3c</chem> 90              |
| 3     | <chem>1d</chem>      | <chem>2a</chem> | <chem>3d</chem> 88              |
| 4     | <chem>1e</chem>      | <chem>2a</chem> | <chem>3e</chem> 74 <sup>b</sup> |
| 5     | <chem>1f</chem>      | <chem>2a</chem> | <chem>3f</chem> 75              |
| 6     | <chem>1g</chem>      | <chem>2a</chem> | <chem>3f</chem> 70 <sup>c</sup> |

- The cis isomers were formed exclusively
- Only small excess of boronic acid required (1.1 eq. for most cases)
- Choice of base, phosphorous ligand

Proposed mechanism:



# Catalytic Enantioselective Ring Opening Reaction: Pd/BINAP

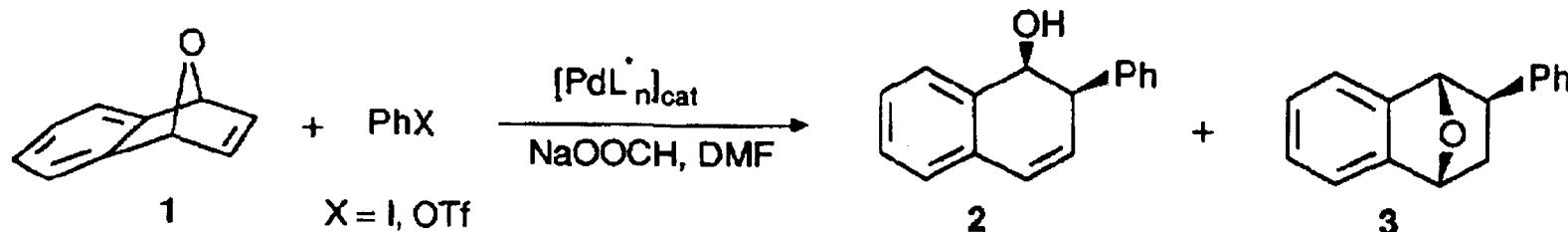


Table: Hydrophenylation of 1,4-Dihydro-1,4-epoxynaphthalene **1**

| X   | $L_n^*$ ( $Pd/L_n^*$ )         | temp.<br>°C, hrs | ratio <sup>c</sup> of <b>2</b> : <b>3</b><br>(yield <sup>d</sup> %) | <b>2</b><br>% ee <sup>e</sup> | <b>3</b><br>% ee <sup>e</sup> |
|-----|--------------------------------|------------------|---|-------------------------------|-------------------------------|
| I   | (R)-BINAP (1:2)                | 55 (16)          | 60:40 (85)  | 0                             | 0                             |
| I   | (S,S)-BDPPA <sup>a</sup> (1:1) | 55 (60)          | 52:48 (87)  | 3 (+)                         | 0                             |
| I   | (S,S)-Chiraphos (1:1)          | 55 (72)          | 100:0 (26)  | 9 (+)                         | -                             |
| I   | (R,R)-Norphos (1:2.1)          | 55 (72)          | 73:27 (72)  | 7 (+)                         | 0                             |
| OTf | (R,R)-Norphos (1:1)            | 55 (89)          | 16:84 (68)  | 43 (-)                        | 28                            |
| OTf | (S,S)-BDPPA <sup>a</sup> (1:1) | 60 (57)          | 50:50 (77)  | 30 (-)                        | 64                            |
| OTf | (R)-BINAP (1:2.1)              | 55 (166)         | 15:85 (83)  | 96 (+) <sup>f</sup>           | 64                            |
| OTf | (S,S)-Chiraphos (1:2)          | 55 (96)          | 29:71 (60)  | 14 (-)                        | 16                            |
| OTf | (S)-BINAP (1:2.1) <sup>b</sup> | 55 (66)          | 100:0 (41)  | 54 (-)                        | -                             |

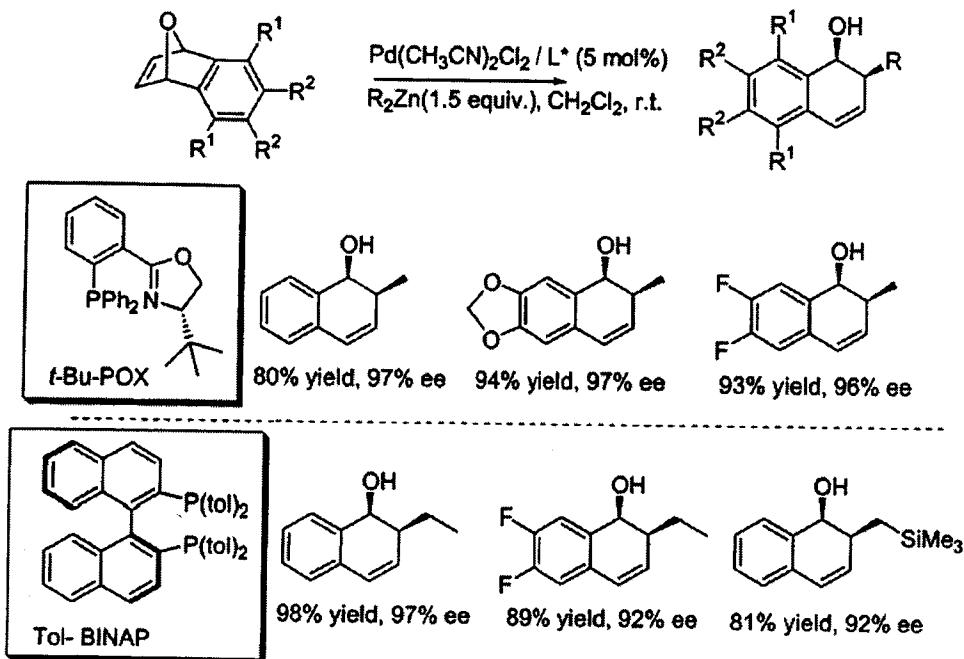
<sup>a</sup> BDPP stands for 2,4-Bis(diphenylphosphino)pentane. <sup>b</sup>  $ZnCl_2$  (2 equiv.) were added. <sup>c</sup> Determined by gas chromatography.

<sup>d</sup> Isolated yield. <sup>e</sup> Determined by HPLC using a chiral stationary phase column (Chiralcel OD-H). <sup>f</sup>  $[\alpha]_D^{28} +10$  (c 1.2, ethanol)

- The ratio of **2**/**3** dependent on phosphine: bulky phosphines favour **2** (88% with  $PPh_3$ )
- Addition of Zn-salt lead to exclusive formation of **2**

# Catalytic Enantioselective Ring Opening Reaction- Pd/phosphines

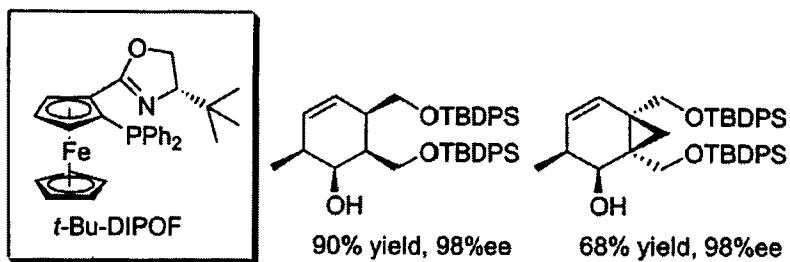
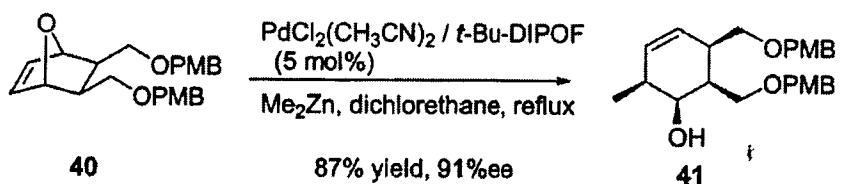
Scheme 8



- Variety of chiral phosphines are effective in inducing asymmetry, but each system requires optimization
- Reaction at lower temperature leads to rate deceleration but no significant improvement in enantioselectivity

- DIPOF is also good for [3,2,1]-system.

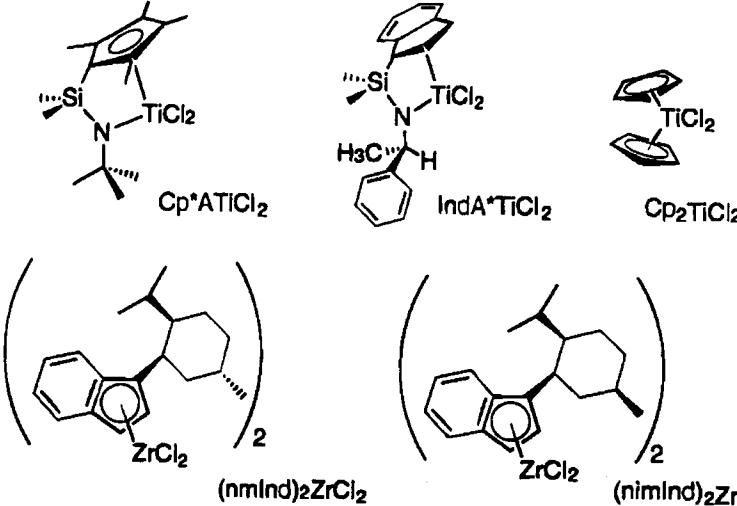
Scheme 9



Lautens, M. *et. al.* *J. Am. Chem. Soc.* **2000**, *122*, 1804.  
Lautens, M. *et. al.* *Org. Lett.* **2000**, *2*, 1971.

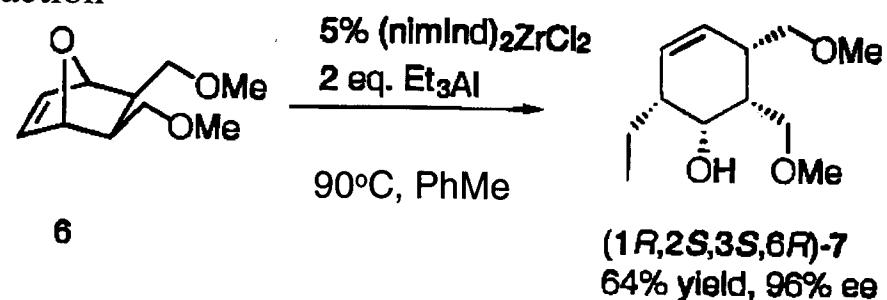
# Catalytic Enantioselective Ring Opening Reaction: Zr/Nimind

- Low valent metallocene can effect the ring opening reaction

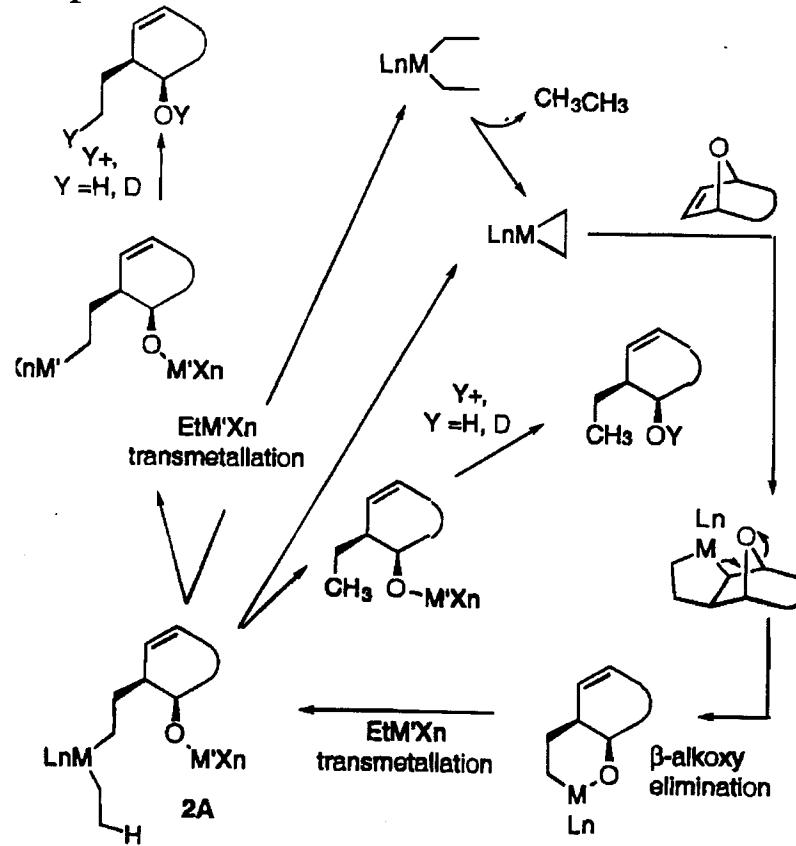


**Figure 1.** Structures of catalyst precursors.

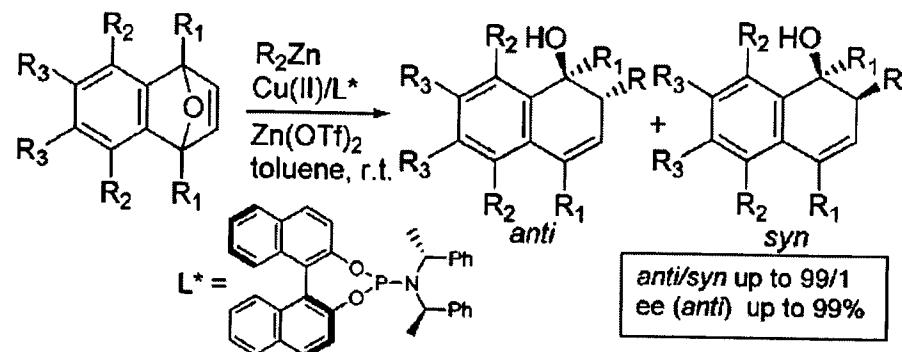
- Zr-nimind catalyst is the only selective catalyst, but only for **6**.
- Opening of [3,2,1]-bicycle gave 17% ee
- Deuterium exchange experiments consistent with the proposed mechanism



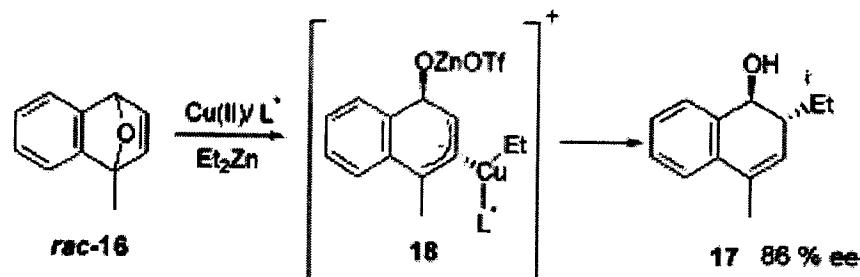
Proposed mechanism:



# Catalytic Enantioselective Ring Opening Reaction-Cu/Phosphoramidite



- chiral monodentate ligand effective
- minor syn products obtained were all racemic
- syn product arise from opening by  $\text{Zn}(\text{OTf})_2$
- high anti selectivity:  $\pi$ -allyl copper intermediate

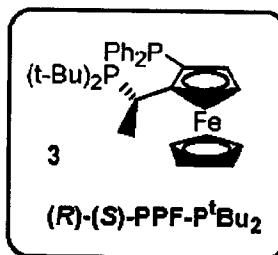
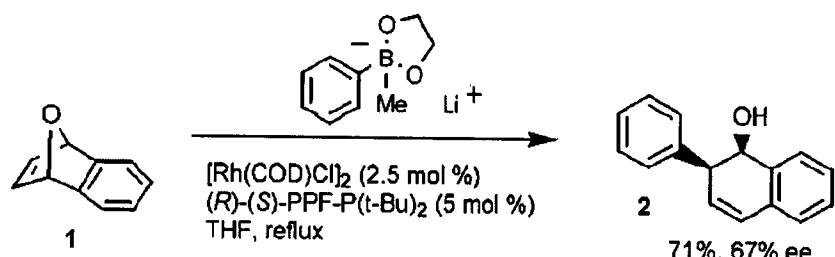


| entry | Substrate | time (h) | Product | yield (%) <sup>b</sup> | anti /syn | ee (%) |
|-------|-----------|----------|---------|------------------------|-----------|--------|
| 1     | 6         | 70       | 11      | 58                     | 83/17     | 80     |
| 2     | 7         | 70       | 12      | 65                     | 90/10     | 88     |
| 3     | 8         | 16       | 13      | 90                     | 99/1      | >99    |
| 4     | 9         | 48       | 14      | 82                     | 90/10     | 97     |
| 5     | 10        | 40       | 15      | 85                     | 92/8      | 92     |

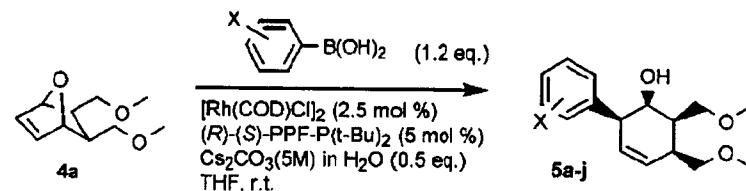
<sup>a</sup> All reactions were run as described in the typical procedure.<sup>16</sup> <sup>b</sup> Isolated yields of anti products.

Feringa, B. L. et al. Org. Lett. 2002, 4, 2703.

# Rh-Catalyzed Ring Opening with Organoboron Compounds



**Table 2.** ARO of Oxabicycle **4a** with Arylboronic Acids<sup>a</sup>



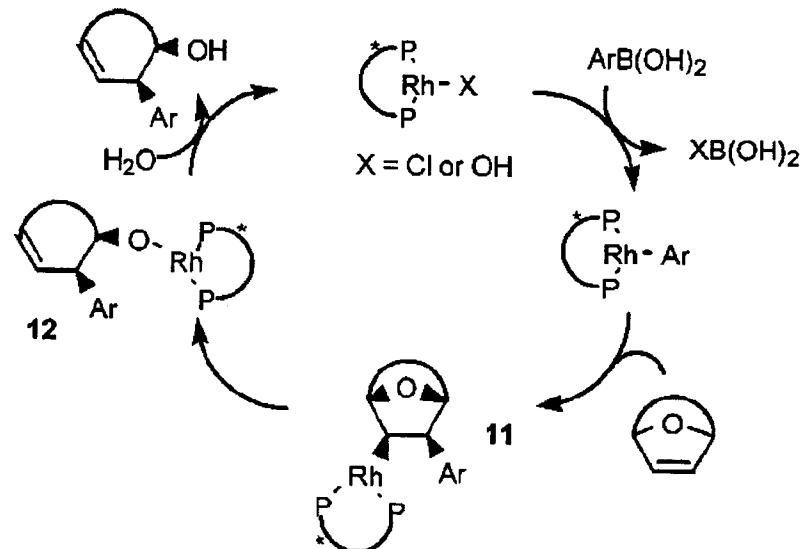
| entry          | phenyl substituent | product <sup>b</sup> | yield (%) <sup>c</sup> | ee (%) <sup>d</sup> |
|----------------|--------------------|----------------------|------------------------|---------------------|
| 1              | 4-Me               | 5a                   | 88                     | 95                  |
| 2              | none               | 5b                   | 91                     | 95                  |
| 3              | 2-Me               | 5c                   | n.r.                   |                     |
| 4              | 4-Cl               | 5d                   | 95                     | 95                  |
| 5              | 3-Cl               | 5e                   | 73                     | 99                  |
| 6              | 2-Cl               | 5f                   | n.r.                   |                     |
| 7 <sup>e</sup> | 3-I                | 5g                   | 85                     | 95                  |
| 8              | 4-Ac               | 5h                   | 71                     | 94                  |
| 9              | 4-OMe              | 5i                   | 87                     | 96                  |
| 10             | 3-OMe              | 5j                   | 91                     | 95                  |

<sup>a</sup> Reactions performed with 50 mg (0.271 mmol) of **4a**. <sup>b</sup> Products are diastereomerically pure. <sup>c</sup> Isolated yield after column chromatography. <sup>d</sup> As determined by chiral HPLC (Chiracel OD or AD columns). <sup>e</sup> Required 5 mol % of  $[\text{Rh}(\text{COD})\text{Cl}]_2$  to proceed to completion.

- syn addition of aryl and alkenyl boronic acids
- Ferrocenyl ligand showed the best reactivity and selectivity

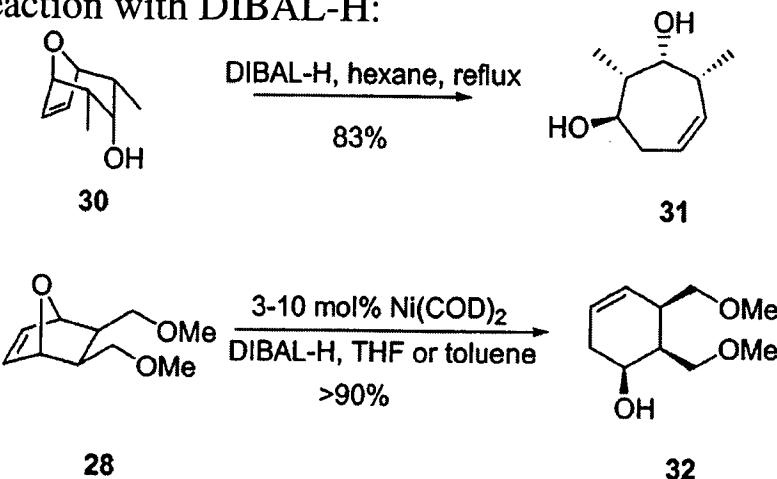
Proposed mechanism:

**Scheme 5**

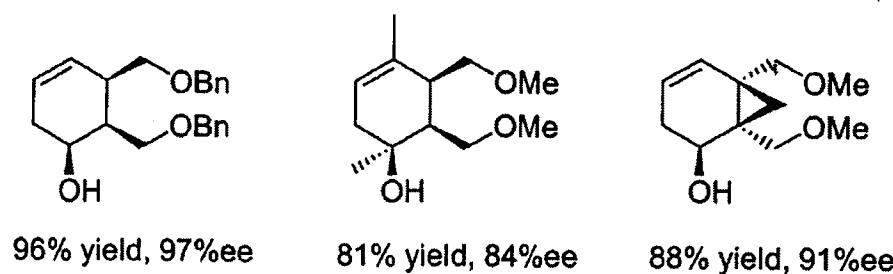
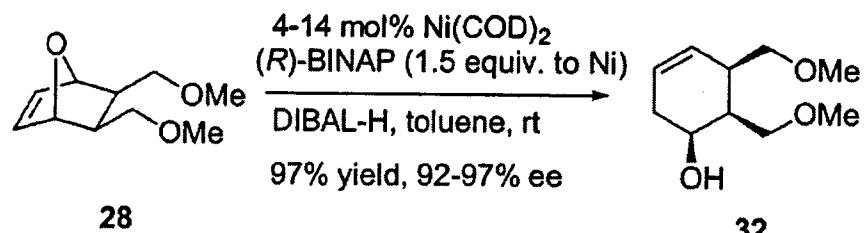


# Ni-catalyzed Ring Opening Reaction with Hydride

Reaction with DIBAL-H:

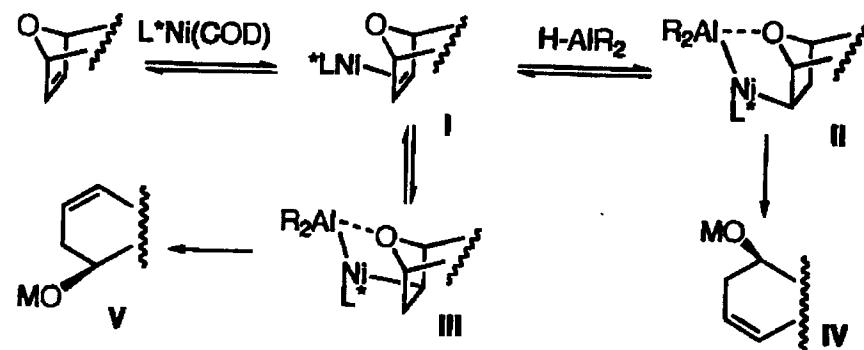


Use of chiral ligand:



Proposed mechanism:

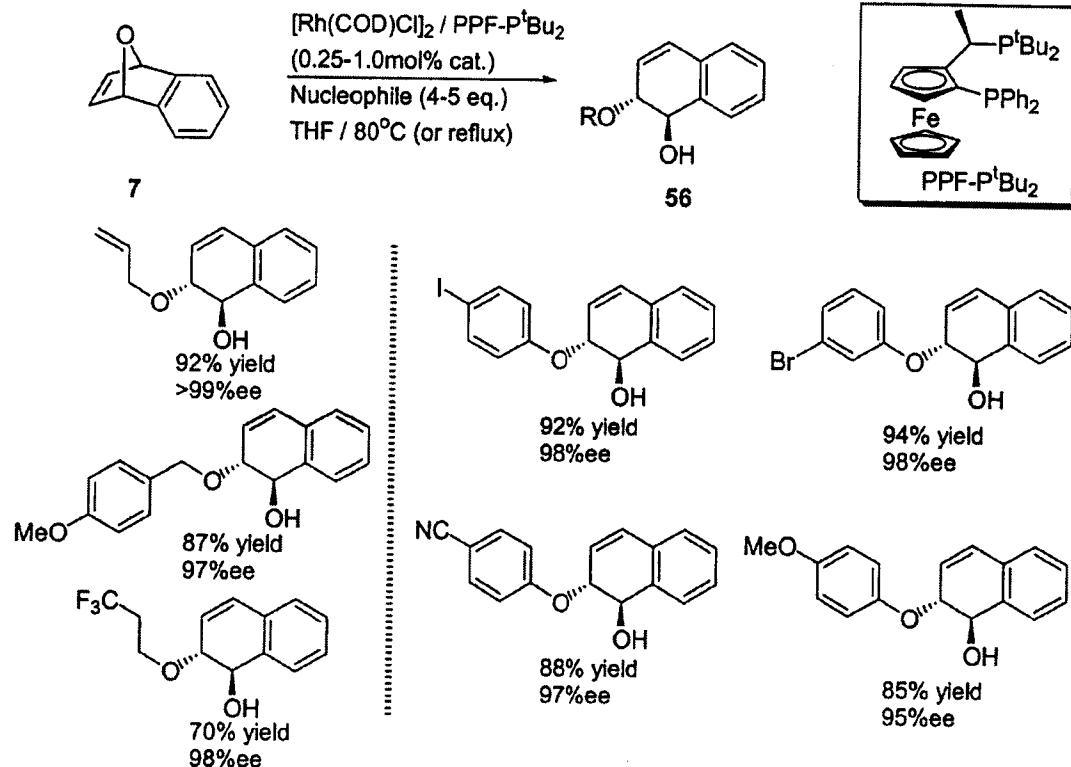
Scheme 2



- Slow addition of DIBAL-H is crucial for obtaining high enantioselectivity
- Presence of phosphine necessary to obtain the ring opening product selectively

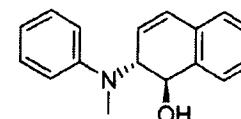
# Rh-Catalyzed Ring Opening with Heteronucleophiles

Scheme 13

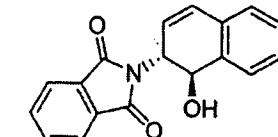


Scheme 15

## Activated Nitrogen Nucleophiles

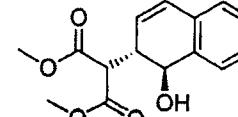


[Rh-I] cat: 97% yield, 92% ee  
[Rh-Cl] cat: 92% yield, 74% ee

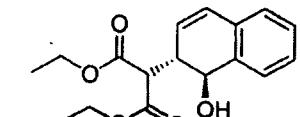


[Rh-I] cat: 90% yield, 98% ee  
[Rh-Cl] cat: 55% yield, 45% ee

## Malonate Nucleophiles

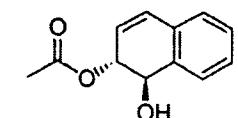


[Rh-I] cat: 97% yield, 98% ee  
[Rh-Cl] cat: 56% yield, 51% ee

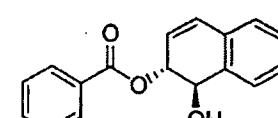


[Rh-I] cat: 95% yield, 97% ee

## Ammonium Carboxylate Nucleophiles



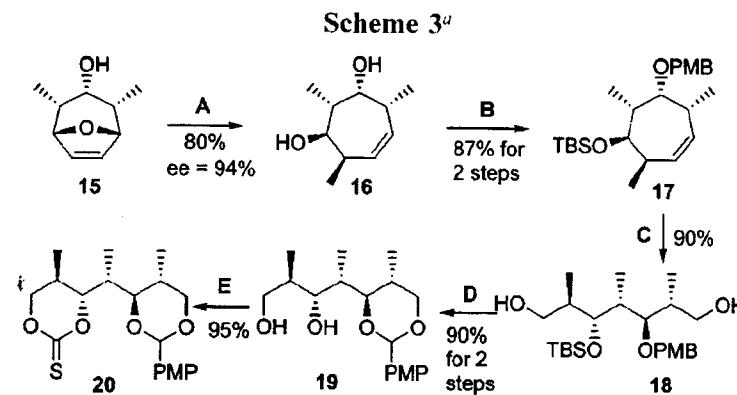
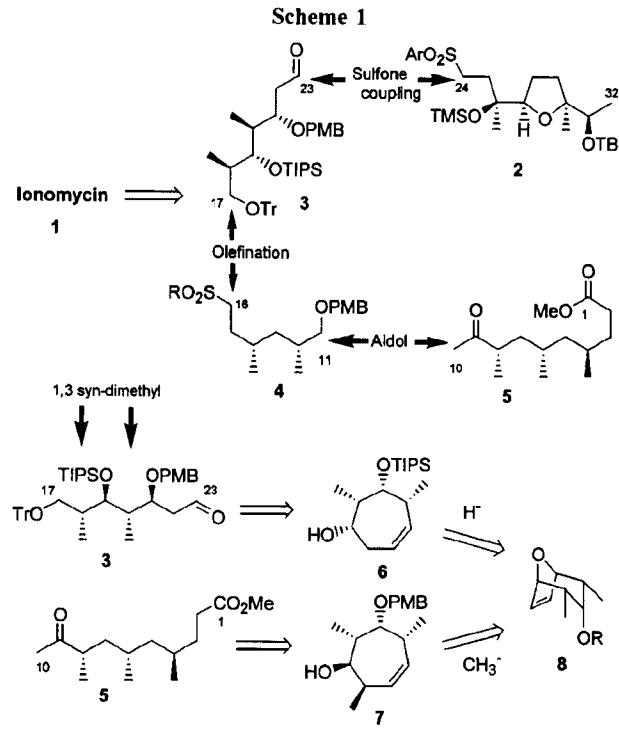
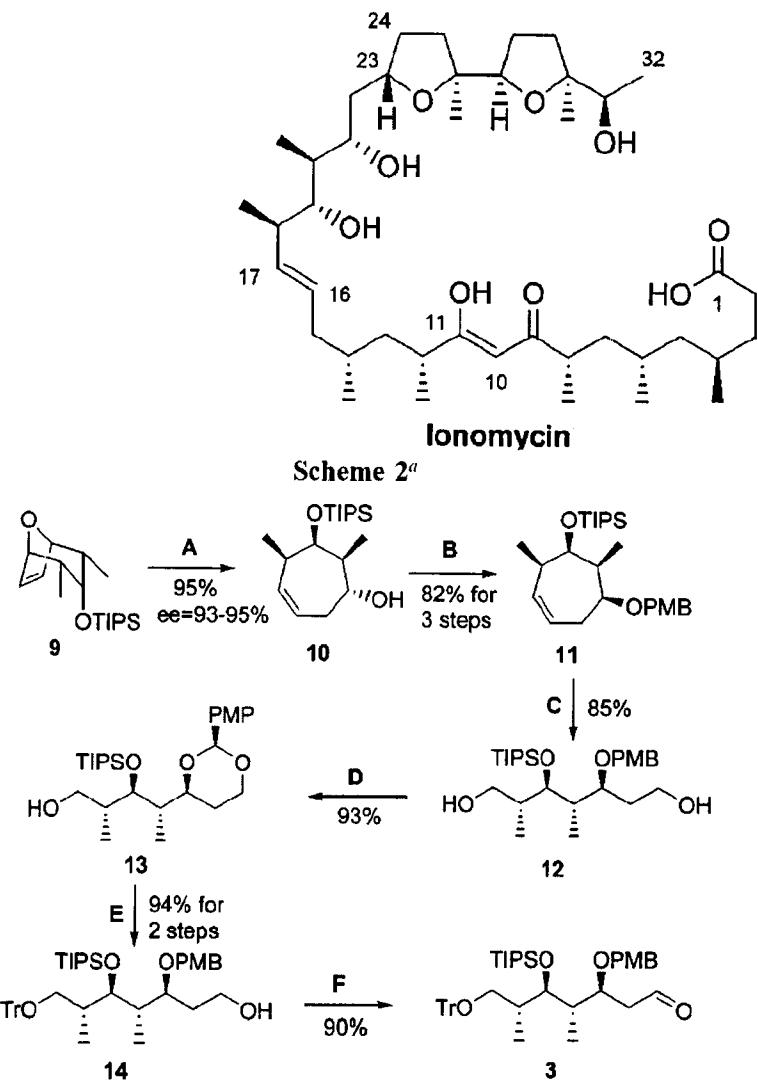
[Rh-I]: 95% (92% ee)  
[Rh-Cl]: 81% (61% ee)



[Rh-I]: 81% (90% ee)  
[Rh-Cl]: 72% (31% ee)

- Variety of nucleophiles: alcohol, amine, carboxylate, malonate
- Exclusive anti product formation
- Addition of ammonium iodide (*in situ* generation of Rh-I complex) improved reactivity and selectivity for amines

# Applications in Synthesis: Ionomycin



<sup>a</sup> (A) 5 mol % Ni(COD)<sub>2</sub>, 10 mol % (S)-BINAP, toluene, 65 °C, 1.1 equiv of DIBAL-H (added over 20 h); (B) (a) DMSO, (COCl)<sub>2</sub>, NEt<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C; (b) PhMe, DIBAL-H, -78 °C; (c) THF, KHMDS, PMBCl; (C) O<sub>3</sub>, MeOH/CH<sub>2</sub>Cl<sub>2</sub>, -78 °C then NaBH<sub>4</sub>, rt; (D) CH<sub>2</sub>Cl<sub>2</sub>, DDQ, mol sieves, rt; (E) (a) TrCl, NEt<sub>3</sub>, DMAP, CH<sub>2</sub>Cl<sub>2</sub>; (b) CH<sub>2</sub>Cl<sub>2</sub>, DIBAL-H, -78 to 0 °C; (F) DMSO, (COCl)<sub>2</sub>, NEt<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C.

<sup>a</sup> (A) 5 mol % Pd[(R)-'Pr-(R)-DIPOF]Cl<sub>2</sub>, 10 mol % Zn(OTf)<sub>2</sub>, 2.5 equiv of Me<sub>2</sub>Zn, dichloroethane, reflux; (B) (a) TBDMSCl, imidazole, DMF; (b) NaH, PMBBr, Bu<sub>4</sub>Ni (cat.), DMF; (C) O<sub>3</sub>, MeOH/CH<sub>2</sub>Cl<sub>2</sub>, -78 °C then NaBH<sub>4</sub>, rt; (D) (a) CH<sub>2</sub>Cl<sub>2</sub>, DDQ, mol sieves, rt; (b) TBAF, THF, rt; (E) TCDDI, THF, 50 °C; (F)

# Conclusion

- Asymmetric-Ring-Opening reactions of oxabicycloalkenes provide useful synthetic intermediates.
- Various transition metals can be used as catalysts for addition of nucleophiles in these substrates.

Organohalides: Ni, Pd (with Zn)

Organozinc: Pd

Organomagnesium: Ni, Cu, Fe

Organoboron: Rh

Organoaluminum: Zr, Ti

Terminal acetylene: Ni (with Zn)

Hydrides: Ni

Alkohol, amine and malonate: Rh

- Two different mechanisms:
  - carbometallation leads to syn product
  - $\pi$ -allyl metal intermediates lead to anti product
- Application in total synthesis demonstrated