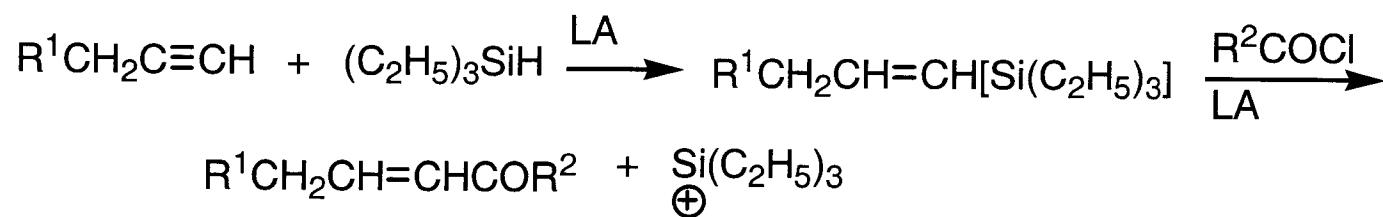
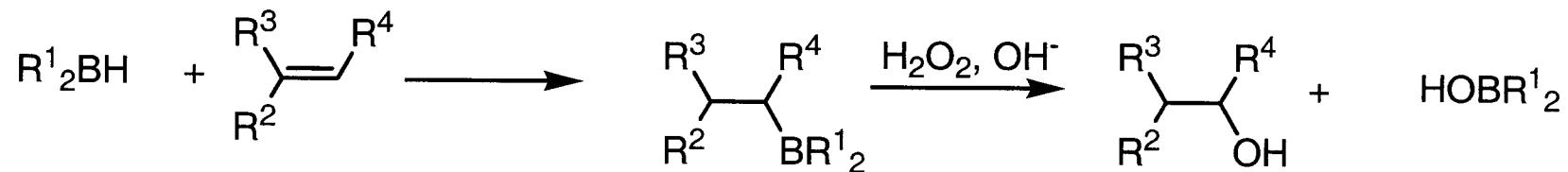

Rhodium Catalyzed C-C Bond Forming Hydrogenation

Monica Jo Patten
Group Meeting
January 25, 2005

Reductive Coupling: Why hydrogenation?

□ Conventional reductive coupling



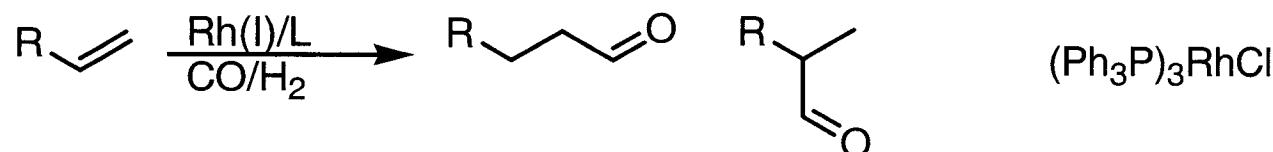
Conventional reductive coupling produces stoichiometric byproducts.

Outline

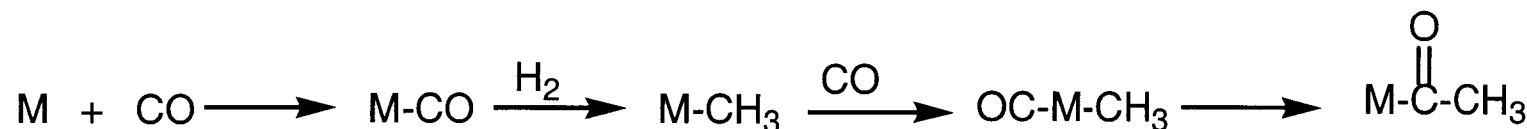
- Early C-C bond formation utilizing hydrogen
- Activation of hydrogen
- Classes of C-C bond formation reactions by hydrogen
 - Mechanistic proposals/support

Early C-C bond formation

□ Hydroformylation



□ Fischer-Tropsch Synthesis



Early methods of C-C bond formation utilizing Hydrogenation involved the migratory insertion of CO.

Breit, B. *Acc. Chem. Res.* **2003**, 36, 264-275.

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Isomerization vs. Hydrogenation

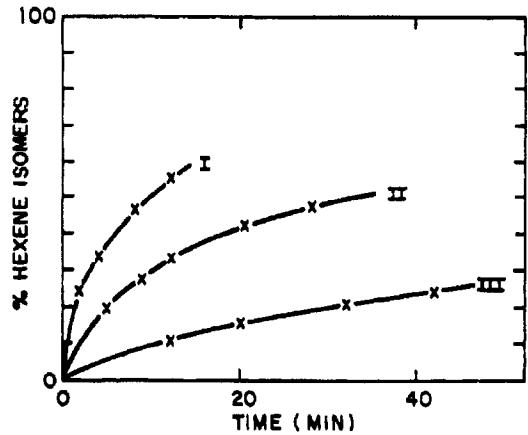
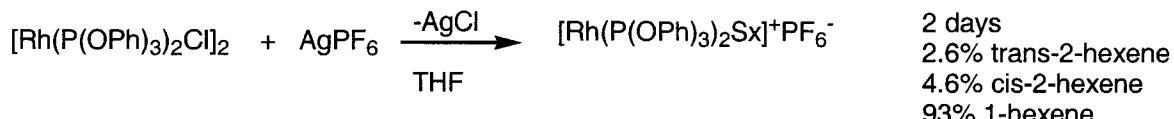
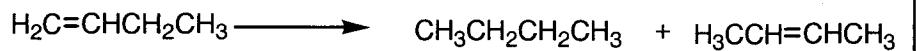


Figure 3. The isomerization of *cis*-2-hexene by prepared catalytic solutions after removal of hydrogen: I = 6.2 mM $[\text{Rh}(\text{NBD})(\text{PMe}_3)_3]^+\text{PF}_6^-$ in acetone; II = 5.3 mM $[\text{Rh}(\text{NBD})(\text{PPh}_2\text{Me})_2]^+\text{PF}_6^-$ in acetone; III = 4.7 mM $[\text{Rh}(\text{NBD})(\text{PPh}_2\text{Me})_2]^+\text{PF}_6^-$ in acetone.

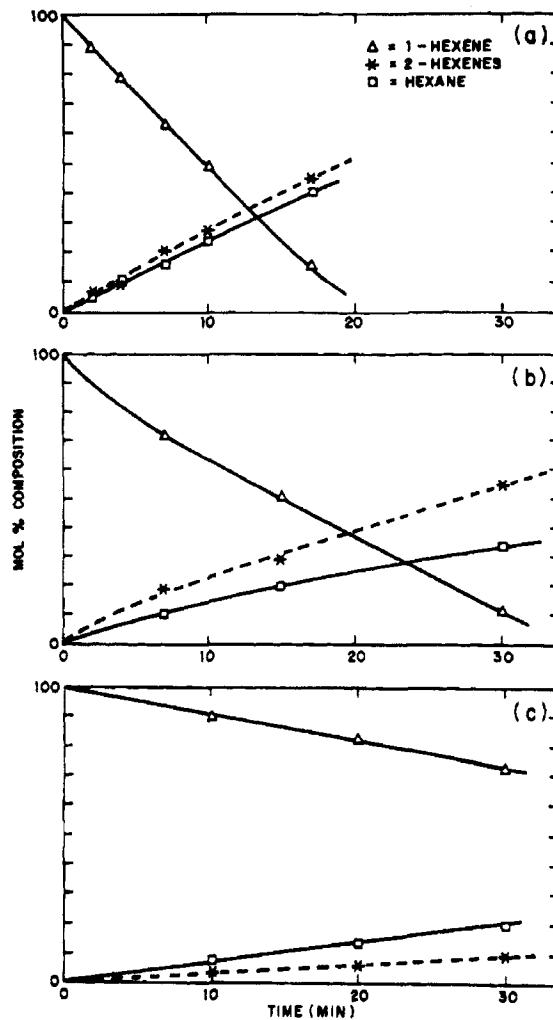
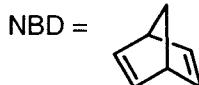


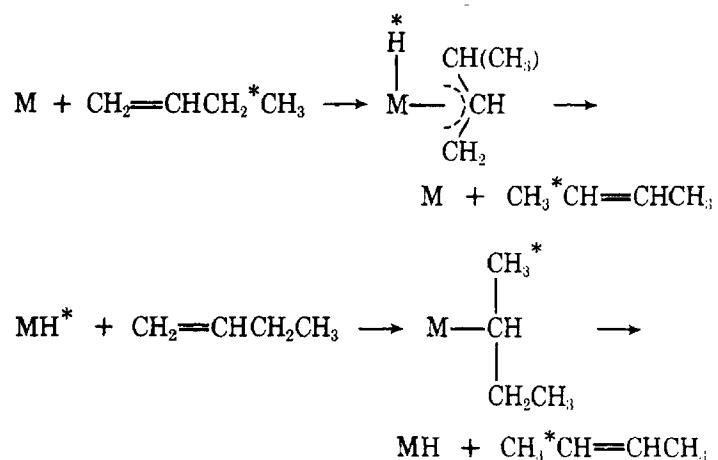
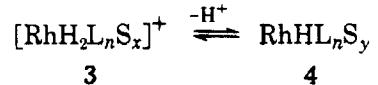
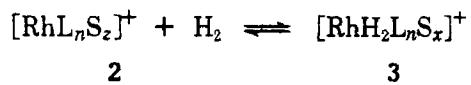
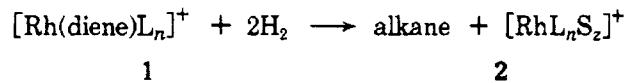
Figure 4. The hydrogenation of 1-hexene in acetone: (a) 3.7 mM $\text{Rh}(\text{CH}_3)(\text{NBD})(\text{PPh}_2\text{Me})$; (b) 3.7 mM $[\text{Rh}(\text{NBD})(\text{PPh}_2\text{Me})_2]^+\text{PF}_6^-$; (c) 5.3 mM $[\text{Rh}(\text{NBD})(\text{PPh}_2\text{Me})_2]^+\text{PF}_6^-$ in the presence of 2.2 mol of HClO_4 .

Schrock, R.; Osborn, J. *J. Am. Chem. Soc.*
1976, 98, 2134.

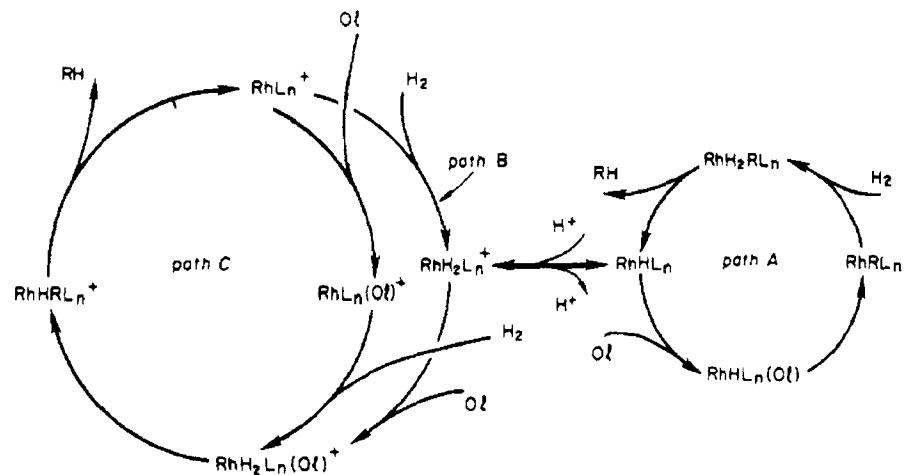
Question 1: Isomerization vs. Hydrogenation

- What are active catalyst(s)?
- Mechanisms for isomerization?

Dihyride/Monohydride Equilibrium



Scheme I. Pathways for Olefin Hydrogenation and Isomerization
($n = 2$ or 3, OI = olefin, R = alkyl, RH = alkane, L = a ligand, e.g., PPhMe₂; S_x and S_y omitted).



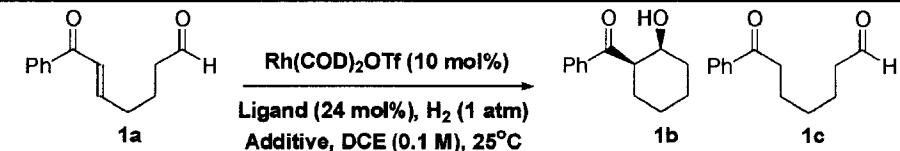
Schrock, R.; Osborn, J. *J. Am. Chem. Soc.* **1976**, 98, 2134.
Schrock, R.; Osborn, J. *J. Am. Chem. Soc.* **1976**, 98, 4450.

Reductive Coupling Utilizing Hydrogenation

- Aldol Condensation
- Intermolecular reductive coupling of 1,3-cyclohexadiene with α -keto aldehydes
- Intermolecular reductive coupling of 1,3-enynes and 1,3-diynes with α -keto aldehydes
- Reductive cyclization of 1,6-diynes and 1,6-enynes

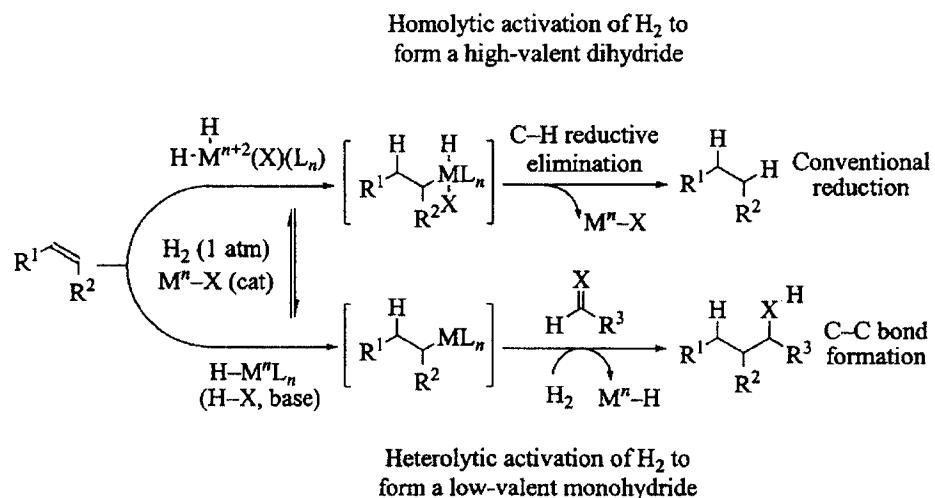
Jang, H.-Y.; Krische, M. *Acc. Chem. Res.* **2004**, 37, 653-661.

Adjusting Catalyst Equilibrium Away from Simple Hydrogenations

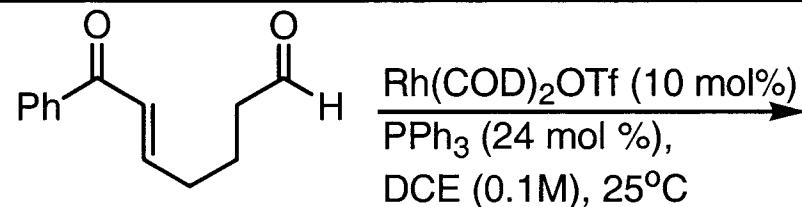


| entry | ligand | additive (mol %) | yield ^b aldol (syn-anti) | yield ^b 1,4-reduction |
|-------|--|------------------|-------------------------------------|----------------------------------|
| 1 | PPh ₃ | | 21% (99:1) | 25% |
| 2 | PPh ₃ | KOAc (30%) | 59% (58:1) | 21% |
| 3 | (<i>p</i> -CF ₃ Ph) ₃ P | | 57% (14:1) | 22% |
| 4 | (<i>p</i> -CF ₃ Ph) ₃ P | KOAc (30%) | 89% (10:1) | 0.1% |

^a As product ratios were found to vary with surface-to-volume ratio of the reaction mixture, all transformations were conducted on a 1.48 mmol scale in 50 mL round-bottomed flasks. ^b Isolated yields after purification by silica gel chromatography.



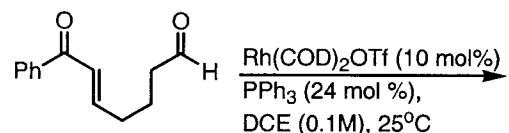
Question 2: Control Experiment



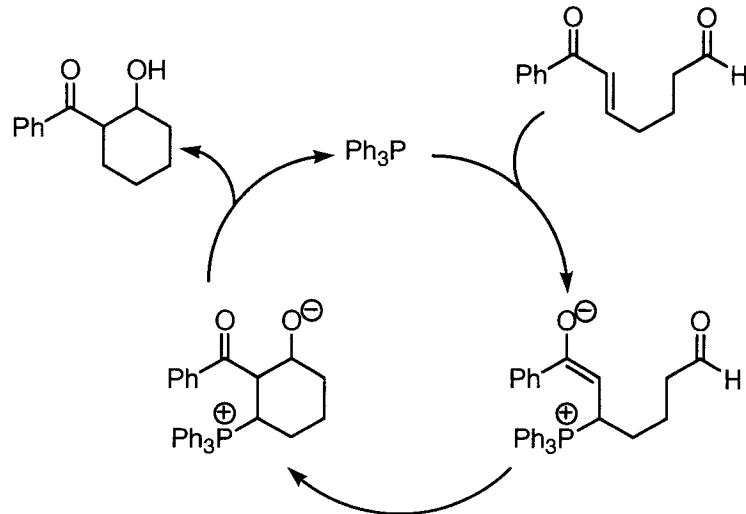
- Mechanism of the reaction the control experiment is testing for:

- What is the name of this transformation?

Question 2: Control Experiment

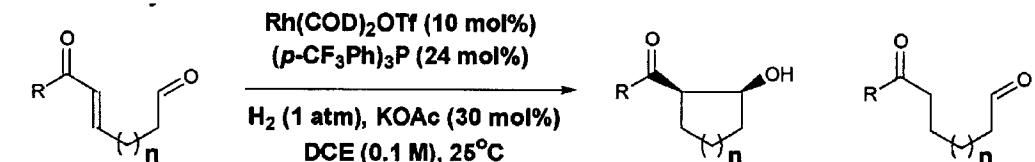


- Mechanism of the reaction the control experiment is testing for:



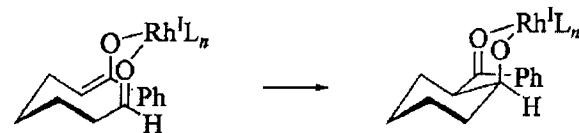
- What is the name of this transformation?
 - Morita-Baylis-Hillman Reaction

Aldol cycloreduction of aldehyde-enones



| substrate | product (syn:anti) | 1,4-reduction |
|--------------------------------|--------------------|---------------|
| 1a, n = 2, R = Ph | 1b, 89% (10:1) | 1c, 0.1% |
| 2a, n = 2, R = p-MeOPh | 2b, 74% (5:1) | 2c, 3% |
| 3a, n = 2, R = 2-naphthyl | 3b, 90% (10:1) | 3c, 1% |
| 4a, n = 2, R = 2-thiophenyl | 4b, 76% (19:1) | 4c, 2% |
| 5a, n = 2, R = 2-furyl | 5b, 70% (6:1) | 5c, 10% |
| 6a, n = 1, R = Ph | 6b, 71% (24:1) | 6c, 1% |
| 7a, n = 2, R = CH ₃ | 7b, 65% (1:5) | |

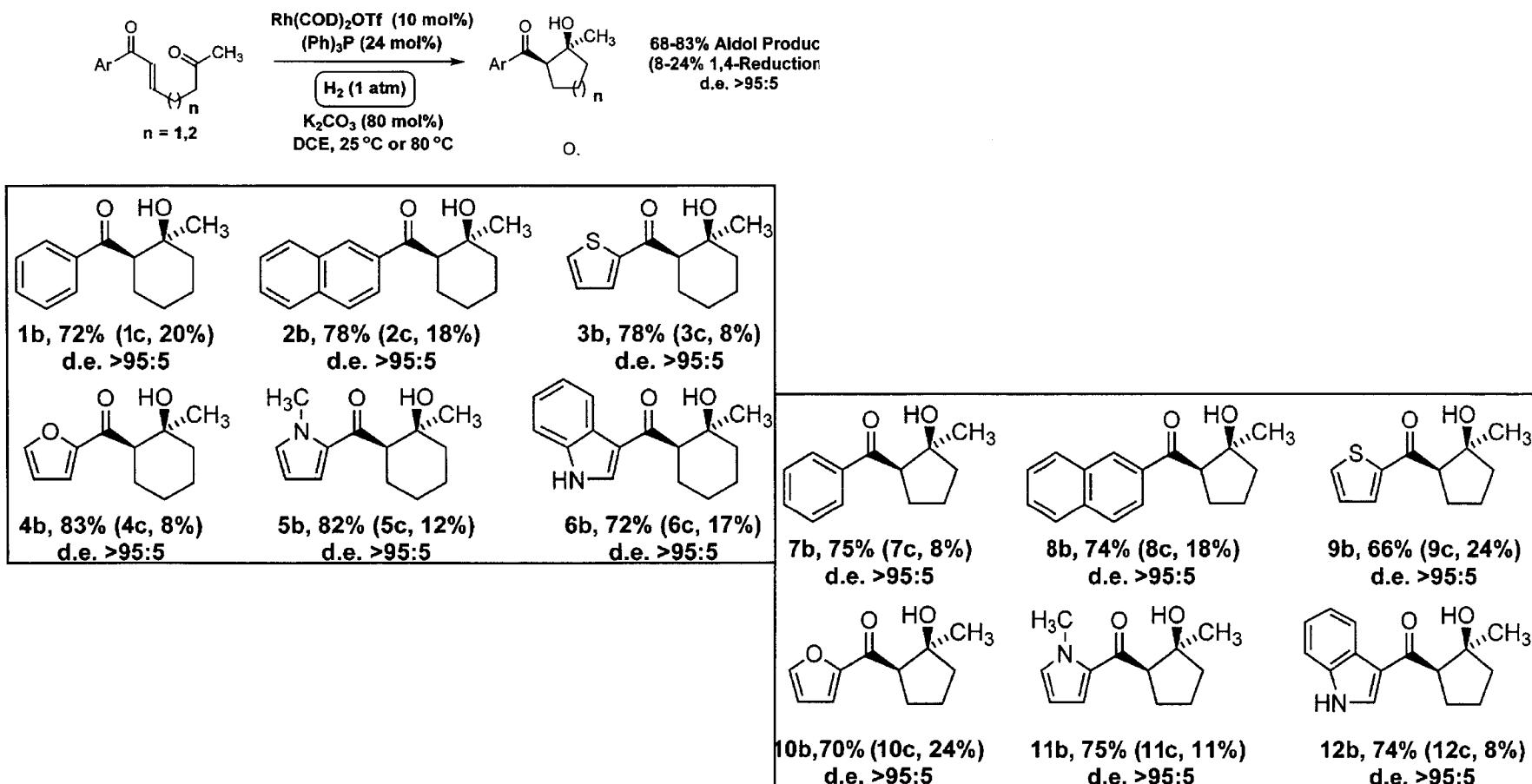
Stereochemical model



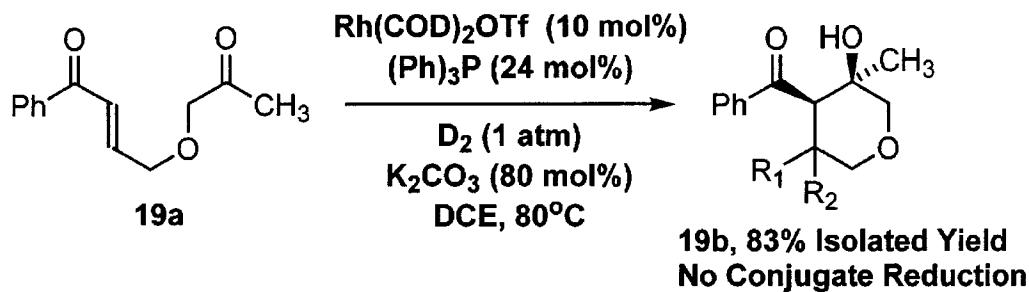
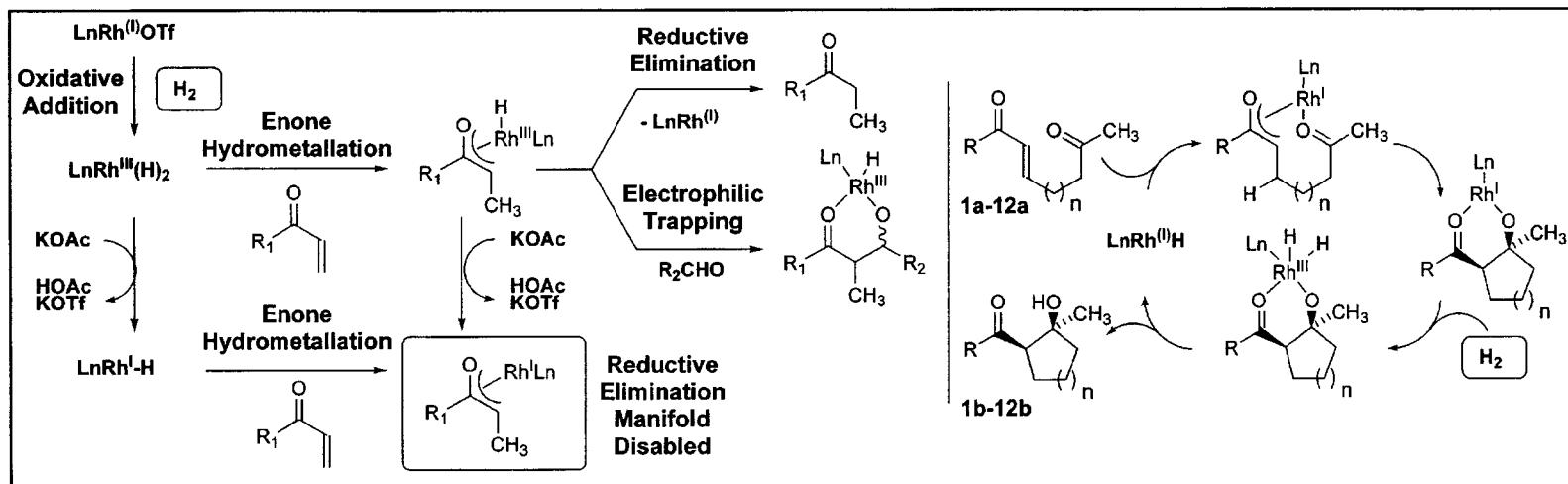
(Z)-enolate, Zimmerman-Traxler-type transition state

ang, H.-Y.; Huddleston, R.; Krische, M. *J. Am. Chem. Soc.* **2002**, 124, 15156-15157.
 ang, H.-Y.; Krische, M. *Eur. J. Org. Chem.* **2004**, 3953-3958.

Aldol cycloreduction of keto-enones



Mechanism of aldol cycloreduction



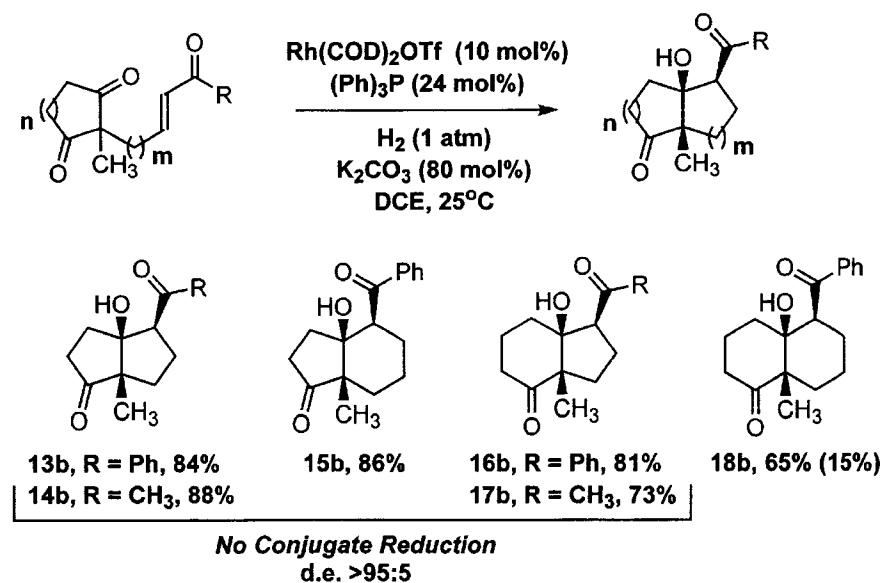
$\text{R}_1 = \text{R}_2 = \text{H}, 11\% +/- 5\%$

$\text{R}_1 = \text{D}, \text{R}_2 = \text{H}, 81\% +/- 5\%$

$\text{R}_1 = \text{R}_2 = \text{D}, 8\% +/- 5\%$

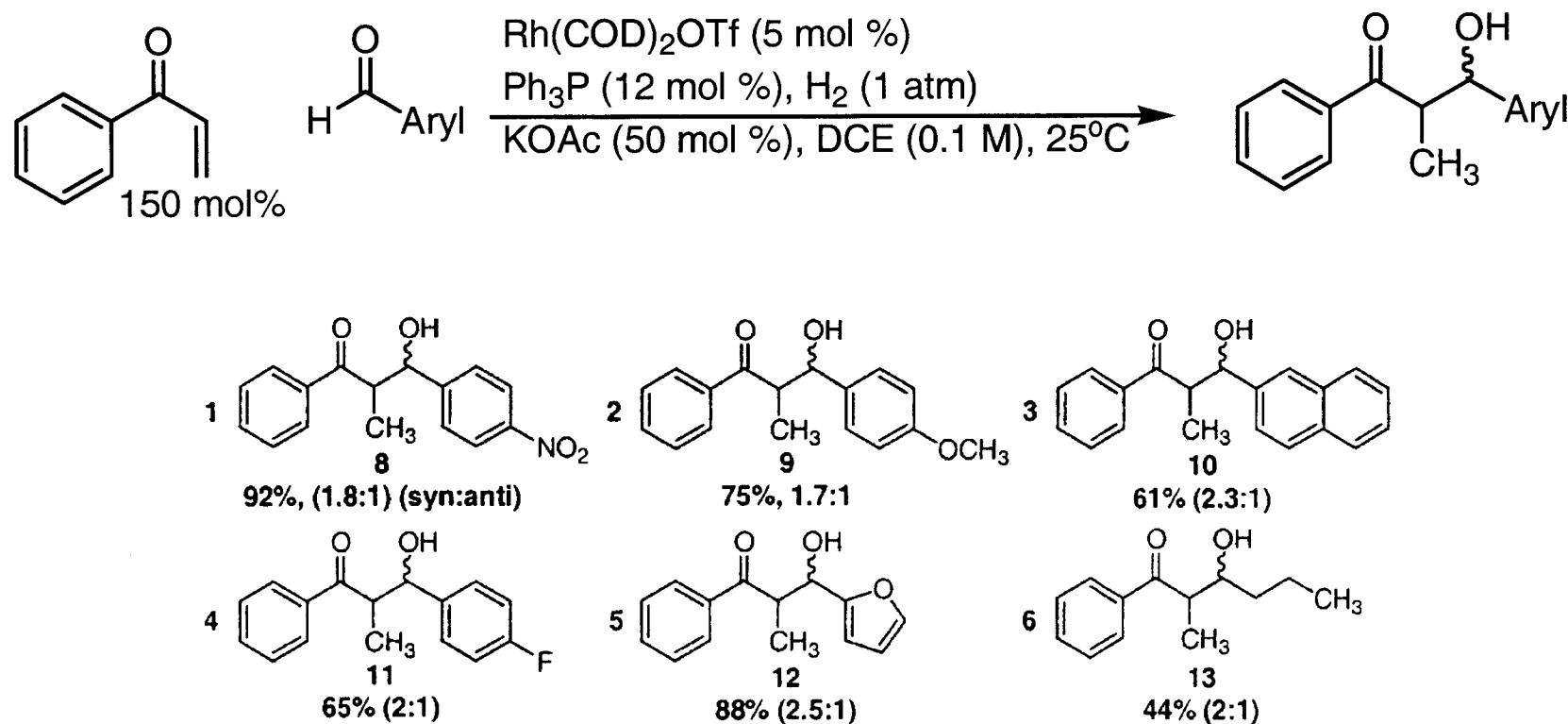
Huddleston, R.; Krische, M. *Org. Lett.* **2003**, *5*, 1143-1146.

Aldol Cycloreduction of Dione-enones



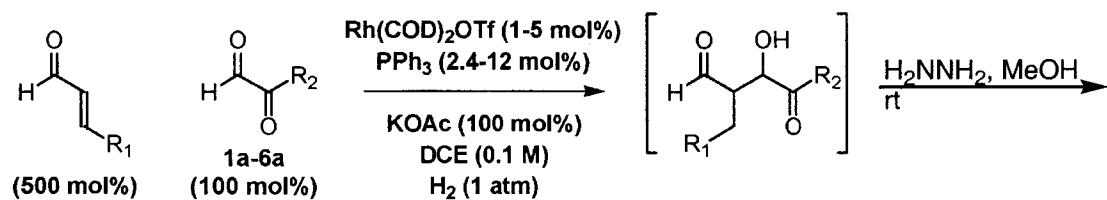
Huddleston, R.; Krische, M. *Org. Lett.* **2003**, 5, 1143-1146.

Intermolecular Aldol Condensation



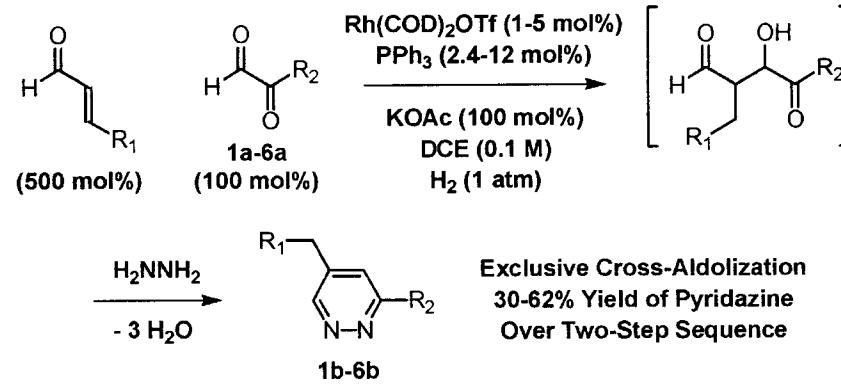
Jang, H.-Y.; Huddleston, R.; Krische, M. *J. Am. Chem. Soc.* **2002**, 124, 15156-15157.

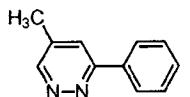
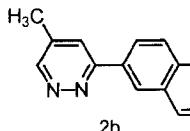
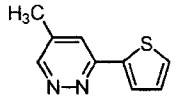
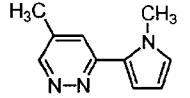
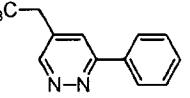
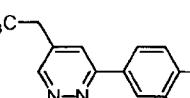
Reductive Coupling of Unsaturated aldehydes and glyoxals: Question 3



- What is the stabilized product?
- What is the name of this class of compounds?

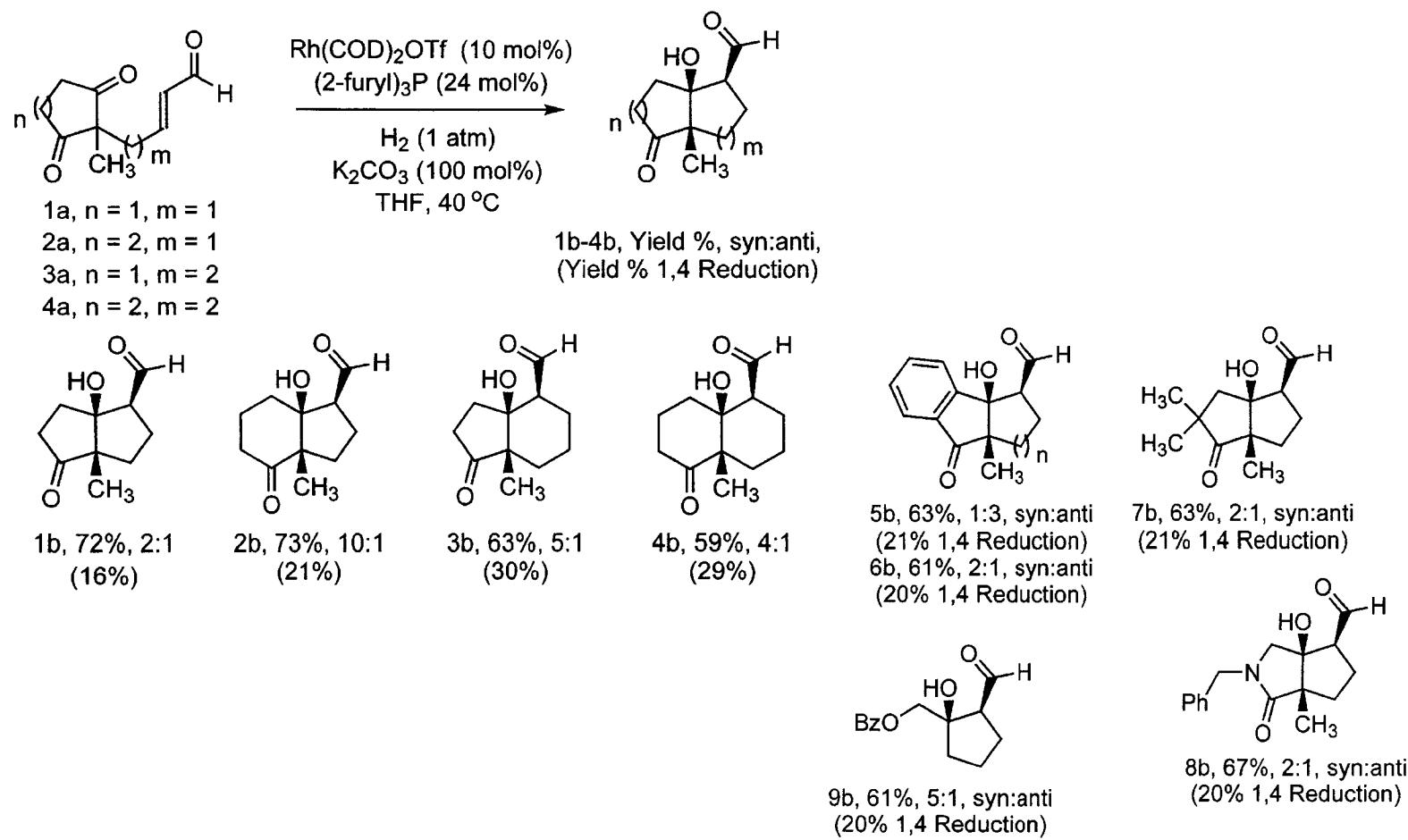
Reductive Coupling of Unsaturated aldehydes and glyoxals: Question 3



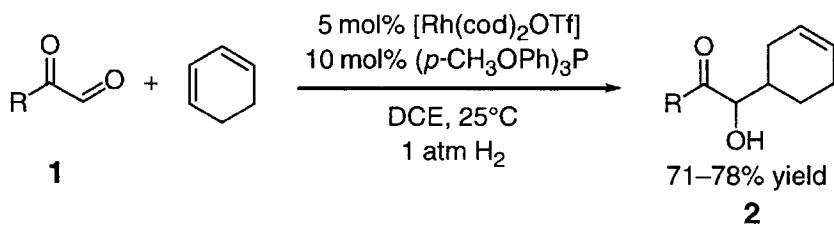
| Entry | R_1 | R_2 | Procedure ^a | | Product | Yield |
|-------|-----------------|-----------------------------------|------------------------|-------|---|-----------------|
| | | | 1a-4a | 1b-6b | | |
| 1 | H | Ph | | |  | 62 |
| 2 | H | 2-naphthyl | | |  | 59 |
| 3 | H | 2-thiophenyl | | |  | 31 |
| 4 | H | 2-(N-methylpyrrolyl) ^b | | |  | 30 ^c |
| 5 | CH_3^d | Ph | | |  | 47 |
| 6 | CH_3^d | 2-naphthyl ^b | | |  | 50 |

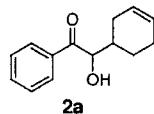
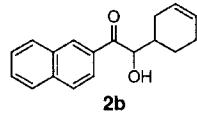
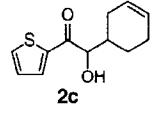
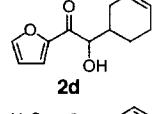
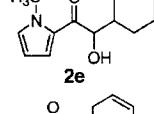
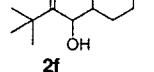
□ pyridazines

Aldol Cycloreduction of Dione-enones



Reductive Coupling of Cyclohexene and Glyoxals

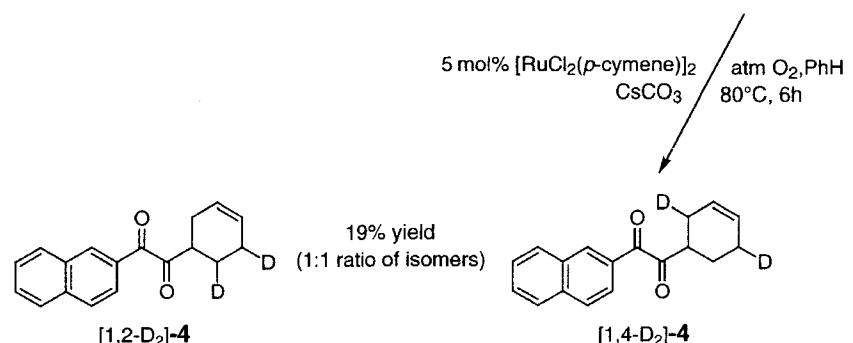
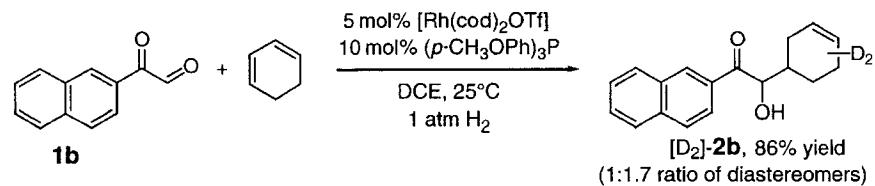
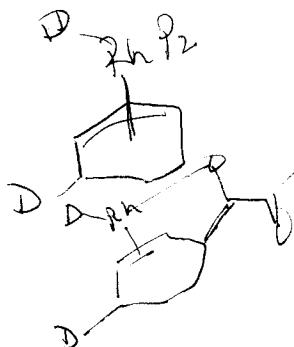
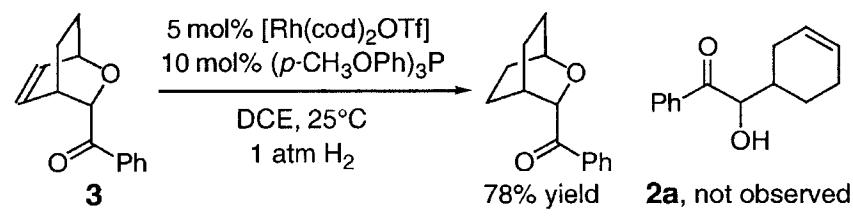


| Product | Yield | Ratio of isomers |
|--|-------|------------------|
|  2a | 76% | 1:1.6 |
|  2b | 77% | 1:1.5 |
|  2c | 74% | 1:1.4 |
|  2d | 78% | 1:1.3 |
|  2e | 73% | 1:1.4 |
|  2f | 71% | 1:1.6 |

Angew. Chem. Int. Ed. **2003**, *42*, 4074–4077.

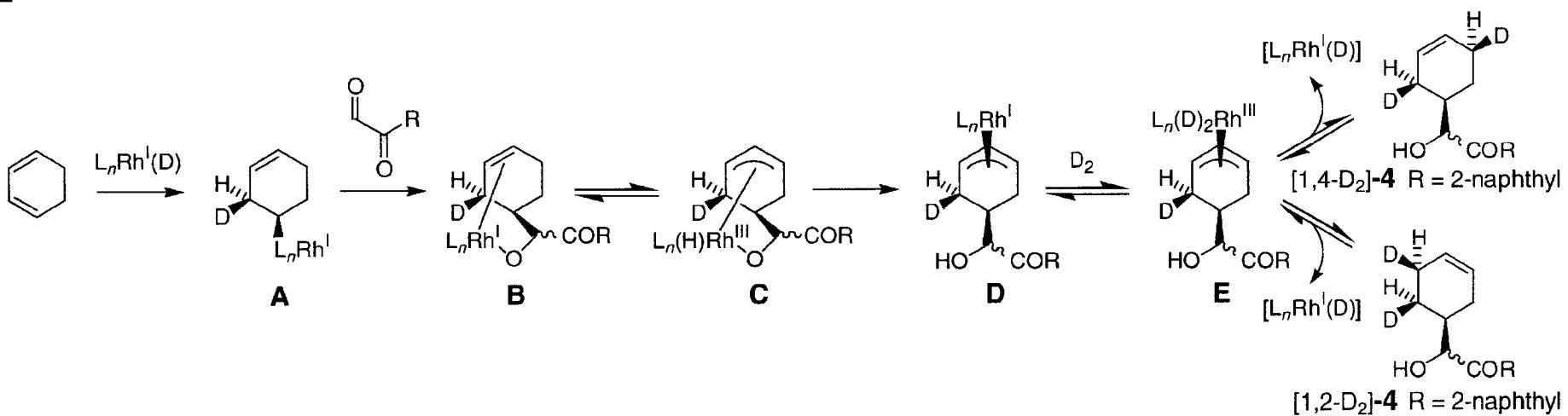
Question 4: Mechanistic insight

- Propose a mechanism which is consistent with the following results:

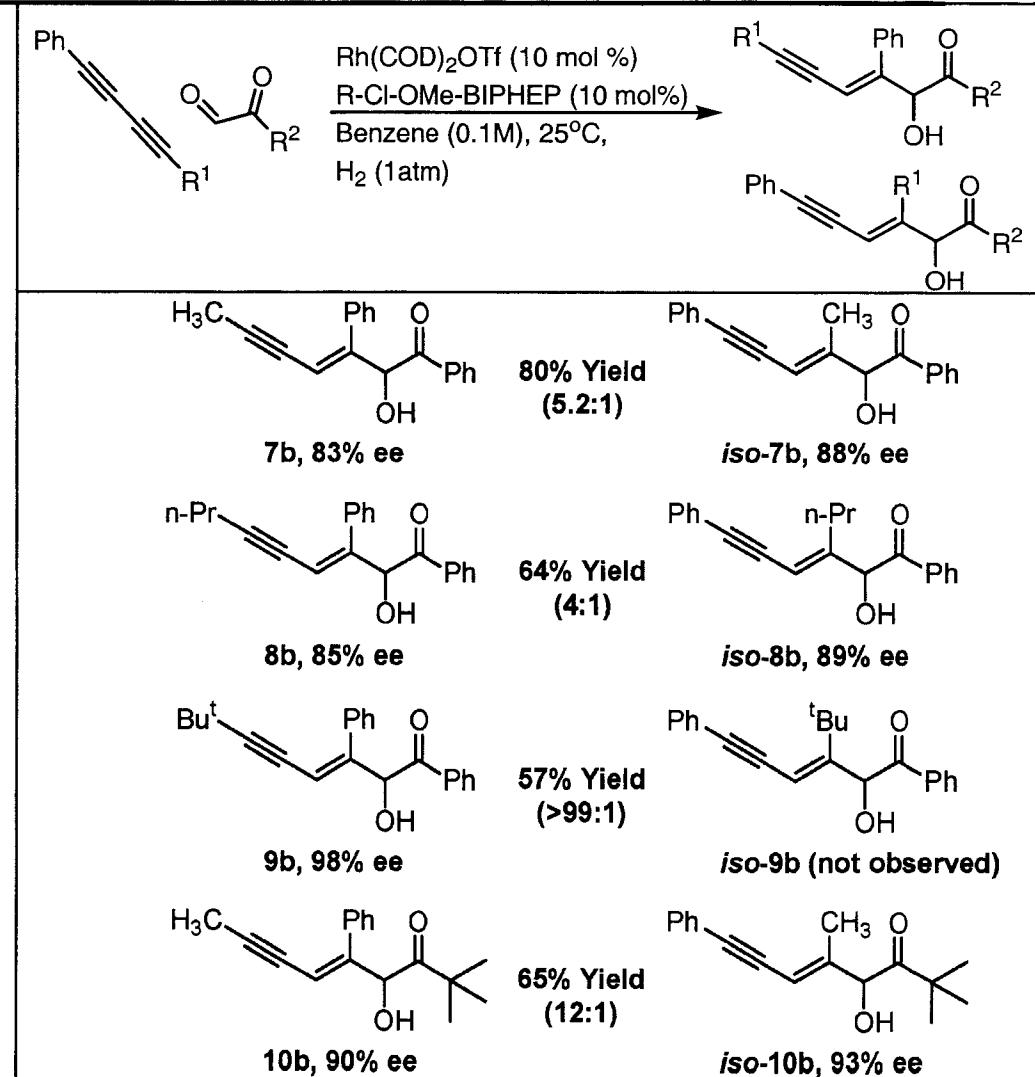
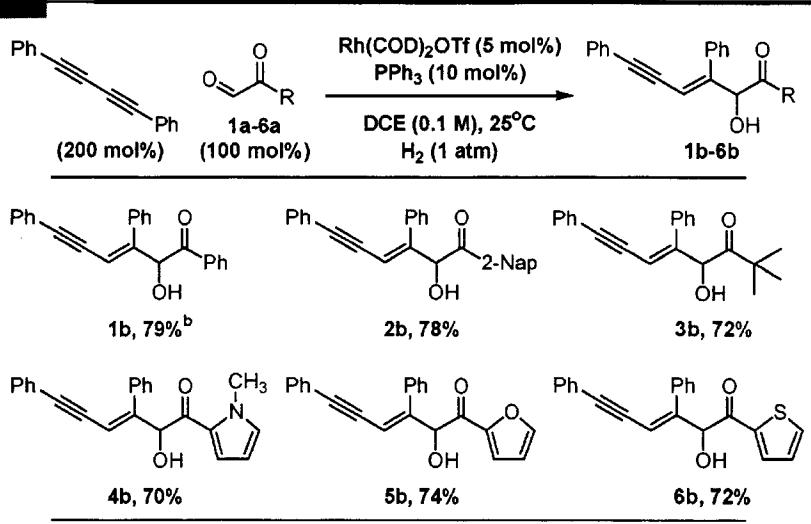


Question 4: Mechanistic insight

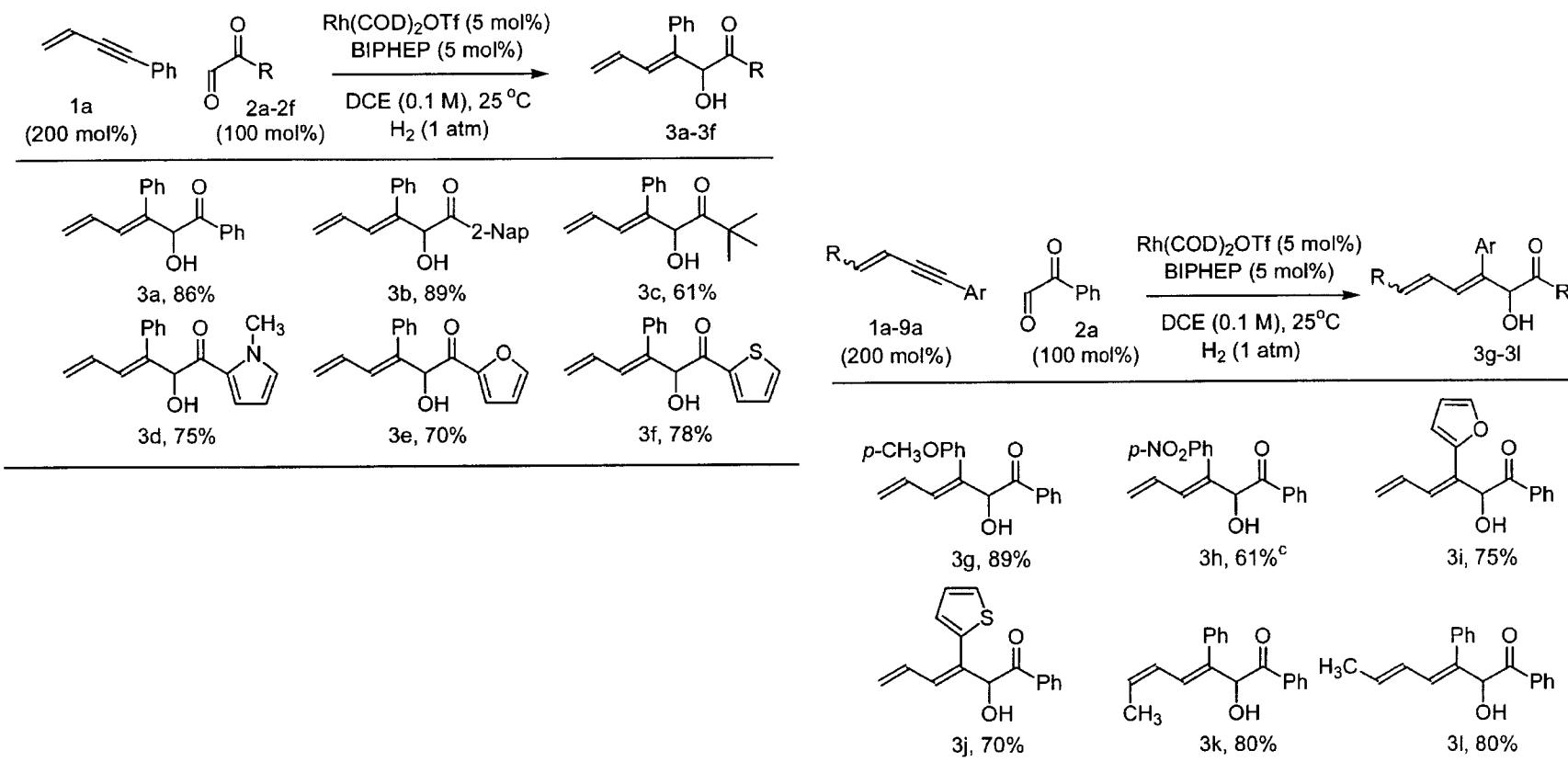
□ Model proposed in literature:



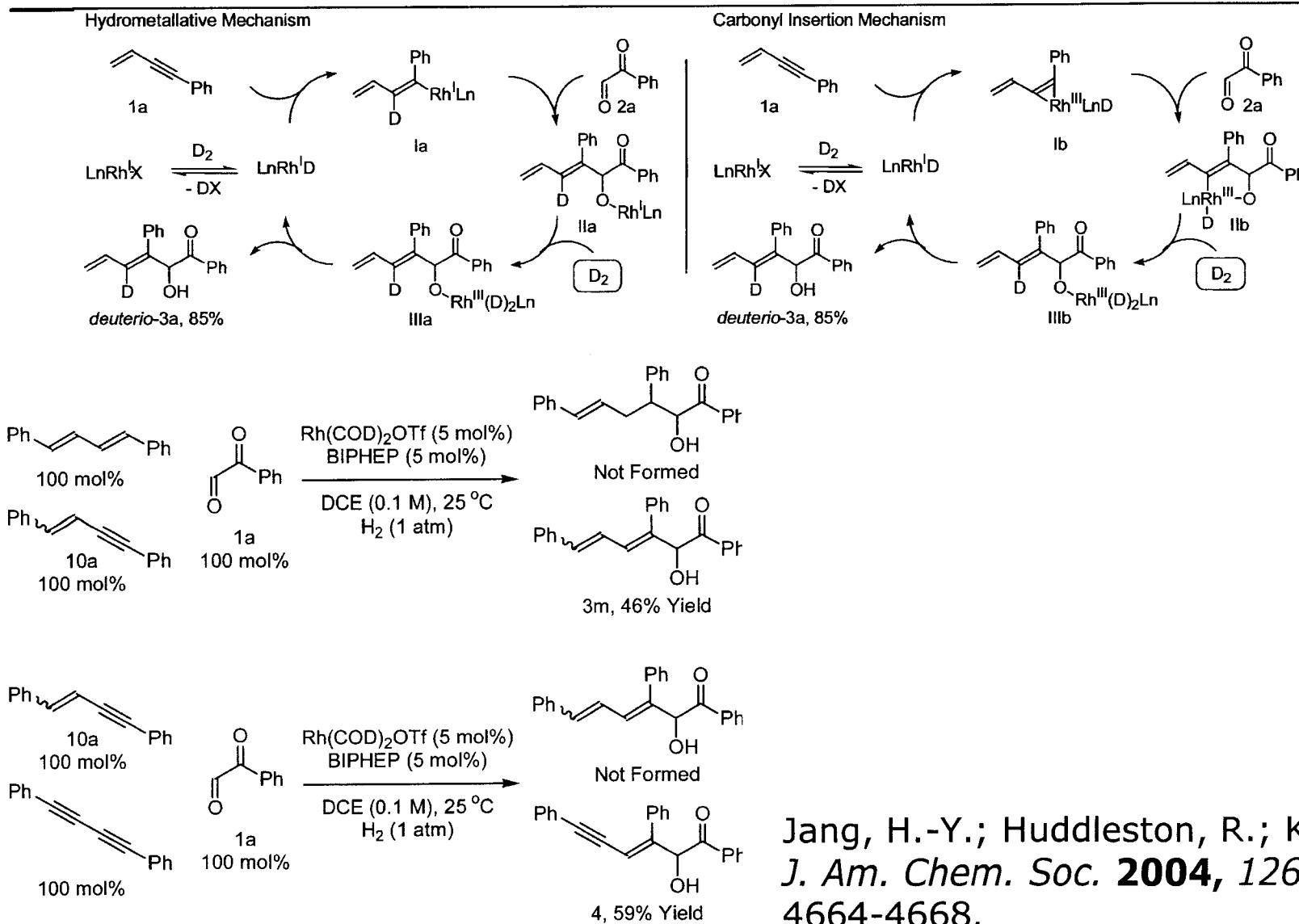
Catalytic Reductive Coupling of 1,3-Diynes to Glyoxals



Reductive Condensation of α -Keto Aldehydes and 1,3-Enynes

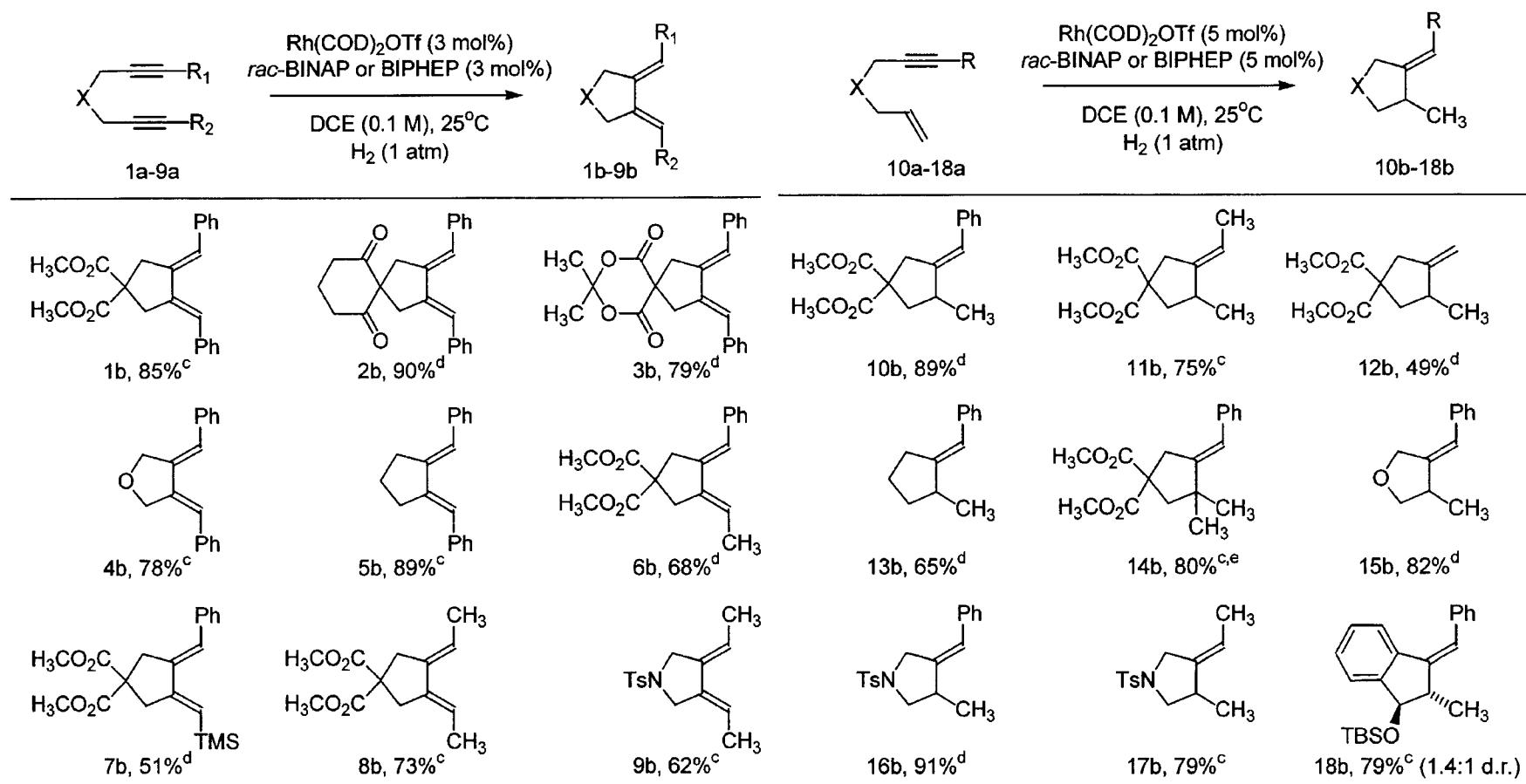


Mechanism of Reductive Coupling of 1,3-Enynes and 1,3-Diyne s with α -Keto Aldehydes



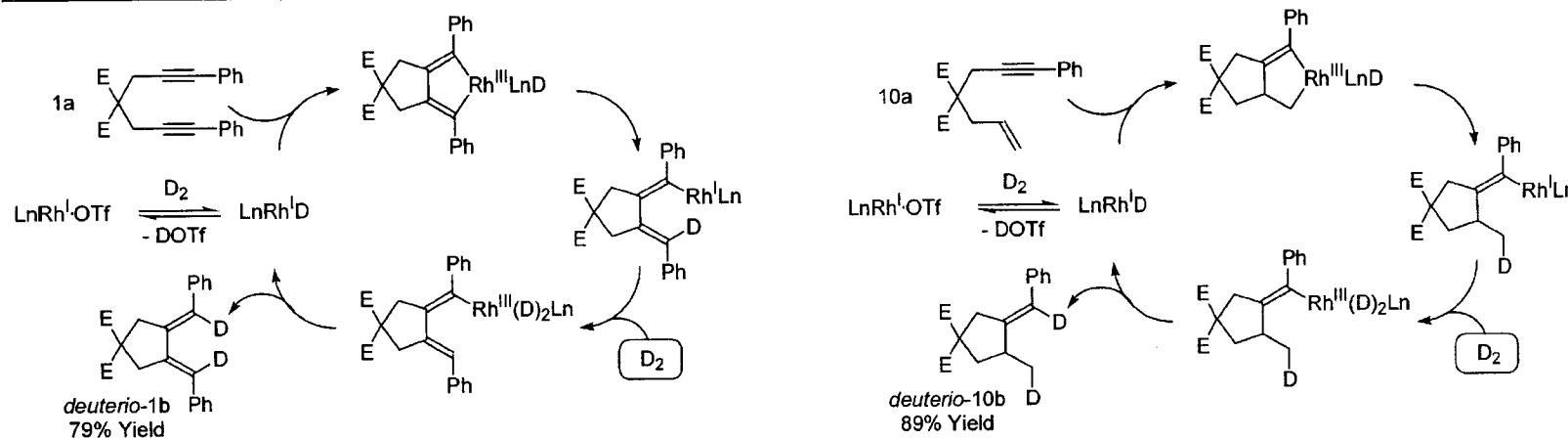
Jang, H.-Y.; Huddleston, R.; Krische, M.
J. Am. Chem. Soc. **2004**, *126*,
 4664-4668.

Reductive Cyclization of 1,6-Diynes and 1,6-Enynes

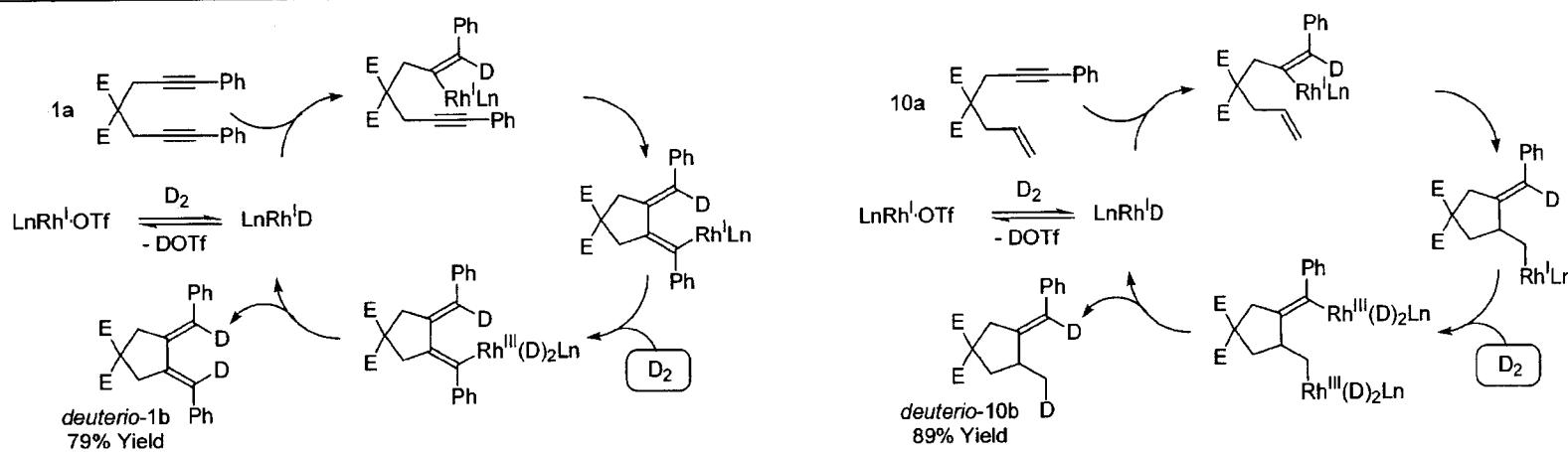


Mechanism of Reductive Cyclization of 1,6-Diynes and 1,6-Enynes

Catalytic Mechanism Involving Oxidative Cyclization: Regio-Determining C-C Bond Formation Precedes C-H Bond Formation.



Catalytic Mechanism Involving Alkyne Hydrometallation: Regio-Determining C-H Bond Formation Precedes C-C Bond Formation.



Summary

- Traditional methods of reductive coupling produce stoichiometric amounts of byproducts
- Capture of hydrogenation intermediates allows coupling with H₂ as the terminal reductant
- Several types of couplings have been successfully accomplished by capture of hydrogenation intermediates
- Heterolytic cleavage for formation of a monohydride catalyst intermediate is required for successful coupling
- Heterolytic cleavage of hydrogen is accomplished through the use of cationic precatalysts

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 - Jang, H.-Y.; Huddleston, R.; Krische, M. *Angew. Chem. Int. Ed. Engl.* **2003**, *42*, 4074-4077.
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