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## Reductive Enolate Generation From Enones - Application in C-C bond Formation

1. Cauble, D, F.; Gipson, J, D.; Krische, M, J. *J. Am. Chem. Soc.* **2003**, *125*, 1110.
2. Huddleston, R, R.; Krische, M, J. *Org. Lett.* **2003**, *5*, 1143.
3. Jang, H, Y.; Huddleston, R, R.; Krische, M, J. *J. Am. Chem. Soc.* **2002**, *124*, 15156.

Group Presentation

Zhenjie Lu

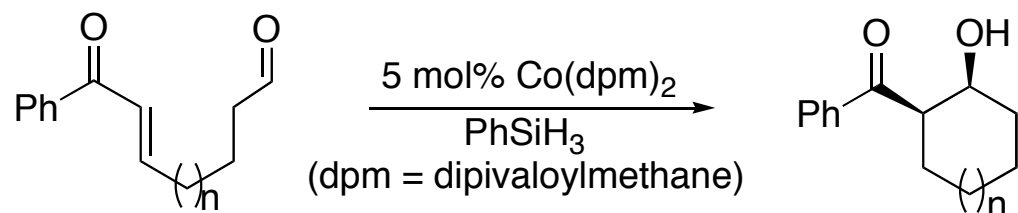
Nov 20, 2003

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## Catalytic Nucleophilic Activation of Enones

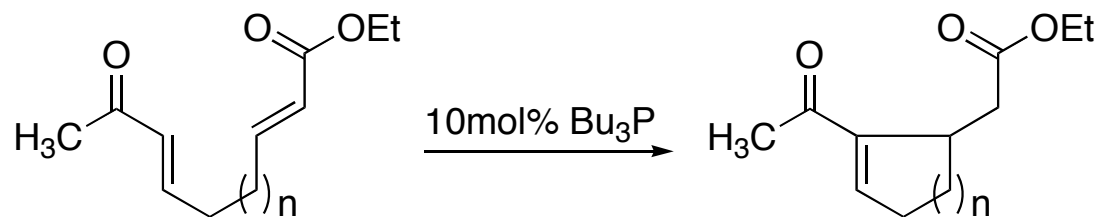
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- Hydrometallative nucleophilic activation via conjugate reduction



\* Co, Ni, Rh catalyst systems, silane, borane, alane, and stannane,  $\text{H}_2$  as reductants

- Nucleophilic organocatalysis via reversible conjugate addition

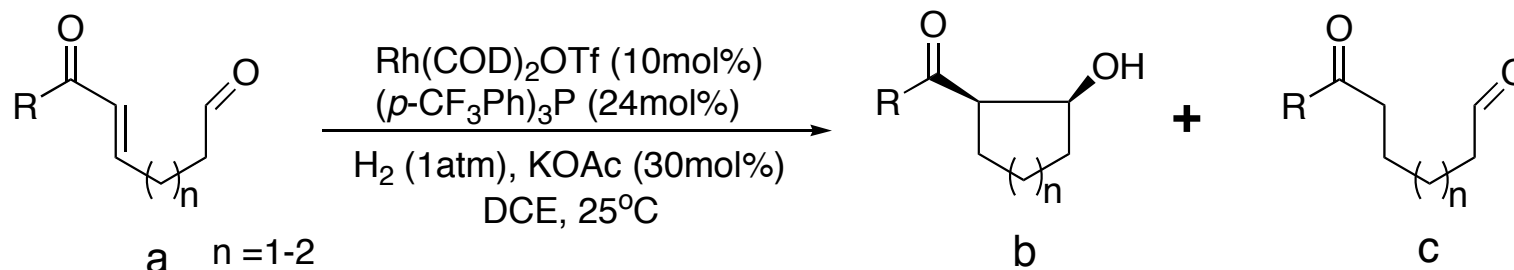


\* Intramolecular Baylis-Hillman reaction, Intramolecular Rauhut-Currier reaction



## Catalytic C-C bond Formation of Monoenone and Monoaldehyde

➤ Hydrogenative aldol cycloreduction of aromatic, heteroaromatic, and aliphatic enone substrates to form 5- and 6- membered rings.

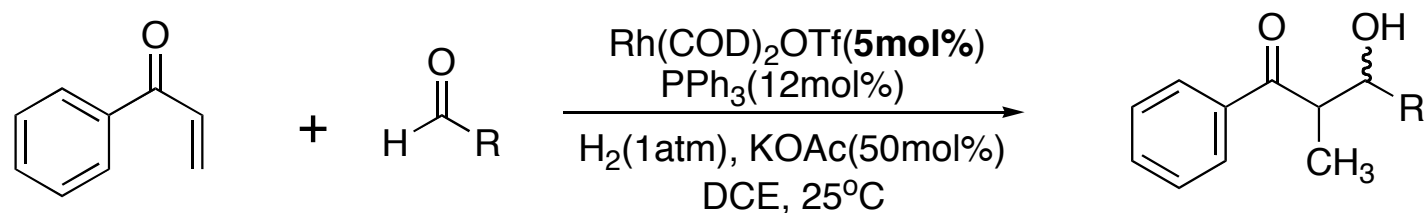


**Table 1.** Rh-Catalyzed Hydrogenative Aldol Cycloreduction of Monoenone Monoaldehydes **1a-7a**

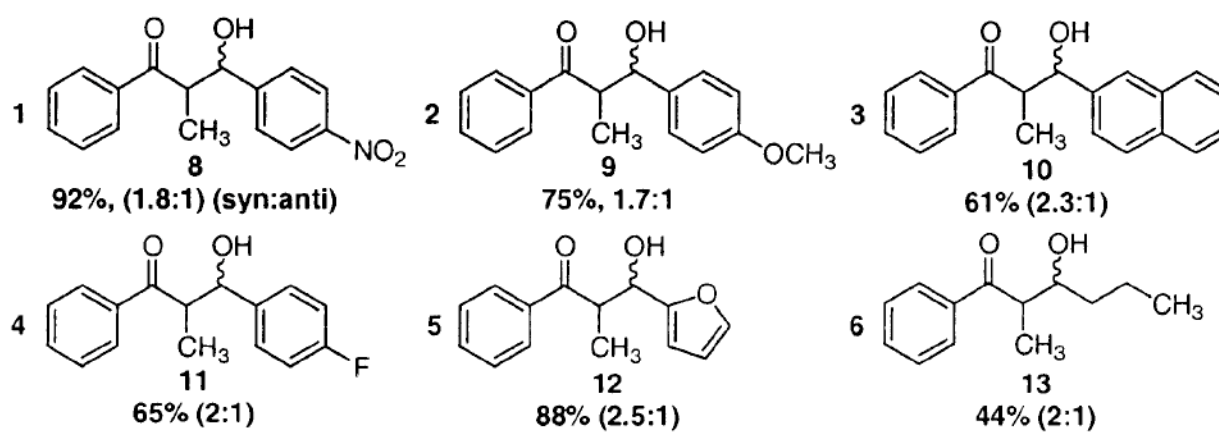
substrate	product (syn:anti)	1,4-reduction
<b>1a</b> , $n = 2$ , R = Ph	<b>1b</b> , 89% (10:1)	<b>1c</b> , 0.1%
<b>2a</b> , $n = 2$ , R = <i>p</i> -MeOPh	<b>2b</b> , 74% (5:1)	<b>2c</b> , 3%
<b>3a</b> , $n = 2$ , R = 2-naphthyl	<b>3b</b> , 90% (10:1)	<b>3c</b> , 1%
<b>4a</b> , $n = 2$ , R = 2-thiophenyl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

## Intermolecular Hydrogenative Aldol Condensation

➤ Phenyl vinyl ketone as preucleophile.



**Table 2.** Intermolecular Rh-catalyzed hydrogenative aldol condensation of phenyl vinyl ketone and various aldehydes



\* Changes of conditions:

Intramolecular: enone: 100mol%, catalyst: 10mol%, conc: 0.5mol/L.

Intermolecular: enone: 150mol%, catalyst: 5mol%, conc: 0.1mol/L.

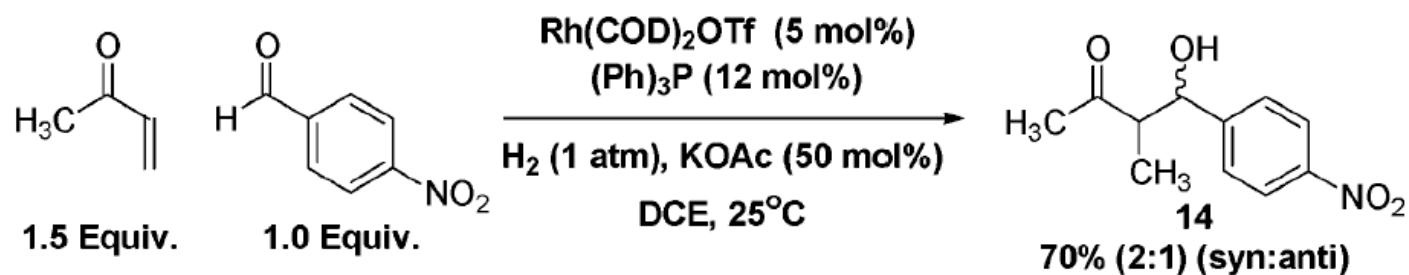
## Variation of the Nucleophilic Partners

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➤ Propiophenone doesn't result in aldolization;

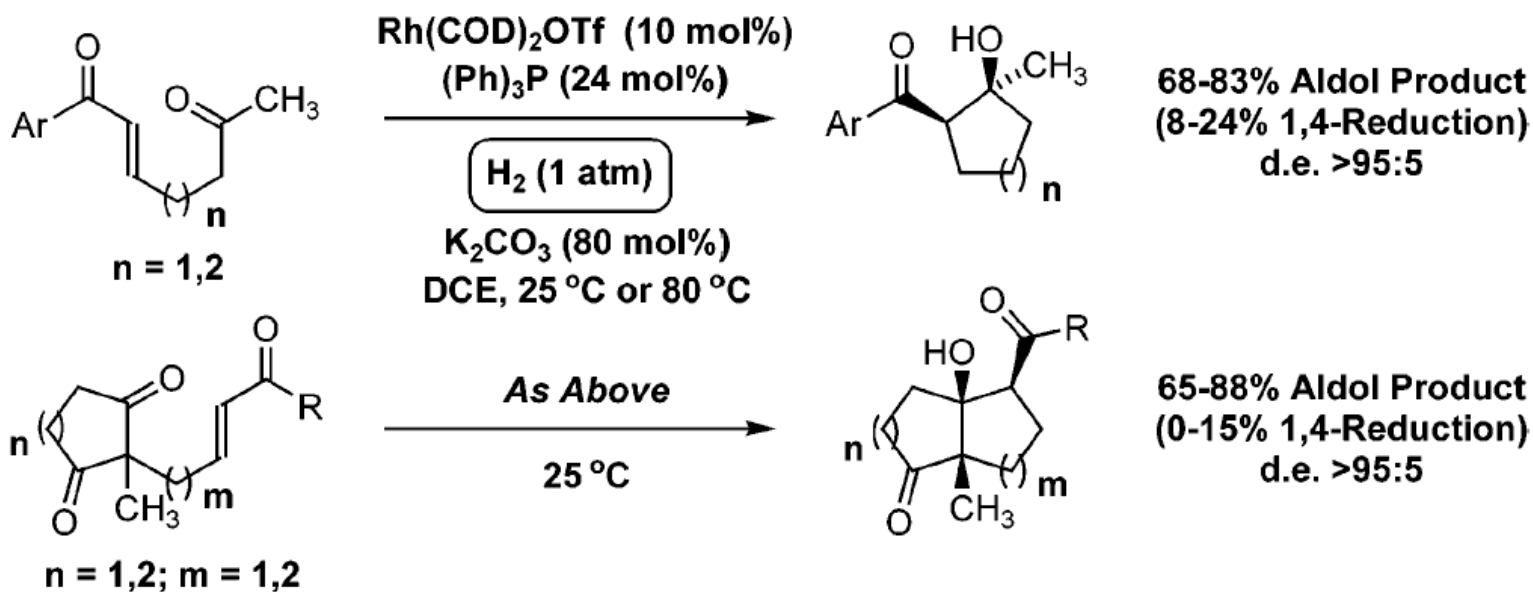
Ethyl acrylate exclusively give 1,4-reduction product;

Methyl vinyl ketone works.



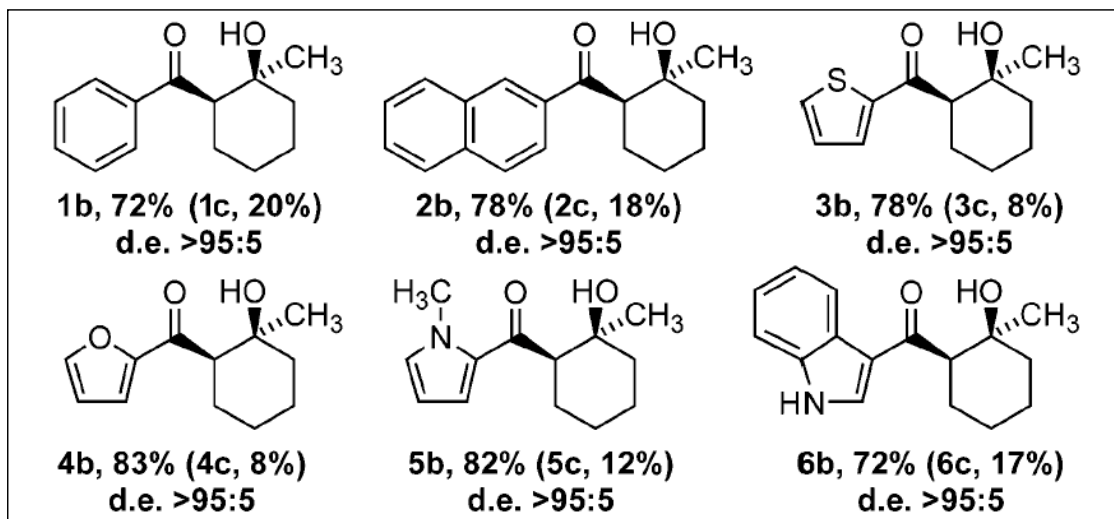
## Catalytic Hydrogenative Cycloredution of Keto-enones

- Ketone and dione partners as electrophiles

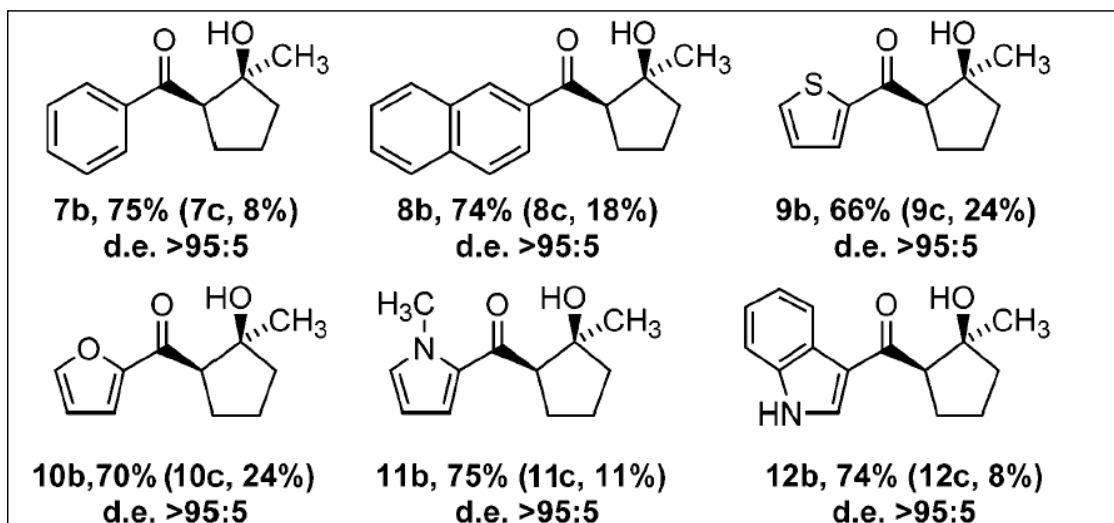


## Catalytic Hydrogenative Cycloreduction of Keto-enones

n = 2

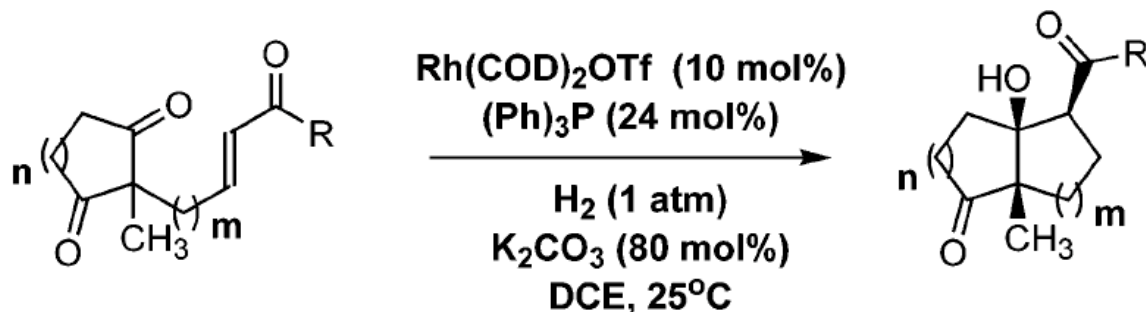


n = 1





## Cycloreduction of Dione-enones



13a,  $n = 1$ ,  $m = 1$ ,  $\text{R} = \text{Ph}$

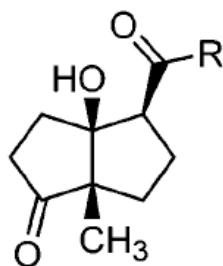
14a,  $n = 1$ ,  $m = 1$ ,  $\text{R} = \text{CH}_3$

15a,  $n = 1$ ,  $m = 2$ ,  $\text{R} = \text{Ph}$

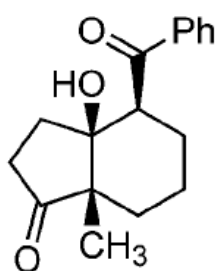
16a,  $n = 2$ ,  $m = 1$ ,  $\text{R} = \text{Ph}$

17a,  $n = 2$ ,  $m = 1$ ,  $\text{R} = \text{CH}_3$

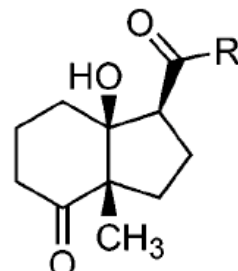
18a,  $n = 2$ ,  $m = 2$ ,  $\text{R} = \text{Ph}$



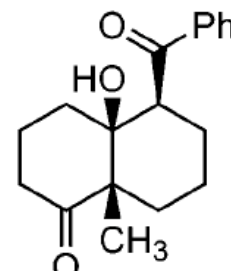
13b,  $\text{R} = \text{Ph}$ , 84%



15b, 86%



16b,  $\text{R} = \text{Ph}$ , 81%



18b, 65% (15%)

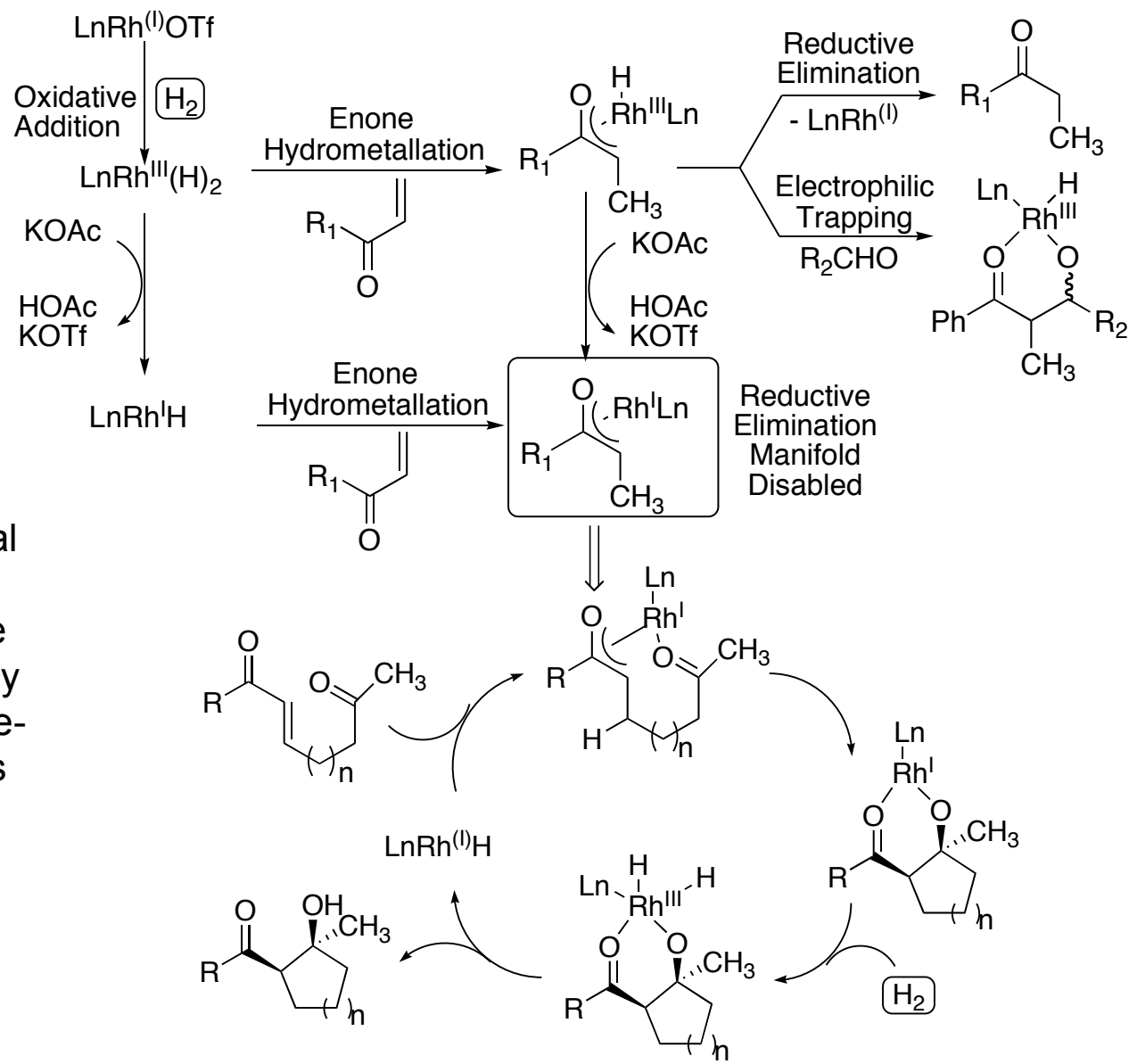
14b,  $\text{R} = \text{CH}_3$ , 88%

17b,  $\text{R} = \text{CH}_3$ , 73%

**No Conjugate Reduction**  
 d.e. >95:5

➤ Diastereoselective formation of 3-contiguous stereogenic centers, including 2-contiguous quaternary centers.

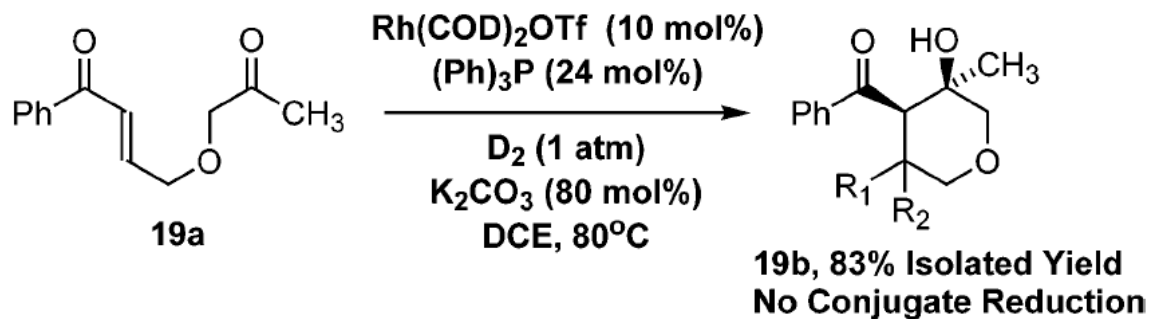
## Monohydride-based Catalytic Cycle



➤ Formal heterolytic activation of elemental hydrogen mitigates competitive conjugate reduction manifolds by enabling monohydride-based catalytic cycles

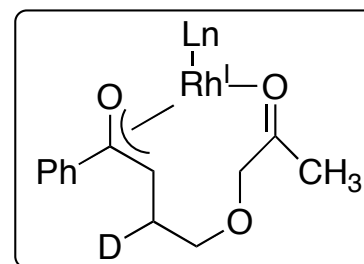
## Mechanism Study on the Conjugate Reduction

- Catalytic cycloaddition employing elemental deuterium



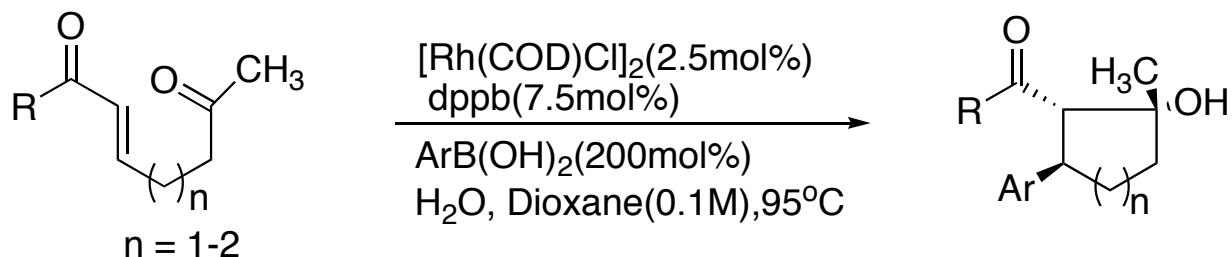
$R_1 = R_2 = \text{H}$ , 11% +/- 5%  
 $R_1 = \text{D}$ ,  $R_2 = \text{H}$ , 81% +/- 5%  
 $R_1 = R_2 = \text{D}$ , 8% +/- 5%

⇓  
The enone hydrometalation is reversible.  
Such as  $\beta$ -hydride elimination of Rh-enolate.



## Carbometallative Aldol Cycloreduction: Tandem Conjugate Addition Aldol Cyclization

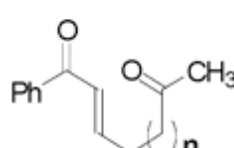
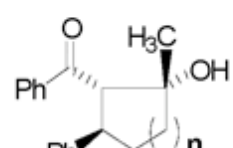
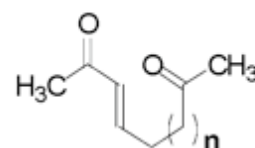
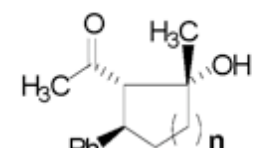
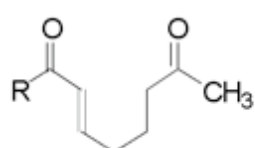
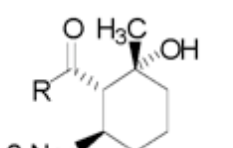
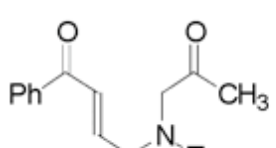
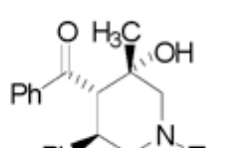
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- \* Rh-catalyzed conjugate addition is performed:
  1. Aqueous organic media  $\Rightarrow$  adding water (5 equiv with respect to substrate)
  2. Avoid the addition of arylboronic acids to aldehyde  $\Rightarrow$  methyl ketones
- \* Three contiguous stereogenic centers are created in one manipulation with high relative and absolute stereochemical control. A single diastereomer was obtained, no epimeric material detected.
- \* The stereochemical assignment was corroborated by X-ray analysis.

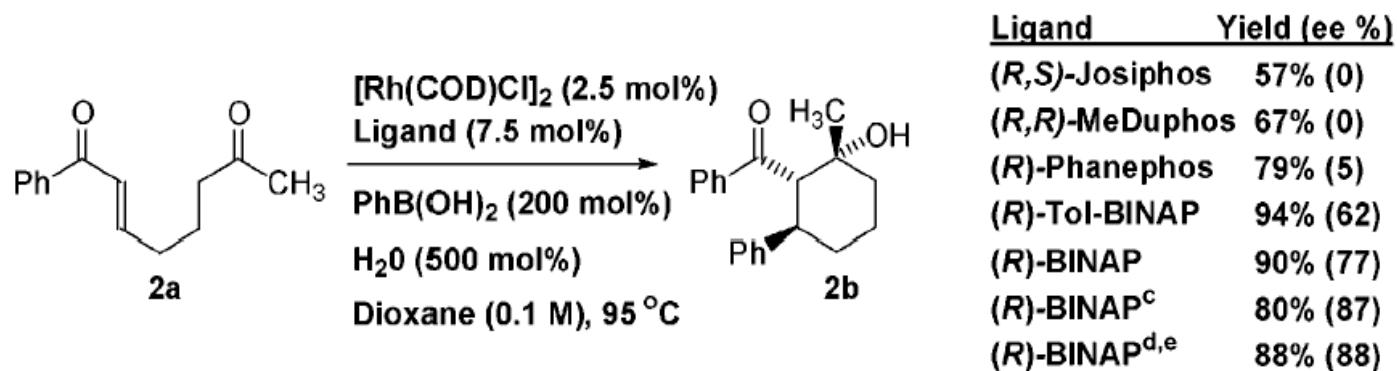
## Carbometallative Aldol Cycloreduction

**Table .** Catalytic diastereoselective carbometallative aldol cycloreduction

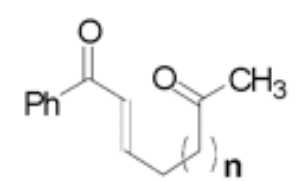
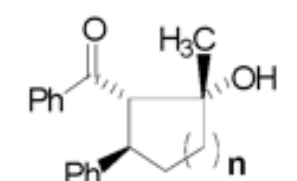
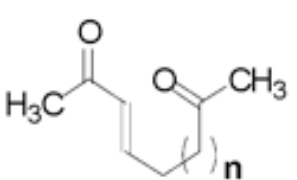
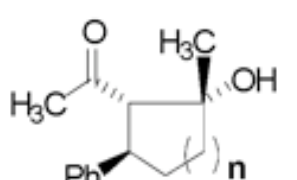
Entry	Substrate	Product	Isolated Yield
1	 <b>1a, n = 1</b> <b>2a, n = 2</b>	 <b>1b</b> <b>2b</b>	 <b>73%</b> <b>87%</b>
2	 <b>3a, n = 1</b> <b>4a, n = 2</b>	 <b>3b</b> <b>4b</b>	 <b>75%</b> <b>45%</b>
3	 <b>4a, R = CH<sub>3</sub></b> <b>2a, R = Ph</b>	 <b>4c</b> <b>2c</b>	 <b>40%</b> <b>70%</b>
4	 <b>5a</b>	 <b>5b</b>	 <b>84%</b>

## Catalytic Enantioselective Carbometallative Aldol Cycloreduction

➤ Optimization of the enantioselective carbometallative cycloreduction of **2a**

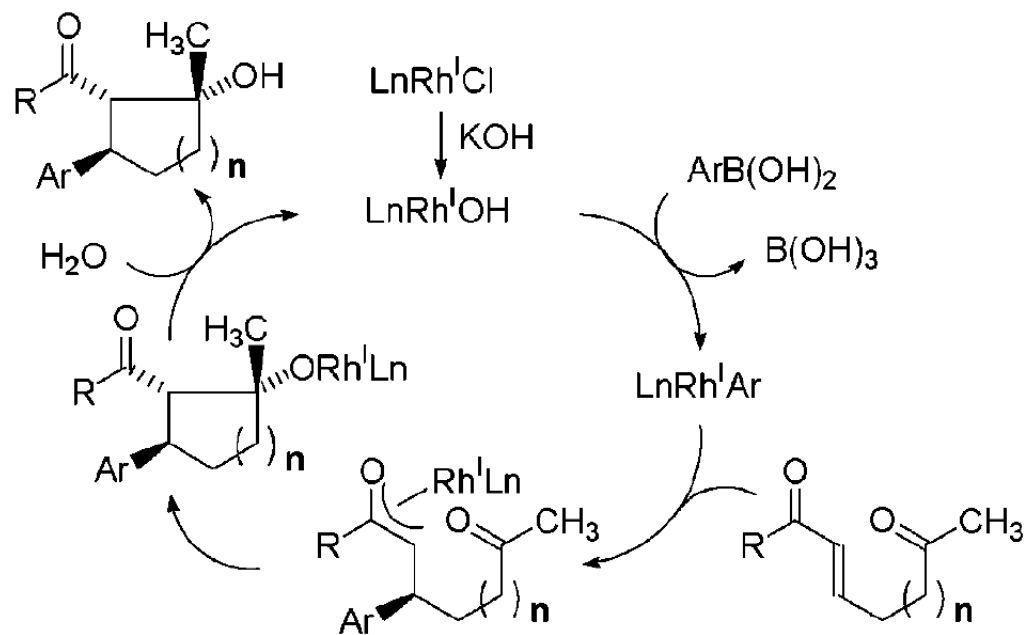


**Table** . Catalytic enantioselective carbometallative aldol cycloreduction

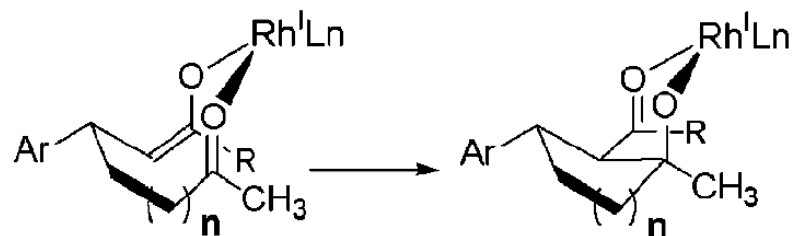
Entry	Substrate	Product	Isolated Yield (ee%)
1	 <b>1a, n = 1</b>	 <b>1b</b>	<b>78% (77)</b>
	<b>2a, n = 2</b>	<b>2b</b>	<b>88% (88)</b>
2	 <b>3a, n = 1</b>	 <b>3b</b>	<b>88% (94)</b>
	<b>4a, n = 2</b>	<b>4b</b>	<b>69% (95)</b>

## Proposed Mechanism

### ➤ Proposed catalytic cycle



### ➤ Model of Z-enolate and Zimmerman-Traxler type Transition state



## Summary

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- A catalytic C-C bond formation under hydrogenative conditions via selectively generate and transform transition metal enolates.
  - A mild and economical hydrometallative method which circumvents 1,4-reduction byproduct.
  - Aldehyde, ketone, and dione used as electrophiles in aldol cycloreduction to form 5- or 6- membered rings.
  - The ability of creating three contiguous stereogenic centers in a single manipulation with high relative and absolute stereochemical control.
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