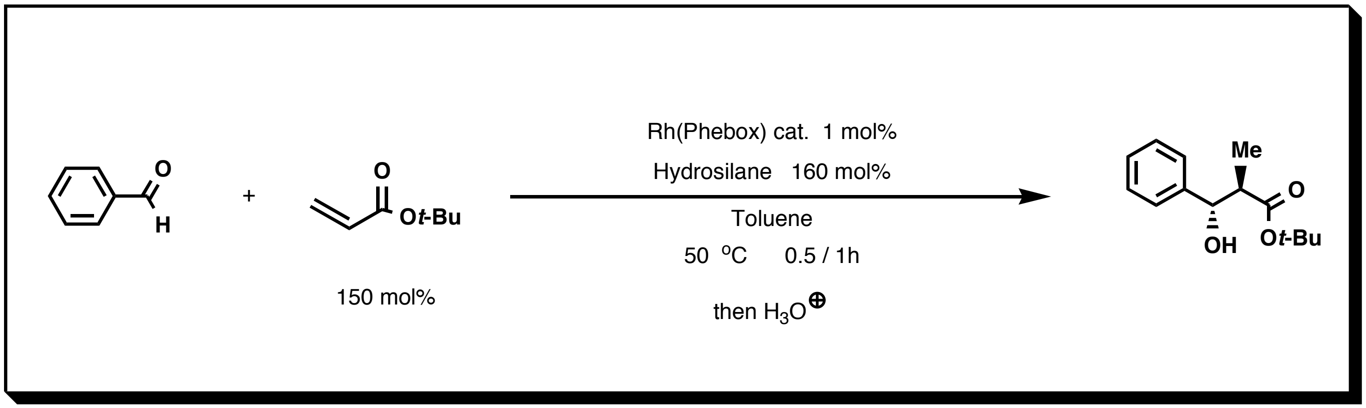
High Performance of Rh(Phebox) Catalysts in Asymmetric Reductive Aldol Reaction: High Anti-Selectivity



Nishiyama,* H.; Shiomi, T.; Tsuchiya, Y.; Matsuda, I.

Nagoya University, Japan

J. Am. Chem. Soc. **2005**, *127*, 6972-6973.

Introduction

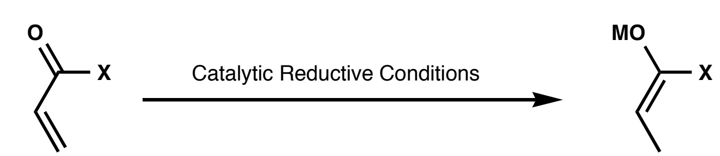
POLYPROPIONATE DERIVED NATURAL PRODUCTS

⇓

STATE OF THE ART OF ENOLATE CHEMISTRY ⇒ **GENERAL LEVEL OF SYNTHETIC ORGANIC CHEMISTRY**

A GENERAL CATALYTIC ASYMMETRIC *DIRECT ALDOL* REACTION IS STILL MISSING

An Alternative Approach: ENONES as LATENT ENOLATES

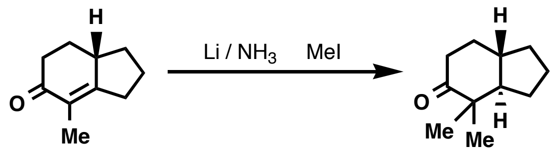


HIGHLIGHTS: --- **The enolate is generated *in situ***

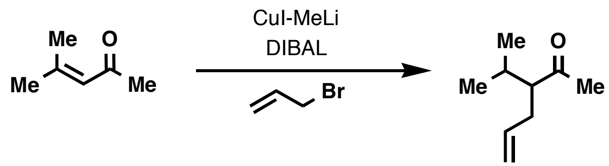
--- **Multicomponent Reaction**

Reductive Aldol Reactions: Background (I)

Reductive Alkylation of α,β-Unsaturated Compounds

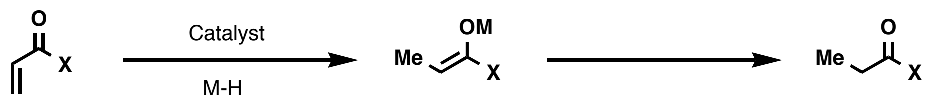


Stork, G. and coworkers *J. Am. Chem. Soc.* **1965**, *87*, 275



Tsuda, T.; Saegusa, T. and coworkers *J. Org. Chem.* **1987**, *52*, 439

Catalytic 1,4-Hydrometalation

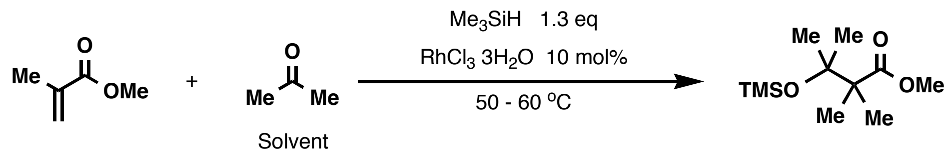


M	*First Report*
Si	Speier, J. L. and coworkers *J. Am. Chem. Soc.* **1957**, *79*, 974
Sn	Four, P. and Guibe, P. *Tetrahedron Lett.* **1982**, *23*, 1825 Keinan, E. and Geize, P. A. *Tetrahedron Lett.* **1982**, *23*, 477
Al	Tsuda, T.; Saegusa, T. and coworkers *J. Org. Chem.* **1986**, *51*, 537
B	Evans, D. A. and Fu, G. C. *J. Org. Chem.* **1990**, *55*, 5678

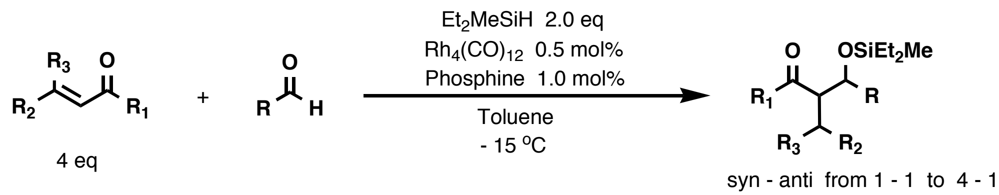
Is It Possible to Suppress the 1,4-Reduction Pathway and Use the Intermediate Enolate in an Aldol Reaction ?

Reductive Aldol Reactions: Background (II)

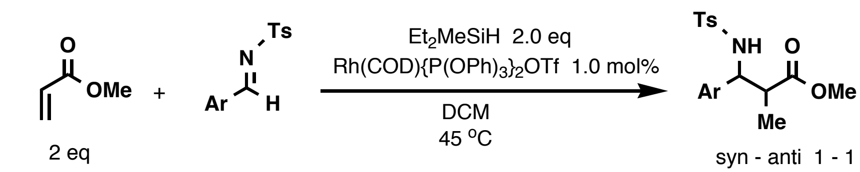
Rhodium-Catalyzed Reductive Aldol Reactions



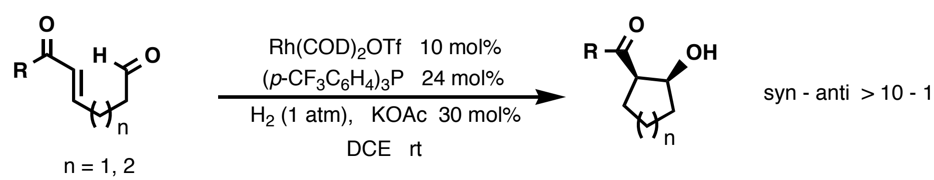
Revis, A. and Hilty, T. K. *Tetrahedron Lett.* **1987**, *28*, 4809

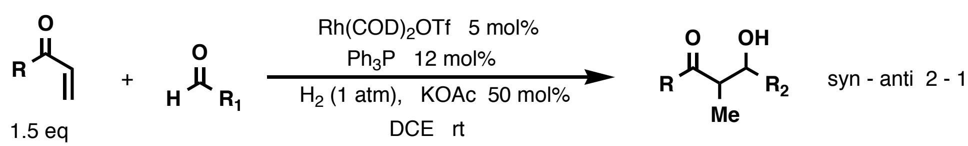


Matsuda, I. and coworkers *Tetrahedron Lett.* **1990**, *31*, 5331



Matsuda, I. and coworkers *Chem. Commun.* **2002**, 1284

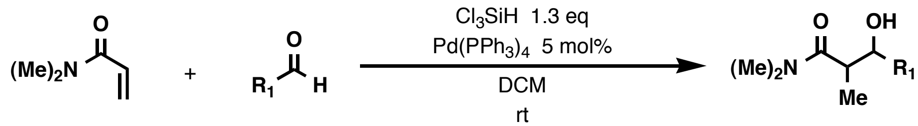




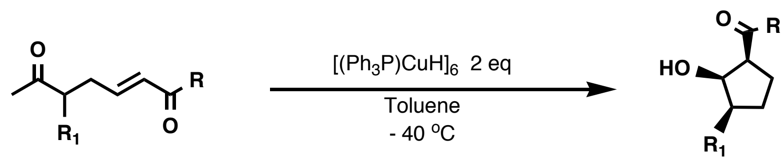
Krische, M. J. and coworkers *J. Am. Chem. Soc.* **2002,** *124*, 15156

Reductive Aldol Reactions: Background (III)

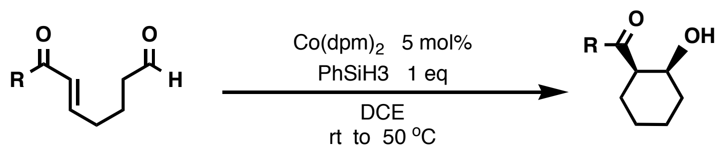
Others Metal-Promoted Reductive Aldol Reactions



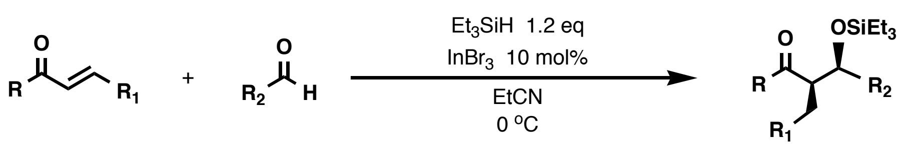
Kiyooka, S. and coworkers *Tetrahedron Lett.* **1998**, *39*, 5237



Chiu, P. and coworkers *Org. Lett.* **2001**, *3*, 1901



Krische, M. J. and coworkers *J. Am. Chem. Soc.* **2002**, *124*, 9448

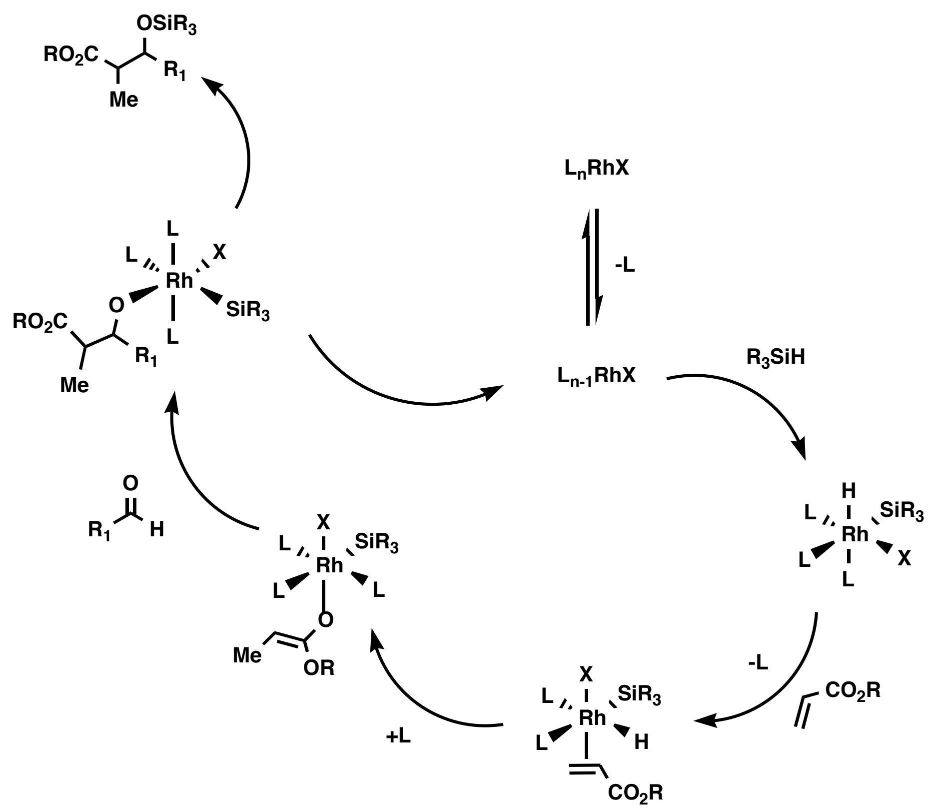


Shibata, I.; Baba, A. and coworkers *Angew. Chem. Int. Ed. Engl.* **2004**, *43*, 711

Reductive Aldol Reactions: Background (IV)

Proposed Mechanism

\

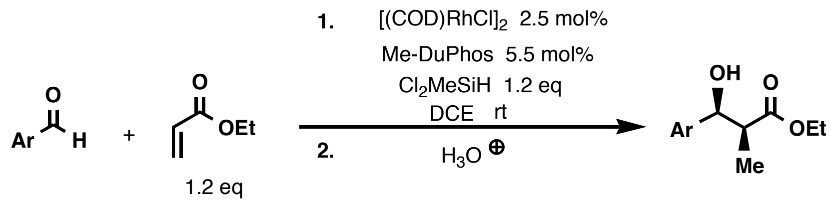


For an example of Rh-O enolate see: Bergman, R. G. and Heathcock, C. H. *J. Am. Chem. Soc.* **1989**, *111*, 938

For an example of Rh-oxa-π complex see: Hayashi, T. and coworkers *J. Am. Chem. Soc.* **2002**, *124*, 5052

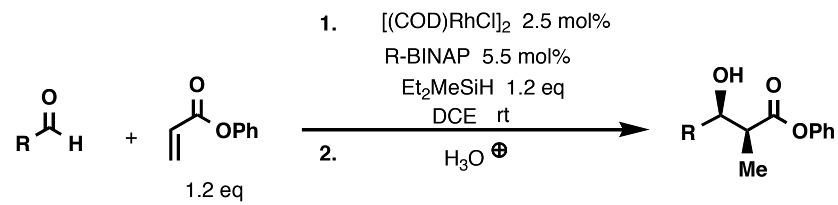
Reductive Aldol Reactions: Background (V)

The Development of a Catalytic Asymmetric Version



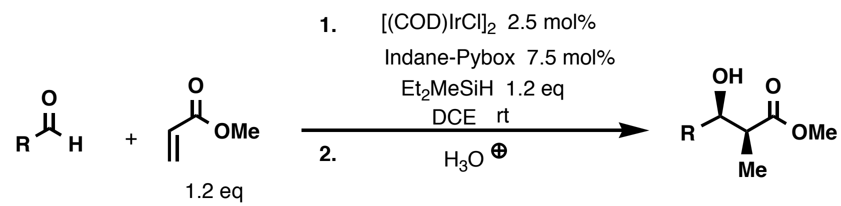
syn - anti > 20 - 1
ee 0%

Morken, J. P. and Taylor, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 12202



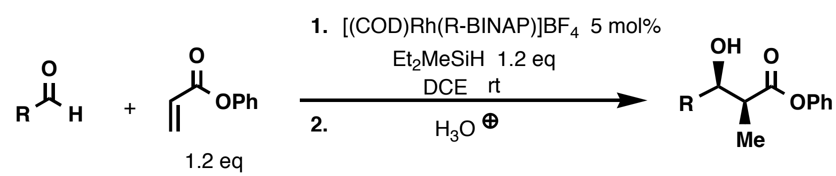
syn - anti from 2 - 1 to 5 - 1
ee (syn) 45 - 87%

Morken, J. P. and coworkers. *J. Am. Chem. Soc.* **2000**, *122*, 4528



syn - anti from 3 - 1 to 10 - 1
ee (syn) 91 - 97%

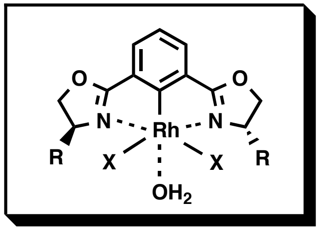
Morken, J. P. and coworkers. *Org. Lett.* **2001**, *3*, 1829



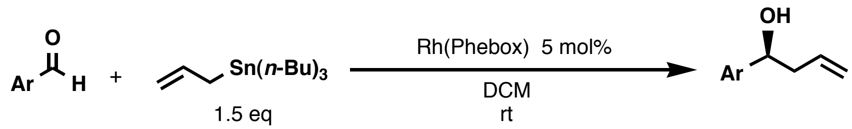
syn - anti from 3 - 1 to 7 - 1
ee (syn) 75 - 83%

Morken, J. P. and coworkers. *Org. Lett.* **2004**, *6*, 2309

Rh(Phebox) Catalysts in Organic Synthesis

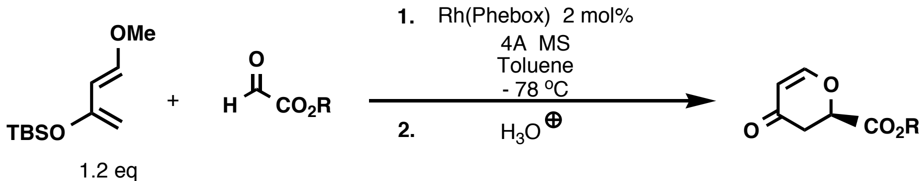


R = *i*-Pr or Bn
X = Cl, Br, OAc



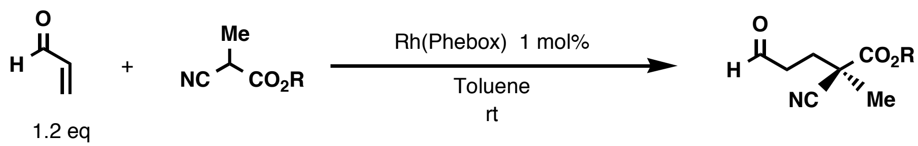
ee (43 - 80)%

Nishiyama, H. and coworkers *Chem. Commun.* **1999**, 131
Nishiyama, H. and Motoyama, Y. and coworkers *Synlett* **2003**, 1883



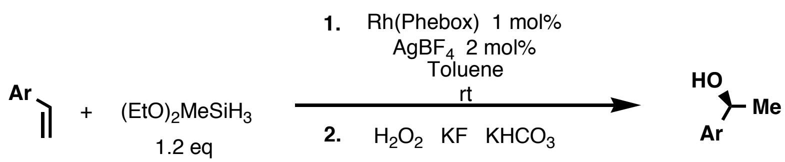
ee (36 - 82)%

Nishiyama, H. and coworkers *Tetrahedron.* **2001**, *57*, 853



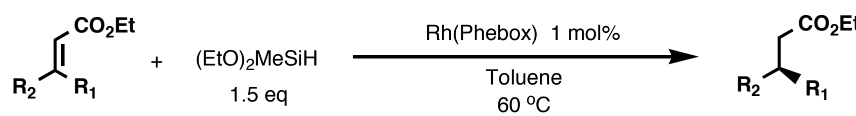
ee (69 - 85)%

Nishiyama, H. and Motoyama, Y. and coworkers *Chem. Eur. J.* **2002**, *8*, 2968



ee (37 - 95)%

Nishiyama, H. and coworkers *Synlett* **2004**, 2099

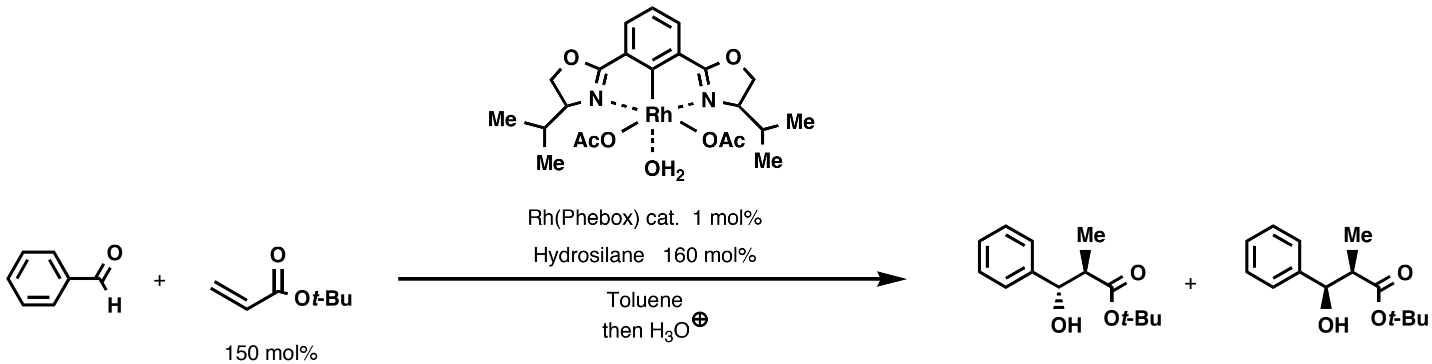


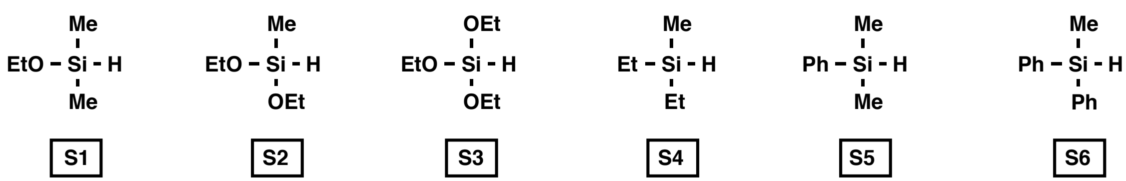
ee (43 - 98)%

Nishiyama, H. and coworkers *Synlett* **2004**, 2493

High Performance of Rh(Phebox) Catalysts in Asymmetric Reductive Aldol Reaction: High Anti-Selectivity (I)

Preliminary Studies

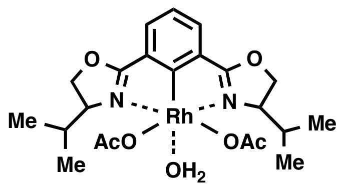




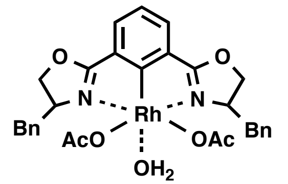
Entry	Silane	T / t (°C / h)	Yield (%)	anti / syn	ee % anti	ee % syn
1	**S1**	50 / 0.5	93	94 / 6	94	2
2	**S2**	50 / 0.5	91	95 / 5	91	11
3	**S3**	50 / 0.5	87	94 / 6	88	4
4	**S4**	60 / 3.0	89	93 / 7	93	7
5	**S5**	50 / 0.5	93	94 / 6	95	5
6	**S6**	50 / 5.0	95	93 / 7	96	34

High Performance of Rh(Phebox) Catalysts in Asymmetric Reductive Aldol Reaction: High Anti-Selectivity (II)

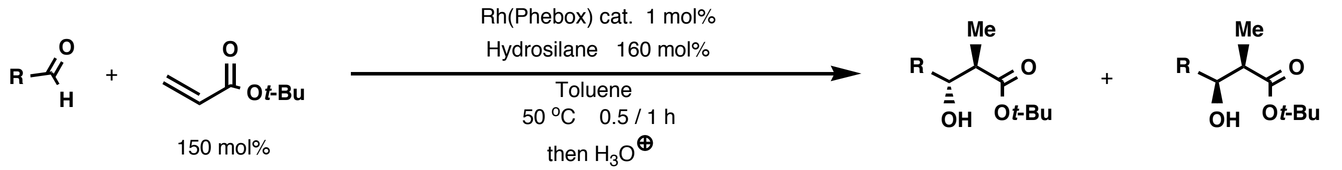
Reaction Scope



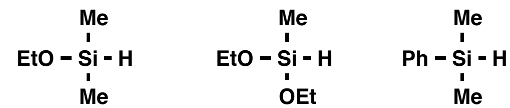
1



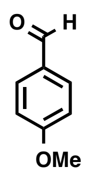
2



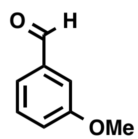
[Catalyst / Silane : yield of aldols (%), ratio of anti / syn, ee (%) of anti and syn]



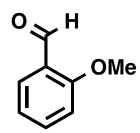
S1 S2 S3



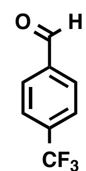
[**1** / **S1**: 94 93 / 7 94, 1]
[**1** / **S2**: 82 94 / 6 93, 1]
[**1** / **S3**: 90 92 / 8 95, 5]
[**2** / **S2**: 98 94 / 6 94, 42]



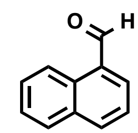
[**1** / **S2**: 92 93 / 7 92, 28]
[**1** / **S3**: 96 93 / 7 96, 15]
[**2** / **S2**: 99 91 / 9 93, 64]



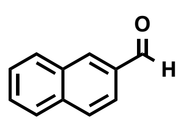
[**1** / **S2**: 84 92 / 8 87, 5]
[**1** / **S3**: 95 87 / 13 93, 27]



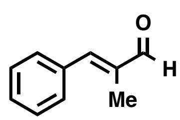
[**1** / **S2**: 93 92 / 8 89, 34]
[**1** / **S3**: 95 87 / 13 93, 27]



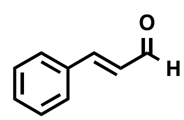
[**1** / **S1**: 93 95 / 5 95, 13]
[**1** / **S2**: 95 98 / 2 95, 23]
[**1** / **S3**: 92 81 / 19 90, 0]
[**2** / **S2**: 97 98 / 2 96, nd]



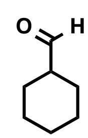
[**1** / **S2**: 92 93 / 7 93, 17]
[**1** / **S3**: 93 93 / 7 96, 5]



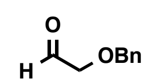
[**1** / **S2**: 76 93 / 7 92, 52]
[**1** / **S3**: 78 68 / 32 55, 8]



[**1** / **S2**: 56 81 / 19 93, 79]
[**1** / **S3**: 32 90 / 10 72, 58]



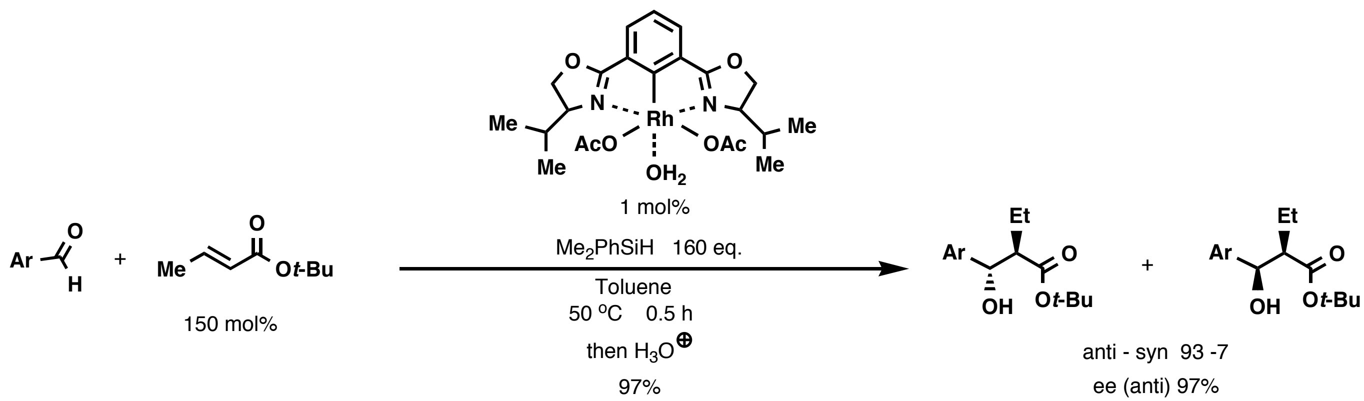
[**1** / **S1**: 70 87 / 13 93, 12]
[**1** / **S2**: 58 95 / 5 95, 5]
[**1** / **S3**: product not observed]
[**2** / **S2**: 72 86 / 14 93, 57]

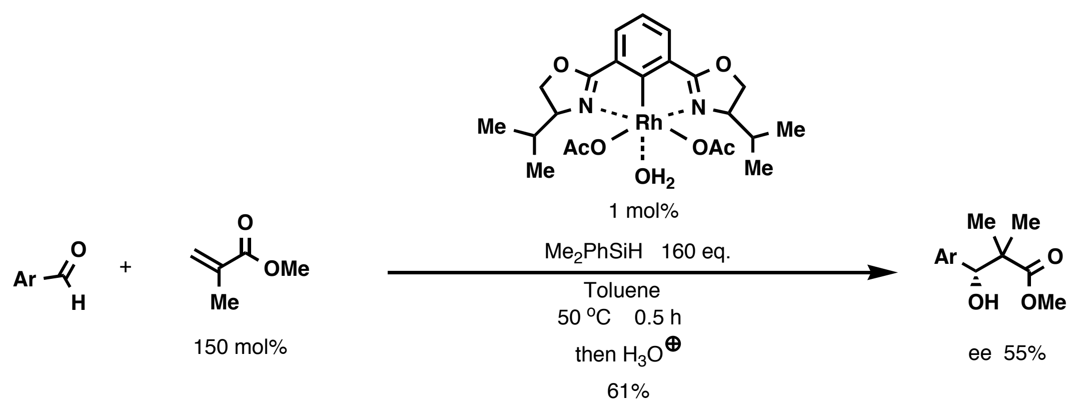


[**1** / **S2**: 75 72 / 28 93, 77]
[**2** / **S2**: 81 59 / 41 91, 87]

High Performance of Rh(Phebox) Catalysts in Asymmetric Reductive Aldol Reaction: High Anti-Selectivity (III)

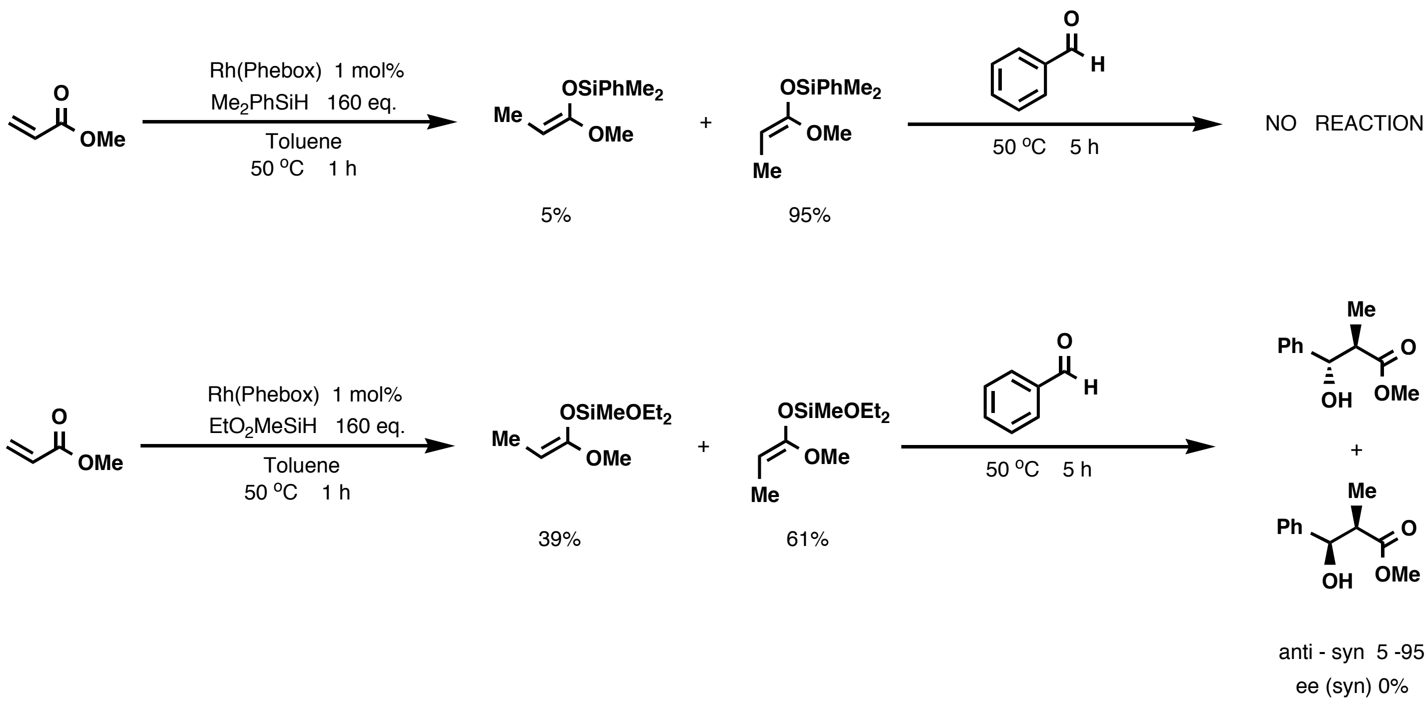
Substitution on the Acrylate Moiety





High Performance of Rh(Phebox) Catalysts in Asymmetric Reductive Aldol Reaction: High Anti-Selectivity (IV)

Mechanistic Speculations



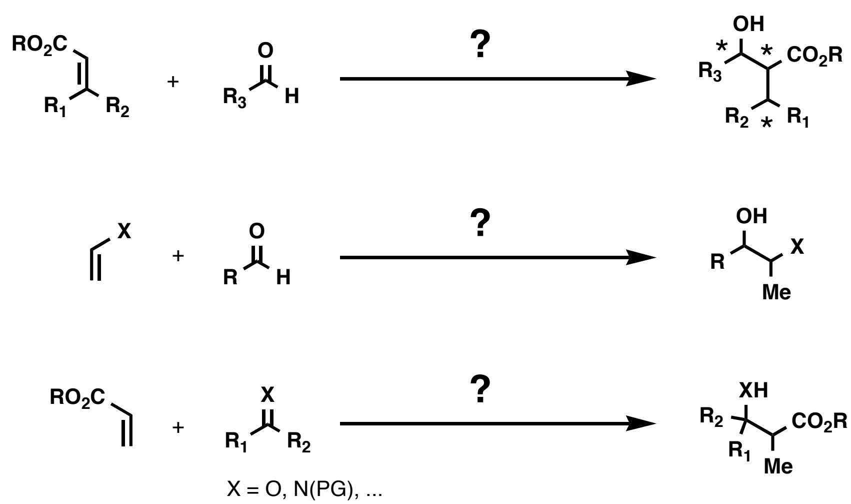
Summary

- **A new catalytic system for the reductive aldol reaction of acrylates with aldehydes and hydrosilanes was described.**

- **The process is extremely efficient and highly *anti* selective.**

Future Work

- **An investigation of the Scope and Limitations of this multicomponent asymmetric C-C bond forming reaction is required.**



- **A Mechanistic Investigation is required.**

- **An improvement of the Reaction Conditions would be of great value: a 50 ºC Temperature is still required.**

- **Application in Total Synthesis.**