Dynamic Kinetic Resolution: Practical Applications in Synthesis

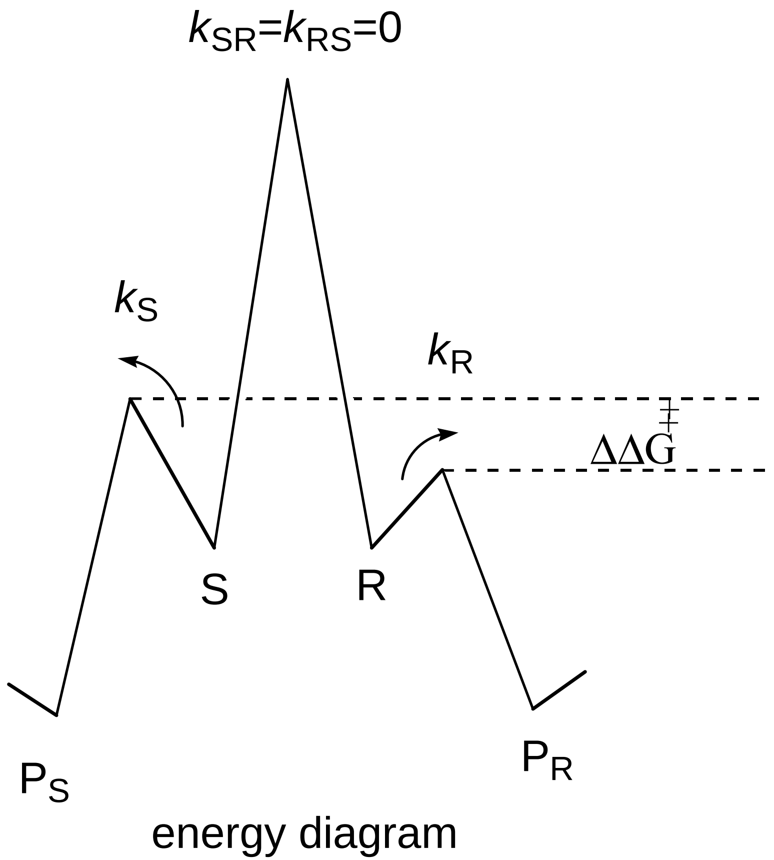
Valerie Keller

November 1, 2001

Outline

- Types of resolution reactions
  - Kinetic Resolution (KR)
  - Dynamic Kinetic Resolution (DKR)
  - Dynamic Thermodynamic Resolution
- Types of DKR
- Case study of KR vs. DKR

Kinetic Resolution



- Assume R is fast reacting enantiomer

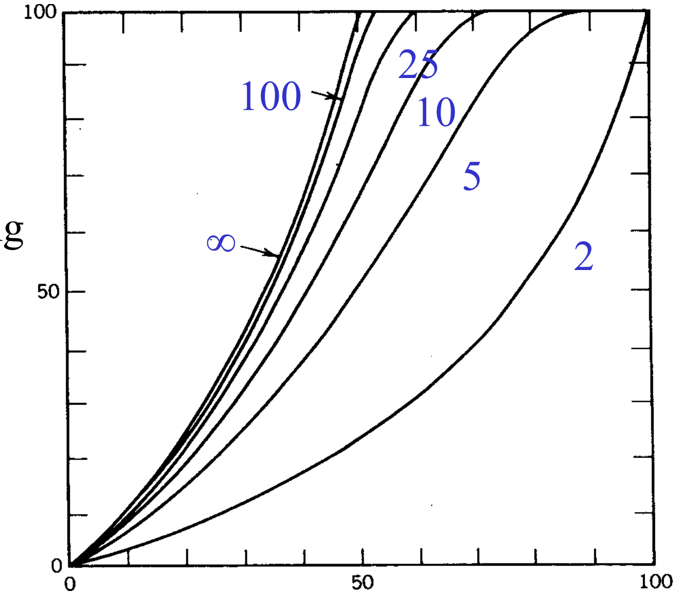
$$R \xrightarrow{k_R} P_R$$

$$S \xrightarrow{k_S} P_S$$

Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249-330.

Kinetic Resolution

%*ee* remaining starting material



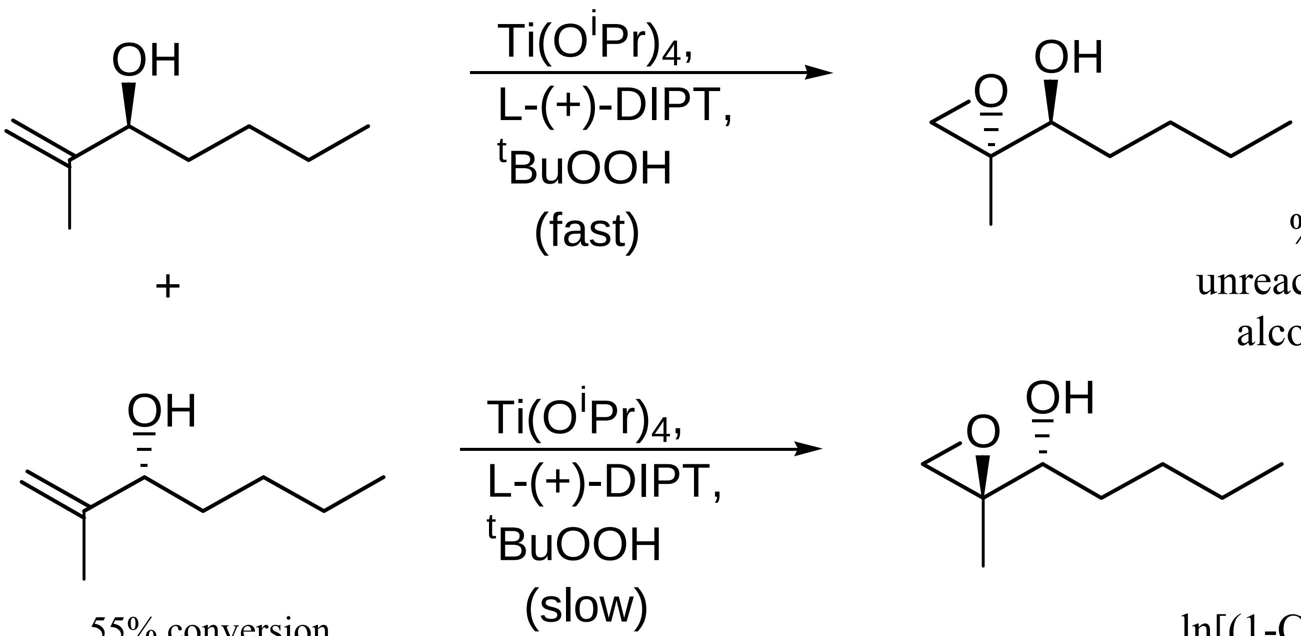
% conversion

- *ee* of SM increases as time increases, *ee* of product decreases as time increases
- Only when $k_R >> k_S$ does the yield approach 50% and *ee* approach 100%
- In practice, one cannot maximize both high yield and high *ee*

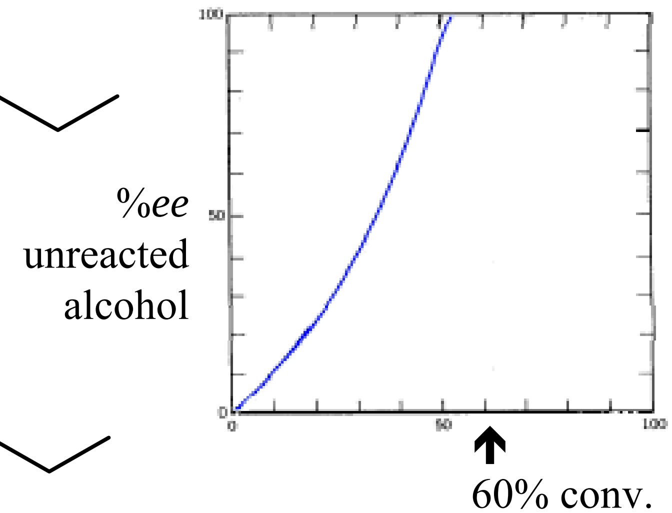
$$\textbf{relative rate} = \frac{\ln[(1-C)(1-ee)]}{\ln[(1-C)(1+ee)]} = \frac{k_R}{k_S} = e^{\Delta\Delta G^{\ddagger}/RT}$$

Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249-330.
Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 5-27.

Kinetic Resolution by Sharpless Asymmetric Epoxidation



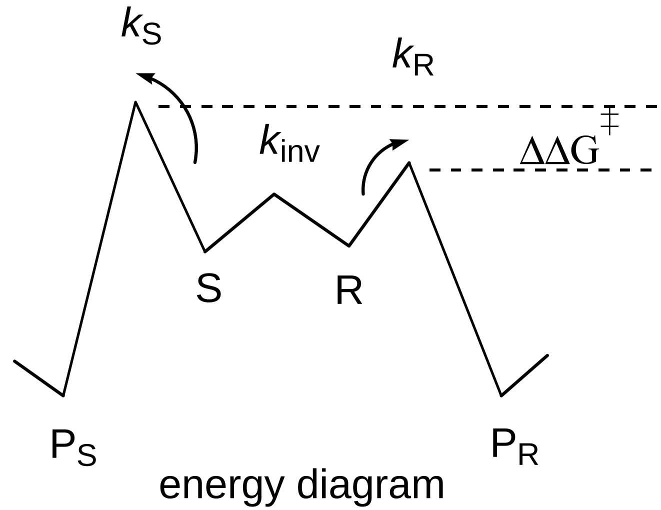
55% conversion
>96% *ee*

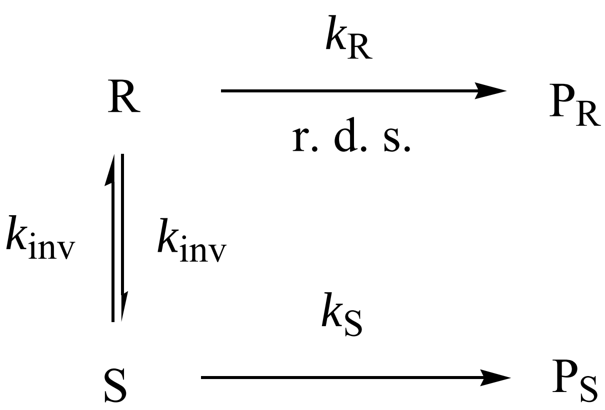


$$\frac{\ln[(1\text{-}C)(1\text{-}ee)]}{\ln[1\text{-}C)(1\text{+}ee)]} = k_R/k_S = 138$$

Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ideda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237-6240.

Dynamic Kinetic Resolution

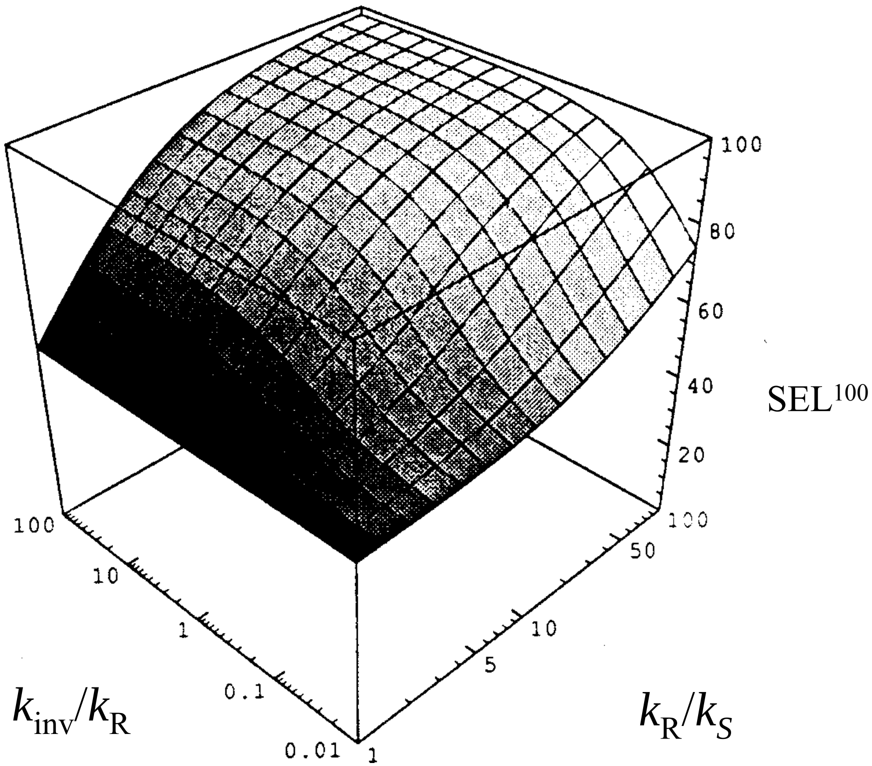


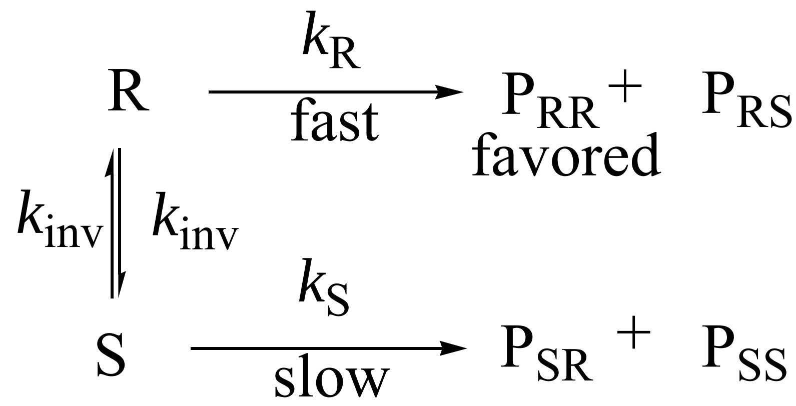


- Assume R is fast reacting enantiomer
- Rates are pseudo 1st order
- S and R racemize at the same rate
- Reaction is irreversible
- Products do not racemize under reaction conditions

Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36-56.
Kitamura, M.; Tokunaga, M.; Noyori, R. *J. Am. Chem. Soc.* **1993**, *115*, 144-152.

Dynamic Kinetic Resolution

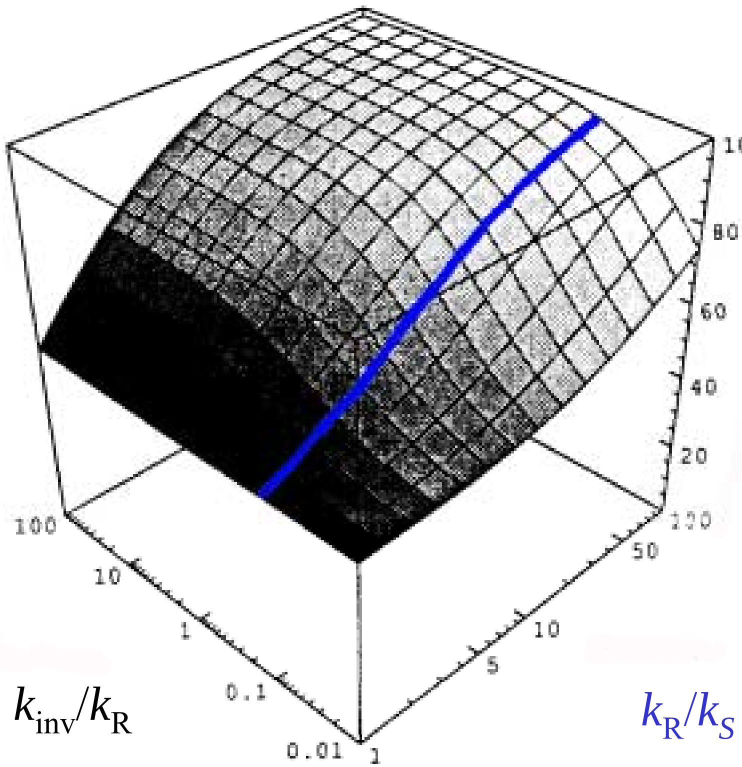


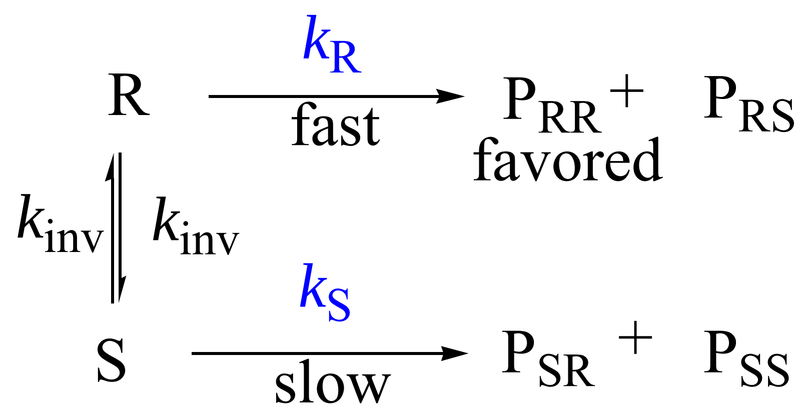


$$\mathrm{SEL}(t) = \frac{\mathrm{P_{RR}}(t)}{\mathrm{P_{RR}}(t) + \mathrm{P_{RS}}(t) + \mathrm{P_{SR}}(t) + \mathrm{P_{SS}}(t)}$$

Kitamura, M.; Tokunaga, M.; Noyori, R. *J. Am. Chem. Soc.* **1993**, *115*, 144-152.

Dynamic Kinetic Resolution

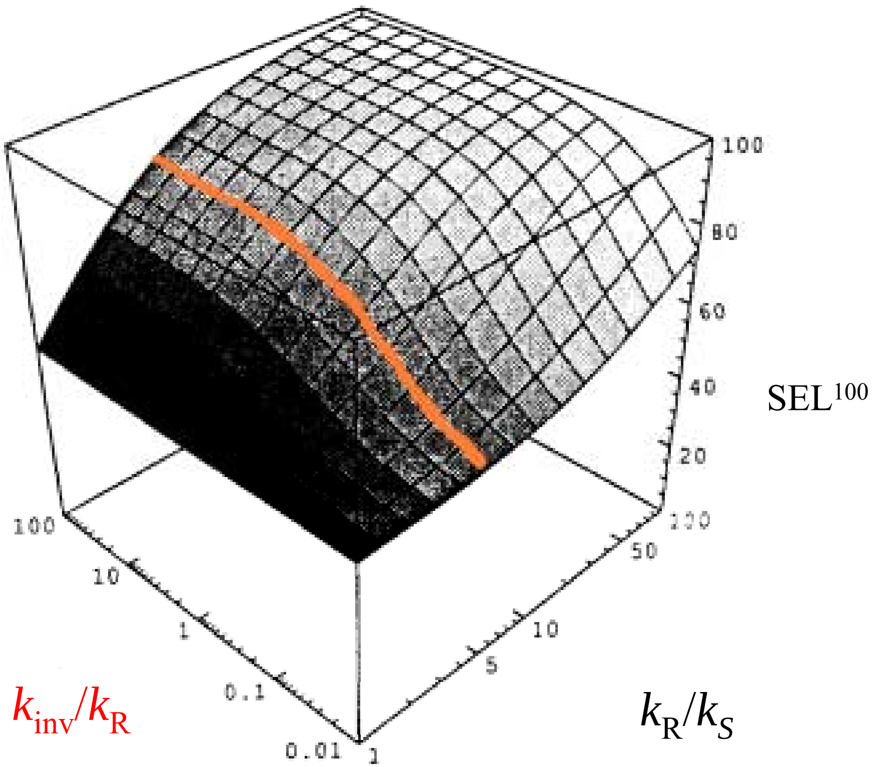


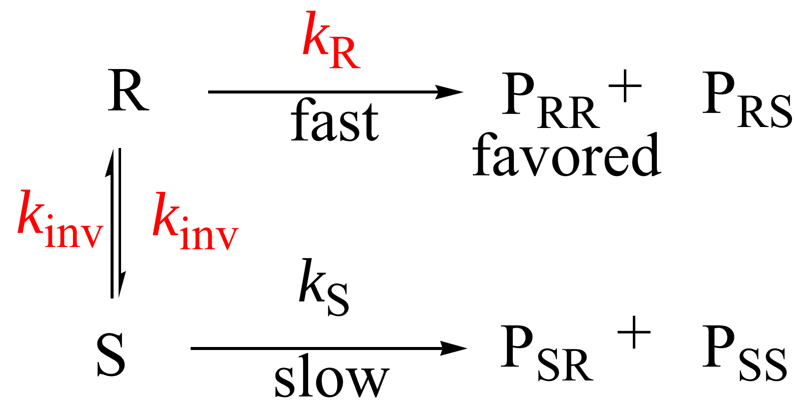


$$SEL(t) = \frac{P_{RR}(t)}{P_{RR}(t) + P_{RS}(t) + P_{SR}(t) + P_{SS}(t)}$$

Kitamura, M.; Tokunaga, M.; Noyori, R. *J. Am. Chem. Soc.* **1993**, *115*, 144-152.

Dynamic Kinetic Resolution

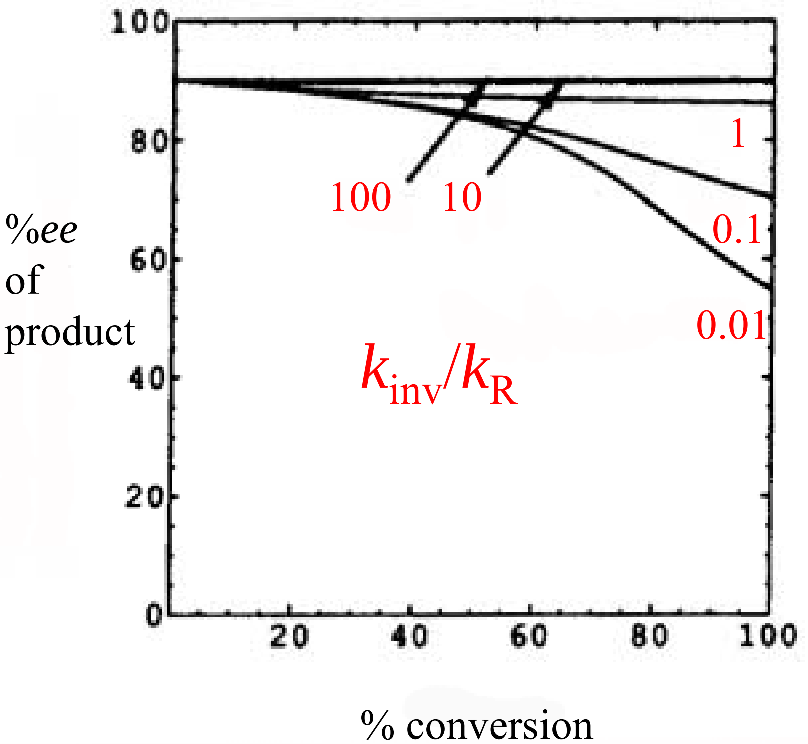




$$\mathrm{SEL}(t) = \frac{P_{RR}(t)}{P_{RR}(t) + P_{RS}(t) + P_{SR}(t) + P_{SS}(t)}$$

Kitamura, M.; Tokunaga, M.; Noyori, R. *J. Am. Chem. Soc.* **1993**, *115*, 144-152.

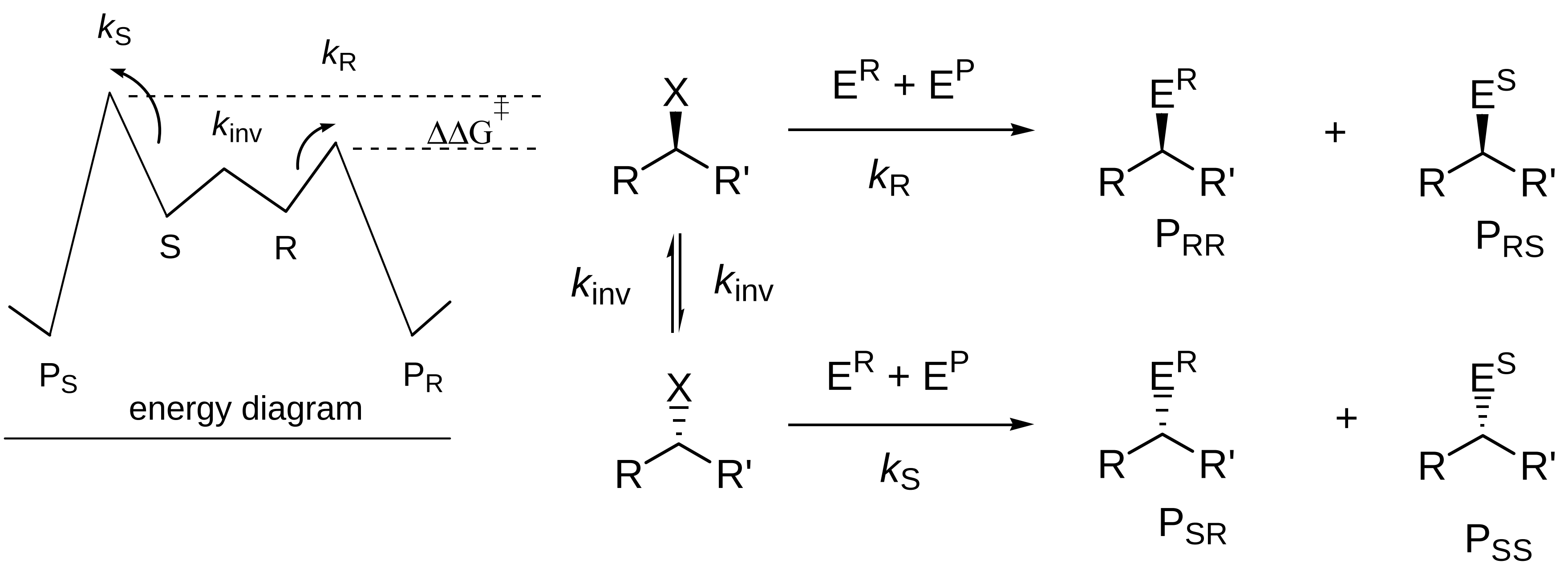
k_{inv} and k_R



- $k_R/k_S = 6.14$ (relative rate)
- If $k_{inv} >> k_R$, the S/R ratio remains steady
- If $k_{inv} \leq k_R$, R is consumed faster than it is replaced

Kitamura, M.; Tokunaga, M.; Noyori, R. *J. Am. Chem. Soc.* **1993**, *115*, 144-152.

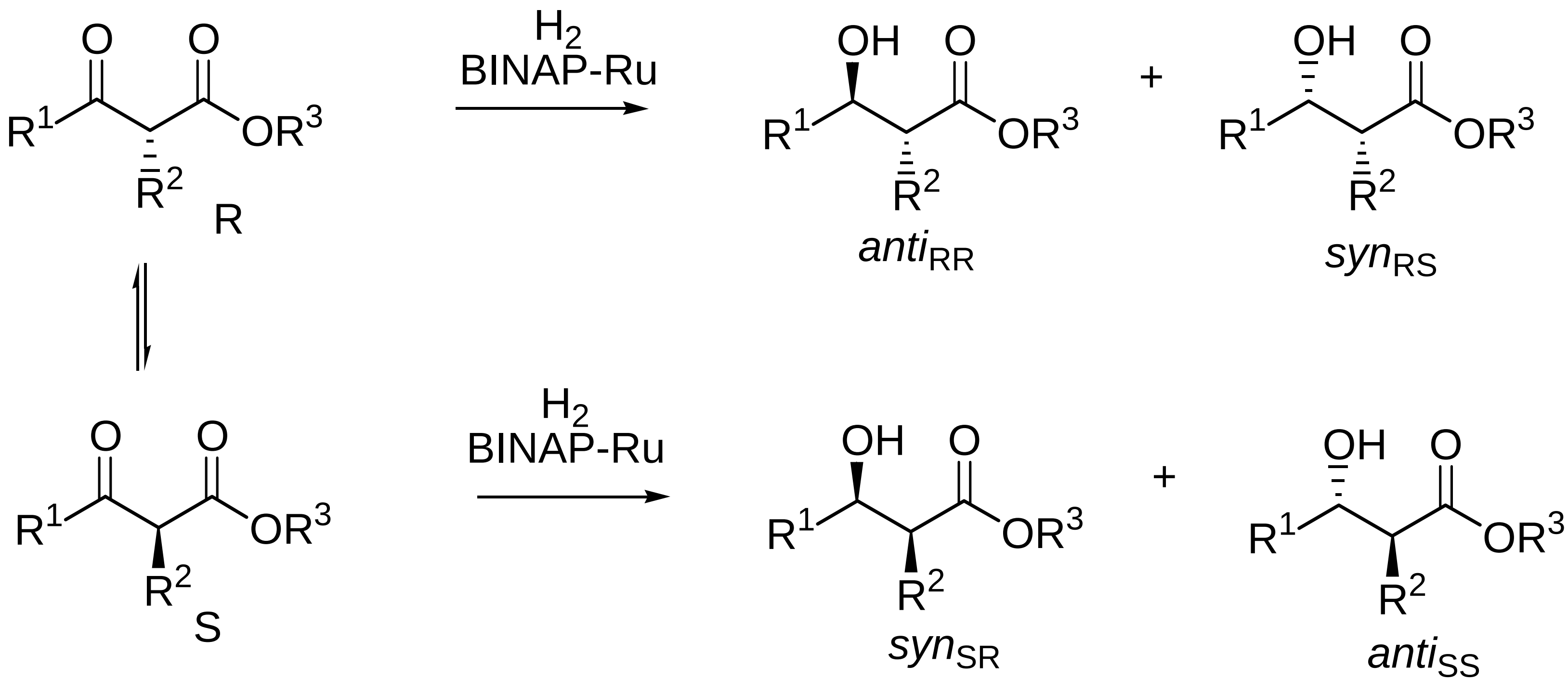
Hoffmann Test



$$\frac{k_R}{k_S} = e^{\Delta\Delta G^{\ddagger}/RT} = \frac{P_{RR} + P_{RS}}{P_{SR} + P_{SS}}$$

Hirsch, R.; Hoffmann, R. W. *Chem. Ber.* **1992**, *125*, 975-982.

First Published Example of Chemical DKR

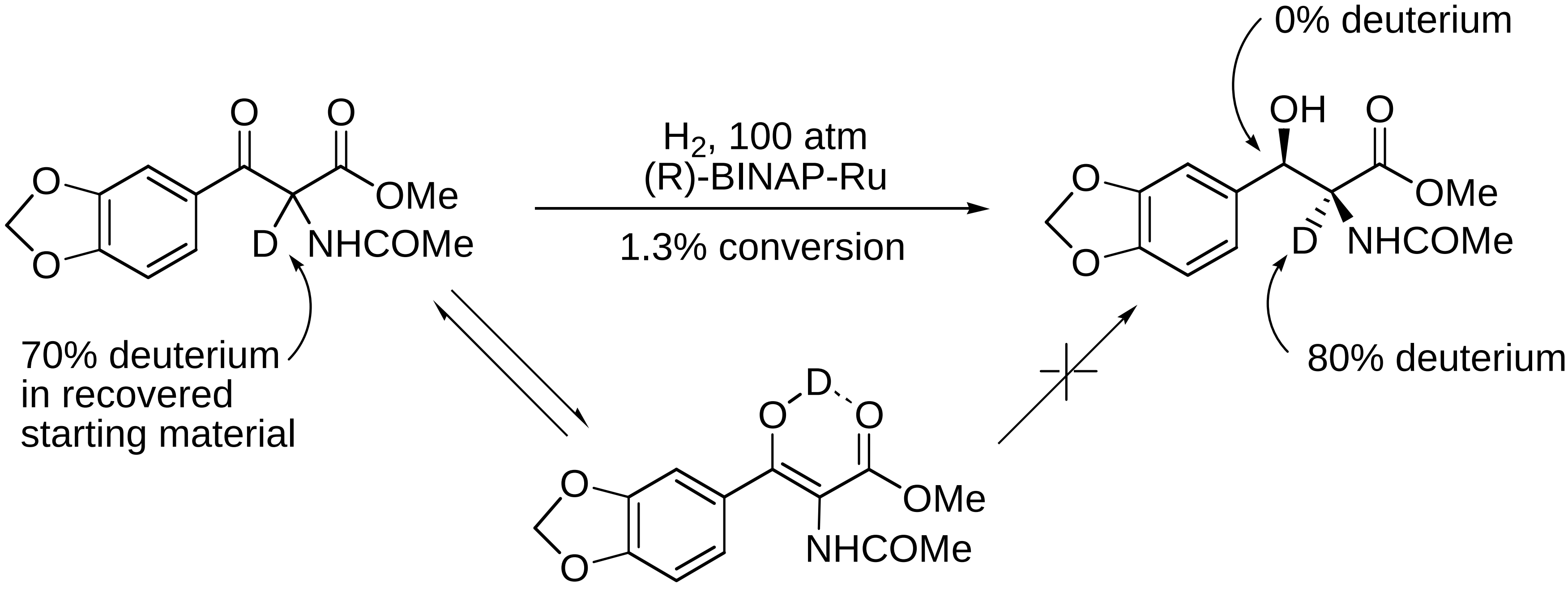


R^1, R^3 = Me, R^2 = $CH_2NHCOMe$, (R)-BINAP-Ru

major product is *syn*$_{SR}$ 98% de and ee

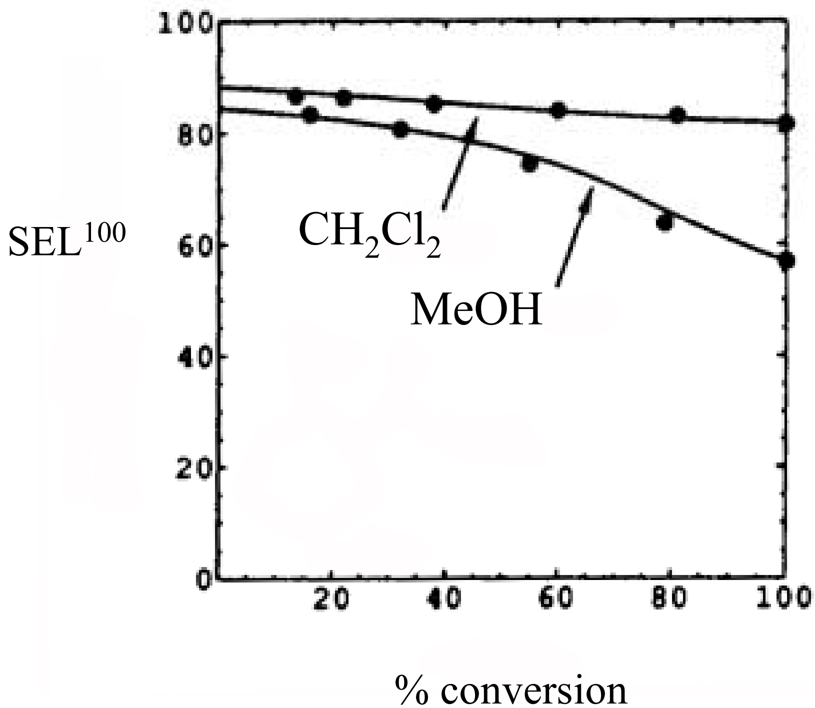
Noyori, R.; Ideda, T.; Ohkuma, T.; Widhalm, M.; Kitamura, M.; Takaya, H.; Sayo, N. Saito, T.; Taketomi, T.; Kumobayashi, H. *J. Am. Chem. Soc.* **1989**, *111*, 9134-9135.

Labeling Experiment

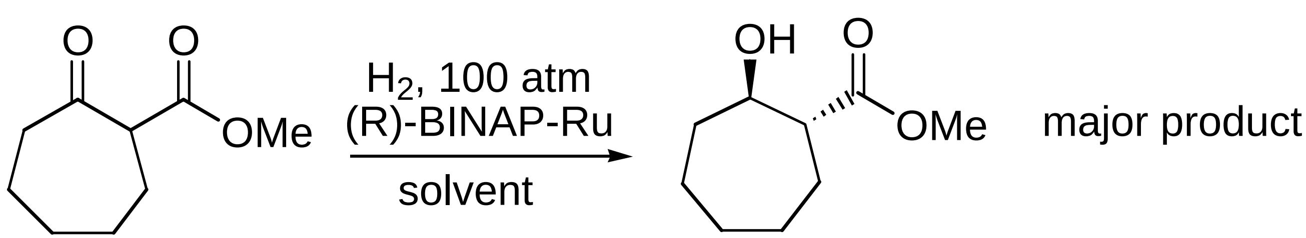


Noyori, R.; Ideda, T.; Ohkuma, T.; Widhalm, M.; Kitamura, M.; Takaya, H.; Sayo, N. Saito, T.; Taketomi, T.; Kumobayashi, H. *J. Am. Chem. Soc.* **1989**, *111*, 9134-9135.

Solvent Effects



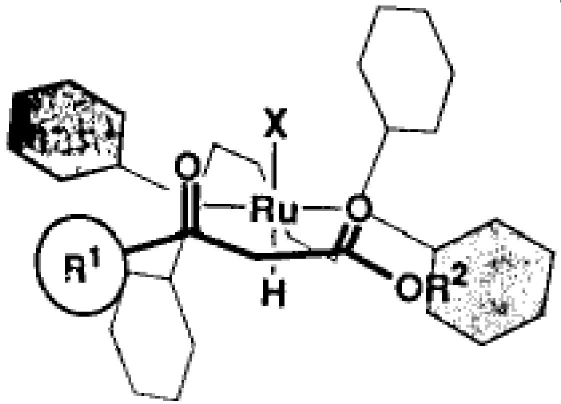
- Hydrogenation in CH_2Cl_2 is much slower than in MeOH
- In MeOH, $k_{inv}/k_R = 0.04$
- In CH_2Cl_2, $k_{inv}/k_R = 0.44$



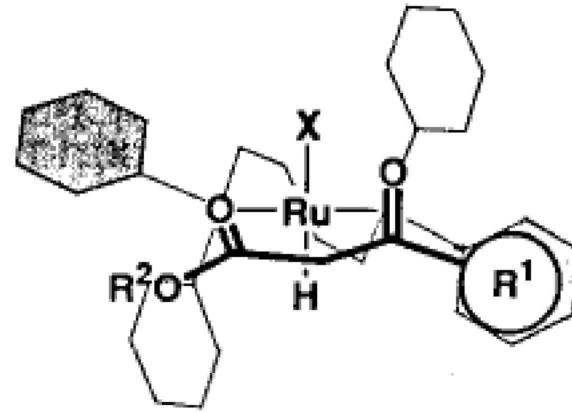
Kitamura, M.; Tokunaga, M.; Noyori, R. *J. Am. Chem. Soc.* **1993**, *115*, 144-152.

Stereochemical Rationale

enantiomer preference

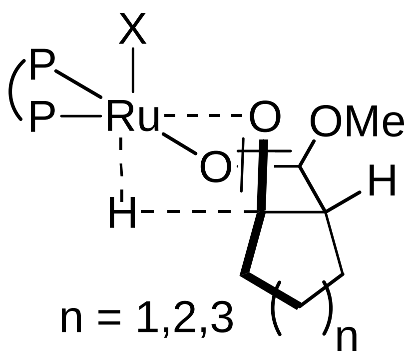


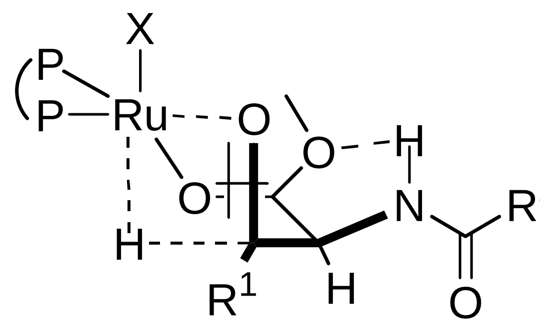
$\mathbf{2}_R$ (side view)
favored



$\mathbf{2}_S$ (side view)
unfavored

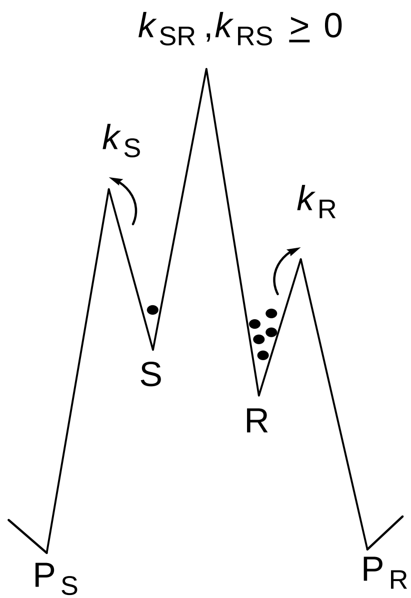
diastereomer preference



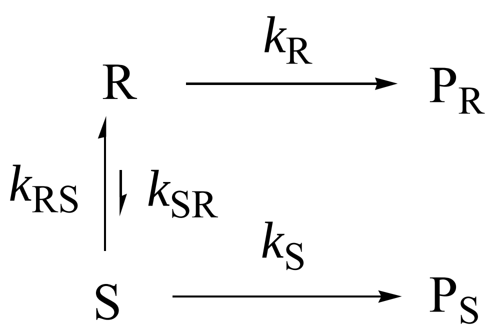


Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36-56.

Dynamic Thermodynamic Resolution



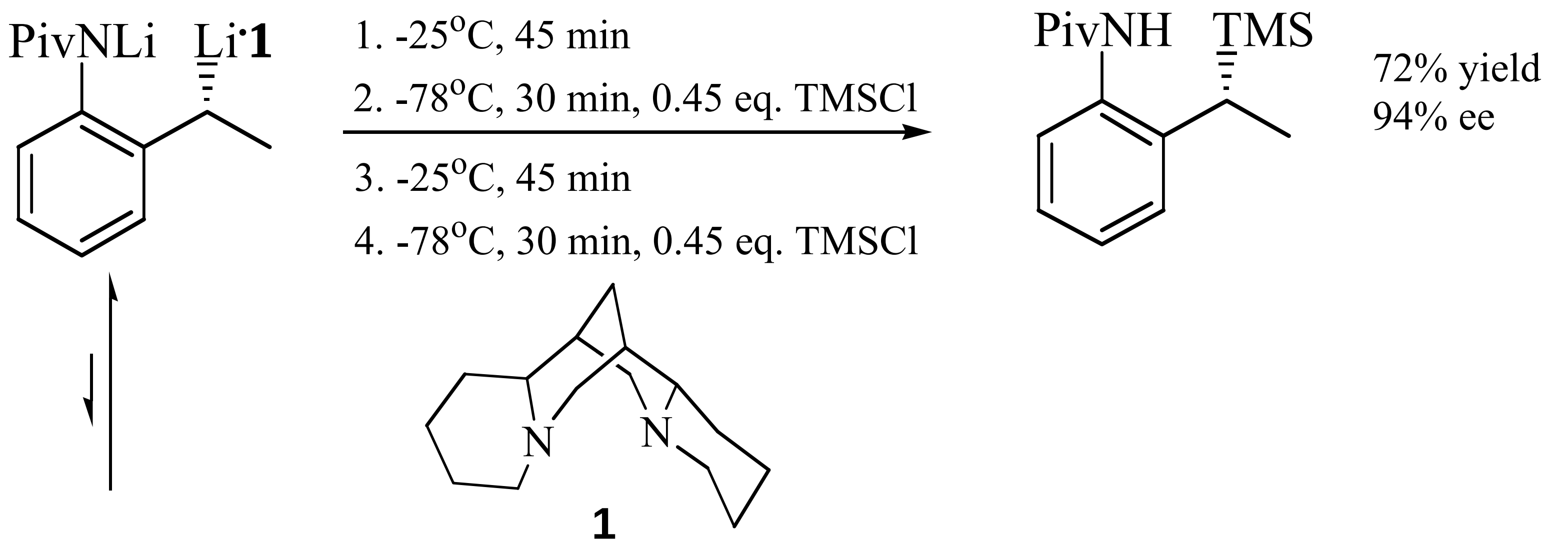
energy diagram

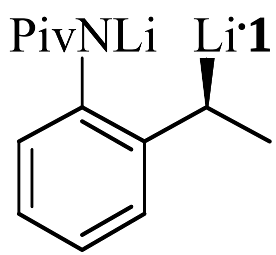


- First equilibrate to thermodynamically favored enantiomer
- Second rely on kinetic differences to enhance selectivity
- Rates of equilibration are not equal
- $k_R >> k_S >> k_{SR}, k_{RS}$

Beak, P.; Anderson, D. R; Curtis, M. D.; Laumer, J. M.; Pippel, D. J.; Weisenburger, G. A. *Acc. Chem. Res.* **2000**, *33*, 715-727.

Dynamic Thermodynamic Resolution





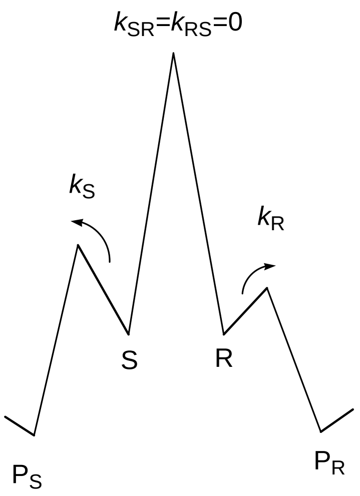
- Li*sparteine complex stable at -78°C, but equilibrates at -25°C

Basu, A.; Gallagher, D. J.; Beak, P. *J. Org. Chem.* **1996**, *61*, 5718-5719.

Summary of Resolution Reactions

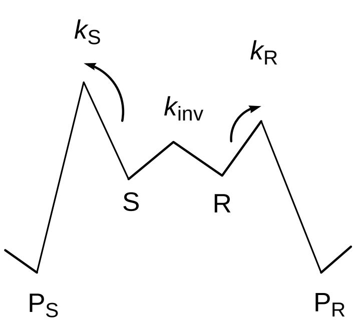
Kinetic Resolution

no equilibration



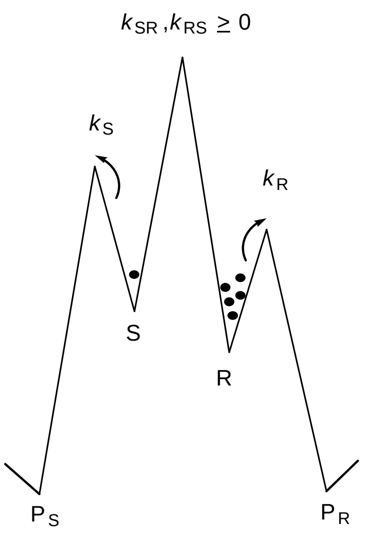
Dynamic Kinetic Resolution

equilibration rate fast compared to reaction



Dynamic Thermodynamic Resolution

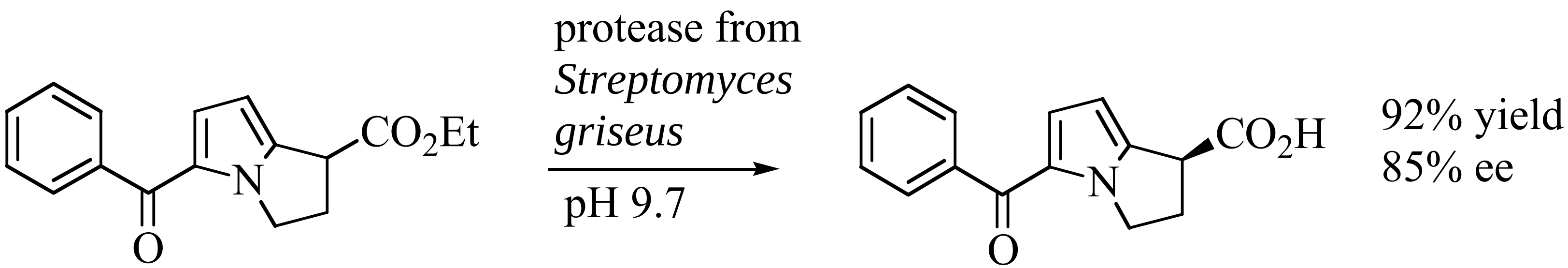
equilibration rate slow compared to reaction



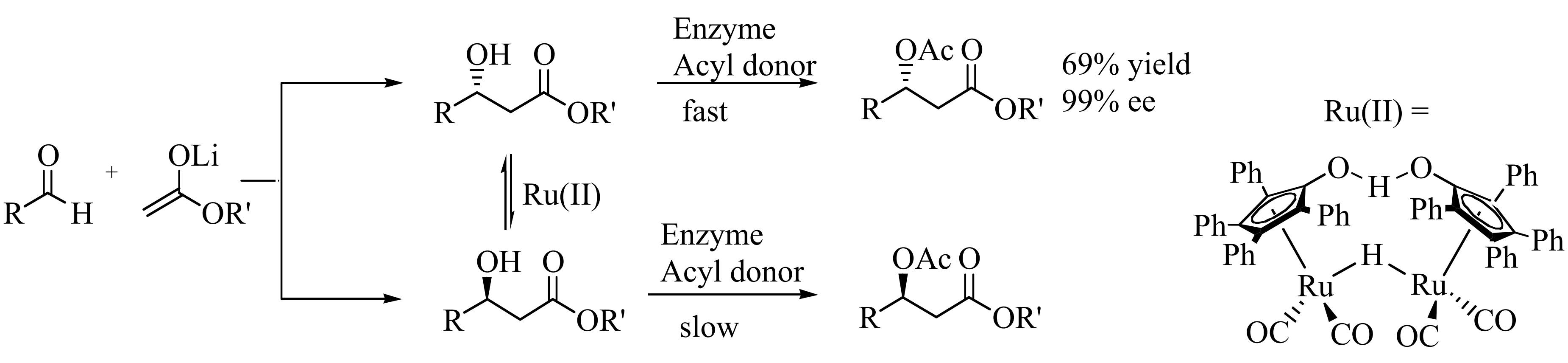
Outline

- Types of resolution reactions
- Types of DKR
  - Enzymatic DKR
  - Substrate controlled DKR
  - Reagent controlled DKR
  - Catalyst controlled DKR
- Case study of KR vs. DKR

Enzymatic DKR

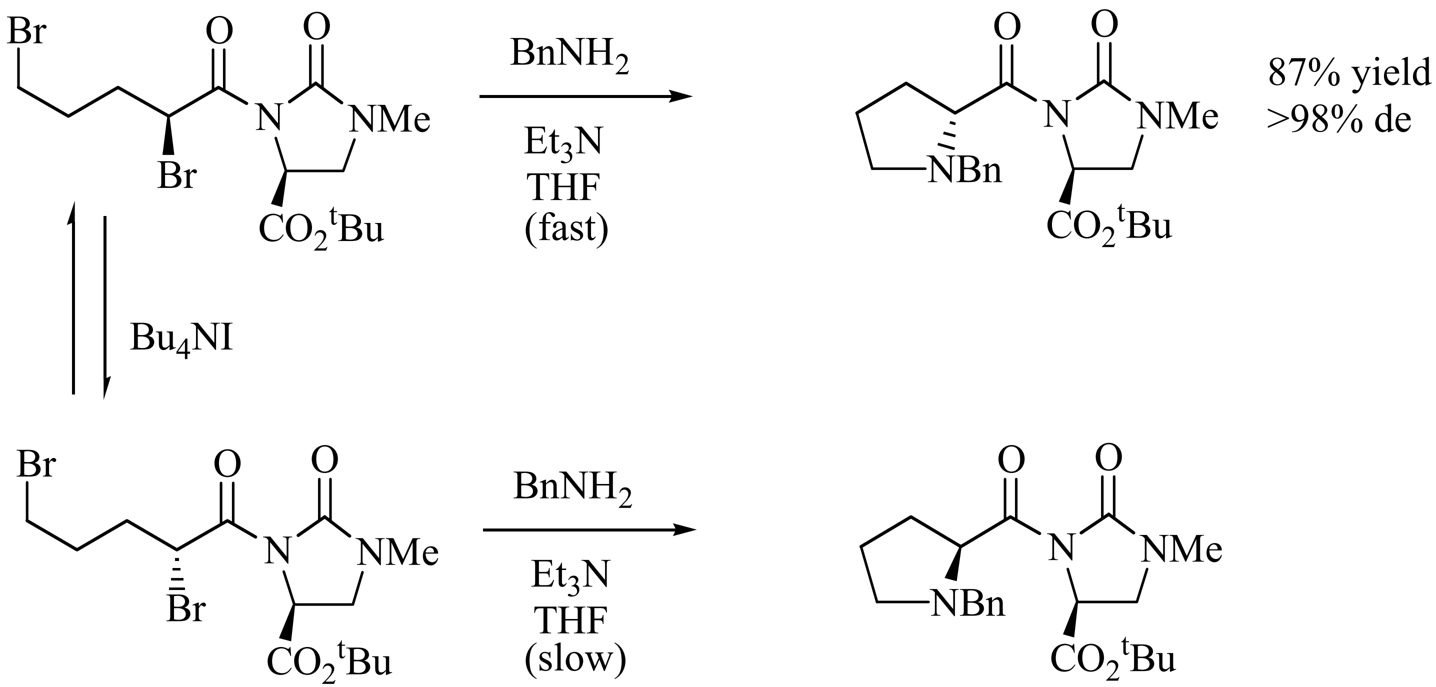


Fülling, G.; Sih, C. J. *J. Am. Chem. Soc.* **1987**, *109*, 2845-2846.



Huerta, F. F.; Bäckvall, J.-E. *Org. Lett.* **2001**, *3*, 1209-1212.

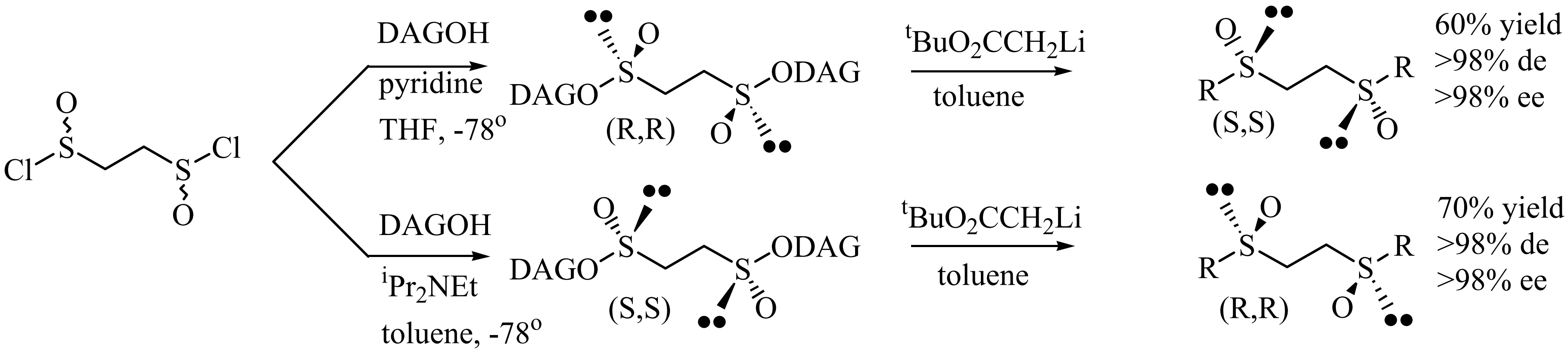
Nunami Chiral Auxiliary
Substrate Controlled DKR



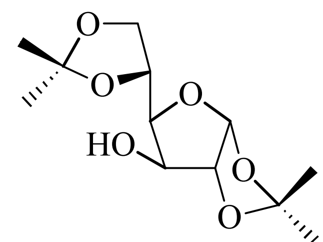
- Chiral auxiliary must be removed
- Starting material takes several steps to synthesize

O'Meara, J. A.; Jung, M.; Durst, T. *Tetrahedron Lett.* **1995**, *36*, 2559-2562.
O'Meara, J. A.; Jung, M.; Durst, T. *Tetrahedron Lett.* **1995**, *36*, 5096

Reagent Controlled DKR



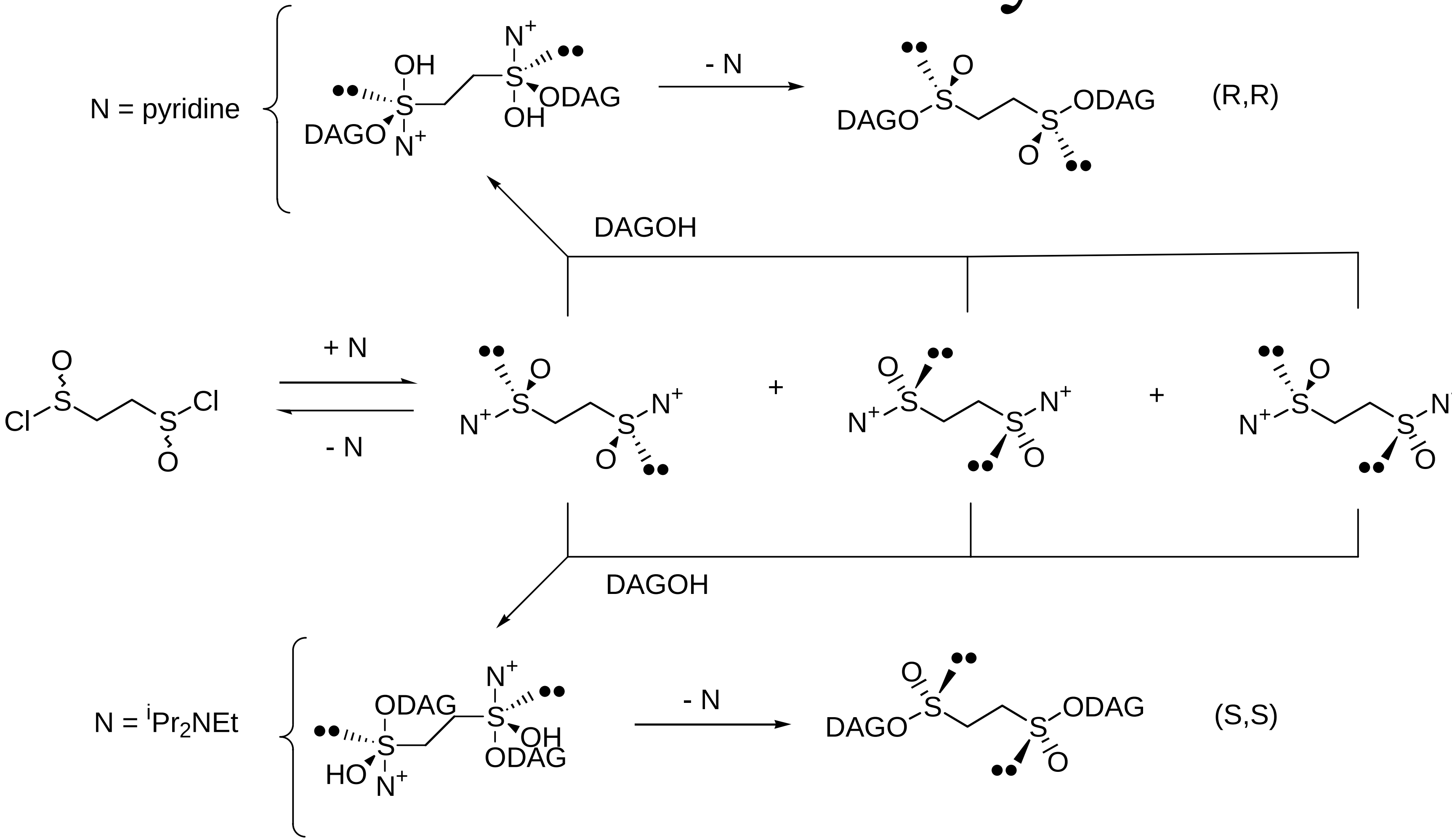
DAGOH = diacetone-D-glucose



Stereochemistry controlled by base used

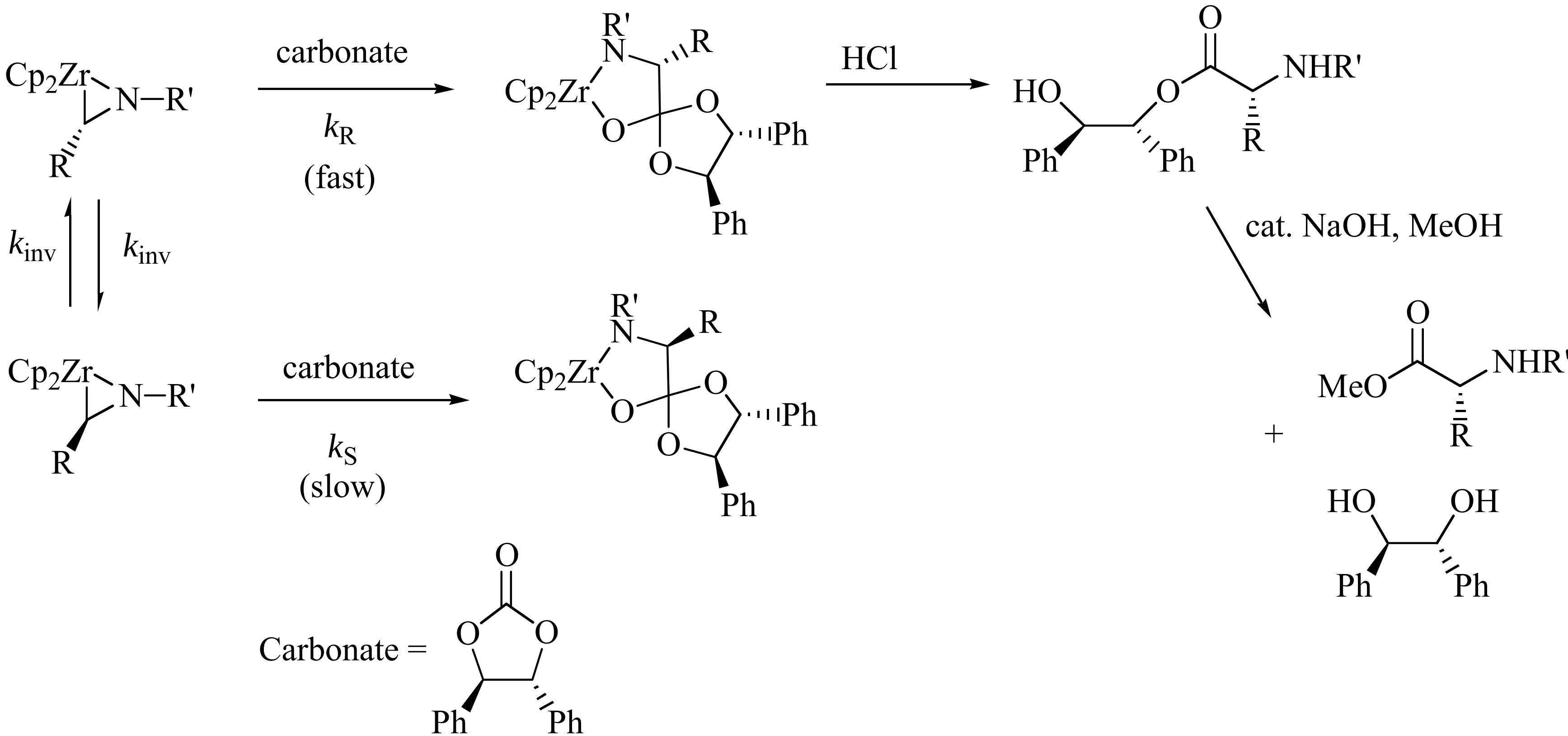
Khiar, N.; Alcudia, F.; Espartero, J.-L.; Rodríguez, L.; Fernández, I. *J. Am. Chem. Soc.* **2000**, *122*, 7598-7599.

Effect of Base on Stereochemistry



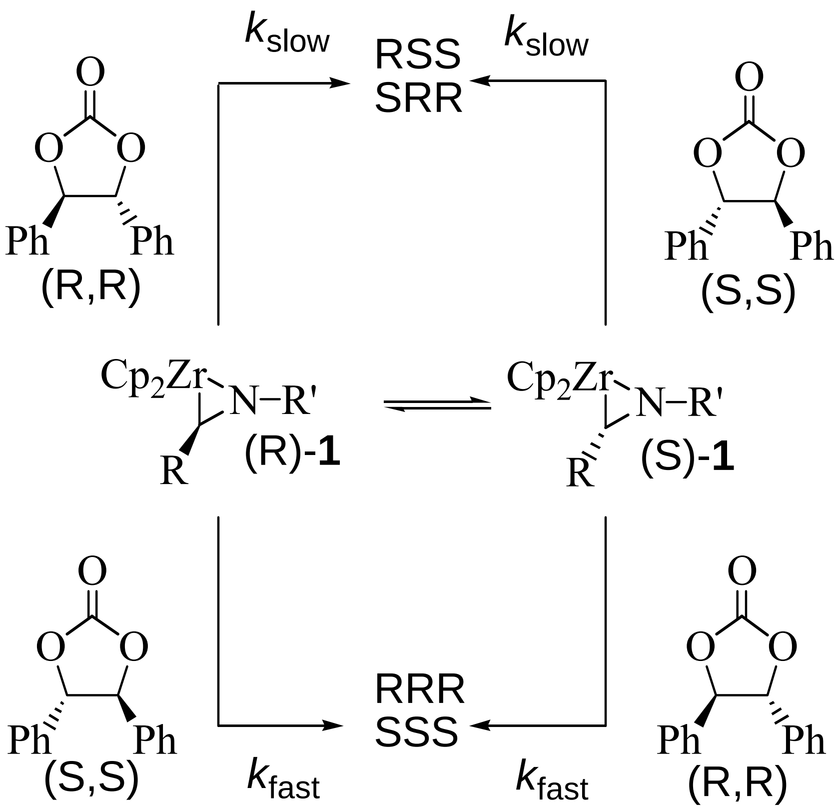
Fernández, I.; Khiar, N.; Llera, J. M.; Alcudia, F. *J. Org. Chem.* **1992**, *57*, 6789-6796.
Khiar, N.; Alcudia, F.; Espartero, J.-L.; Rodríguez, L.; Fernández, I. *J. Am. Chem. Soc.* **2000**, *122*, 7598-7599.

Reagent Controlled DKR



Tunge, J. A.; Gately, D. A.; Norton, J. R. *J. Am. Chem. Soc.* **1999**, *121*, 4520-4521.

Kinetic Studies



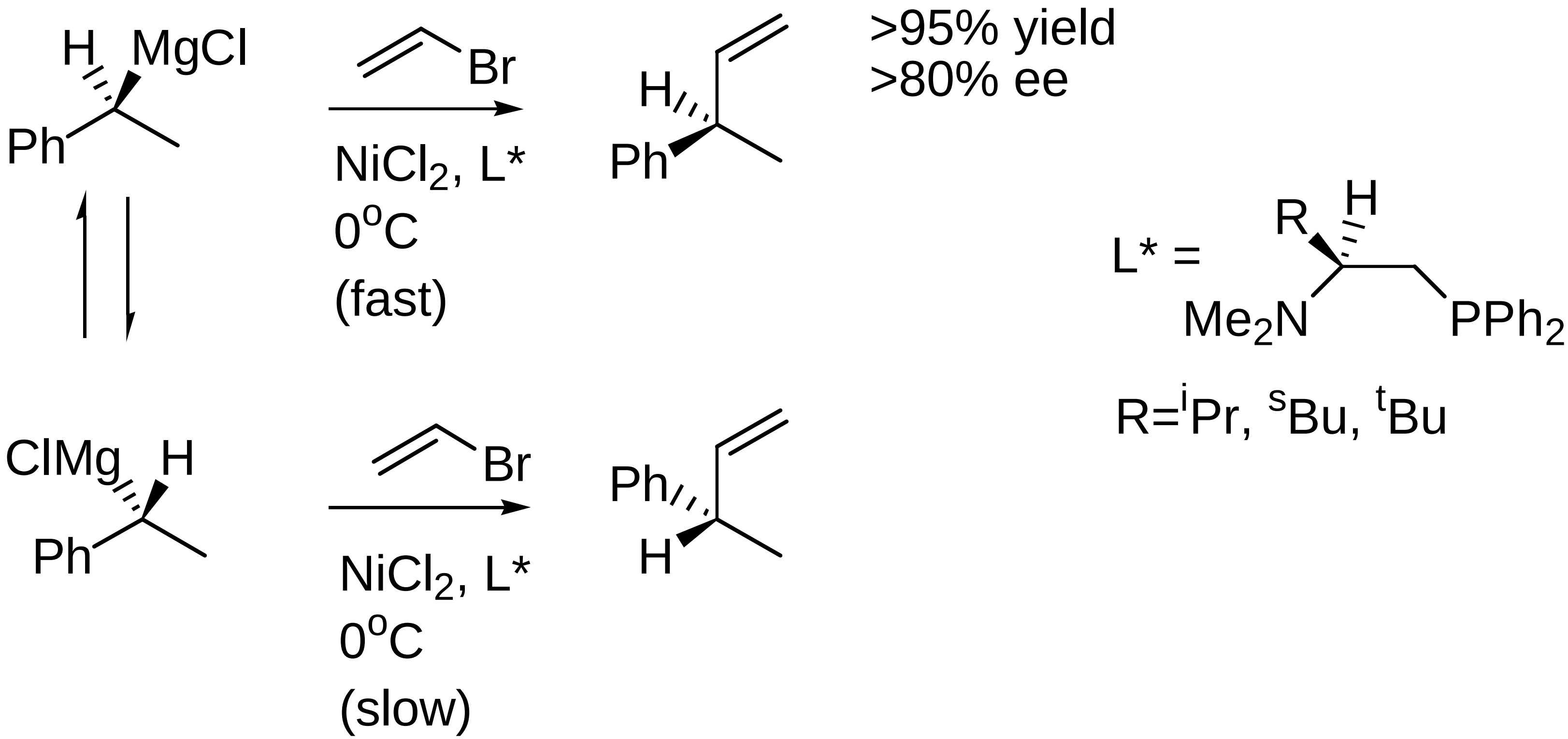
complex	calculated de (%)	relative rate	observed de (%)
1a	76	7.3	76
1b	90	19	90
1c	21	1.5	18
1d	74	6.7	71
1e	82	10.1	77

1a R' = R = Ph
1b R' = TMS, R = Ph
1c R' = TMS, R = ^{i}Pr
1d R' = R = CH_2Ph
1e R' = TMS, R = $CH_2{}^{i}$Pr

$$\text{relative rate} = \frac{k_{fast}}{k_{slow}} = \frac{\text{SSS + RRR}}{\text{SRR + RSS}}$$

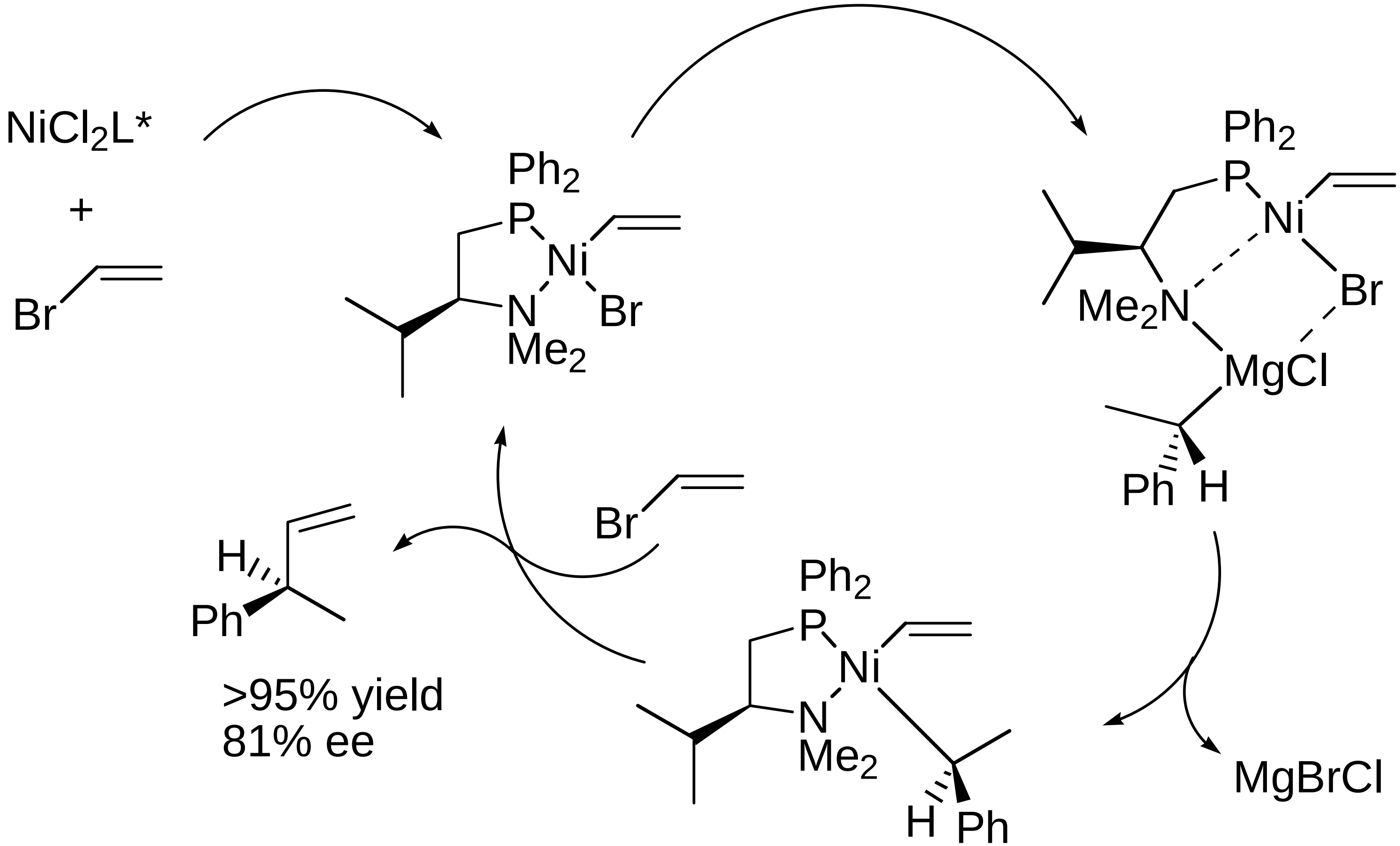
Tunge, J. A.; Gately, D. A.; Norton, J. R. *J. Am. Chem. Soc.* **1999**, *121*, 4520-4521.

Catalyst Controlled DKR



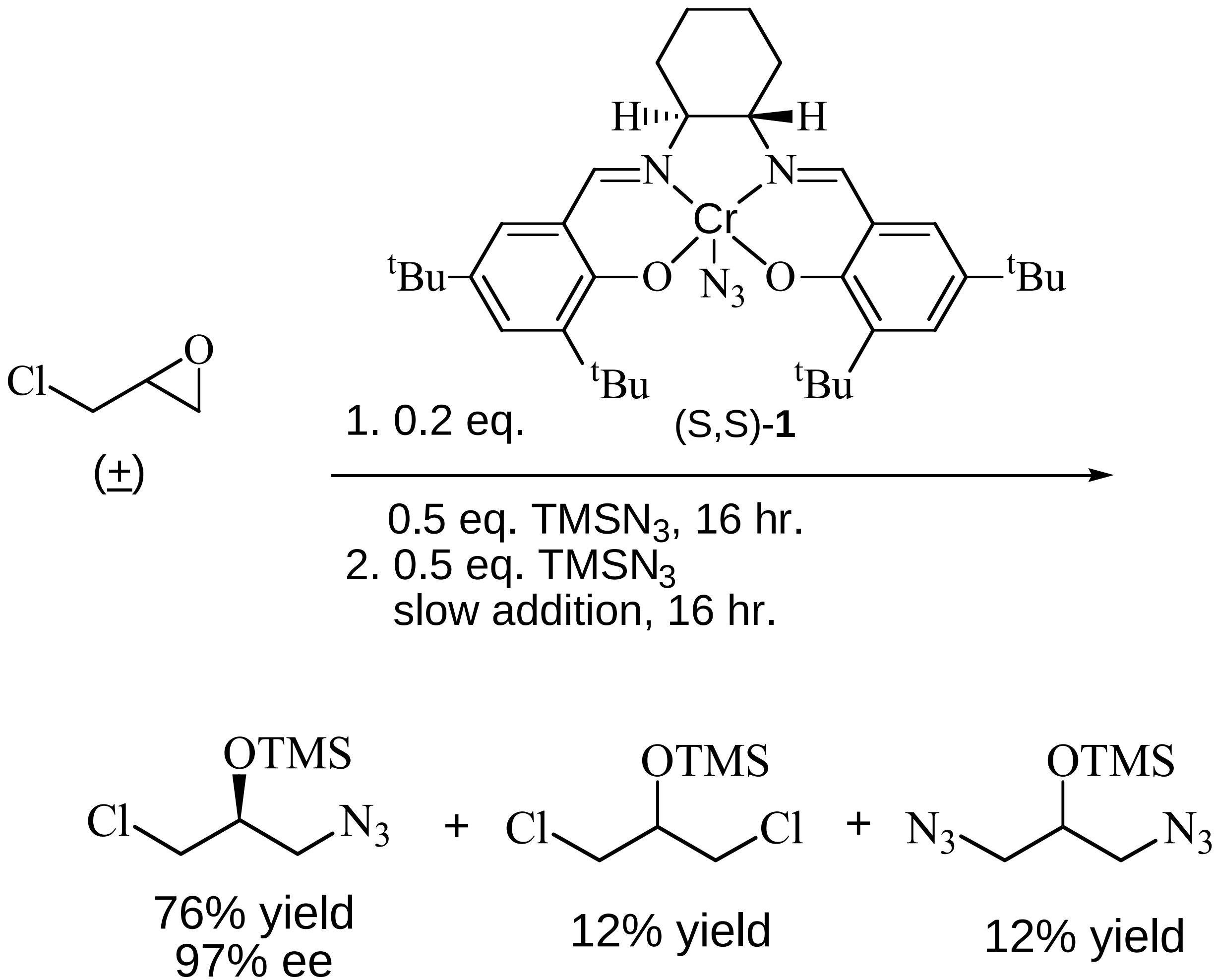
Hayashi, T.; Konishi, M.; Fukushima, M.; Kanehira, K.; Hioki, T.; Kumada, M. *J. Org. Chem.* **1983**, *48*, 2195-2198.

Catalytic Cycle



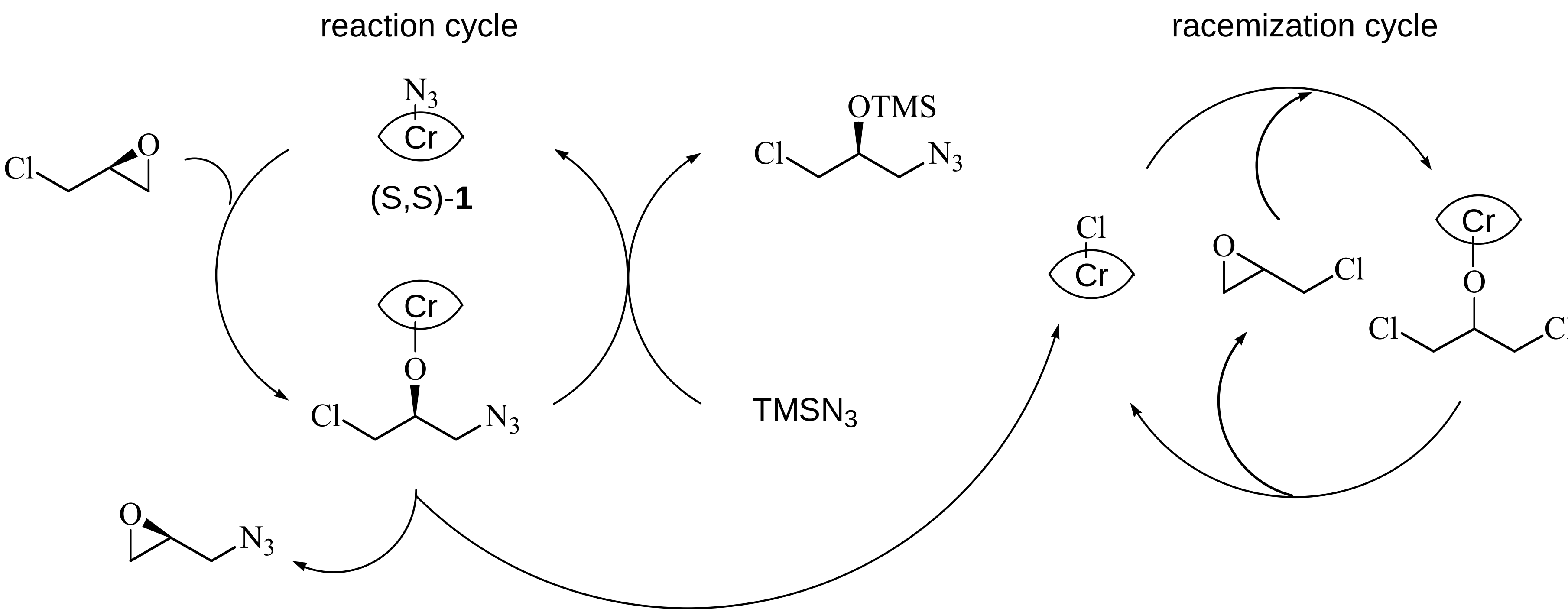
Hayashi, T.; Konishi, M.; Fukushima, M.; Kanehira, K.; Hioki, T.; Kumada, M. *J. Org. Chem.* **1983**, *48*, 2195-2198.

Catalyst Control of DKR



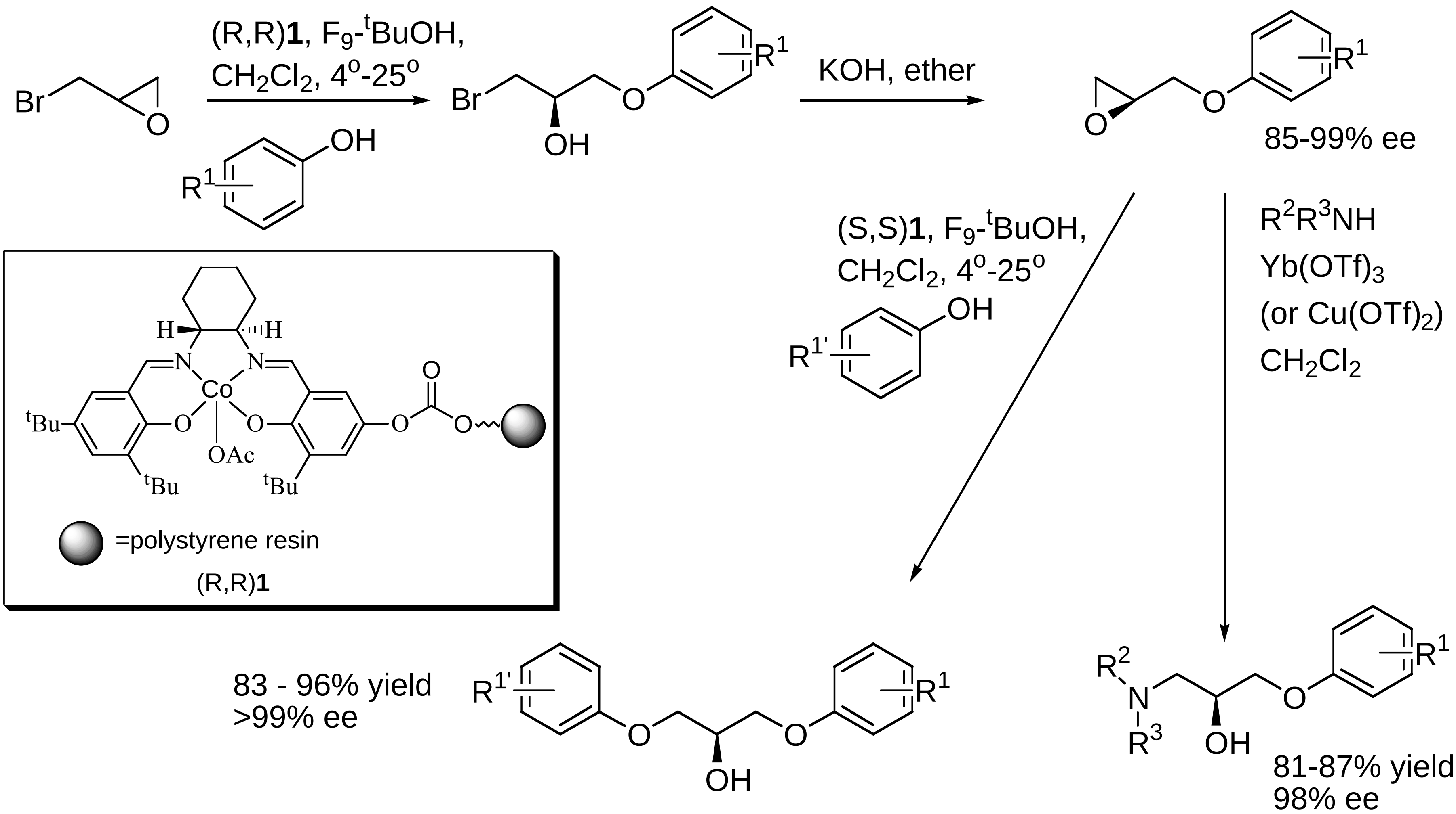
Schaus, S. E.; Jacobsen, E. N. *Tetrahedron Lett.* **1996**, *37*, 7937-7940.

Salen Catalytic Cycle



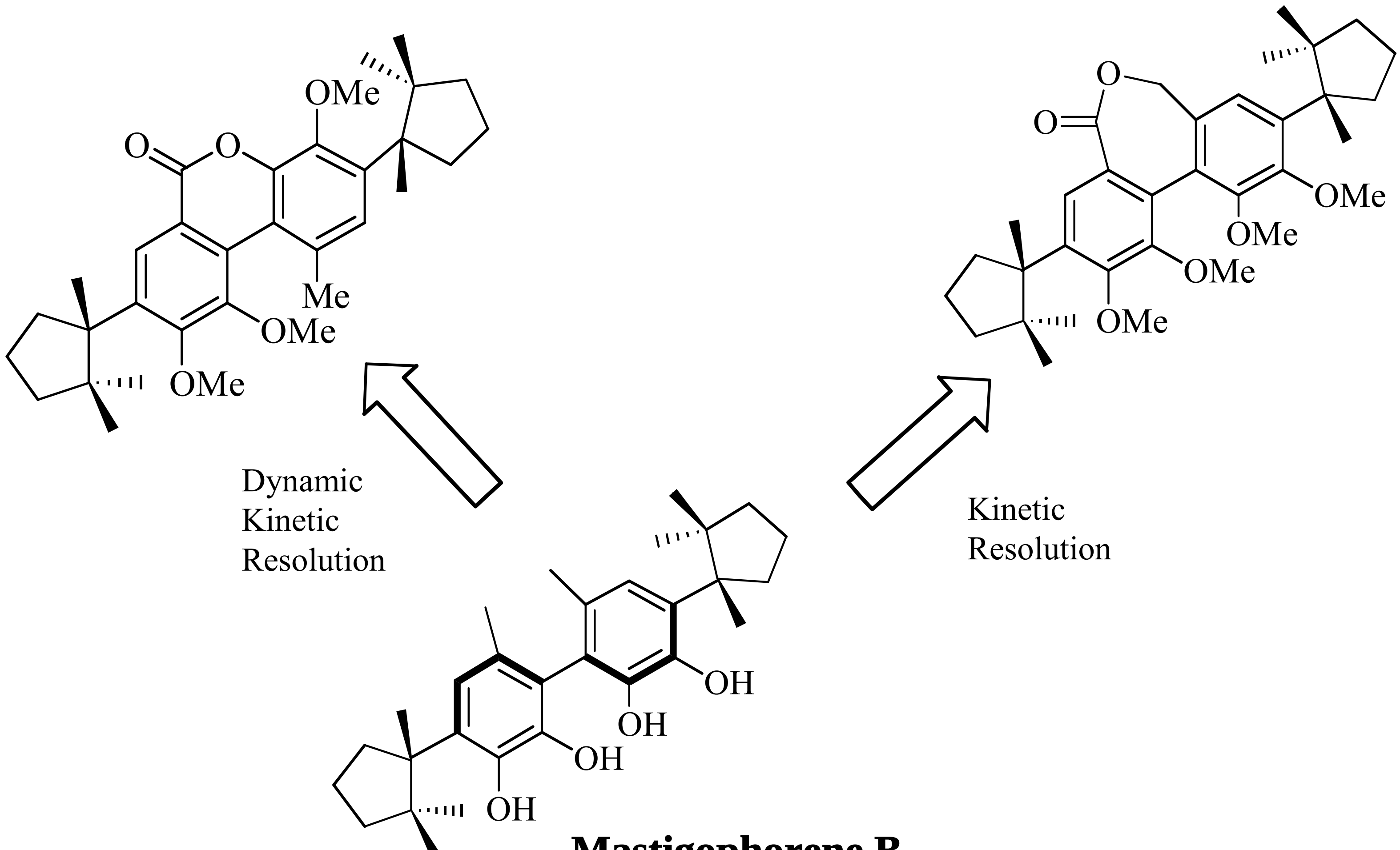
Schaus, S. E.; Jacobsen, E. N. *Tetrahedron Lett.* **1996**, *37*, 7937-7940.

DKR in Small Library Synthesis



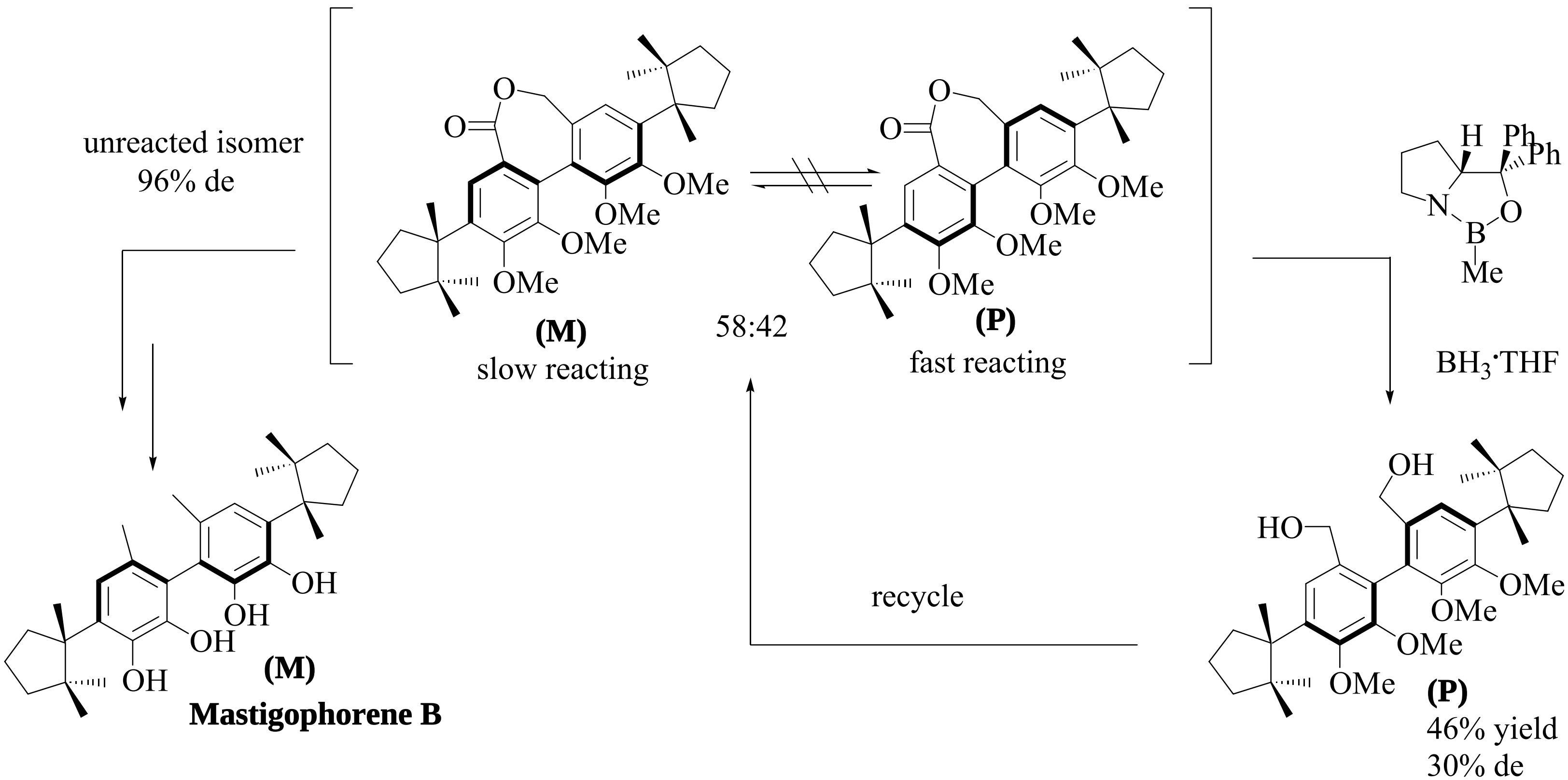
Peukert, S.; Jacobsen, E. N. *Org. Lett.* **1999**, *1*, 1245-1248.

KR vs. DKR



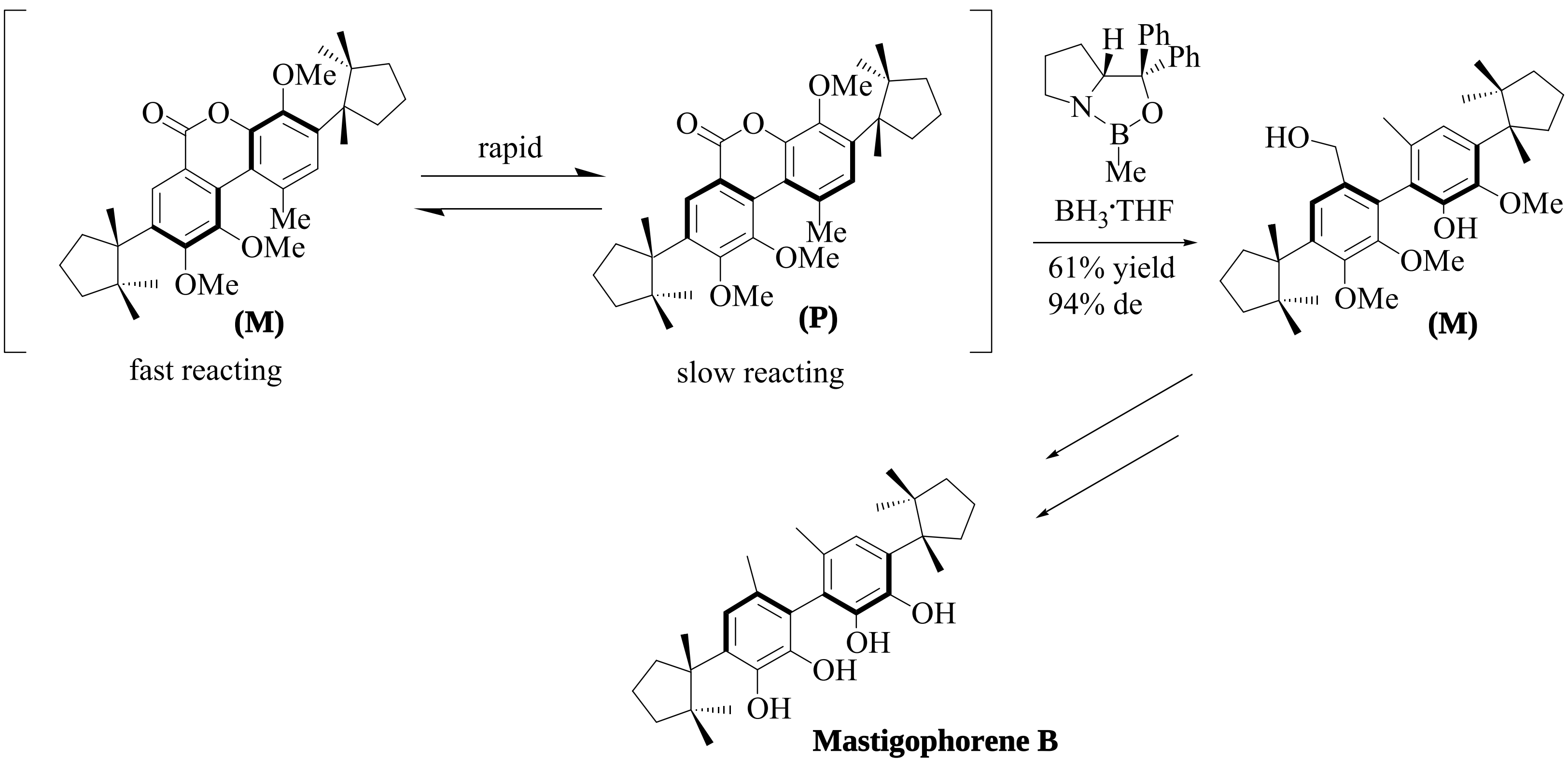
Mastigophorene B

Mastigophorene B: Kinetic Resolution



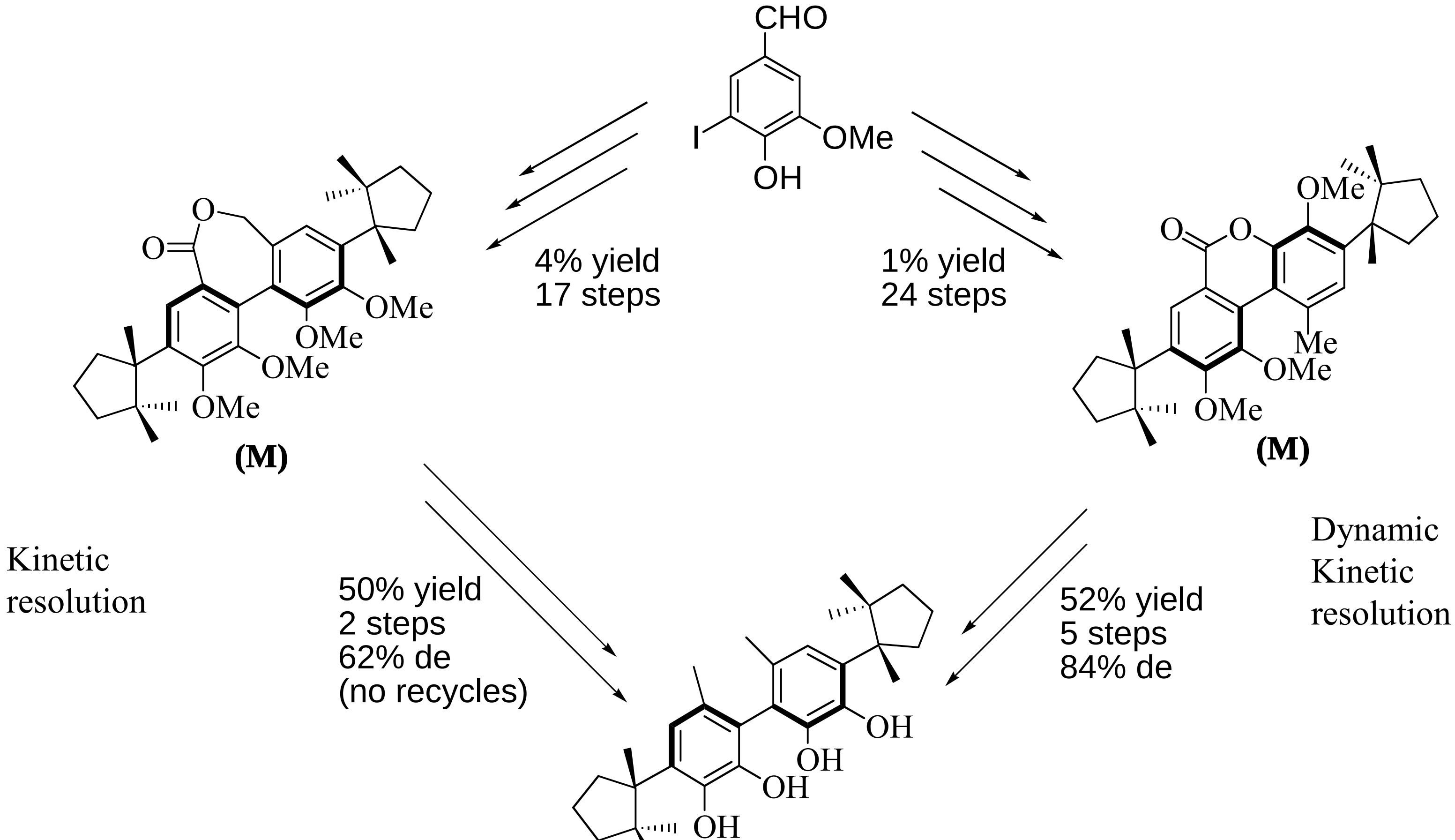
Bringmann, G.; Hinrichs, J.; Pabst, T.; Henschel, P,; Peters, K.; Peters, E.-M. *Synthesis* **2001**, 155-167.

Mastigophorene B: Dynamic Kinetic Resolution



Bringmann, G.; Pabst, T.; Henschel, P.; Kraus, J.; Peters, K.; Peters, E.-M.; Rycroft, D. S.; Connolly, J. D. *J. Am. Chem. Soc.* **2000**, *122*, 9127-9133.

Kinetic vs. Dynamic Kinetic Resolution



Mastigophorene B

Bringmann, G.; Pabst, T.; Henschel, P.; Kraus, J.; Peters, K.; Peters, E.-M.; Rycroft, D. S.; Connolly, J. D. *J. Am. Chem. Soc.* **2000**, *122*, 9127-9133.

Bringmann, G.; Hinrichs, J.; Pabst, T.; Henschel, P.; Peters, K.; Peters, E.-M. *Synthesis* **2001**, 155-167.

Conclusions

- *In situ* racemization of dynamic kinetic resolution can compensate for limitations of kinetic resolution
- Ratios of k_{inv}, k_{R}, and k_{S} important for *ee* of products
- Wide variety of reactions possible

Thank you

Lei Jiang
Bill Lambert
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Joe Martinelli
Susie Martins
Jason Pontrello

John Herbert
Jen Slaughter
Whitney Erwin
Margaret Biddle
Jason Adasiewicz
Belshaw Group
Tolga Gulmen
Lisa Jungbauer