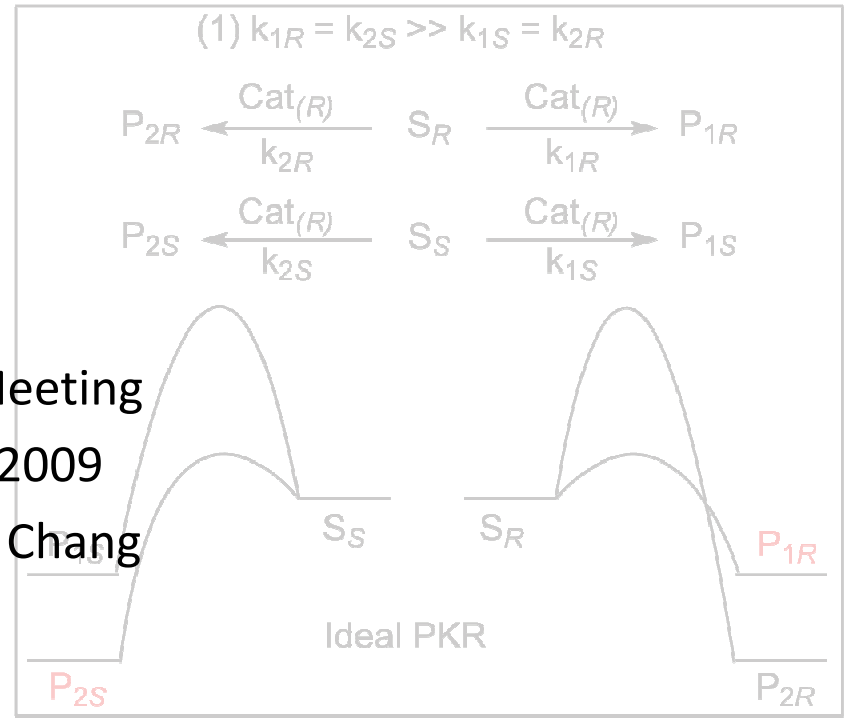
Parallel Kinetic Resolution (PKR)



Group Meeting

09-29-2009

Timothy Chang

KR versus PKR

KR: One enantiomer is transformed into a product relatively rapidly, while the other enantiomer reacts slowly (resulting in the enantioenrichment of product or starting material).

PKR (coined by Vedejs, 1997): Both enantiomers react efficiently, but they are converted into non-enantiomeric products.

KR

$$S_R + \text{Reagent} \xrightarrow[k_R]{\text{Cat}_{(R)}} P_R$$

$$S_S + \text{Reagent} \xrightarrow[k_S]{\text{Cat}_{(R)}} P_S$$

$k_R >> k_S$ or $k_S >> k_R$
resulting in resolution

PKR

$$S_R + \text{Reagent} \xrightarrow[k_1]{\text{Cat}_{(R)}} P_1$$

$$S_S + \text{Reagent} \xrightarrow[k_2]{\text{Cat}_{(R)}} P_2$$

$P_1 \leftrightarrow P_2$ non-enantiomeric

$k_1 = k_2$
resulting in resolution

P_1 and P_2 are
1. diastereomers (stereodivergent)
2. constitutional isomers (regiodivergent)
3. different compounds (chemodivergent, one product can be achiral)

Vedejs, E.; Chen, X. *J. Am. Chem. Soc.* **1997**, *119,* 2584.
Tanaka, K.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125,* 8078.

The Basic of KR (1)

$$S_R + \text{Reagent} \xrightarrow[k_R]{Cat_{(R)}} P_R$$

$$S_S + \text{Reagent} \xrightarrow[k_S]{Cat_{(R)}} P_S$$

Efficiency (relative rate or selectivity factor)

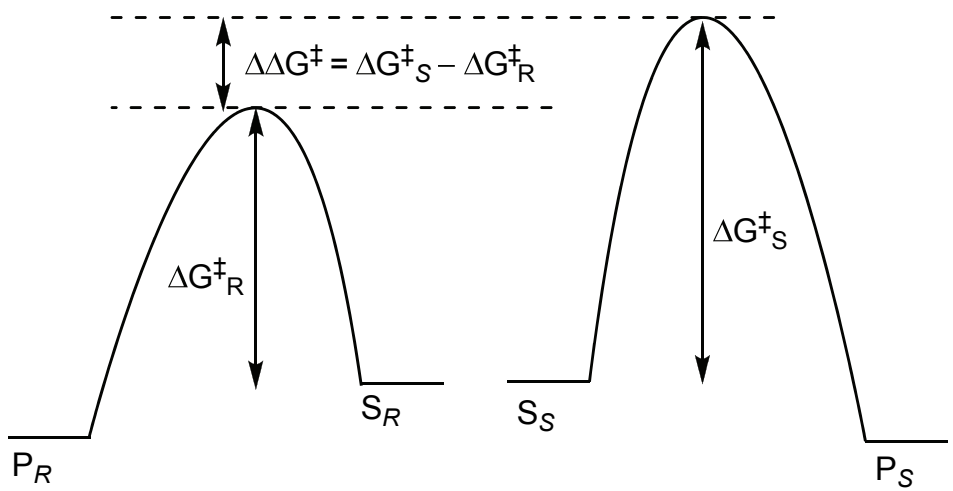
$s = k_{rel} = k_{fast}/k_{slow}$

$= k_R / k_S$

$= \exp(\Delta\Delta G^{\ddagger}/RT)$

Why perform KR:
1. Racemate is cheap
2. No reasonable enantioselective approach
3. Classical resolution (stoichiometric) does not provide high ee

For $k_R > k_S$



"selectivity-determining diastereomeric transition states"

KR Consideration:
1. S and P are easily separated
2. High yield (~50%), high ee
3. Short reaction time
4. Scalibility
5. Low cat. loading
6. Inexpensive cat.
7. Minimal waste
8. Reproducibility
9. Broad scope
10. Functional group compatibility

Walsh P. J.; Kozlowski, M. C. *Fundamentals of Asymmetric Catalysis* Chapter 7

The Basic of KR (2)

$$S_R + \text{Reagent} \xrightarrow[k_R]{Cat_{(R)}} P_R$$

$$S_S + \text{Reagent} \xrightarrow[k_S]{Cat_{(R)}} P_S$$

$s = k_{rel} = \ln[(1 - C)(1- ee) / \ln[(1 - C)(1 + ee)]$ (1)

C = conversion

ee = ee of S

s can be measured experimentally by knowing C and ee

$s = k_{rel} = \ln[1 - C(1 + ee')] / \ln[1 - C(1 - ee')]$ (2)

ee' = ee of P

Combine (1) and (2): ee / ee' = C / (1-C)

Realistically, s factor is often moderate. It is impossible to obtain both good yield and high ee at the same time with moderate s.

KR is useful if s is at least 10. However, the yield of S is sacrified.

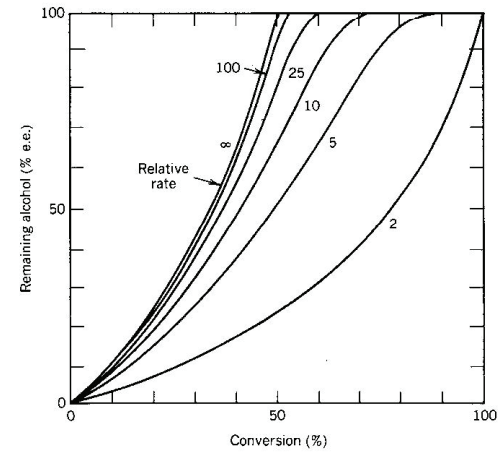


Figure 5. Dependence of e.e.% of recovered material on **s** factor (relative rate) and on conversion. Reprinted with permission from Martin et al., *J. Am. Chem. Soc. 103*, 6237–6240. Copyright 1981 American Chemical Society.

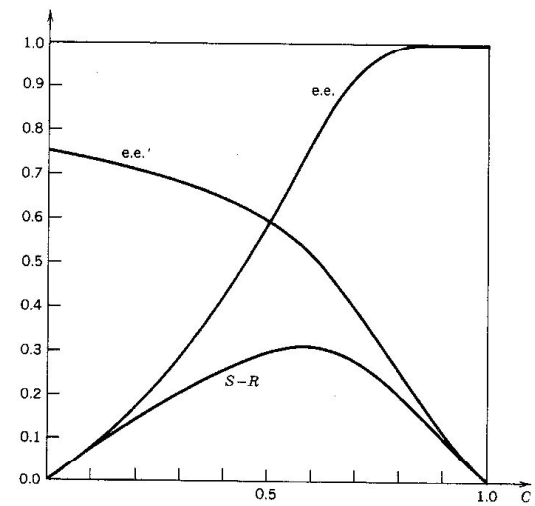


Figure 2. Pseudo-first-order kinetic resolution with conversion *C* as parameter. Computed curves for relative rate **s** = 7.

Kagan, H. B.; Fiaud, J. C. *Topics in Stereochemistry Vol.18,* Kinetic Resolution

A Problem of Relative Rate

$[S_S] - [S_R] = 0.5[\exp(-k_S t) - \exp(-k_R t)]$

$d[S_R]/dt = - k_R[S_R]$
$d[S_S]/dt = - k_S[S_S]$

At time t_{max}, $-d[S_R]/dt = -d[S_S]/dt$

so $k_R[S_R] = k_S[S_S]$
since $k_R/k_S = s = [S_S]/[S_R]$
then ee = (s-1)/(s+1) at t_{max} can be derived

S_S is consumerd faster at $t > t_{max}$

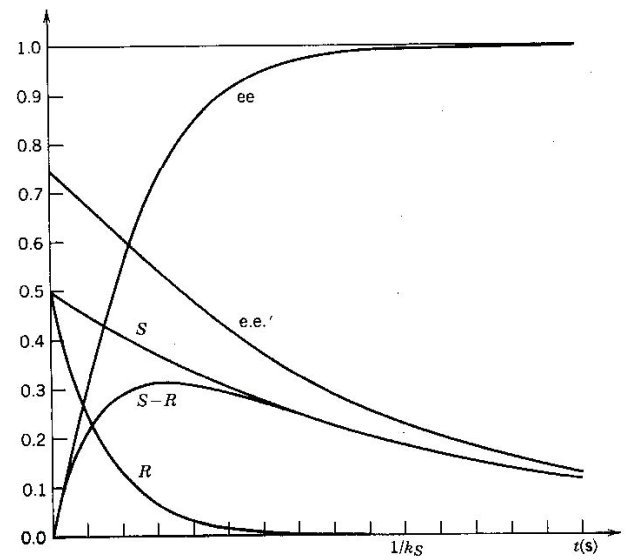


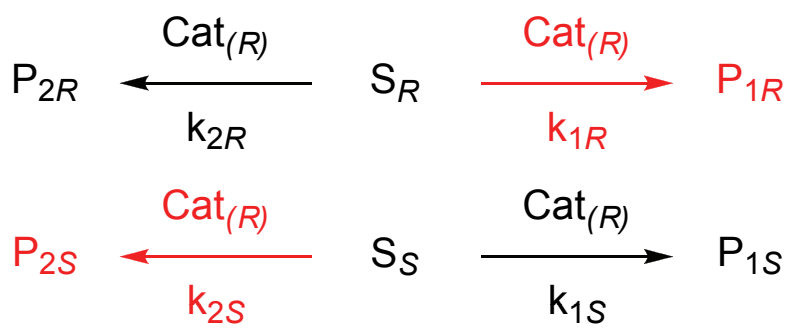
Figure 1. Pseudo-first-order kinetic resolution with time as parameter. Computed curves for relative rate s = 7.

Smaller s factor means that the relative rate reaches 1 earlier. Consequently, conversion must go higher to comsume S_R to leave S_S with satisfactory ee. Higher conversion also means <u>lower</u> <u>yield</u> for S_S.

Kagan, H. B.; Fiaud, J. C. *Topics in Stereochemistry Vol.18,* Kinetic Resolution.

The Basic of PKR

Solution:
Minimize built up of the less reactive substrate (S_S) by a simultaneous transformation of S_S.



Ideal situation:

$k_{1R} = k_{2S} >> k_{1S} = k_{2R}$ $\quad$ P_{1R} / P_{2S} is constant during the course of resolution

$[S_R]/[S_S] = 1$ $\quad$ ee = 0 $\quad$ S_R / S_S is constant during the course of resolution

Example:

If $s_1 = s_2 = 49$ $\quad$ $P_{1R}:P_{1S} = 49:1$ $\quad$ $ee(P_{1R}) = 96\%$
$P_{2S}:P_{2R} = 49:1$ $\quad$ $ee(P_{2S}) = 96\%$ $\quad$ ee = (49 - 1) / (49 + 1)

To achieve the same result in KR, s needs to be 200:

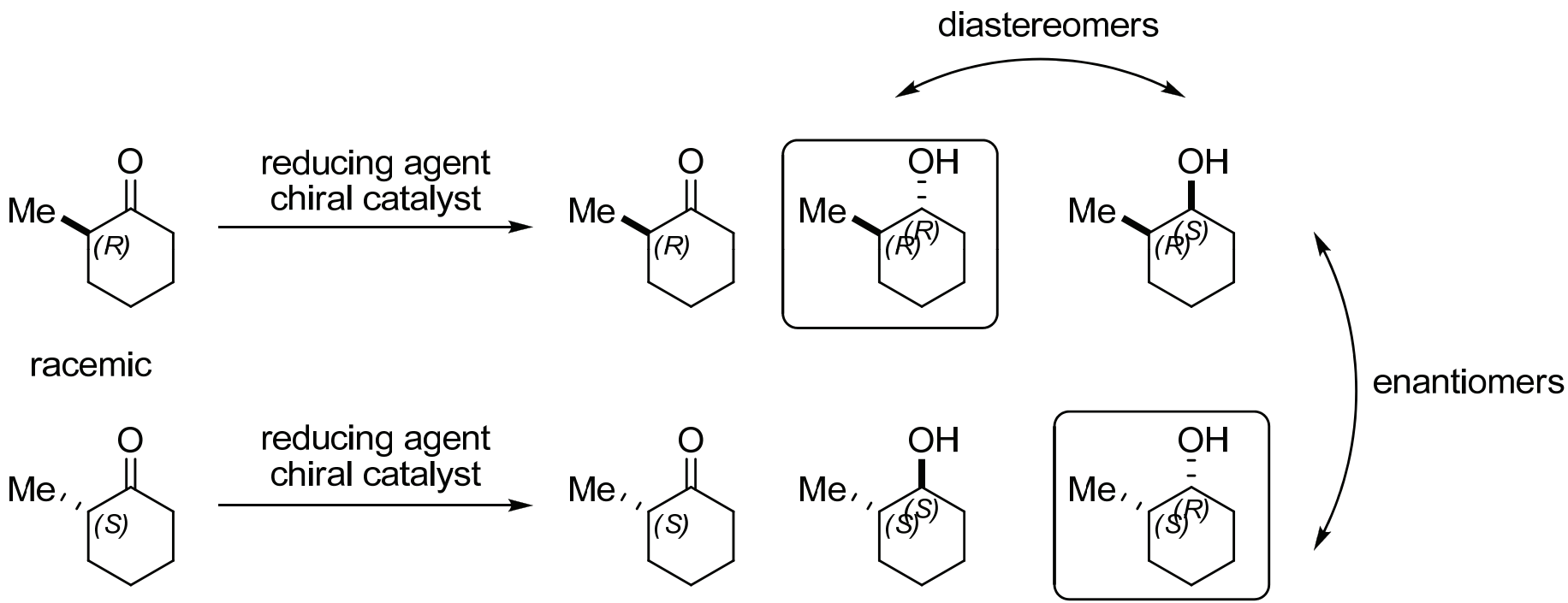
$s = \ln[1 - C(1 + ee')] / \ln[1 - C(1 + ee')]$ $\quad$ C = 0.5, ee = 96%, s =200

s (or k_{rel}) can be lower in PKR than in KR to achieve high ee

Vedejs, E.; Chen, X. *J. Am. Chem. Soc.* **1997**, *119*, 2584.

PKR Mathematical Treatment (1)

Consider the following hypothetical examples (stereodivergent):

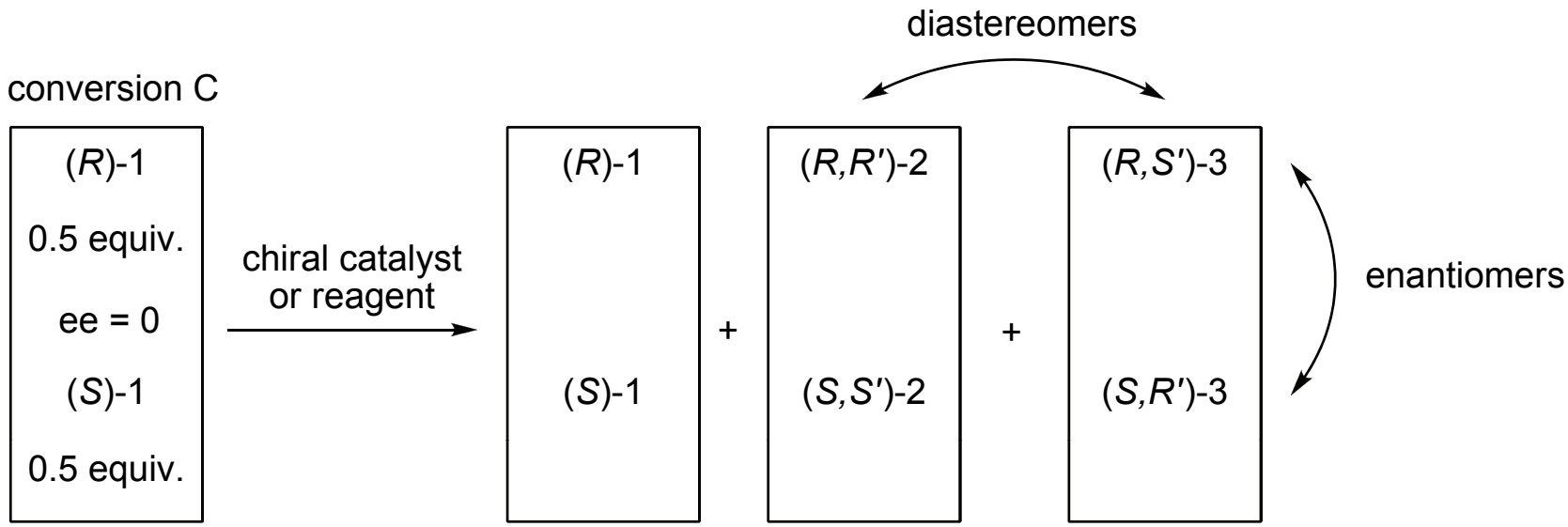


Assuming no racemization through the enolate/enol intermediates, no dynamic process, no side products.

Kagan, H. B. *Tetrahedron* **2001**, 57, 2449.

Kagan, H. B.; Fiaud, J. C. *Topics in Stereochemistry Vol.18,* Kinetic Resolution.

PKR Mathematical Treatment (2)



$C = x_2 + x_3$
$0 \leq C \leq 1$
$x_1 + x_2 + x_3 = 1$

$$\mathrm{ee}_1 x_1 + \mathrm{ee}_2 x_2 + \mathrm{ee}_3 x_3 = 0, \quad (1)$$

$$\mathrm{dr} = x_2/x_3 = [C(\mathrm{ee}_1 - \mathrm{ee}_3) - \mathrm{ee}_1]/[C(\mathrm{ee}_2 - \mathrm{ee}_1) + \mathrm{ee}_1], \quad (2)$$

$$\boxed{\mathrm{ee}_1 = C[\mathrm{dr}\ \mathrm{ee}_2 + \mathrm{ee}_3]/[(C-1)(1+\mathrm{dr})], \quad (3)}$$

$$\mathrm{ee}_2 = [(C-1)(1+1/\mathrm{dr})\mathrm{ee}_1]/C - \mathrm{ee}_3/\mathrm{dr} \quad (4)$$

$$\mathrm{ee}_3 = [(C-1)(1+\mathrm{dr})\mathrm{ee}_1]/C - \mathrm{dr}\ \mathrm{ee}_2. \quad (5)$$

$$a = [RR']/[RS'] = \mathrm{dr}[(1+\mathrm{ee}_2)/(1+\mathrm{ee}_3)], \quad (6)$$

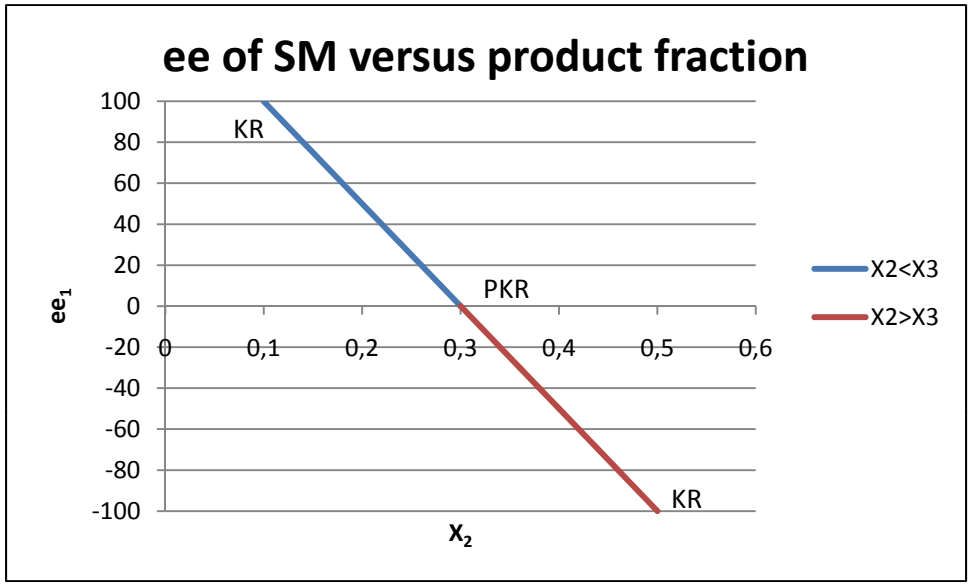
$$b = [SS']/[SR'] = \mathrm{dr}[(1+\mathrm{ee}_2)/(1+\mathrm{ee}_3)]. \quad (7)$$

$$C = [(1+\mathrm{dr})\mathrm{ee}_1]/[\mathrm{dr}(\mathrm{ee}_1 - \mathrm{ee}_2) + \mathrm{ee}_1 - \mathrm{ee}_3]. \quad (8)$$

Kagan, H. B. *Tetrahedron* **2001**, 57, 2449.
Kagan, H. B.; Fiaud, J. C. *Topics in Stereochemistry Vol.18,* Kinetic Resolution.

PKR Mathematical Treatment (3)

<Example 1>
Looking back at the ideal PKR:
Assume C = 0.6,
$ee_2 = ee_3 = 1$,
$x_2 = x_3 = 0.3$
dr = 1,
$ee_1 = C[dr\ ee_2 + ee_3]/[(C - 1)(1 + dr)]$ (3)
$ee_1 = 0.6[1x1-1]/[(0.6-1)(1+1)] = 0$



<Example 2>
$x_2 = 0.29$, $x_3=0.31$
Assume C = 0.6
$ee_2 = ee_3 = 1$,
then ee_1 should be close to 0, but not 0
dr = 0.29/0.31 = 0.93548
$ee_1 = 0.05$ (5% ee)

At complete conversion, C = 1
ee and yield are inversely related

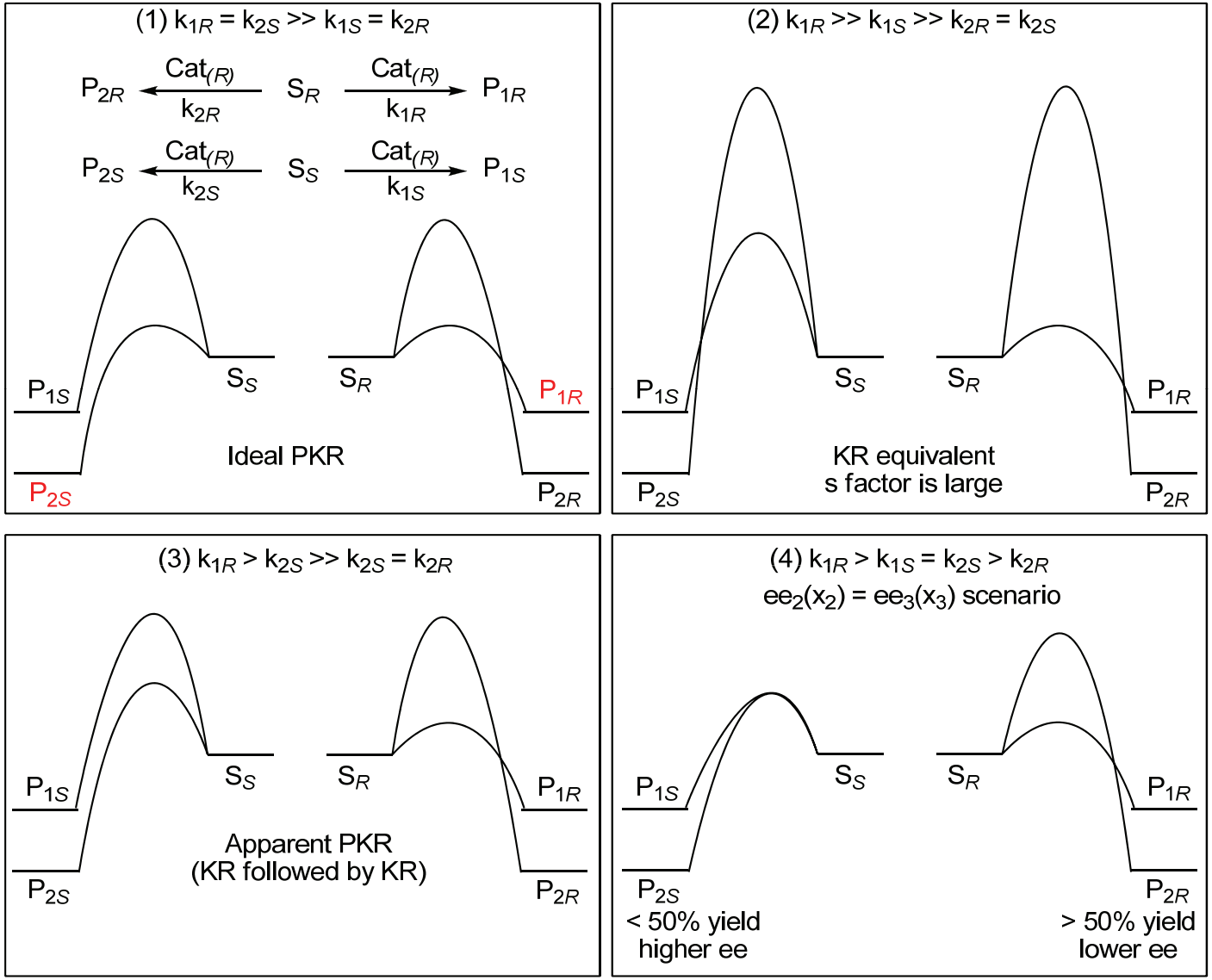
$ee_1x_1 + ee_2x_2 + ee_3x_3 = 0$ (1)

when C = 1, $x_1 = 0$,
then $-ee_2(x_2) = ee_3(x_3)$

Remember to make either ee_2 or ee_3 -ve in the calculation to satisfy equation (1)
e.g.
+ve sign indicates products are derived from (R)-1
-ve sign indicates products are derived from (S)-1

Kagan, H. B. *Tetrahedron* **2001**, 57, 2449.
Kagan, H. B.; Fiaud, J. C. *Topics in Stereochemistry Vol.18,* Kinetic Resolution.

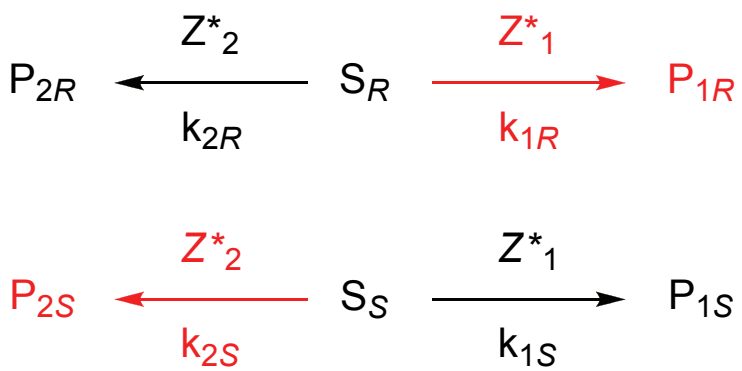
Relative Energy Considerations



A relative energy diagram can be drawn from yields and enantioselectivities (assuming no other side products or their origins are known).

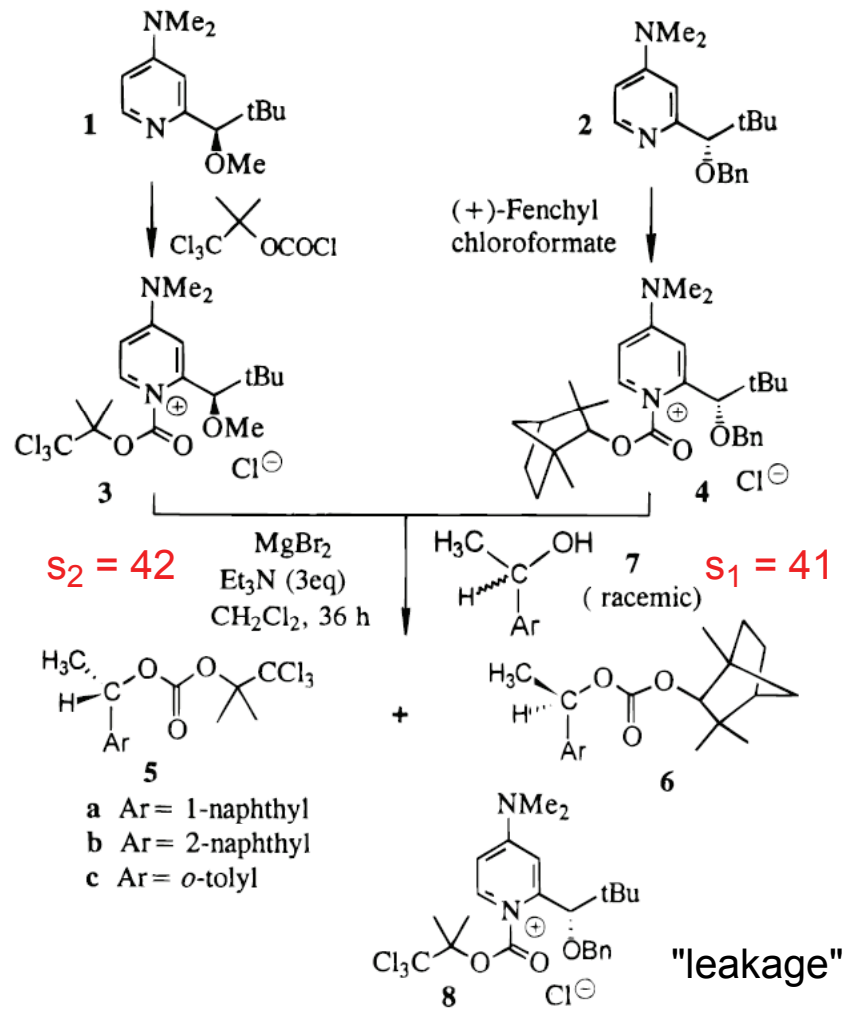
Proof of Principle using Quasienantiomeric Electrophiles

Z* = stoichiometric chiral reagents (quasienantiomers)



P_{1R} and P_{2S} are quasienantiomers

Basic criteria for a successful PKR:
1. Minimal mutual interference wrt catalyst or reagents
2. Have similar rates
3. Have opposite enantiocontrol wrt S_R and S_S
4. P_{1R} and P_{2S} are easily separated



Vedejs, E.; Chen, X. *J. Am. Chem. Soc.* **1997**, *119*, 2584.

Proof of Principle

Table 1. PKR Experiments Using **3** and **4** to Resolve **7**[a]

entry	Ar	**5**:**6**[b]	yield (**5**)	ee (**5**)[d]	yield (**6**)	ee (**6**)[d]
1	1-naphthyl	1.0:1.0	46% (49%)[c]	88%	49% (49%)[c]	95%
2	2-naphthyl	1.0:1.0	49% (49%)[c]	86%	43% (49%)[c]	93%
3	*o*-tolyl	1.13:1.0	46% (53%)[c]	83%	46% (47%)[c]	94%

[a] 0.56 mol equiv each of **3** and **4**, 2.25 mol equiv of $MgBr_2$, 3 mol equiv of Et_3N, 1 mol equiv if racemic $ArCH(OH)CH_3$ in CH_2Cl_2 at room temperature, 36 h. [b] NMR ratio of crude products. [c] Yield vs internal standard, NMR assay. [d] hplc assay; see Supporting Information.

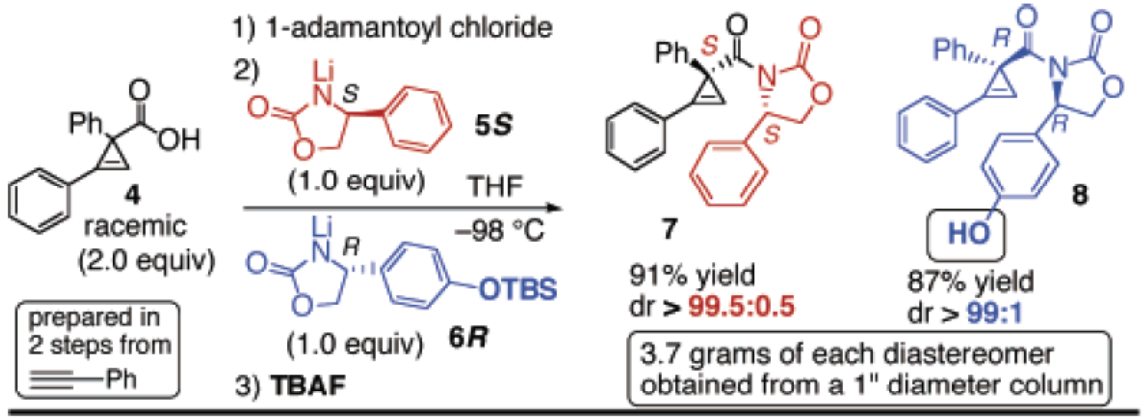
What is the s factor required to achieve the same yield and selectivity in KR?
<Example>
entry 1, compound 6:
49% yield
95% ee
s = ln[1 - C(1 + ee')] / ln[1 - C(1 - ee')]
= ln[1 - 0.49(1 + 0.95)] / ln[1 - 0.49(1 - 0.95)]
s = 125
A higher s factor is required to achieve the same results in KR.

Can you achieve an effective PKR if k_{1R} is different to k_{1S}?
In principle, it should be possible to adjust the relative concentration of $[Z_1^*]$ and $[Z_2^*]$ to make up the difference between k_{1R} and k_{1S}, i.e. to achieve the same rate of consumption (Not experimentally proven yet).

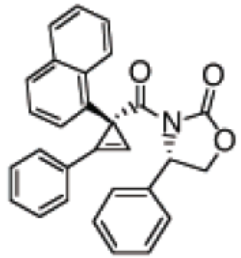
Vedejs, E.; Chen, X. *J. Am. Chem. Soc.* **1997**, *119*, 2584.

PKR using Quasienantiomeric Nucelophiles

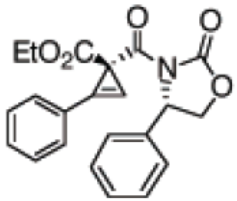
Table 1. One-Pot Parallel Kinetic Resolution of Cyclopropenes



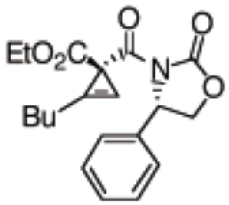
Note: products from **6*R*** are not shown below



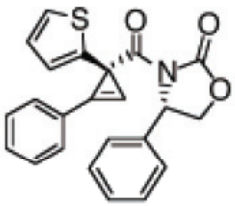
from **5*S***: 93%, dr=97:3
from **6*R***: 90%, dr=97:3



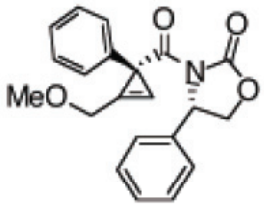
from **5*S***: 91%, dr=98:2
from **6*R***: 89%, dr=97:3



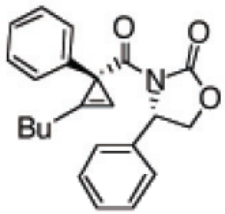
from **5*S***: 90%, dr=97:3
from **6*R***: 86%, dr=96:4



from **5*S***: 91%, dr=97:3
from **6*R***: 87%, dr=97:3



from **5*S***: 93%, dr=96:4
from **6*R***: 89%, dr=97:3



from **5*S***: 87%, dr=90:10
from **6*R***: 83%, dr=91:9

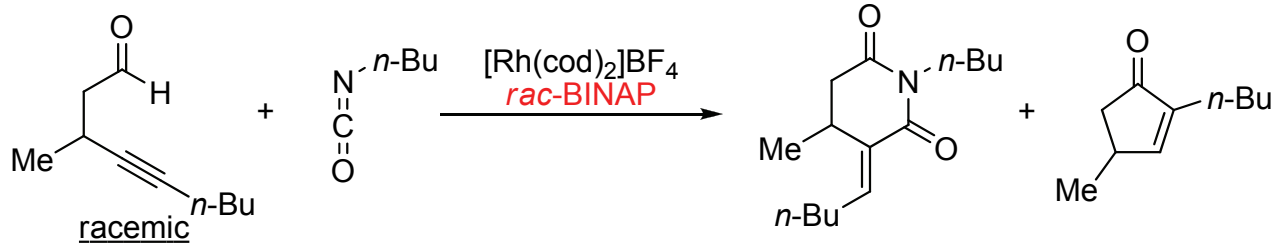
Fox et. al. *J. Am. Chem. Soc.* **2004**, *126,* 4490.

How to Spot a Potential PKR

Ligand survey

<Expt 1>

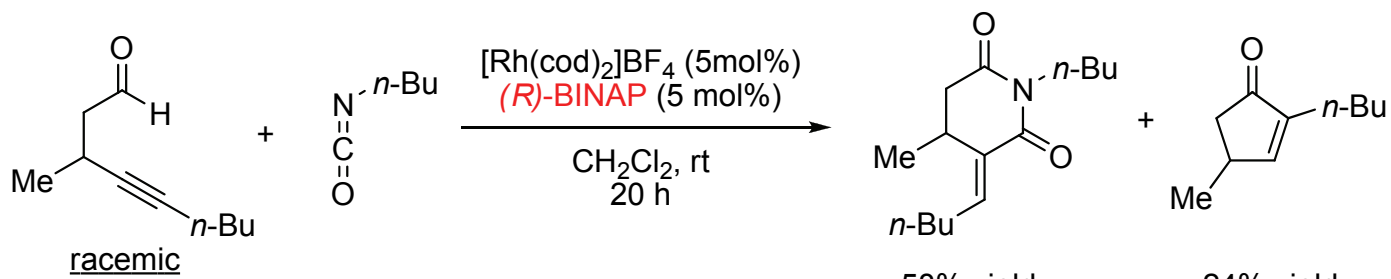
Using a racemic ligand:



Result: poor yield
Action: bad reaction, bad ligand, discard this reaction --> no publication :-(
A better action: identify the side product

<Expt 2>

Subject the enantiopure ligand to the reaction



"Serendipity" discovery of PKR

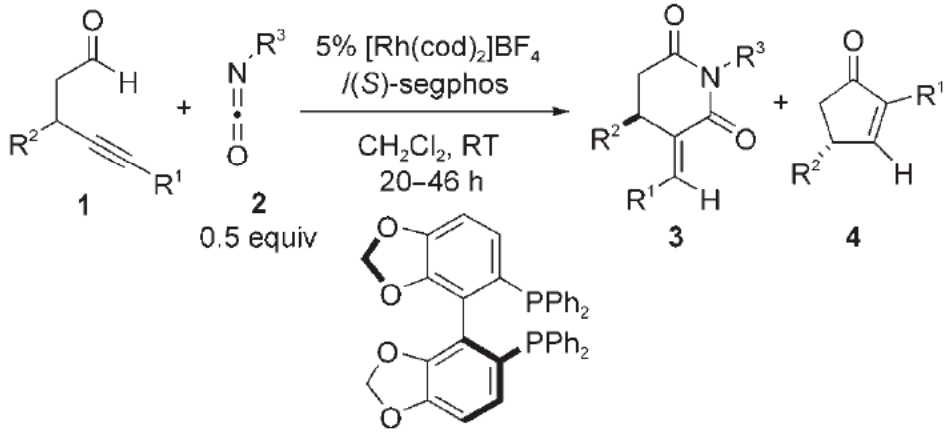
<Expt 3> Confirm PKR by using enantioenriched SM
Expect the formation of one product (out of the two possibilities)

<Expt 4...> Screen more enantiopure ligands, reaction optimization...

Publication in JACS or ACIEE :-) (happy graduate student)

Chemodivergent PKR (1)

Table 2: Rhodium-catalyzed parallel kinetic resolution of 3-substituted 4-alkynals to yield enantioenriched 2-alkylideneglutarimides and cyclopentenones.[a]

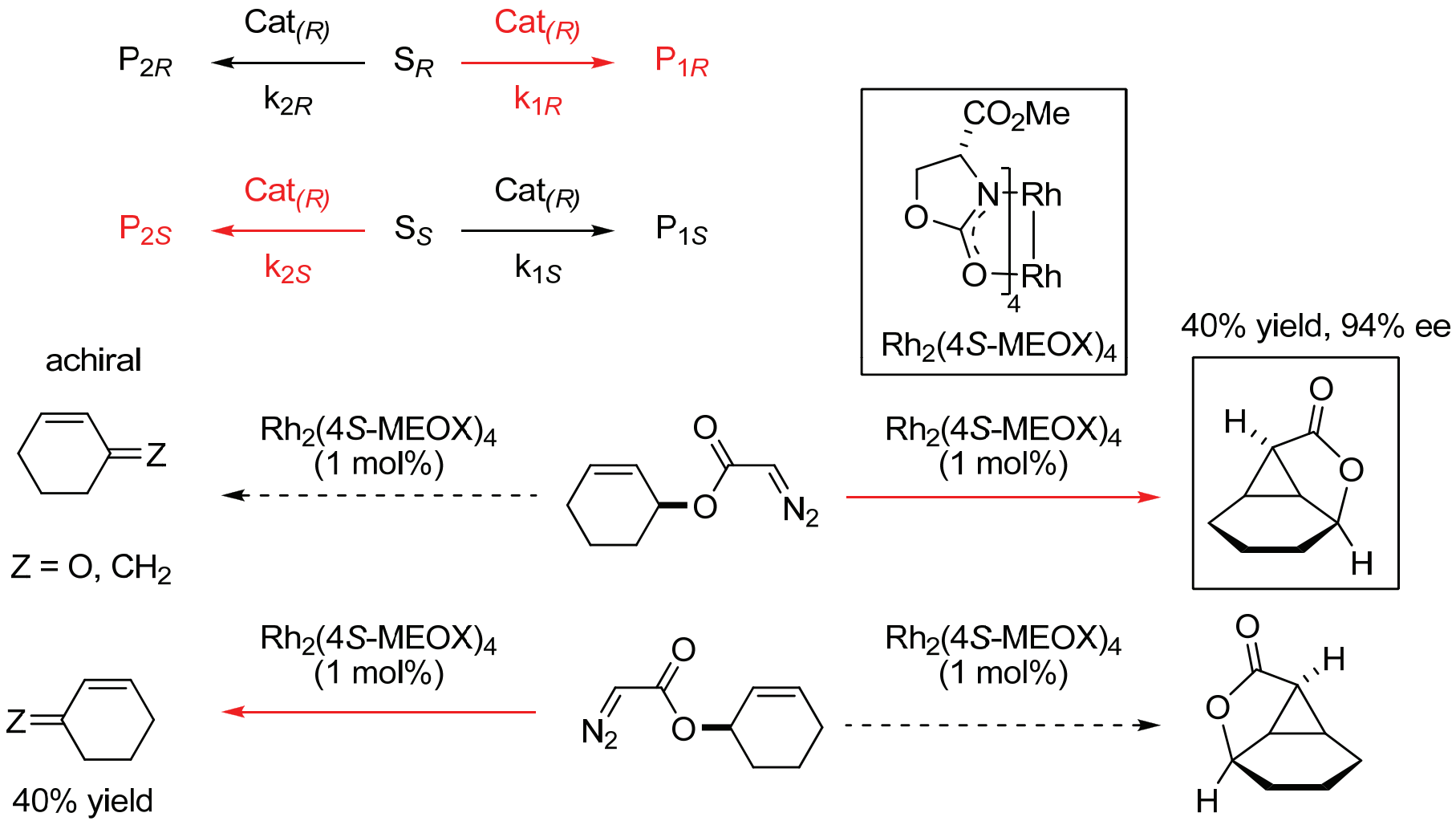


Entry	1	R^1	R^2	2	R^3	3 Yield [%][b]	3 *ee* [%][c]	4 Yield [%][b]	4 *ee* [%][c]
1	**1h**	*n*Bu	*n*Bu	**2a**	*n*Bu	34	91	28	92
2	**1h**	*n*Bu	*n*Bu	**2b**	Cy	30	81	38	94
3	**1h**	*n*Bu	*n*Bu	**2c**	Bn	36	88	26	91
4	**1h**	*n*Bu	*n*Bu	**2d**	Ph	20	52	38	94
5	**1a**	*n*Bu	Me	**2a**	*n*Bu	38	87	39	83
6[d]	**1i**	*n*Bu	Ph	**2a**	*n*Bu	22	97	36	78
7[d]	**1c**	Cy	Me	**2a**	*n*Bu	33	64	30	98
8	**1e**	1-cyclohexenyl	Me	**2a**	*n*Bu	49	56	26	85
9[d]	**1f**	Ph	Me	**2a**	*n*Bu	35	72	31	76

[a] Reactions were carried out with **1** (0.40 mmol), **2** (0.20 mmol), $[Rh(cod)_2]BF_4$ (0.020 mmol), (*S*)-segphos (0.020 mmol), and CH_2Cl_2 (2.0 mL). [b] Yields of the isolated products. [c] The *ee* values were determined by chiral HPLC or GC analysis. [d] Catalyst = 10 mol %.

Tanaka et. al. *ACIEE* **2006**, *45,* 2734.

Chemodivergent PKR (2)

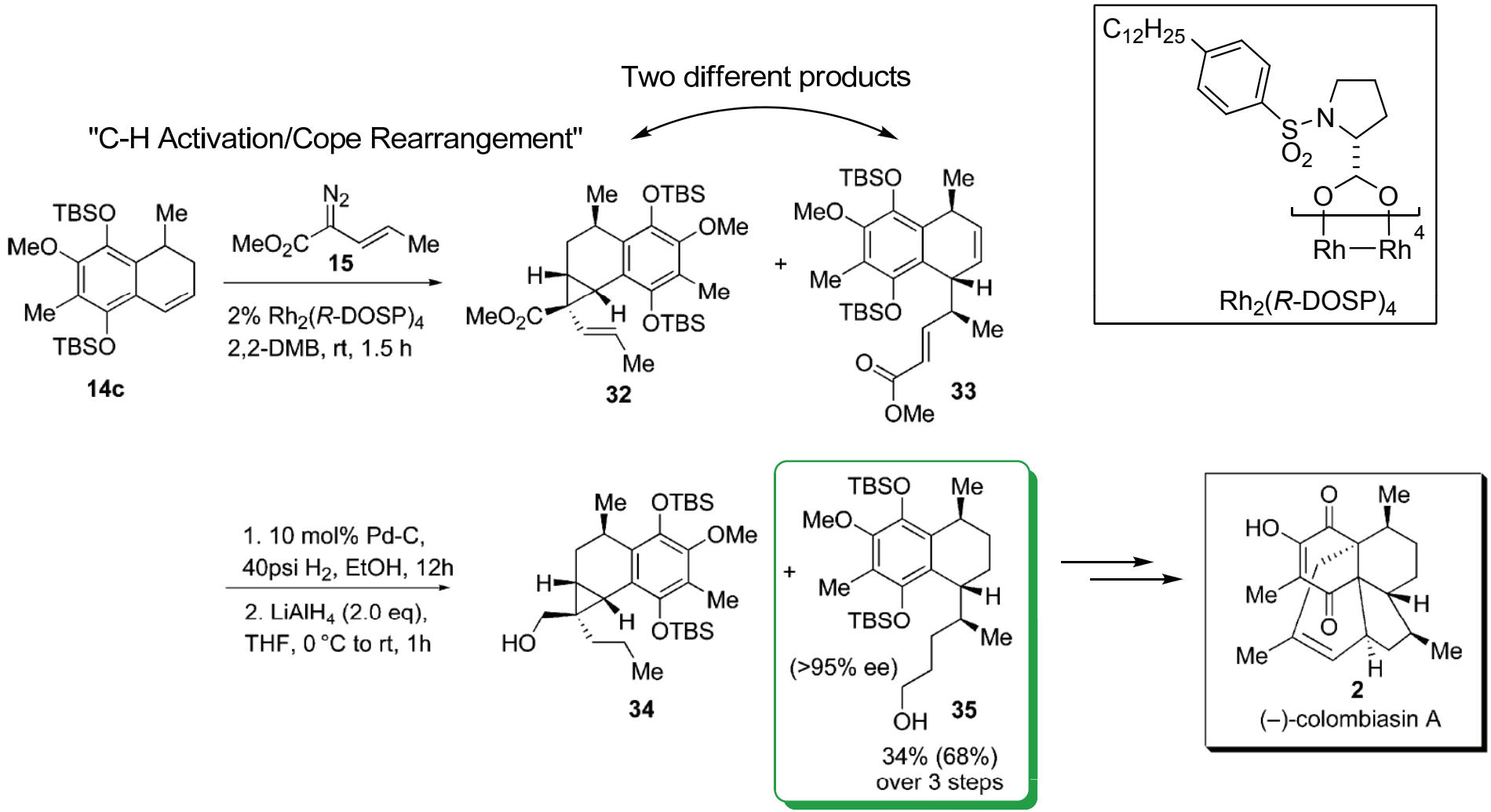


The same reaction was perforemd with $Rh_2(4R\text{-MEOX})_4$ to confirm PKR.

One of the resulting products does not need to be chiral to be a PKR.

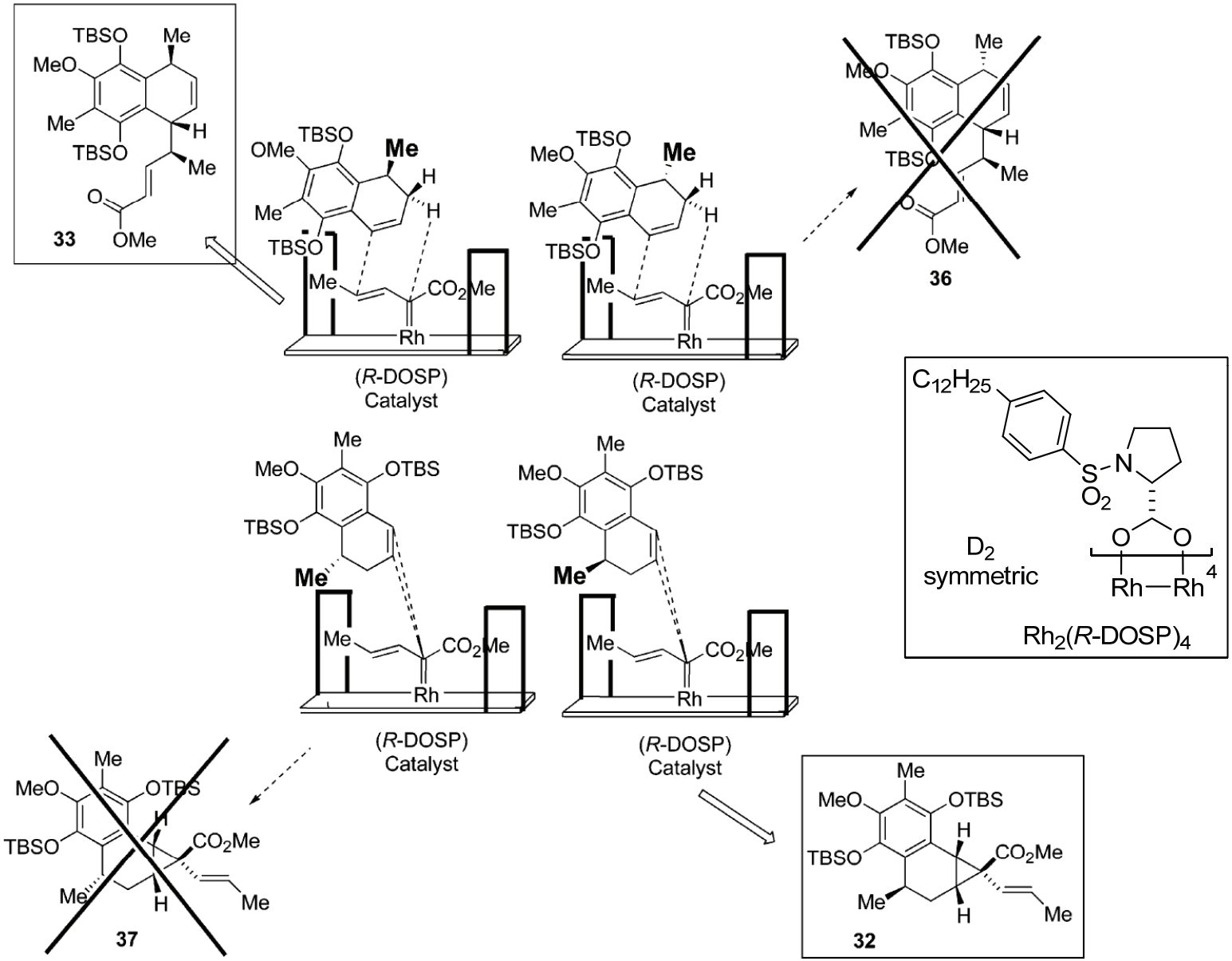
Dolye and Martin et. al. *J. Am. Chem. Soc.* **1995**, *117*, 11021.

Application of Chemodivergent PKR in Synthesis



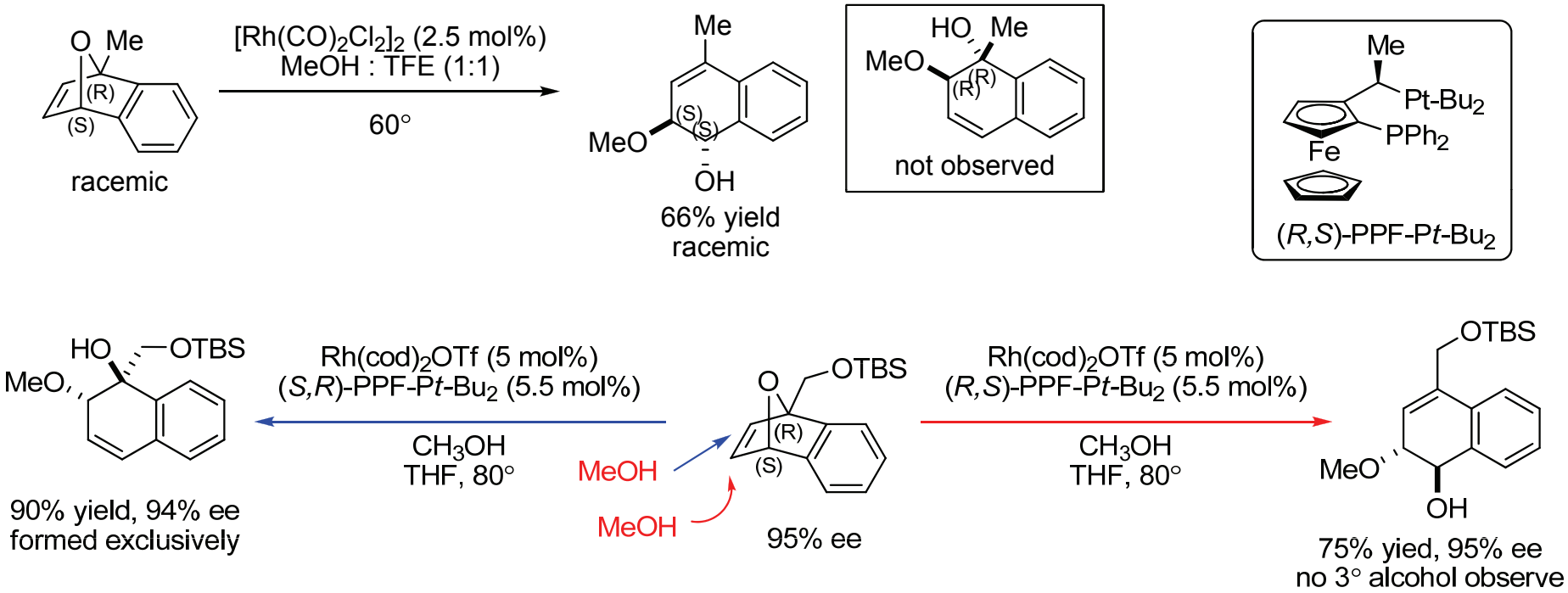
Davies et. al. *J. Am. Chem. Soc.* **2006**, *128,* 2485.

Model/Rational Behind the Divergent Reactivities



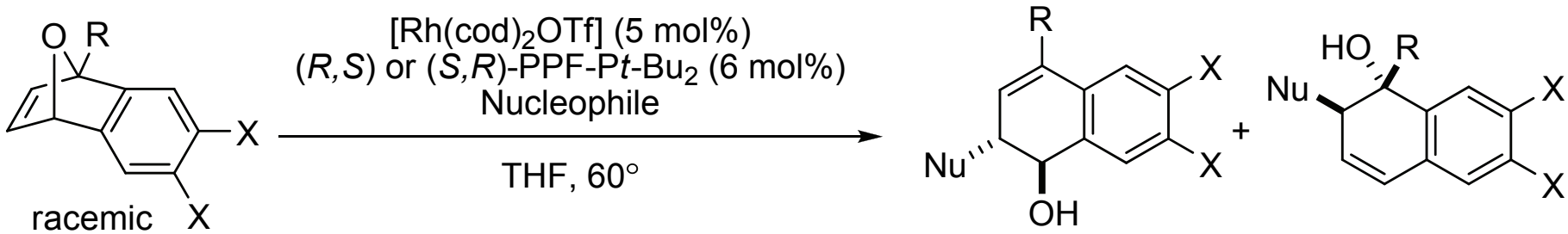
Davies et. al. *J. Am. Chem. Soc.* **2006**, *128,* 2485.

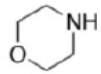
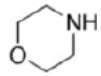
Regiodivergent PKR (1) Group Question Coming Up…



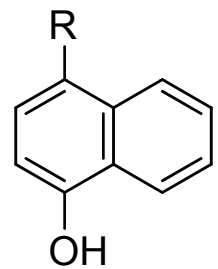
Webster, R.; Böing, C.; Lautens, M. *J. Am. Chem. Soc.* **2009**, *131,* 444.

Regiodivergent PKR (1), Group Question



entry	R	X	nucleophile	product A yield (%)	product A ee[d] (%)	product B yield (%)	product B ee[d] (%)
1[b]	CH_3	H	CH_3OH	(50)[a]	-	42	90
2[b]	CH_3	H	Bn_2NH	29	86	32	>99
3[b]	CH_3	H	Et_2NH	48	79[e]	35	>99
4[b]	CH_3	H	$PhNHCH_3$	43	80	35	99
5[c]	CH_3	H		50	75	39	>99
6[c]	CH_3	Br	Bn_2NH	50	83	30	99
7[c]	CH_3	F	Bn_2NH	50	90	45	>99
8[c,f]	CH_3	F		50	90	48	>99

[a] Aromatized naphthol product **1c** was isolated.

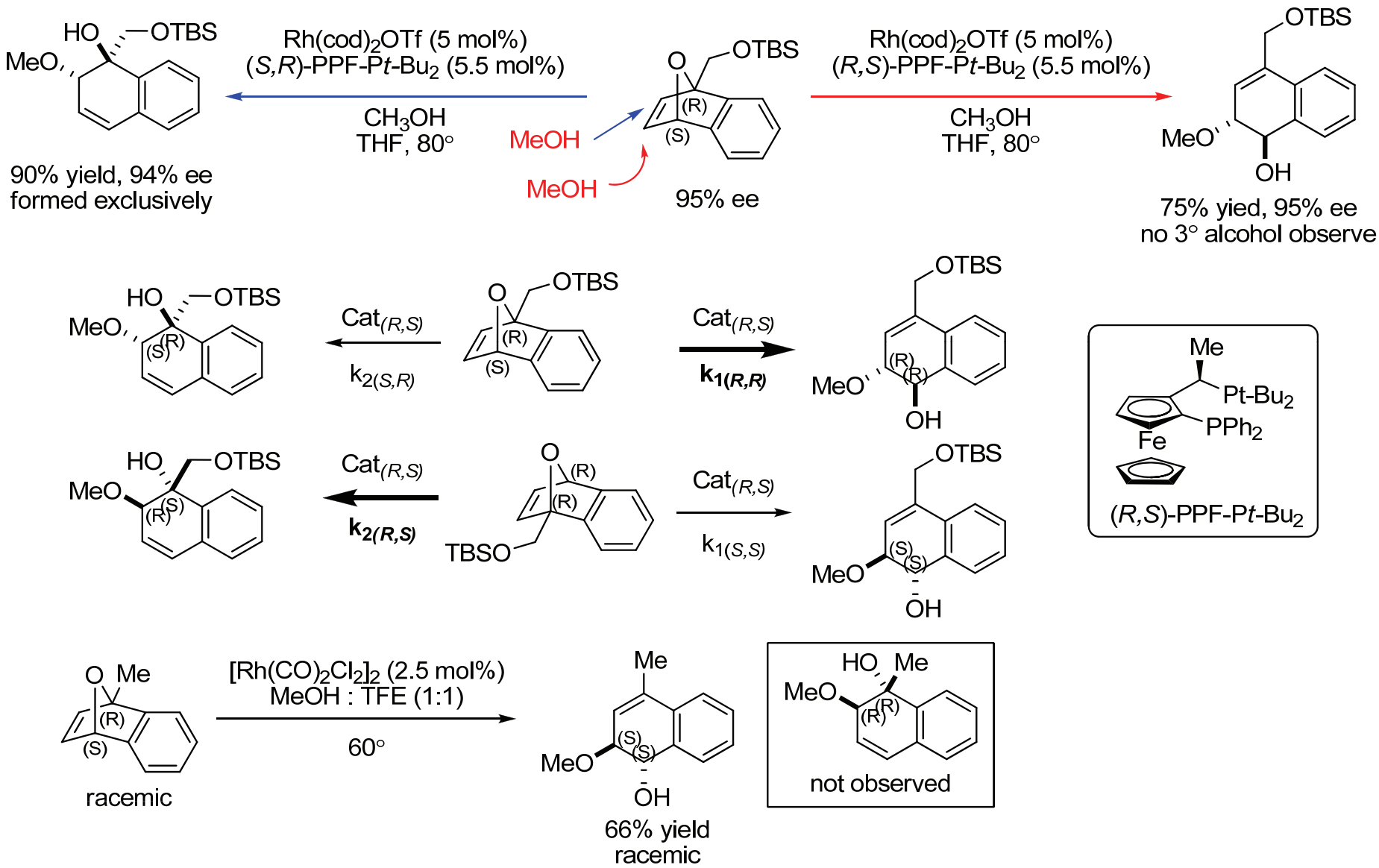


side product, **1c**

1. Find a general trend in yield and ee between the two products in the table.
2. Provide a rational for this trend.
3. Propose a energy diagram to correlate with your hypothesis in 2.

Webster, R.; Böing, C.; Lautens, M. *J. Am. Chem. Soc.* **2009**, *131,* 444.

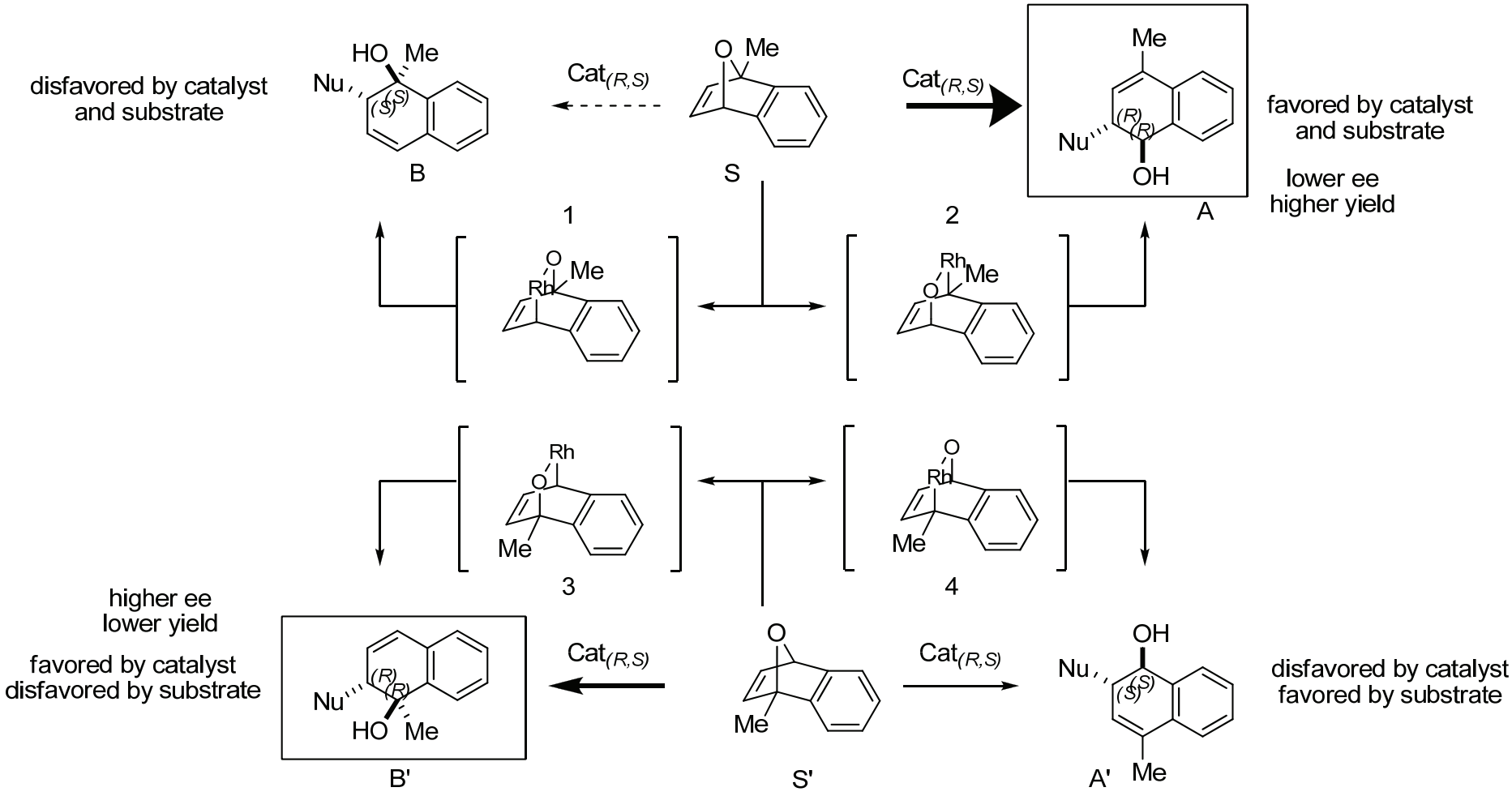
Group Question Answers



Catalyst control overrides the inherent preference of the substrate.

Webster, R.; Böing, C.; Lautens, M.
J. Am. Chem. Soc. **2009**, *131*, 444.

Group Question Answers, Cont.



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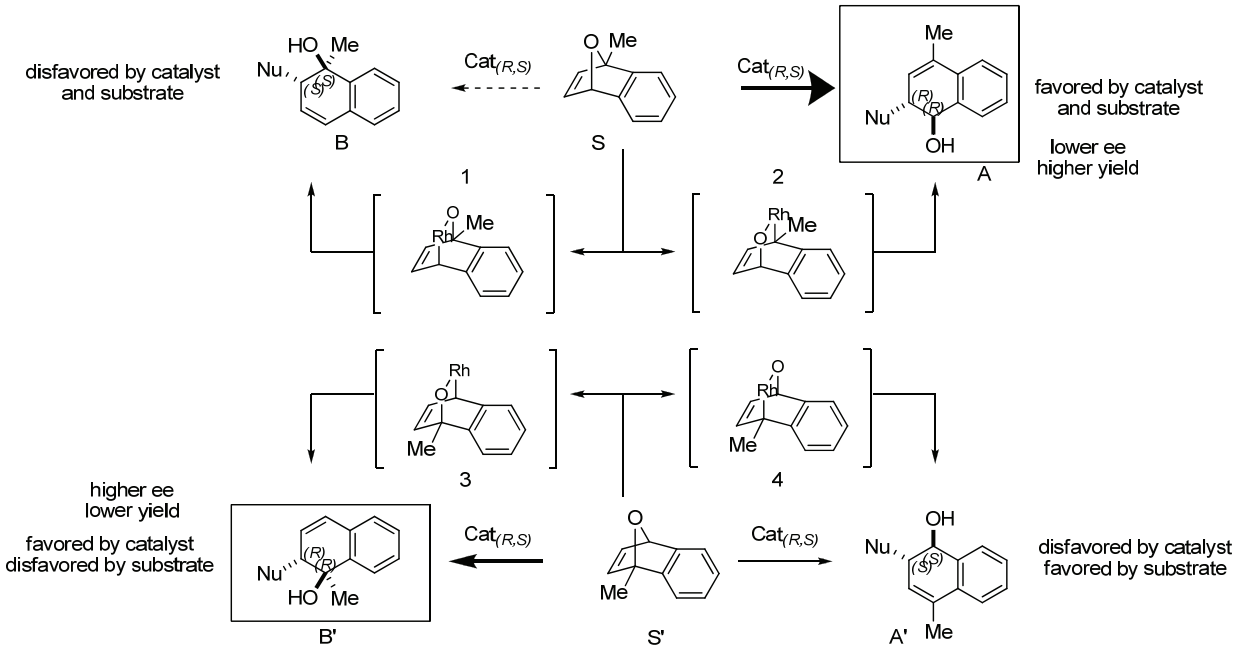
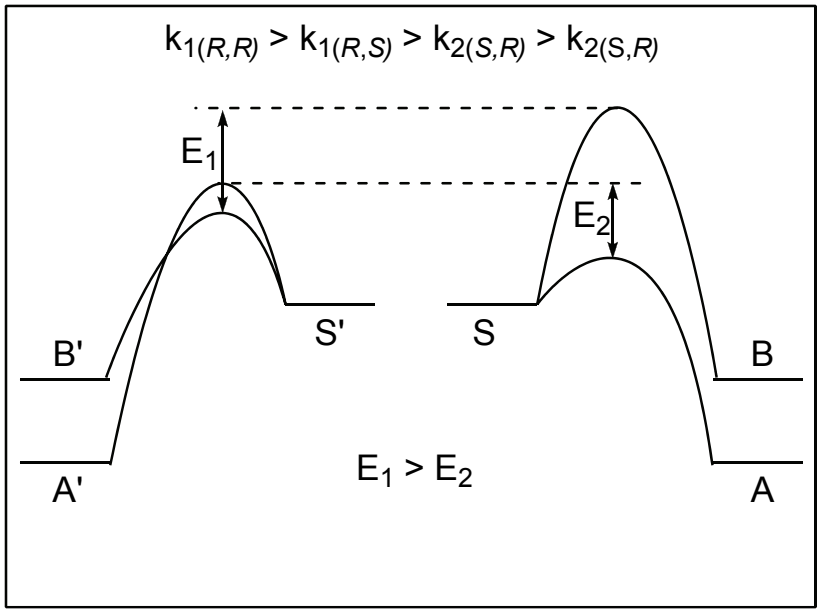
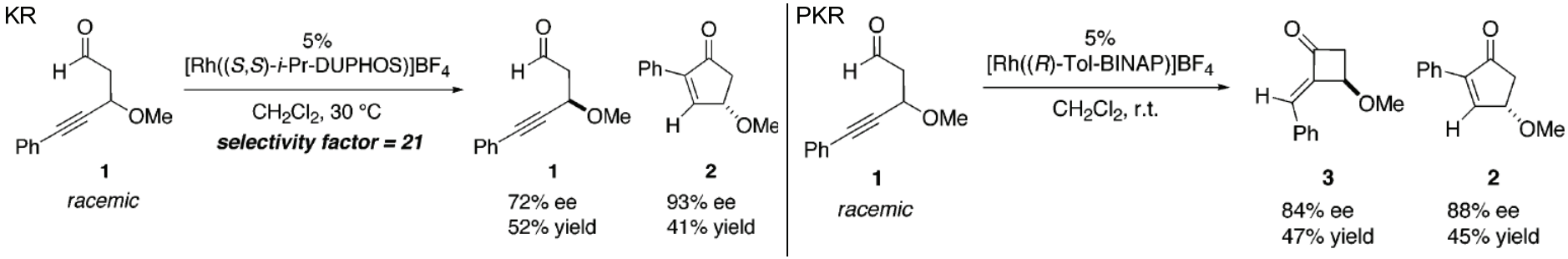
Group Question Answers, Cont.



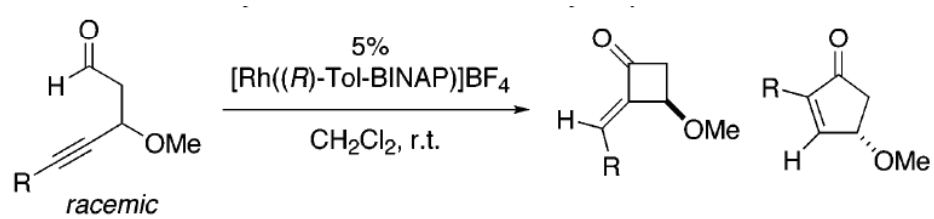


Webster, R.; Böing, C.; Lautens, M. *J. Am. Chem. Soc.* **2009**, *131,* 444.

Regiodivergent PKR (2)



Amazing ligand effect!

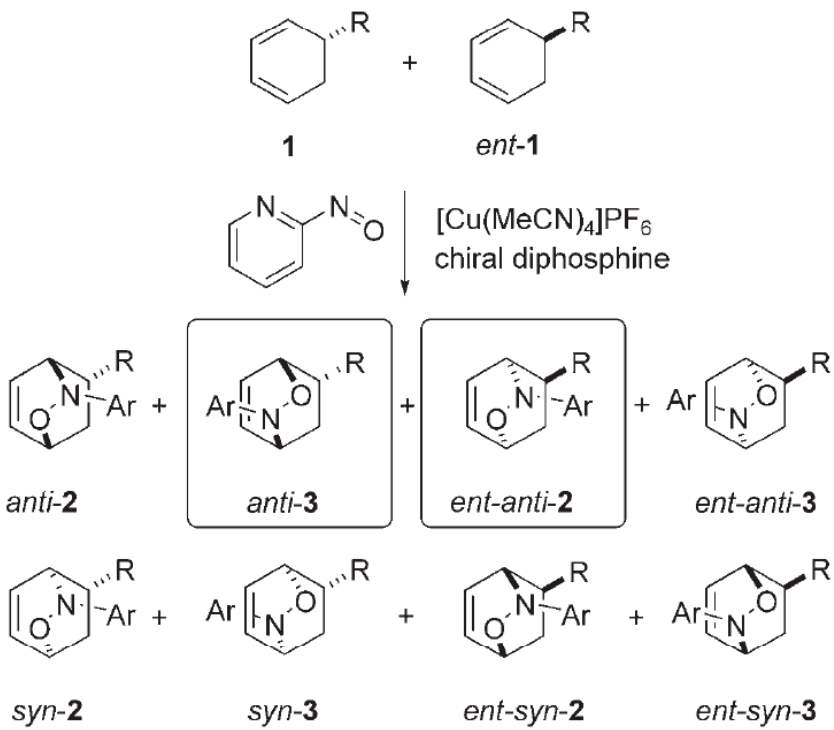


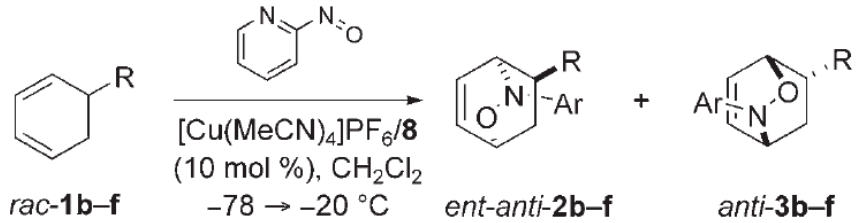
entry	R	cyclobutanone ee (%)	cyclobutanone yield (%)	cyclopentenone ee (%)	cyclopentenone yield (%)
1	Ph	**84**	47	**88**	45
2	4-MeO(C_6H_4)	**81**	43[a]	**81**	36[a]
3[b]	4-CF_3(C_6H_4)	>**99**	32	**62**	58
4[b]	*o*-tol	>**99**	27	**85**	41
5	2-furyl	**98**	26	**46**	66
6	Cy	>**99**	25	**84**	41

All yields are isolated yields. [a] Isolated as a mixture of cyclobutanone and cyclopentenone (the yields are distributed according to the ^{1}H NMR spectrum). [b] The reaction was carried out at 40 °C.

Tanaka, K.; Fu, G. C. *J. Am. Chem. Soc.* **2009**, *131*, 444.

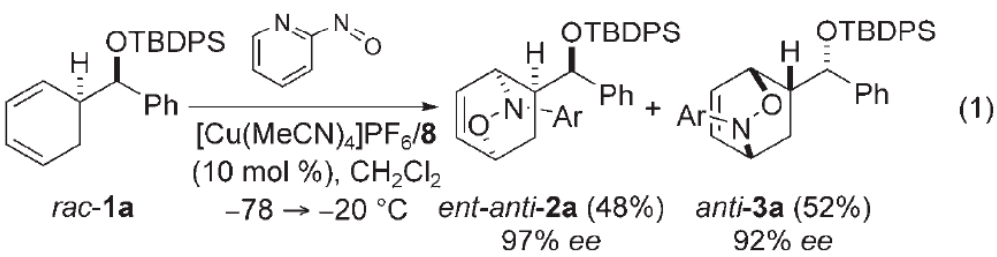
Regiodivergent PKR (3)



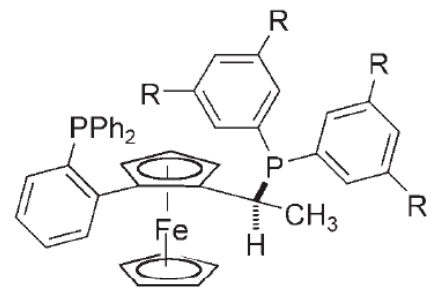


Diene	R	*ent-anti*-**2**		*anti*-**3**	
		Yield [%]	*ee* [%]	Yield [%]	*ee* [%]
1 b	CMe_2OTMS[e]	48	95	52	89
1 c[a]	$CH_2OTBDPS$	42	99	45	88
1 d[b]	CH_2Ph	40	98	43	84
1 e[c]	CH_2OAc	39	98	42	82
1 f[d]	Ph	45	98	54	94

[a] One of the *syn* isomers, **2 c** or **3 c**, was formed in 13% yield. [b] The *syn* isomers **2 d** and **3 d** were formed in 17% combined yield. [c] The *syn* isomers **2 e** and **3 e** were formed in 19% combined yield. [d] The *syn* isomers were formed in trace amounts (< 1%). [e] TMS = trimethylsilyl.



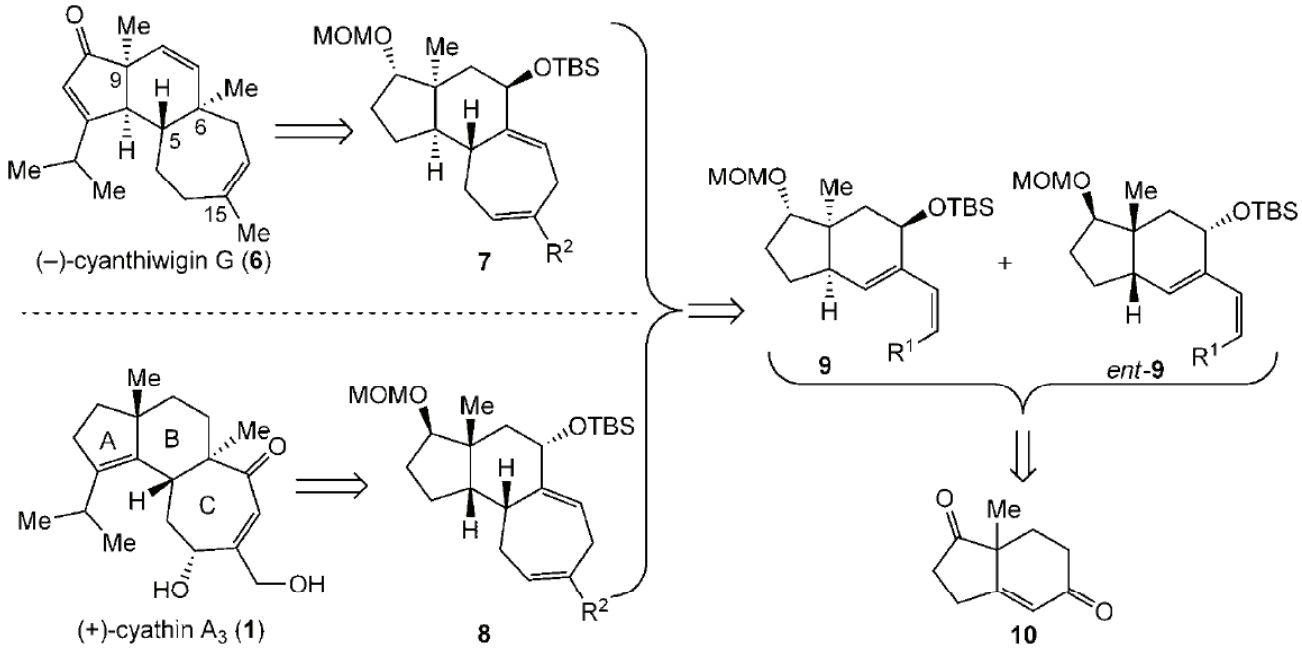
(1)



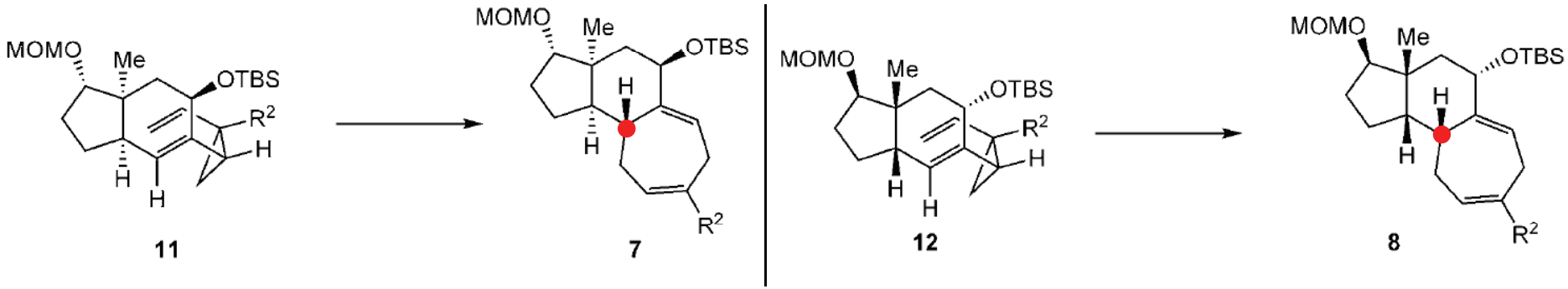
Jana, C. K.; Studer, A. *ACIEE* **2007**, *46,* 6542.

Stereodivergent PKR in Total Synthesis

Vision:



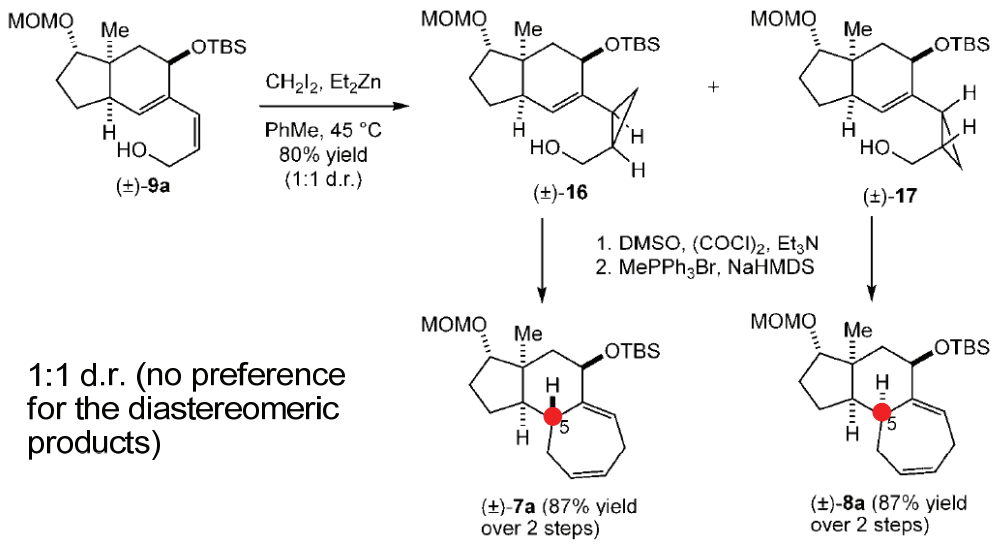
7 and 8 are diastereomers



Strategy: Cyclopropanation/Cope Rearrangement

Sarpong et. al. *ACIEE* **2009**, *48,* 2398.

Stereodivergent PKR in Total Synthesis



1:1 d.r. (no preference for the diastereomeric products)

facial selectivity is not perfect

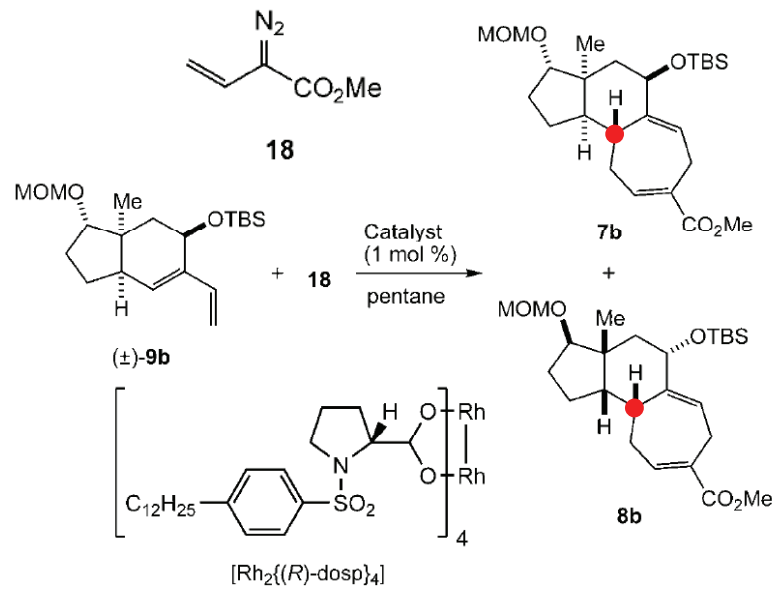


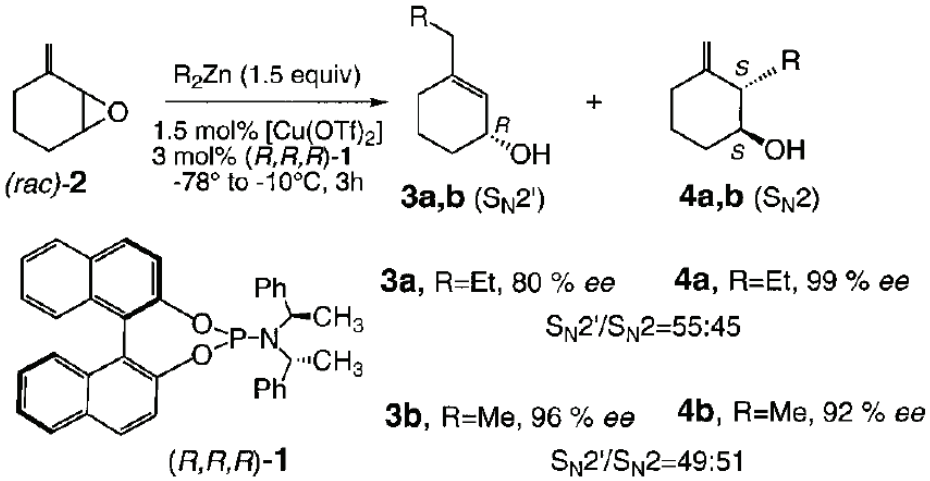
Table 1: Rh^{II}-catalyzed PKR of diene (±)-**9b**.

Entry	Catalyst	Ratio[a] **7b**/**8b**	e.r.[b] (−)-**7b**/(+)-**7b**	e.r.[b] (+)-**8b**/(−)-**8b**
1[c]	$[Rh_2(OOct)_4]$	1:1	–	–
2	$[Rh_2\{(R)\text{-dosp}\}_4]$	1:1	12:88	88:12
3	$[Rh_2\{(S)\text{-dosp}\}_4]$	1:1	89:11	15:85

[a] Determined by ^{1}H NMR spectroscopy. [b] Determined on samples of **19** and **20** by HPLC on a Chiralcel OD-H column; eluent: 2.0% 2-propanol in hexanes. [c] On multiple runs there was no enrichment within error (±1.5%). Oct = octonate.

Sarpong et. al. *ACIEE* **2009**, *48,* 2398.

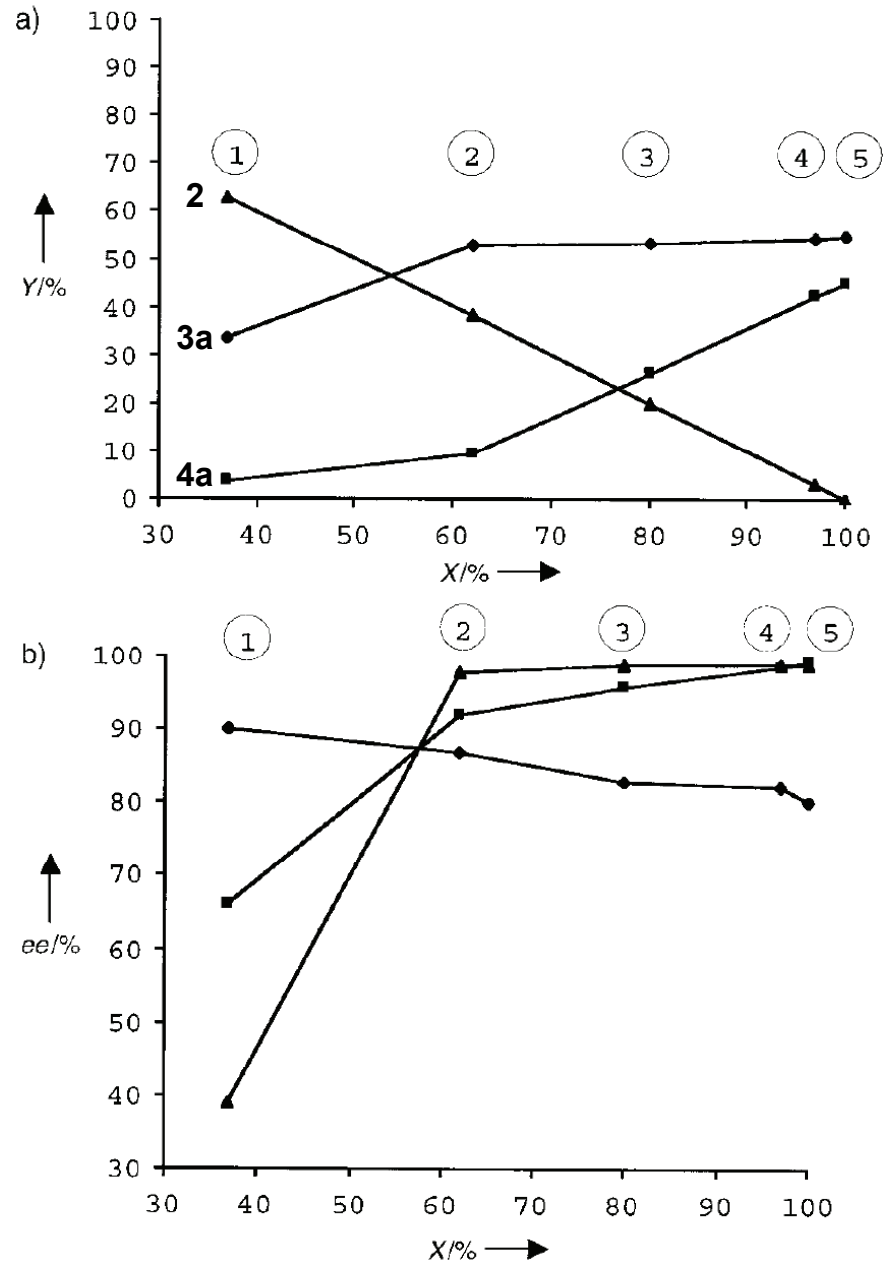
Apparent PKR



	1	2	3	4	5
t [min]	3	15	120	150	180
T [°C]	– 78	– 78	– 55	– 35	– 10

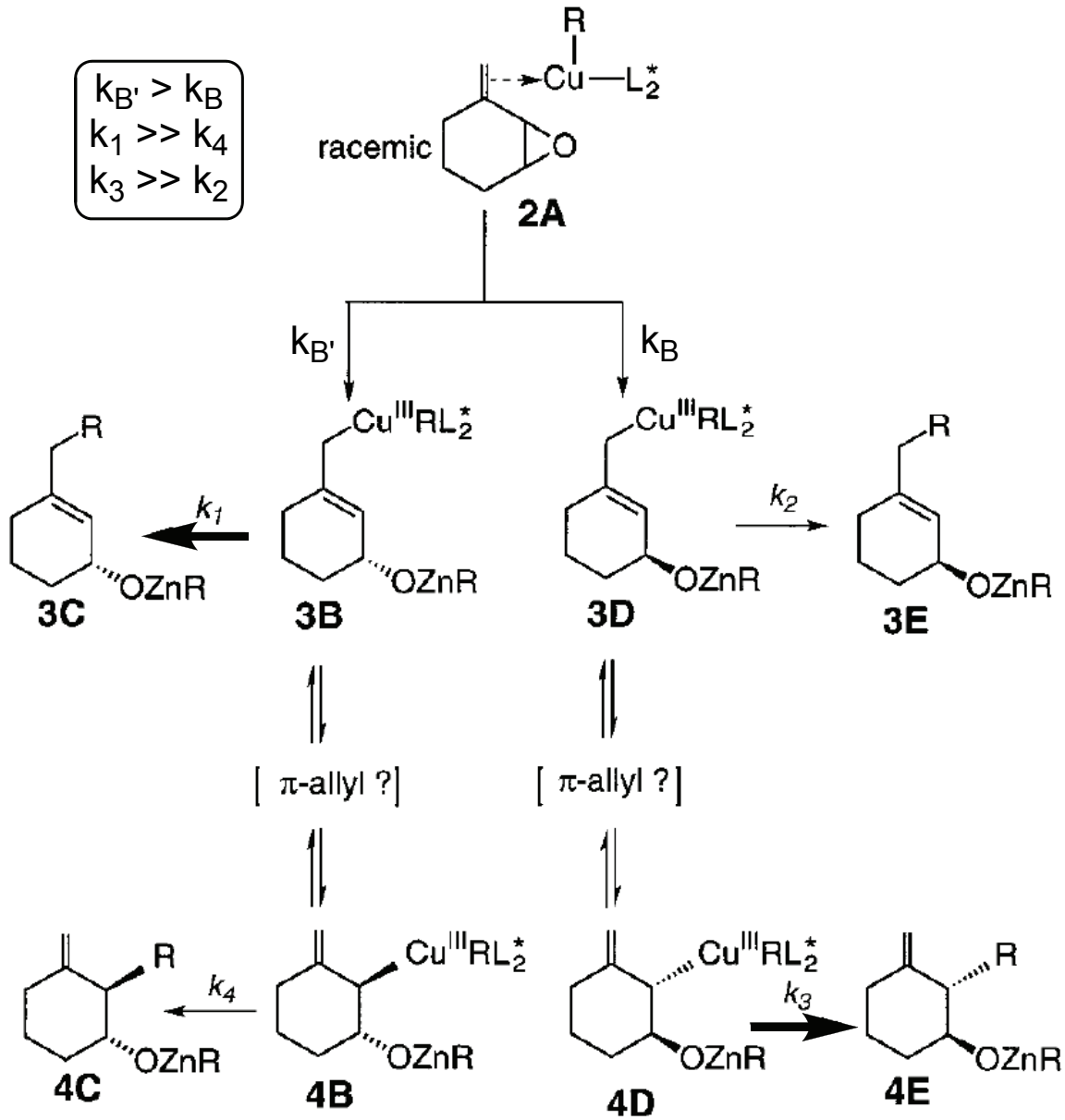
Figure 1. GC yield Y [%] (a) and enantiomeric excesses [%] (b) of compounds **2** (-▲-), **3a** (-◆-), **4a** (-■-) present in the reaction mixture at different conversions X of **2**. Values determined by GC using a β-cyclodextrin column (see Supporting Information).

Using *rac*-**1** gave S_N2':S_N2 = 98:2



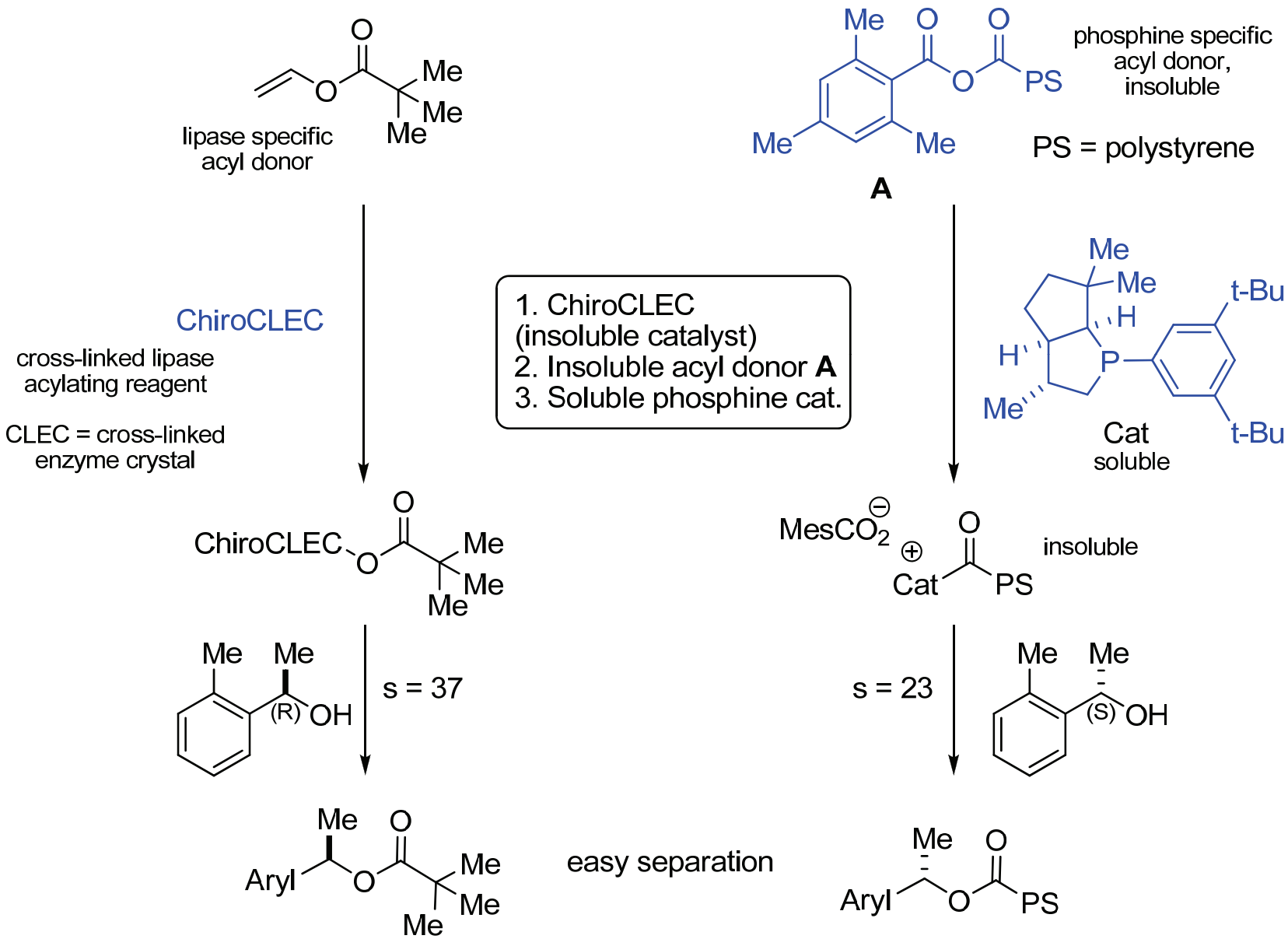
Feringa et. al. *ACIEE* **2001**, *40,* 930.

A Hypothesis for Apparent PKR



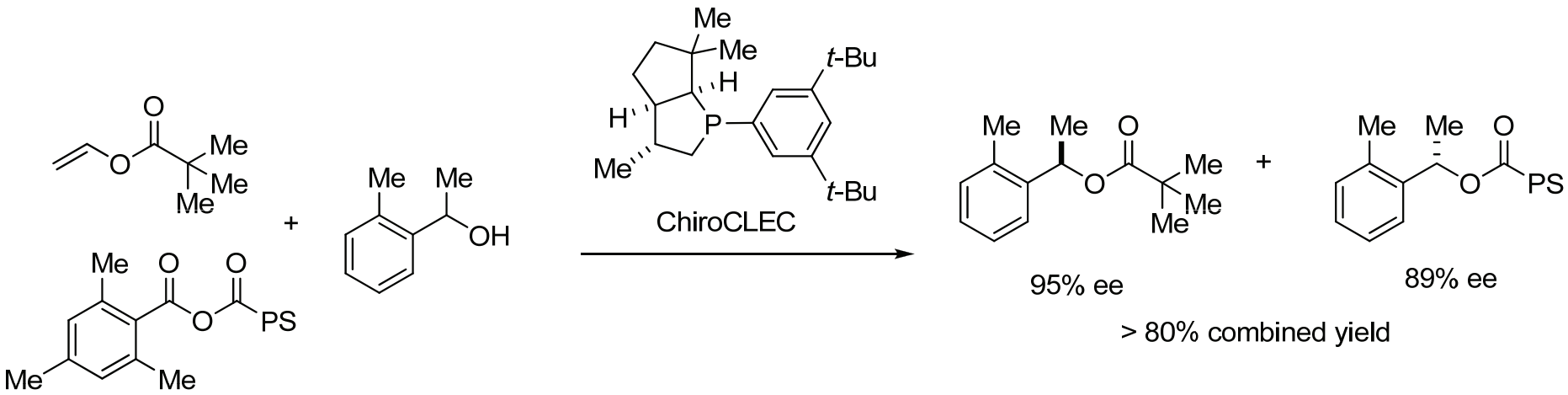
Feringa et. al. *ACIEE* **2001**, *40,* 930.

Using Two Catalysts in a Three-Phase System



Vedejs, E.; Rozners, E. *J. Am. Chem. Soc.* **2001**, *123*, 2428.

Using Two Catalysts in a Three-Phase System



Calculation based on s = 23

Conversion (%)	SM ee (%)	Max. yield (%)	Product ee (%)	Max. yield (%)
50	81	50	81	50
54	89	46	77	54
56	94	44	74	56

Vedejs, E.; Rozners, E. *J. Am. Chem. Soc.* **2001**, *123,* 2428.

Summary

"Pseudo" Stereodivergent
Stoichiometric Resolving Agent

Quasienantiomeric Nucleophiles
(Fox)

Quasienantiomeric Electrophiles
(Vedejs)

PKR

Biological or Enzymatic Approach

Chiral Catalyst + (Reagent)

Chemodivergent
(Tanaka)
(Doyle)
(Davies)
One of the two products can be achiral

Regiodivergent
(Lautens)
(Fu)
(Studer)

Stereodivergent
(Sarpong)

Summary

- PKR minimizes the built-up of the slower reacting enantiomer.

- The s factor can be significantly less to achieve comparable results to KR.

- If s factor is greater than 125, it is not worthwhile to perform a PKR.

- Rational design of a PKR is very challenging.

- Discovery of a PKR depends on careful analysis of the products.

- For an ideal PKR, the chiral catalyst should have complete control for the Regio- or Stereoselelctivity over substrate control.