

**IS IT POSSIBLE TO EVALUATE CHIRAL AUXILIARIES
FROM THEIR RACEMIC MIXTURES ?**

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VARIOUS USES OF CHIRAL AUXILIARIES

ASYMMETRIC SYNTHESIS

DIASTEREOSELECTIVE

substrate ---- chiral auxiliary

Stoichiometric *

ENANTIOSELECTIVE

achiral substrate $\left\{ \begin{array}{l} \text{reagent} \text{ ----- chiral auxiliary} \\ \text{catalyst} \text{ ----- chiral auxiliary} \end{array} \right.$

Stoichiometric
Catalytic

KINETIC RESOLUTION

reagent ----- chiral auxiliary
catalyst ----- chiral auxiliary

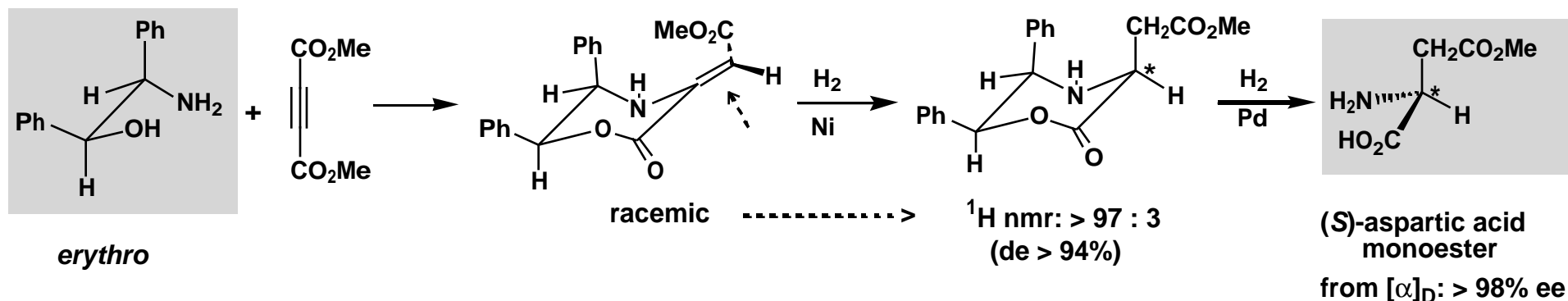
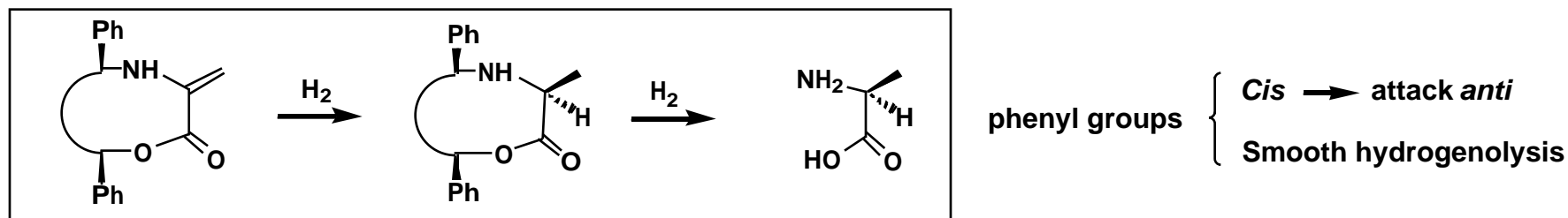
Stoichiometric *
Catalytic *

THE EVALUATION OF CHIRAL AUXILIARIES FROM THEIR RACEMIC MIXTURES

AUXILIARY FIXED TO THE SUBSTRATE

The diastereomeric excess (*de*) of the intermediate is equal to the enantiomeric excess of the product. With a racemic auxiliary *de* is unchanged, while the product becomes racemic.

Example : an early strategy of aminoacid synthesis



H.B. Kagan et al, *Tetrahedron Lett.*, 1968, 5681.

STUDY OF RACEMIC CATALYSTS

SOME STRATEGIES : chiral additives

Chiral poisoning

J. Brown, J. Faller

Activation-deactivation

K. Mikami

**IS IT POSSIBLE TO EVALUATE A CATALYST FROM
ITS RACEMIC MIXTURE ?**

H. KAGAN, F. LAGASSE, M. TSUKAMOTO

Université Paris-Sud, Orsay

C. WELCH

Merck Co, Rahway

***J. Am. Chem. Soc.*, 2003, 125, 7490**

ENANTIOSELECTIVE CATALYTIC REACTIONS

Use of a substrate with two , or more , prochiral centers



Measurement of a diastereoselectivity



Evaluation of the enantioselectivity

Similarity with some cases of isotactic polymerization

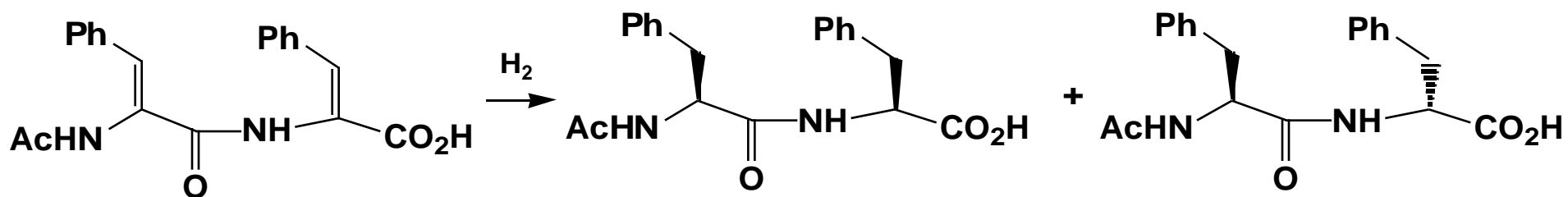
**Sequential asymmetric reactions on a substrate with two prochiral centers
with an enantiopure catalyst**

Some examples on C_1 and C_2 symmetric substrates

Product distribution

C₁-SYMMETRIC SUBSTRATES

One early example :



L* = (S,S)-diop 60% ee (S,S) 55 : 45 85% ee (S,R)

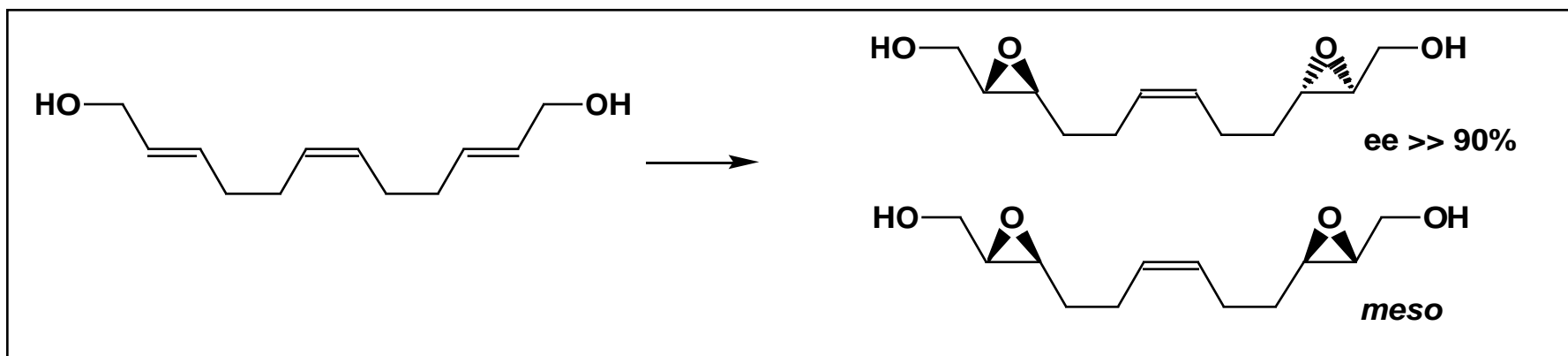
Catalyst: RhCIL*

L* = (R,R)-dipamp >95% ee (S,S) 98 : 2

J.-C. Poulin, H. B. Kagan , *J. C. S. Chem. Commun.* 1982, 1268

J.-C. Poulin, D. Meyer, H. B. Kagan , *C. R. Acad. Sci. Ser.C*, 291, 1980, 69

**CREATION OF TWO INDEPENDENT STEREOGENIC CENTERS
USE OF A DOUBLE SHARPLESS EPOXIDATION**



The distribution of isomers which results from a series of sequential chemical processes, each of which can occur with generation of 2 isomers, can be represented as the expression of the polynomial $(A_1 + B_1)(A_2 + B_2) \dots (A_n + B_n)$ where $A_i : B_i$ is the ratio of major / minor isomer for the i th process.

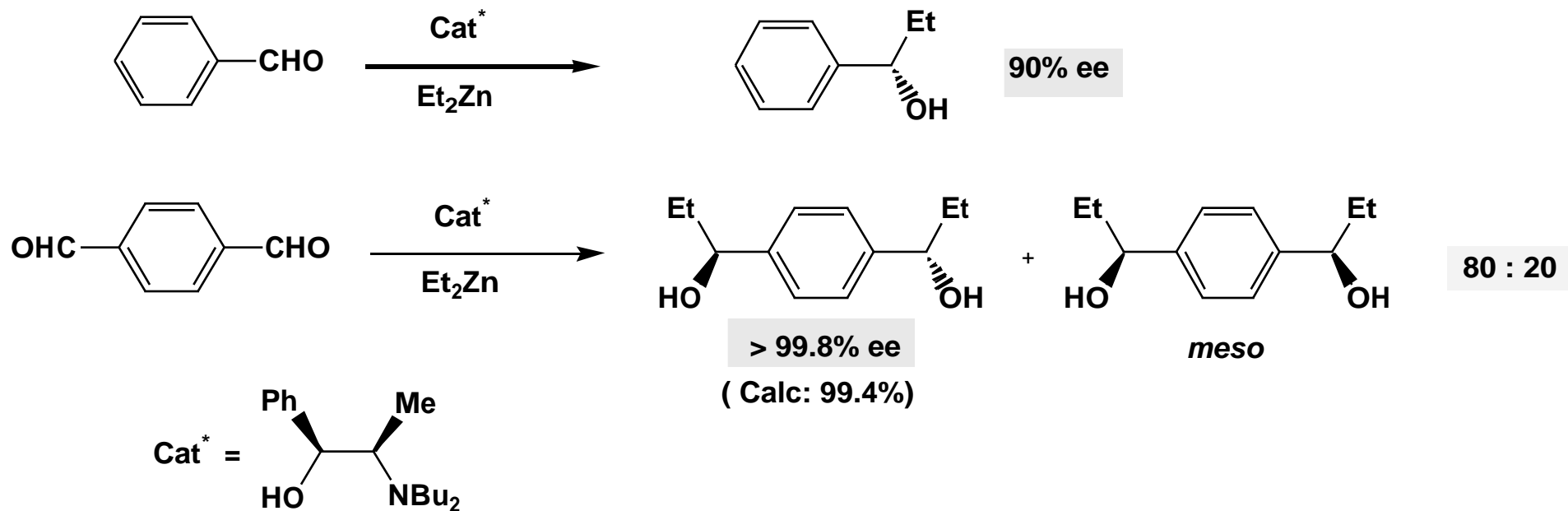
Simple AE with 90% ee (19 : 1)

Double AE with $(A_1 : B_1) = (A_2 : B_2) = 19 : 1 \rightarrow 361 : 38 : 1$

chiral diepoxide: 361: 1 or 99.4% ee

T. R. Hoye et al., *J. Am. Chem. Soc.*, 1985, 107, 5312

DOUBLE ORGANOZINC ADDITION



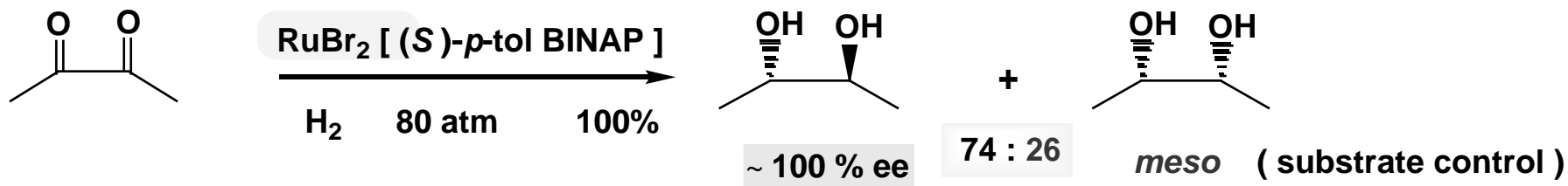
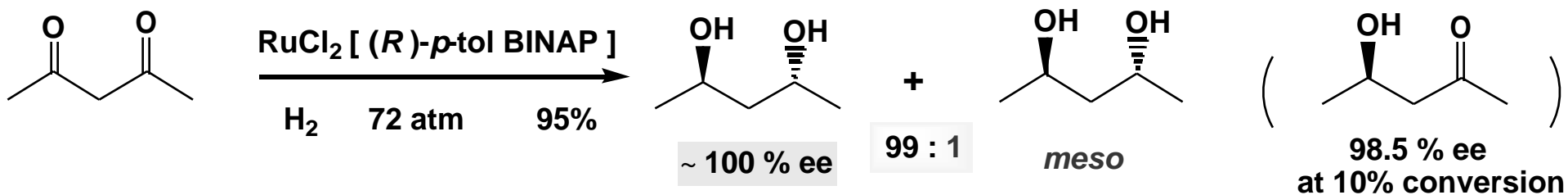
Relationship between ee of monofunctional and bifunctional substrates, calculated for equivalent stereoselectivities at each step.

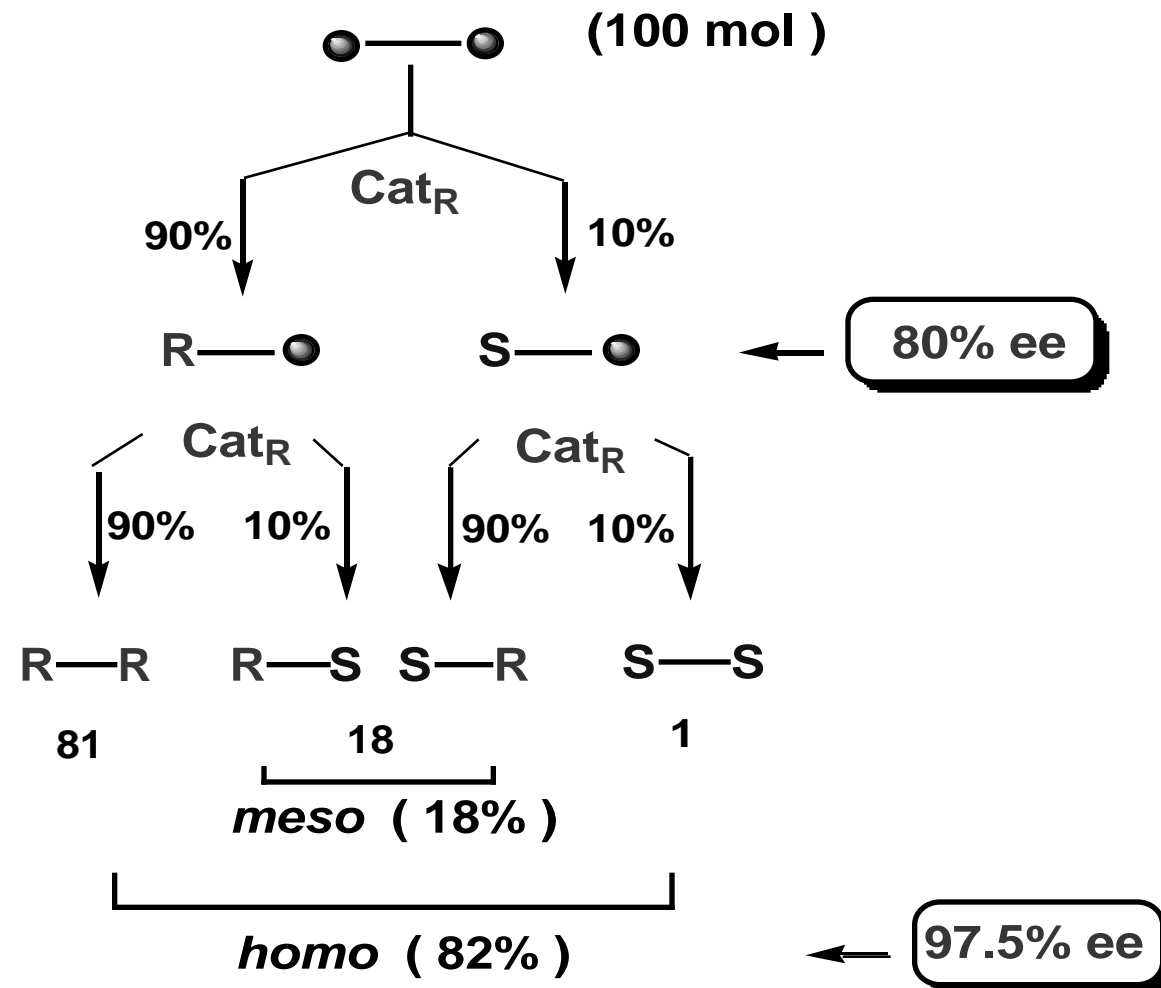
K. Soai et al., *JCS Chem. Commun.*, 1992, 106

REDUCTION OF DIKETONES

Hydrogenation of functionalized ketones catalyzed by Ru / BINAP complexes

R. Noyori, M. Kitamura et al., *J. Am. Chem. Soc.*, 1988, 110, 629

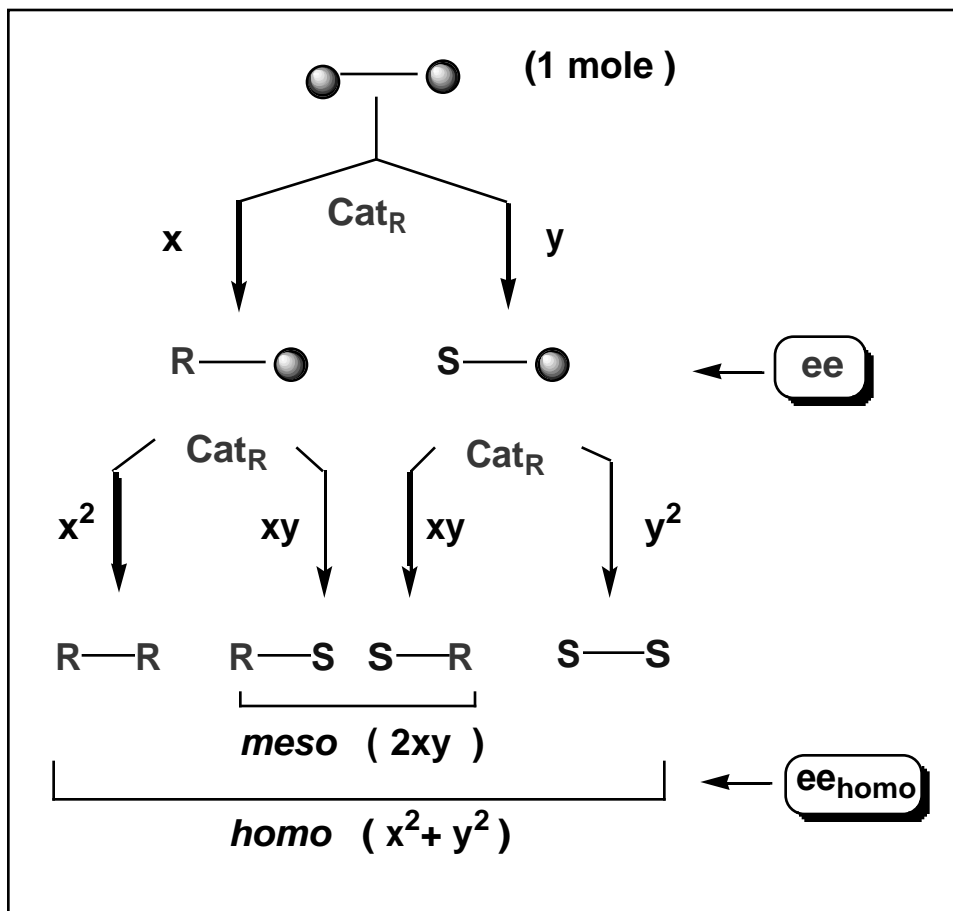




ee (homo) > initial ee

The major diastereomer has an amplified ee

Complete conversion of C₂-symmetric substrates with identical stereocontrol at each step of the tandem reaction



$$\begin{cases} \text{each stereofacial control : } x / y \\ x + y = 1 \end{cases}$$



$$\begin{aligned} (R - R) / (S - S) &= (x / y)^2 = (R / S)^2 \\ (homo) / (meso) &= 2xy / (x^2 + y^2) \end{aligned}$$

$$\begin{cases} R / S = \frac{1 + ee}{1 - ee} \\ de_{homo} = \frac{homo - meso}{homo + meso} \end{cases}$$



$$ee_{homo} = \frac{2 ee}{1 + ee^2}$$

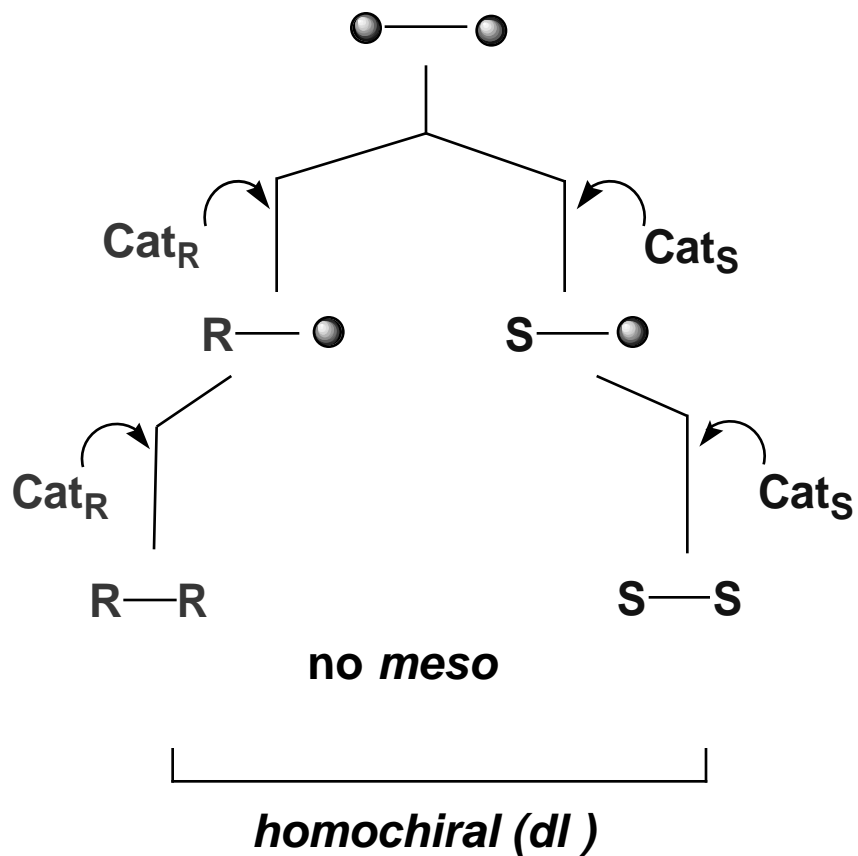
$$ee^2 = de_{homo}$$

$$ee (homo) > \text{initial } ee$$

The *homo* / *meso* ratio is directly correlated to the enantioselectivity at the first stage:
small amount of *meso* product is related to a high enantioselectivity of the catalyst

Two consecutive reactions with *fully enantioselective* catalysts

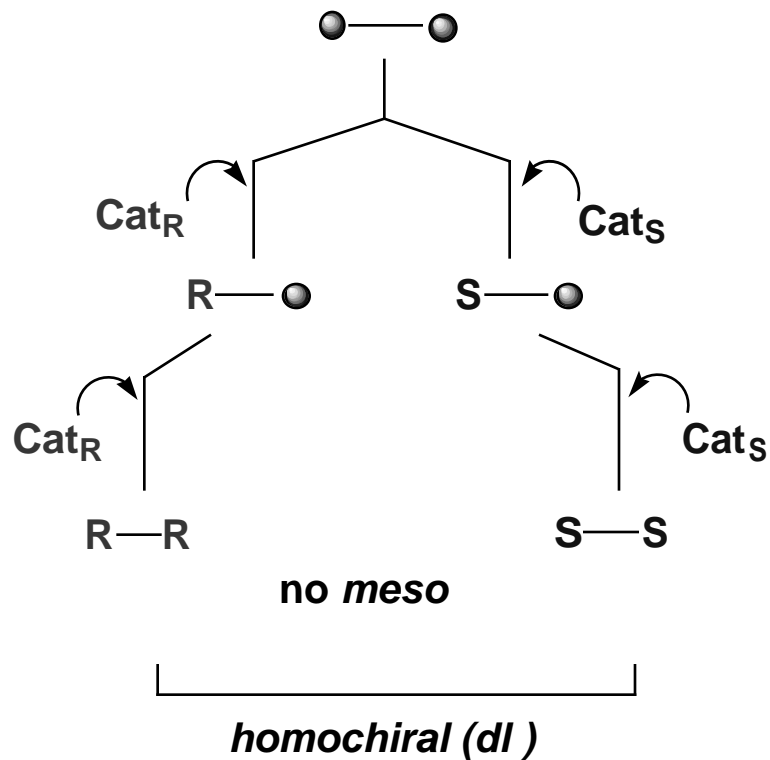
(racemic catalyst : $\text{Cat}_R + \text{Cat}_S$)



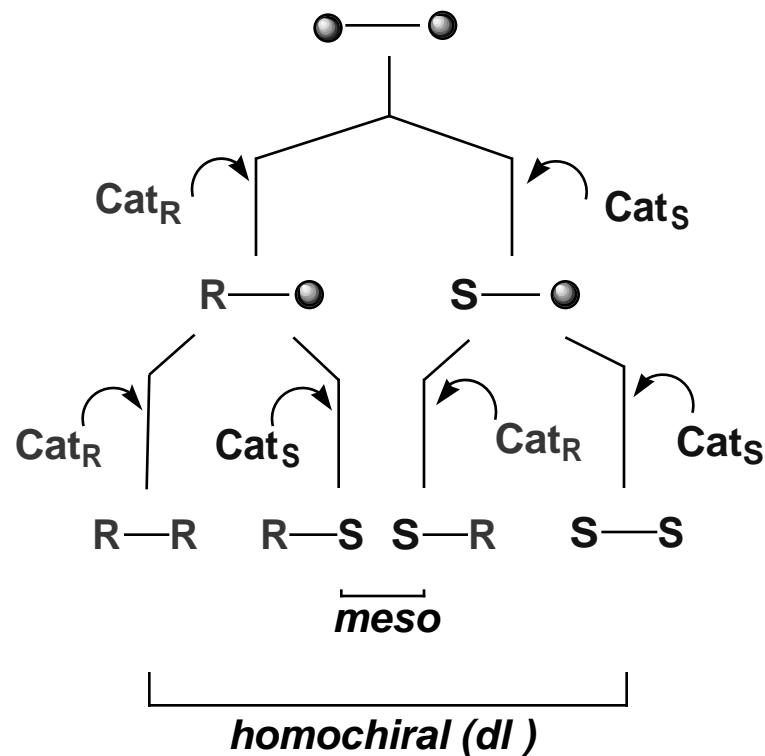
The same catalyst (Cat_R or Cat_S) reacts twice

Two consecutive reactions with *fully enantioselective* catalysts

(racemic catalyst : $\text{Cat}_R + \text{Cat}_S$)



The same catalyst (Cat_R or Cat_S) reacts twice



The bifunctional substrate reacts also with two enantiomeric catalysts

--> *homo (dl) / meso* = 1 / 1

INFORMATIONS ON EACH ENANTIOMER OF A RACEMIC CATALYST

SOME CONDITIONS

Reaction

Double reaction on a molecule of the substrate by the same molecule of the catalyst

Measurement of the diastereoselectivity de_{homo}

→ enantioselectivity ee_1 of the first step

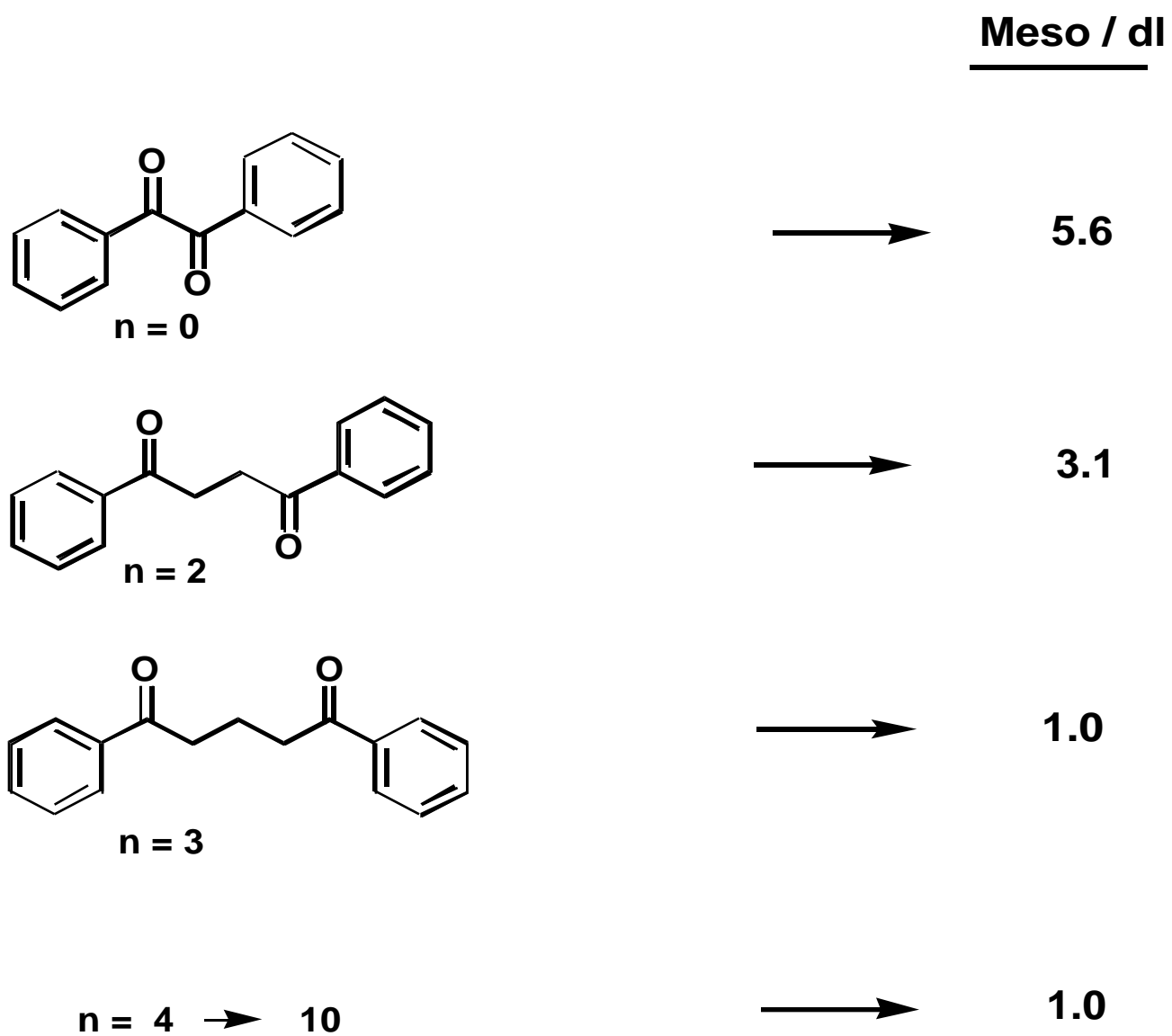
Substrate

$$ee_1^2 = de_{\text{homo}}$$

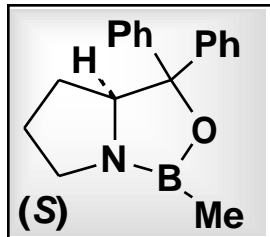
Two equivalent prochiral units, not too far from each other, for avoiding escape of the catalyst

Two prochiral units, not too close to each other, for avoiding substrate control at the second step

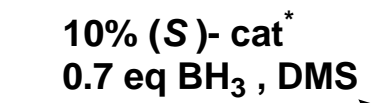
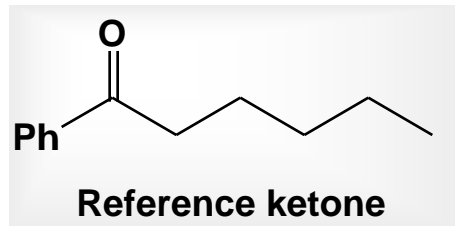
Diastereoselectivity of reduction by 2.5 BH₃, DMS / toluene



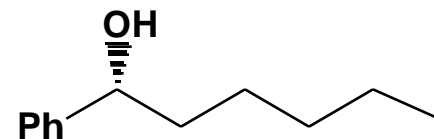
ASYMMETRIC REDUCTION OF A DIKETONE



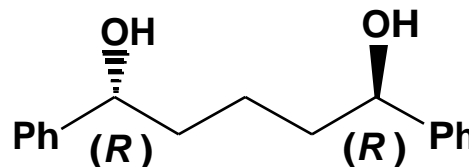
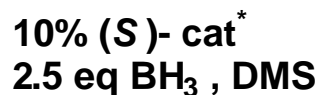
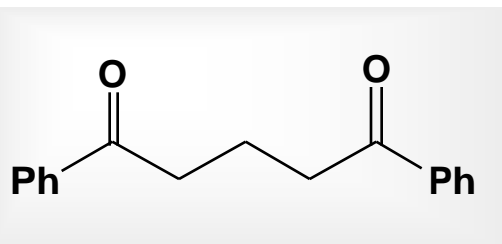
Catalyst



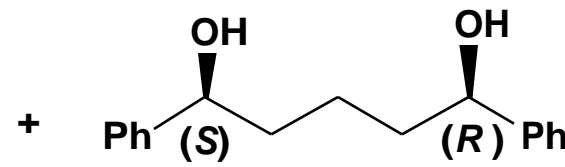
THF, 0°C
THF, 66°C
toluene, 110°C



87.5% ee (R)
83.5% ee (R)
86.0% ee (R)



homo



meso

THF, 0°C

$ee_{homo} = 99.5\%$ ee (calc. 99.4)
 ee_1 (calc.)= 90.0%

$de_{homo} = 80.6\%$

THF, 66°C

$ee_{homo} = 99.5\%$ ee (calc. 99.0)
 ee_1 (calc.)= 85.0%

$de_{homo} = 72.0\%$

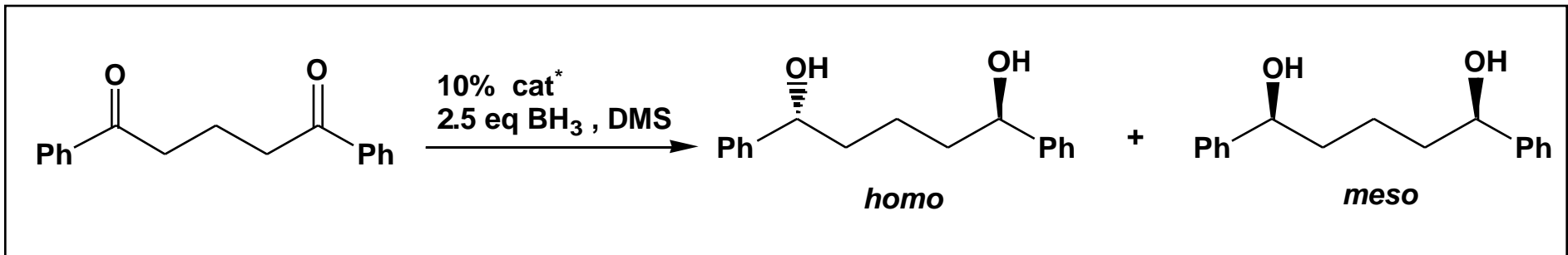
toluene, 110°C

$ee_{homo} = 99.5\%$ ee (calc. 99.6)
 ee_1 (calc.)= 90.5%

$de_{homo} = 82.0\%$

Calculated values of ee_{homo} and ee_1 using de_{homo} : good agreement with experimental values of ee_{homo} ,
calculated values of ee_1 are slightly higher than ees in hexaphenone reduction.

RACEMIC CATALYST

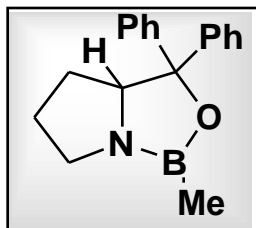


(*S*)- catalyst

[toluene, 110°C	$d_{\text{homo}} = 82.0\%$	$ee_{\text{homo}} = 99.5\% ee$
	THF, 66°C	$d_{\text{homo}} = 72.0\%$	$ee_{\text{homo}} = 99.4\% ee$

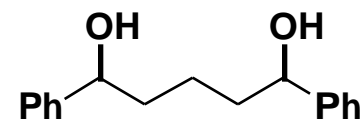
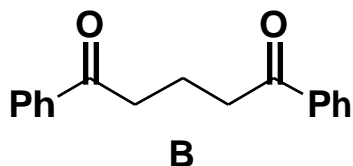
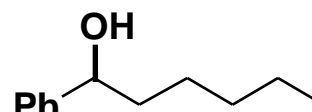
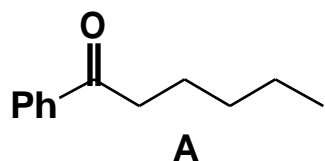
racemic catalyst

[toluene, 110°C	$d_{\text{homo}} = 67.8\%$	$ee_1 \text{ (calc.)} = 82.3\% [86.0]$
	THF, 66°C	$d_{\text{homo}} = 82.7\%$	$ee_1 \text{ (calc.)} = 91.0\% [83.5]$



Catalyst

The diastereoselectivity is retained with the racemic catalyst, allowing to calculate approximate value of ee_1



[Ru (*p*-cymene) ephedrine] Cl

i-PrOH, 45°C, 1 h

(+)-ephedrine 100% ee

monoketone A \longrightarrow 68 % ee (*R*)

diketone B \longrightarrow diol 96 % ee (*R*)
 ee₁ = 76% (calc.)

de_{homo} = 58%

racemic ephedrine

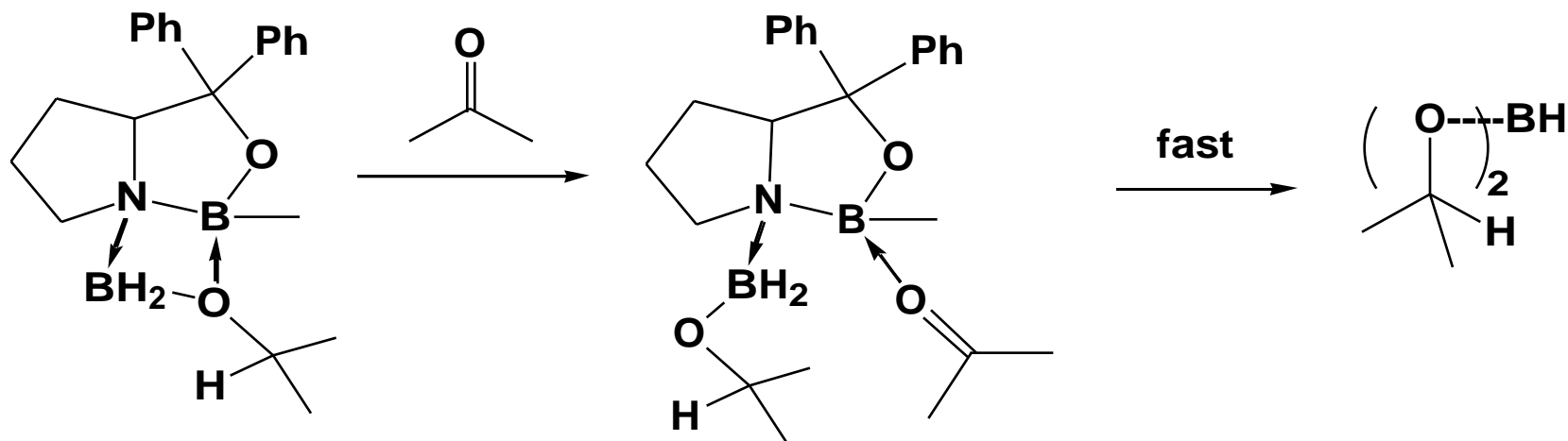
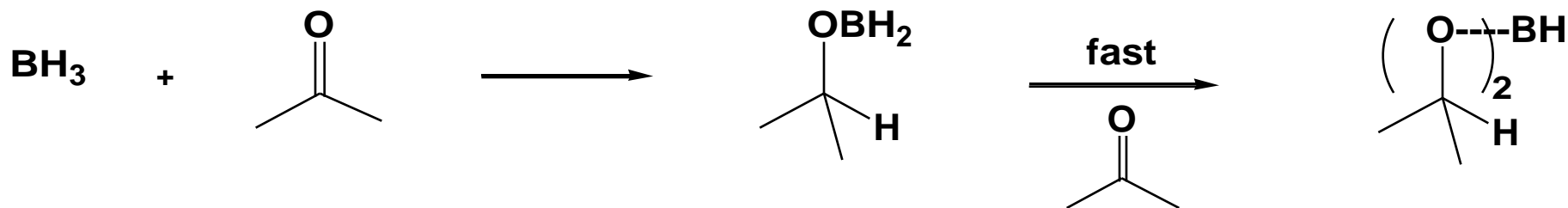
diketone B \longrightarrow diol 0 % ee

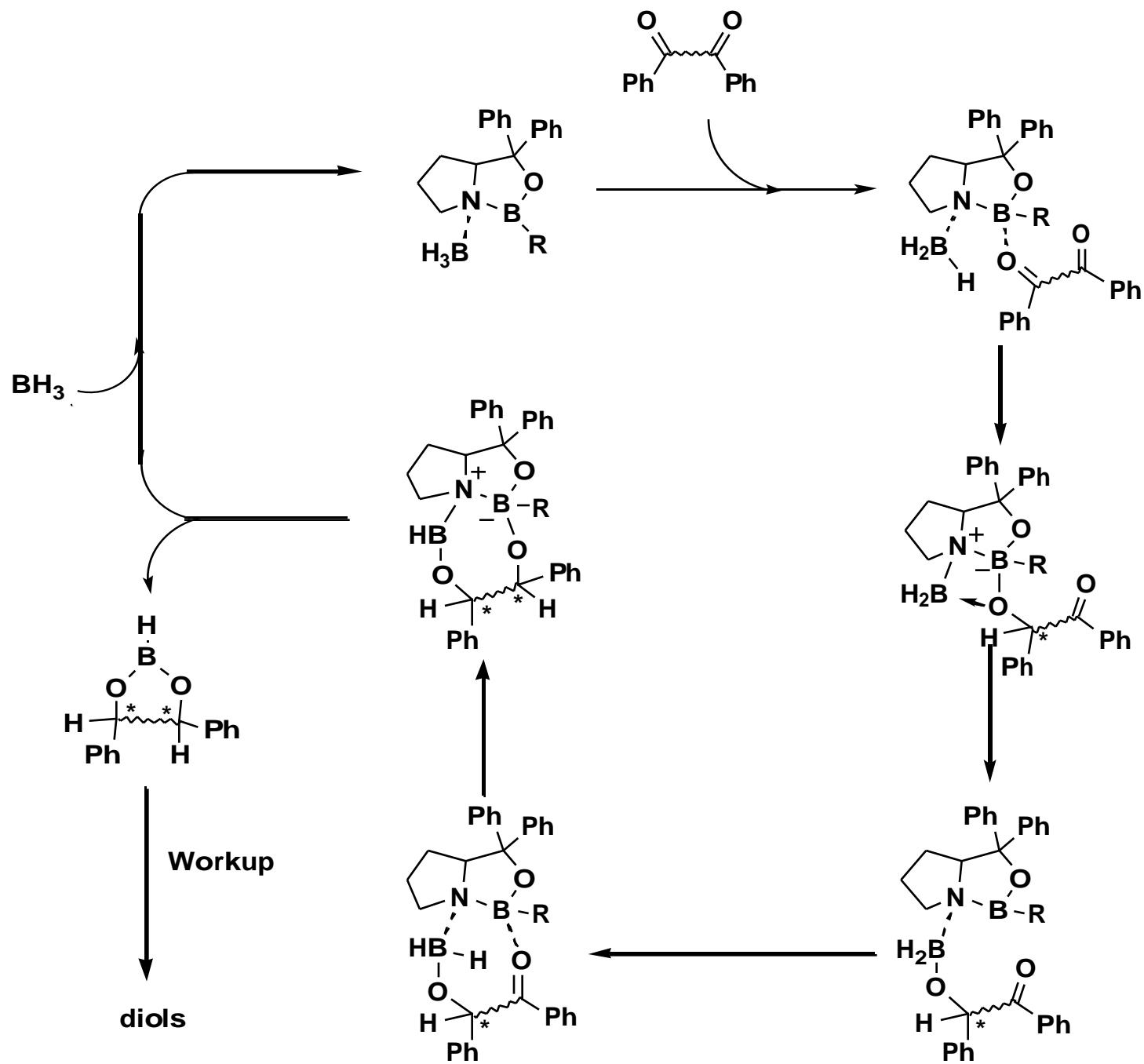
de_{homo} = 0%

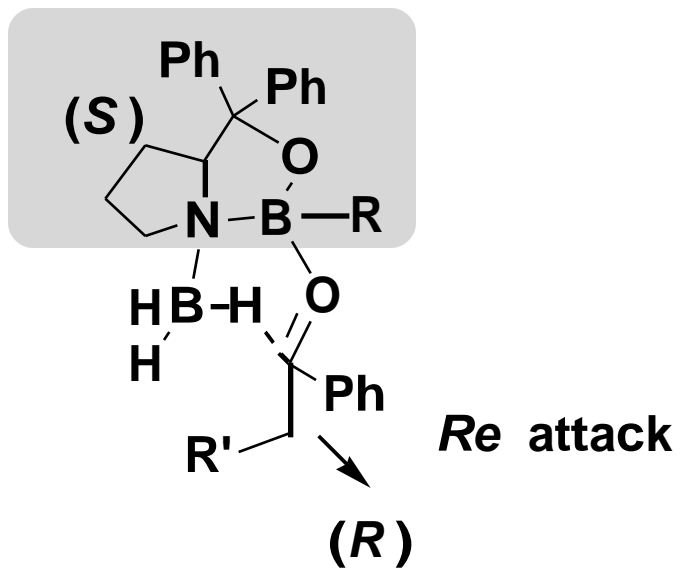
Conclusion:

With the racemic catalyst there is a scrambling of the enantiomeric catalysts at the second stage of the process. Similar results with the system RhCl(diop) / Ph₂SiH₂

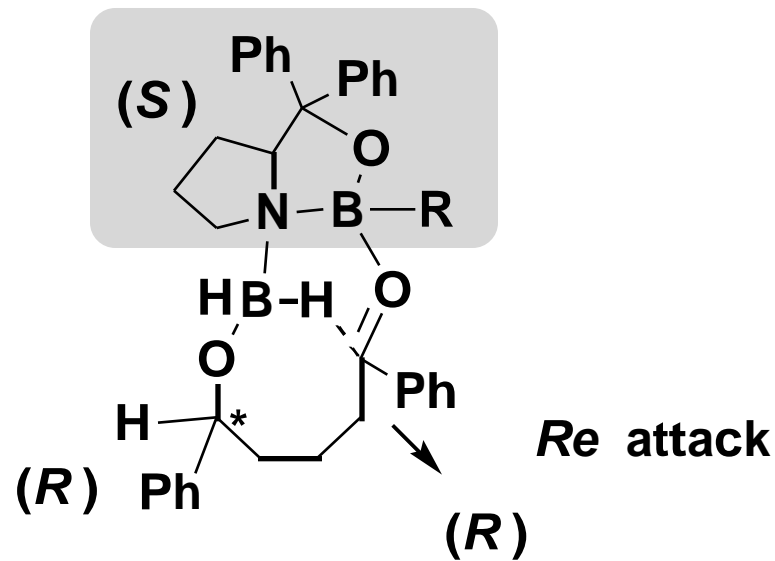
It is known that 2 H of BH_3 are delivered in ketone reductions
Usual stoichiometry: 0.7 eq BH_3 / carbonyl



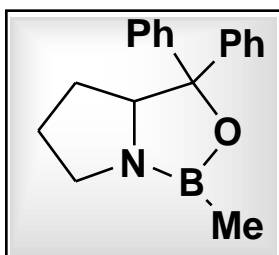




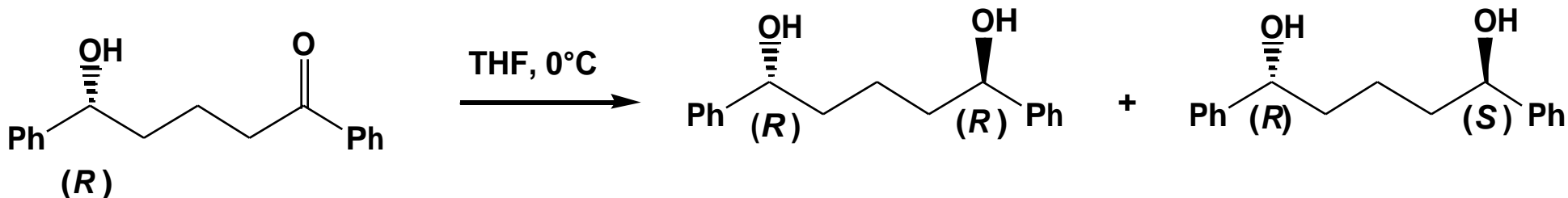
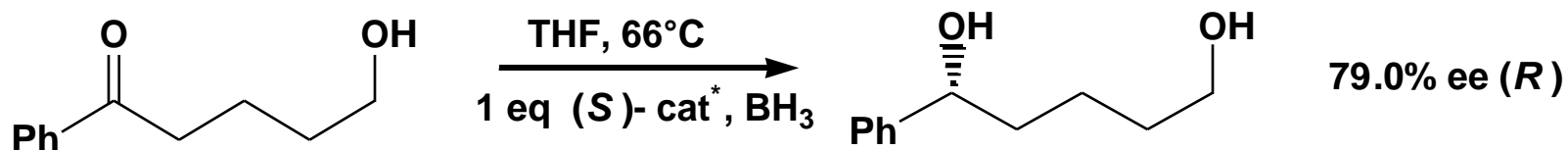
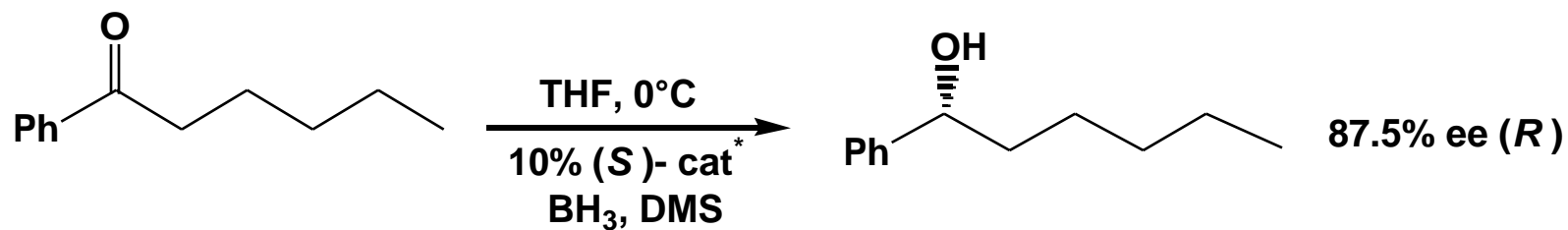
catalyst control



catalyst control ?



Catalyst



BH₃, DMS

50 : 50 (de_{homo} = 0%)

1 eq (S)-cat^{*}, BH₃

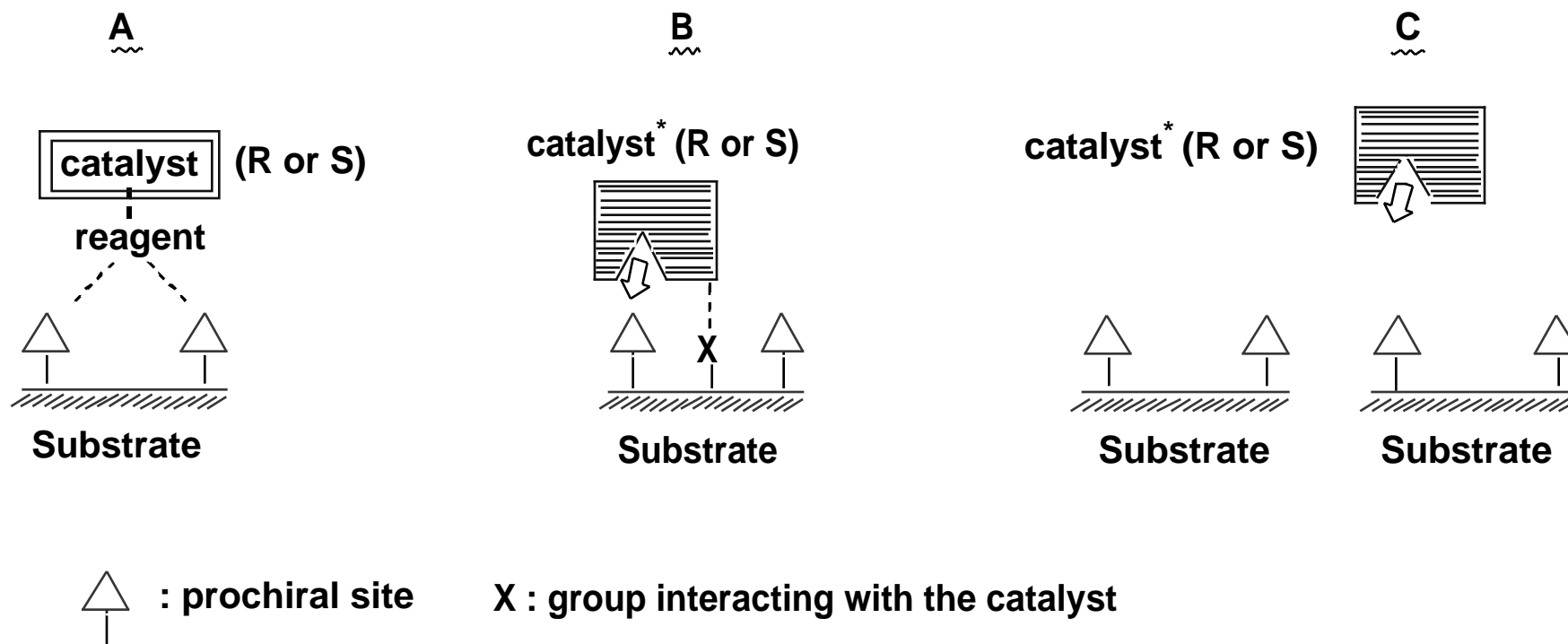
95 : 5 (de_{homo} = 90%)

1 eq (R)-cat^{*}, BH₃

5 : 95 (de_{meso} = 90%)

Results in agreement with a catalyst control in the second step of the diketone reduction, in an intramolecular process

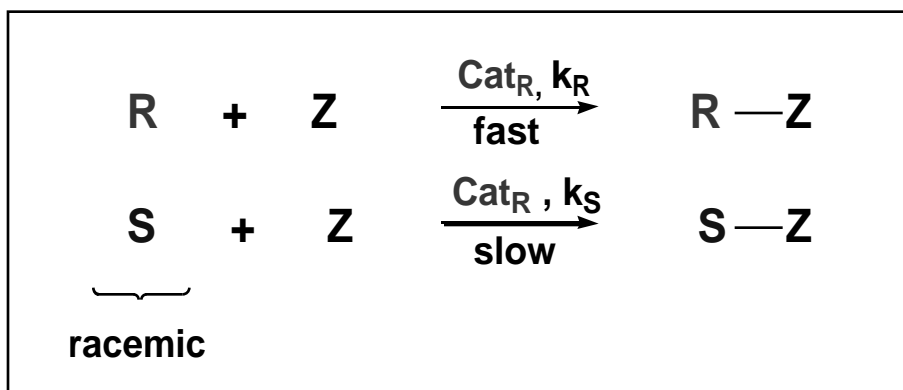
STRATEGIES TO RETAIN THE CATALYST IN THE VICINITY OF THE SUBSTRATE



In **A** or **B** : an interacting group retains the catalyst

In **C** : one enantiomer of the catalyst is surrounded by an assembly of substrates : microcavity, solid phase etc ?

THE EVALUATION OF RACEMIC AUXILIARIES FOR KINETIC RESOLUTION



knowledge of *er* and conversion

$$\longrightarrow s = k_{\text{rel}} = k_R / k_S$$

Racemic catalyst



Use of a partially resolved substrate:

G. Lloyd-Jones et al., *Angewandte Chem. Int. Ed.*, 2001, 40, 4289.

STUDY OF RACEMIC AUXILIARIES

Diastereoselective syntheses

measurement of de

Enantioselective syntheses (catalytic)

substrate with two remote prochiral centers, measurement of de

$de_{homo} = 0$ → no enantioselectivity for the catalyst, or catalyst scrambling

$de_{homo} \neq 0$ → calculation of enantioselectivity ee_1

Kinetic resolution (catalytic) : partially resolved substrate

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