

Considerations in Kinetic Resolution Reactions

----- the design of chiral DMAP analogues and the kinetic resolution of secondary alcohols

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- ⦿ The design of chiral DMAP analogues and their kinetic resolution of secondary alcohols
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Introductions

Methods to prepare an enantioenriched compound

Asymmetric
synthesis

Resolution

Chiral
pool

Use of enantiopure starting materials provided by nature

Separation of enantiomers by chemical or physical means

Preparation from achiral precursors using chiral reagents or catalysts

Practical considerations in the three methods:

◎ Chiral pool:

Unfortunately, the range of compounds provided by nature is limited with respect to structure and stereochemistry. (limited)

◎ Resolution:

Except in those cases where both enantiomers can be employed productively, resolution have a maximum yield of 50% based on racemic starting materials. (inefficiency)

◎ Asymmetric synthesis:

With a lot of advantages in synthesizing asymmetric products, it's still much easier and less expensive to access racemates in a great number of cases. (racemic products in most cases)

D. Wistuba, V. Schurig. *J. Chromatogr. A* **2000**, 875, 255-276.

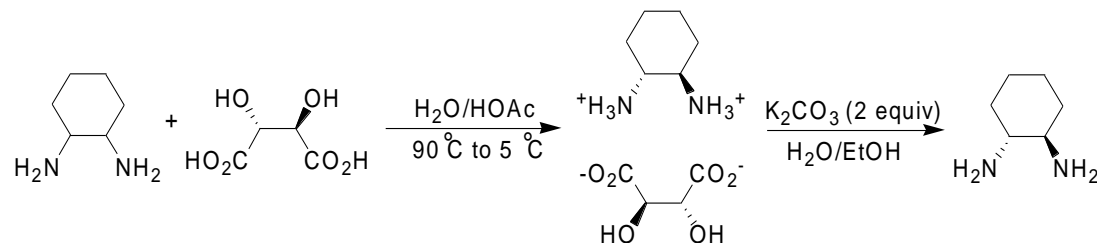
B. M. Trost, *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 259-281.

Classifications of resolutions

Classical resolutions

Involve the use of a stoichiometric amount of a chiral resolving agent.

Scheme 1. Classical resolution of trans-1,2-cyclohexanediamine



Chiral chromatography

Generally relies on the use of a chiral stationary phase to resolve enantiomers contained in a mobile phase

Kinetic resolution

Involves using a chiral catalyst or reagent to promote selective reaction of one enantiomer over the other giving a mixture of enantioenriched starting materials and product, and the desired component is isolated.

Scheme 2. catalytic kinetic resolution



J. Jacques, A. Collet, S. H. Wilen. *Enantiomers, Racemates and Resolutions*, Krieger, Malabar, FL, 1991.

J. F. Larrow, E. N. Jacobsen. *Org. Synth.* **1998**, 75, 1-11.

A. H. Hoveyda, M. T. Didiuk. *Curr. Org. Chem.* **1998**, 2, 537-574.

Theoretical considerations

Categories of kinetic resolution

A

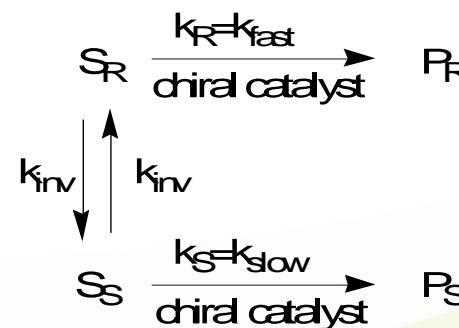
Standard kinetic resolution

B

Dynamic kinetic resolution

The substrate undergoes racemization at a rate greater than that of its transformation to product. (100% yield)

Scheme 3. Dynamic kinetic resolution



C

Parallel kinetic resolution

Enantiomers undergo reaction at comparable rates to give different products. (constant ee value)

Standard kinetic resolution

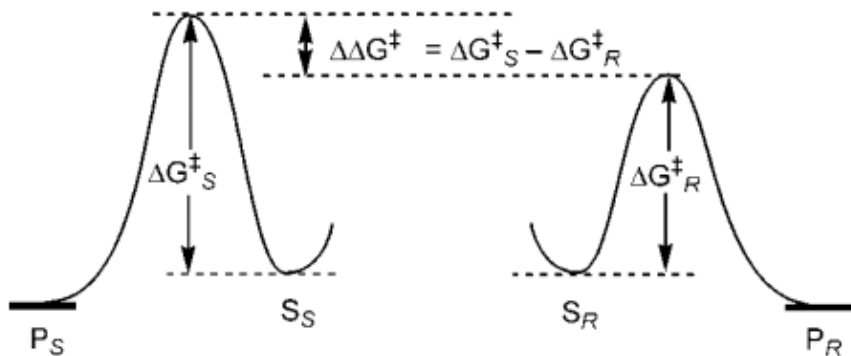
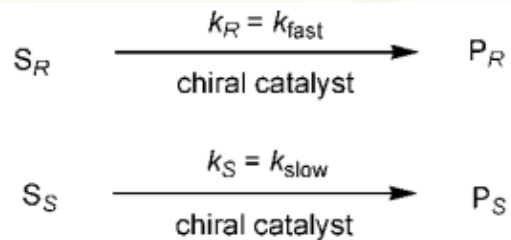


Figure 1. Relative rate constants in kinetic resolution

$$k_{\text{rel}} = s = k_{\text{fast}}/k_{\text{slow}} = e^{\Delta\Delta G^\ddagger/RT} \quad (1)$$

In kinetic resolutions, enantiomers of a racemic substrate (S) react at different rates to form a product (P) that may or may not be chiral.

In a catalytic kinetic resolution, the relative rates of reaction for the enantiomers, typically expressed as s or $k_{\text{rel}} = k_{\text{fast}}/k_{\text{slow}}$, are dictated by the magnitude of $\Delta\Delta G^\ddagger$ (though it's in the same manner with an enantioselective reaction of a prochiral substrate, there is still an important difference)

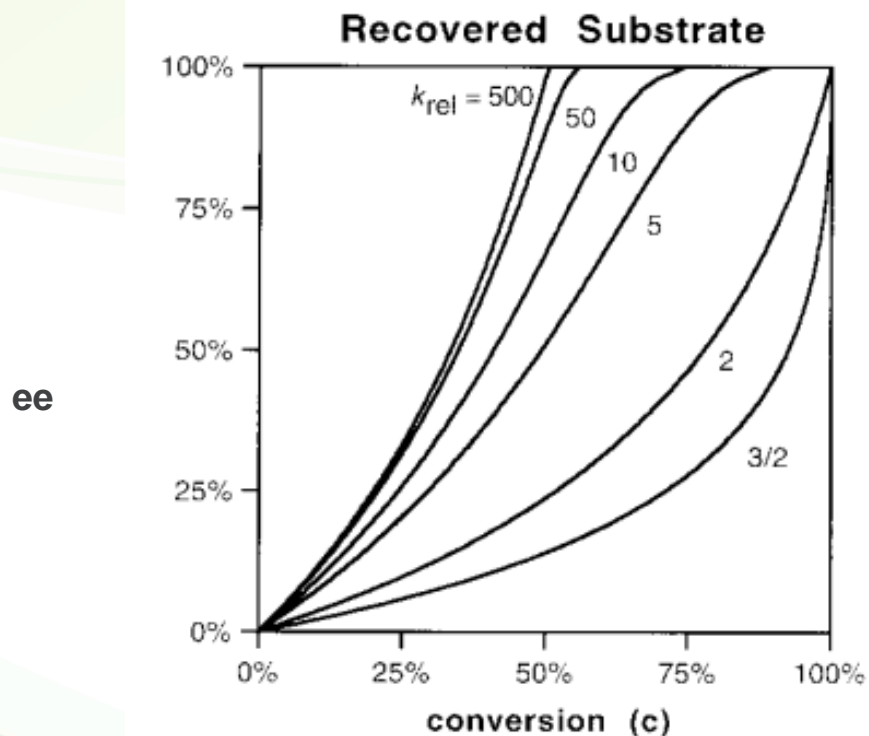


Figure 2a. plots of ee vs. conversion as a function of k_{rel} for recovered substrate

$$k_{rel} = \frac{\ln[(1-c)(1-ee)]}{\ln[(1-c)(1+ee)]} \quad (2)$$

The ee obtained in a kinetic resolution changes as a function of conversion. Even if the k_{rel} is not especially high, unreacted substrate can be recovered in high ee simply by carrying the reaction to high enough conversion.

Table 1. Representative k_{rel} and $\Delta\Delta G^\ddagger$ values, along with the conversions required to attain recovered substrates in 90, 98, and >99% ee

k_{rel}	$\Delta\Delta G^\ddagger$ (kcal/mol)	Conversion (%) required to attain:		
		90% ee	98% ee	>99% ee
1.5	0.24	99.9	99.99	>99.999
2	0.41	97.2	99.5	>99.7
5	0.95	74.8	84.0	>86.6
10	1.35	62.1	69.7	>72.1
50	2.31	50.4	54.0	>54.9
100	2.72	48.9	51.8	>52.4
500	3.66	47.7	50.0	>50.3

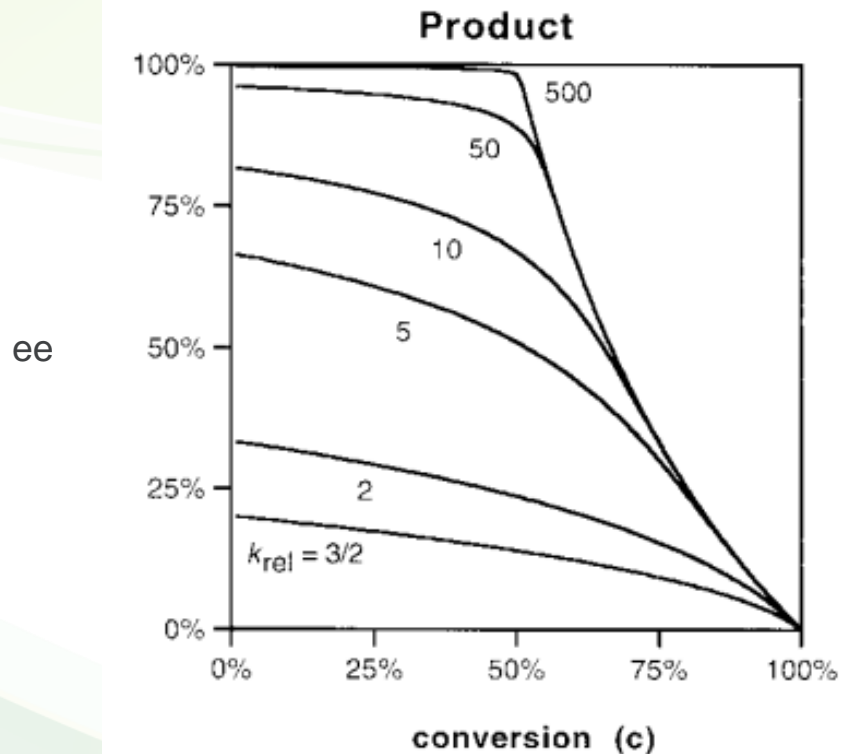


Figure 2b. plots of ee vs. conversion as a function of k_{rel} for product

$$k_{rel} = \frac{\ln[1-c(1+ee)]}{\ln[1-c(1-ee)]} \quad (3)$$

In contrast, high selectivity factors are necessary in order to obtain high ee product from kinetic resolution.

As reflected by the plot in Figure 2b, k_{rel} values in excess of 50 are generally required if product of high enantiomeric purity is to be obtained in useful yield.

$$k_{rel} = \frac{\ln[(1-c)(1-ee)]}{\ln[(1-c)(1+ee)]} \quad (2) \quad k_{rel} = \frac{\ln[1-c(1+ee)]}{\ln[1-c(1-ee)]} \quad (3)$$

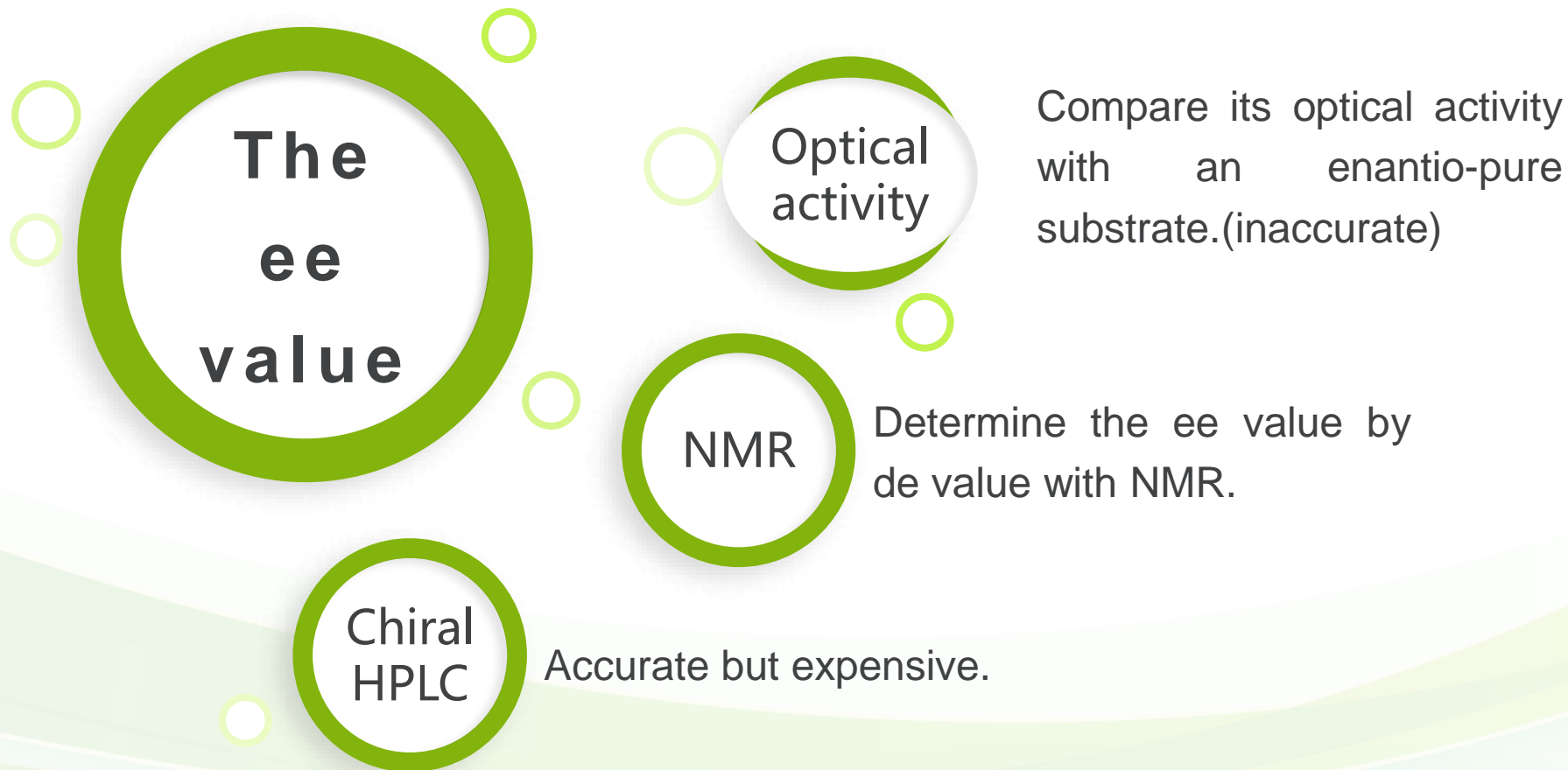
It is by no means a straightforward matter to determine k_{rel} values accurately using equation 2 and 3. And it is found that k_{rel} values calculated using equation 2 and 3 vary significantly with conversion.

Therefore, we often describe reactions in terms of recovered substrate or product yields and ee's.

T. O. Luukas, C. Girard, D. R. Fenwick, H. B. Kagan. *J. Am. Chem. Soc.* **1999**, *121*, 9299-9306.

D. W. Johnson Jr, D. A. Singleton. *J. Am. Chem. Soc.* **1999**, *121*, 9307-9312.

How to determine the ee value?



The design of chiral DMAP analogues

A basic principle to design a chiral catalyst:

A compound that possesses a mirror plane of symmetry is not chiral.

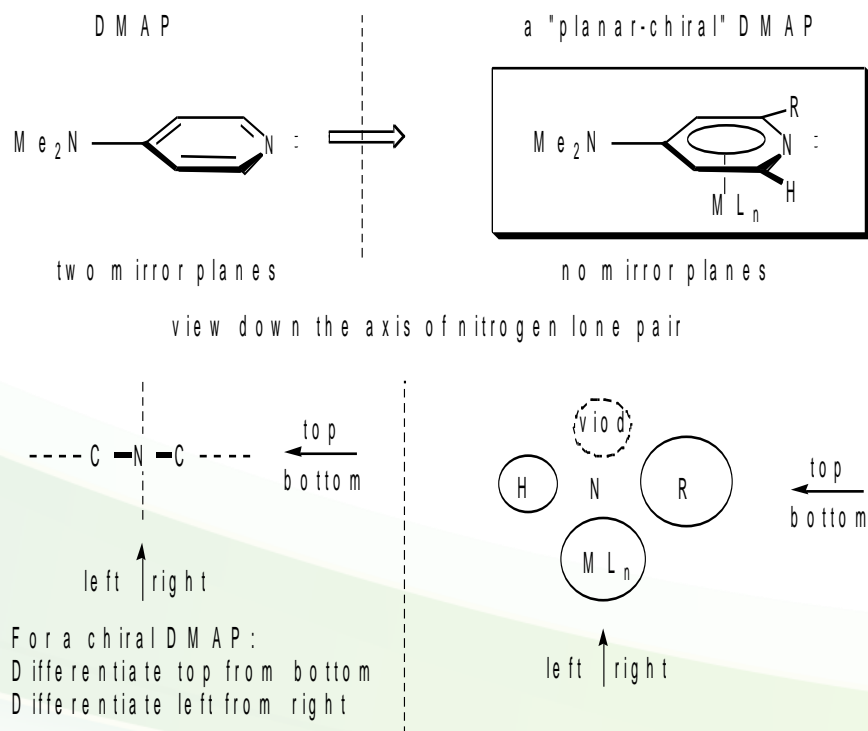


Figure 3. Design of a "planar-chiral" derivative of DMAP

Chirality that results from π complexation to a metal is commonly referred to as "planar chirality".

Considerations in choosing the metal fragment, ML_n :

1. It should be electron-rich, thereby enhancing the nucleophilicity of the catalyst;
2. Its steric environment should be "tunable";
3. It should lead to robust planar-chiral complexes, for maximum versatility and for ease of handling.

P. J. Reider, *Chimia*. **1997**, *51*, 306-308.

G. C. Fu. *Acc. Chem. Res.* **2000**, *33*, 412-420.

The design of chiral DMAP analogues

- On the basis of the first two criteria, the iron cyclopentadienyl group (FeCp' ; Cp' is a cyclopentadienyl-derived ligand) appeared to be a suitable choice for ML_n .

Two modifications of the original design:

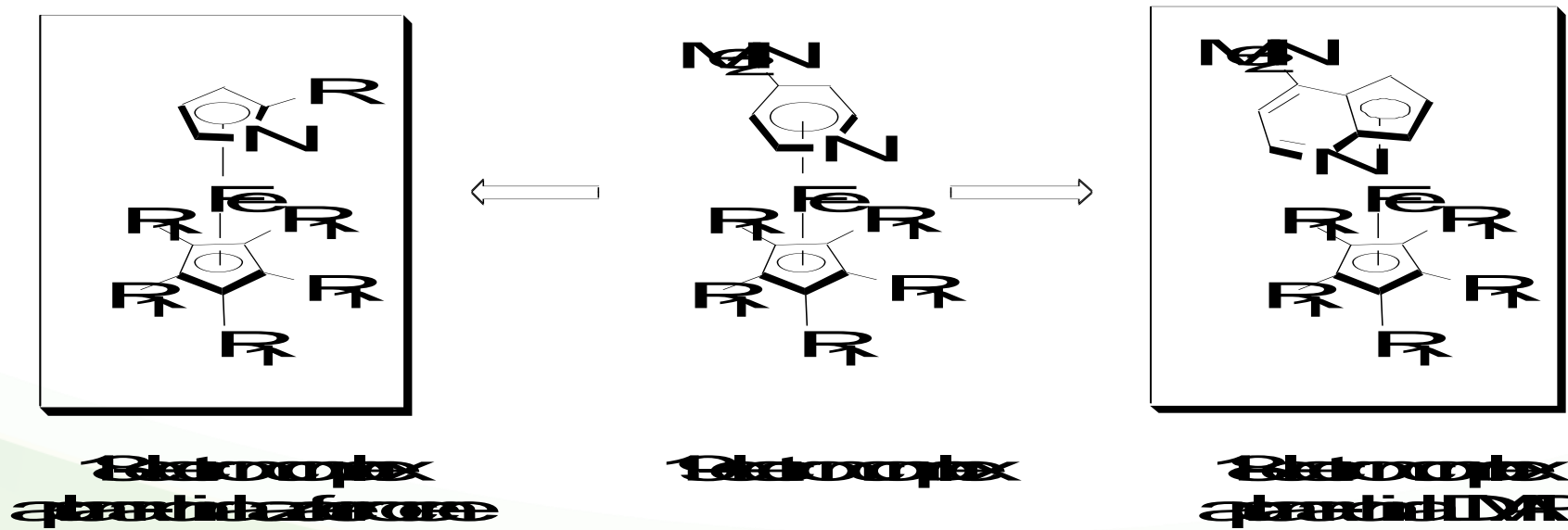


Figure 4. Eighteen-electron planar-chiral heterocycle complex

G. C. Fu, *Am. Chem. Soc.* **1998**, *120*, 7479-7483.

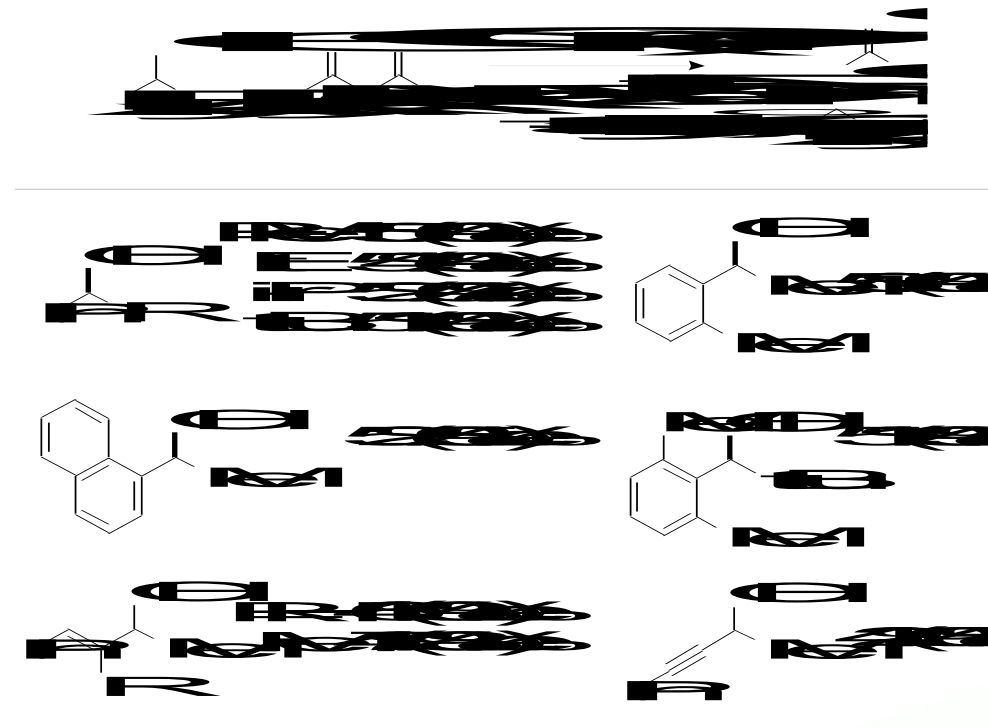
G. C. Fu, *Acc. Chem. Res.* **2000**, *33*, 412-420.

kinetic resolution of secondary alcohols (DMAP analogues)

Possible mechanism:



Figure 5. possible mechanism for the catalytic acylation of alcohol



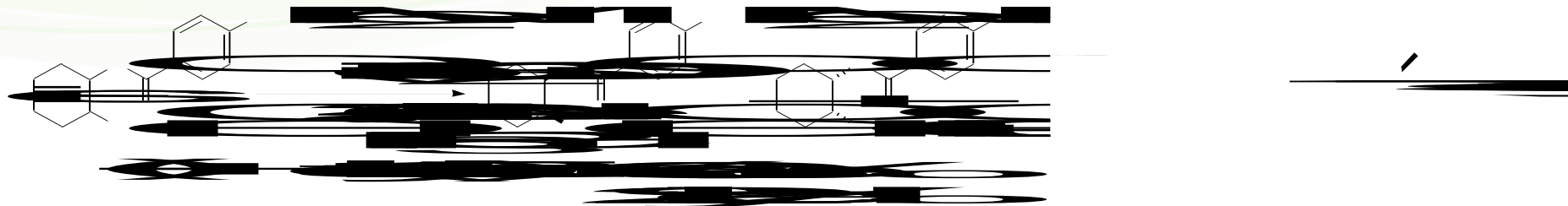
Scheme 1. Fu's kinetic resolution of secondary alcohols

E. F. Scriven. *V. Soc. Rev.* **1983**, *12*, 129-161.

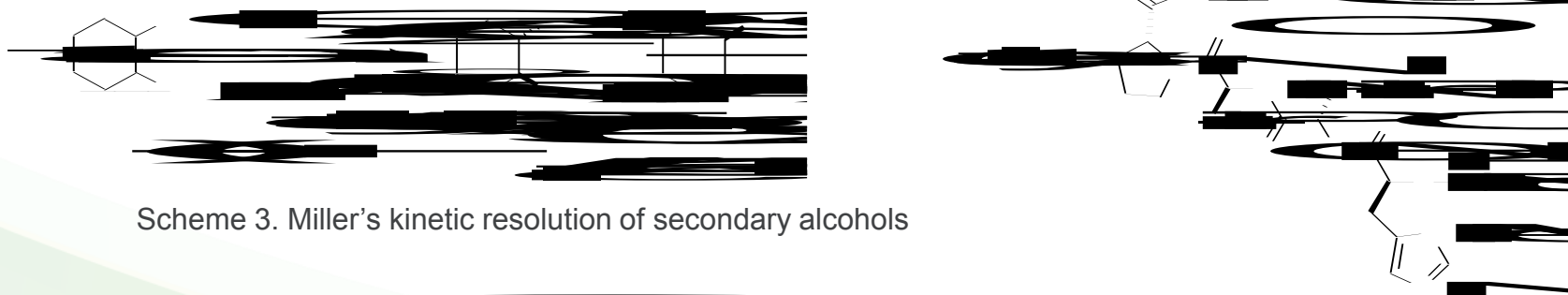
J. C. Ruble, H. A. Latham, G. C. Fu, *J. Am. Chem. Soc.* **1997**, *119*, 1492-1493.

A. C. Spivey, T. Fekner, S. E. Spey, *J. Org. Chem.* **2000**, *65*, 3154-3159.

Other examples of kinetic resolution of secondary alcohols



Scheme 2. Fuji's kinetic resolution of secondary alcohols



Scheme 3. Miller's kinetic resolution of secondary alcohols

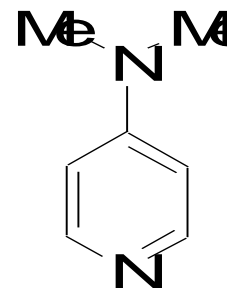


Scheme 4. Oriyama's kinetic resolution of secondary alcohols

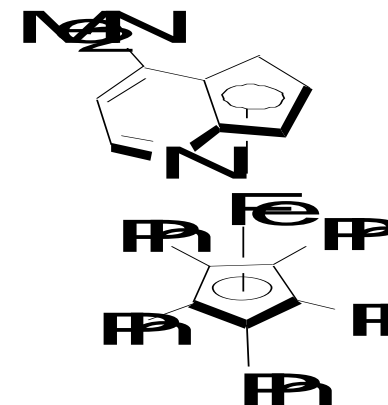
Helicene and DMAP

Helical structures attract extensive interest within the chemistry community by virtue of their chirality. The Lewis base catalyst dimethylaminopyridine (DMAP) is the prototypical synthetic nucleophilic catalyst, dramatically enhancing the rate of transfer of C-electrophiles to O-,N-,and C-nucleophiles.

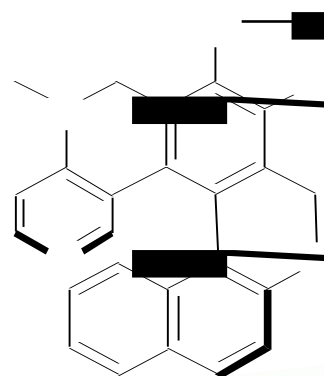
The drive to synthesize chiral molecules with non-traditional stereoelements, such as those which **contain planar or axial chiral elements**, has arguably been motivated by the continued development of novel catalyst–ligand designs and the advancement of modern asymmetric synthetic methodologies.



DMAP



Fu's DMAP analogue



Carbery's DMAP analogue

Figure 6. DMAP, planar chiral and axially chiral DMAP analogue

Helicene and DMAP

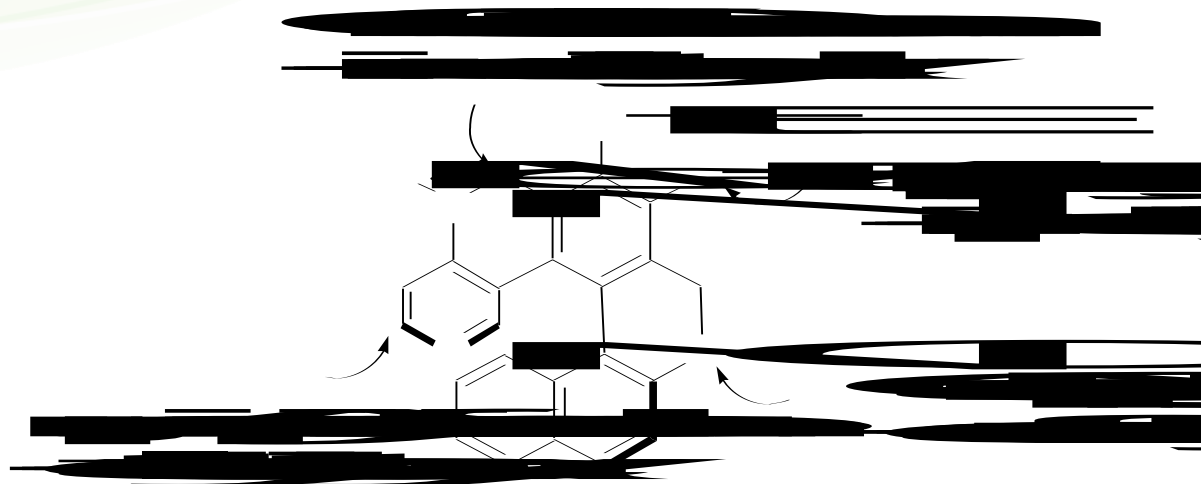
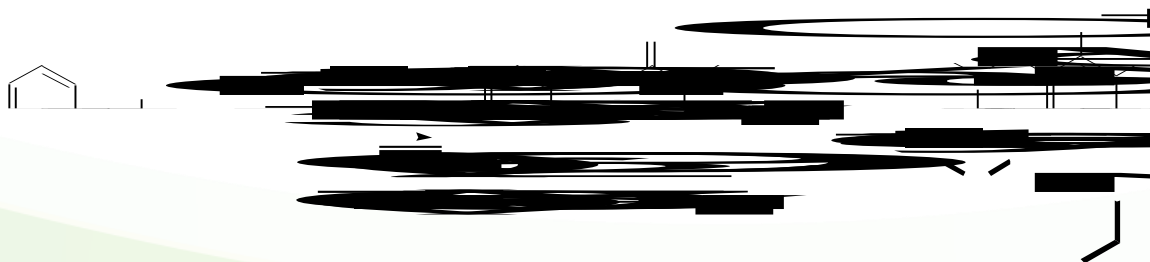


Figure 7. Design concept of helicoidal DMAP catalyst



Scheme 5. Kinetic resolution of secondary alcohol with Carbery's helicoidal DMAP catalyst

Summary

- ⦿ Theoretical considerations in kinetic resolution(s, ee value and its determination)
- ⦿ The design of chiral DMAP analogues and their kinetic resolution of secondary alcohols
- ⦿ Other examples of kinetic resolution of secondary alcohols
- ⦿ Helicene and DMAP

Thanks for your attention!