# Atropisomers

## *Fundamentals, Pharmaceutical Considerations, & Selective Syntheses*

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Literature Group Meeting

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# Atropisomers

*Fundamentals, Pharmaceutical Considerations, & Selective Syntheses*

I. Historical Development & Fundamentals

II. Considerations in Drug Development

III. Overview of Atroposelective Synthetic Methods

IV. Summary & Conclusions

# The Moirai

## "The Fates"

Κλωθω
Clotho

Ατροπος
Atropos

Λαχεσις
Lachesis

Κλωθω
Clotho

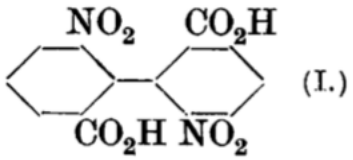
Ατροπος
Atropos

Λαχεσις
Lachesis

# Atropisomerism—Historical Development

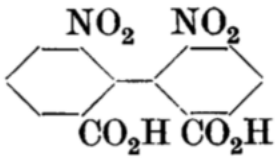
- **G. H. Christie & J. Kenner — 1922**
  - What is the molecular configuration of the ***diaryl*** scaffold, as in 6,6'-dinitro-2,2'-diphenic acid?

**Leading Hypothesis—Planar Structures**




(I.)

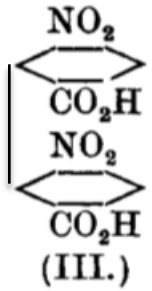
*trans*




(II.)

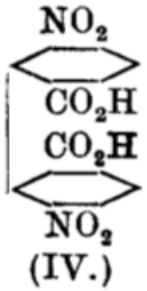
*cis*

**Kauffler Formulae—Parallel Planes**




(III.)

*cis*

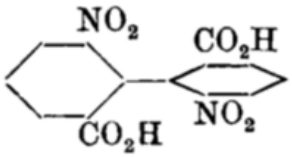



(IV.)

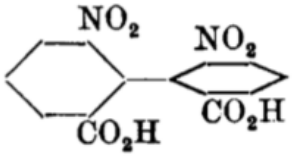
*trans*

- Christie & Kenner reasoned that 6,6'-dinitro-2,2'-diphenic acid would not be ***resolvable*** if co-planar or if *cis*-parallel planar due to the existence of ***internal symmetry planes***.

- Perhaps "…the two benzene nuclei possess a common axis but do not lie in the same plane. In this case, it will be seen that both forms of the acid (V and VI) should be resolvable."




(V.)

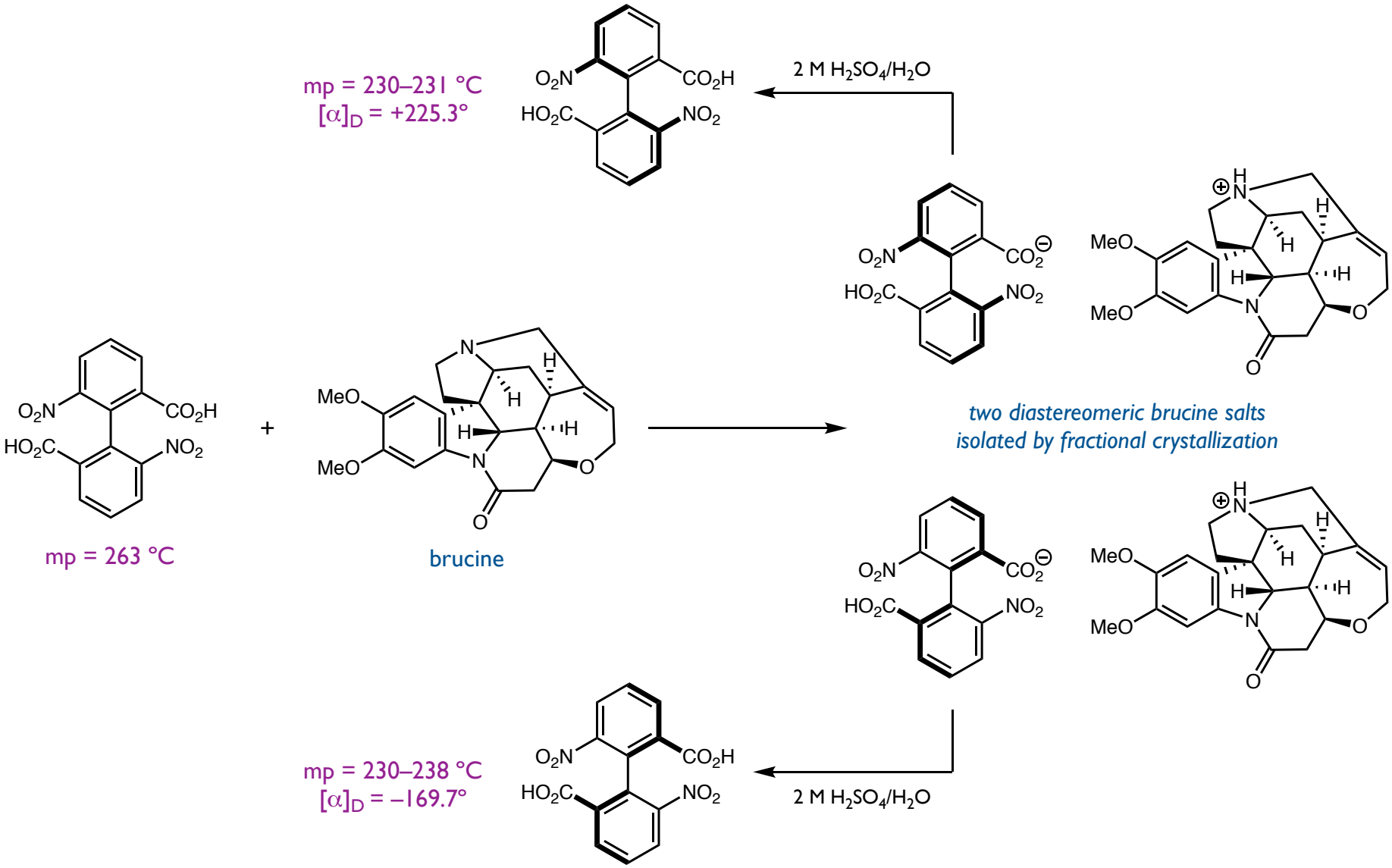



(VI.)



Christie, G. H.; Kenner, J. *J. Chem. Soc., Trans.* **1922**, *121*, 614–620.

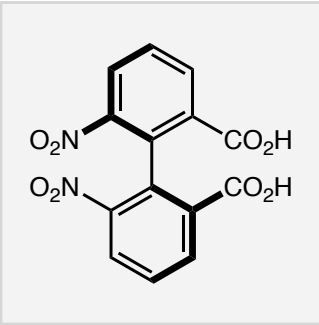
# Fractional Crystallization of Brucine Salts



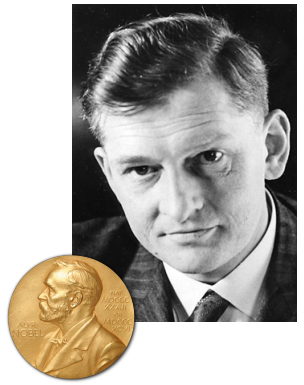

Christie, G. H.; Kenner, J. *J. Chem. Soc., Trans.* **1922**, *121*, 614–620.

# Atropisomerism—Historical Development

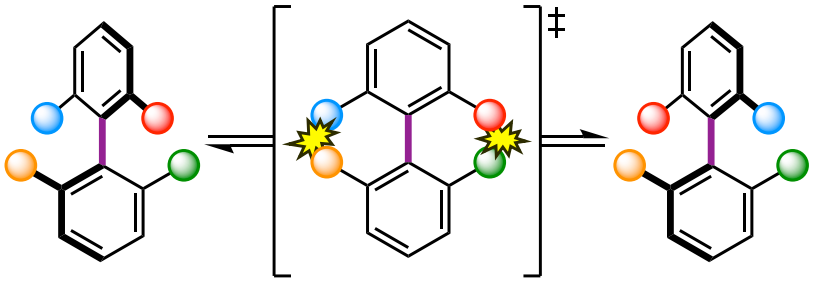
- **G. H. Christie & J. Kenner — 1922**
  - First to observe ***enantiomers*** about a chiral axis in 6,6'-dinitro-2,2'-diphenic acid.



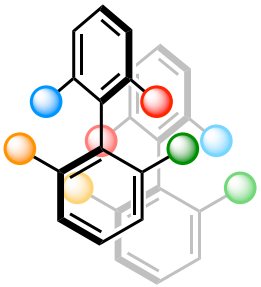

- **R. Kuhn — 1933**
  - Coins the term ***atropisomer*** to describe stereoisomers arising from "freezing" internal rotation about a single bond.
  - From the Greek word ***atropos*** (ατροπος), meaning "without turn."
  - The term originally referred specifically to ***biaryls***.



**Richard Kuhn**
**Nobel Prize in Chemistry**
**1938**



*strained coplanar transition state*



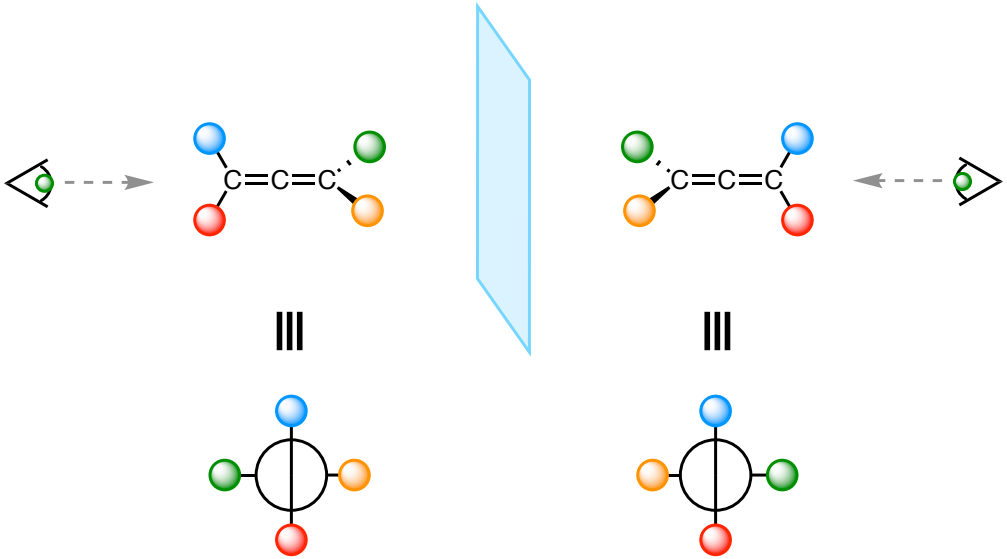
*non-superimposable mirror images*

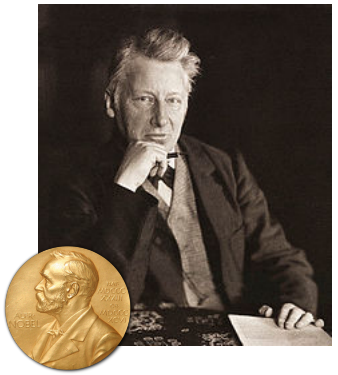


Kuhn, R. "Molekulare Asymmetrie." In *Stereochemie;* Freudenberg, K., Ed.;Franz Deutike: Leipzig-Wien, Germany, 1933, pp. 803–824.

# Axial Chirality—Allenes

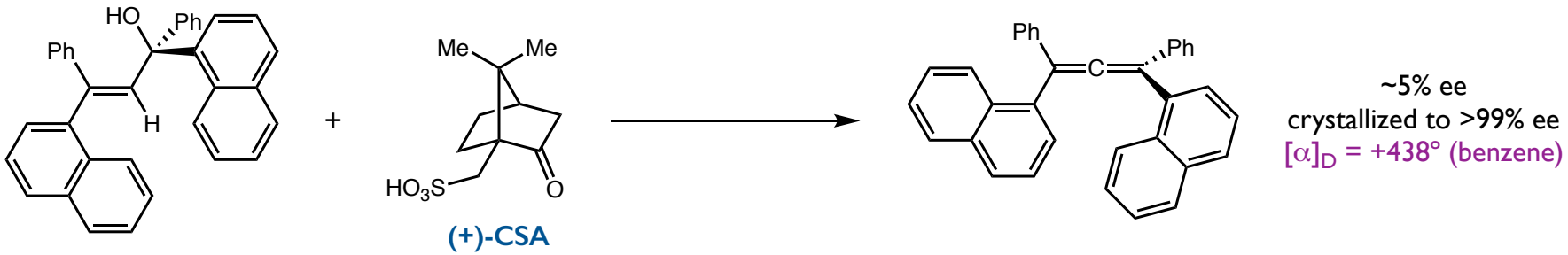
- The concept of ***axial chirality*** was originally formulated by van 't Hoff in 1875 with regard to allenes.





**Jacobus Henricus van 't Hoff**
**Nobel Prize in Chemistry**
**1901**

- Verification of van 't Hoff's proposal came six decades later, when Maitland & Mills synthesized the first ***optically pure allene***.

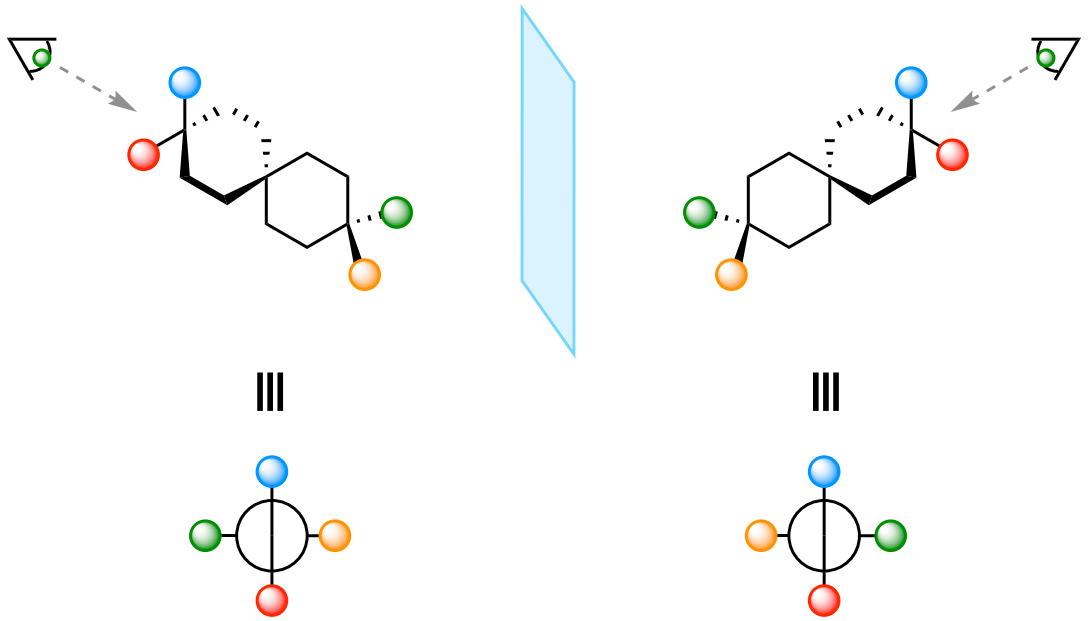




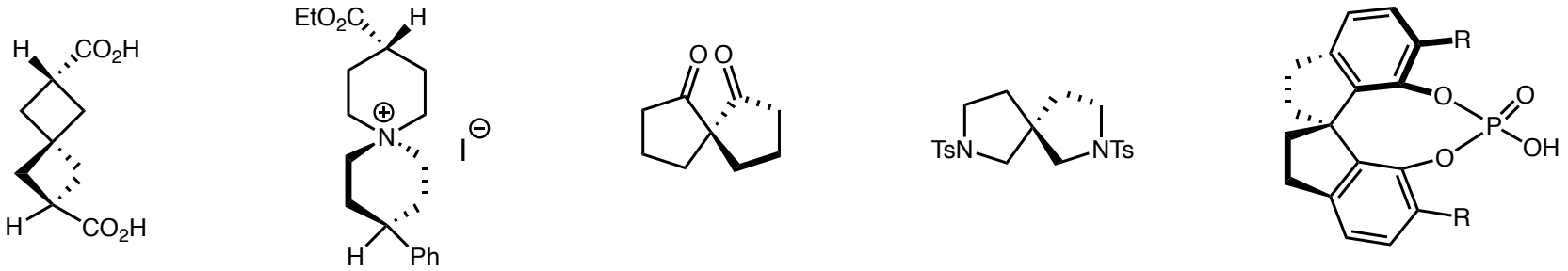

Eliel, E. L.; Wilen, S.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley Interscience: New York, 1994, pp. 1119–1190.

# Axial Chirality—Spiranes

- *Spiranes* have also been found to exhibit *axial chirality* in much the same way as allenes.



- A number of *optically active spiranes* are known.

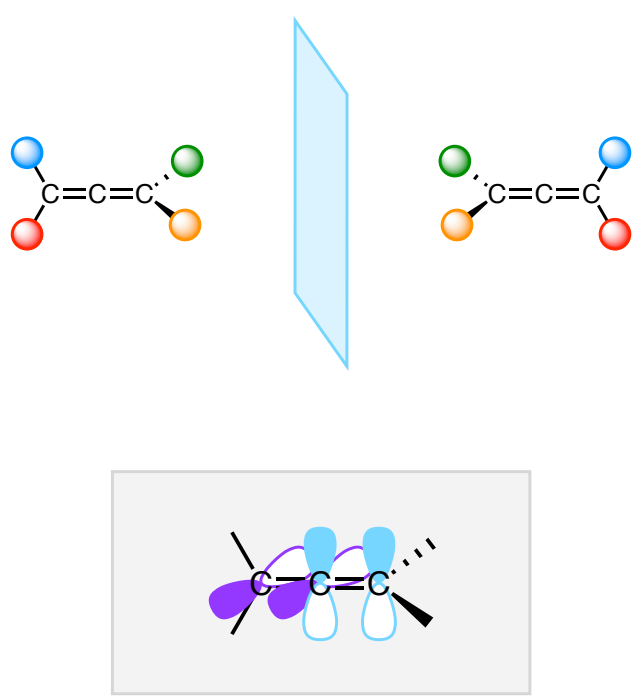





Eliel, E. L.; Wilen, S.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley Interscience: New York, 1994, pp. 1119–1190.

# Axial Chirality & Atropisomerism

- ***Allenes***, ***spiranes***, and ***biaryls*** are axially chiral, but are they all considered to be ***atropisomeric***?



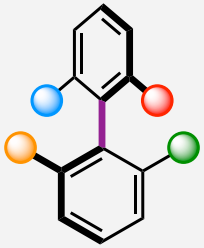

- In order to classify as an ***atropisomeric compound***, a molecule must be chiral due to hindered rotation about a single bond, the sense of chirality being maintained through steric interference.
  - Allenes are axially chiral but not atropisomeric; ***Biaryls are axially chiral and atropisomeric***.



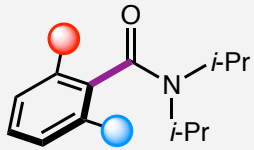
Eliel, E. L.; Wilen, S.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley Interscience: New York, 1994, pp. 1119–1190.

# Types of Atropisomeric Scaffolds

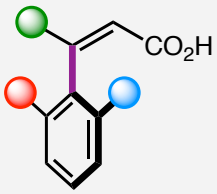
## Chiral C–C Axes



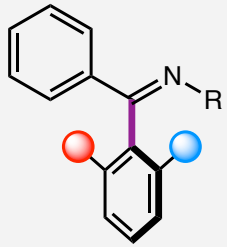
biaryls




tertiary benzamides

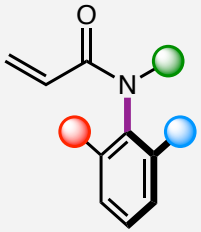



α-styrenes

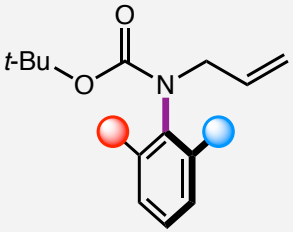



imines

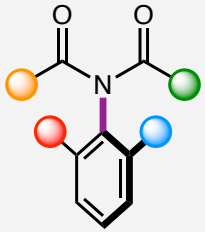
## Chiral C–N Axes



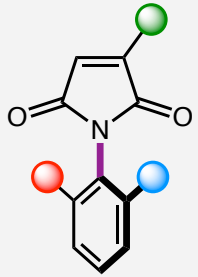

anilides

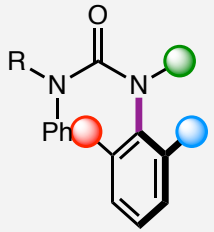



carbamates

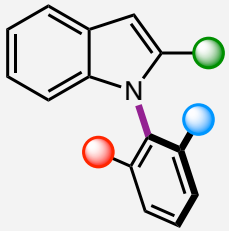



imides

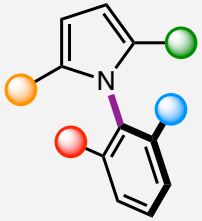


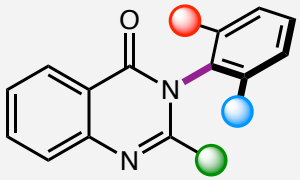

ureas



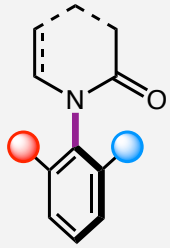

indoles



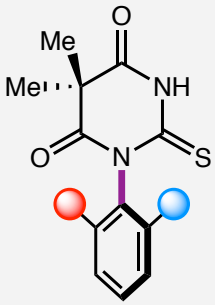

pyrroles




quinazolinones




lactams



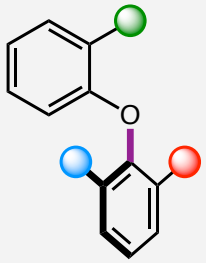

barbiturates



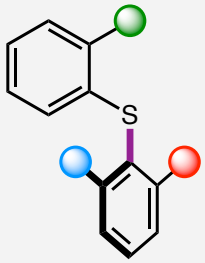
Kumarasamy, E.; Raghunathan, R.; Sibi, M. P.; Sivarugu, J. *Chem. Rev.* **2015**, *115*, 11239–11300.

# Types of Atropisomeric Scaffolds

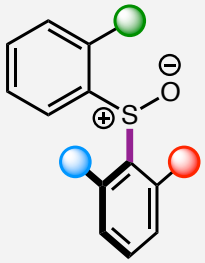
## Chiral C–O & C–S Axes



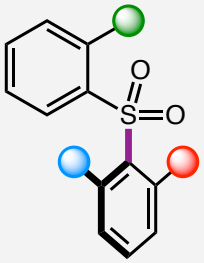

diaryl ethers

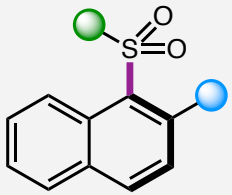



diaryl sulfides



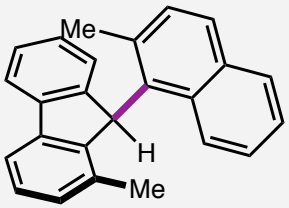

sulfoxides



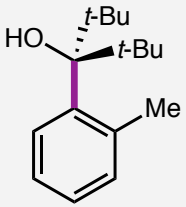




sulfones

## Chiral C($sp^2$)–C($sp^3$) Axes

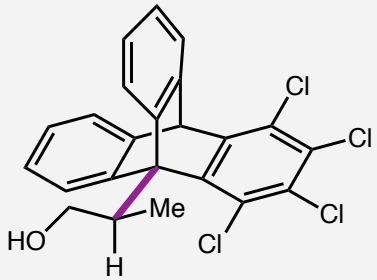



9-arylfluorenes
$\Delta G^{\ddagger}$ = 33.3 kcal/mol

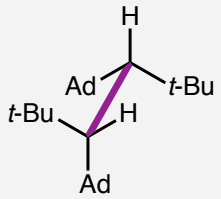



3° benzylic alcohols
$\Delta G^{\ddagger}$ = 25.9 kcal/mol

## Chiral C($sp^3$)–C($sp^3$) Axes




triptycenes
$\Delta G^{\ddagger}$ = 23.5 kcal/mol

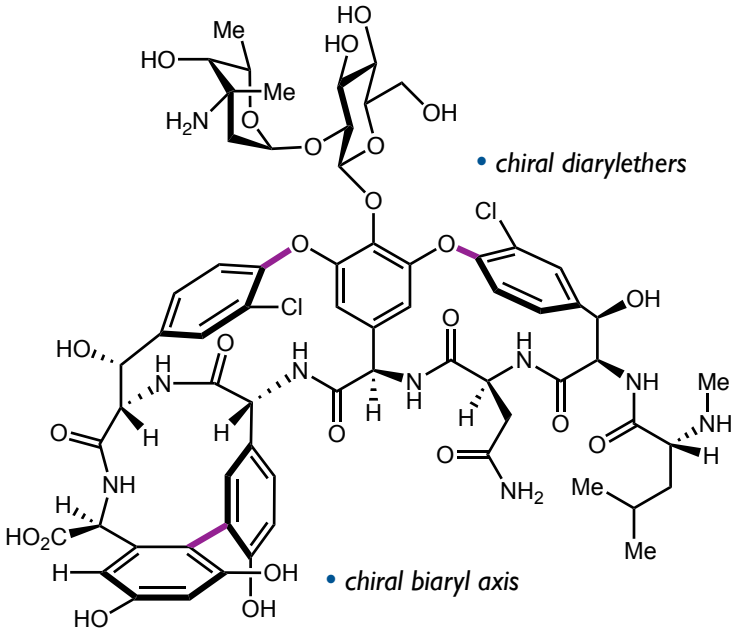



ethanoids


Kumarasamy, E.; Raghunathan, R.; Sibi, M. P.; Sivarugu, J. *Chem. Rev.* **2015**, *115*, 11239–11300.

Ōki, M. "Recent Advances in Atropisomerism," in *Topics in Stereochemistry*; Allinger, N. L.; Eliel, E. L.; Wilen, S. H., Eds.; Wiley: Hoboken, NJ, 1983; Vol. 14, pp. 1–81.

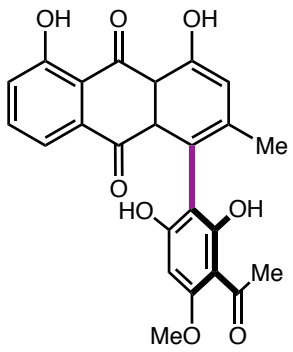
# Atropisomeric Natural Products



- *chiral diarylethers*
- *chiral biaryl axis*

**vancomycin**

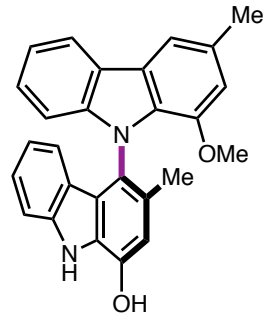
- *antibiotic of "last resort"*



**knipholone**

- *antimalarial & antitumor activity*

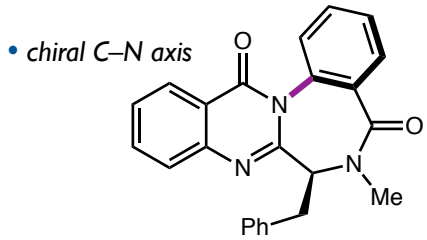
- *chiral C–N axis*



**murrastifoline-F**

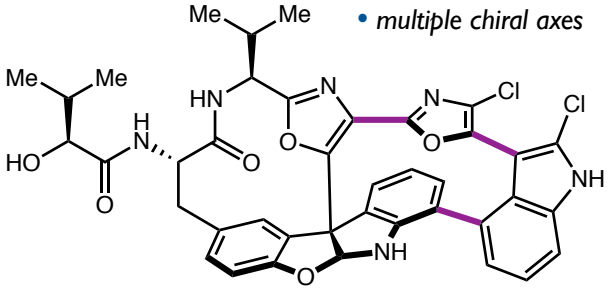
- *antiplasmoidal activity*

- *chiral C–N axis*



**benzomalvin A**

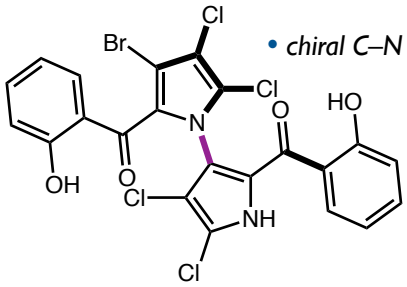
- *substance P inhibitor & antidepressant*



- *multiple chiral axes*

**diazonamide A**

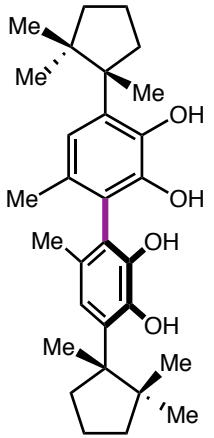
- *antimitotic agent*



- *chiral C–N axis*

**marinopyrrole B**

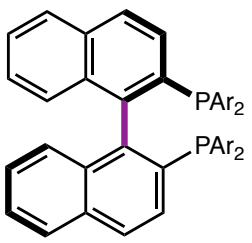
- *antibiotic & anticancer activity*



**murrastifoline**

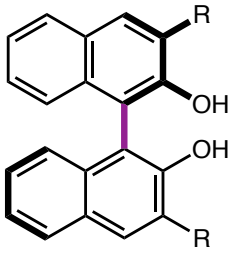
- *stimulates nerve growth*

# Atropisomeric Scaffolds as Ligands for Transition Metals

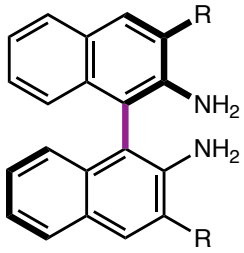



(*R*)-BINAP

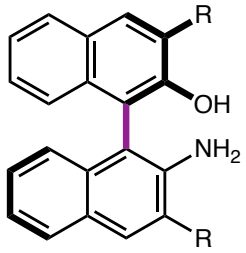
- *asymmetric hydrogenation*



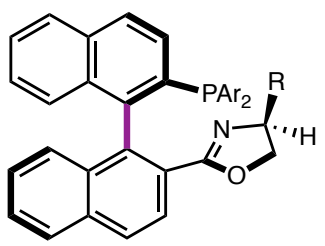

(*R*)-BINOL



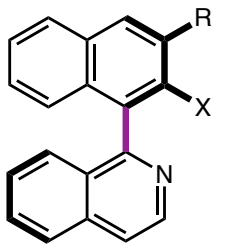

(*R*)-BINAM



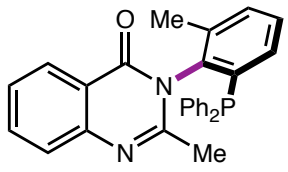

(*R*)-NOBIN



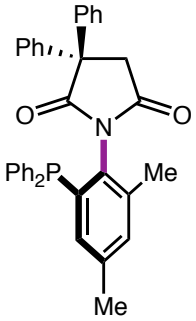

(*R*)-IPHOX



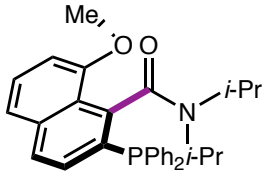

(*R*)-QUINAP/OL/AM




**1**




**2**

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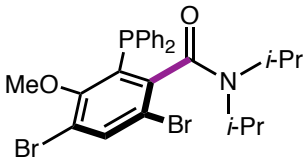


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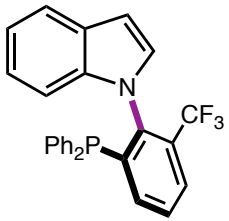
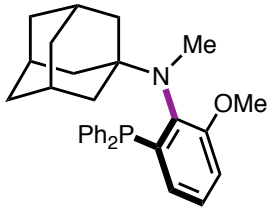
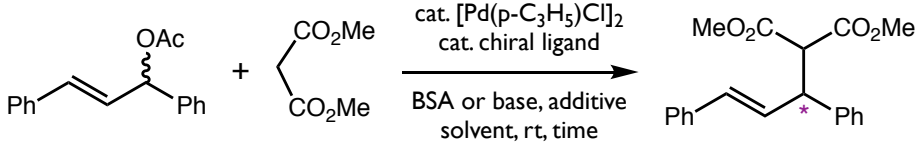



**5**




**6**

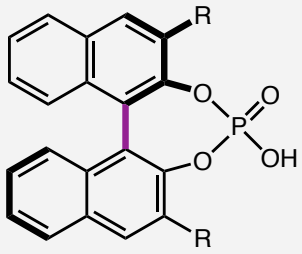



| Ligand | Additive | Solvent | Time (h) | yield (%) | ee (%) |
|---|---|---|---|---|---|
| 1 | 15-C-5 | $CH_2Cl_2$ | 96 | 30 | 52 |
| 2 | – | $CH_2Cl_2$ | 24 | 23 | 52 |
| 3 | NaOAc | $CH_2Cl_2$ | 4 | 89 | 94 |
| 4 | – | $CH_2Cl_2$ | 5 | 93 | 92 |
| 5 | LiOAc | $Et_2O$ | 24 | 99 | 99 |
| 6 | LiOAc | MeCN | 48 | 98 | 88 |

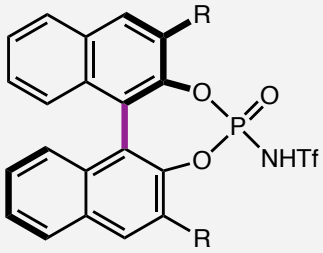

Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029–3069; Wang, Y.-B.; Tan, B. *Acc. Chem. Res.* **2018**, *51*, 534–547.
Kumarasamy, E.; Raghunathan, R.; Sibi, M. P.; Sivarugu, J. *Chem. Rev.* **2015**, *115*, 11239–11300.

# Atropisomeric Scaffolds as Organocatalysts

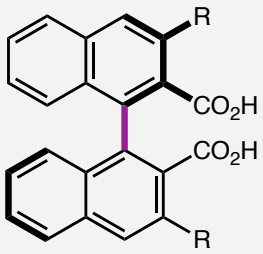
*Brønsted Acid Organocatalysts*



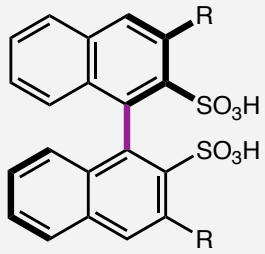

CPAs



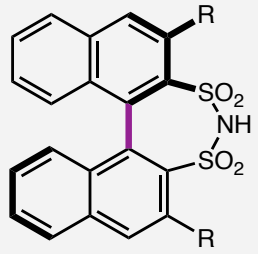

CPIs




CCAs

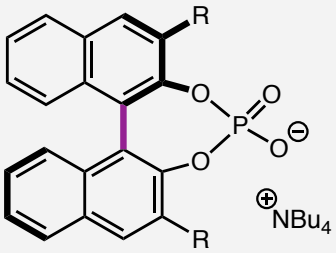



CSAs

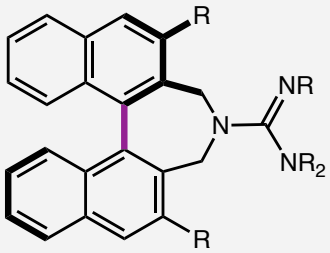



CSIs

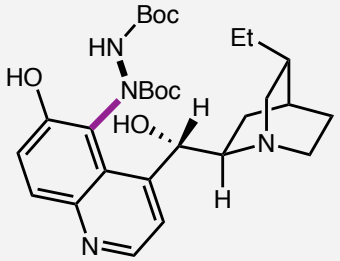
*Brønsted Base Organocatalysts*



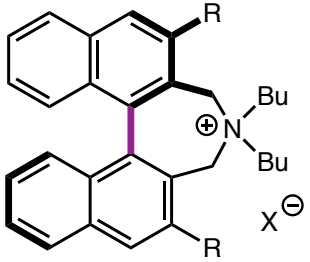

BINOL Phosphates



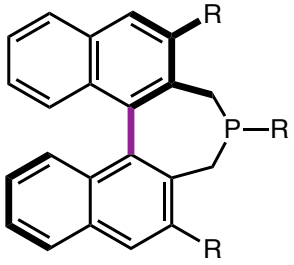

Gaunidines




Modified Cinchona Alkaloids




Phase Transfer Catalysts

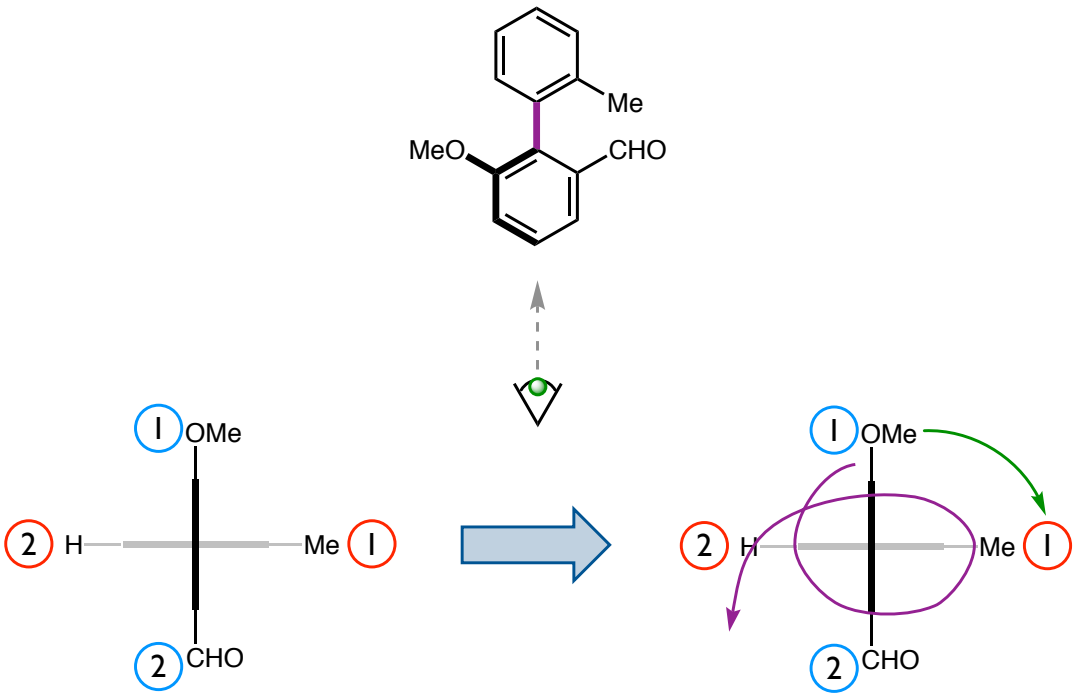



Phosphines


Wang, Y.-B.; Tan, B. *Acc. Chem. Res.* **2018**, *51*, 534–547.
Parmar, D.; Sugiono, E.; Raja, S.; Reuping, M. *Chem. Rev.* **2014**, *114*, 9047–9153.
Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999–1010.
Brandes, S.; Niess, B.; Bella, M.; Prieto, A.; Overgaard, J.; Jørgensen, K. A. *Chem.–Eur. J.* **2006**, *12*, 6039–6052.

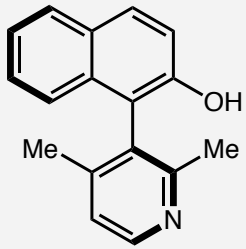
# Absolute Configuration of Atropisomeric Compounds

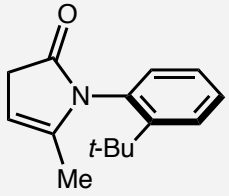
- The configuration of atropisomeric compounds can be described in two ways:
  1. the Cahn–Ingold–Prelog convention: (a*R*) or (a*S*), or
  2. using the helical analogy: *M* (minus) or *P* (plus).

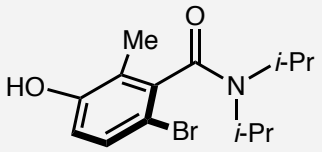



**CIP**
counterclockwise—(a*S*)
**helical**
clockwise—(*P*)

***Let's Practice!***



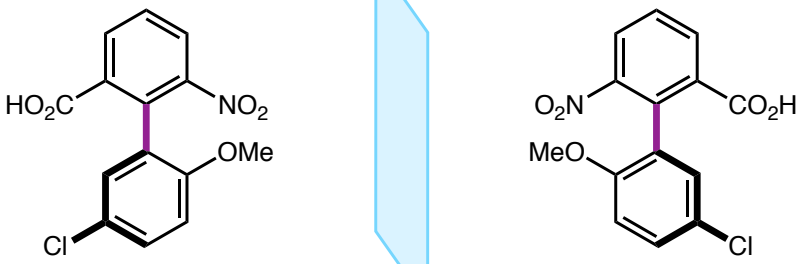



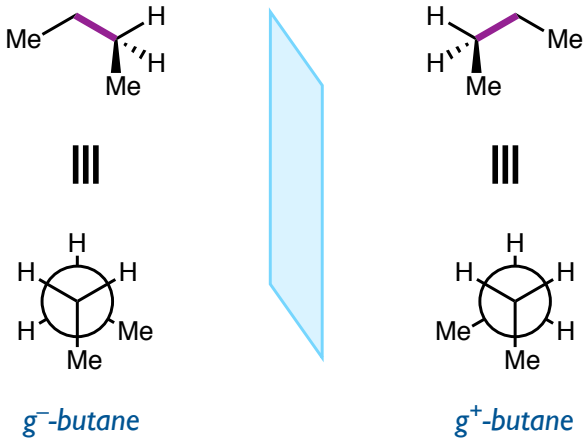



Eliel, E. L.; Wilen, S.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley Interscience: New York, 1994, pp. 1119–1190.

# Atropisomers & Conformers—What's the Difference?



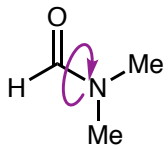

• *Rotation about the biaryl bond gives rise to enantiomers.*




*g*$^{-}$-butane *g*$^{+}$-butane

• *Rotation about the internal C–C bond of butane can also give enantiomers.*

- Ōki proposed an arbitrary, yet practically useful criterion for ***atropisomerism***:
  - $t_{1/2}$ **> 1000s** for rotation about the single bond in question at any given temperature.



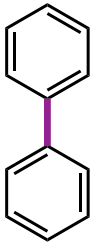

$\Delta G^{\ddagger}$ = 20.6 kcal/mol

| Temperature (K) | $\Delta G^{\ddagger}$ (kcal/mol) | |
|---|---|---|
| | *K* = 1.0 | *K* = 10.0 |
| 200 | 14.73 | 14.49 |
| 250 | 18.52 | 18.23 |
| 300 | 22.34 | 21.98 |
| 350 | 26.17 | 25.75 |
| 400 | 30.01 | 29.53 |
| 450 | 33.87 | 33.33 |
| 500 | 37.74 | 37.14 |

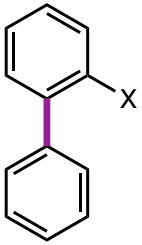
Ōki, M. "Recent Advances in Atropisomerism," in *Topics in Stereochemistry*; Allinger, N. L.; Eliel, E. L.; Wilen, S. H., Eds.; Wiley: Hoboken, NJ, 1983; Vol. 14, pp. 1–81.

# Atropisomerism & Rotational Barriers

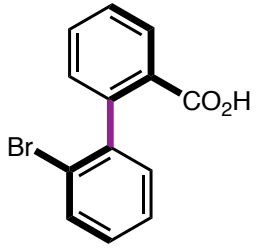
- Atropisomeric compounds exhibit ***time-resolved chirality*** owing to the barrier-dependence on configurational stability.



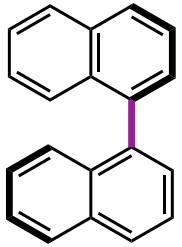
$\Delta G^{\ddagger}$ = 1.4–2.0 kcal/mol
$t_{1/2}$ = 1.2–3.3 x $10^{-12}$ s



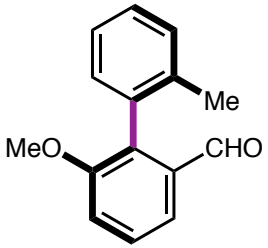

X = F, $\Delta G^{\ddagger}$ = 3.7 kcal/mol
X = Me, $\Delta G^{\ddagger}$ = 7.4 kcal/mol
X = Cl, $\Delta G^{\ddagger}$ = 7.6 kcal/mol
X = Br, $\Delta G^{\ddagger}$ = 8.6 kcal/mol
X = *t*-Bu, $\Delta G^{\ddagger}$ = 15.4 kcal/mol
$t_{1/2}$ = 5.7 x $10^{-11}$ to 2.1 x $10^{-2}$ s



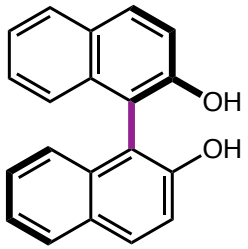

$\Delta G^{\ddagger}$ = 22.1 kcal/mol
$t_{1/2}$ = 0.5 h



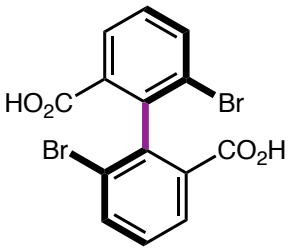
$\Delta G^{\ddagger}$ = 24.0 kcal/mol
$t_{1/2}$ = 11.5 h



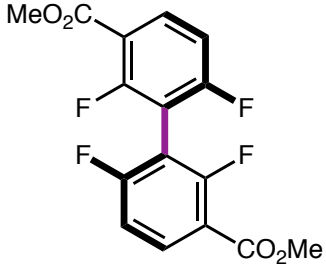

$\Delta G^{\ddagger}$ = 29.8 kcal/mol
$t_{1/2}$ = 23.0 y




$\Delta G^{\ddagger}$ = 37.8 kcal/mol
$t_{1/2}$ = 1.7 x $10^{4}$ millennia




$\Delta G^{\ddagger}$ >50 kcal/mol
$t_{1/2}$ ~ ∞
*decomposes first*



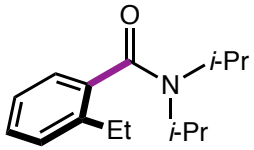

$\Delta G^{\ddagger}$ = 25.8 kcal/mol
$t_{1/2}$ = 9.9 d



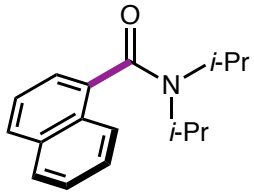
Mazzanti, A.; Lunazzi, L.; Minzoni, M.; Anderson, J. E. *J. Org. Chem.* **2006**, *71*, 5474–5481.

# Steric Trends in Benzamide Atropisomers

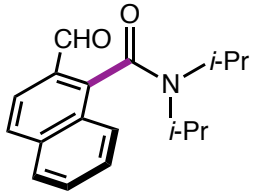
- Similar trends have also been observed in non-biaryl atropisomers, such as this tertiary benzamide series.



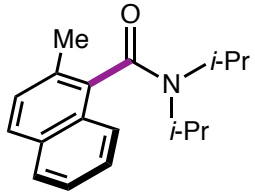

$\Delta G^{\ddagger}$ = 14.2 kcal/mol
$t_{1/2}$ = 0.002 s



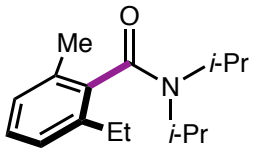

$\Delta G^{\ddagger}$ = 17.9 kcal/mol
$t_{1/2}$ = 1 s



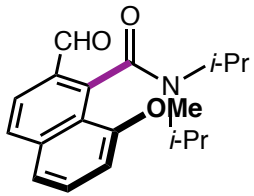

$\Delta G^{\ddagger}$ = 21.6 kcal/mol
$t_{1/2}$ = 1.5 min



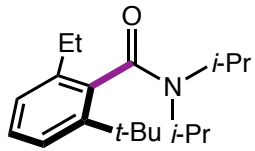

$\Delta G^{\ddagger}$ = 25.1 kcal/mol
$t_{1/2}$ = 75 h




$\Delta G^{\ddagger}$ = 25.7 kcal/mol
$t_{1/2}$ = 8.4 d




$\Delta G^{\ddagger}$ = 29.2 kcal/mol
$t_{1/2}$ >10 y

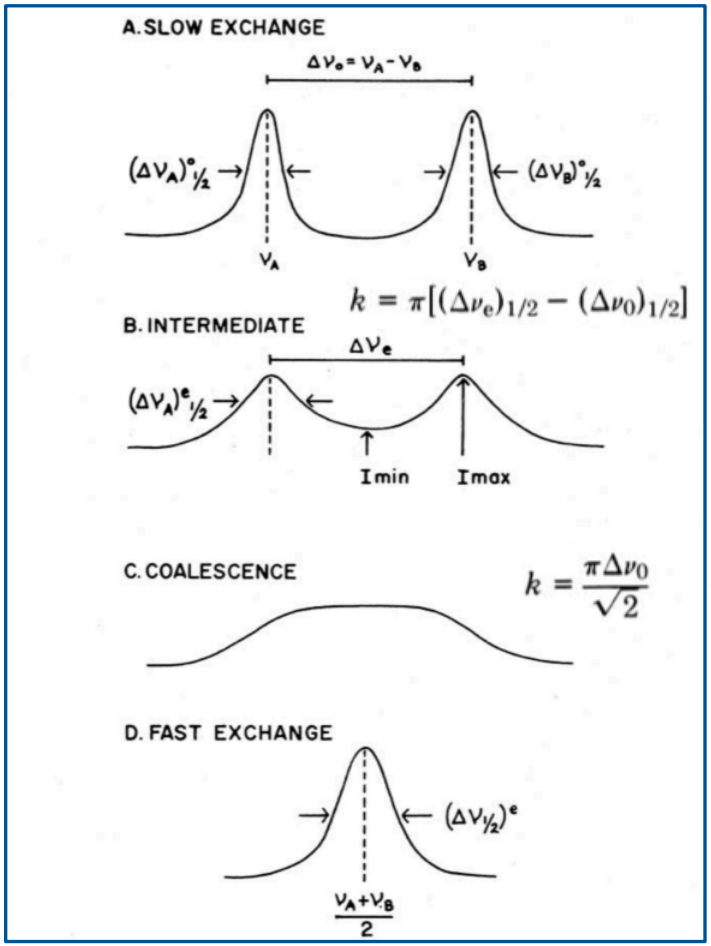



$\Delta G^{\ddagger}$ = 30.0 kcal/mol
$t_{1/2}$ >30 y

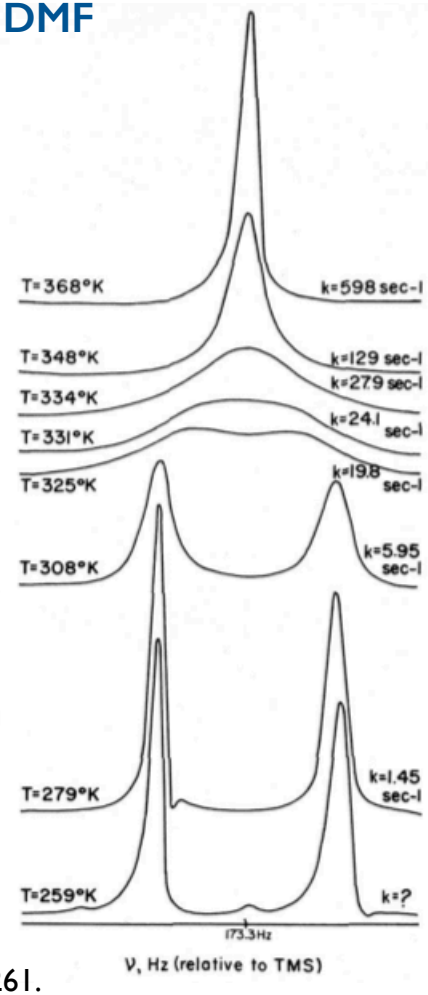
Ahmed, A.; Bragg, R. A.; Clayden, J.; Lai, L. W.; McCarthy, C.; Pink, J. H. *Tetrahedron* **1998**, *54*, 13277–13294.
Clayden, J. *Chem. Commun.* **2004**, 127–135.

# Measuring Rotational Barriers—NMR Lineshape Analysis

- The advent of NMR spectroscopy and development of dynamic NMR techniques was historically quite enabling for the study of atropisomeric compounds.
- *Lineshape Analysis* is a technique that is often employed to measure rotational barriers.




**DMF**



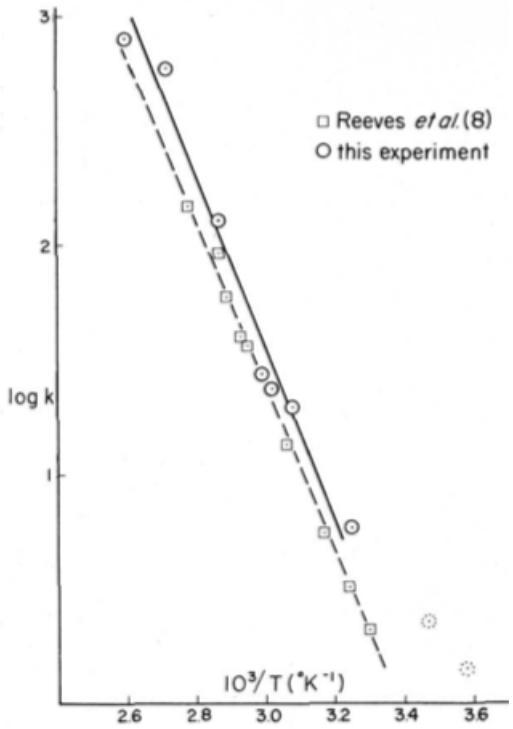



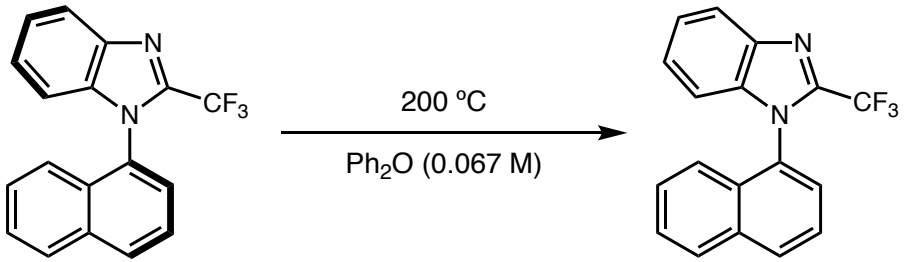

Table 2. Comparison to Values of Reeves, et al. (9)

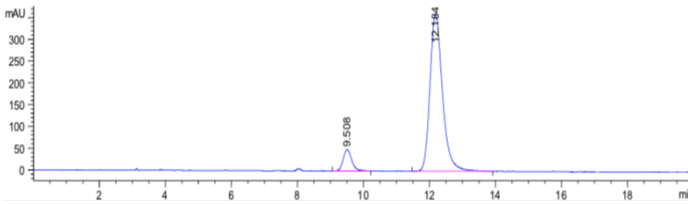
| | This study | Reeves et al. (9) |
|---|---|---|
| $T_c$, (°K) | 331 | 339 |
| $E_a$ (kcal/mole) | 17(14)[a] | 16.8 |
| $\Delta G^{\ddagger}$ (kcal/mole) | 17 | 17.3 |
| $\Delta H^{\ddagger}$ (kcal/mole) | 16 | 16.3 |
| $\Delta S^{\ddagger}$ (e.u.) | −2.1 | −3.59 |

Gasparro, F. P.; Kolodny, N. H. *J. Chem. Educ.* **1977**, *54*, 258–261.

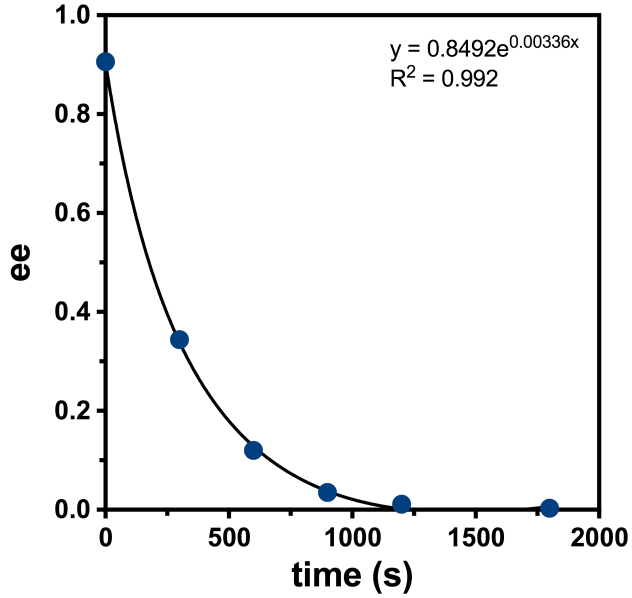
# Measuring Rotational Barriers—HPLC Methods

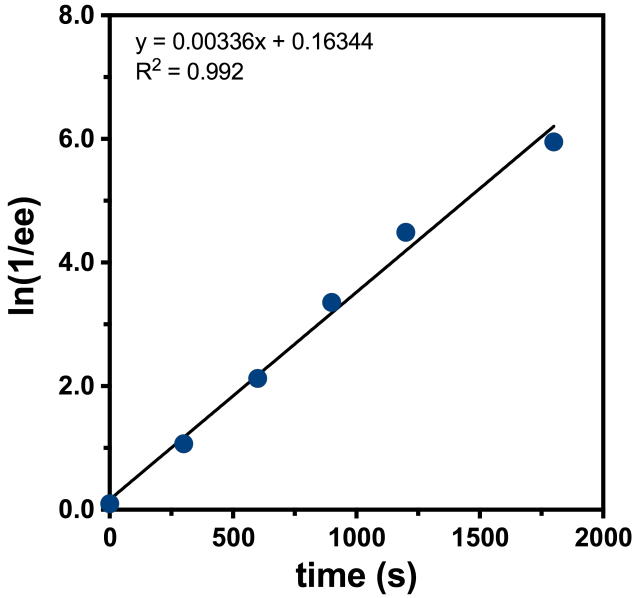
- NMR lineshape analysis cannot be used to directly measure the equilibration rates between enantiomers (unless diastereomers are involved).
- It is often simpler to use ***chiral HPLC*** to measure rotational barriers atropisomeric scaffolds.




- *measure the ee of the material at various time points*



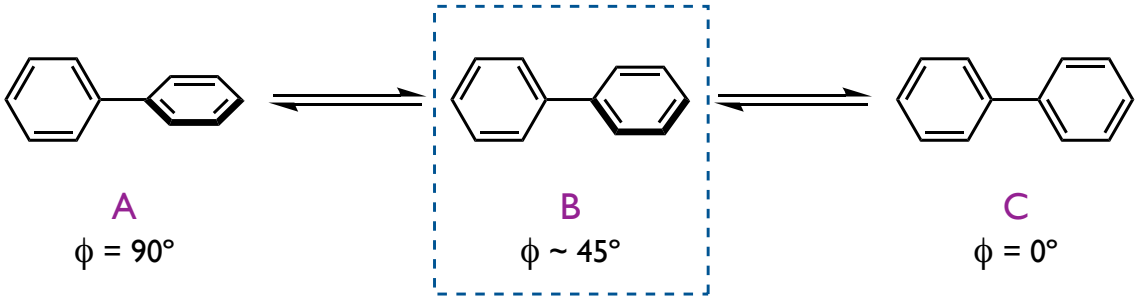

$$slope = k_{enant}$$
$$k_{rac} = 2k_{enant}$$

$$\Delta G^{\ddagger}_{rac} = -RT\ln\left(\frac{k_{rac}h}{k_B T}\right) = 33.5 \text{ kcal/mol}$$

$$t_{1/2} = ln(2)/k_{rac}$$

For example, see: Barrett, K. T.; Miller, S. J. *Org. Lett.* **2015**, *17*, 580–583.

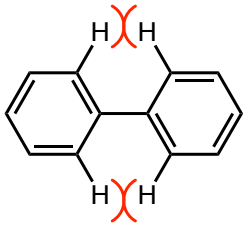
# Torsional Energy Profile of Biphenyl



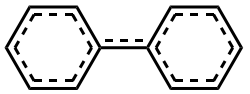
A
$\phi$ = 90°

B
$\phi$ ~ 45°

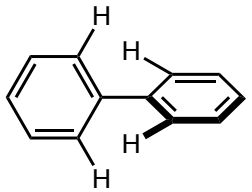
C
$\phi$ = 0°



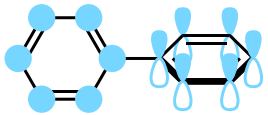

• *co-planar conformer destabilized by steric interactions between ortho-Hs*



• *co-planar conformer stabilized by conjugation/$\pi$-delocalization*

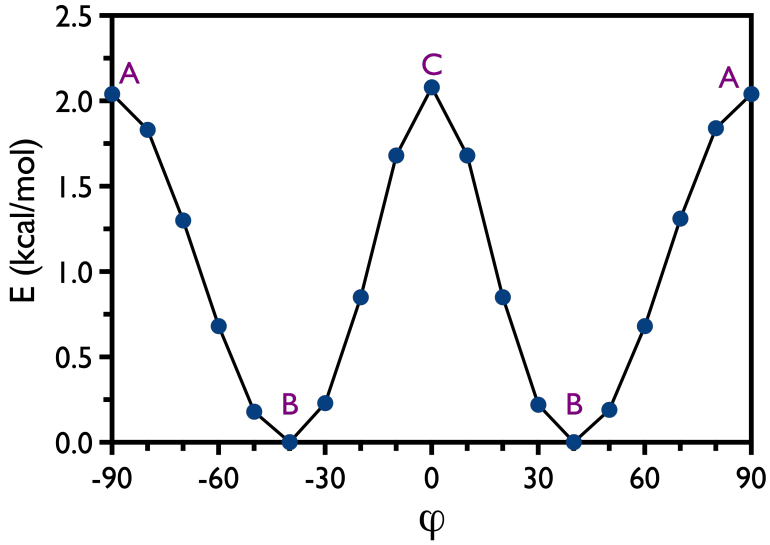



• *orthogonal conformer avoids severe destabilization between ortho-Hs*



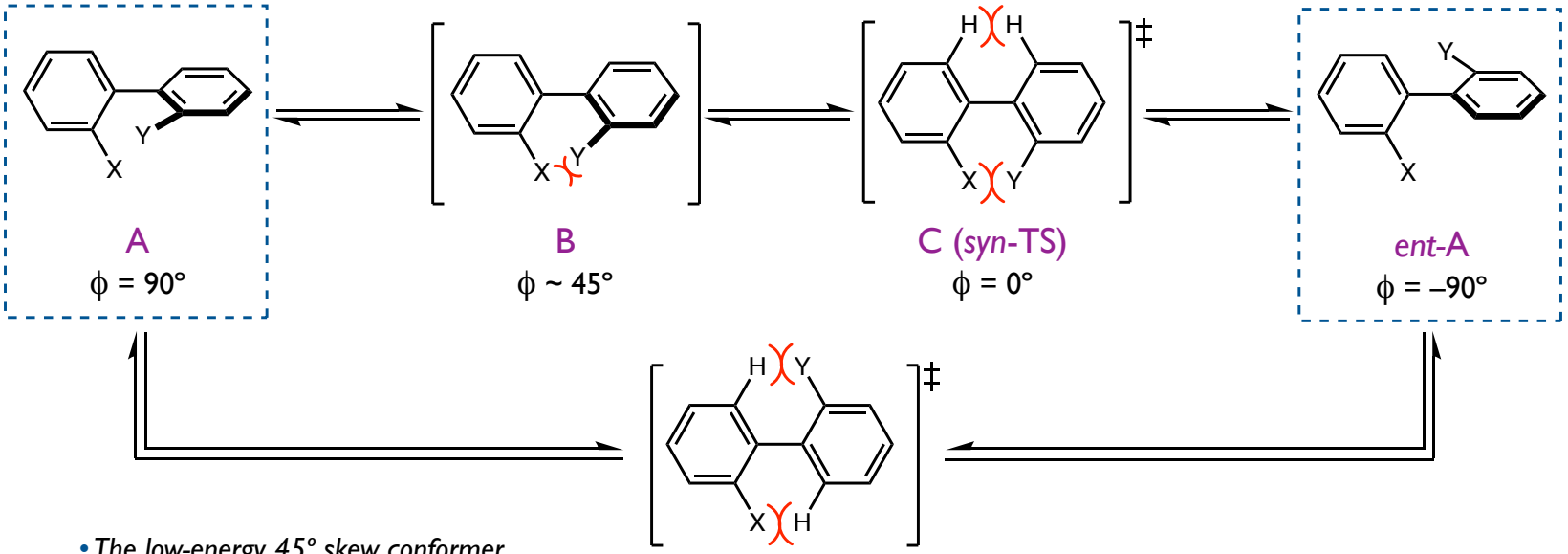
• *orthogonal conformer lacks conjugation between phenyl rings*

Torsional Energy Profile of Biphenyl

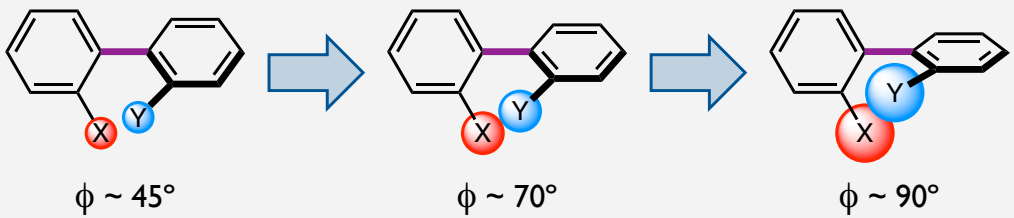



Torsional PES calculated at the B3LYP/6-31+G(d,p) level of theory using *Gaussian 16*.

# Torsional Energy Profiles of More Hindered Biaryls




• *The low-energy 45° skew conformer of biphenyl disappears as X and Y increase in size.*




• *As the ortho-substituents increase in size, the ground state conformation shifts from ~45° skew to an orthogonal orientation.*

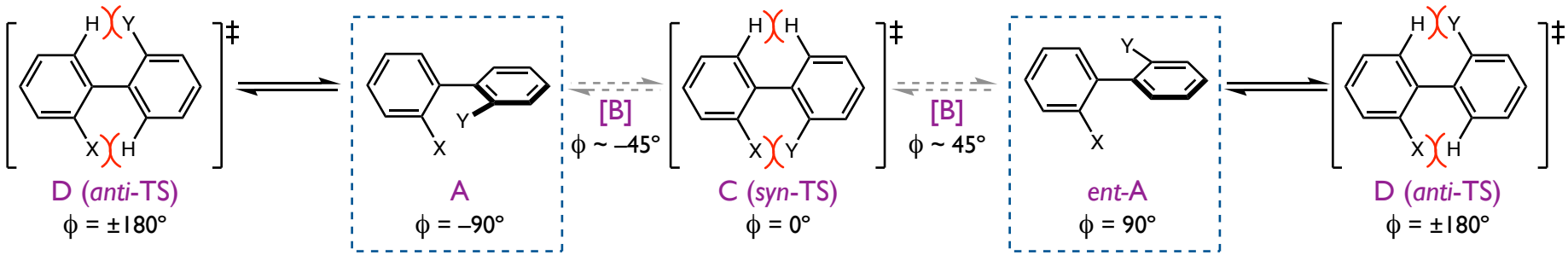
| X | Y | $\Delta G^{\ddagger}$ (kcal/mol) | ϕ |
|---|---|---|---|
| H | H | 2.2 | 42.5° |
| H | F | 3.0 | 45.1° |
| H | Cl | 7.6 | 59.9° |
| H | Br | 8.6 | 63.6° |
| H | I | 8.3 | 60.4° |
| F | F | 4.8 | 57.9° |
| Cl | Cl | 17.6 | 84.9° |
| Br | Br | 20.0 | 91.5° |
| I | I | 21.7 | 94.8° |

• *Calculated using B3LYP/6-311+G(d,p).*

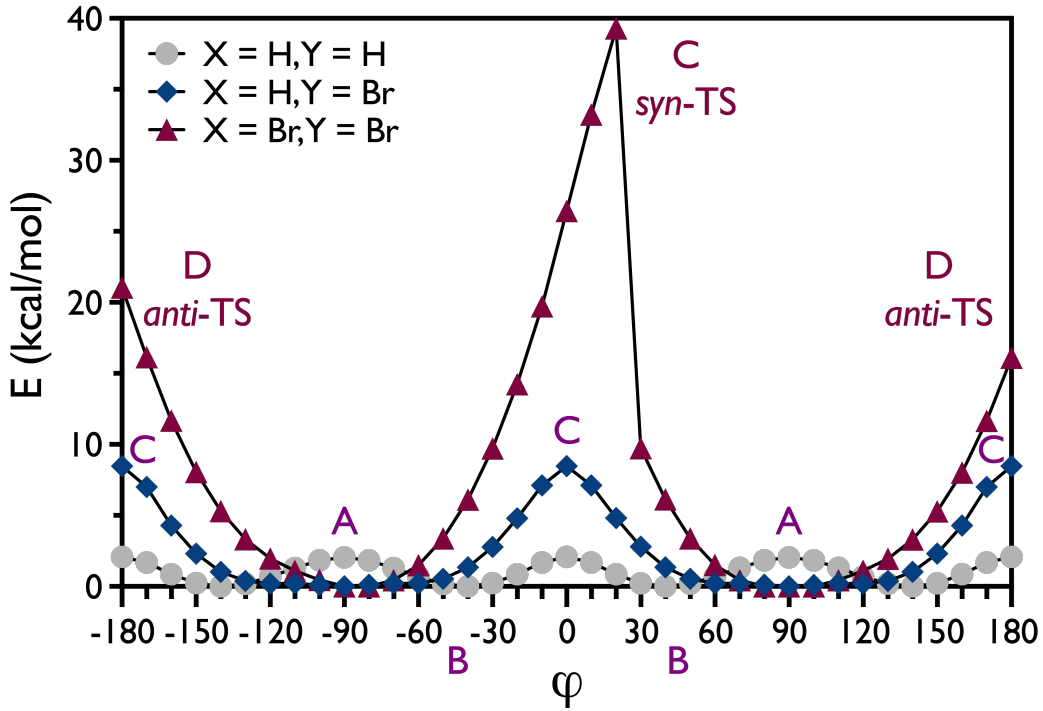

Leroux, F. *ChemBioChem* **2004**, *5*, 644–649.
Grein, F. *J. Phys. Chem. A* **2002**, *106*, 3823–3827.

Torsional PESs calculated at the B3LYP/6-31+G(d,p) level of theory using *Gaussian 16*.

# Torsional Energy Profiles of More Hindered Biaryls




- *When X,Y ≠ H, enantiomerization will occur via the lower-energy anti-TS.*




Torsional PESs calculated at the B3LYP/6-31+G(d,p) level of theory using *Gaussian 16*.

# Quantifying Steric Interactions in Biaryl Atropisomers

- Sternhell & co-workers were interested in rationally designing a system that would allow for the quantification of steric effects.

- The ideal system should have the following characteristics:
  1. The process should be intramolecular.
  2. Steric effects should be dominant over electronic effects.
  3. The system must be amenable to the study of many functional groups.
  4. The conformational energy landscape of the process should be well-defined.
  5. Either the ground state or transition state should be insensitive to size.
  6. The framework should be synthetically accessible.

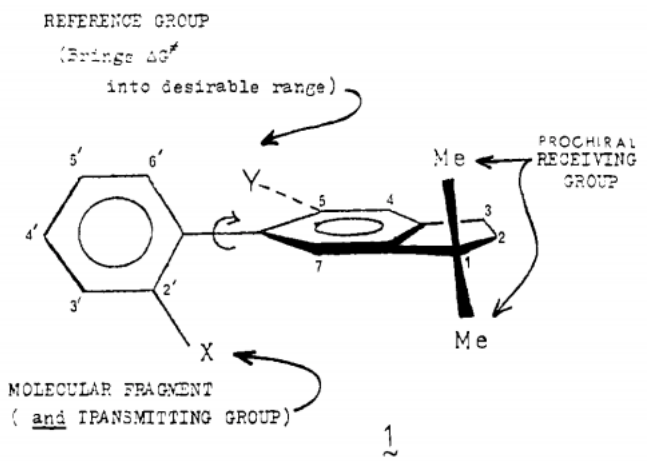
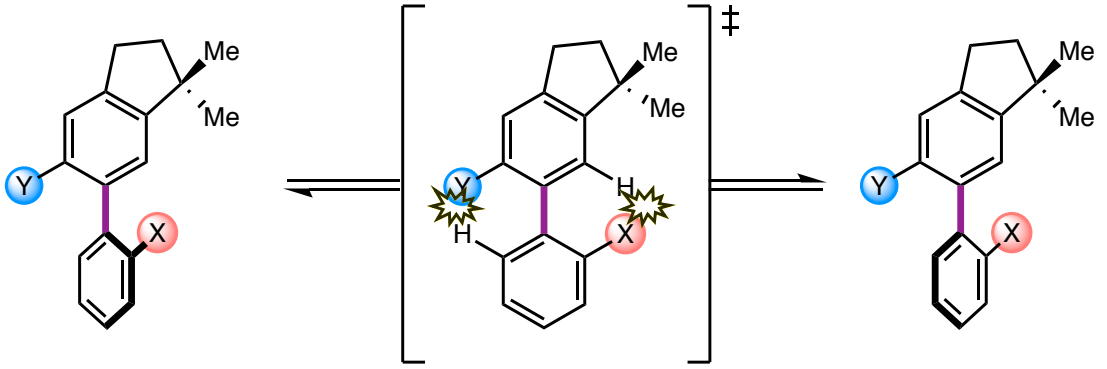



**Figure 1.** A rationally designed molecular framework for the study of steric interactions.




- *Steric repulsion between X)(H and Y)(H in the coplanar TS determine the barrier, yet X and Y do not interact in the ground state.*

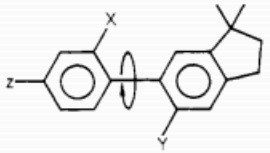
- *gem-dimethyl group provides a handle for NMR lineshape analysis.*



Bott, G.; Field, L. D.; Sternhell, S. *J. Am. Chem. Soc.* **1980**, *102*, 5618–5626.

# Activation Parameters

**Table I.** Activation Parameters for 6-(2-X-4-Z-Phenyl)-5-Y-1,1-dimethylindans




| | Y | X | Z | temp range, K | $\Delta G^{\ddagger}_{m}$,[a] kJ mol$^{-1}$ | $\Delta H^{\ddagger}$, kJ mol$^{-1}$ | $\Delta S^{\ddagger}$, J mol$^{-1}$ K$^{-1}$ | $\Delta G^{\ddagger}_{340}$,[b] kJ mol$^{-1}$ | $\Delta G^{\ddagger}_{340}$,[c] kJ mol$^{-1}$ |
|---|---|---|---|---|---|---|---|---|---|
| 1 | $CH_3$ | I | H | 356–415 | 89.9 ± 0.7 | 55.7 ± 1.3 | −88 ± 3.5 | 85.8 ± 1.0 | 86.3 ± 1.8 |
| 2 | $OCH_3$ | I | H | 299–325 | 69.8 ± 0.6 | 55.4 ± 1.5 | −46 ± 5 | 71.1 ± 0.7 | 72.0 ± 1.3 |
| 3 | $CH_3$ | Br | H | 335–367 | 83.8 ± 1.1 | 66.2 ± 1.5 | −50 ± 4 | 83.3 ± 1.2 | 82.9 ± 1.4 |
| 4 | $CH_3$ | Cl | H | 308–362 | 78.1 ± 1.0 | 49.4 ± 0.9 | −86 ± 2.5 | 78.6 ± 1.0 | 78.5 ± 1.1 |
| 5 | $CH_3$ | F | H | 210–273 | 51.8 ± 0.6 | 22.9 ± 2.0 | −120 ± 2 | 63.6 ± 0.8 | 59.6 ± 3.0 |
| 6 | $CH_3$ | $CH_3$ | H | 337–350 | 81.2 ± 1.0 | | | | 80.9 ± 1.0 |
| 7 | $OCH_3$ | $CH_3$ | H | 258–308 | 62.3 ± 0.7 | 39.6 ± 0.4 | −80 ± 1.5 | 66.8 ± 0.7 | 66.8 ± 2.1 |
| 8 | $CH_3$ | $OCH_3$ | H | 259–281 | 61.4 ± 0.7 | 48.0 ± 5.5 | −50 ± 5.5 | 64.9 ± 1.0 | 66.9 ± 2.4 |
| 9 | $CH_3$ | OH | H | 256–269 | 61.4 ± 0.8 | | | | 67.5 ± 2.7 |
| 10 | $CH_3$ | OAc | H | 275–290 | 65.3 ± 0.7 | 44.1 ± 1.5 | −75 ± 5 | 69.6 ± 1.0 | 69.8 ± 2.1 |
| 11 | $CH_3$ | COOMe | H | 297–322 | 70.8 ± 0.7 | 52.8 ± 0.9 | −58 ± 3 | 72.6 ± 0.7 | 73.2 ± 1.5 |
| 12 | $OCH_3$ | COOMe | H | 237–273 | 55.6 ± 0.5 | 37.2 ± 0.6 | −73 ± 2 | 61.8 ± 0.7 | 62.3 ± 2.5 |
| 13 | $CH_3$ | $COCH_3$ | H | 273,277 | 64.9 ± 0.7 | | | | 70.0 ± 2.3 |
| 14 | $CH_3$ | Ph | H | 293–311 | 70.5 ± 0.7 | 40.6 ± 1.5 | −99 ± 5 | 74.2 ± 0.9 | 73.5 ± 1.6 |
| 15 | $CH_3$ | $CH_2OH$ | H | 336–364 | 82.4 ± 0.9 | 64.0 ± 1.4 | −53 ± 4 | 81.9 ± 0.9 | 81.6 ± 1.2 |
| 16 | $CH_3$ | $CH_2OAc$ | H | 333–404 | 84.6 ± 0.9 | 67.3 ± 1.0 | −47 ± 2.5 | 83.2 ± 1.0 | 82.4 ± 1.6 |
| 17 | $CH_3$ | $CH(CH_3)_2$ | H | 420–457 | 100.8 ± 0.7 | 51.5 ± 2.1 | −113 ± 5 | 89.7 ± 1.9 | 93.0 ± 3.0 |
| 18 | $CH_3$ | $CF_3$ | H | 392–422 | 97.3 ± 1.1 | 77.8 ± 3.7 | −48 ± 9 | 94.1 ± 1.7 | 92.0 ± 2.7 |
| 19 | $OCH_3$ | $CF_3$ | H | 307–332 | 74.3 ± 0.8 | 57.0 ± 1.7 | −53 ± 5 | 75.4 ± 0.9 | 75.9 ± 1.3 |
| 20 | $CH_3$ | $NO_2$ | H | 275–304 | 68.8 ± 1.0 | | | | 72.8 ± 2.2 |
| 21 | $OCH_3$ | $NO_2$ | H | 233–253 | 55.3 ± 0.6 | | | | 63.0 ± 3.0 |
| 22 | $CH_3$ | $NH_2$ | H | 323–361 | 80.8 ± 0.9 | 53.1 ± 1.3 | −81 ± 4 | 80.7 ± 0.9 | 80.6 ± 1.0 |
| 23 | $CH_3$ | $NHCH_3$ | H | 352–376 | 86.6 ± 0.8 | 52.7 ± 3.3 | −93 ± 10 | 84.4 ± 1.1 | 84.7 ± 1.4 |
| 24 | $CH_3$ | $N(CH_3)_2$ | H | 301–338 | 71.5 ± 0.6 | 44.5 ± 1.0 | −84 ± 3 | 73.2 ± 0.7 | 73.1 ± 1.1 |
| 25 | $CH_3$ | $N(CH_3)_3^+$ | H | >422 | | | | | >94 |
| 26 | $CH_3$ | $NHCOCH_3$ | H | 284–308 | 67.6 ± 0.6 | 42.6 ± 0.3 | −84 ± 1 | 71.3 ± 0.7 | 71.1 ± 1.7 |
| 27 | $CH_3$ | $Si(CH_3)_3$ | H | 366–427 | 92.1 ± 0.8 | 53.6 ± 1.3 | −97 ± 3.5 | 86.6 ± 1.0 | 87.6 ± 2.2 |
| 28 | $CH_3$ | SH | H | 333–349 | 81.2 ± 0.9 | 45.9 ± 1.6 | −103 ± 5 | 81.1 ± 0.9 | 81.1 ± 0.9 |
| 29 | $CH_3$ | $SCH_3$ | H | 337–356 | 82.2 ± 0.8 | 53.1 ± 1.2 | −84 ± 3.5 | 81.6 ± 0.9 | 81.7 ± 1.0 |
| 30 | $CH_3$ | CN | H | 244–254 | 58.8 ± 0.8 | | | | 66.0 ± 3.0 |
| 31 | $CH_3$ | HgCl | H | 320–351 | 73.7 ± 0.5 | 39.9 ± 1.6 | −102 ± 5 | 74.6 ± 0.5 | 74.1 ± 0.6 |
| 32 | $CH_3$ | Cl | $NO_2$ | 310–344 | 76.5 ± 0.9 | 56.2 ± 0.9 | −62 ± 3 | 77.3 ± 0.9 | 77.5 ± 1.2 |
| 33 | $CH_3$ | F | $NO_2$ | 213–243 | 48.6 ± 0.6 | 19.6 ± 0.8 | −127 ± 3.5 | 62.9 ± 0.9 | 57.4 ± 3.3 |

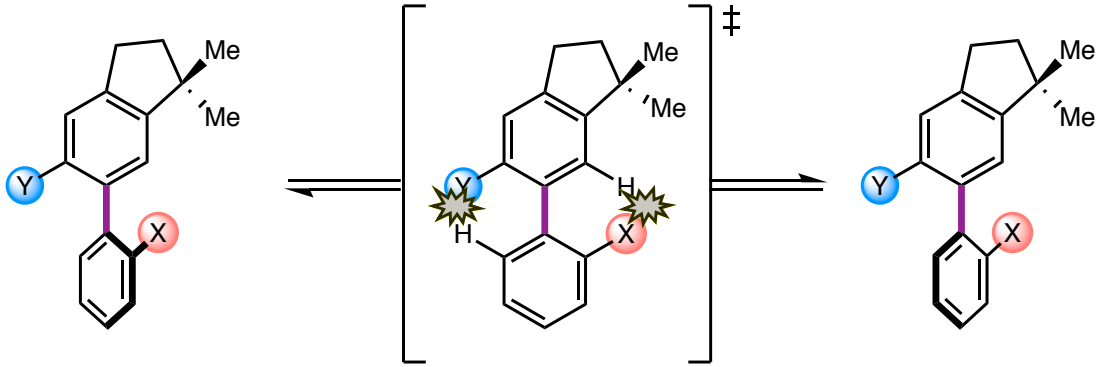
[a] $\Delta G^{\ddagger}$ at the temperature at the center of the range over which kinetic data was obtained. [b] $\Delta G^{\ddagger}$ at 340 K, calculated using $\Delta G^{\ddagger}_{m}$ and $\Delta S^{\ddagger}$. [c] $\Delta G^{\ddagger}$ at 340 K, calculated using $\Delta G^{\ddagger}_{m}$ and $\Delta S^{\ddagger}_{av}$.



Bott, G.; Field, L. D.; Sternhell, S. *J. Am. Chem. Soc.* **1980**, *102*, 5618–5626.

# Sternhell Interference Values—Steric Parameters

- Recognizing the additivity of the steric interactions in the biaryl system, simple algebraic manipulation of the $\Delta G^{\ddagger}$ values led Sternhell & co-workers to identify "***interference values***."



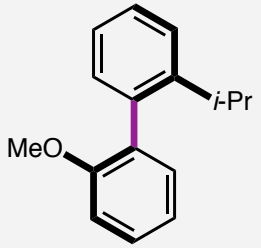

$$\Delta G^{\ddagger}(\text{tot}) = \Delta G^{\ddagger}(\text{X–H}) + \Delta G^{\ddagger}(\text{Y–H})$$

- *The constituent $\Delta G^{\ddagger}$ terms are interference values.*

**Table III.** $I_{340}^{X-H}$ Values for the Rotational Barriers of Biphenyls

| interacting group (X or Y) | $I_{340}^{X-H}$, kJ mol$^{-1}$ | interacting group (X or Y) | $I_{340}^{X-H}$, kJ mol$^{-1}$ |
|---|---|---|---|
| I | 45.7 ± 2.7 | $CH(CH_3)_2$ | 52.6 ± 4.1 |
| Br | 42.5 ± 2.5 | *t*-Bu | 76.6 ± 4.3[a] |
| Cl | 38.1 ± 2.2 | COOMe | 34.3 ± 3.1 |
| F | 19.2 ± 4.1 | $COCH_3$ | 29.6 ± 3.4 |
| H | ~4[a] | Ph | 33.1 ± 2.7 |
| MeO | 26.6 ± 1.2 | CN | 25.6 ± 4.1 |
| HO | 27.1 ± 3.8 | $NMe_2$ | 32.7 ± 2.2 |
| AcO | 29.4 ± 3.2 | NHMe | 44.3 ± 2.5 |
| SMe | 41.3 ± 2.1 | $NH_2$ | 40.2 ± 2.1 |
| SH | 40.7 ± 2.0 | $NMe_3^+$ | >53.6 |
| $CH_3$ | 40.4 ± 1.1 | $NCOCH_3$ | 30.7 ± 2.8 |
| $CF_3$ | 50.6 ± 3.1 | $NO_2$ | 32.4 ± 3.3 |
| $CH_2OH$ | 41.2 ± 2.3 | HgCl | 33.7 ± 1.7 |
| $CH_2OAc$ | 42.0 ± 2.7 | $SiMe_3$ | 47.2 ± 3.3 |

***Independent Verification***




$\Delta G^{\ddagger}$ = 18.8 kcal/mol (NMR)
$\Delta G^{\ddagger}$ = 18.9 kcal/mol (Sternhell)



Bott, G.; Field, L. D.; Sternhell, S. *J. Am. Chem. Soc.* **1980**, *102*, 5618–5626.

# Effective Radii—Another Steric Parameter

- Sternhell & co-workers were also able to derive the ***effective radius*** of each functional group studied, a useful parameter describing the size of a substituent.

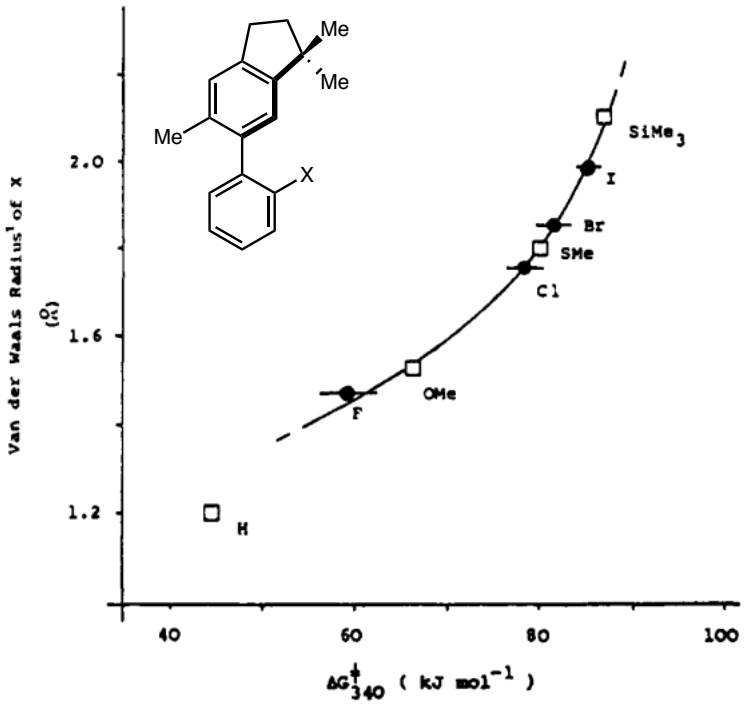



**Figure 3.** Plot of $\Delta G_{340}^{\ddagger}$ against the van der Waals radius[1] of X in some 6-(2-X-phenyl)-1,1,5-trimethylindans (**1**, Y = Me).

**Table II.** Effective van der Waals Radii (Å) Derived from Rotational Barriers in 6-Aryl-1,1,5-trimethylindans (**1**, Y = Me)

| X | effective radius (this work)[a] | van der Waals radius (Bondi)[1] | effective radius (Charton)[3] |
|---|---|---|---|
| I | 1.97 ± 0.06 | 1.98 | 1.97 |
| Br | 1.86 ± 0.04 | 1.85 | 1.85 |
| Cl | 1.73 ± 0.03 | 1.75 | 1.73 |
| F | 1.47 ± 0.01 | 1.47 | 1.47 |
| OMe | 1.52 ± 0.03 | 1.52 (O) | 1.56 |
| OH | 1.53 ± 0.03 | | 1.52 |
| OAc | 1.56 ± 0.03 | | |
| SMe | 1.82 ± 0.03 | 1.80 (S) | 1.84 |
| SH | 1.80 ± 0.03 | | 1.80 |
| $CH_3$ | 1.80 ± 0.03 | 2.0 | 1.72, 2.23[b] |
| $CF_3$ | 2.2 ± 0.13 | | 2.11, 2.74[b] |
| $CH_2OH$ | 1.82 ± 0.04 | | 1.73 |
| $CH_2OAc$ | 1.84 ± 0.05 | | |
| $CH(CH_3)_2$ | 2.2 ± 0.12 | | 1.96 |
| *t*-Bu | 3.6 ± 0.5[c] | | 2.4, 3.2[b] |
| COOMe | 1.62 ± 0.03 | | |
| $COCH_3$ | 1.56 ± 0.04 | | |
| Ph | 1.62 ± 0.03 | 1.77 | 1.77 |
| CN | 1.51 ± 0.03 | 1.78 | 1.60 |
| $NMe_2$ | 1.61 ± 0.02 | 1.55 (N) | 1.63 |
| NHMe | 1.91 ± 0.05 | | |
| $NH_2$ | 1.79 ± 0.03 | | |
| $NMe_3^+$ | >2.27 | | 2.42, 3.11[b] |
| $NCOCH_3$ | 1.58 ± 0.03 | | |
| $NO_2$ | 1.61 ± 0.04 | | 1.79 |
| HgCl | 1.63 ± 0.01 | 1.5–1.65 (Hg) | |
| $SiMe_3$ | 2.01 ± 0.08 | 2.1 | 2.6, 3.99[b] |

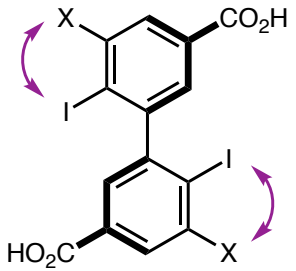
[a] Derived by intrapolation (see Figure 3, Table I, and text). Confidence limits reflect those of the activation parameters (Table I). [b] Charton's value of $r_{min}$ and $r_{max}$. [c] See text. The $\Delta G^{\ddagger}_{340}$ for this compound is well beyond the range encompassed by the halogens so the effective radius of *tert*-butyl is not well defined.



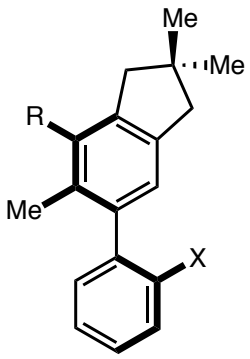
Bott, G.; Field, L. D.; Sternhell, S. *J. Am. Chem. Soc.* **1980**, *102*, 5618–5626.

# Other Factors that Affect Rotational Barriers in Atropisomers

- ***Buttressing Effects***

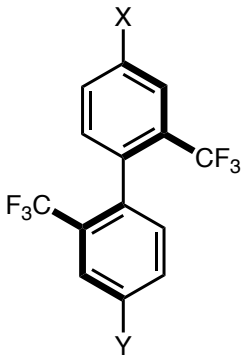



X = H, $\Delta G^{\ddagger}$ = 23.4 kcal/mol
X = I, $\Delta G^{\ddagger}$ = 30.1 kcal/mol

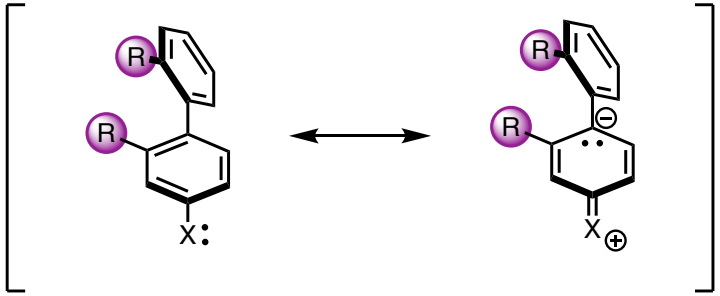



| X | R | $\Delta G^{\ddagger}$ (kcal/mol) | $\Delta\Delta G^{\ddagger}$ (kcal/mol) |
|---|---|---|---|
| F | H | 14.2 | 2.0 |
| F | Br | 16.2 | |
| Cl | H | 18.8 | 2.2 |
| Cl | Br | 21.0 | |
| $NO_2$ | H | 17.4 | 2.0 |
| $NO_2$ | Br | 19.4 | |

- ***Electronic Effects***




| X | Y | $\Delta G^{\ddagger}$ (kcal/mol) |
|---|---|---|
| H | H | 25.6 |
| OMe | H | 24.9 |
| OMe | OMe | 24.4 |
| $NO_2$ | H | 25.8 |
| $NO_2$ | $NO_2$ | 26.3 |

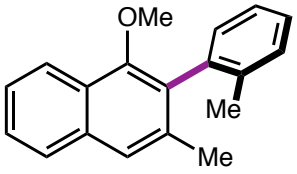



- *n → π* donation into arene increases $sp^3$-character of at biaryl C-atom*


Wolf, C.; Hochmuth, D. H.; König, W. A.; Roussel, C. *Liebigs Ann.* **1996**, *357*–363.
Rieger, M.; Westheimer, F. H. *J. Am. Chem. Soc.* **1950**, *72*, 19–28.
Bringmann, G.; Mortimer, A. J.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 5384–5427.

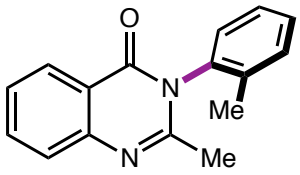
# Other Factors that Affect Rotational Barriers in Atropisomers

- *Bond Length Effects*

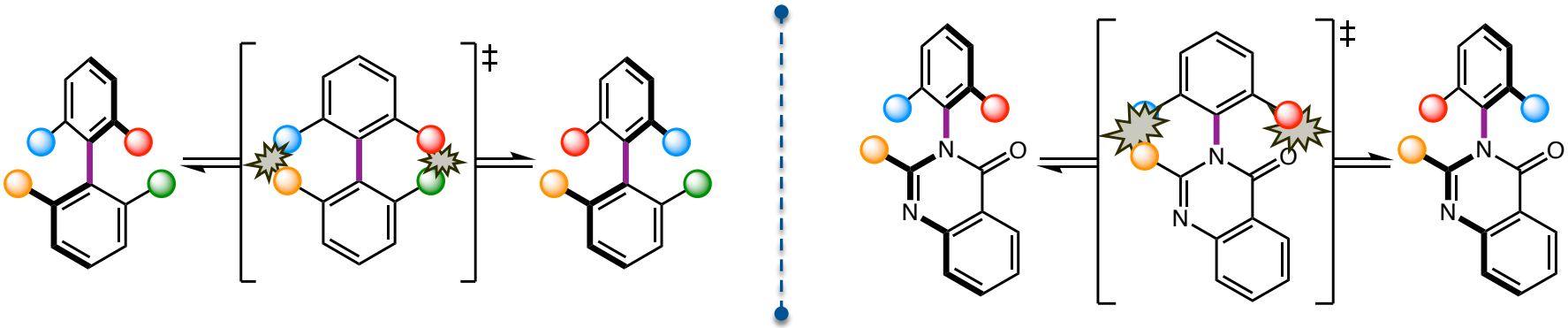



$\Delta G^{\ddagger}$ = ca. 30 kcal/mol
$t_{1/2}$ > 30 y
$r_{C-C}$ = 1.49 Å

*vs.*




$\Delta G^{\ddagger}$ = ca. 36 kcal/mol
$t_{1/2}$ ~ 800,000 y
$r_{C-C}$ = 1.37 Å

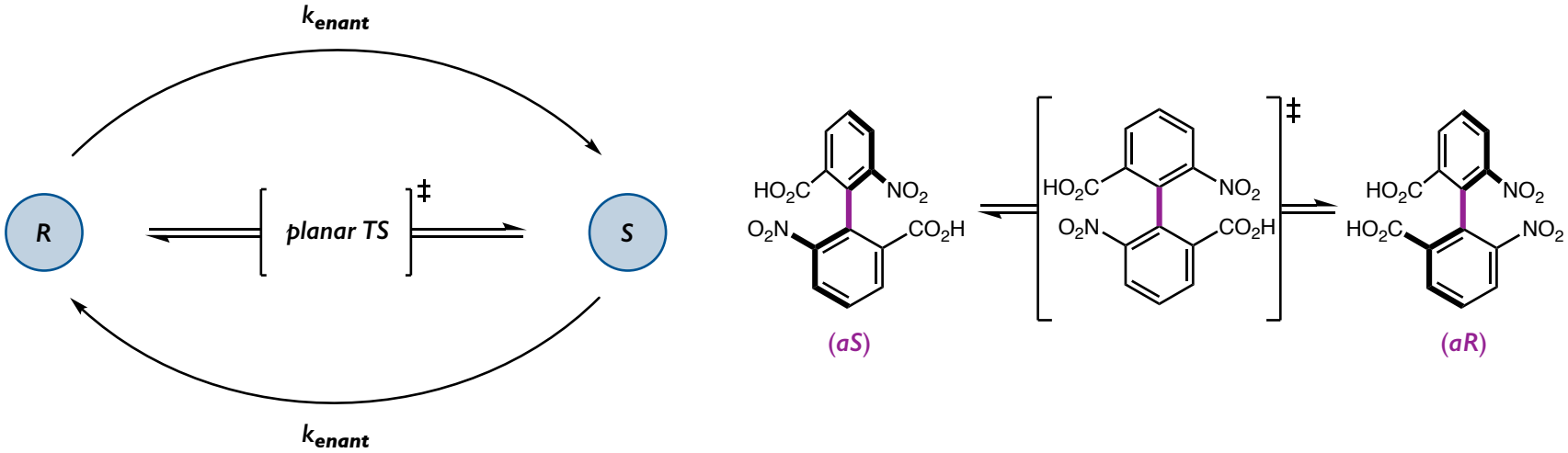



• *Strain is exacerbated in the coplanar TS when the atropisomeric bond is shorter in length.*

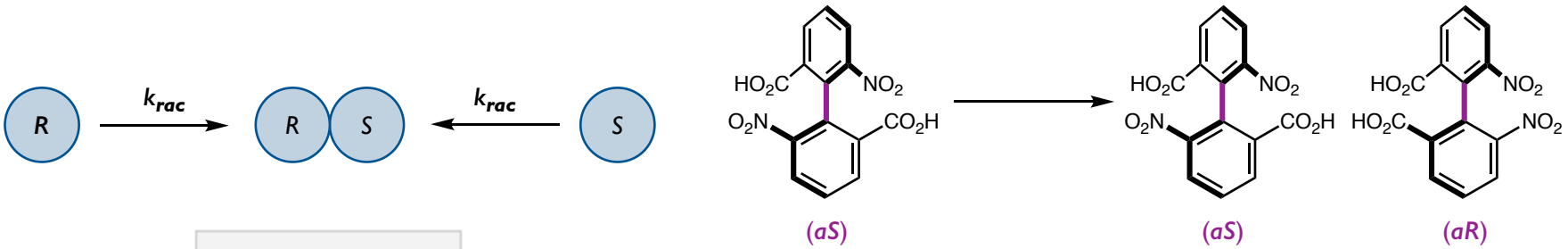

Kumarasamy, E.; Raghunathan, R.; Sibi, M. P.; Sivarugu, J. *Chem. Rev.* **2015**, *115*, 11239–11300.
Bringmann, G.; Mortimer, A. J.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 5384–5427.

# Racemization vs. Enantiomerization

- ***Enantiomerization*** is the (microscopic) reversible process in which an a molecule switches its configuration (e.g., *R* to *S*, or *vice versa*).




- ***Racemization*** is a macroscopic process, whereby an enantiopure or enantioenriched compound becomes racemic (loses its optical activity).




$$k_{rac} = 2k_{enant}$$

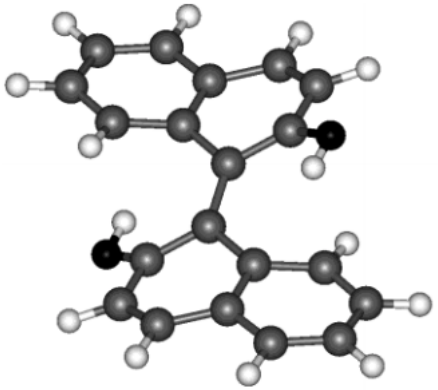


Reist, M.; Testa, B.; Carrupt, P.-A.; Jung, M.; Schurig, V. *Chirality* **1995**, *7*, 396–400.

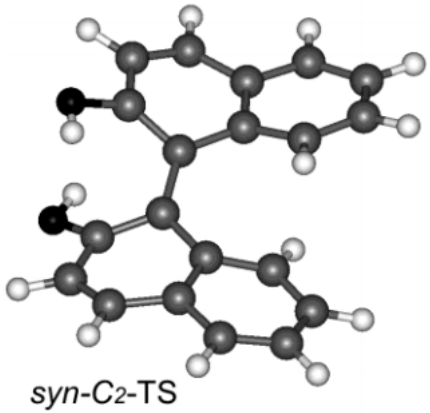
# Modes of Racemization—Bond Rotation

- Many atropisomeric compounds thermally racemize *via* bond rotation about the chiral axis. If barriers are significantly high, decomposition will occur before racemization.

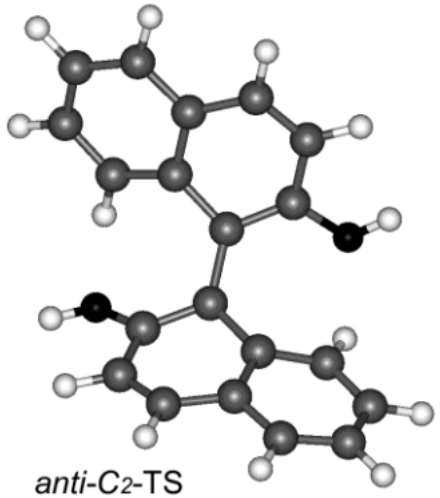
- ***Thermal Racemization of BINOL*—B3LYP/6-31G(d,p)**



*anti*-$C_i$-TS



*syn*-$C_2$-TS



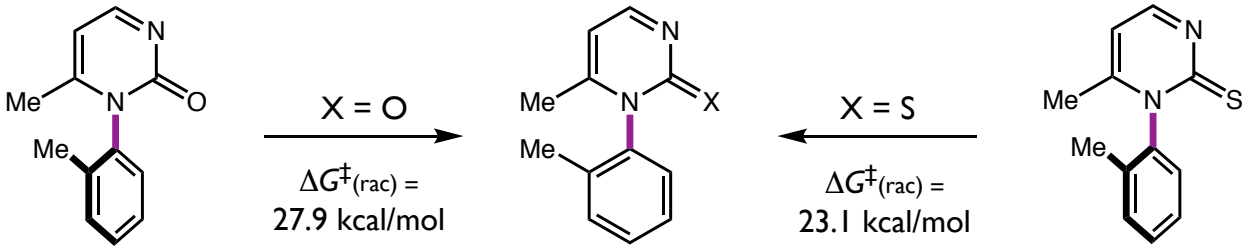
*anti*-$C_2$-TS

| structure | rel energy (kJ/mol) | angle C(2)–C(1)–C(1′)–C(2′) (deg) | distance (pm) | | | |
|---|---|---|---|---|---|---|
| | | | C(1)–C(1′) | H(2)–H(8′) | H(2)–H(2′) | H(8)–H(8′) |
| GS | 0 | 94.8 | 150 | 327 | 336 | 375 |
| *anti*-$C_i$-TS | 158.3 | 180 | 149 | 218 | dist C(8)–H(2′) 209 | |
| *syn*-$C_2$-TS | 175.3 | 25.6 | 150 | | 255 | 202 |
| *anti*-$C_2$-TS | 249.4 | 172.7 | 152 | | dis. O(1)–H(8′) 201 | |

Meca, L.; Reha, D.; Havlas, Z. *J. Org. Chem.* **2003**, *68*, 5677–5680.

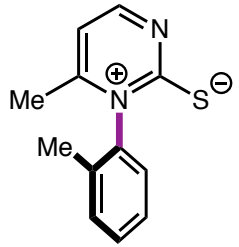
# Heteroatom Considerations in Bond Rotation

- Racemization modes, and the barriers that enable them, will vary on a case-by-case basis.
- In heterobiaryl-type atropisomers, it is important to consider the possible heteroatom effects on the racemization mode/barrier.

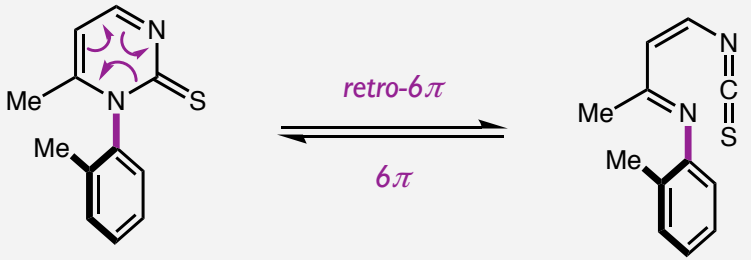



*pyrimidinone* *pyrimidinethione*

**Hypothesis**




- *Long C–S bond with more single bond character is more readily distorted during transition through coplanar TS.*

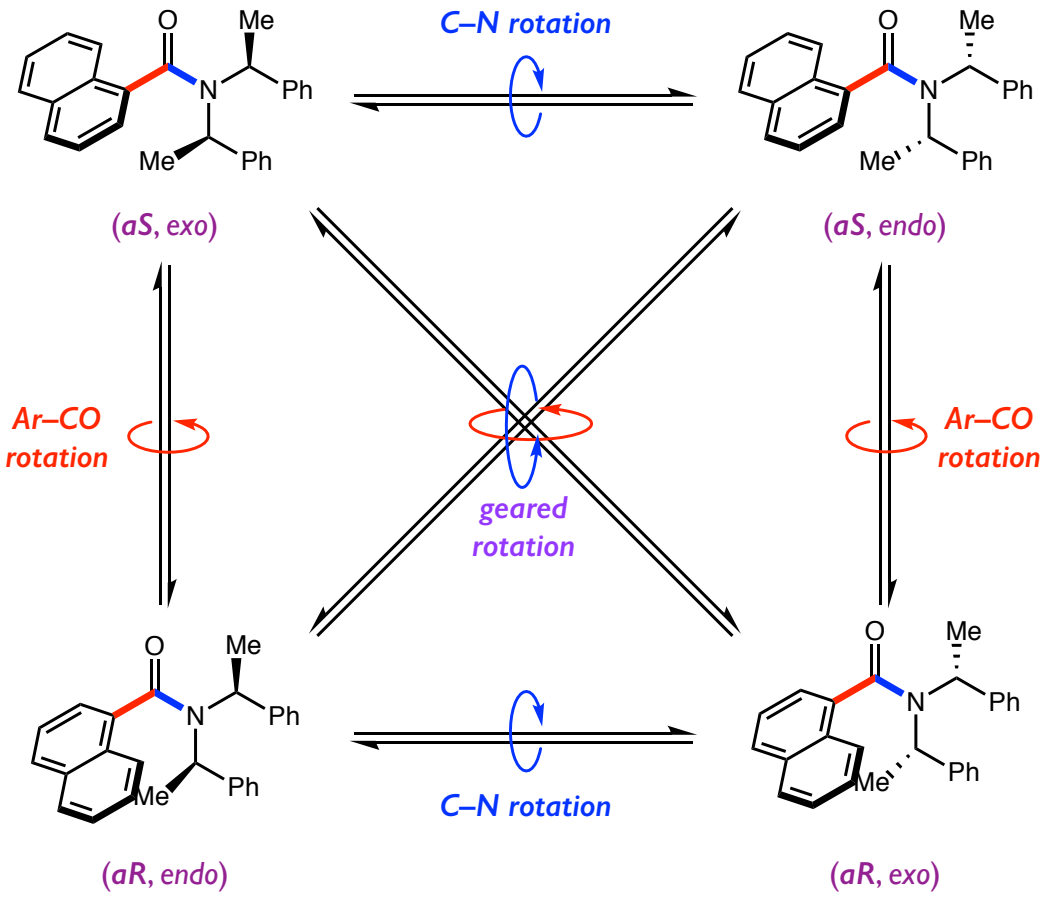




Kashima, C.; Katoh, A. *J. Chem. Soc., Perkin Trans.* **1980**, 1599–1602.
Roussel, C.; Adjimi, M.; Chemlal, A.; Djafri, A. *J. Org. Chem.* **1988**, *53*, 5076–5080.

# Modes of Racemization—Gearing

- Clayden & co-workers have extensively studied the stereodynamics of tertiary benzamide atropisomers using NMR lineshape analysis.




- *C–N or Ar–CO rotations are expected to exchange all NMR signals.*
- *Geared rotation will only exchange signals rising from a given diastereomer, and only the N-substituents should be affected.*

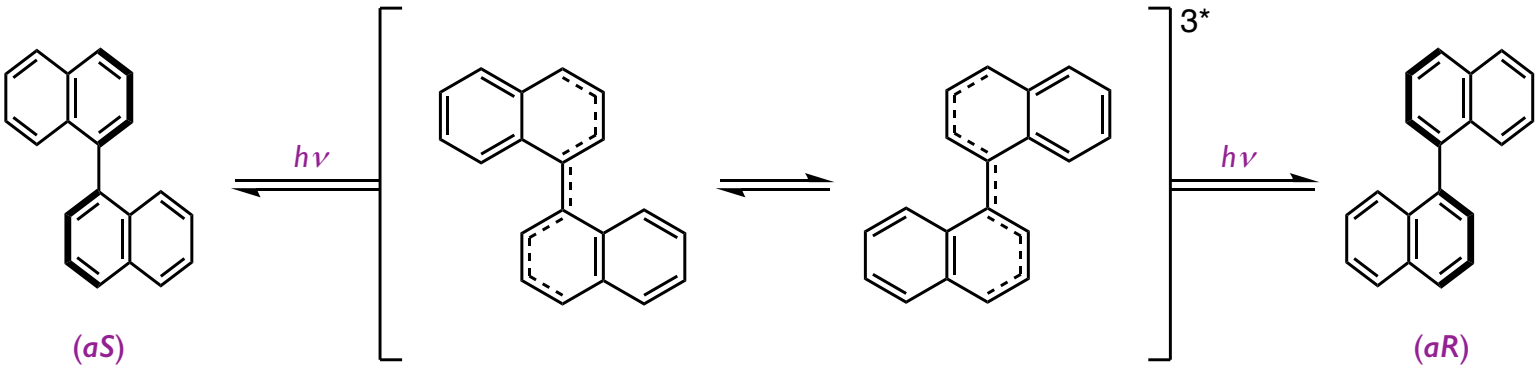
$\Delta G^{\ddagger}$(Ar–CO) = 16.8 kcal/mol
$\Delta G^{\ddagger}$(geared) = 16.2 kcal/mol

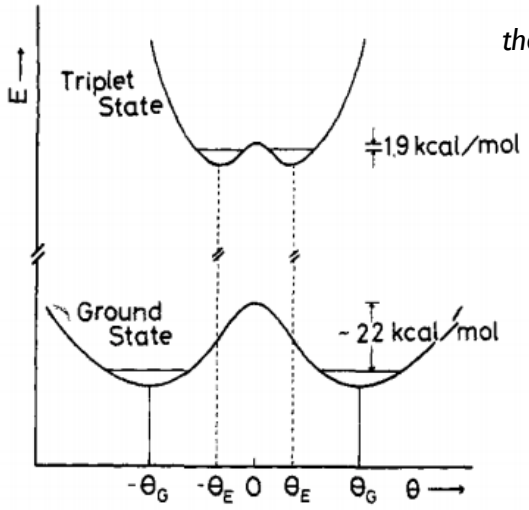
*Geared rotation is ~3x faster!*


Bragg, R. A.; Clayden, J.; Morris, G. A.; Pink, J. H. *Chem.—Eur. J.* **2002**, *8*, 1279–1289.
Clayden, J.; Pink, J. H. *Angew. Chem. Int. Ed.* **1998**, *37*, 1937–1939.

# Modes of Racemization—Photochemical

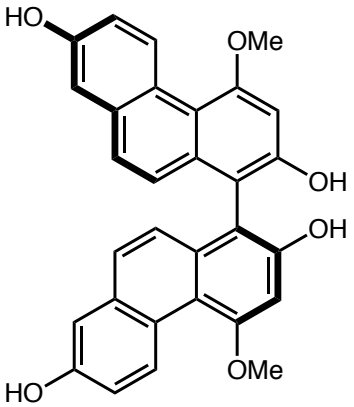
- Binaphthyl-type scaffolds are able to racemize *via* the ***triplet excited state***.
  - The biradical character of the triplet has a higher bond order between the two naphthyl nuclei, resulting in a more planar structure.




• *Flattening in triplet excited state destabilizes the structure, such that enantiomerization is rapid.*

$\Delta G^{\ddagger}$ = 24.1 kcal/mol in GS
$\Delta G^{\ddagger}$ = 1.9 kcal/mol in T*

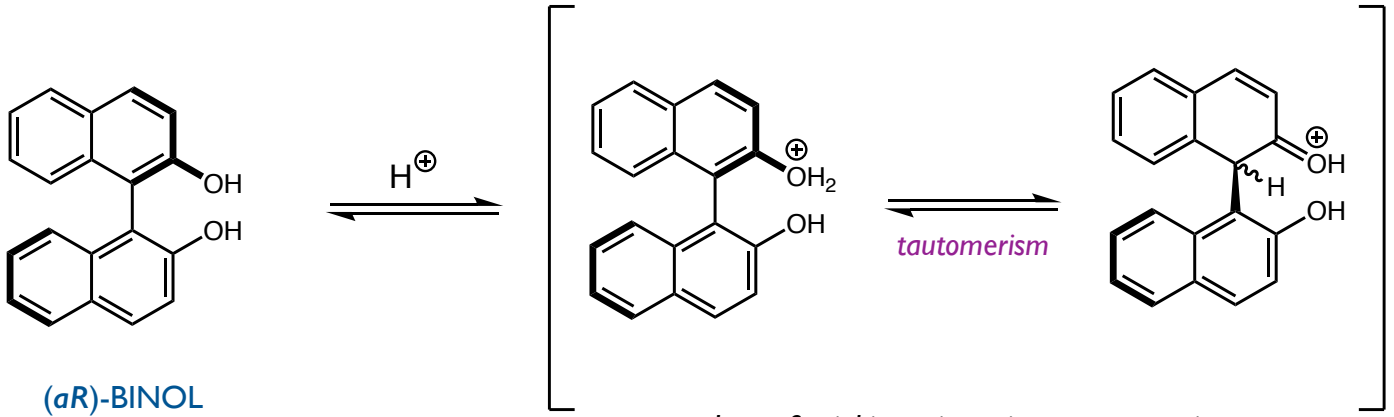



***blestriarene C***
$t_{1/2}$(rac) = 30 min under *hν*


Irie, M.; Yoshida, K.; Hayashi, K. *J. Phys. Chem.* **1977**, *81*, 969–972.
Hattori, T.; Shimazumi, Y.; Goro, H.; Yamabe, O.; Morohashi, N.; Kawai, W.; Miyano, S. *J. Org. Chem.* **2003**, *68*, 2099–2108.

# Modes of Racemization—Acid/Base Reactivity

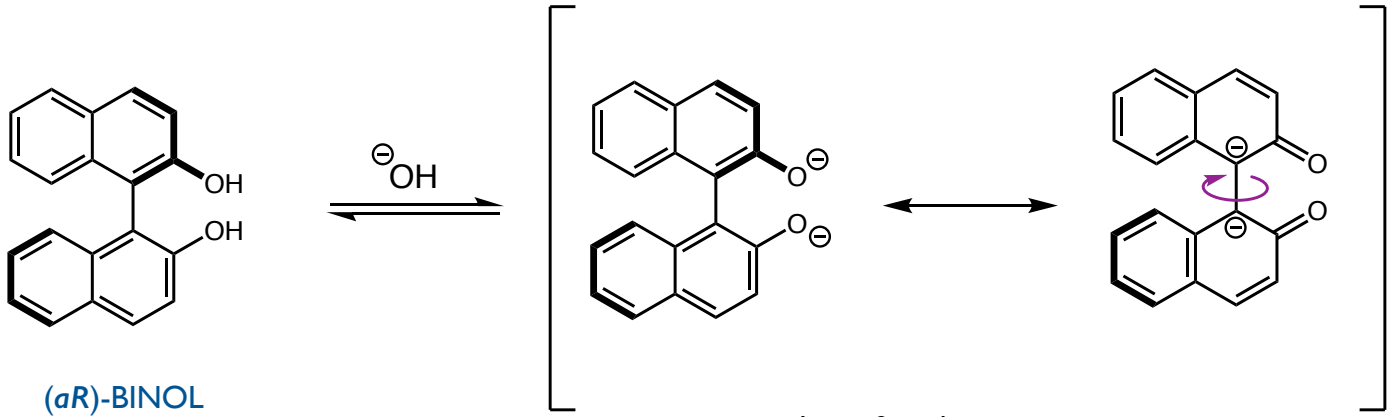
- *Acid-Catalyzed Racemization of BINOL*




(*aR*)-BINOL
$\Delta G^{\ddagger}$ = 37.8 kcal/mol
$t_{1/2}$ = 1.7 x $10^4$ millennia

- *Loss of axial integrity owing to tautomerism.*
- *Full loss of optical activity after 24 h at 100 °C.*

- *Base-Catalyzed Racemization of BINOL*




(*aR*)-BINOL

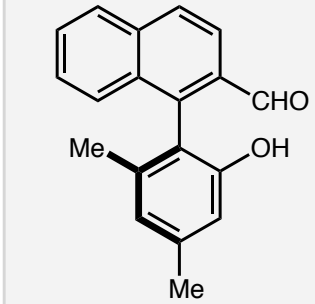
- *Loss of axial integrity owing to accumulation of $sp^3$-character at biaryl bond.*

Kyba, E. P.; Gokel, G.W.; de Jong, F.; Koga, K.; Sousa, L. R.; Sielgel, M. G.; Kaplan, L.; Sogah, G. D.Y.; Cram, D. J. *J. Org. Chem.* **1977**, *42*, 4173–4184.

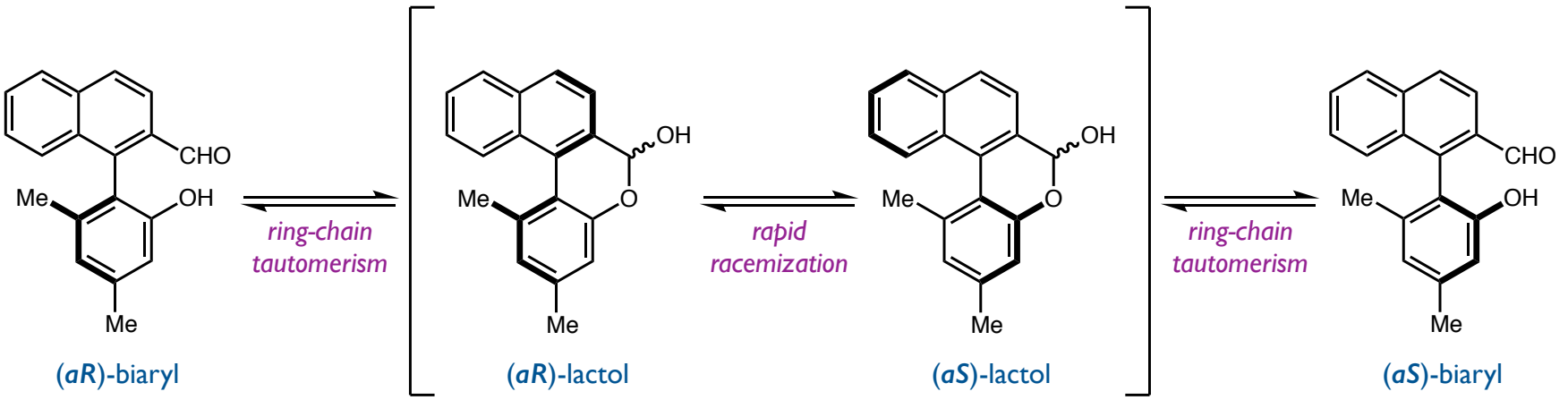
# Modes of Racemization—Formation of a Bridge

- Bringmann & co-workers prepared the enantiopure biaryl aldehyde compound shown and observed that it ***racemized slowly at rt despite being tetra-ortho-substituted***.

- DFT calculations provided insight into the mechanism of racemization, which was found to involve a ***transient lactol species***.



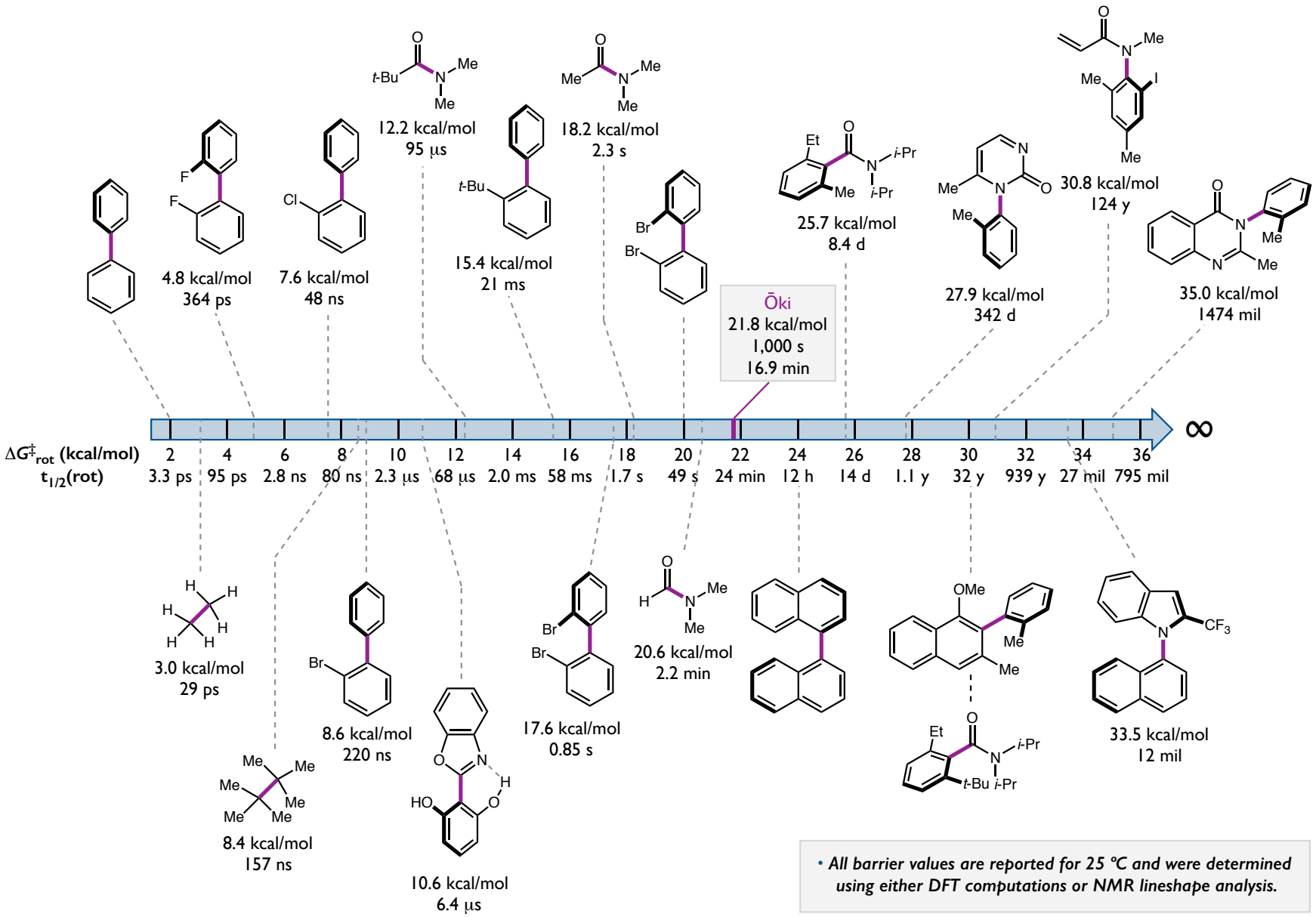

(*aR*)-biaryl
$t_{1/2}$(rac) = 6.5 h at rt
$\Delta G^{\ddagger}$(rac) = 23.7 kcal/mol




• *Formation of 6-membered lactol bridge decreases enantiomerization barrier via ground state destabilization.*


Bringmann, G.; Hartung, T. *Liebigs Ann.Chem.* **1994**, 313–316.
Bringmann, G.; Vitt, D.; Kraus, J.; Breuning, M. *Tetrahedron* **1998**, *54*, 10691–10698.

# Overview of Rotational Barriers




- *All barrier values are reported for 25 °C and were determined using either DFT computations or NMR lineshape analysis.*

# Atropisomers

*Fundamentals, Pharmaceutical Considerations, & Selective Syntheses*

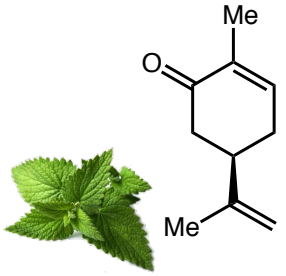
I. Historical Development & Fundamentals

II. **Considerations in Drug Development**

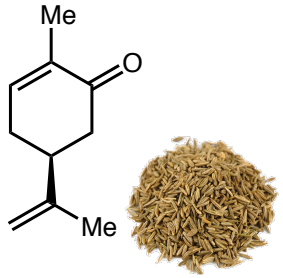
III. Overview of Atroposelective Synthetic Methods

IV. Summary & Conclusions

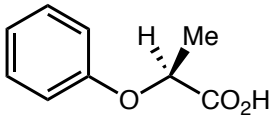
# Biological Discrimination of Enantiomers



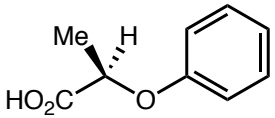

(*R*)-(–)-carvone
- *spearmint odor*



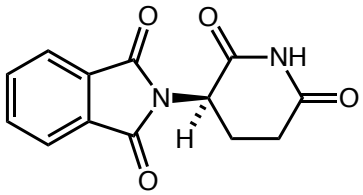

(*S*)-(+)-carvone
- *caraway odor*



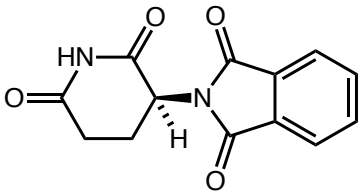

(*S*)-(+)-α-(2-bromophenoxy)-propionic acid
- *plant growth stimulant (auxin)*




(*R*)-(–)-α-(2-bromophenoxy)-propionic acid
- *plant growth antagonist (anti-auxin)*



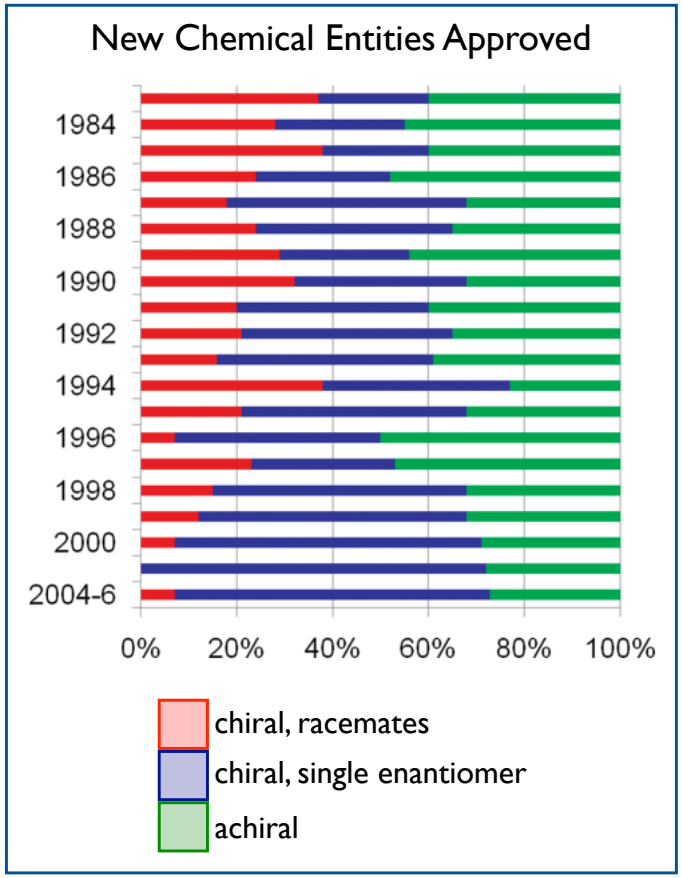

(*R*)-thalidomide (eutomer)
- *anti-nausea*
- *sedative*



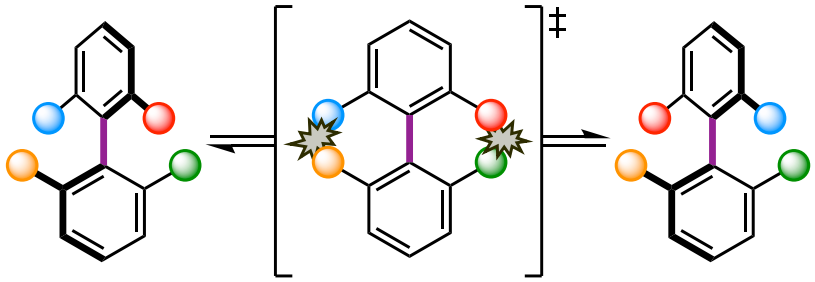

(*S*)-thalidomide (distomer)
- *teratogen*


Eriksson, T.; Bjorkman, S.; Roth, B.; Fyge, A.; Hoglund, P. *Chirality* **1995**, *7*, 44–52.
Reist, M.; Carrupt, P.-A.; Francotte, E.; Testa, B. *Chem. Res. Toxicol.* **1998**, *11*, 1521–1528.

# Atropisomers in Pharmaceutical Chemistry




- ***What does this mean for atropisomeric drugs and drug candidates?***



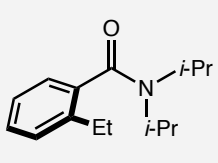
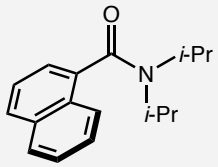
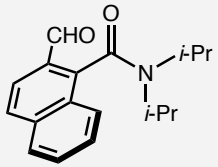
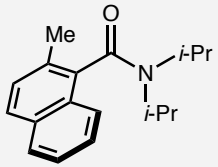
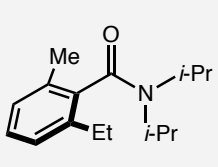
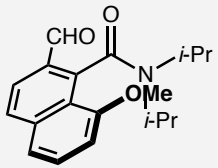
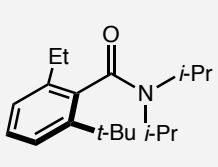

- *Enantiomers equilibrate via bond rotation.*
- *Drug stability/composition is therefore time-dependent.*

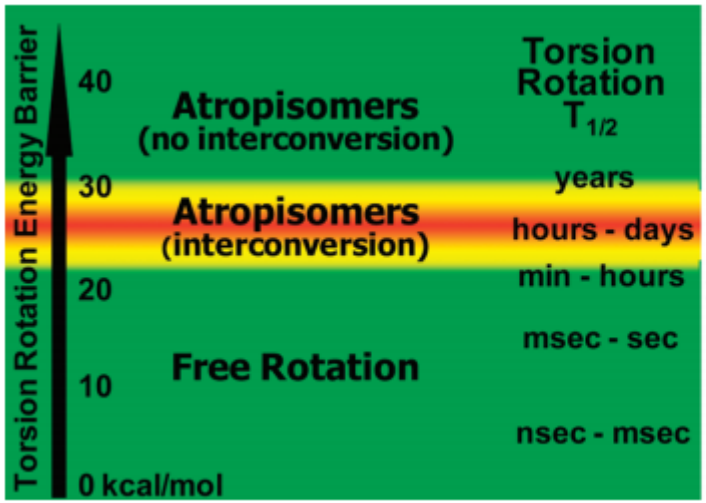
- Configurational stability of atropisomeric drugs is dependent on their rotational barriers, which in turn are dependent on steric and electronic effects, temperature, solvent, medium, etc.

- "Overall, many view atropisomer chirality as a lurking menace with the potential to…derail drug development programs…"


Clayden, J.; Moran, W. J.; Edwards. P. J.; LaPlante, S. R. *Angew. Chem. Int. Ed.* **2009**, *48*, 6398–6401.
LaPlante, S. R.; Edwards, P. J.; Fader, L. D.; Jakalian, A.; Hucke, O. *ChemMedChem* **2011**, *6*, 505–513.
LaPlante, S. R.; Fader, L. D.; Fandrick, K. R.; Fandrick, D. R.; Hucke, O.; Kemper, R.; Miller, S. P. F.; Edwards, P. J. *J. Med. Chem.* **2011**, *54*, 7005–7022.

# Guidelines for Atropisomer Classification

| |  |  |  |  |  |  |  |
|---|---|---|---|---|---|---|---|
| $\Delta G^{\ddagger}$ (kcal/mol) | 14.2 | 17.9 | 21.6 | 25.1 | 25.7 | 29.2 | 30.0 |
| $t_{1/2}$ | 0.002 s | 1 s | 12 min | 75 h | 10 d | > 10 y | >>10 y |




***Class 3:***
**Generally developed as a single compound.**

***Class 2:***
**Development pathway customized case-by-case, but usually as a mixture.**

***Class 1:***
**Develop as a single compound (rapidly equilibrating mixture).**

**Rule-of-Thumb**

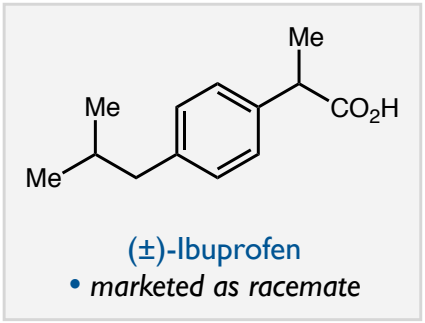
- *A drug compound should maintain 99.5% homogeneity over 24 h in vivo.*
- *$\Delta G^{\ddagger}$ > 27.3 kcal/mol & $t_{1/2}$ > 138 d*


Ahmed, A.; Bragg, R. A.; Clayden, J.; Lai, L. W.; McCarthy, C.; Pink, J. H. *Tetrahedron* **1998**, *54*, 13277–13294.
LaPlante, S. R.; Edwards, P. J.; Fader, L. D.; Jakalian, A.; Hucke, O. *ChemMedChem* **2011**, *6*, 505–513.

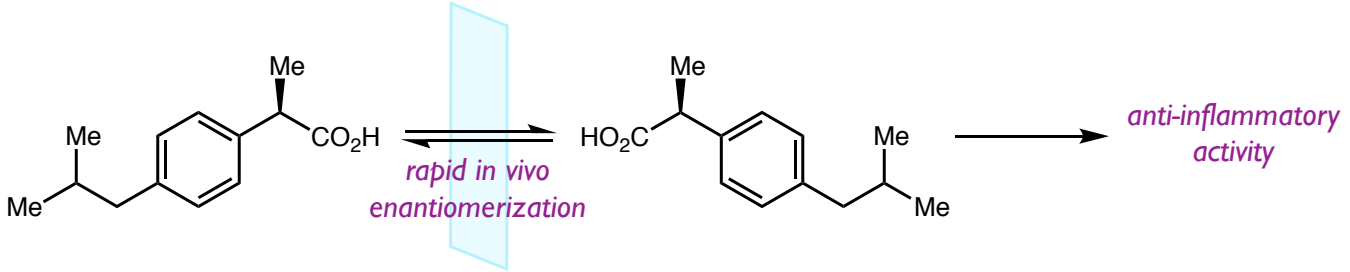
# Class 1 (Non)Atropisomers

- According to the LaPlante scheme, ***Class 1 Atropisomers*** are those compounds with ***rotational barriers of 0–20 kcal/mol at 25 °C***—freely rotating, inseparable mixture of stereoisomers.

- This situation can be dealt with in much the same way as a point-chiral drug that racemizes rapidly *in vivo*, such as Ibuprofen.




(±)-Ibuprofen
- *marketed as racemate*




(*R*)-(–)-Ibuprofen
- *distomer*

(*S*)-(–)-Ibuprofen
- *eutomer*



Friary, R. F.; Spangler, M.; Osterman, R.; Schulman, L.; Schwerdt, J. H. *Chirality* **1996**, *8*, 364–371.
LaPlante, S. R.; Fader, L. D.; Fandrick, K. R.; Fandrick, D. R.; Hucke, O.; Kemper, R.; Miller, S. P. F.; Edwards, P. J. *J. Med. Chem.* **2011**, *54*, 7005–7022.

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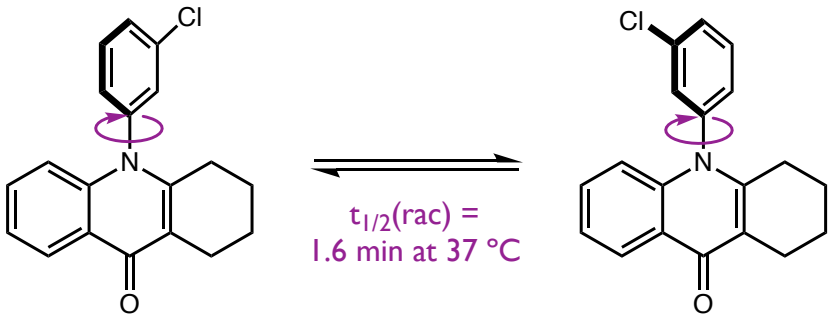



Sch 40120

- *5-Lipoxygenase inhibitor for acute inflammatory diseases (e.g., psoriasis).*
- *Individual enantiomers observed analytically on chiral HPLC, but equilibrating.*
- *Rapid in vivo racemization led to development of drug as a racemic mixture.*

- It is still appropriate to investigate the critical pharmacological attributes of both isomers in order to demonstrate that it has favorable ADMET(E) properties.

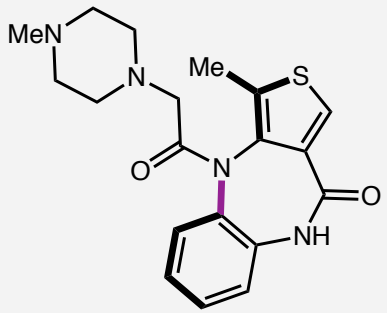


Friary, R. F.; Spangler, M.; Osterman, R.; Schulman, L.; Schwerdt, J. H. *Chirality* **1996**, *8*, 364–371.
LaPlante, S. R.; Fader, L. D.; Fandrick, K. R.; Fandrick, D. R.; Hucke, O.; Kemper, R.; Miller, S. P. F.; Edwards, P. J. *J. Med. Chem.* **2011**, *54*, 7005–7022.

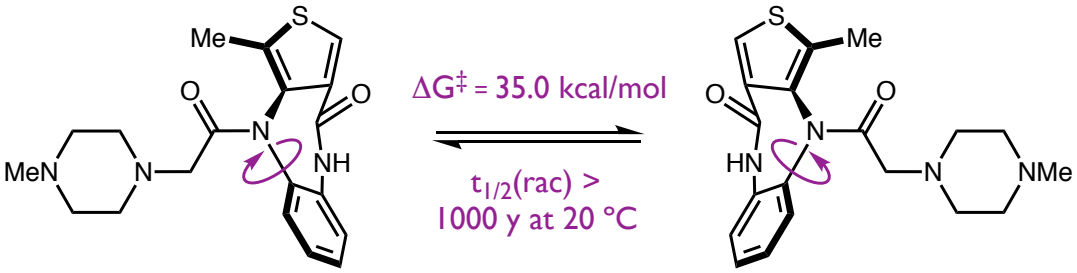
# Class 3 Atropisomers

- Compounds in which the ***barrier to rotation about the chiral axis is >30 kcal/mol*** are considered to be ***Class 3 Atropisomers***—configurationally stable on the order of years.

- If configurational stability can be clearly demonstrated under physiological conditions, it is recommended to ***develop the drugs as single-enantiomer compounds***.




Telenzepine
- *selective muscarinic antagonist*
- *used to treat peptidic ulcers*




(–)-Telenzepine
- *distomer (inactive)*

(+)-Telenzepine
- *eutomer (500x more active)*



Eveleigh, P.; Hulme, E. C.; Schudt, C.; Birdsall, N. J. M. *Mol. Pharmacol.* **1989**, *35*, 477–483.
LaPlante, S. R.; Fader, L. D.; Fandrick, K. R.; Fandrick, D. R.; Hucke, O.; Kemper, R.; Miller, S. P. F.; Edwards, P. J. *J. Med. Chem.* **2011**, *54*, 7005–7022.

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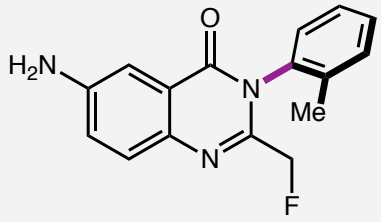
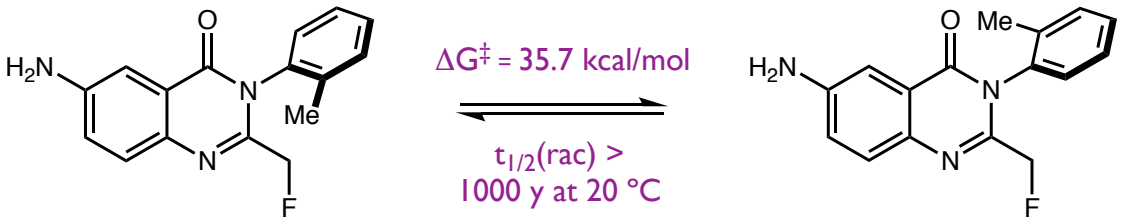



Afloqualone
- *$GABA_a$ receptor agonist*
- *sedative & muscle relaxant*
- *recreational hypnotic*




- *quinazolinone-type drugs have high barriers to rotation owing, in part, to the short C–N bond of the chiral anilide axis.*



Yamada, Y.; Otsuka, M.; Tani, J.; Oine, T. *Chem. Pharm. Bull.* **1983**, *31*, 1158–1165.
LaPlante, S. R.; Fader, L. D.; Fandrick, K. R.; Fandrick, D. R.; Hucke, O.; Kemper, R.; Miller, S. P. F.; Edwards, P. J. *J. Med. Chem.* **2011**, *54*, 7005–7022.

# Class 2 Atropisomers

- Compounds characterized by ***rotational barriers of 20–30 kcal/mol*** about the chiral axis give rise to Class 2 Atropisomers—racemization half-lives on the order of hours-days-years.

- These are the most problematic type of atropisomers for drug development, as the ***enantiomeric composition of the substance may change*** as a function of time—quality control issues.

- The pharmaceutical industry has handled atropisomers of this type in three ways:

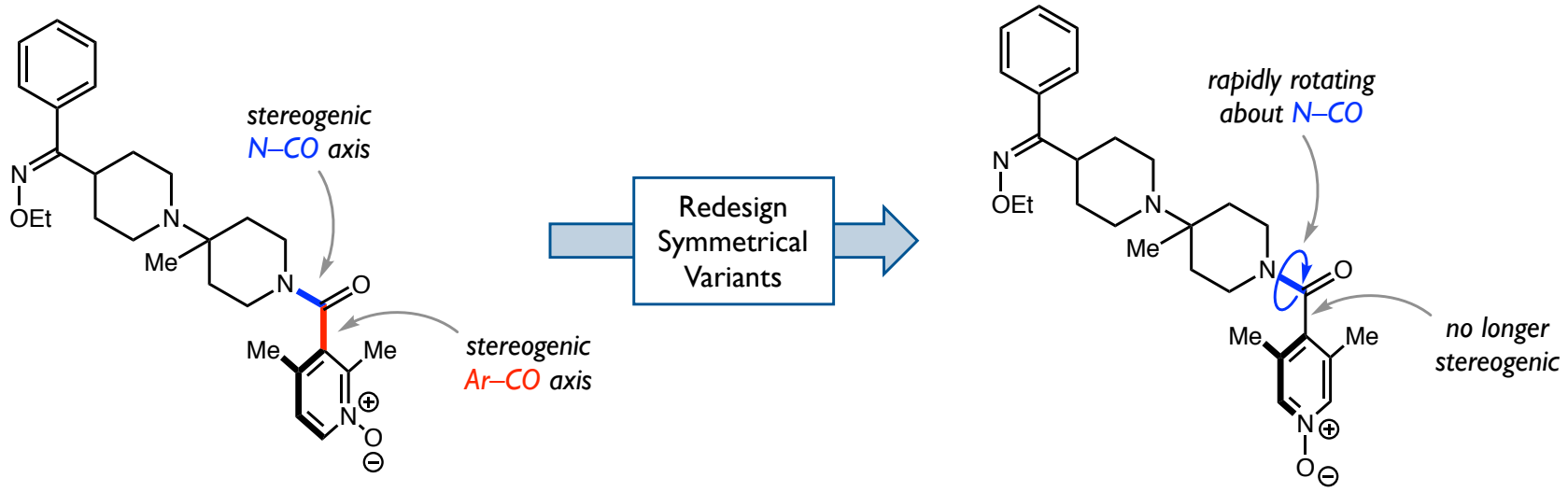
1. ***Symmetrization*** **(chiral axis to achiral axis)**
2. ***Redesigning Higher Barriers*** **(Class 2 to Class 3 transition)**
3. ***Redesigning Smaller Barriers*** **(Class 2 to Class 1 transition)**



LaPlante, S. R.; Fader, L. D.; Fandrick, K. R.; Fandrick, D. R.; Hucke, O.; Kemper, R.; Miller, S. P. F.; Edwards, P. J. *J. Med. Chem.* **2011**, *54*, 7005–7022.

# Symmetrizing a Class 2 Atropisomer

- Schering–Plough identified **Sch 351125** as a hit HIV therapeutic, and found that it existed as an equilibrating mixture of four stereoisomers, owing to restricted rotation about the two stereogenic axes.




Sch 351125
- *CCR5 antagonist*
- *inhibits HIV entry into host cells*
- *mixture of four atropisomeric steroisomers*

Symmetrized Derivative
- *now rapidly equilibrating racemate*
- *similar efficacy in binding & viral entry assays*
- *overall pharmacological profile inferior*

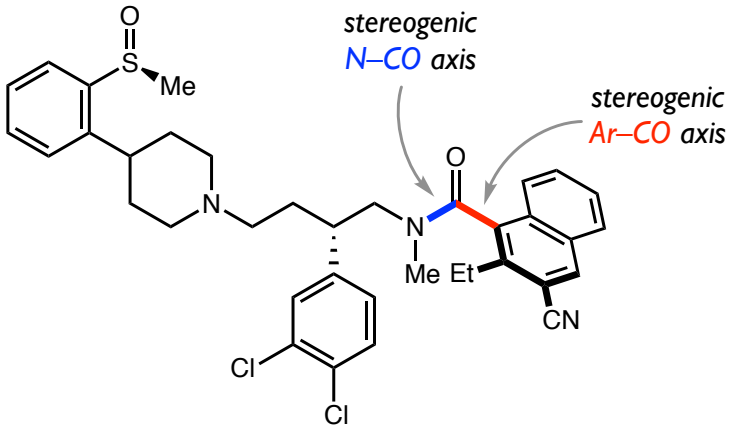
- Attempts to simplify the stereochemical composition of the target resulted in an inferior drug.



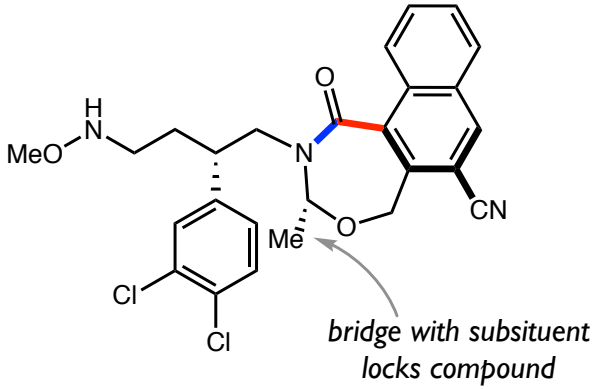
Palani, A; Tagat, J. R. *J. Med. Chem.* **2006**, 49, 2851–2857.

# Designing a Higher Rotational Barrier

- AstraZeneca discovered a potent $NK_1$ antagonist, but complications arose due to thermal equilibration about the two stereogenic axes at physiological temperature.








AstraZeneca $NK_1$ Antagonist
- *treatment for depression*
- *mixture of four atropisomeric steroisomers equilibrating through geared rotation ($t_{1/2}$ ~ days)*

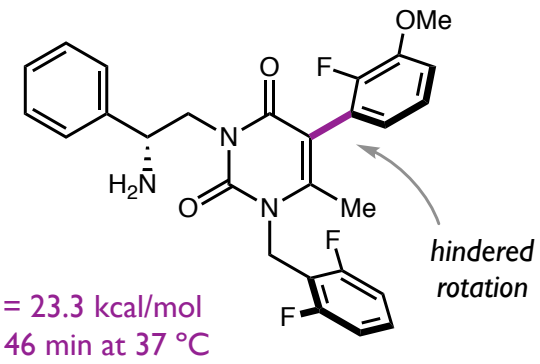
Bridged Variant
- *single isomer*
- *potent activity in vitro and in vivo*

- The structure was redesigned with a ***seven-member bridge*** possessing a substituent; this locked the the molecule into a single, highly bioactive conformer with Class 3 characteristics.

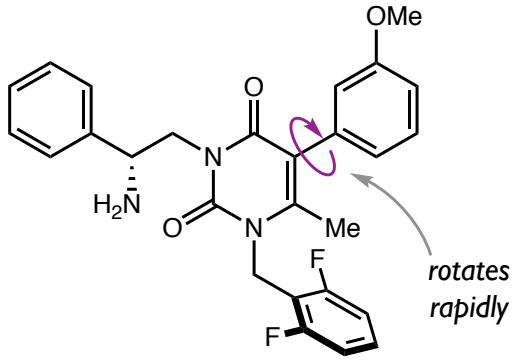

Albert, J. S. *et al. J. Med. Chem.* **2002**, *45*, 3972–3983.
Albert, J. S. *et al. Tetrahedron* **2004**, *60*, 4337–4347.

# Designing a Lower Rotational Barrier

- Tucci & co-workers (Neurocrine Biosciences, Inc.) identified ***NBI 42902*** as a potent therapeutic for the treatment endometriosis and uterine fibroids. The compound existed a mixture of diastereomers that equilibrated with a half-life of 46 min at physiological temperature.




$\Delta G^{\ddagger}$ = 23.3 kcal/mol
$t_{1/2}$ = 46 min at 37 °C


NBI 42902
- *human gonadotropin-releasing hormone receptor antagonist*
- *treatment of endomitriosis and uterine fibroids*
- *diastereomers observed owing to atropisomerization*

Defluorinated Analog
- *no diastereomers observed*
- *~equal potency & pharmacological profile*

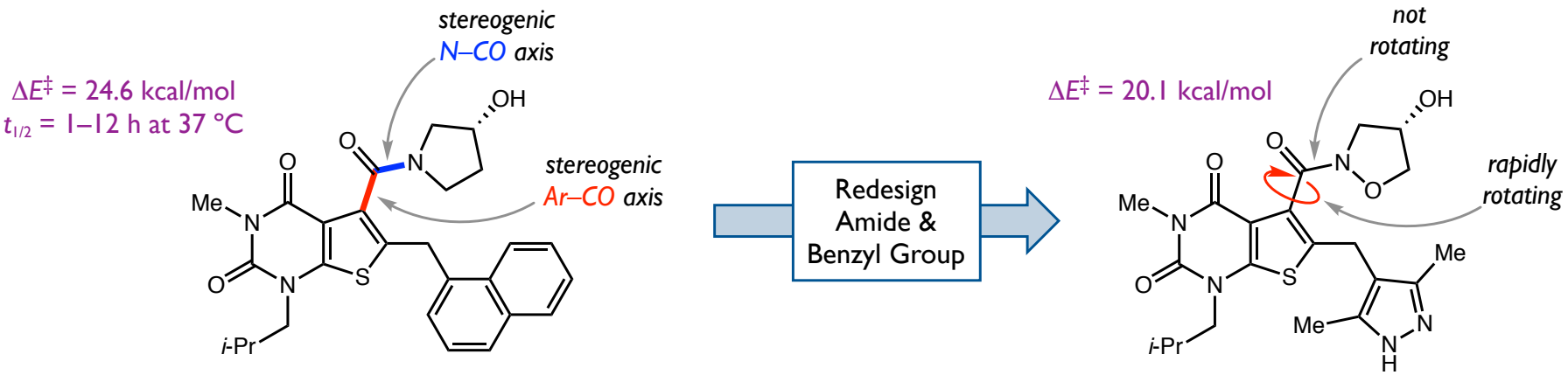
- Redesign of the structure without the *ortho*-fluoride resulted in a single isomer—consistent with a transition from a Class 2 Atropisomer to a Class 1 Non-atropisomer.



Tucci, F. C. *et al. Chirality* **2005**, *17*, 559–564.

# Designing a Lower Rotational Barrier

- Researcher from AstraZeneca identified a potent ***MCT1 blocker*** for immunosuppression therapy, but analysis was complicated by the existence of ***four, equilibrating stereoisomers***, all of which demonstrated different potencies toward the target.




AstraZeneca MCT1 Blocker
- *monocarboxylate transporter blocker*
- *used in imunosuppresion therapy*
- *four equilibrating stereoisomers all have different potencies*

MCT1 Blocker Derivative
- *only a single isomer observed*
- *exhibited acceptable druglike properties*

- Redesign of the target led to a loss of atropisomerism consistent with a shift from a Class 2 barrier to Class 1 non-atropisomer.



Guile, S. D. *et al. Bioorg. Med. Chem. Lett.* **2006**, *16*, 2260–2265.

# Developing a Racemic Mixture

- It can be appropriate to develop an atropisomeric drug as an equilibrating racemate if:
  1. racemization is very rapid *in vivo*,
  2. the enantiomers are analytically or preparatively inseparable,
  3. the pharmacological profile and ADMET(E) properties of each enantiomer are favorable.

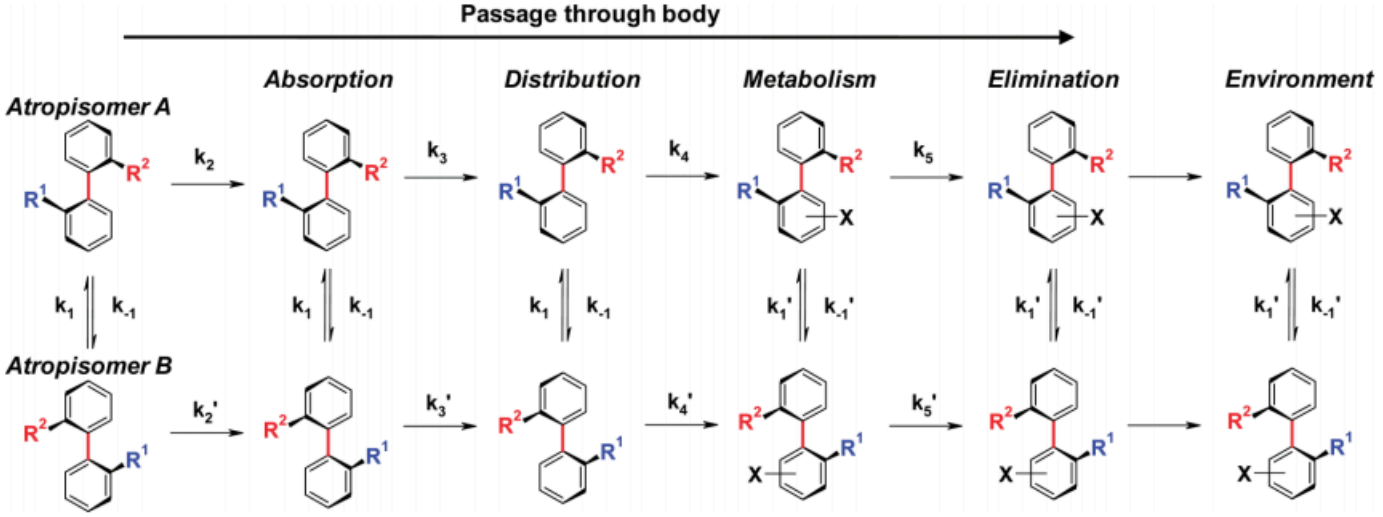



**Figure 9.** Atropisomer compounds should have addition equilibria and rotation rates that may need to be considered for dosing patients with stable and safe drug substances. The chiral axes are colored red.



Clayden, J.; Moran, W. J.; Edwards. P. J.; LaPlante, S. R. *Angew. Chem. Int. Ed.* **2009**, *48*, 6398–6401.
LaPlante, S. R.; Fader, L. D.; Fandrick, K. R.; Fandrick, D. R.; Hucke, O.; Kemper, R.; Miller, S. P. F.; Edwards, P. J. *J. Med. Chem.* **2011**, *54*, 7005–7022.

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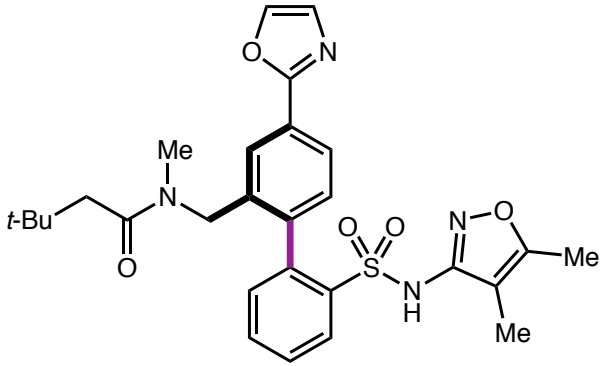
  3. the pharmacological profile and ADMET(E) properties of each enantiomer are favorable.

- BMS developed the following endothelin receptor agonist to treat congestive heart failure as a racemic mixture owing to the rapid *in vivo* racemization and the favorable simulated pharmacokinetics of elimination.




BMS-207940
- *endothelin receptor antagonist*
- *used in treatment of congestive heart failure*
- *medium- and concentration-dependent barrier*

$t_{1/2}$(rac) = 15.8 h (aqueous medium)

$t_{1/2}$(rac) = 2.5 h (human plasma, 400 μg/mL)

$t_{1/2}$(rac) = 0.1 h (human plasma, 20 μg/mL)

*Devloped as a Racemic Mixture*

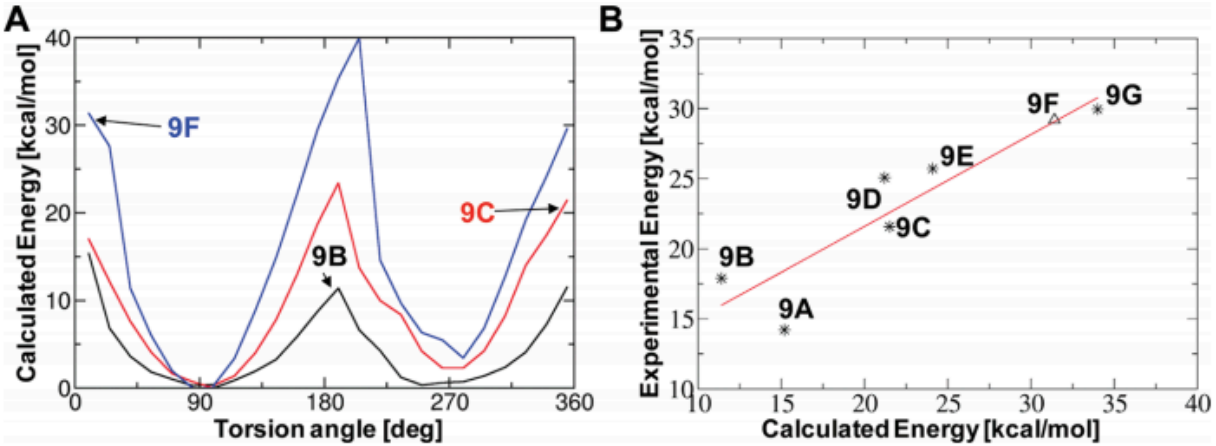

Zhou, Y. S.; Tay, L. K.; Hughes, D.; Donahue, S. *J. Clin. Pharmacol.* **2004**, *44*, 680–688.
Clayden, J.; Moran, W. J.; Edwards. P. J.; LaPlante, S. R. *Angew. Chem. Int. Ed.* **2009**, *48*, 6398–6401.
LaPlante, S. R.; Fader, L. D.; Fandrick, K. R.; Fandrick, D. R.; Hucke, O.; Kemper, R.; Miller, S. P. F.; Edwards, P. J. *J. Med. Chem.* **2011**, *54*, 7005–7022.

# Atropisomers in Drug Discovery & Development

- Atropisomers of ***Classes 1 and 3*** are relatively easy to handle in terms of drug development:
  - If rapidly racemizing under physiological conditions (Class 1), develop as a racemic mixture.
  - If the configurationally stable on the order of years or more (Class 3), develop as a single enantiomer substance.

- ***Class 2 atropisomers*** present more significant challenges to drug development, as their configurational integrity changes as a function of time.

- It is important for pharmaceutical chemists to be able to ***identify potential atropisomers*** and ***institute plans to handle them*** EARLY in the development process.





Clayden, J.; Moran, W. J.; Edwards. P. J.; LaPlante, S. R. *Angew. Chem. Int. Ed.* **2009**, *48*, 6398–6401.

LaPlante, S. R.; Edwards, P. J.; Fader, L. D.; Jakalian, A.; Hucke, O. ChemMedChem **2011**, *6*, 505–513.

LaPlante, S. R.; Fader, L. D.; Fandrick, K. R.; Fandrick, D. R.; Hucke, O.; Kemper, R.; Miller, S. P. F.; Edwards, P. J. *J. Med. Chem.* **2011**, *54*, 7005–7022.

# Atropisomers

*Fundamentals, Pharmaceutical Considerations, & Selective Syntheses*

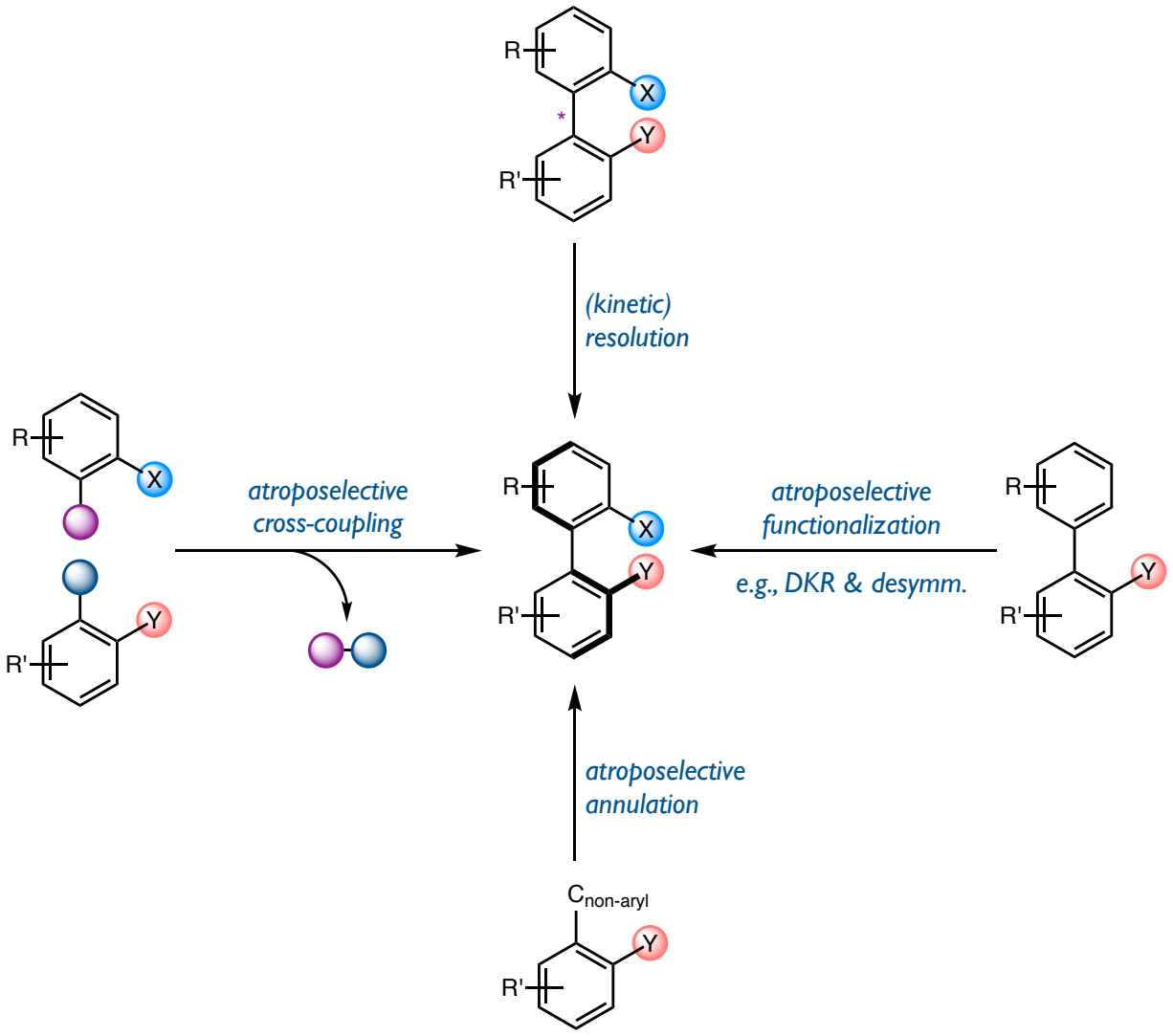
I. Historical Development & Fundamentals

II. Considerations in Drug Development

**III. Overview of Atroposelective Synthetic Methods**

IV. Summary & Conclusions

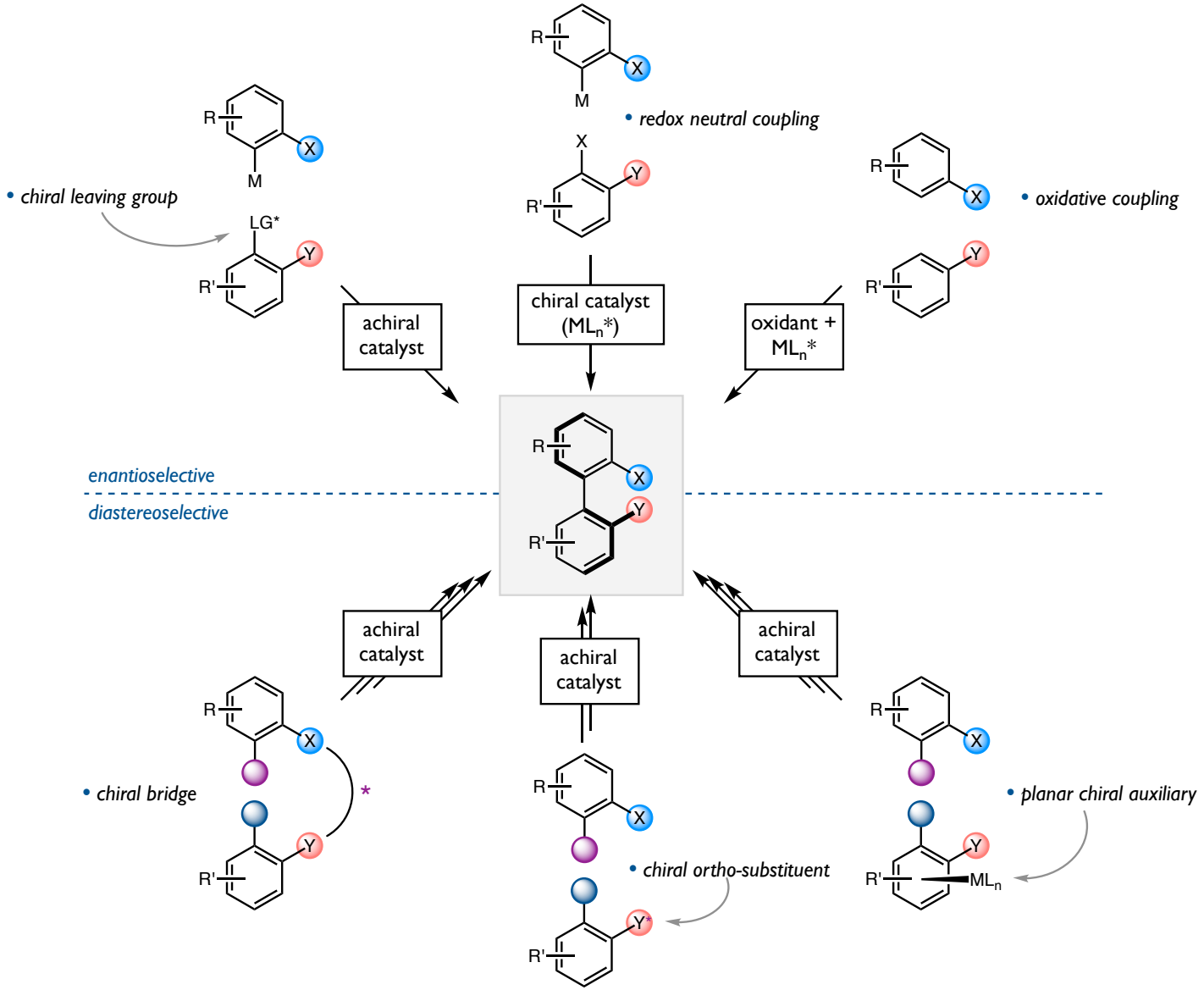
# General Strategies for Atroposelective Synthesis





Bringmann, G.; Mortimer, A. J.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 5384–5427.
Kumarasamy, E.; Raghunathan, R.; Sibi, M. P.; Sivarugu, J. *Chem. Rev.* **2015**, *115*, 11239–11300.
Zilate, B.; Castgrogiovanni, A.; Sparr, C. *ACS Catal.* **2018**, *8*, 2981–2988.

# Atroposelective Cross-Coupling

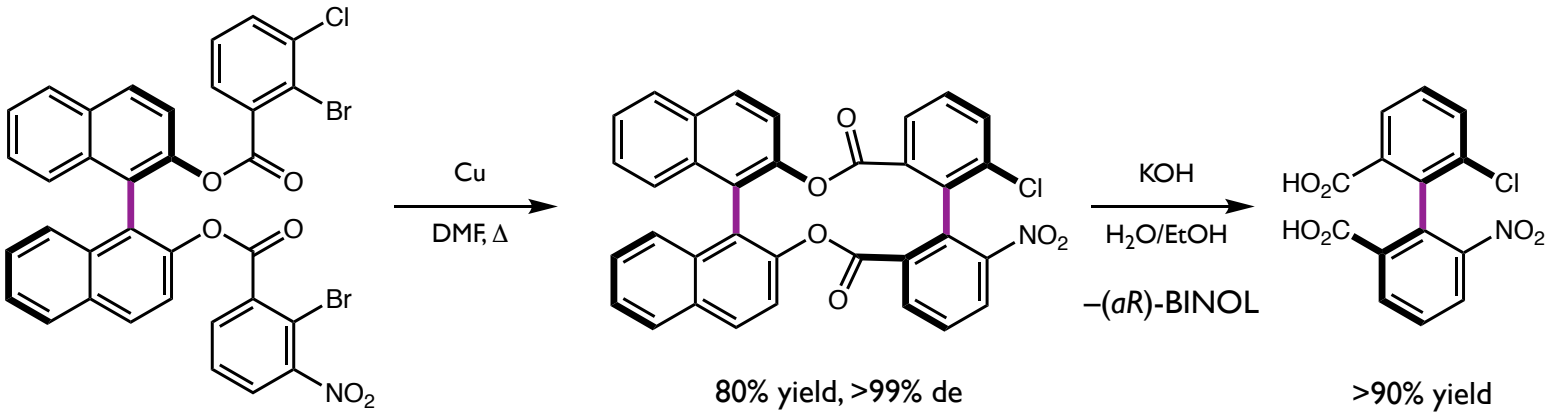





Bringmann, G.; Mortimer, A. J.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 5384–5427.

# Select Cross-Coupling Examples

## *Chiral Bridge Strategy*

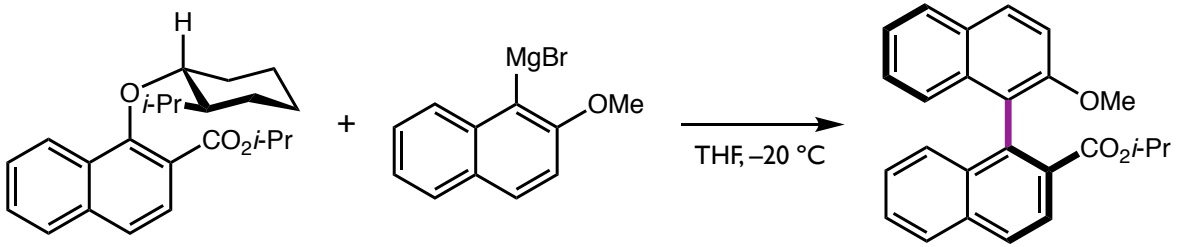



80% yield, >99% de

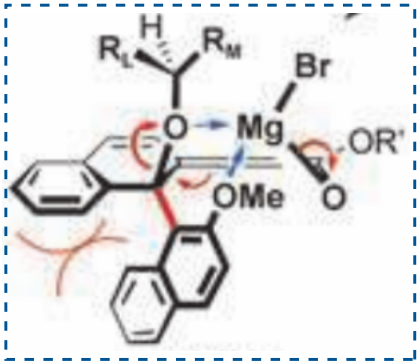
>90% yield

Miyano, S.; Tobita, M.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3522–3526.

## *Chiral Leaving Group Strategy*



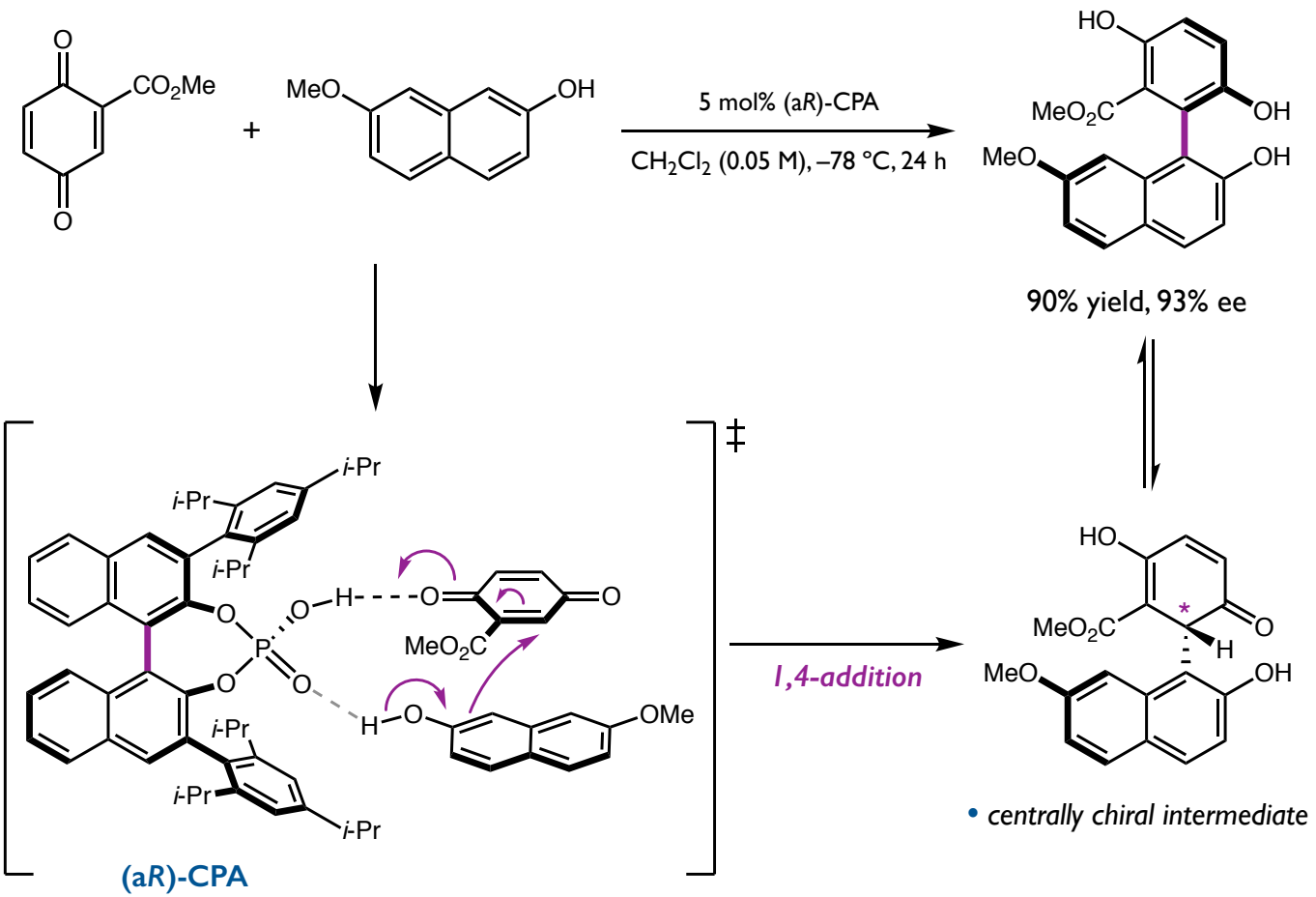

92% yield, 97% ee




• *chelation controlled $S_NAr$*

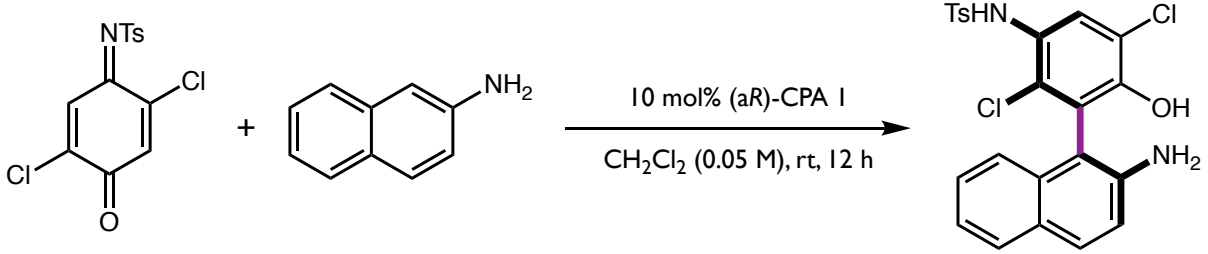
Suzuki, T.; Hotta, H.; Hattori, T.; Miyano, S. *Chem. Lett.* **1990**, 807–810.

# Naphthol Couplings with Point–to-Axis Chirality Transfer

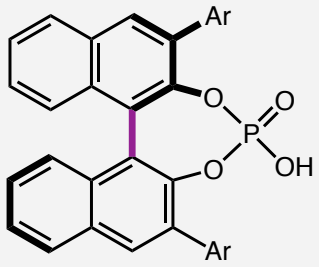



Chen, Y.-H.; Cheng, D.-J.; Zhang, J.; Wang, Y.; Liu, X.-Y.; Tan, B. *J. Am. Chem. Soc.* **2015**, *137*, 15062−15065.
Wang, J.-Z.; Zhou, J.; Xu, C.; Sun, H.; Kürti, L. s.; Xu, Q.-L. *J. Am. Chem. Soc.* **2016**, *138*, 5202−5205.

# Point–to-Axis Chirality Transfer



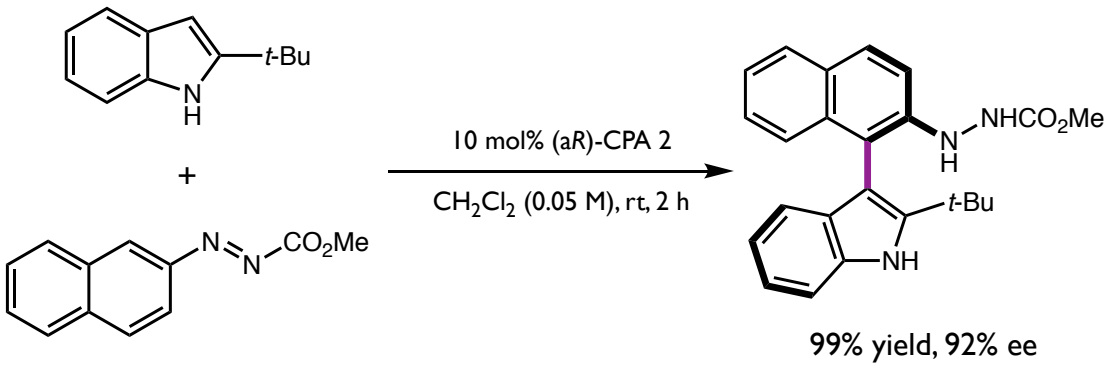

98% yield, 91% ee



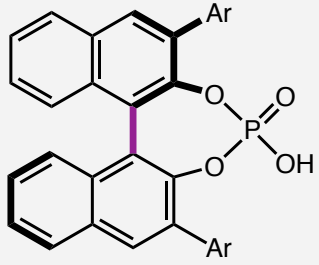

**(a*R*)-CPA 1**

Ar = 2,4,6-(*i*-Pr)$C_6H_2$

Chen, Y.-H.; Qi, L.-W.; Fang, F.; Tan, B. *Angew. Chem. Int. Ed.* **2017**, *56*, 16308–16312.




99% yield, 92% ee



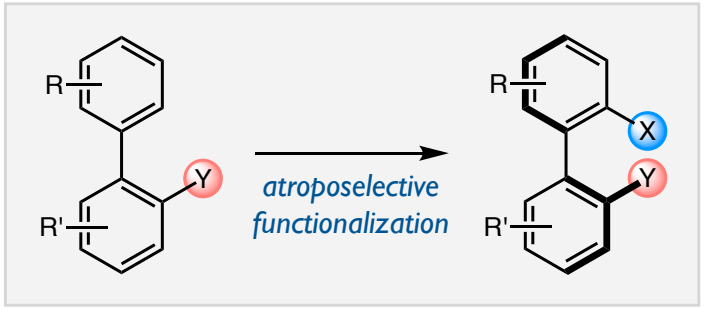

**(a*R*)-CPA 2**

Ar = $C_6F_5$



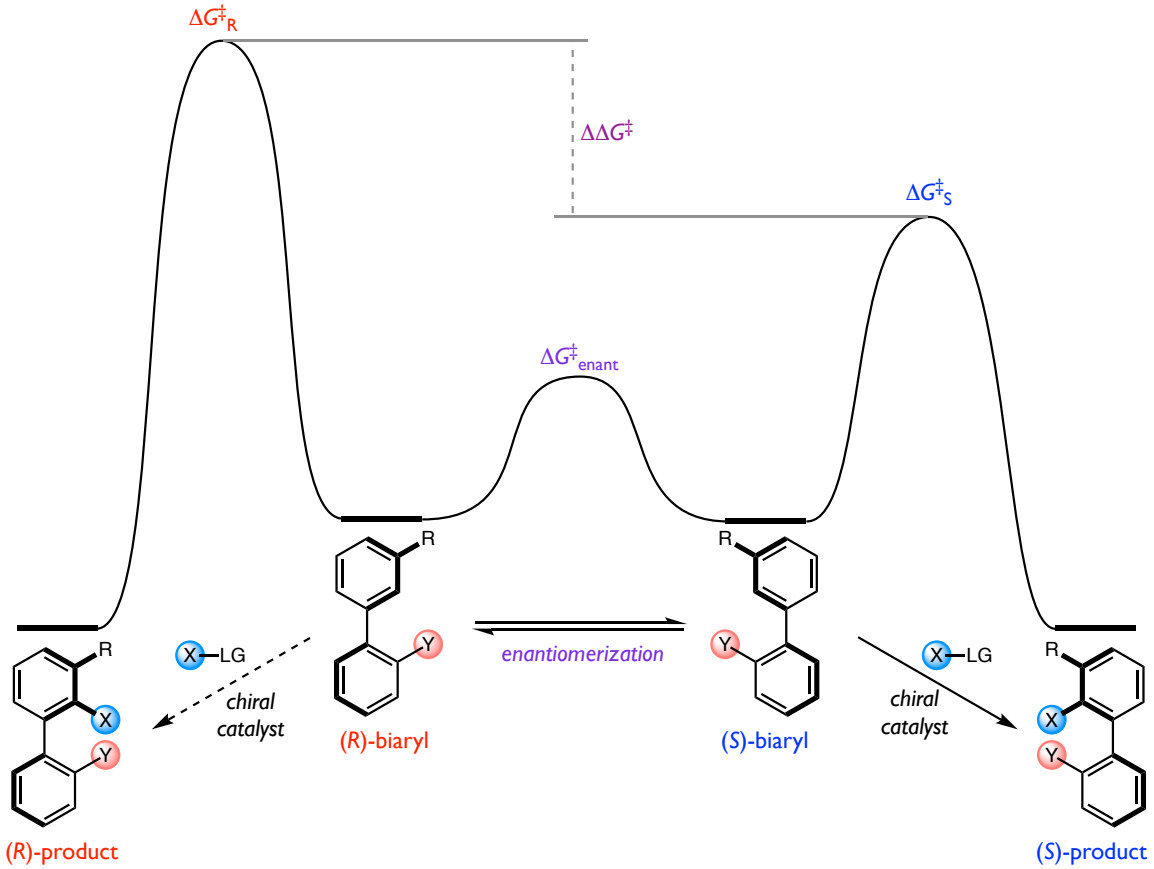
Qi, L.-W.; Mao, J.-H.; Zhang, J.; Tan, B. *Nat. Chem.* **2017**, *10*, 58–64.

# Atroposelective Functionalization

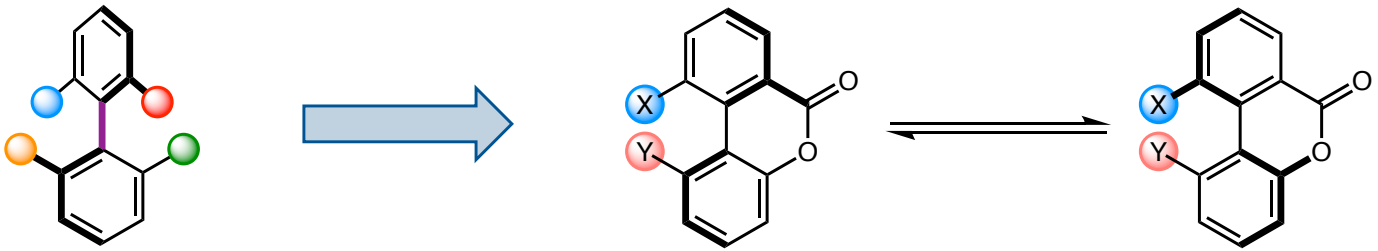



- In this strategy, either (1) a chiral, but rapidly racemizing, scaffold is functionalized in such a way that the enantiomerization barrier is raised, or (2) a symmetrical scaffold is desymmetrized.

*Dynamic Kinetic Resolution (DKR)*



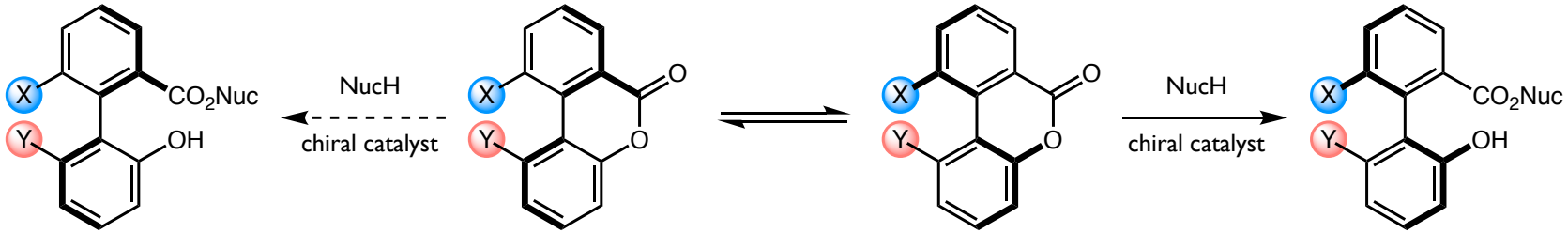
# Ring-Opening of Bringmann Lactones—DKR




- *tetrasubstituted biaryls are typically configurationally stable*

- *constrained, tetrasubstituted biaryls racemize rapidly at rt due to ground state destabilization*

## *Dynamic Kinetic Resolution (DKR)*



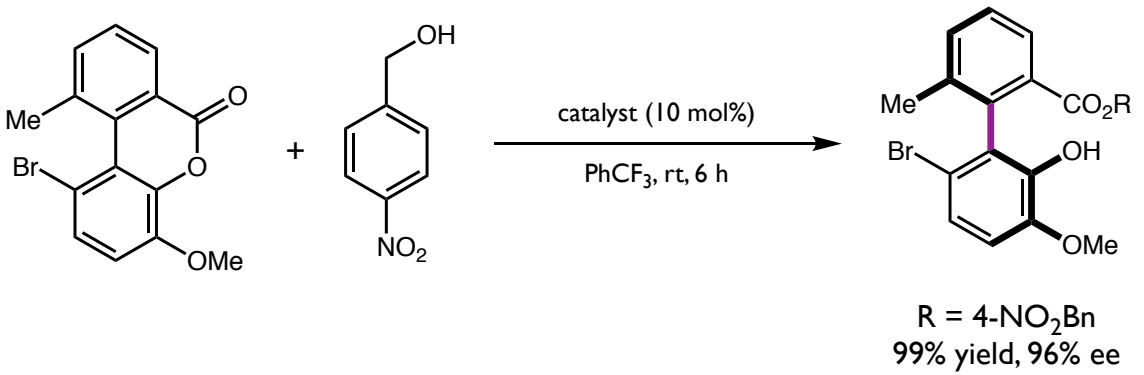

- *Use a chiral catalyst or chiral nucleophile to effect a DKR of configurationally labile Bringmann lactones.*

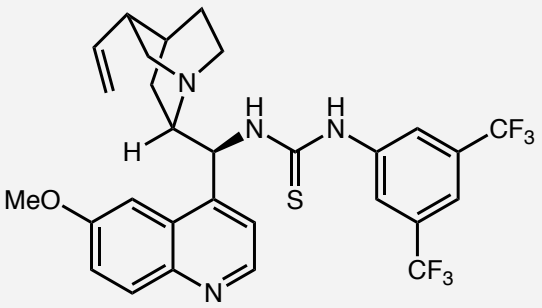


Bringmann, G.; Mortimer, A. J.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 5384–5427.

# Ring-Opening of Bringmann Lactones—DKR


## *Catalytic Ring Opening of Bringmann Lactones*

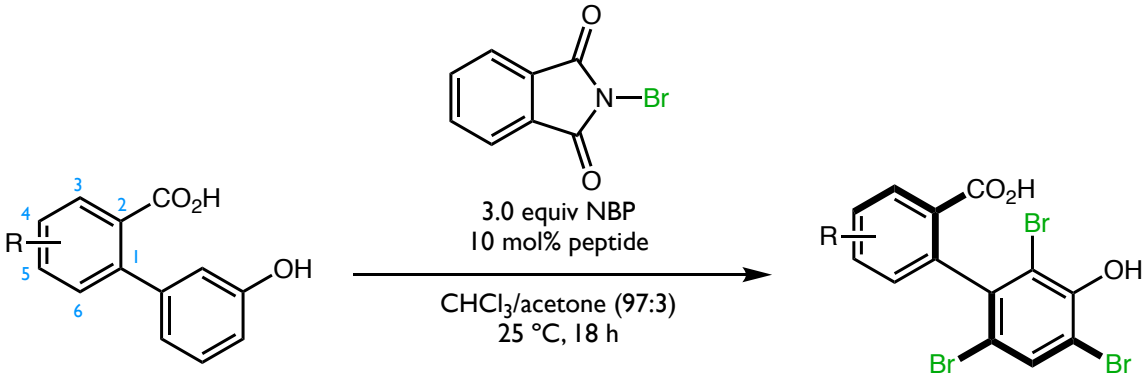




Bringmann, G.; Mortimer, A. J.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 5384–5427.
Yu, C.; Huang, H.; Li, X.; Zhang, Y.; Wang, W. *J. Am. Chem. Soc.* **2016**, *138*, 6956–6959.

# Peptide-Catalyzed, Atroposelective Bromination—DKR

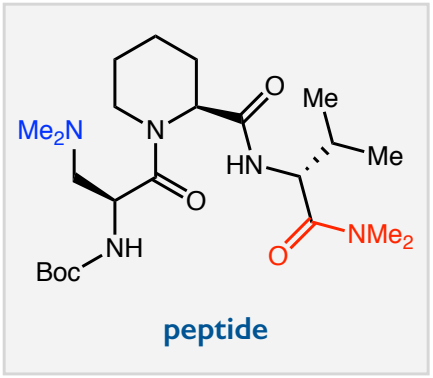



**(±)-biaryl**

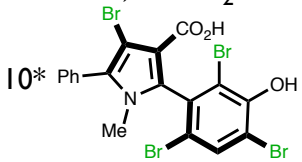
- *rapidly racemizing (~7 kcal/mol barrier)*

**enantioenriched tribromide**

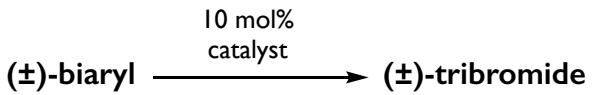
- *atropisomerically stable (>30 kcal/mol barrier)*



**peptide**

| Entry | R | Yield (%) | er |
|---|---|---|---|
| 1 | H | 80 | 97.0:3.0 |
| 2 | 4-$NO_2$ | 85 | 97.0:3.0 |
| 3 | 5-$NO_2$ | 75 | 96.5:3.5 |
| 4 | 4-OMe | 80 | 94.0:6.0 |
| 5 | 5-OMe | 70 | 96.0:4.0 |
| 6 | 4-F | 65 | 96.5:3.5 |
| 7 | 5-F | 70 | 97.0:3.0 |
| 8 | 3-Me | 85 | 87.0:13.0 |
| 9 | 4,5-$OCH_2O$ | 70 | 95.0:5.0 |
| 10* |  | 77 | 85.0:15.0 |

* 4 equiv NBS



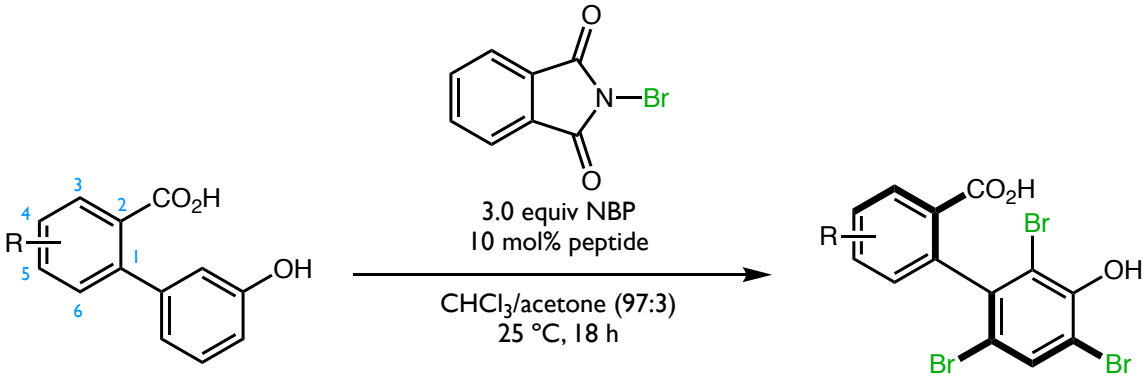

| Catalyst | Yield (%) |
|---|---|
| none | 15% |
| i-$Pr_2NEt$ | 31% |
| (±)-Boc-Val-$NMe_2$ | 91% |

- *backbone amides involved in catalysis*



Gustafson, J. L.; Lim, D.; Miller, S. J. *Science* **2010**, *328*, 1251–1255.

# Peptide-Catalyzed, Atroposelective Bromination—DKR

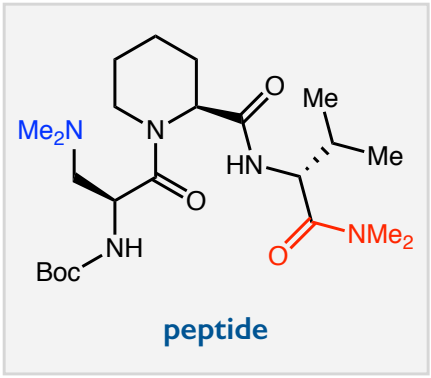



**(±)-biaryl**

- *rapidly racemizing (~7 kcal/mol barrier)*

**enantioenriched tribromide**

- *atropisomerically stable (>30 kcal/mol barrier)*



**peptide**

| Entry | R | Yield (%) | er |
|---|---|---|---|
| 1 | H | 80 | 97.0:3.0 |
| 2 | 4-$NO_2$ | 85 | 97.0:3.0 |
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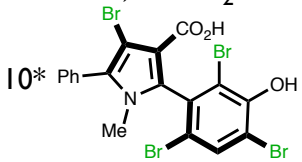
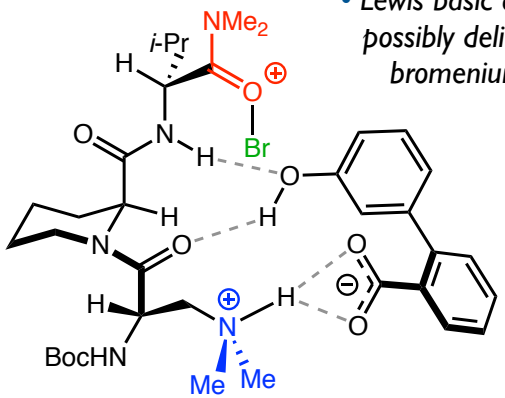
| 4 | 4-OMe | 80 | 94.0:6.0 |
| 5 | 5-OMe | 70 | 96.0:4.0 |
| 6 | 4-F | 65 | 96.5:3.5 |
| 7 | 5-F | 70 | 97.0:3.0 |
| 8 | 3-Me | 85 | 87.0:13.0 |
| 9 | 4,5-$OCH_2O$ | 70 | 95.0:5.0 |
| 10* |  | 77 | 85.0:15.0 |

* 4 equiv NBS

- *Lewis basic amide possibly delivers bromenium*

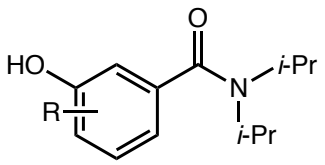


- *salt-bridge formation with substrate*



Gustafson, J. L.; Lim, D.; Miller, S. J. *Science* **2010**, *328*, 1251–1255.

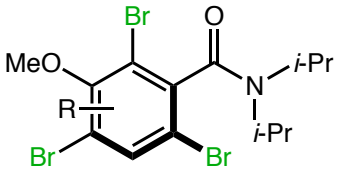
# Peptide-Catalyzed, Atroposelective Bromination—DKR



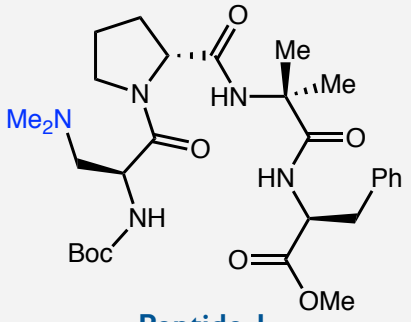

(±)-benzamide

1.5 equiv DBDMH
10 mol% peptide 1

$CHCl_3$ (0.02 M)
–40 °C, 4–48 h
*then* $TMSCHN_2$/MeOH

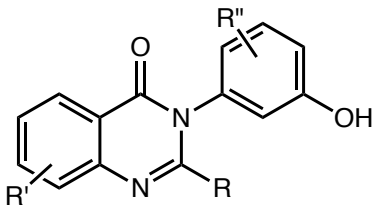



**13 Examples**
75–92% yield, 75:25 to 96:4 er




**Peptide 1**

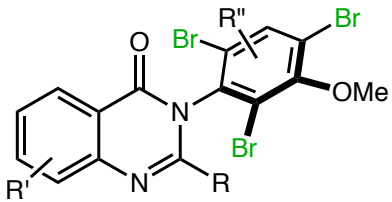
Barrett, K. T.; Miller, S. J. *J. Am. Chem. Soc.* **2013**, *135*, 2963–2966.



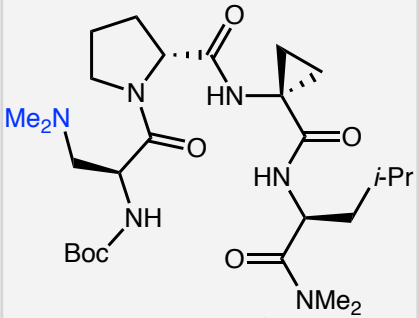

(±)-quinazolinone

3.0 equiv NBS
(slow addn. over 2.5 h)
10 mol% peptide 2

$PhMe/CHCl_3$ (9:1, 0.01 M)
5 vol% acetone
0 °C, 3 h total
*then* $TMSCHN_2$/MeOH



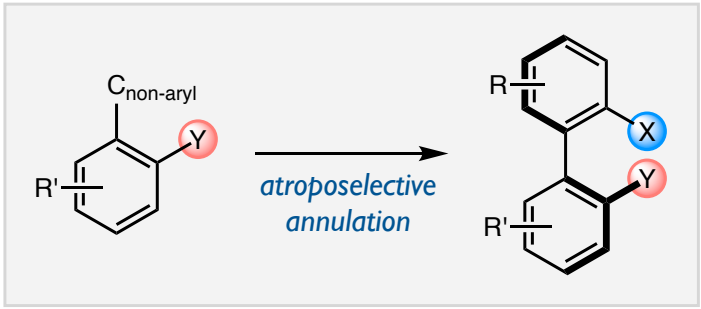

**14 Examples**
63–93% yield, 56:44 to
99:1 er




**Peptide 2**

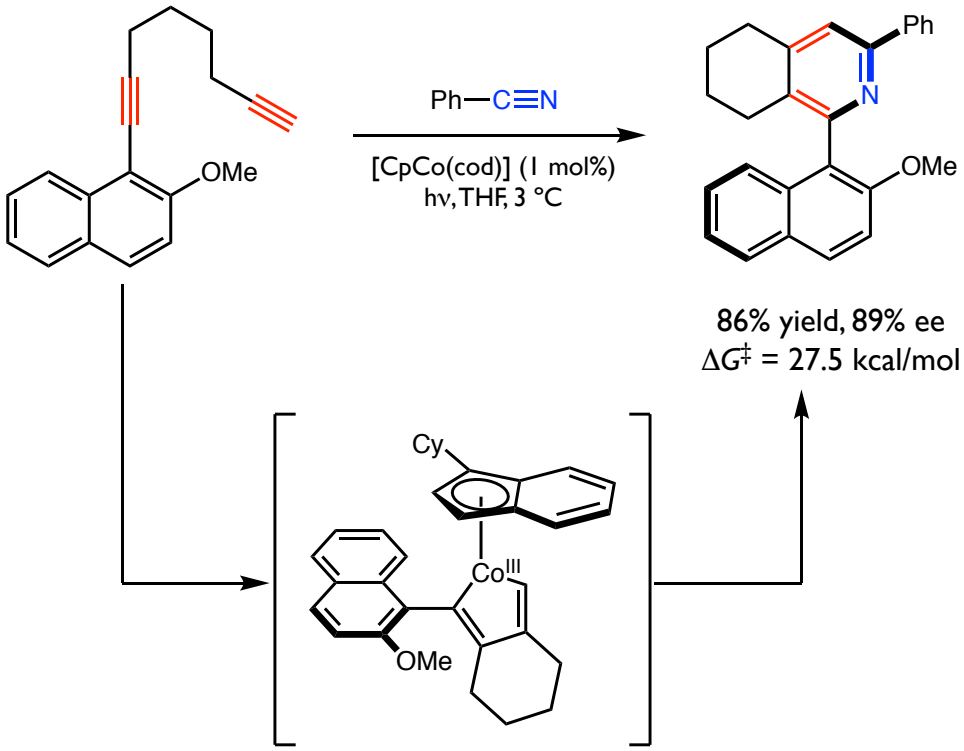
Diener, M. E.; Metrano, A. J.; Kusano, S.; Miller, S. J. *J. Am. Chem. Soc.* **2015**, *137*, 12369–12377.

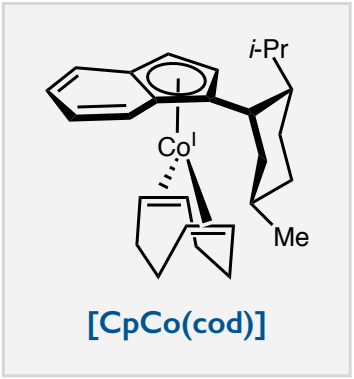
# Atroposelective Annulation




- In this strategy, a new ring, often an arene, is formed through the action of a chiral catalyst, leading to atropisomers about the newly formed biaryl bond.

*Co(I)-Catalyzed [2+2+2]*

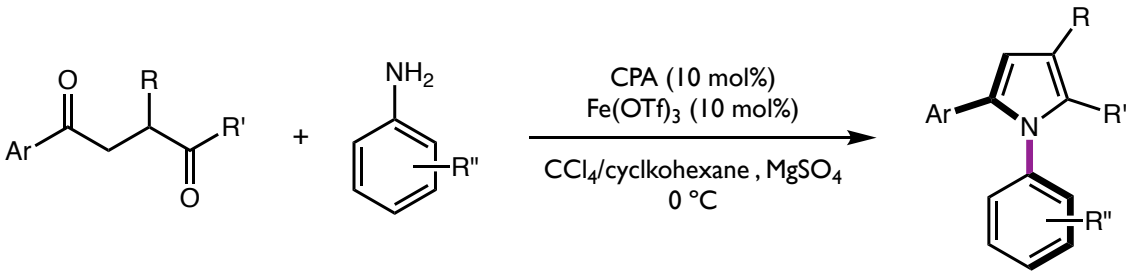


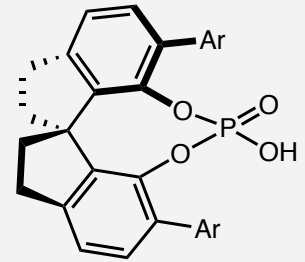



Gutnov, A.; Heller, B.; Fischer, C.; Drexler, H.-J.; Spannenberg, A.; Sundermann, B.; Sundermann, C. *Angew. Chem. Int. Ed.* **2004**, *43*, 3795–3797.

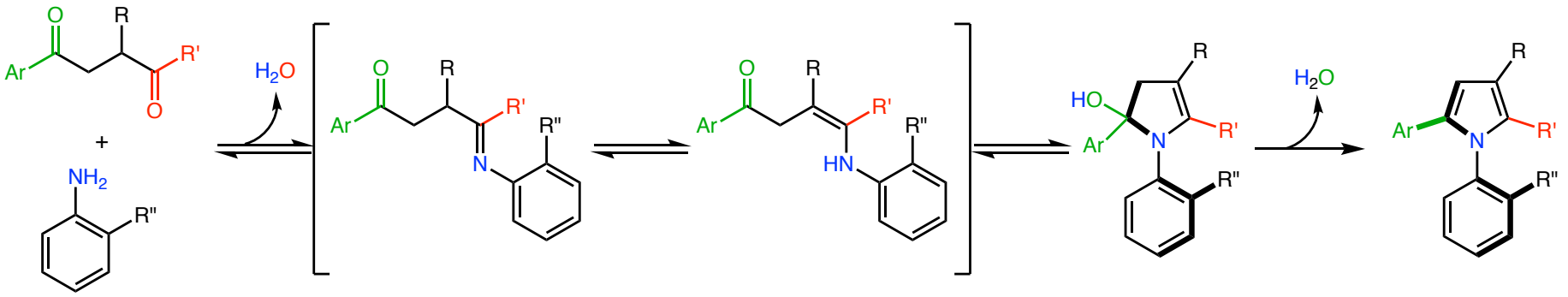
# Atroposelective Paal–Knorr Annulation




31 Examples
83–95% yield, 86–97% ee



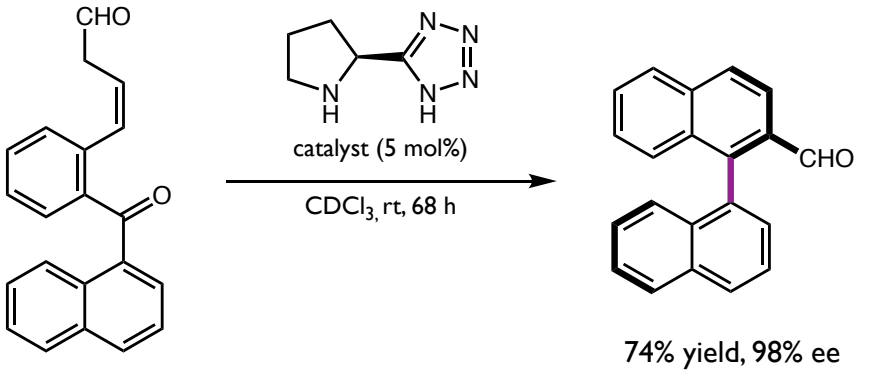
(a*R*)-*spiro*-CPA
Ar = 9-anthryl



- *key intermediate for catalyst-control in enantiodetermining cyclization*

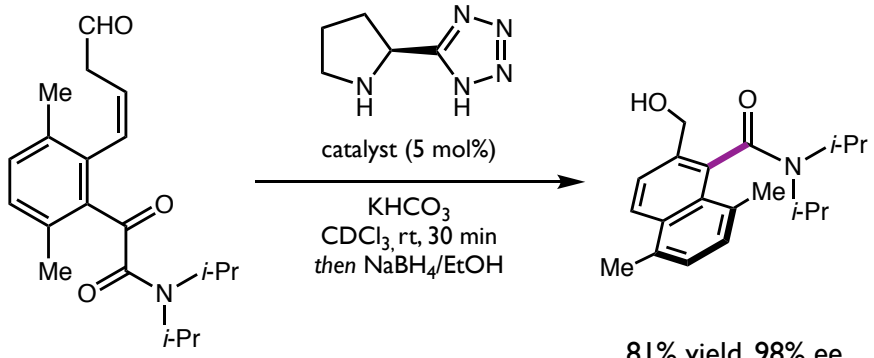
Zhang, L.; Zhang, J.; Ma, J.; Cheng, D.-J.; Tan, B. *J. Am. Chem. Soc.* **2017**, *139*, 1714–1717.

# Atroposelective Aldol & Michael Reactions



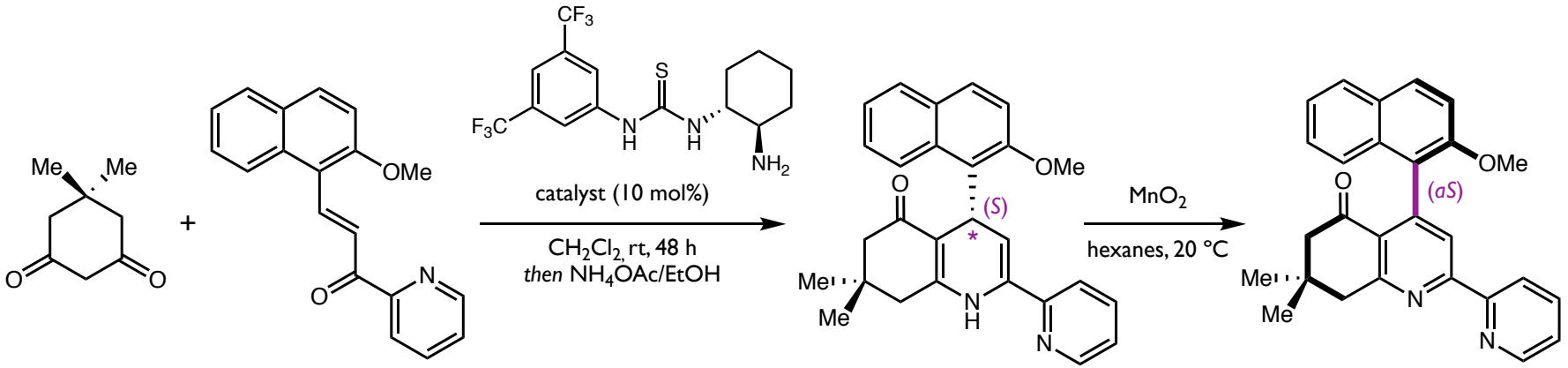

74% yield, 98% ee

Link, A.; Sparr, C. *Angew. Chem. Int. Ed.* **2014**, *53*, 5458–5461.




81% yield, 98% ee

Faseke, V. C.; Sparr, C. *Angew. Chem. Int. Ed.* **2016**, *55*, 7261–7264.




77% yield, 94% ee

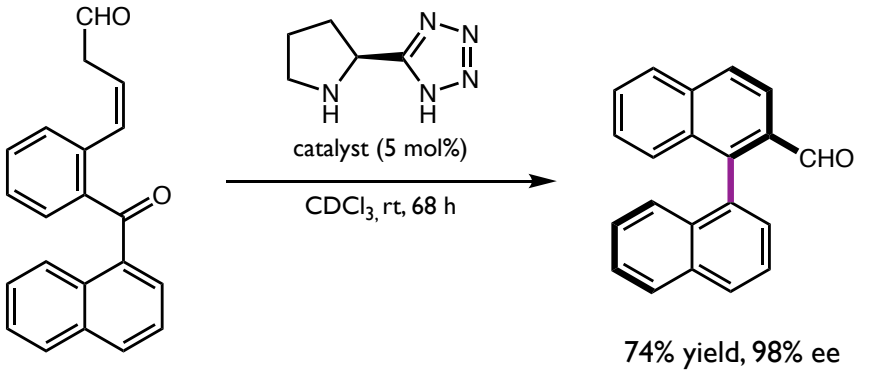
86% ee (91% cp)

$\Delta G^{\ddagger}$ = 27.5 kcal/mol

$t_{1/2}$ = 91 d at 25 °C

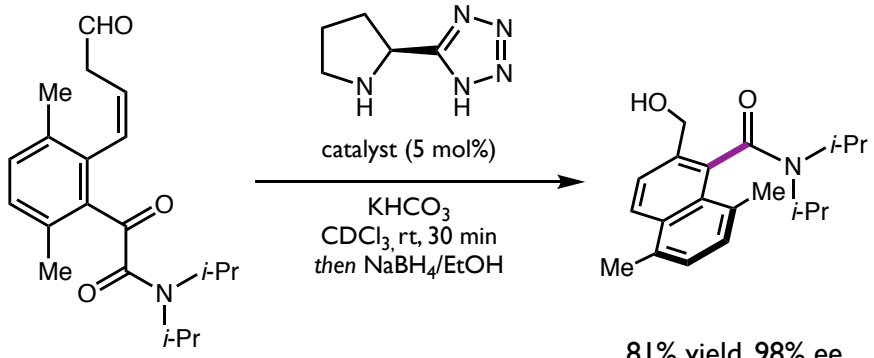
Quinonero, O.; Jean, M.; Vanthuyne, N.; Roussel, C.; Bonne, D.; Constantieux, T.; Bressy, C.; Bugaut, X.; Rodriguez, J. *Angew. Chem. Int. Ed.* **2016**, *55*, 1401–1405.

# Atroposelective Aldol & Michael Reactions




74% yield, 98% ee

Link, A.; Sparr, C. *Angew. Chem. Int. Ed.* **2014**, *53*, 5458–5461.

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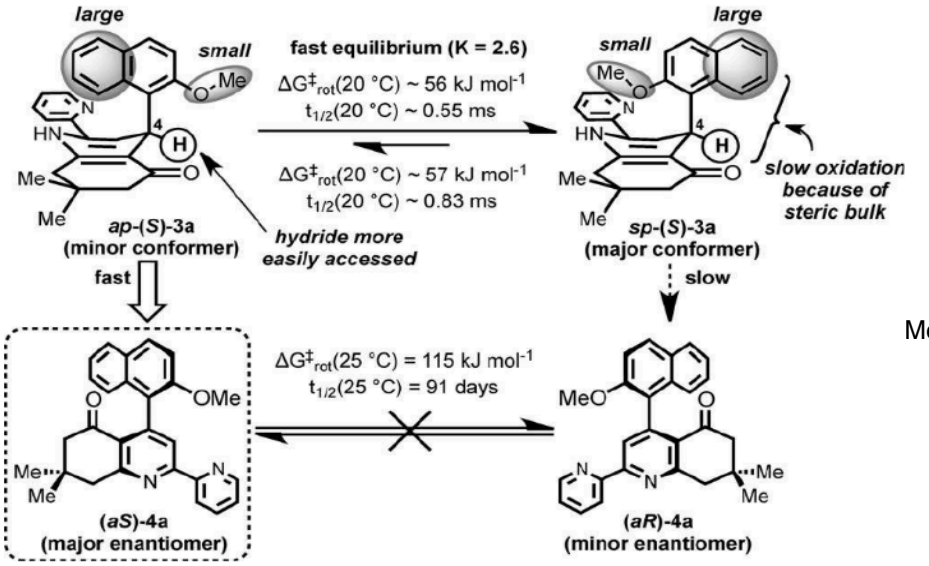
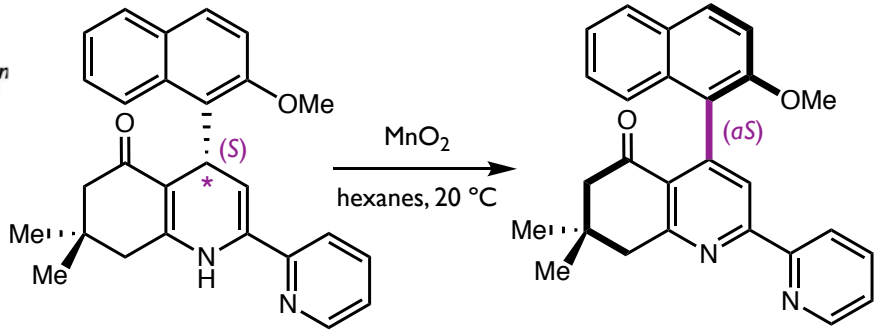
Faseke, V. C.; Sparr, C. *Angew. Chem. Int. Ed.* **2016**, *55*, 7261–7264.

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Quinonero, O.; Jean, M.; Vanthuyne, N.; Roussel, C.; Bonne, D.; Constantieux, T.; Bressy, C.; Bugaut, X.; Rodriguez, J. *Angew. Chem. Int. Ed.* **2016**, *55*, 1401–1405.

# Atropisomers

*Fundamentals, Pharmaceutical Considerations, & Selective Syntheses*

I. Historical Development & Fundamentals

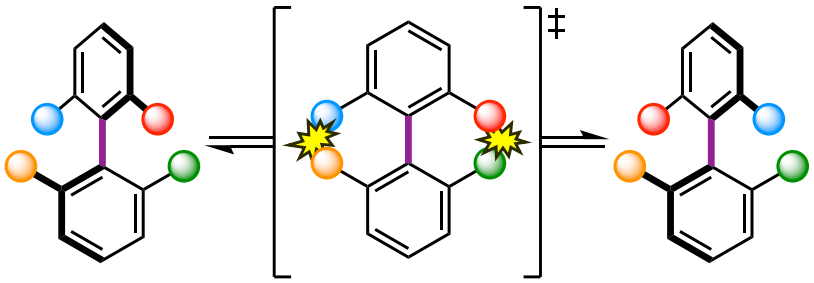
II. Considerations in Drug Development

III. Overview of Atroposelective Synthetic Methods

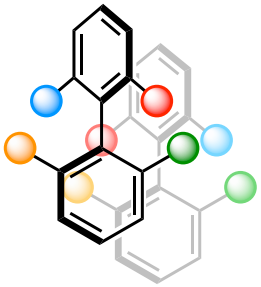
**IV. Summary & Conclusions**

# Summary

## Fundamentals

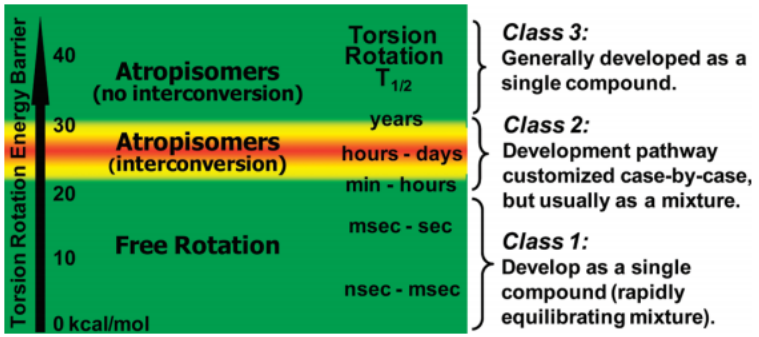


*strained coplanar transition state*



*non-superimposable mirror images*

## Pharmaceutical Considerations

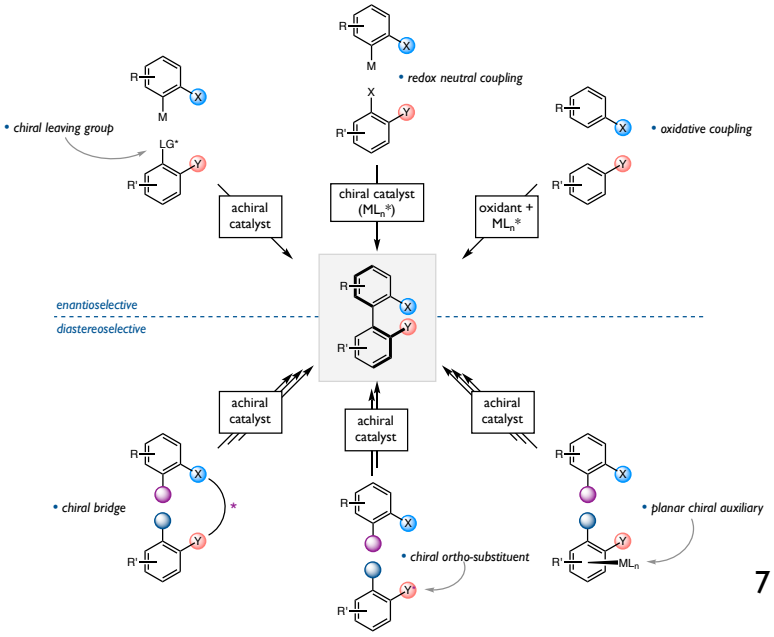



***Class 3:*** Generally developed as a single compound.

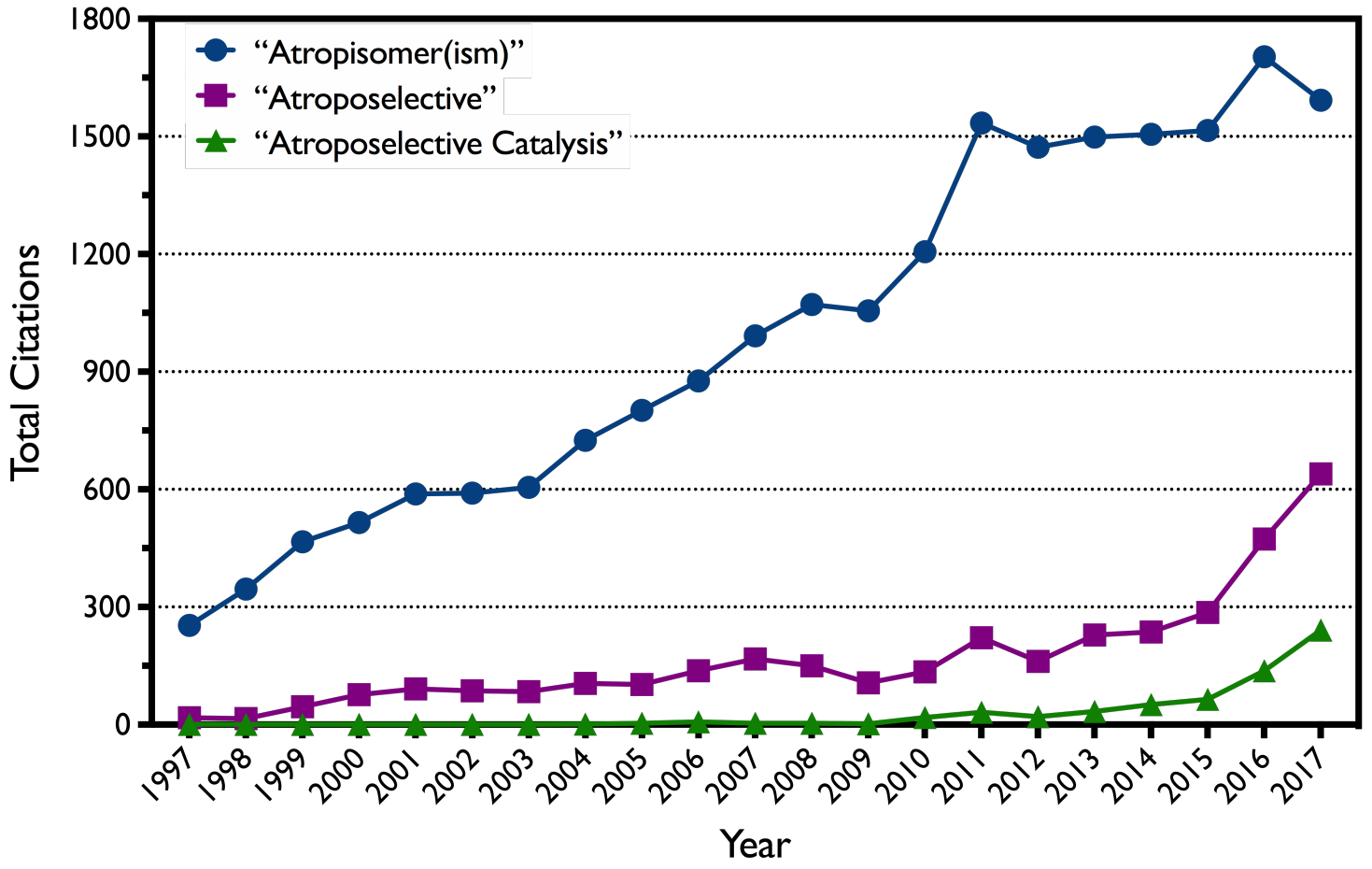
***Class 2:*** Development pathway customized case-by-case, but usually as a mixture.

***Class 1:*** Develop as a single compound (rapidly equilibrating mixture).

## Methods for Synthesis



# Outlook




Data compiled from *Web of Science* topic searches, accessed 14 June 2018.

# The Extra Mile

## General Text on Stereochemistry

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Bringmann, G.; Mortimer, A. J.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 5384–5427.

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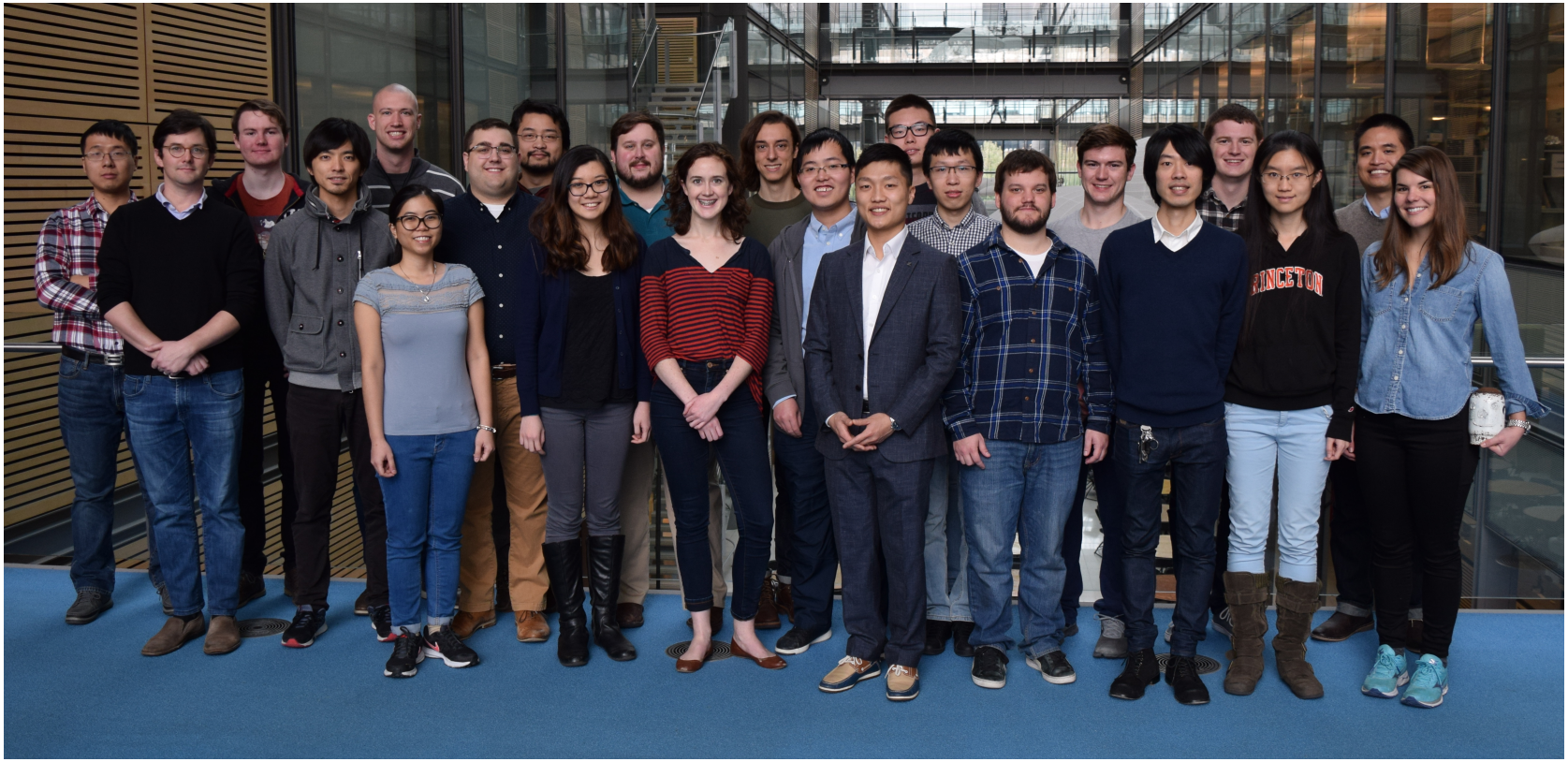
Wang, Y.-B.; Tan, B. *Acc. Chem. Res.* **2018**, *51*, 534–547.

# Thank You!




NIH NIGMS