Atropisomers
Fundamentals, Pharmaceutical Considerations, & Selective Syntheses

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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”
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

Kauffler Formulae—Parallel Planes

- 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.”
Fractional Crystallization of Brucine Salts

mp = 230–231 °C  
[α]D = +225.3°

2 M H2SO4/H2O

mp = 230–238 °C  
[α]D = -169.7°

two diastereomeric brucine salts isolated by fractional crystallization

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.

Axial Chirality—Allenes

- The concept of *axial chirality* was originally formulated by van ‘t Hoff in 1875 with regard to allenes.

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

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.

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Axial Chirality & Atropisomerism

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

![Diagram showing axial chirality and atropisomerism](image)

- 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**.

# Types of Atropisomeric Scaffolds

## Chiral C–C Axes

- Biaryls
- Tertiary benzamides
- \( \alpha \)-styrenes
- Imines

## Chiral C–N Axes

- Anilides
- Carbamates
- Imides
- Ureas
- Indoles
- Pyrroles
- Quinazolinones
- Lactams
- Barbiturates

Types of Atropisomeric Scaffolds

Chiral C–O & C–S Axes

- Diaryl ethers
- Diaryl sulfides
- Sulfoxides
- Sulfones

Chiral C(sp²)–C(sp³) Axes

- 9-arylfuorenes
  \[ \Delta G^\ddagger = 33.3 \text{ kcal/mol} \]

- 3° benzylic alcohols
  \[ \Delta G^\ddagger = 25.9 \text{ kcal/mol} \]

Chiral C(sp³)–C(sp³) Axes

- Triptycenes
  \[ \Delta G^\ddagger = 23.5 \text{ kcal/mol} \]

- Ethanoids


Atropisomeric Natural Products

vancomycin
• antibiotic of “last resort”

knipholone
• antimalarial & antitumor activity

murrastifoline
• antiplasmodial activity

diazoneamide A
• antimitotic agent

benzomalvin A
• substance P inhibitor & antidepressant

murrastifoline-F
• stimulates nerve growth

marinopyrrole B
• antibiotic & anticancer activity

knipholone
• chiral C–N axis

murrastifoline-F
• antiplasmodial activity

knipholone
• chiral C–N axis

murrastifoline
• chiral C–N axis

• multiple chiral axes

• chiral biaryl axis

• chiral diarylethers

• chiral C–N axis
Atropisomeric Scaffolds as Ligands for Transition Metals

\[ \text{Ph} \text{Me}_2 \text{P} \text{Ph}_{Ar_2} \text{R} \]
\[ \text{(R)-BINAP} \]
- asymmetric hydrogenation

\[ \text{Ph} \text{OH} \text{Me} \text{OH} \text{R} \]
\[ \text{(R)-BINOL} \]

\[ \text{Ph} \text{NH}_2 \text{NH}_2 \text{R} \]
\[ \text{(R)-BINAM} \]

\[ \text{Ph} \text{OH} \text{NH}_2 \text{R} \]
\[ \text{(R)-NOBIN} \]

\[ \text{Ph} \text{N} \text{O} \text{R} \]
\[ \text{(R)-IPHOX} \]

\[ \text{Ph} \text{N} \text{X} \text{R} \]
\[ \text{(R)-QUINAP/OL/AM} \]

\[ \text{Ph} \text{Ph} \text{OAc} \]
\[ \text{CO}_2 \text{Me} + \text{CO}_2 \text{Me} \]
\[ \text{cat. [Pd(p-C}_3\text{H}_5\text{)Cl]_2} \]
\[ \text{BSA or base, additive solvent, rt, time} \]

\[ \text{MeO}_2 \text{C} \text{CO}_2 \text{Me} \]

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Additive</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>yield (%)</th>
<th>ee (%)</th>
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</thead>
<tbody>
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<td>15-C-5</td>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>96</td>
<td>30</td>
<td>52</td>
</tr>
<tr>
<td>2</td>
<td>–</td>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>24</td>
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<td>52</td>
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<tr>
<td>3</td>
<td>NaOAc</td>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>4</td>
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<td>94</td>
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<tr>
<td>4</td>
<td>–</td>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>5</td>
<td>93</td>
<td>92</td>
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<tr>
<td>5</td>
<td>LiOAc</td>
<td>Et\textsubscript{2}O</td>
<td>24</td>
<td>99</td>
<td>99</td>
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<tr>
<td>6</td>
<td>LiOAc</td>
<td>MeCN</td>
<td>48</td>
<td>98</td>
<td>88</td>
</tr>
</tbody>
</table>

Atropisomeric Scaffolds as Organocatalysts

**Brønsted Acid Organocatalysts**

<table>
<thead>
<tr>
<th>CPAs</th>
<th>CPIs</th>
<th>CCAs</th>
<th>CSAs</th>
<th>CSIs</th>
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</thead>
<tbody>
<tr>
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<td><img src="image2.png" alt="CPI" /></td>
<td><img src="image3.png" alt="CCA" /></td>
<td><img src="image4.png" alt="CSA" /></td>
<td><img src="image5.png" alt="CSI" /></td>
</tr>
</tbody>
</table>

**Brønsted Base Organocatalysts**

<table>
<thead>
<tr>
<th>BINOL Phosphates</th>
<th>Gaunidines</th>
<th>Modified Cinchona Alkaloids</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image6.png" alt="BINOL Phosphate" /></td>
<td><img src="image7.png" alt="Gaunidine" /></td>
<td><img src="image8.png" alt="Modified Cinchona Alkaloid" /></td>
</tr>
</tbody>
</table>

**Phase Transfer Catalysts**

<table>
<thead>
<tr>
<th>Phosphines</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image9.png" alt="Phosphine" /></td>
</tr>
</tbody>
</table>

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

Let’s Practice!
Atropisomers & Conformers—What’s the Difference?

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

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

<table>
<thead>
<tr>
<th>Temperature (K)</th>
<th>$\Delta G^\ddagger$ (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$K = 1.0$</td>
</tr>
<tr>
<td>200</td>
<td>14.73</td>
</tr>
<tr>
<td>250</td>
<td>18.52</td>
</tr>
<tr>
<td>300</td>
<td>22.34</td>
</tr>
<tr>
<td>350</td>
<td>26.17</td>
</tr>
<tr>
<td>400</td>
<td>30.01</td>
</tr>
<tr>
<td>450</td>
<td>33.87</td>
</tr>
<tr>
<td>500</td>
<td>37.74</td>
</tr>
</tbody>
</table>

$\Delta G^\ddagger$ is the free energy of activation.

Atropisomerism & Rotational Barriers

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

\[
\Delta G^\ddagger = 1.4-2.0 \text{ kcal/mol} \\
\frac{t}{2} = 1.2-3.3 \times 10^{-12} \text{ s}
\]

\[
\Delta G^\ddagger = 3.7 \text{ kcal/mol} \\
\text{X} = \text{F, } \frac{t}{2} = 23.0 \text{ y}
\]

\[
\Delta G^\ddagger = 7.4 \text{ kcal/mol} \\
\text{X} = \text{Me, } \frac{t}{2} = 0.5 \text{ h}
\]

\[
\Delta G^\ddagger = 7.6 \text{ kcal/mol} \\
\text{X} = \text{Cl, } \frac{t}{2} = 1.7 \times 10^{-12} \text{ millennia}
\]

\[
\Delta G^\ddagger = 8.6 \text{ kcal/mol} \\
\text{X} = \text{Br, } \frac{t}{2} = \infty
\]

\[
\Delta G^\ddagger = 15.4 \text{ kcal/mol} \\
\text{X} = \text{t-Bu, } \frac{t}{2} = 5.7 \times 10^{-11} \text{ to } 2.1 \times 10^{-2} \text{ s}
\]

\[
\Delta G^\ddagger = 22.1 \text{ kcal/mol} \\
\frac{t}{2} = 11.5 \text{ h}
\]

\[
\Delta G^\ddagger = 24.0 \text{ kcal/mol} \\
\frac{t}{2} = 9.9 \text{ d}
\]

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

\[ \Delta G^\ddagger = 14.2 \text{ kcal/mol} \quad t_{1/2} = 0.002 \text{ s} \]

\[ \Delta G^\ddagger = 17.9 \text{ kcal/mol} \quad t_{1/2} = 1 \text{ s} \]

\[ \Delta G^\ddagger = 21.6 \text{ kcal/mol} \quad t_{1/2} = 1.5 \text{ min} \]

\[ \Delta G^\ddagger = 25.1 \text{ kcal/mol} \quad t_{1/2} = 75 \text{ h} \]

\[ \Delta G^\ddagger = 25.7 \text{ kcal/mol} \quad t_{1/2} = 8.4 \text{ d} \]

\[ \Delta G^\ddagger = 29.2 \text{ kcal/mol} \quad t_{1/2} > 10 \text{ y} \]

\[ \Delta G^\ddagger = 30.0 \text{ kcal/mol} \quad t_{1/2} > 30 \text{ y} \]
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.

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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.

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

\[ t_{1/2} = \ln(2)/k_{\text{rac}} \]

For example, see: Barrett, K. T.; Miller, S. J. Org. Lett. 2015, 17, 580–583.
Torsional Energy Profile of Biphenyl

A
\( \phi = 90^\circ \)

B
\( \phi \sim 45^\circ \)

C
\( \phi = 0^\circ \)

- 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 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.

<table>
<thead>
<tr>
<th>X</th>
<th>Y</th>
<th>$\Delta G^\ddagger$ (kcal/mol)</th>
<th>$\phi$</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>H</td>
<td>2.2</td>
<td>42.5°</td>
</tr>
<tr>
<td>H</td>
<td>F</td>
<td>3.0</td>
<td>45.1°</td>
</tr>
<tr>
<td>H</td>
<td>Cl</td>
<td>7.6</td>
<td>59.9°</td>
</tr>
<tr>
<td>H</td>
<td>Br</td>
<td>8.6</td>
<td>63.6°</td>
</tr>
<tr>
<td>H</td>
<td>I</td>
<td>8.3</td>
<td>60.4°</td>
</tr>
<tr>
<td>F</td>
<td>F</td>
<td>4.8</td>
<td>57.9°</td>
</tr>
<tr>
<td>Cl</td>
<td>Cl</td>
<td>17.6</td>
<td>84.9°</td>
</tr>
<tr>
<td>Br</td>
<td>Br</td>
<td>20.0</td>
<td>91.5°</td>
</tr>
<tr>
<td>I</td>
<td>I</td>
<td>21.7</td>
<td>94.8°</td>
</tr>
</tbody>
</table>

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

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 $X, Y \neq H$, 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.
# Activation Parameters

Table I. Activation Parameters for 6-(2-X-4-Z-Phenyl)-S-Y-1,1-dimethylenedans

<table>
<thead>
<tr>
<th>Y</th>
<th>X</th>
<th>Z</th>
<th>Temp range, K</th>
<th>$\Delta G^\ddagger_{m}$, kJ mol$^{-1}$</th>
<th>$\Delta H^\ddagger$, kJ mol$^{-1}$</th>
<th>$\Delta S^\ddagger$, J mol$^{-1}$ K$^{-1}$</th>
<th>$\Delta G^\ddagger_{exp}$, kJ mol$^{-1}$</th>
<th>$\Delta G^\ddagger_{calc}$, kJ mol$^{-1}$</th>
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</thead>
<tbody>
<tr>
<td>CH$_3$</td>
<td>I</td>
<td>H</td>
<td>356-415</td>
<td>89.9 ± 0.7</td>
<td>55.7 ± 1.3</td>
<td>-88 ± 3.5</td>
<td>85.8 ± 1.0</td>
<td>86.3 ± 1.8</td>
</tr>
<tr>
<td>OCH$_3$</td>
<td>I</td>
<td>H</td>
<td>289-325</td>
<td>69.8 ± 0.6</td>
<td>55.4 ± 1.5</td>
<td>-46 ± 5</td>
<td>71.1 ± 0.7</td>
<td>72.9 ± 1.9</td>
</tr>
<tr>
<td>CH$_3$</td>
<td>Br</td>
<td>H</td>
<td>335-367</td>
<td>83.8 ± 1.1</td>
<td>66.2 ± 1.5</td>
<td>-50 ± 4</td>
<td>83.3 ± 1.2</td>
<td>82.9 ± 1.4</td>
</tr>
<tr>
<td>CH$_3$</td>
<td>Cl</td>
<td>H</td>
<td>308-362</td>
<td>78.1 ± 1.0</td>
<td>49.4 ± 0.9</td>
<td>-96 ± 2.5</td>
<td>78.6 ± 1.0</td>
<td>78.5 ± 1.1</td>
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<tr>
<td>CH$_3$</td>
<td>F</td>
<td>H</td>
<td>210-273</td>
<td>51.8 ± 0.6</td>
<td>22.9 ± 2.0</td>
<td>-120 ± 2</td>
<td>63.6 ± 0.8</td>
<td>63.6 ± 0.8</td>
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<tr>
<td>CH$_3$</td>
<td>CH$_2$</td>
<td>H</td>
<td>237-350</td>
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<td></td>
<td></td>
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<td></td>
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<tr>
<td>OCH$_3$</td>
<td>CH$_3$</td>
<td>H</td>
<td>258-308</td>
<td>62.3 ± 0.7</td>
<td>39.6 ± 0.4</td>
<td>-80 ± 1.5</td>
<td>66.8 ± 0.7</td>
<td>66.8 ± 0.7</td>
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<td>48.0 ± 5.5</td>
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<td>61.4 ± 0.8</td>
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<td>CH$_3$</td>
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<td>H</td>
<td>275-290</td>
<td>65.3 ± 0.7</td>
<td>44.1 ± 1.5</td>
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<td>69.8 ± 2.1</td>
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<td>COONa</td>
<td>H</td>
<td>297-322</td>
<td>70.8 ± 0.7</td>
<td>52.8 ± 0.9</td>
<td>-58 ± 3</td>
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<td>72.2 ± 1.5</td>
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<td>237-273</td>
<td>55.6 ± 0.6</td>
<td>37.2 ± 0.6</td>
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<td>Ph</td>
<td>H</td>
<td>293-311</td>
<td>70.5 ± 0.7</td>
<td>40.6 ± 1.5</td>
<td>-99 ± 5</td>
<td>74.2 ± 0.9</td>
<td>73.5 ± 1.6</td>
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<tr>
<td>CH$_3$</td>
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<td>H</td>
<td>336-364</td>
<td>82.4 ± 0.9</td>
<td>64.0 ± 1.4</td>
<td>-53 ± 4</td>
<td>81.9 ± 0.9</td>
<td>81.6 ± 1.2</td>
</tr>
<tr>
<td>CH$_3$</td>
<td>CH$_3$OAc</td>
<td>H</td>
<td>333-404</td>
<td>84.6 ± 0.9</td>
<td>67.3 ± 1.0</td>
<td>-47 ± 2.5</td>
<td>83.2 ± 1.0</td>
<td>82.4 ± 1.6</td>
</tr>
<tr>
<td>CH$_3$</td>
<td>CH(CH$_3$)$_2$</td>
<td>H</td>
<td>420-457</td>
<td>100.0 ± 0.7</td>
<td>51.5 ± 2.1</td>
<td>-113 ± 5</td>
<td>89.7 ± 1.9</td>
<td>92.0 ± 3.0</td>
</tr>
<tr>
<td>CH$_3$</td>
<td>CF$_3$</td>
<td>H</td>
<td>392-422</td>
<td>97.3 ± 1.1</td>
<td>77.8 ± 3.7</td>
<td>-48 ± 9</td>
<td>94.1 ± 1.7</td>
<td>92.0 ± 2.7</td>
</tr>
<tr>
<td>OCH$_3$</td>
<td>CF$_3$</td>
<td>H</td>
<td>307-332</td>
<td>74.3 ± 0.8</td>
<td>57.0 ± 1.7</td>
<td>-53 ± 5</td>
<td>75.4 ± 0.9</td>
<td>75.9 ± 1.3</td>
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<tr>
<td>CH$_3$</td>
<td>NO$_2$</td>
<td>H</td>
<td>275-304</td>
<td>68.8 ± 1.0</td>
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<tr>
<td>CH$_3$</td>
<td>NO$_2$</td>
<td>H</td>
<td>233-256</td>
<td>55.3 ± 0.6</td>
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<td></td>
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<td></td>
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<tr>
<td>CH$_3$</td>
<td>NH$_2$</td>
<td>H</td>
<td>223-251</td>
<td>80.8 ± 0.9</td>
<td>53.1 ± 1.3</td>
<td>-81 ± 4</td>
<td>80.7 ± 0.9</td>
<td>80.6 ± 1.0</td>
</tr>
<tr>
<td>CH$_3$</td>
<td>NH$_2$</td>
<td>H</td>
<td>252-276</td>
<td>86.6 ± 0.8</td>
<td>52.7 ± 3.3</td>
<td>-92 ± 10</td>
<td>84.4 ± 1.1</td>
<td>84.7 ± 1.4</td>
</tr>
<tr>
<td>CH$_3$</td>
<td>N(CH$_3$)$_2$</td>
<td>H</td>
<td>301-338</td>
<td>71.5 ± 0.6</td>
<td>44.5 ± 1.0</td>
<td>-84 ± 3</td>
<td>73.2 ± 0.7</td>
<td>73.1 ± 1.1</td>
</tr>
<tr>
<td>CH$_3$</td>
<td>N(CH$_3$)$_2$</td>
<td>H</td>
<td>&gt;422</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CH$_3$</td>
<td>NHCOCH$_3$</td>
<td>H</td>
<td>284-308</td>
<td>67.6 ± 0.6</td>
<td>42.6 ± 0.3</td>
<td>-84 ± 1</td>
<td>71.3 ± 0.7</td>
<td>71.1 ± 1.7</td>
</tr>
<tr>
<td>CH$_3$</td>
<td>NHCOCH$_3$</td>
<td>H</td>
<td>284-308</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CH$_3$</td>
<td>S(CH$_3$)$_2$</td>
<td>H</td>
<td>266-287</td>
<td>92.1 ± 0.8</td>
<td>53.6 ± 1.3</td>
<td>-97 ± 3.5</td>
<td>86.6 ± 1.0</td>
<td>87.6 ± 2.2</td>
</tr>
<tr>
<td>CH$_3$</td>
<td>SH</td>
<td>H</td>
<td>333-349</td>
<td>81.2 ± 0.9</td>
<td>45.9 ± 1.6</td>
<td>-103 ± 5</td>
<td>81.1 ± 0.9</td>
<td>81.1 ± 0.9</td>
</tr>
<tr>
<td>CH$_3$</td>
<td>SCl$_2$</td>
<td>H</td>
<td>327-356</td>
<td>82.2 ± 0.8</td>
<td>53.1 ± 1.2</td>
<td>-84 ± 3.5</td>
<td>81.6 ± 0.9</td>
<td>81.7 ± 1.0</td>
</tr>
<tr>
<td>CH$_3$</td>
<td>CN</td>
<td>H</td>
<td>244-254</td>
<td>58.8 ± 0.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CH$_3$</td>
<td>HgCl</td>
<td>H</td>
<td>320-351</td>
<td>73.7 ± 0.5</td>
<td>39.9 ± 1.6</td>
<td>-102 ± 5</td>
<td>74.6 ± 0.5</td>
<td>74.1 ± 0.6</td>
</tr>
<tr>
<td>CH$_3$</td>
<td>Cl</td>
<td>NO$_2$</td>
<td>310-344</td>
<td>76.5 ± 0.9</td>
<td>56.2 ± 0.9</td>
<td>-62 ± 3</td>
<td>77.3 ± 0.9</td>
<td>77.5 ± 1.2</td>
</tr>
<tr>
<td>CH$_3$</td>
<td>F</td>
<td>NO$_2$</td>
<td>213-243</td>
<td>48.6 ± 0.6</td>
<td>19.6 ± 0.8</td>
<td>-127 ± 3.5</td>
<td>62.9 ± 0.9</td>
<td>57.4 ± 3.3</td>
</tr>
</tbody>
</table>

* $\Delta G^\ddagger$ at the temperature at the center of the range over which kinetic data was obtained.  
* $\Delta G^\ddagger$ at 340 K, calculated using $\Delta G^\ddagger_{m}$ and $\Delta S^\ddagger$.  
* $\Delta G^\ddagger$ at 340 K, calculated using $\Delta G^\ddagger_{m}$ and $\Delta S^\ddagger_{av}$. 

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.”

\[ \Delta G^\ddagger(\text{tot}) = \Delta G^\ddagger(X-H) + \Delta G^\ddagger(Y-H) \]

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

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

<table>
<thead>
<tr>
<th>Interacting Group (X or Y)</th>
<th>$I_{340}^{X-H}$, kJ mol(^{-1})</th>
<th>Interacting Group (X or Y)</th>
<th>$I_{340}^{X-H}$, kJ mol(^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>45.7 ± 2.7</td>
<td>CH(CH(_3))(_2)</td>
<td>52.6 ± 4.1</td>
</tr>
<tr>
<td>Br</td>
<td>42.5 ± 2.5</td>
<td>r-Bu</td>
<td>76.6 ± 4.3(^a)</td>
</tr>
<tr>
<td>Cl</td>
<td>38.1 ± 2.2</td>
<td>COOMe</td>
<td>34.3 ± 3.1</td>
</tr>
<tr>
<td>F</td>
<td>19.2 ± 4.1</td>
<td>COCH(_3)</td>
<td>29.6 ± 3.4</td>
</tr>
<tr>
<td>H</td>
<td>~4(^a)</td>
<td>Ph</td>
<td>33.1 ± 2.7</td>
</tr>
<tr>
<td>MeO</td>
<td>26.6 ± 1.2</td>
<td>CN</td>
<td>25.6 ± 4.1</td>
</tr>
<tr>
<td>HO</td>
<td>27.1 ± 3.8</td>
<td>NMe(_2)</td>
<td>32.7 ± 2.2</td>
</tr>
<tr>
<td>AcO</td>
<td>29.4 ± 3.2</td>
<td>NHMe</td>
<td>44.3 ± 2.5</td>
</tr>
<tr>
<td>SMe</td>
<td>41.3 ± 2.1</td>
<td>NH(_3)</td>
<td>40.2 ± 2.1</td>
</tr>
<tr>
<td>SH</td>
<td>40.7 ± 2.0</td>
<td>NMe(_3)^*</td>
<td>&gt;53.6</td>
</tr>
<tr>
<td>CH(_3)</td>
<td>40.4 ± 1.1</td>
<td>NO(_2)</td>
<td>32.4 ± 3.3</td>
</tr>
<tr>
<td>CF(_3)</td>
<td>50.6 ± 3.1</td>
<td>HgCl</td>
<td>33.7 ± 1.7</td>
</tr>
<tr>
<td>CH(_2)OH</td>
<td>41.2 ± 2.3</td>
<td>SiMe(_3)</td>
<td>47.2 ± 3.3</td>
</tr>
<tr>
<td>CH(_2)OAc</td>
<td>42.0 ± 2.7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Independent Verification

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

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

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

<table>
<thead>
<tr>
<th>X</th>
<th>effective radius (this work)</th>
<th>van der Waals radius (Bondi)</th>
<th>effective radius (Chariton)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>1.97 ± 0.06</td>
<td>1.98</td>
<td>1.97</td>
</tr>
<tr>
<td>Br</td>
<td>1.86 ± 0.04</td>
<td>1.85</td>
<td>1.85</td>
</tr>
<tr>
<td>Cl</td>
<td>1.73 ± 9.03</td>
<td>1.75</td>
<td>1.73</td>
</tr>
<tr>
<td>F</td>
<td>1.47 ± 0.01</td>
<td>1.47</td>
<td>1.47</td>
</tr>
<tr>
<td>OMe</td>
<td>1.52 ± 0.03</td>
<td>1.52 (O)</td>
<td>1.56</td>
</tr>
<tr>
<td>OH</td>
<td>1.53 ± 0.03</td>
<td>1.53</td>
<td>1.52</td>
</tr>
<tr>
<td>OAc</td>
<td>1.56 ± 0.03</td>
<td>1.56</td>
<td></td>
</tr>
<tr>
<td>SMc</td>
<td>1.82 ± 0.03</td>
<td>1.80 (S)</td>
<td>1.84</td>
</tr>
<tr>
<td>SH</td>
<td>1.80 ± 0.03</td>
<td>1.80</td>
<td>1.80</td>
</tr>
<tr>
<td>CH$_3$</td>
<td>1.80 ± 0.03</td>
<td>1.80</td>
<td>1.72, 2.22</td>
</tr>
<tr>
<td>CF$_3$</td>
<td>2.2 ± 0.13</td>
<td>2.11, 2.74</td>
<td></td>
</tr>
<tr>
<td>CH$_3$OH</td>
<td>1.82 ± 0.04</td>
<td>1.73</td>
<td></td>
</tr>
<tr>
<td>CH$_2$OAc</td>
<td>1.84 ± 0.05</td>
<td>1.96</td>
<td></td>
</tr>
<tr>
<td>CH$_2$(CH$_3$)$_2$</td>
<td>2.2 ± 0.12</td>
<td>2.4, 3.2</td>
<td></td>
</tr>
<tr>
<td>t-Bu</td>
<td>3.6 ± 0.5</td>
<td>2.42, 3.11</td>
<td></td>
</tr>
<tr>
<td>COOMe</td>
<td>1.62 ± 0.03</td>
<td>1.77</td>
<td>1.77</td>
</tr>
<tr>
<td>COCH$_3$</td>
<td>1.56 ± 0.04</td>
<td>1.77</td>
<td>1.60</td>
</tr>
<tr>
<td>Ph</td>
<td>1.62 ± 0.03</td>
<td>1.78</td>
<td>1.60</td>
</tr>
<tr>
<td>CN</td>
<td>1.51 ± 0.03</td>
<td>1.53 (N)</td>
<td>1.63</td>
</tr>
<tr>
<td>NMe$_2$</td>
<td>1.61 ± 0.02</td>
<td>1.79</td>
<td>1.63</td>
</tr>
<tr>
<td>NH$_2$</td>
<td>1.79 ± 0.03</td>
<td>2.27</td>
<td>2.42, 3.11</td>
</tr>
<tr>
<td>NMe$_3$</td>
<td>&gt; 2.27</td>
<td>2.42, 3.11</td>
<td></td>
</tr>
<tr>
<td>NCOCH$_3$</td>
<td>1.58 ± 0.03</td>
<td>1.58</td>
<td>1.79</td>
</tr>
<tr>
<td>NO$_3$</td>
<td>1.61 ± 0.04</td>
<td>1.58</td>
<td>1.79</td>
</tr>
<tr>
<td>HgCl</td>
<td>1.63 ± 0.01</td>
<td>1.58</td>
<td>1.79</td>
</tr>
<tr>
<td>SiMe$_3$</td>
<td>2.01 ± 0.08</td>
<td>2.1</td>
<td>2.1</td>
</tr>
</tbody>
</table>

$^a$ Derived by interpolation (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 $\Delta G_{340}^{\pm}$ for this compound is well beyond the range encompassed by the halogens so the effective radius of tert-butyl is not well defined.

Other Factors that Affect Rotational Barriers in Atropisomers

- **Buttressing Effects**

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

- **Electronic Effects**

<table>
<thead>
<tr>
<th>X</th>
<th>Y</th>
<th>( \Delta G^\ddagger ) (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>H</td>
<td>25.6</td>
</tr>
<tr>
<td>OMe</td>
<td>H</td>
<td>24.9</td>
</tr>
<tr>
<td>OMe</td>
<td>OMe</td>
<td>24.4</td>
</tr>
<tr>
<td>NO₂</td>
<td>H</td>
<td>25.8</td>
</tr>
<tr>
<td>NO₂</td>
<td>NO₂</td>
<td>26.3</td>
</tr>
</tbody>
</table>

  \[ n \rightarrow \pi^* \text{ donation into arene increases} \]
  \[ \text{sp}^3\text{-character of at biaryl C-atom} \]
Other Factors that Affect Rotational Barriers in Atropisomers

- **Bond Length Effects**

\[
\Delta G^\ddagger = \text{ca. 30 kcal/mol} \\
\frac{t_{1/2}}{} > 30 \text{ y} \\
\text{r}_{C-C} = 1.49 \text{ Å}
\]

\[
\Delta G^\ddagger = \text{ca. 36 kcal/mol} \\
\frac{t_{1/2}}{} \sim 800,000 \text{ y} \\
\text{r}_{C-C} = 1.37 \text{ Å}
\]

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

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

\[ k_{\text{enant}} \]

\[ \text{planar TS} \]

\[ \text{R} \leftrightarrow \text{S} \]

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

\[ k_{\text{rac}} = 2k_{\text{enant}} \]

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)**

<table>
<thead>
<tr>
<th>structure</th>
<th>rel energy (kJ/mol)</th>
<th>angle C(2)–C(1)–C(1′)–C(2′) (deg)</th>
<th>distance (pm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GS</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>anti-C1′TS</td>
<td>158.3</td>
<td>94.8</td>
<td></td>
</tr>
<tr>
<td>syn-C2′TS</td>
<td>175.3</td>
<td>180</td>
<td></td>
</tr>
<tr>
<td>anti-C2′TS</td>
<td>249.4</td>
<td>150</td>
<td></td>
</tr>
</tbody>
</table>

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.

\[
\Delta G^\ddagger_{(rac)} = 27.9 \text{ kcal/mol}
\]

\[
\Delta G^\ddagger_{(rac)} = 23.1 \text{ kcal/mol}
\]

---

Modes of Racemization—Gearing

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

\[
\begin{align*}
\text{(aS, exo)} & \quad \text{(aS, endo)} \\
\text{(aR, endo)} & \quad \text{(aR, exo)}
\end{align*}
\]

- C–N 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.

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

Geared rotation is ~3x faster!

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.

![Diagram showing racemization process](image)

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

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

\[ \tau_{1/2}^{(\text{rac})} = 30 \text{ min under } h\nu \]

Modes of Racemization—Acid/Base Reactivity

- **Acid-Catalyzed Racemization of BINOL**

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

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

- **Base-Catalyzed Racemization of BINOL**

  (aR)-BINOL

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

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.*

\[
\tau_{1/2}(\text{rac}) = 6.5 \text{ h at rt} \\
\Delta G^\ddagger(\text{rac}) = 23.7 \text{ kcal/mol}
\]

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

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

Atropisomers in Pharmaceutical Chemistry

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

- 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…”

![New Chemical Entities Approved](image)

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


Guidelines for Atropisomer Classification

<table>
<thead>
<tr>
<th>ΔG‡ (kcal/mol)</th>
<th>t_{1/2}</th>
</tr>
</thead>
<tbody>
<tr>
<td>14.2</td>
<td>0.002 s</td>
</tr>
<tr>
<td>17.9</td>
<td>1 s</td>
</tr>
<tr>
<td>21.6</td>
<td>12 min</td>
</tr>
<tr>
<td>25.1</td>
<td>75 h</td>
</tr>
<tr>
<td>25.7</td>
<td>10 d</td>
</tr>
<tr>
<td>29.2</td>
<td>&gt; 10 y</td>
</tr>
<tr>
<td>30.0</td>
<td>&gt;&gt;10 y</td>
</tr>
</tbody>
</table>

**Rule-of-Thumb**

- A drug compound should maintain 99.5% homogeneity over 24 h in vivo.
- ΔG‡ > 27.3 kcal/mol & t_{1/2} > 138 d
Class I (Non)Atropisomers

• According to the LaPlante scheme, *Class I 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.

Class I (Non)Atropisomers

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

![Chemical structure](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.

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.

Class 3 Atropisomers

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

Afloqualone
- $GABA_\alpha$ 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.

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)
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.

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

---

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

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

---

Designing a Higher Rotational Barrier

- AstraZeneca discovered a potent NK\textsubscript{1} antagonist, but complications arose due to thermal equilibration about the two stereogenic axes at physiological temperature.

\begin{itemize}
  \item The structure was redesigned with a \textit{seven-member bridge} possessing a substituent; this locked the molecule into a single, highly bioactive conformer with Class 3 characteristics.
\end{itemize}

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.

\[ \Delta G^\ddagger = 23.3 \text{ kcal/mol} \]
\[ t_{1/2} = 46 \text{ min at 37 } ^\circ \text{C} \]

- 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.

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.

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

---

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

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

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.

![Diagram](image)

*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.

Developing a Racemic Mixture

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- 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.

\[
\begin{align*}
\text{BMS-207940} & \\
& \text{endothelin receptor antagonist} \\
& \text{used in treatment of congestive heart failure} \\
& \text{medium- and concentration-dependent barrier}
\end{align*}
\]

\[
\begin{align*}
\frac{t_1}{2} (\text{rac}) &= 15.8 \text{ h (aqueous medium)} \\
\frac{t_1}{2} (\text{rac}) &= 2.5 \text{ h (human plasma, 400 µg/mL)} \\
\frac{t_1}{2} (\text{rac}) &= 0.1 \text{ h (human plasma, 20 µg/mL)}
\end{align*}
\]

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.

---

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

Atroposelective Cross-Coupling

- Chiral leaving group
- Achiral catalyst
- Oxidant + MLₙ*

Enantioselective
Diastereoselective

- Chiral bridge
- Chiral ortho-substituent
- Planar chiral auxiliary

Select Cross-Coupling Examples

**Chiral Bridge Strategy**


**Chiral Leaving Group Strategy**

Naphthol Couplings with Point–to-Axis Chirality Transfer

Point–to-Axis Chirality Transfer

\[
\begin{align*}
\text{NTs} & \quad \text{Cl} \\
\text{Cl} & \quad \text{Cl} \\
\end{align*}
\]

\[
\begin{align*}
+ & \quad \text{NH}_2 \\
\text{CH}_2\text{Cl}_2 (0.05 \text{ M}), \text{rt}, 12 \text{ h} & \quad \text{NH}_2 \\
\end{align*}
\]

98% yield, 91% ee

(aR)-CPA 1

\[
\begin{align*}
\text{Ar} & = \text{2,4,6-(i-Pr)C}_6\text{H}_2 \\
\end{align*}
\]


\[
\begin{align*}
\text{N} & \quad \text{CO}_2\text{Me} \\
\text{t-Bu} & \quad \text{t-Bu} \\
\end{align*}
\]

\[
\begin{align*}
\text{NH} & \quad \text{NH} \\
\text{NHCO}_2\text{Me} & \quad \text{NHCO}_2\text{Me} \\
\end{align*}
\]

99% yield, 92% ee

(aR)-CPA 2

\[
\begin{align*}
\text{Ar} & = \text{C}_6\text{F}_5 \\
\end{align*}
\]

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.

Catalytic Ring Opening of Bringmann Lactones

Peptide-Catalyzed, Atroposelective Bromination—DKR

(±)-biaryl
- rapidly racemizing
  (~7 kcal/mol barrier)

3.0 equiv NBP
10 mol% peptide
CHCl₃/acetone (97:3)
25 ºC, 18 h

enantioenriched tribromide
- atropisomerically stable
  (>30 kcal/mol barrier)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Yield (%)</th>
<th>er</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>80</td>
<td>97.0:3.0</td>
</tr>
<tr>
<td>2</td>
<td>4-NO₂</td>
<td>85</td>
<td>97.0:3.0</td>
</tr>
<tr>
<td>3</td>
<td>5-NO₂</td>
<td>75</td>
<td>96.5:3.5</td>
</tr>
<tr>
<td>4</td>
<td>4-OMe</td>
<td>80</td>
<td>94.0:6.0</td>
</tr>
<tr>
<td>5</td>
<td>5-OMe</td>
<td>70</td>
<td>96.0:4.0</td>
</tr>
<tr>
<td>6</td>
<td>4-F</td>
<td>65</td>
<td>96.5:3.5</td>
</tr>
<tr>
<td>7</td>
<td>5-F</td>
<td>70</td>
<td>97.0:3.0</td>
</tr>
<tr>
<td>8</td>
<td>3-Me</td>
<td>85</td>
<td>87.0:13.0</td>
</tr>
<tr>
<td>9</td>
<td>4,5-OCH₂O</td>
<td>70</td>
<td>95.0:5.0</td>
</tr>
<tr>
<td>10*</td>
<td>Ph</td>
<td>77</td>
<td>85.0:15.0</td>
</tr>
</tbody>
</table>

* 4 equiv NBS

(±)-biaryl "catalyst"

Catalyst Yield (%)
- none 15%
- i-Pr₂NEt 31%
- (±)-Boc-Val-NMe₂ 91%

- backbone amides involved in catalysis

Peptide-Catalyzed, Atroposelective Bromination—DKR

(±)-biaryl
• rapidly racemizing (~7 kcal/mol barrier)

enantioenriched tribromide
• atropisomERICally stable (>30 kcal/mol barrier)

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* 4 equiv NBS

Peptide-Catalyzed, Atroposelective Bromination—DKR


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]**

86% yield, 89% ee

\[ \Delta G^\ddagger = 27.5 \text{ kcal/mol} \]
Atroposelective Paal–Knorr Annulation

\[
\text{Ar} \text{O} \text{R'} \text{O} \text{R''} + \text{NH}_2 \text{Ar} \text{O} \text{R''} \xrightarrow{\text{CPA (10 mol%) Fe(OTf)}_3 (10 \text{ mol%})} \text{CCl}_4/\text{cyclkohexane} , \text{MgSO}_4 \xrightarrow{0 \text{ } ^\circ\text{C}} \]

31 Examples
83–95% yield, 86–97% ee

(aR)-spiro-CPA
Ar = 9-anthryl

• key intermediate for catalyst-control in enantiodetermining cyclization
Atroposelective Aldol & Michael Reactions


Atroposelective Aldol & Michael Reactions


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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

- Chiral leaving group
- Chiral catalyst
- Oxidant
- Product

- Redox neutral coupling
- Planar chiral auxiliary
- Chiral ortho-substituent
- Chiral bridge
- Chiral ortho-substituent
- Chiral leaving group
- Chiral catalyst
- Oxidant
- Product

Pharmaceutical Considerations

- Torsion Rotation
- Energy Barrier
- Atropisomers
- (no interconversion)
- 40 years
- 30 hours - days
- 20 min - hours
- 10 msec - sec
- Free Rotation
- 0 kcal/mol
Outlook

Data compiled from Web of Science topic searches, accessed 14 June 2018.
The Extra Mile

General Text on Stereochemistry

General Text on Atropisomerism

Comprehensive Review on Biaryl Atropisomers

Comprehensive Review on Non- & Heterobiaryl Atropisomers

Atropisomers in Drug Development

Recent Reviews on Catalytic, Atroposelective Methods
Thank You!