Helicenes: Synthesis and Applications

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Outline

Background

Synthesis
  ◦ Early methods
  ◦ Photochemical strategy
  ◦ Diels-Alder strategy

Application
  ◦ Chiral ligands in asymmetric catalysis
  ◦ Helicenes as organocatalysts
Helicenes

Class of polyaromatic molecules
- Characterized by several (4 or more) ortho-fused benzene (or hetero-aromatic) rings
- Adopt a helical structure
- Very large specific rotation
  - $\pm 1670^\circ$ (for [5]helicene) up to $\pm 9620^\circ$ (for [13]helicene)
  - $[\alpha]_\lambda^T = \frac{\alpha}{l \cdot c}$
- “Continuously chiral”

Nomenclature

Use \([n]\)helicene for unsubstituted systems
- \(n\) = number of ortho-fused rings
- Also common to use prefixes

Directionality
- Right-handed helicenes are denoted \(P\) (plus) or \(\Delta\)
- Left-handed helicenes are denoted \(M\) (minus) or \(\Lambda\)
Some terminology...

Axial Chirality:
- No stereogenic centers
- Molecule contains an axis (single bond) whose substituents are held in a particular arrangement due to steric bulk

Helicity:
- Defined by a 3-dimensional space curve

Axial Chirality: (S)-BINOL  
(S)-VAPOL: Both?  
Helicity: (P)-hexahelicene
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Hexahelicene - Synthesis

First synthesis (Newman and Lednicer, 1956)

M. S. Newman and D. Lednicer. J. Am. Chem. Soc. 1956, 78(18), 4765-4770
Hexahelicene - Resolution

Resolution with TAPA
- 2-(2,4,5,7-tetranitro-9-fluorenylideneaminoxy)-propionic acid
- Novel technique at the time for resolution of a neutral molecule
- Formation of a diastereomeric charge-transfer complex

Specific rotations:
- (−)-helicene: \([\alpha]^{24}_D = -3640^\circ\)
- (+)-helicene: \([\alpha]^{25}_D = +3707^\circ\)
A sample of hexahelicene (I) was sent to Prof. H. S. Gutowsky, University of Illinois, who is interested in nuclear magnetic resonance phenomena. He reports the following concerning I.

“The proton magnetic resonance of hexahelicene was observed (L. H. Meyer, A. Saika and H. S. Gutowsky, THIS JOURNAL, 75, 4567 (1953)) in chloroform and in carbon tetrachloride solutions. The spectrum consisted of two main components, with relative integrated intensities of 3:2, located at δ-values of +0.325 and +0.391, respectively. The weaker of these components was broader and appeared to contain two sub-components of unequal intensity. On the basis of intensities, as well as by their chemical shifts, the main component at +0.325 can be assigned to the 10 peripheral protons (4–13, incl.) and the weaker double line at +0.391 to the 6 terminal protons at the 'split' in the polycyclic ring (1, 2, 15, 16 and 3, 14). The chemical shift in the resonance of the peripheral protons from the resonance of the terminal protons is comparable to that found (H. J. Bernstein and W. G. Schneider, J. Chem. Phys., 24, 468 (1956)) in compounds such as phenanthrene. There do not appear to be any sizable effects due to the 'helical type' overlap of the rings.”
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Photochemical Approach

Oxidative photocyclization of stilbene-like molecules

- The intermediate trans-dihydrophenanthrene is trapped with I$_2$ or O$_2$
- Only the cis-isomer is reactive, but the trans-isomer can still be used since cis-trans isomerization of stilbene derivatives occurs readily under the conditions

\[
\text{Cis-stilbene} \xrightarrow{\text{hv}} \left[ \begin{array}{c} \text{trans-dihydrophenanthrene} \\ H \\ H \end{array} \right] \xrightarrow{\text{oxidant (I$_2$ or O$_2$)}} \text{Phenanthrene}
\]
Mechanism

Cyclization:

Oxidative Trapping:

- I$_2$ is typically used rather than oxygen, since hydrogen abstraction by iodide is more exothermic
Competing Reactions

Problem: [2+2] cycloadditions

Stilbene dimerization

Phenanthrene-Stilbene Cycloaddition

Solution: Run reaction at low concentrations (0.001 M or less)
Hexahelicene (revisited)

R. H. Martin, 1968

- Cyclization precursor accessed through Wittig chemistry

[Chemical reactions and structures with notes on yields]
Larger...

Heptahelicene (R. H. Martin, 1967)
- Stilbene-like precursor accessed by dehydration reaction

Racemic synthesis – resolution was achieved by hand-picking crystals!!

66% yield

... and larger


- Wittig reaction proceeds in 97% yield
- Photocyclization proceeds in 84% yield
- Up to [14] helicenes prepared in this manner

Substituted Helicenes

[6]-Heliphos (Reetz, 1997)
- Cyclization precursor accessed with Wittig chemistry
- Photocyclodehydrogenation proceeds in 10-50 % yield

Substituted Helicenes

- Precursor accessed via Heck reaction
- Propylene oxide traps HI as it forms

\[
\begin{align*}
\text{R} &= \text{H, Me, OMe, OH, CN} \\
\end{align*}
\]
Regioselectivity

Controlling regioselectivity

- How can unwanted constitutional isomers be discriminated against?
- Often, π-stacking interactions help organize the transition state
- Another option is to use a “bromine auxiliary”

75 % yield for cyclization step (as opposed to 20 % when bromine auxiliary is not used)

Heterohelicenes

- Photochemical approach is easily applied

Asymmetric Photocyclization

Asymmetric synthesis with circularly polarized light (first example)
- Enantiomeric excess < 0.20% (determined by optical rotation), but still outside the margin of experimental error

(M)-helicene: \([\alpha]^{23}_D = -7.5 \pm 0.3^\circ\)

(P)-helicene: \([\alpha]^{23}_D = +7.9 \pm 0.6^\circ\)

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Diels-Alder Approach

2 General Classes

◦ Addition of dienophile to 3,3’,4,4’-tetrahydro-1,1’-binapthalenes

◦ Addition of dienophile to vinylbenzenes

Early Work

[5]-Helicene (Weidlich, 1938)
- First example of using the Diels-Alder approach
- Tetrahydrobinaphthalene used as diene
- Cycloaddition step proceeds in 75% yield

Addition to vinylbenzenes

[5]-Helicenebisquinone (Katz, 1990)
- Cycloaddition proceeds in 17 % yield
- Immediate Diels-Alder product is oxidized by excess benzoquinone

How to increase yield?
Diels-Alder: Increasing the Yield

Substituted [5] and [6]-Helicenebisquinones (Katz, 1997)

- Yields can be increased by increasing electron density on the diene

\[
\begin{align*}
\text{R} & \quad \text{\(\text{O}_2\text{C} \quad (12 \text{ equiv})\)} \\
\text{110 °C, 3 days} & \quad \text{Rearomatization}
\end{align*}
\]

17 %, \( R = \text{H} \) (previous slide)
50 %, \( R = \text{OC}_{12}\text{H}_{25} \)

\[
\begin{align*}
\text{R}_1 & \quad \text{\(\text{O}_2\text{C} \quad \text{O} \quad \text{R}_1 \quad \text{R}_2 \)} \\
\text{toluene, reflux} & \quad \text{R}_1 & \quad \text{\(\text{O}_2\text{C} \quad \text{O} \quad \text{R}_2 \quad \text{R}_1 \)}
\end{align*}
\]

6 %, \( R_1 = \text{H}, R_2 = \text{H} \)
13%, \( R_1 = \text{H}, R_2 = \text{OMe} \)
47%, \( R_1 = \text{OMe}, R_2 = \text{H} \)
42%, \( R_1 = \text{OTBDMS}, R_2 = \text{H} \)

Asymmetric Diels-Alder

Asymmetric synthesis with chiral sulfinylquinones

\[(M)\text{-helicenebisquinone}\]

80 % ee, 22 % yield

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Asymmetric catalysis

Why use helicenes in asymmetric catalysis?

- Rigidity/thermal stability
- Define a large chiral pocket (“continuously chiral”)
- Highly amenable to charge-transfer complexation (polarizable)
Early Applications

Epoxidation (Martin, 1986)
- Stoichiometric additive
- First application of a helicene in an enantioselective reaction

\[
\text{(P)-(+)\text{-}2\text{-cyano-}[7]\text{helicene}} 
\]

92% yield, 99.8% ee

\[
\text{(M)-(\text{-})\text{-}2\text{-cyano-}[7]\text{helicene}} 
\]

84% yield, 97.6% ee
Early Applications

Hydrogenation (Reetz, 1997)

- First example of catalytic use of a helicene in asymmetric synthesis

\[
\begin{align*}
\text{MeO}_2\text{C} & \quad \text{CO}_2\text{Me} \\
\xrightarrow{(P)\text{-PHelix (0.1 mol %)} \quad [\text{Rh(COD)}_2\text{BF}_4 \text{ (0.1 mol %)}]} \\
\text{H}_2 \quad (1 \text{ atm), r.t.} & \quad \text{MeO}_2\text{C} & \quad \text{CO}_2\text{Me}
\end{align*}
\]

54% yield, 39% ee

(P)-PHelix:

Helical Phosphines

Kinetic Resolution with PHelix (Reetz, 2000)

\[ \text{racemic} + \text{MeO}_2\text{C} = \text{CO}_2\text{Me} \quad \text{(2.9 equiv)} \quad \xrightarrow{(+)-(P)-PHelix (1.0 mol \%), [(allyl)PdCl]_2 (0.25 mol \%), BSA (2.9 equiv), KOAc (cat.)} \quad \text{MeO}_2\text{C} = \text{CO}_2\text{Me} \quad 82.7\% \text{ ee (R)} + \quad \text{MeO}_2\text{C} = \text{CO}_2\text{Me} \quad 99\% \text{ ee (R)} \]
Helical Phosphines

Kinetic Resolution with PHelix (Reetz, 2000)

- Although PHelix is formally a diphosphine, it is more likely behaving as a monodentate ligand
- Multiple signals in $^{31}\text{P}$ NMR
  - $\eta^3$-C$_3$H$_5$PdCl-PHelix complex
  - Main peak at 33.6 ppm
  - Smaller signals at 24.1, 27.2, 27.9, and 28.0 ppm
- Crystal structure
  - P1–P2 distance in PHelix is too large to chelate metal


6.481(1) Å [P1–P2]
Unfunctionalized Helicenes

Soai (2001)

- First example of a hydrocarbon as an asymmetric catalyst
- “Chiral inducer” to an asymmetric autocatalytic process
- Origin of enantioselectivity arises from formation of a charge-transfer complex between the aldehyde and helicene
- Evidence of a charge-transfer complex can be observed in proton NMR
  - Upfield shift of aldehyde and pyrimidine ring proton signals
  - Shift shows a linear correlation with amount of helicene added (up to 6.3 equiv)

<table>
<thead>
<tr>
<th>Proton signal</th>
<th>$\Delta \delta$ (per equiv. of helicene)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>-13.3 Hz</td>
</tr>
<tr>
<td>B</td>
<td>-9.1 Hz</td>
</tr>
<tr>
<td>C</td>
<td>-1.1 Hz</td>
</tr>
</tbody>
</table>

![Chemical structure](image)

Helicenes in Organocatalysis

Modular synthesis of 1-azahelicenes (Takenaka, 2008)

- Cyclization is achieved through an intramolecular Stille coupling
- Variation of Wittig partner allows access to a number of azahelicenes

Takenaka et al. *Angew. Chem., Int. Ed.* 2008, 47(50), 9708-9710
Helicenes in Organocatalysis

Desymmetrization of *meso* epoxides with chlorosilane

- Degree of stereoselectivity is highly substrate-dependent

\[
\text{catalyst (10 mol %)} \\
\text{SiCl}_4, \text{ DIPEA, CH}_2\text{Cl}_2 \\
48 \text{ hrs, } -78 ^\circ \text{C}
\]

Substrate scope:

- \( R = \text{Ph} \): 77 % yield, 94 % ee
- \( R = 2\text{-naphthyl} \): 76 % yield, 92 % ee
- \( R = \text{BnOCH}_2 \): 72 % yield, 65 % ee
- \( R = \text{alkyl} \): 74 % yield, 33 % ee

Takenaka et al. *Angew. Chem., Int. Ed.* 2008, 47(50), 9708-9710
Lewis Base Catalysis

Activation of allenyltrichlorosilane (Takenaka, 2011)
- Synthesis and application of a bidentate Lewis basic helicene

1. \( \text{THF, -78 °C} \)
2. \( \text{DDQ, -78 °C} \)

\[ \text{RCH} = \text{CH}_{\text{SiCl}} + \text{catalyst (10 mol %)} \rightarrow \text{RCH} = \text{CHCH} = \text{CH}_2 \]

18 examples, 55-98% yield, 59-96% ee

Lewis Base Catalysis

Activation of allenyltrichlorosilane (Takenaka, 2011)
- Proposed model of stereochemical control

Significant drop in ee when this catalyst was used instead (33% ee)

Significant drop in ee (59% ee) when this substrate was used (R = aryl for all other substrates)
H-Bond Donor Catalysis

Helicene-based 2-aminopyridinium ions (Takenaka, 2010)
- Application: addition of dihydroindoles to nitroalkenes

Catalyst synthesis:

1. TsOH, ad-NH₂ (82%)
2. HCl, EtOH, NaBArF₂₄ (98%)

- 19 examples
- 10-90% yield
- 60:40 to 98:2 er

H-Bond Donor Catalysis

Helicene-based 2-aminopyridinium ions (Takenaka, 2010)

- Stereochemical model:

Enantioselectivity drops off rapidly for this catalyst (adamantyl group removed):

![Chemical structures and reaction scheme](image-url)

Concluding Remarks

Powerful synthetic methods exist to construct helicenes
- Photocyclization strategy and Diels-Alder strategy are most common
- Can generate both functionalized and unfunctionalized helicenes

Helicenes have displayed varied roles in a number of catalytic processes
- Chiral ligands for transition metals
- Organocatalysis
- Lewis basic helicenes

Still a young field!
- Reports of catalytic uses of helicenes date back only to the 1990s
References

Reviews:

All other sources are cited on the slides on which they appear.