Biaryls in Nature and Synthetic Approaches to Axial Chirality

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M.C. Escher’s Drawing Hands
Outline

- Axial chirality in context
- Biaryls in nature
- Synthetic approaches to biaryl axial chirality
  - Classical
  - Selective conversion of pro-stereogenic biaryls
  - Generation of second aromatic ring
- Conclusion
Timeline of Chirality

- **1848**: Louis Pasteur studied the enantiomers of tartaric acid while investigating the mechanism by which wine goes sour.
- **1874**: Van’t Hoff proposed the tetrahedral carbon.
- **1922**: Christie and Kenner first accurately described axial chirality (*J. Chem. Soc.** 1922, 121, 614)*.
- **1933**: Kuhn coined the term *atropisomer* (a=not, tropos=turn). Originally only referred to biaryl compounds (*Stereochemie*, Frans Deuticke, Leipzig, 1933).

Kaufler’s explanation for axial chirality (*Ann.** 1907, 151, 351)*.
Features of Chiral Biaryl Atropisomers

- Stability/rotational barrier factors (a half life of 16.7 min (1,000 s) is considered physically separable):
  - Sterics (I>Br>Me>Cl>NO$_2$>CO$_2$H>OMe>F>H)
    - 3 or 4 ortho substituents generally form stable atropisomers
  - Existence, length and rigidity of bridges
    - 5 membered rings freely rotate at r.t.
  - Atropisomerization mechanisms
    - Physical (e.g. heat)
    - Photochemical
    - Chemically induced

- Chirality criteria:
  - Different substituents on both sides of the axis (A≠B and A’≠B’)
  - Presence and location of hetero-atoms
  - Different meta substituents

Assignment of Chirality

chirality in biaryl compounds (priority: A > B):

M=Minus
P=Plus

prochirality in biaryl compounds:

Gossypol (from *gossypium hirsutum* seeds)
- Discovered in 1899 (absolute stereochemistry determined in 1988)
- The (-) enantiomer is either the major or sole possessor of the following biological activity:
  - Anti-fertility
  - Anti-tumor
  - Anti-amoebic
  - Anti-HIV

*Phytochemistry, 1991, 30, 2655*
Biological Activity (cont.)

- **Antimicrobial Teicoplanin** (*actinoplanes teichomyceticus*)
  - 2-8 fold more potent than vancomycin and less cytotoxic
  - The biological activity of the DE ring atropisomer was 50 fold less active than the parent compound in antimicrobial and cell free binding assays

(Boger *JACS*, *2000*, 122, 10047)
Biosynthetic Pathways

- **Oxidative phenolic coupling**

- **Polyketide cyclization**

Bringmann, *Progress in the Chemistry of Organic Natural Products* Vol. 82, **2001**, 1-249
Biosynthetic Pathways (cont.)

- **Diels-Alder**

- **Aldol type cyclizations**
Biaryls in Nature

- Wherever in nature phenolic aromatics can be found - be they derived from polyketide precursors, from aromatic amino acids and/or shikimic acid, or from terpenoids - the corresponding homo- or hetero-dimeric biaryls have to be expected.

Bringmann

*Progress in the Chemistry of Organic Natural Products* 2001, Vol. 82, 3
Biaryl Ligands
Synthesis

- “Classic concept”
  - C-C bond formation between two aryl systems with simultaneous asymmetric induction

- Transformation of a “pro-chiral” biaryl system into a chiral system through chemical transformation
  - Desymmetrization

- Generation of second aromatic ring from nonaromatic precursor with simultaneous generation of desired chirality
I. Classical Approaches

- Diastereoselective approaches:
  - Chiral bridge linking the two coupling partners
    - Bridge might or might not be present in final product
  - Chiral auxiliary on the arene (usually ortho position)
  - Incorporation of removable chiral unit ($\eta^6$ chromium complex)

- Enantioselective approaches:
  - Chiral leaving group
  - Metal based reagents and chiral ligands

Classical Approach- chiral tethers

  ![Chemical structure](image)
  
  **Chemical Reaction:**  
  \[
  \text{Cu, DMF} \quad 30-80 \% \text{, } 85-100 \text{ de} \]

  ![Chemical structure](image)
  
  **Chemical Reaction:**  
  \[
  \text{KOH} \quad \sim 90\% \]

Favored due to anomeric effect  
Additional Tethers

  - Designed to allow access to BINOL derivatives

\[
\begin{align*}
\text{Acetonide:} & \quad \begin{array}{c}
\text{MeO} \quad \text{OMe} \\
\text{MeO} \\
\text{MeO} \quad \text{OMe}
\end{array} \\
\text{CuCl(OH)TMEDA} & \quad \begin{array}{c}
\text{MeO} \quad \text{OMe} \\
\text{MeO} \\
\text{MeO} \quad \text{OMe}
\end{array} \\
\text{CH}_2\text{Cl}_2, \text{O}_2, \text{rt} 90\% & \quad \begin{array}{c}
\text{MeO} \quad \text{OMe} \\
\text{MeO} \\
\text{MeO} \quad \text{OMe}
\end{array}
\end{align*}
\]


\[
\begin{align*}
\text{Lactone:} & \quad \begin{array}{c}
\text{MeO} \quad \text{OMe} \\
\text{MeO} \\
\text{MeO} \quad \text{OMe}
\end{array} \\
\text{MoCl}_5, \text{CH}_2\text{Cl}_2 & \quad \begin{array}{c}
\text{MeO} \quad \text{OMe} \\
\text{MeO} \\
\text{MeO} \quad \text{OMe}
\end{array} \\
0 \degree \text{C, 50}\% & \quad \begin{array}{c}
\text{MeO} \quad \text{OMe} \\
\text{MeO} \\
\text{MeO} \quad \text{OMe}
\end{array}
\end{align*}
\]
Schreiber’s application to DOS

- A library of axially chiral biaryls (>400) was synthesized to screen for biological activity
  (Schreiber, JACS, 2000, 122, 5656)
  - The kinetic product could be converted to the other atropodiastereomer by heating for 2 days.

\[
\begin{align*}
1. & \text{ t-BuLi} \\
2. & \text{ CuCN} \\
3. & \text{ Oxidant} \\
\end{align*}
\]

R = \((\text{CH}_2)_5\text{Si}^{-} \text{O}^{-}\)

500-560 micrometer polystyrene beads

55%, 6:1 P:M
Schreiber’s DOS results

- 9 and 10-membered rings were synthesized (Org. Lett, 2004, 6, 4021)
- These analogues were submitted to protein-binding, chemical genetic, and phenotype assays.
- When entry I was tested in zebrafish, the P isomer had no activity while the M isomer affected the cardiovascular system during development (J.A.C.S, 2002, 124, 1354)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Biaryl (3)</th>
<th>% Yield</th>
<th>Kinetic dr (P:M)</th>
<th>Thermodynamic dr (P:M)</th>
</tr>
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<tr>
<td>h</td>
<td></td>
<td>94</td>
<td>17:1</td>
<td>1:1.5</td>
</tr>
<tr>
<td>i</td>
<td></td>
<td>94</td>
<td>6:1</td>
<td>1:2</td>
</tr>
<tr>
<td>j</td>
<td>(S)-Bn</td>
<td>1 92</td>
<td>16:1</td>
<td>1:11</td>
</tr>
<tr>
<td>k</td>
<td>(R)-Ph</td>
<td>1 84</td>
<td>1:23</td>
<td>2:1</td>
</tr>
<tr>
<td>l</td>
<td>(S)-i-Bu</td>
<td>1 83</td>
<td>4:1</td>
<td>1:2</td>
</tr>
<tr>
<td>m</td>
<td>(S)-CH$_3$Cy</td>
<td>1 88</td>
<td>22:1</td>
<td>1:11</td>
</tr>
<tr>
<td>n</td>
<td>(S)-i-Bu</td>
<td>n=1 97</td>
<td>35:1</td>
<td>1:10</td>
</tr>
<tr>
<td>o</td>
<td>(R)-Et</td>
<td>1 91</td>
<td>1:25</td>
<td>9:1</td>
</tr>
<tr>
<td>p</td>
<td>(R)-Me</td>
<td>1 94</td>
<td>1:32</td>
<td>6:1</td>
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<tr>
<td>q</td>
<td>(S)-Bn</td>
<td>0 97</td>
<td>3:1</td>
<td>UD$^g$</td>
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<tr>
<td>r</td>
<td>(S)-i-Bu</td>
<td>0 93</td>
<td>2:1</td>
<td>UD$^g$</td>
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<tr>
<td>s</td>
<td>(S)-Me</td>
<td>n=1 77</td>
<td>11:1$^h$</td>
<td>1:3$^h$</td>
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<tr>
<td>t</td>
<td></td>
<td>0 96</td>
<td>&gt;50:1$^i$</td>
<td>UD$^g$</td>
</tr>
<tr>
<td>u</td>
<td></td>
<td>81$^j$</td>
<td>1:&gt;50</td>
<td>UD$^g$</td>
</tr>
<tr>
<td>v</td>
<td></td>
<td>73</td>
<td>1.5:1</td>
<td>UD$^g$</td>
</tr>
<tr>
<td>w</td>
<td></td>
<td>68</td>
<td>1:10</td>
<td>UD$^g$</td>
</tr>
</tbody>
</table>
Total Synthesis Applications- Vancomycin

- Evans (*JACS*, 1993, 115, 6426)

- Boger (*JACS*, 1999, 121, 3226)
Vancomycin Derivatives

- **Boger**
  
  *(J. Am. Chem. Soc. 2006; 128; 2885)*

- The A-B ring system was constructed in the same fashion as the parent compound (Suzuki coupling followed by thermal equilibration)

- Ultimately, **5** exhibited antimicrobial activity against VanA-resistant microorganisms
Vancomycin- Chiral Ligands


![Diagram](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Solvent</th>
<th>Temp</th>
<th>Time (h)</th>
<th>Yield</th>
<th>Ratio</th>
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<tr>
<td>1</td>
<td>PH$_3$P</td>
<td>PhMe</td>
<td>90</td>
<td>2</td>
<td>80</td>
<td>1:1</td>
</tr>
<tr>
<td>2</td>
<td>BINAP</td>
<td>PhMe</td>
<td>90</td>
<td>12</td>
<td>Trace</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>BINAP</td>
<td>THF</td>
<td>65</td>
<td>12</td>
<td>Trace</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>S-BINAP</td>
<td>DMF</td>
<td>80</td>
<td>8</td>
<td>60</td>
<td>2.3:1</td>
</tr>
<tr>
<td>5</td>
<td>S-BINAP</td>
<td>PhMe:THF (1:1)</td>
<td>70</td>
<td>5</td>
<td>40</td>
<td>95:5</td>
</tr>
<tr>
<td>6</td>
<td>R-BINAP</td>
<td>PhMe:THF (1:1)</td>
<td>70</td>
<td>5</td>
<td>40</td>
<td>5:95</td>
</tr>
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</table>
Chiral Ortho Substituents

- **Oxazoline and asymmetric Grignard addition** *(Meyers, *JACS*, 1985, 107, 682)*
  - Grignard reagent essential
  - Low selectivity with aryllithium
  - Good yields of tri-ortho substituted products. Tetra-ortho substituted products are produced in low yields
  - $R'$ and $R''$ = Me, OMe, OMOM or OTBS, $R$=Ph

\[
\begin{align*}
&\text{MeO} \text{Br} \\
&\text{OMe N} \text{Me} \\
&\text{MeO} \text{N} \text{Me} \\
\end{align*}
\]

\[
\begin{align*}
&\text{MeO} \text{Br} \\
&\text{OMe N} \text{Me} \\
&\text{MeO} \text{N} \text{Me} \\
\end{align*}
\]
Chiral Ortho Substituents (cont.)

- **Suzuki** *(Colobert, *Org. Lett.* 2003, 5, 3281)*
  - Methoxy protection of chiral aux prevents hydrodehalogenation of substrate

- **Mechanistic studies** *(Colobert, *Org.Lett.*, 2005, 7, 3737)*
  - Diastereoselectivity when SO₂pTol is replaced with:
    - H=60/40
    - OMe or OBn=70/30
    - NMe₂=<95/5
  - Proposed palladacycle intermediate:
Removable Chiral Unit

- Chromium complex (Uemura, *Synlett* 2000, 938-949)

![Chemical Structure]

- Used in:
  - Pinacol coupling with SmI$_2$ (*J.O.C.* 1996, 61, 6088)
    - Accelerates oxidative addition to aryl halide
    - Poor yields when chromium complexed to aryl boronic acid

- Chromium removed through photooxidative demetalation

- Disadvantages:
  - Laborious to get to single enantiomer of chromium complex
  - Toxic
Removable Chiral Unit

  - Single diastereomer
  - Reagents: (a) BH$_3$·Me$_2$S, (S)-oxazaborolidine, b), (b) Pd(OAc)$_2$, (c) [CpRu(CH$_3$CN)$_3$]PF$_6$, (CH$_2$Cl)$_2$, reflux, (51%), (d) NaOMe, MeOH, (98%), (e) hν, CH$_3$CN, (95%).

- **Cyclophanes** (Miyano *Tetrahedron Lett.* 1996, 37, 2057-2060)
  - Used with Grignard reagents
  - 82-85% yield and 91-99% ee
Enantioselective Approaches

- **Chiral leaving group:**

  - $X=F, \text{OMe, or OEt}$. Yield=81-99%, $ee=82-90\%$
Oxidative Homocoupling

- Metal based with chiral ligand

  ![Chemical structure](image)

- **First report:** Cu(II)(NO$_3$)$_2$·3H$_2$O with chiral amine ligands
  (Wynberg and Feringa, *Bioorganic Chemistry*, 1978, 7, 397-408)
  - $R^1=H$, 1-8% ee; $R^1$=ester, 6-16% ee

- **Copper and 1,5, diazacis-decalin** (Kozlowski, *JOC*, 2003, 68, 5500)
  - $R^1=H$, 4-18% ee; $R^1$=ester, 56-94% ee

- **Photochemical with chiral ruthenium salen catalyst** (Katsuki, *Synlett* 2000, 1433-1436)
  - $R^2=H$, 65% ee; $R^2$=OMe, 33% ee, $R^2$=methyl ester, 0% ee

  - $R^1=H$, 89% ee; $R^1$=Br, 88% ee

  - $R^1=H$, 99% ee
  - Works with both free alcohol and methyl ether
Redox Neutral Cross Coupling

- Enantioselective examples include:
    - Ni or Pd catalyzed with ferrocene derived ligand
    - 40-84 % yield and 16-83 % ee
    - Coupled naphthalenes with Me or Et substituents
    - 40-87% yield and 71-95 % ee
    - Conditions compatible with phosphonate and OMe substituents

- Currently, no examples of asymmetric:
  - Stille
  - Negishi
Buchwald Coupling Conditions

- 3a  \( R=\text{Et} \)
- 3b  \( R=\text{Me} \)
- 4a  \( X=\text{I} \)
- 4b  \( X=\text{Br} \)
- 4c  \( X=\text{Cl} \)

![Chemical Structures]

<table>
<thead>
<tr>
<th>Entry</th>
<th>ArX</th>
<th>ArB(OH)(_2)</th>
<th>Product</th>
<th>mol%</th>
<th>temp (°C)</th>
<th>time (h)</th>
<th>yld (%)</th>
<th>ee (%)</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>3a</td>
<td>( \text{Ph} )</td>
<td>( (\pm))-6a</td>
<td>4</td>
<td>70</td>
<td>88</td>
<td>98</td>
<td>87(^b)</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>( \text{Me} )</td>
<td></td>
<td>1</td>
<td>70</td>
<td>17</td>
<td>93</td>
<td>87(^c,d)</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>( \text{Br} )</td>
<td></td>
<td>8</td>
<td>70</td>
<td>88</td>
<td>90</td>
<td>92(^c,d)</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>( \text{Cl} )</td>
<td></td>
<td>2</td>
<td>70</td>
<td>24</td>
<td>96</td>
<td>92(^c,d)</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>( \text{NO}_2 )</td>
<td>( (\pm))-6b</td>
<td>1</td>
<td>70</td>
<td>24</td>
<td>94</td>
<td>92(^c)</td>
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<tr>
<td>6</td>
<td></td>
<td>( \text{Ph} )</td>
<td>( (\pm))-6c</td>
<td>10</td>
<td>80</td>
<td>140</td>
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<tr>
<td>7</td>
<td></td>
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<td>( (\pm))-6d</td>
<td>2</td>
<td>80</td>
<td>24</td>
<td>89</td>
<td>85(^c,d)</td>
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<td>8</td>
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<td>( \text{Ph} )</td>
<td>( (\pm))-6e</td>
<td>3</td>
<td>60</td>
<td>48</td>
<td>74</td>
<td>74(^c)</td>
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<td>92</td>
<td>97</td>
<td>71(^b)</td>
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<td>( \text{Ph} )</td>
<td>( (\pm))-6g</td>
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<td>40</td>
<td>97</td>
<td>57(^e)</td>
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<td>( (\pm))-6h</td>
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<td>24</td>
<td>91</td>
<td>84(^b)</td>
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<td>12</td>
<td></td>
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<td>( (\pm))-6i</td>
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<td>70</td>
<td>48</td>
<td>86</td>
<td>73(^c,d)</td>
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<tr>
<td>13</td>
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<td>( \text{Cl} )</td>
<td>( (\pm))-6j</td>
<td>10</td>
<td>70</td>
<td>48</td>
<td>82</td>
<td>72(^d)</td>
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<tr>
<td>14</td>
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<td>( \text{NO}_2 )</td>
<td>( (\pm))-6k</td>
<td>4</td>
<td>70</td>
<td>48</td>
<td>83</td>
<td>72(^b)</td>
</tr>
</tbody>
</table>
Redox Neutral Cross Coupling (cont.)

- Advantages:
  - Not restricted to specific substitution patterns
  - Allow regioselective cross coupling of 2 different coupling partners
  - Generally, mild reaction conditions
  - Source of chiral information can be used catalytically

- Disadvantages:
  - No standard protocol (time consuming optimization)
  - Long reaction times (sometimes up to 1 week)
II. Modification of Pro-stereogenic Biaryls

- Generation of axially chirality through reaction with “pro-chiral” biaryl unit
  - Biaryl axis formed, chirality introduced later

- Two possible situations:
  - Rotationally hindered but achiral
  - Chiral, but configurationally unstable
Desymmetrization of Biaryls

- **First example of biaryl enzymatic desymmetrization**
  (Matsumoto, *Synlett*, 2002, 122)

\[
\text{AcO}_2 \text{C}_6 \text{H}_4 \text{R} \xrightarrow{\text{CAL or PCL, pH 7, 30–35°C, 1–7 days}} \text{AcO}_2 \text{C}_6 \text{H}_4 \text{OH}
\]

<table>
<thead>
<tr>
<th>R</th>
<th>Me</th>
<th>Et</th>
<th>CH₃OBn</th>
<th>2,3-benzo</th>
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<tr>
<td>CAL: ee [%] (yield [%])</td>
<td>97 (80)</td>
<td>99 (57)</td>
<td>99 (68)</td>
<td>97 (72)</td>
</tr>
<tr>
<td>PCL: ee [%] (yield [%])</td>
<td>99 (86)</td>
<td>96 (67)</td>
<td>98 (51)</td>
<td>98 (94)</td>
</tr>
</tbody>
</table>

- **Carbonylation**

\[
\text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me}
\]

1. nBuLi
2. CO₂

\[
\text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me}
\text{CO₂H}
\]

\[
\text{HO₂C} \quad \text{Me} \quad \text{Me} \quad \text{Me}
\]

70% 40% ee

Sparteine - (-)
Desymmetrization in Cross Coupling

  - Other triflate still available to react (converted to phosphonate *(P)-229* or ester)
Desymmetrization through Bridge Formation

- **Early work:** 82% overall yield (Harada, *J. Org. Chem.* 2000, 65, 1335)

![Chemical structure 1](image1.png)

**Mitsunobu reaction**

2) desilylation
3) Mitsunobu reaction

- **Improvement:** (*Org. Lett.* 2000, 2, 1319)
  - Using Cs$_2$CO$_3$ as the base, 8 could be obtained in 66% as a single diastereomer and 9 in only 7%.

![Chemical structure 2](image2.png)

\[ \text{OMs} \quad \text{OMs} \quad (S)-7 \]

\[ \text{base} \quad \text{DMF, 80}^\circ \text{C} \]

\[ \begin{align*}
\text{(aS,R)-8} \\
9; R^1 = \text{Me}, R^2 = \text{H} \\
9'; R^1 = \text{H}, R^2 = \text{Me}
\end{align*} \]
Desymmetrization in Total Synthesis


- Single atropisomer was needed for efficient etherification

Erikah Englund @ Wipf Group
Axial Chirality through Ring Cleavage


  \[ \text{fast} \]

  ![Lactone Reaction](image)

- The biaryl lactone is configurationally unstable
  - Opening the lactone with chiral nucleophiles can selectively provide the appropriate axial chirality
  - Drawback: Biaryls possessing a β-keto and β-hydroxy functionality readily racemize. β –ketosulfoxides and chiral c-nucleophiles can not be utilized

  ![β-keto and β-hydroxy functionality](image)

  Configurationally unstable
Ortho Selective Reactions

- **C-H activation**

- **Starting material**
  freely rotates.
  Alkylation of the ortho position results in isolable atropisomers

<table>
<thead>
<tr>
<th>run</th>
<th>biaryl compound</th>
<th>ligand</th>
<th>product</th>
<th>yield</th>
<th>ee ( ^{b} )</th>
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<td>1</td>
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<td>(R),(S)-PPFOMe</td>
<td>4</td>
<td>37%</td>
<td>49% ee</td>
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<td>1</td>
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<td>4</td>
<td>trace</td>
<td></td>
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<tr>
<td>3</td>
<td>1</td>
<td>(R),(S)-PPFOMe</td>
<td>4</td>
<td>15%</td>
<td>15% ee</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>(R)-BINAP</td>
<td>4</td>
<td>no reaction</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>(R)-MeO-MOP</td>
<td>4</td>
<td>49%</td>
<td>0% ee</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>(R),(S)-PPFOMe</td>
<td>6</td>
<td>33%</td>
<td>22% ee</td>
</tr>
<tr>
<td>7</td>
<td>5</td>
<td>(R)-MeO-MOP</td>
<td>6</td>
<td>60%</td>
<td>3% ee</td>
</tr>
</tbody>
</table>

\( ^{a} \) Reaction conditions: biaryl compound (0.5 mmol), ethylene (7 kg/cm\(^{2} \)), [RhCl(cod)]\(_{2}\) (0.025 mmol), ligand (0.15 mmol), toluene (2.5 mL), 120 °C, 20 h. \(^{b} \) All enantioselectivities were determined by HPLC analysis on a Daicel OD-H column. The biaryl compound 1 was recovered in 52% yield. \(^{c} \) The reaction was carried out at 80 °C for 72 h. The biaryl compound 1 was recovered in 90% yield. \(^{d} \) Ru(cod)(cot) and (R),(S)-PPFOMe catalyst system was used. \(^{e} \) The biaryl compound 1 was recovered in 67% yield. The biaryl compound 1 was recovered in 45% yield.
Ortho Selective Reactions

  - The initially coupled product could be converted cleanly to the other atropisomer through heating in toluene for 48 h
  - N-oxide formation with MCPBA followed by chiral auxiliary removal affords the stable atropisomers
III. Second Aromatic Ring Generation

- Generation of chiral biaryls through formation of second aromatic ring
  - One of the newest methodologies to generate axial chirality
  - Chirality achieved through:
    - Metal catalyzed cyclization (chiral ligand source of chirality)
    - Central to axial chirality transfer
Chiral Pyridines

- [2+2+2] cyclization under photochemical conditions
  (Gutnov and Heller, Angew. Chem. Int. Ed. 2004, 43, 3795)

- A series of chiral cobal catalysts were screened. Catalyst 5 afforded the highest ee’s
Little temperature dependence (82% ee at 20 °C, 89% ee at 3 °C)

No observed solvent dependence

When alkyne not tethered, yields were 2-33% and ee’s 32-63% (compared to 74-80%)

Proposed source of selectivity:
Cyclization

  - 74-97% yield and ee s in the 90’s
  - This methodology could also be applied to biaryls (81% ee)
  - Ether linkage was successfully replaced with:
    - Alkene
    - Methylene
    - Nitrogen

![Chemical reaction diagram](image)
Cyclization (cont.)

- **Cross Cyclotrimerization**  
  (Tanaka *Org. Lett.*, 2005, 7, 3119)

- 61-89% yield, 84-96 % ee

- Br, Cl, Me, Et and naphtyl varieties were synthesized
Chirality Exchange

- 47-97% yield, >99% ee
- R1 = Cl, OMe, Me, R2 = H, Cl, Me
Chirality Exchange (cont.)

- **Binaphthalene synthesis** (Hattori and Miyano *Tetrahedron Lett.* 2001, **42**, 8035-8038)

\[
\begin{align*}
\text{141} \quad \text{MgBr} & \quad \text{Yb(OTf)}_3 \\
\text{O} & \quad \text{THF, RT} \\
\underset{R}{\text{O}} & \quad \text{single diastereomer} \\
\text{(R)-311} & \quad \text{(R,R)-312} \\
\text{DDQ} & \quad \text{toluene, 80°C} \\
\underset{M^*}{\text{M}} & \quad \text{95% ee} \\
\text{(M)-314} & \quad \text{(M)-313} \\
\text{74% overall yield} & \quad \text{95% ee}
\end{align*}
\]
Carbenes

- Chirality controlled by:
  
  \[
  (OC)_2Cr\leftarrow\begin{array}{c}
  \text{Ph} \\
  \text{Ph}
  \end{array} \rightarrow \begin{array}{c}
  \text{Ph} \\
  \text{Ph}
  \end{array} + (OC)_2Cr\leftarrow\begin{array}{c}
  \text{Ph} \\
  \text{Ph}
  \end{array} \rightarrow \begin{array}{c}
  \text{Ph} \\
  \text{Ph}
  \end{array}
  \]

  \( (R,R)-315 \quad 316 \quad \text{THF, } \Delta \quad (P)-317 \)

  23%, single stereoisomer

Conclusion

- Axially chiral biaryls are an important structural element in many natural products and can greatly influence biological activity.

- Axial chirality has been recognized for nearly 80 years, but the synthetic tools are still in their infancy. There are many methods whose scope haven’t been fully explored.

- The synthetic methods developed (classical, prosteoreogenic modification and aromatic ring generation) have issues that need to be overcome to permit wider application:
  - Substrate generality (formation of both bi-naphthalenes and biaryls)
  - Standardized reaction conditions (less time on optimization)
  - Functional group tolerance