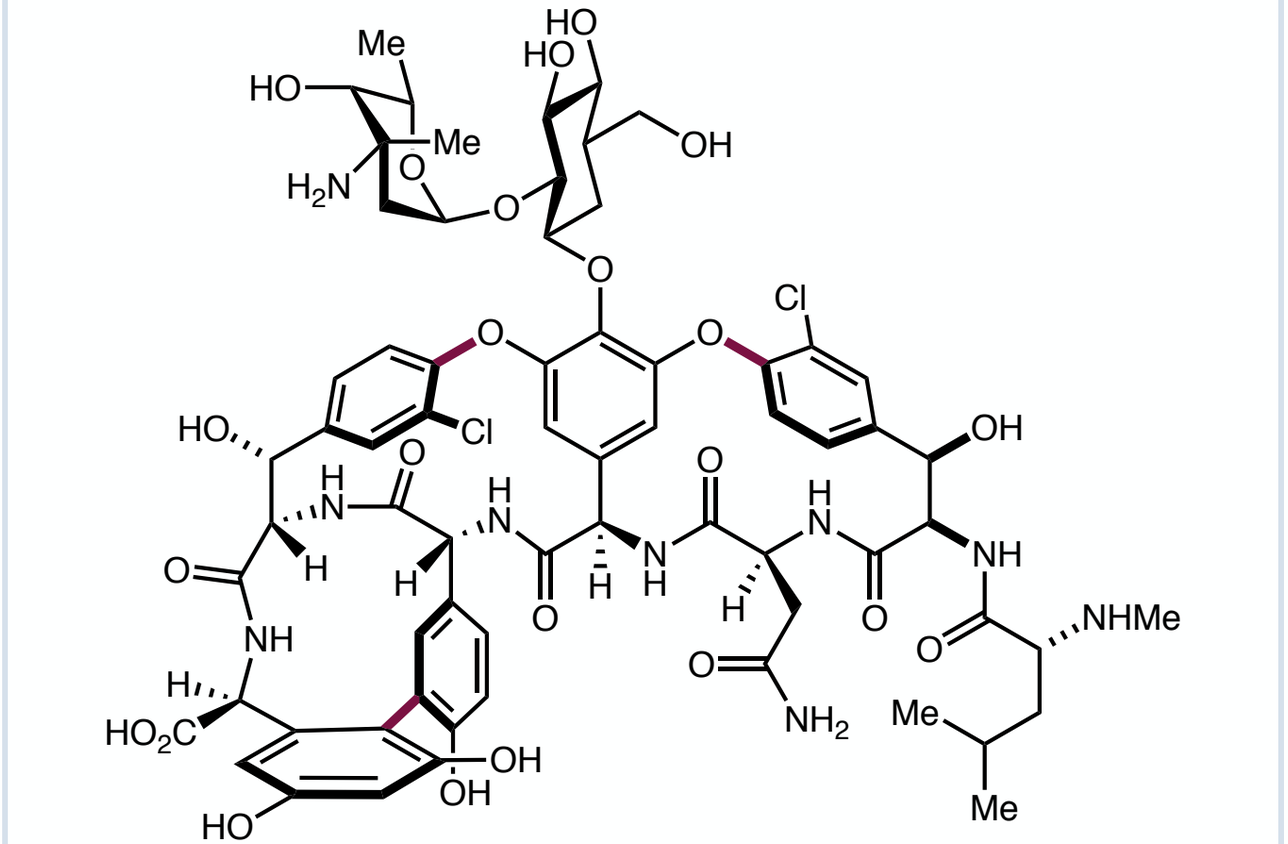
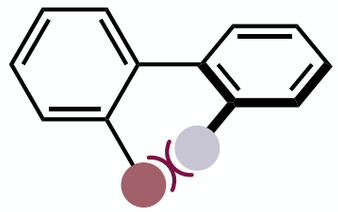
# *Methods and Applications in Atroposelective Chemistry*



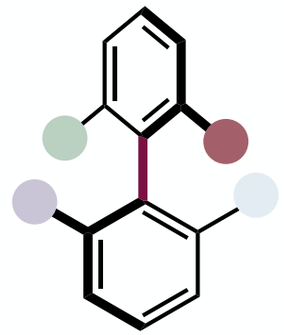

*Nate Dow*
*Group Meeting Literature Talk*
*April 13, 2020*

# *Outline*

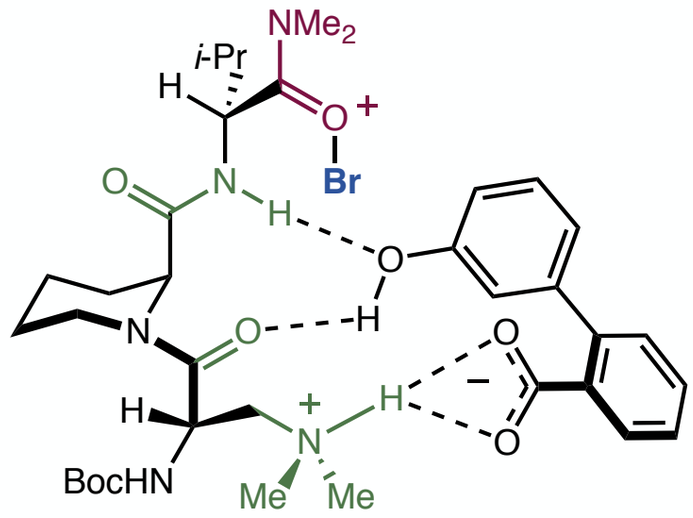
- Introduction and General Considerations
  - Discovery and fundamentals
  - Contributions to rotational barriers
  - Pharmaceutical considerations



- Methods of (Catalytic) Synthesis
  - Diastereoselective methods
  - Dynamic kinetic resolutions and desymmetrization
  - Redox-neutral cross-oupling
  - Oxidative cross-oupling



- Applications
  - Case Study: Tryptorubin A

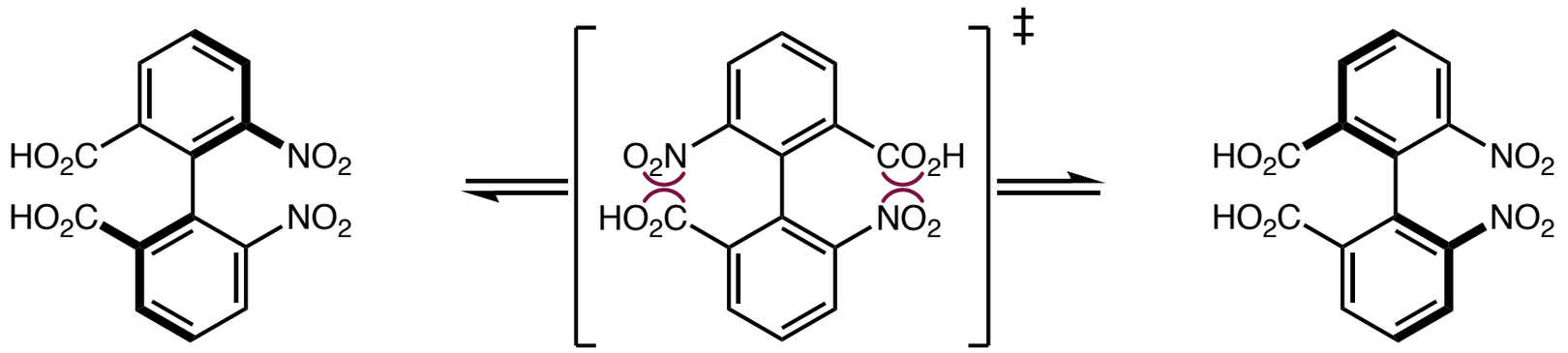


# *Formal Definitions of Atropisomerism*

*Atropos (Greek) - "Without Turn"*

Atropisomers: stereoisomers caused by restricted rotation around a single bond

(a subset of axially chiral compounds)




***strained coplanar transition state***

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

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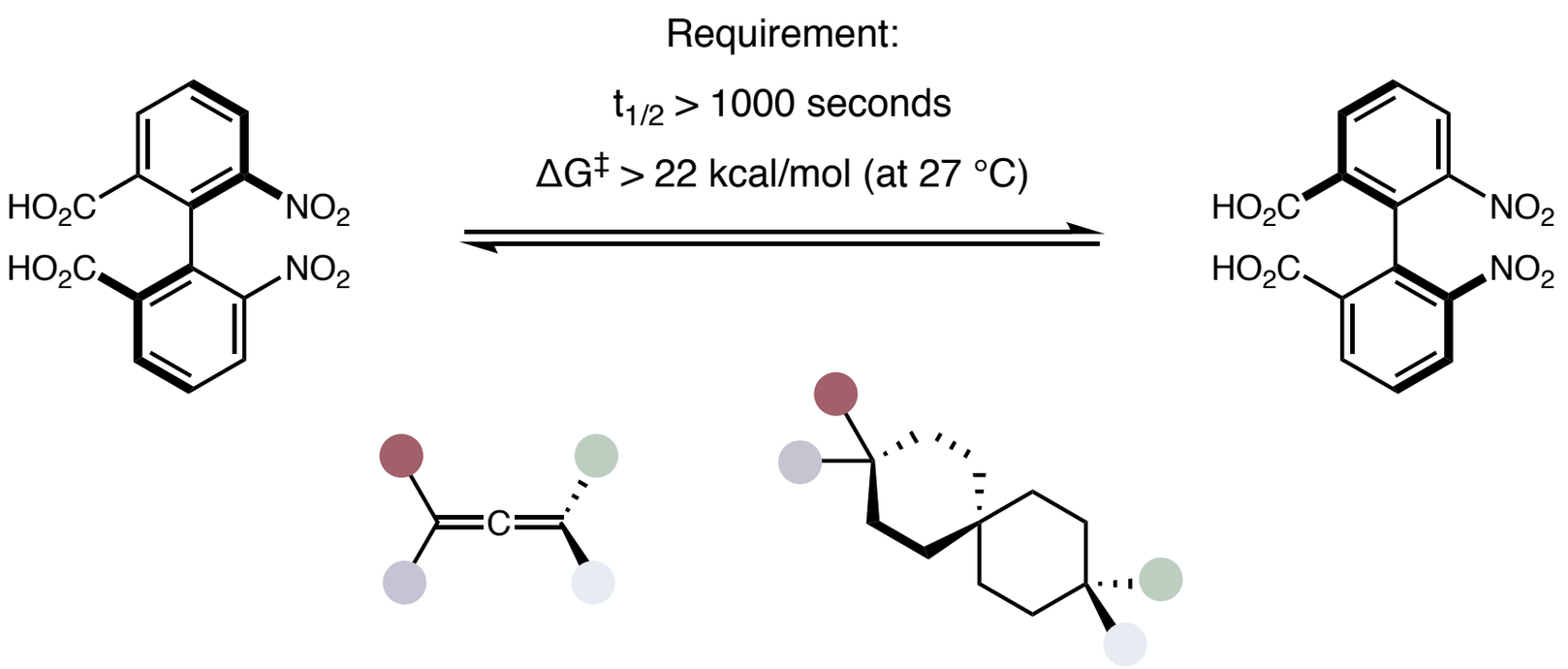


*axially chiral, but no rotational interconversion!*

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

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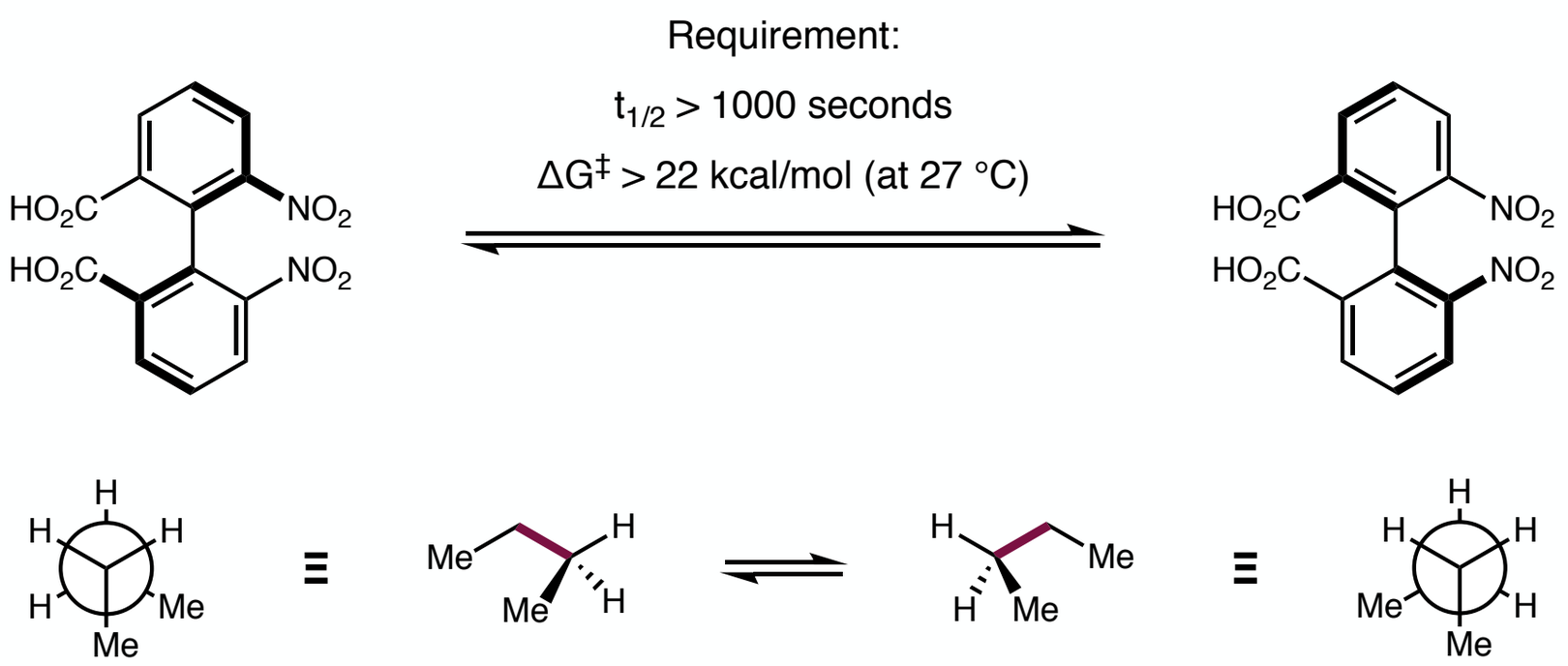


*conformers: rotational interconversion, but barrier too low to produce stable stereoisomers!*

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

# *Formal Definitions of Atropisomerism*

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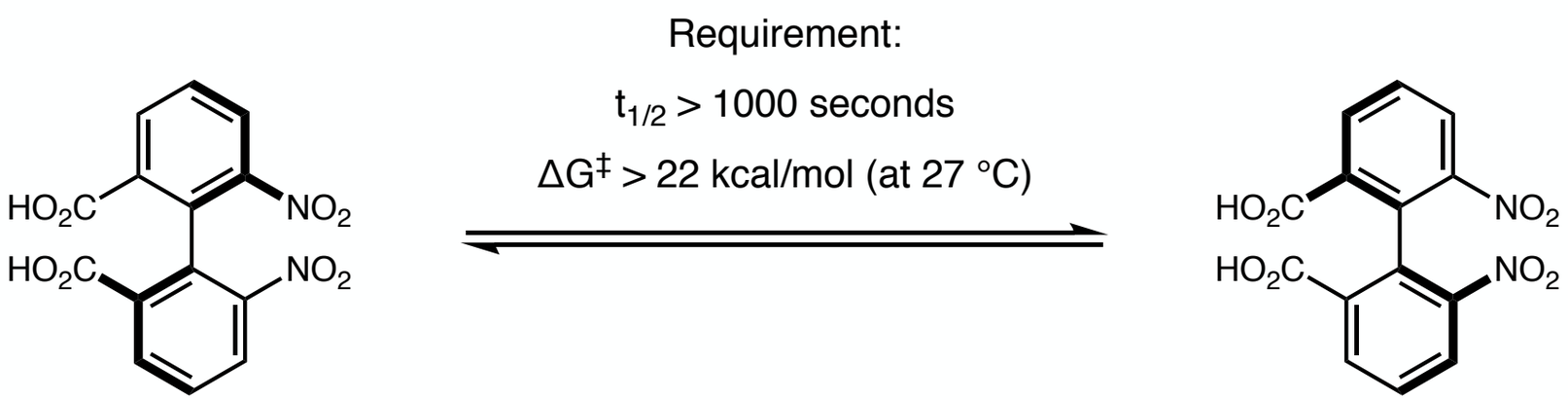
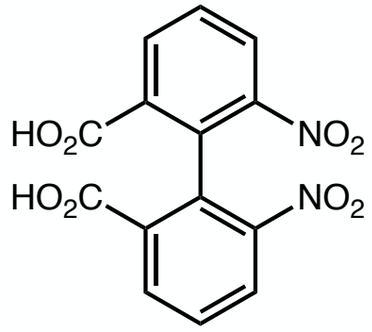


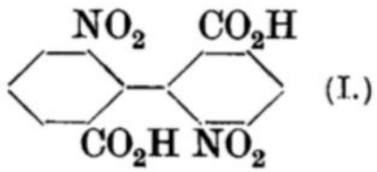

*First reported atropisomeric compound (1922)*

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

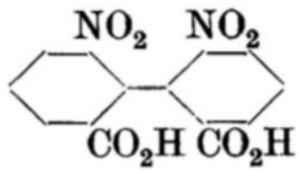
*Initial Discoveries via Alkaloid Resolution*



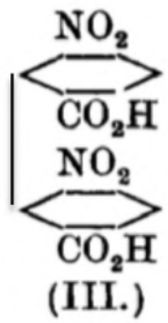

***structural hypotheses***



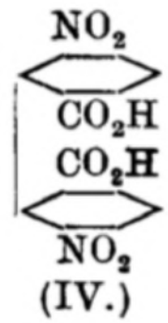

(I.)




(II.)




(III.)




(IV.)

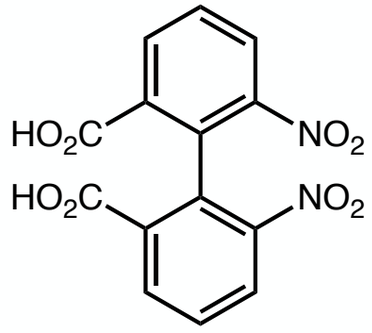
*planar*

*parallel planes (Kauffler)*

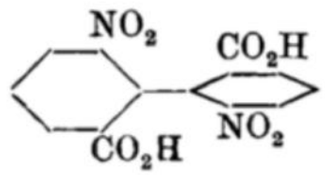
internal symmetry planes, cannot be resolved

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

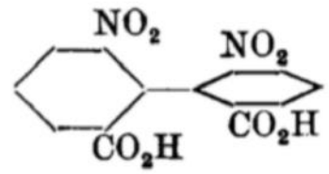
# *Initial Discoveries via Alkaloid Resolution*




***structural hypotheses***




(V.)




(VI.)

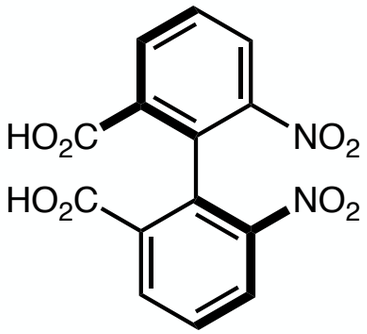
*non-planar*

common axis, but not coplanar

**chiral resolution possible**

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

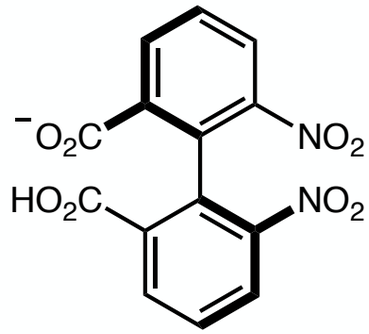
# *Initial Discoveries via Alkaloid Resolution*

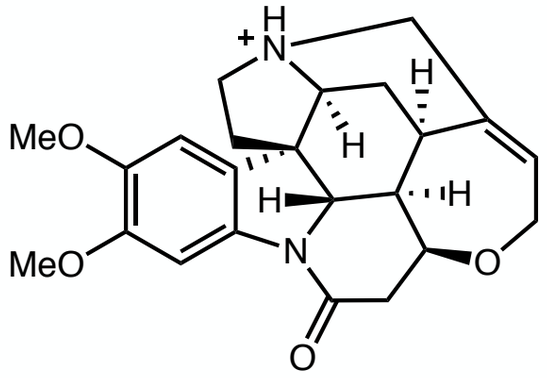


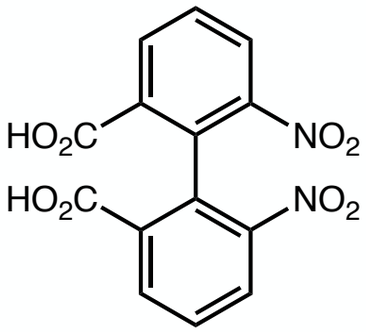

*mp = 230–231 °C*

*$[\alpha]_D$ = +225.3°*

$H_2SO_4/H_2O$ (2 M)

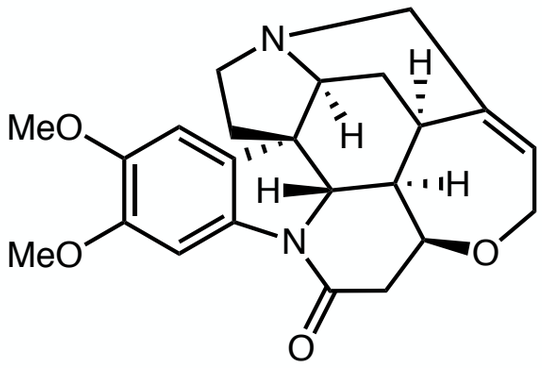


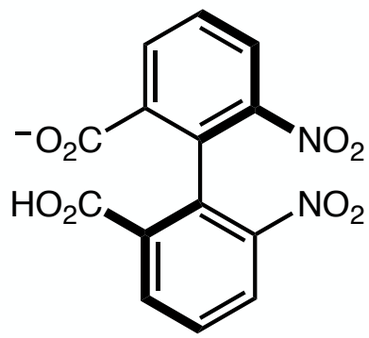

*mp = 263 °C*

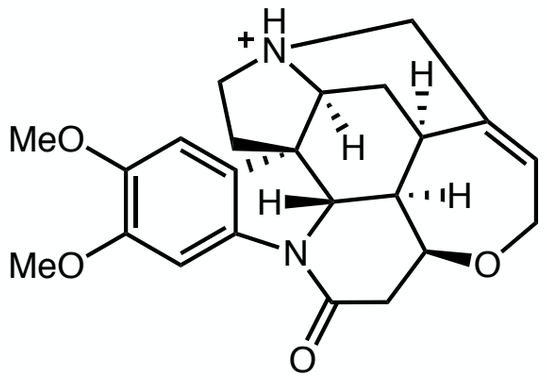
+




*brucine*

***diastereomeric alkaloid salts***

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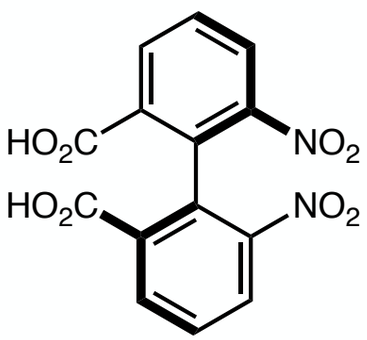



*mp = 230–238 °C*

*$[\alpha]_D$ = −169.7°*

Original theory: 2,2’,6,6’-tetrasubstituted biaryls possess this unique asymmetry

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

# *Formal Definitions of Atropisomerism*

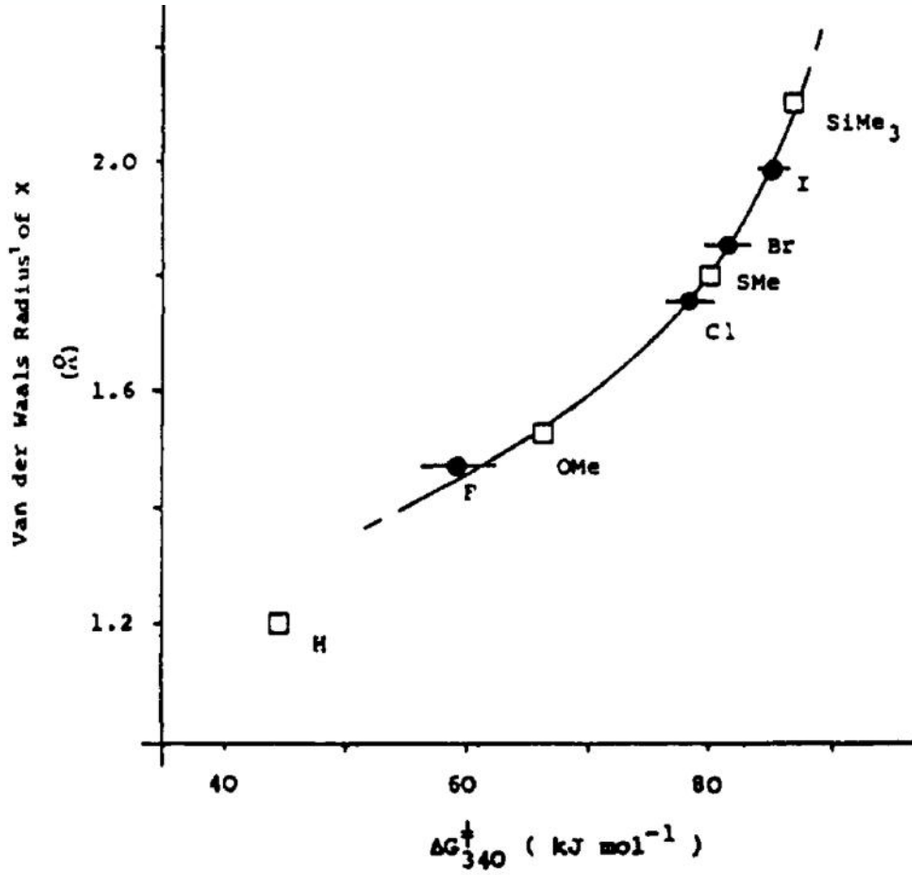
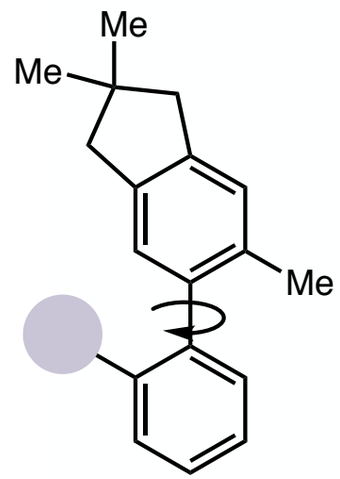



**Figure 3.** Plot of $\Delta G_{340}^{\ddagger}$ against the van der Waals radius[1] of X in some 6-(2-X-phenyl)-1,1,5-trimethylindans (**1**, Y = Me).



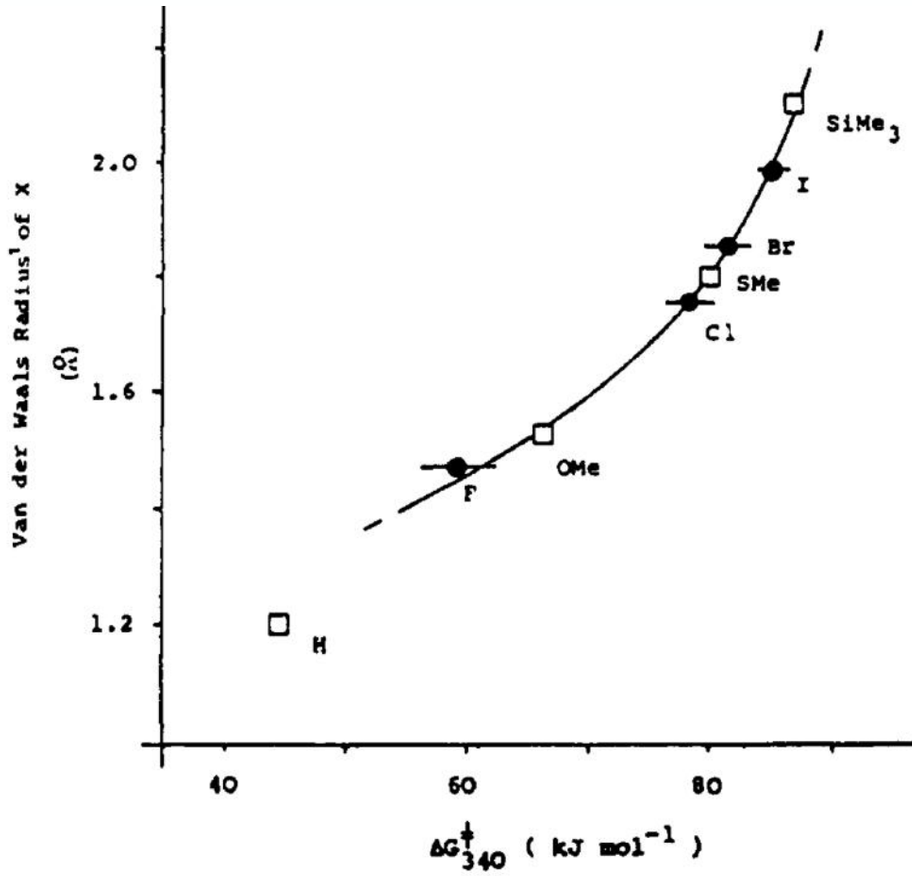

Excellent correlation between rotational barriers and van der Waals radii of ortho substituent

can (roughly) paramaterize LFER via effective radii comparable to Charton values

***most commonly encountered scenario: biaryls containing at least two bulky ortho substituents, steric hindrance between substituents restricts rotation***

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

# *Formal Definitions of Atropisomerism*

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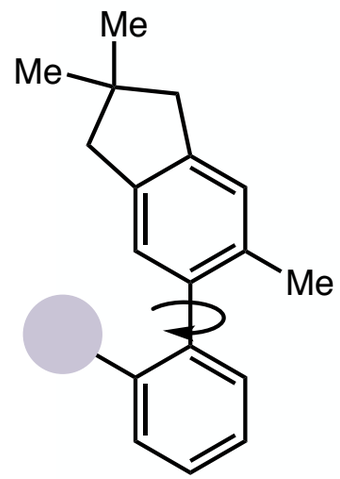



Excellent correlation between rotational barriers and van der Waals radii of ortho substituent

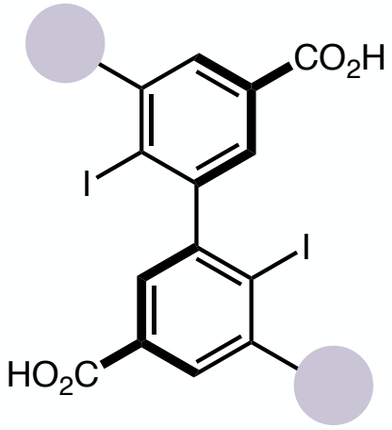
can (roughly) paramaterize LFER via effective radii comparable to Charton values

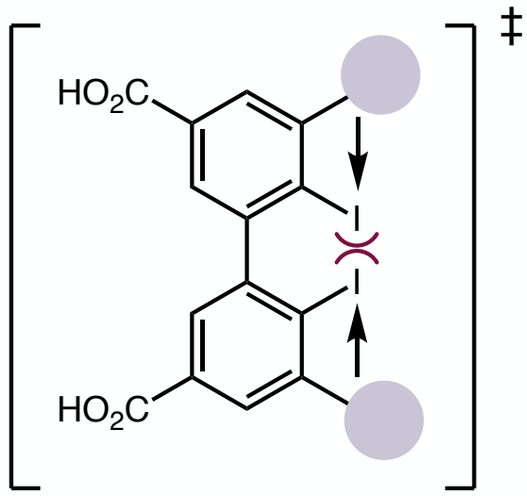
***However, many other factors contribute to the rotational barrier!***

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

# *Other Causes of Restricted Rotation*

## Buttressing Effects



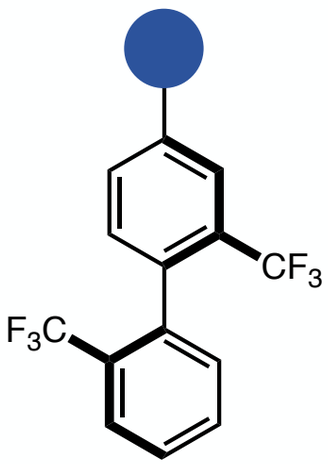




● : H – $\Delta G^{‡}$ = 23.4 kcal/mol

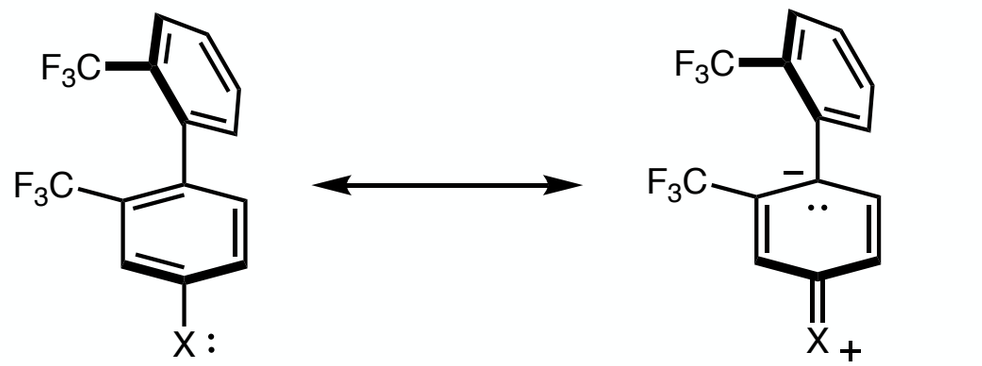
I – $\Delta G^{‡}$ = 30.1 kcal/mol

***meta substitution prevents in-plane bending that could reduce ortho-ortho steric clash***

## Electronic Effects




| ● | $\Delta G^{‡}$ (kcal/mol) |
|---|---|
| H | 25.6 |
| OMe | 24.9 |
| $NO_2$ | 25.8 |

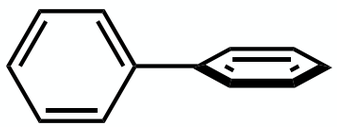



***increased n → π* donation increases $sp^3$-character at axial carbon, lowers rotational barrier***

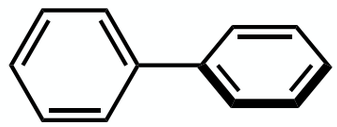
Wolf, C.; Hochmuth, D. H.; König, W. A.; Roussel, C. *Liebigs Ann.* **1996**, 357.

# *Other Causes of Restricted Rotation*

## Stereoelectronic Effects

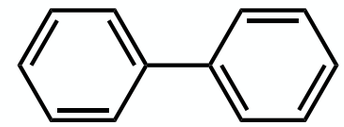


$\phi = 90°$

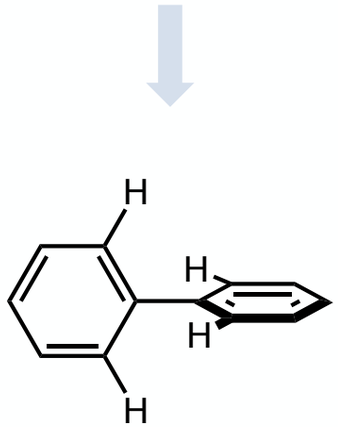


$\phi = 45°$

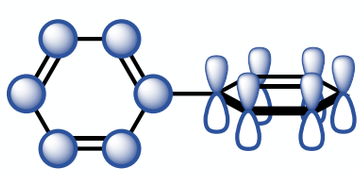
*minimized tortional energy*



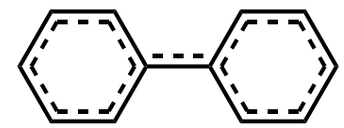
$\phi = 0°$



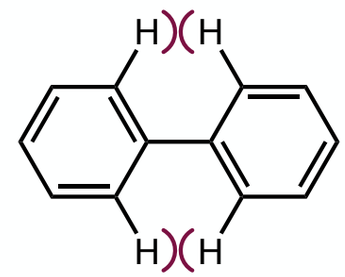

*no coplanar repulsion*



*disrupted conjugation*



*complete electronic delocalization*

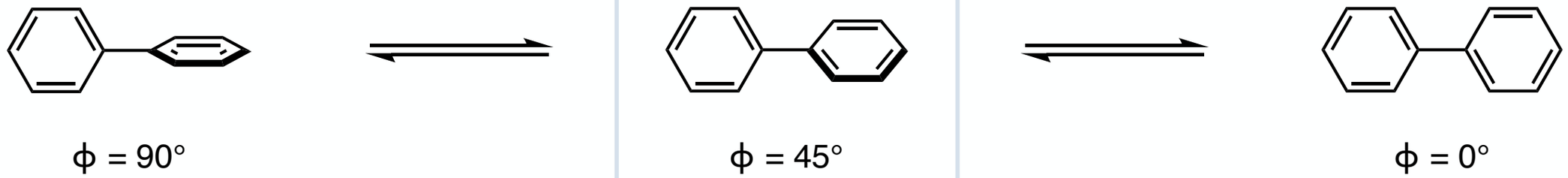


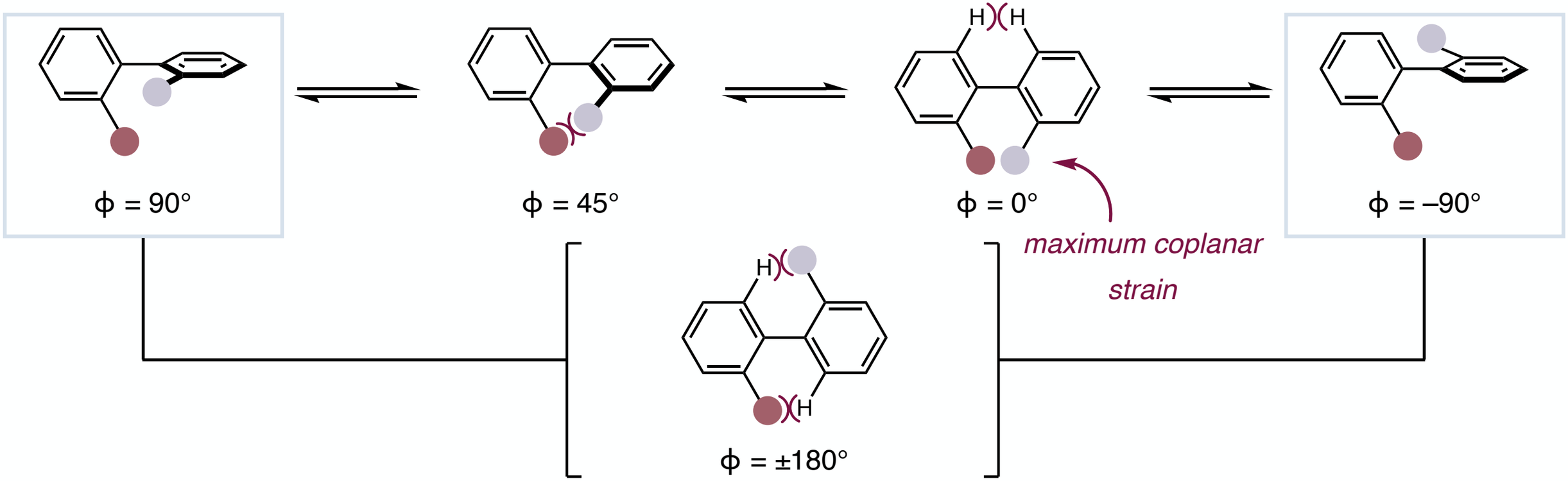

*severe coplanar strain*

Leroux, F. *ChemBioChem* **2004**, *5*, 644.

# *Other Causes of Restricted Rotation*

**Stereoelectronic Effects**

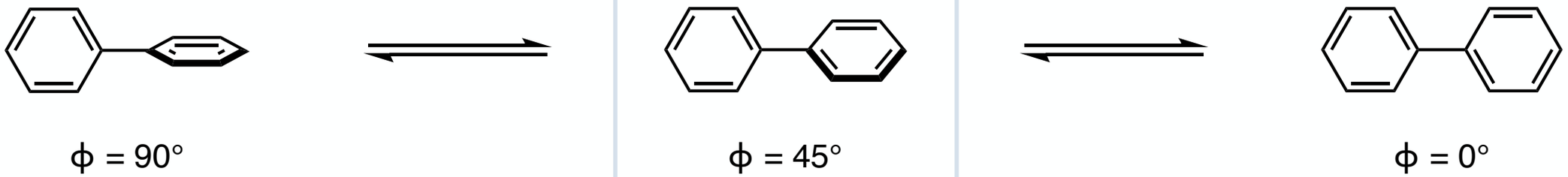


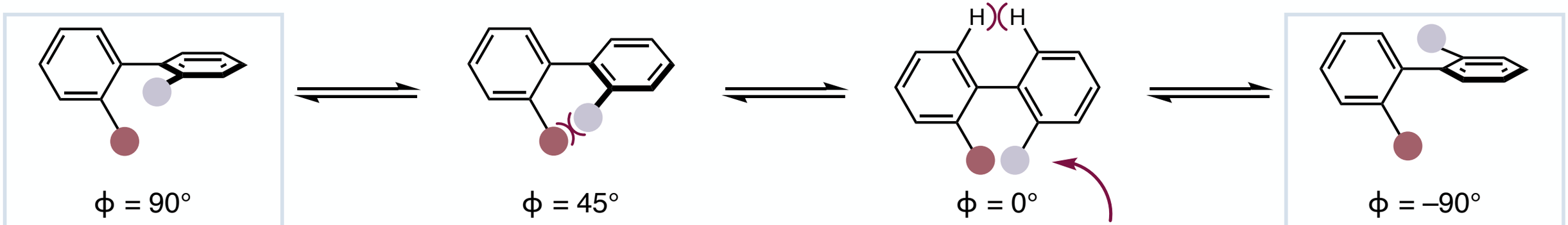




Leroux, F. *ChemBioChem* **2004**, *5*, 644.

# *Other Causes of Restricted Rotation*

**Stereoelectronic Effects**



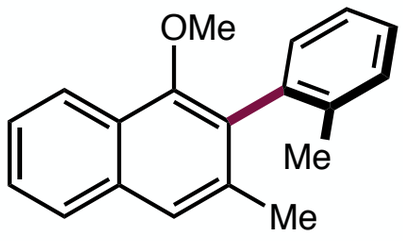




*Increased ortho steric bulk eventually overrides stereoelectronic effects, ground state favors orthogonal orientation*

Leroux, F. *ChemBioChem* **2004**, *5*, 644.

# *Other Causes of Restricted Rotation*

## Bond Length Effects




$\Delta G^{\ddagger}$ = 30 kcal/mol

$t_{1/2}$ > 30 years

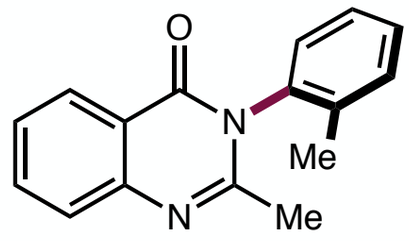
$r_{C–C}$ = 1.49 Å

***vs.***

***shorter bond as chiral axis***

⬇

***higher barrier to rotation***

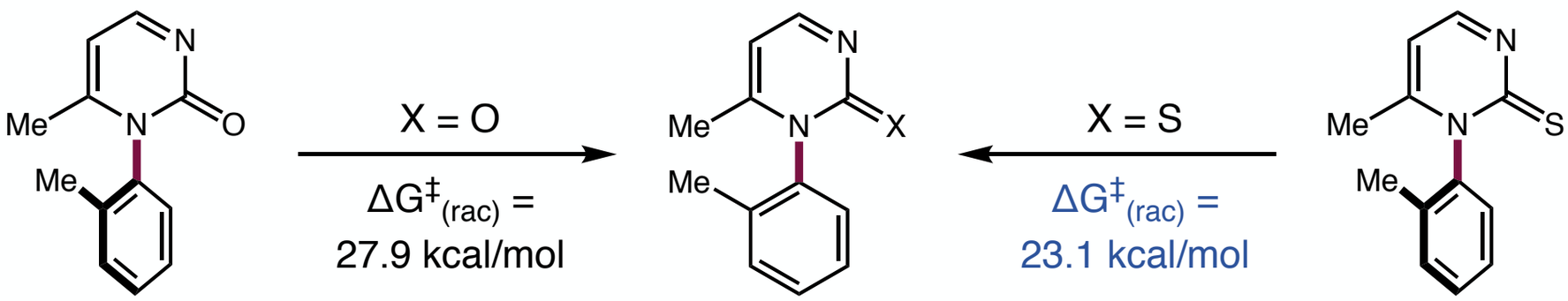


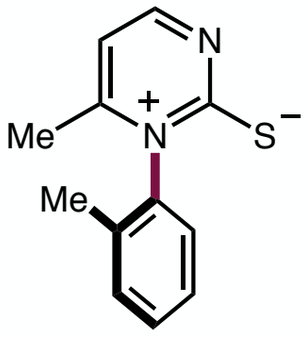

$\Delta G^{\ddagger}$ = 36 kcal/mol

$t_{1/2}$ ~ 800,000 years

$r_{C–N}$ = 1.37 Å

**Also must consider non-axial bond lengths:**




*key resonance form*

***more ground-state single bond character → longer C–S bond,***

***more readily distorted in coplanar transition state***


Kashima, C.; Katoh, A. *J. Chem. Soc., Perkin Trans.* **1980**, 1599.

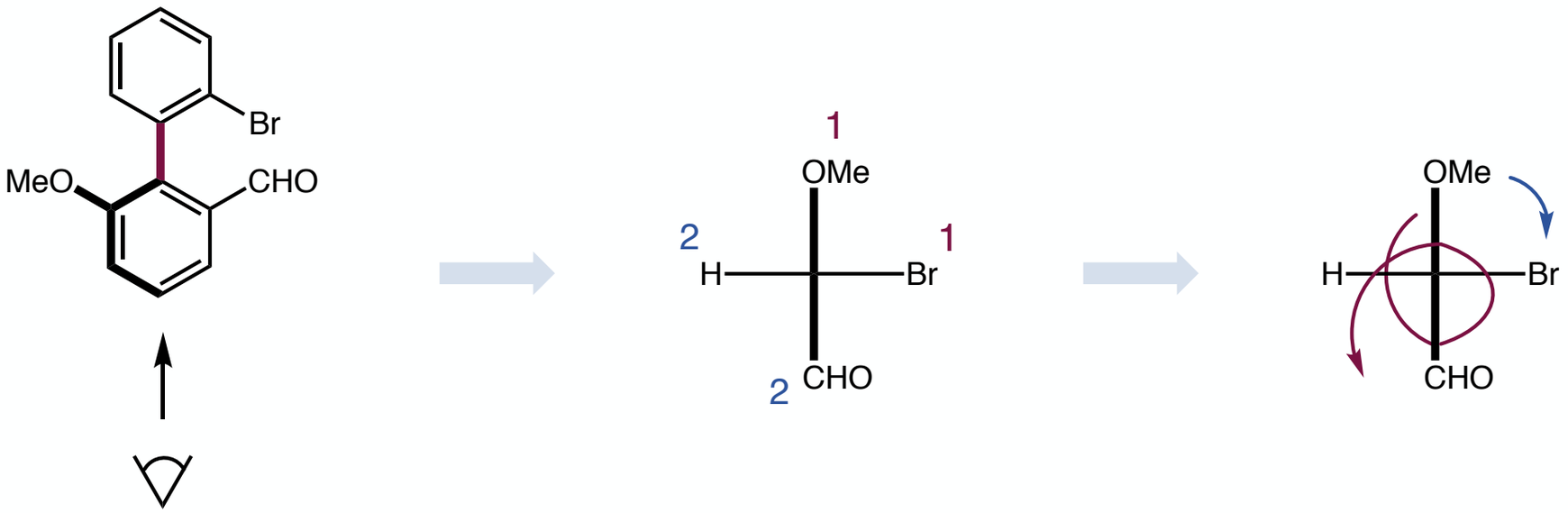
Roussel, C.; Adjimi, M.; Chemlal, A.; Djafri, A. *J. Org. Chem.* **1988**, *53*, 5076.

# *Determination of Absolute Axial Chirality*

*Cahn-Ingold-Prelog notation (aR, aS)*

*OR*

*helical analogy (M - minus, P - plus)*




*Cahn-Ingold-Prelog: counter-clockwise = **aS***

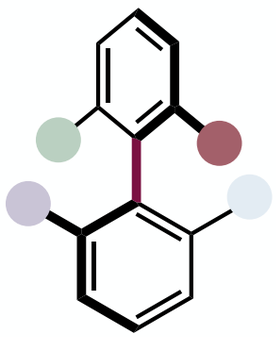
*helical analogy: clockwise = **P***

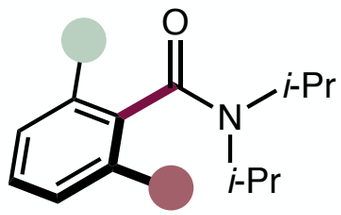
Eliel, E. L.; Wilen, S.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley Interscience: New York, **1994**, pp. 1119.

# *Examples of Atropisomeric Frameworks*

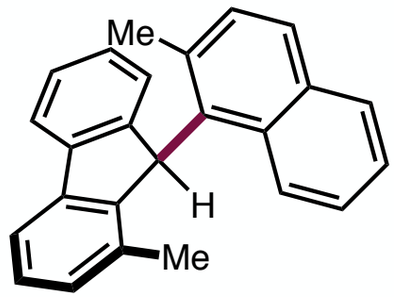
## *C–C bonds*

### *$C(sp^2)$–$C(sp^2)$*



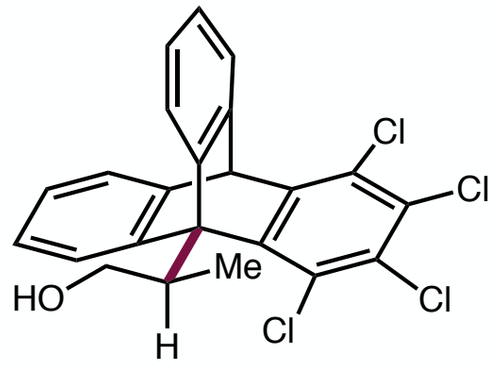



### *$C(sp^2)$–$C(sp^3)$*



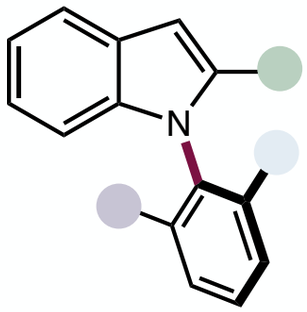

*$\Delta G^{\ddagger}_{(rac)}$ = 33.3 kcal/mol*

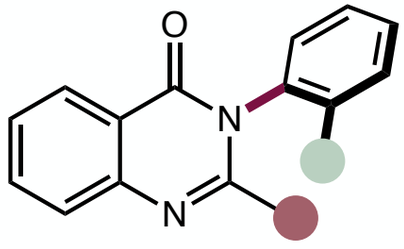
### *$C(sp^3)$–$C(sp^3)$*



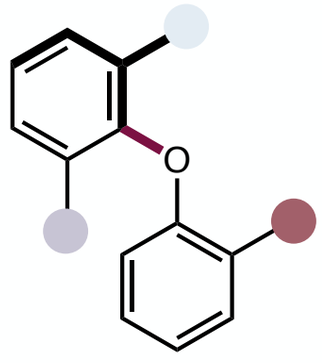

*$\Delta G^{\ddagger}_{(rac)}$ = 23.5 kcal/mol*

## *C–N bonds*

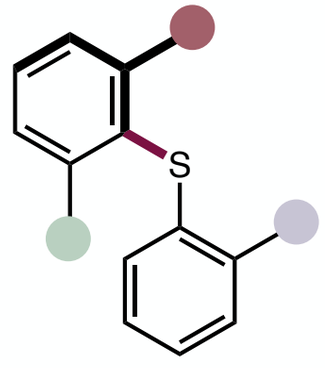


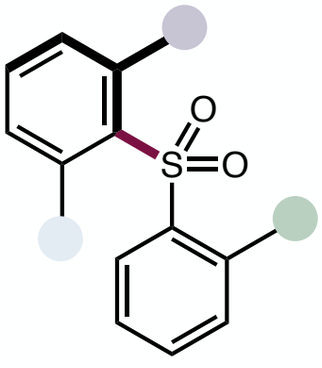




## *C–O bonds*




## *C–S bonds*

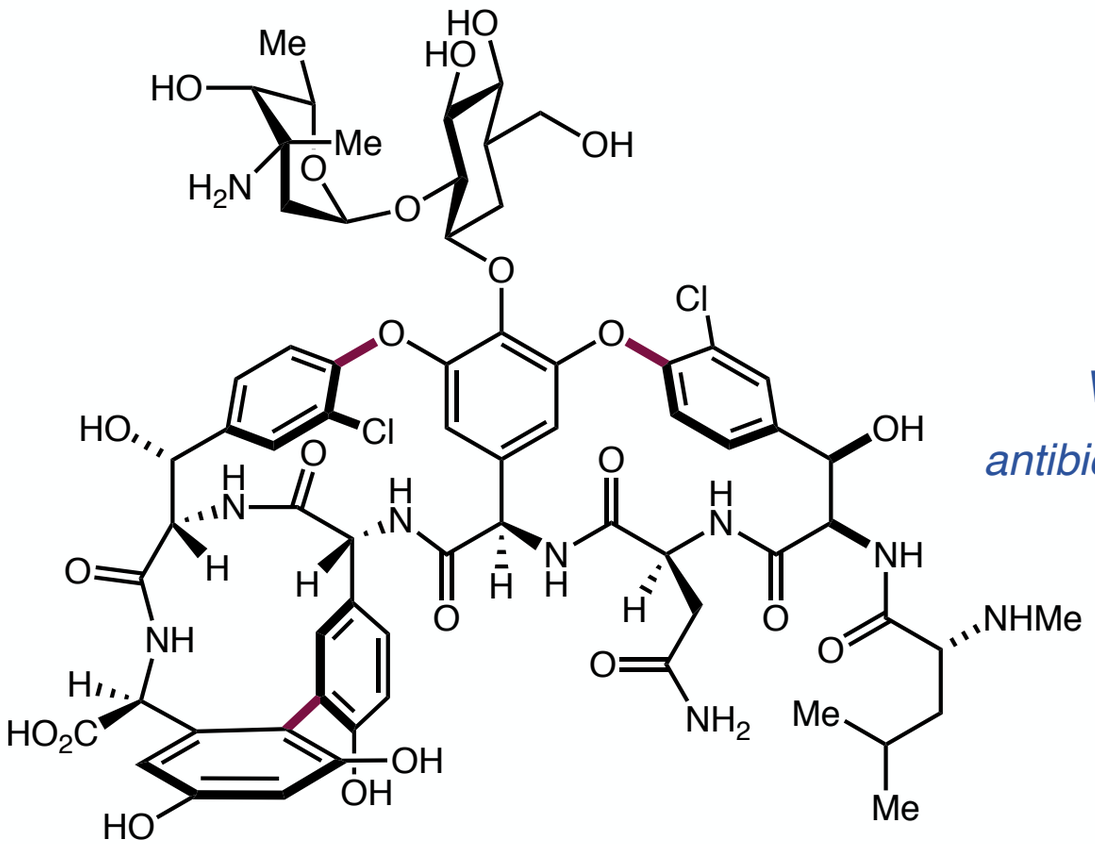



Kumarasamy, E.; Raghunathan, R.; Sibi, M. P.; Sivarugu, *J. Chem. Rev.* **2015**, *115*, 11239.

# *Atropisomers in Nature and Organic Synthesis*

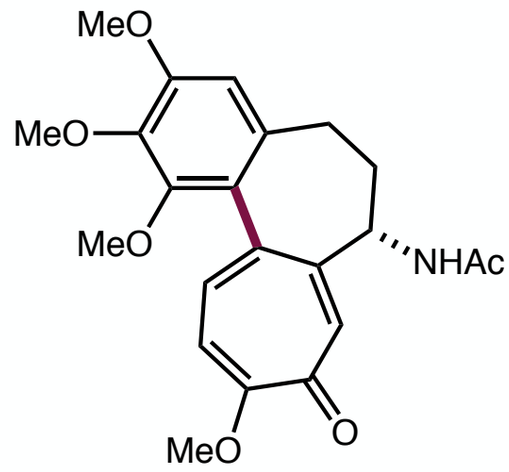
## ***Natural products***




***Vancomycin***

*antibiotic "of last resort"*

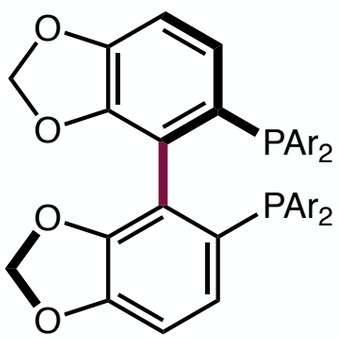
## ***Pharmaceuticals***

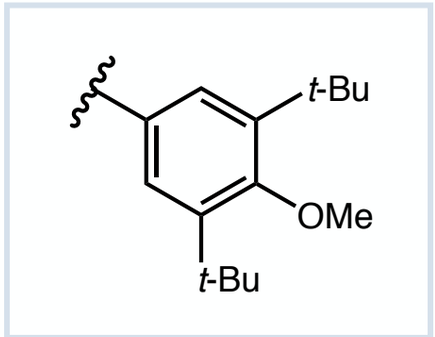



***Colchicine***

*Gout/anti-inflammatory*

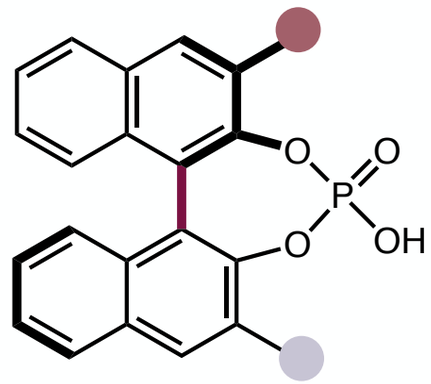
## ***Ligands***

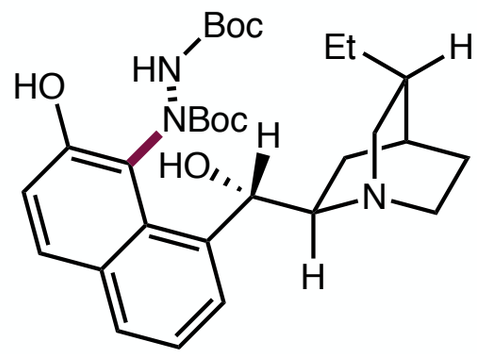



*(R)-DTBM-SEGPHOS*

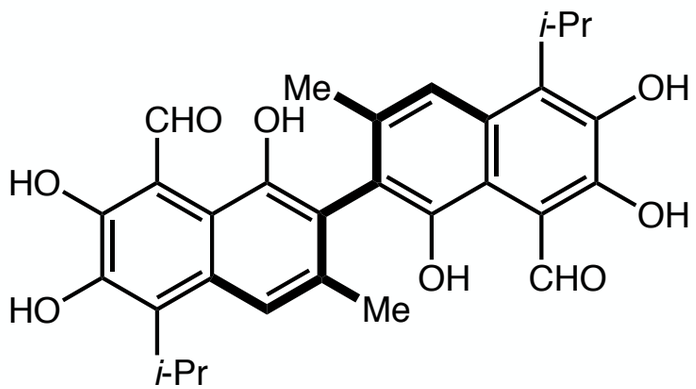
## ***Organocatalysts***



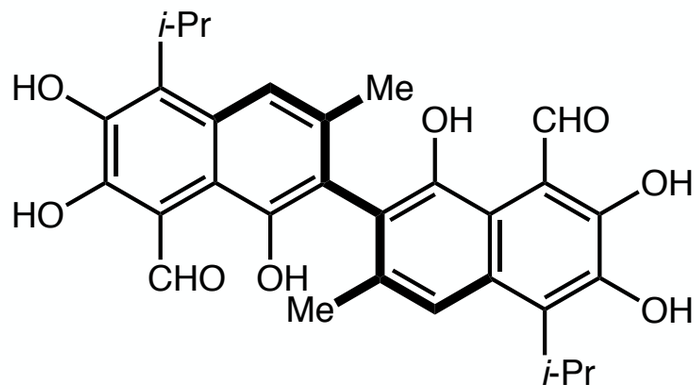




Kumarasamy, E.; Raghunathan, R.; Sibi, M. P.; Sivarugu, *J. Chem. Rev.* **2015**, *115*, 11239.

# *Atropisomers Can Exhibit Potent Bioactivity*

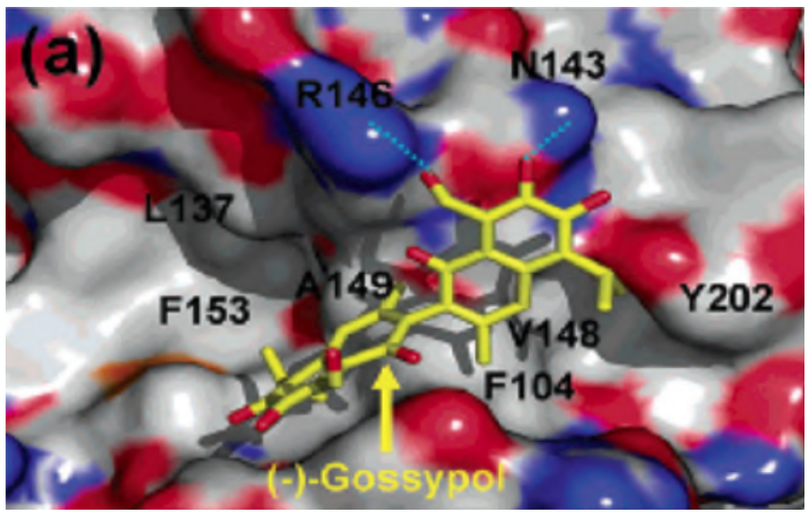



(–)-gossypol




(+)-gossypol

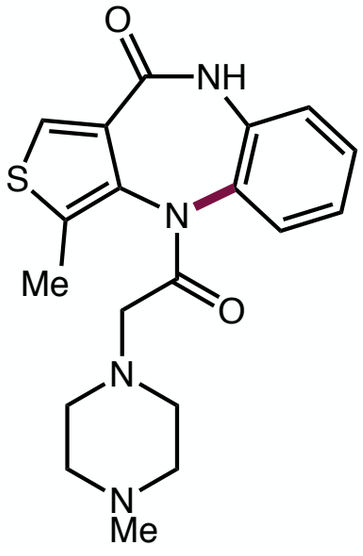
*Eudysmic ratio: fold change in potency (cytotoxicity) between two enantiomers of an inhibitor*




***Eudysmic ratio for (–)-gossypol to (+)-gossypol: 10:1***

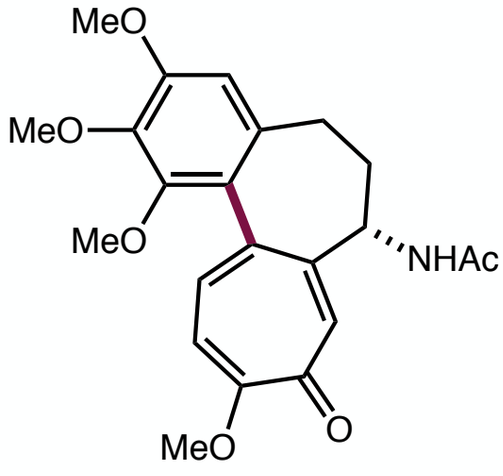
Pellecchia, M. et al. *J. Med. Chem.* **2010**, *53*, 4166.

# *Atropisomeric Representation in Pharmaceuticals*



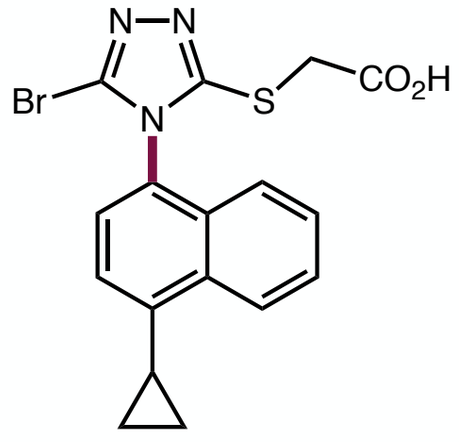

***Telenzepine***

*treatment for peptic ulcers*



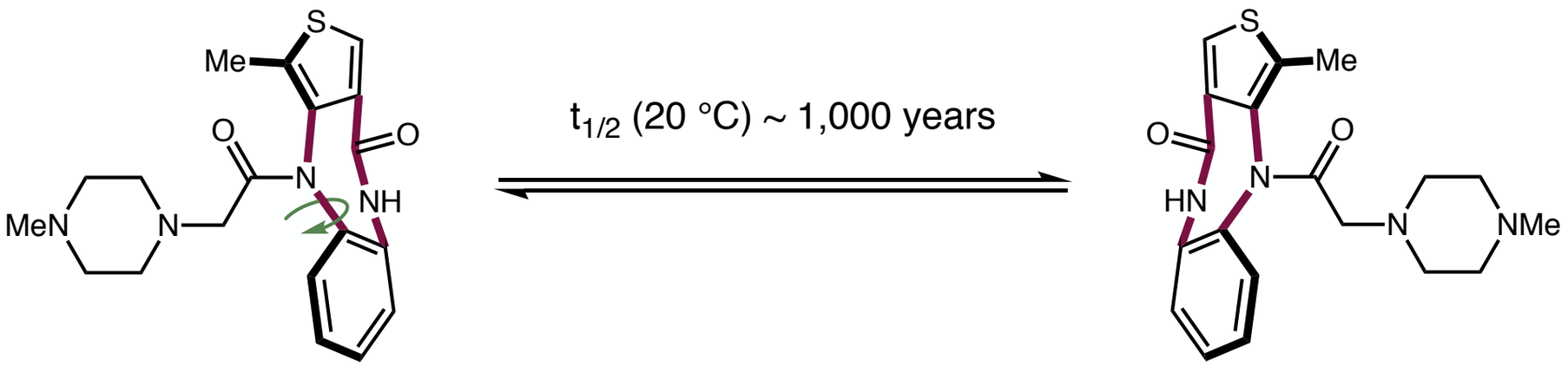

***Colchicine***

*Gout/anti-inflammatory*




***Lesinurad***

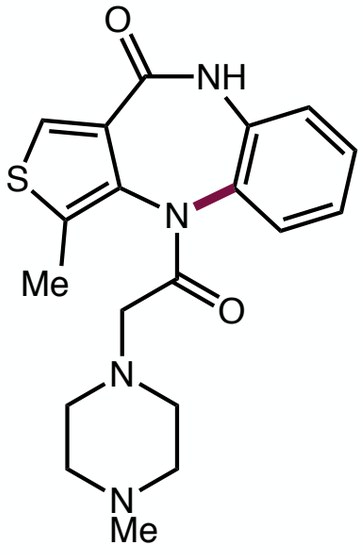
*urate transport inhibitor*




*(+)-isomer: 500-fold greater activity*

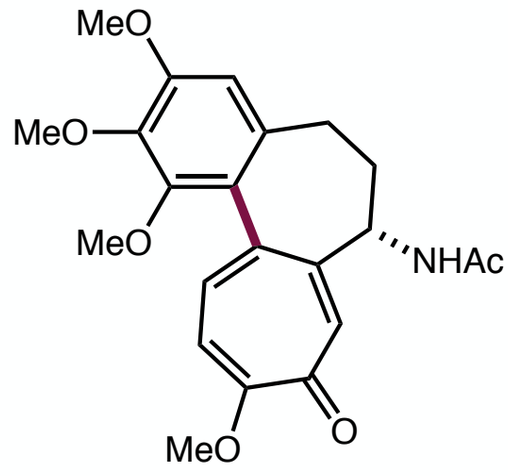
Toenjes, S.; Gustafson, J. *Future Med. Chem.* **2018**, *10*, 4109.

# *Atropisomeric Representation in Pharmaceuticals*



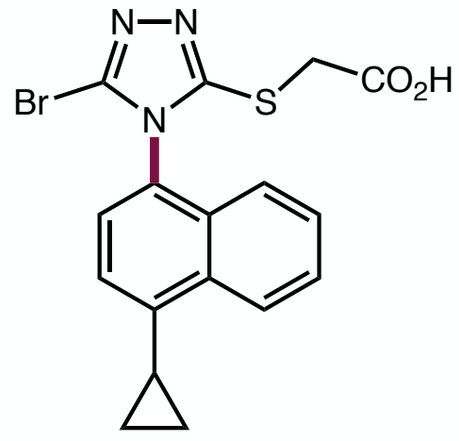

***Telenzepine***

*treatment for peptic ulcers*




***Colchicine***

*Gout/anti-inflammatory*




***Lesinurad***

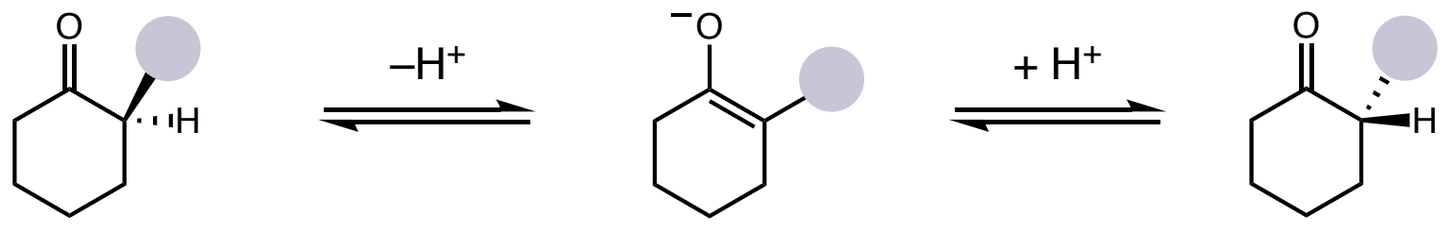
*urate transport inhibitor*

*examples exist of FDA-approved compounds with minimal or no detectable racemization*

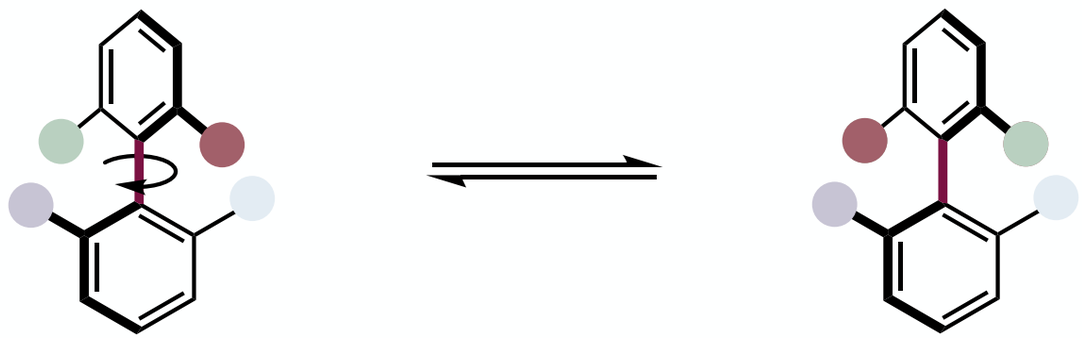
***Historically among chiral drugs, axial chirality is dramatically underrepresented***

Toenjes, S.; Gustafson, J. *Future Med. Chem.* **2018**, *10*, 4109.

# *Considerations in Small Molecule Racemization*




- *bimolecular*
- *multi-step*
- *dependent on environmental conditions (pH, etc.)*



- *unimolecular*
- *single-step*
- *potentially accessible via ambient temperature thermal activation*

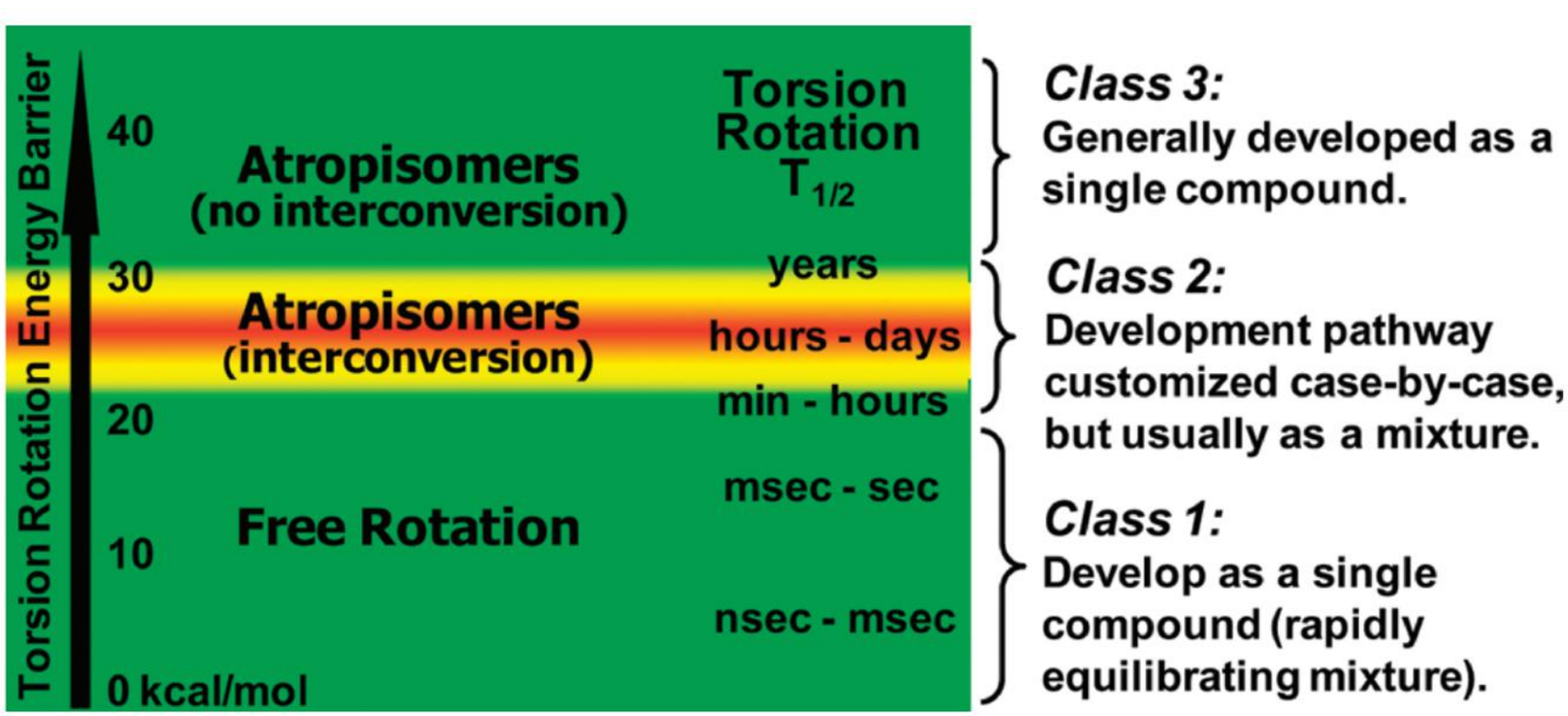
***Potential racemization has overall suppressed efforts to design drugs with chiral atropisomeric axes***

Laplante, S. et. al. *J. Med. Chem.* **2011**, *54*, 7005.

# *A Toolkit and a Renaissance*

*Boehringer Ingelheim and FDA (2011): collaboration to develop practical guide for atropisomerism in medicinal chemistry*

*Computational developments have enabled early-stage prediction of racemization rates based on structural elements*




Laplante, S. et. al. *J. Med. Chem.* **2011**, *54*, 7005.

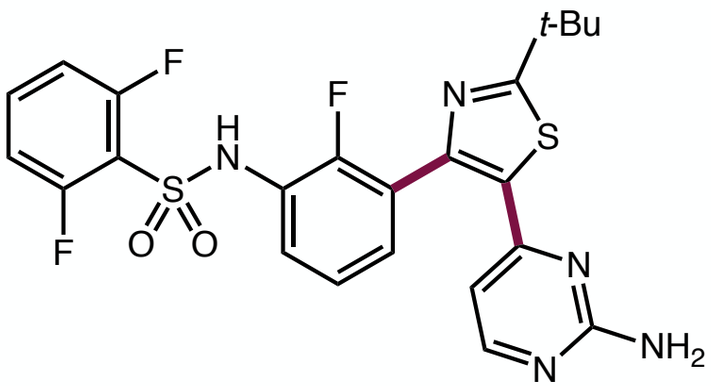
# *Class I Atropisomers*

$t_{1/2}$ < 1 min, $\Delta G^{\ddagger}$ < ~20 kcal/mol

*Extremely rapid interconversion, cannot isolate in stereochemically enriched form*

***Often unaccounted for during synthetic planning!***

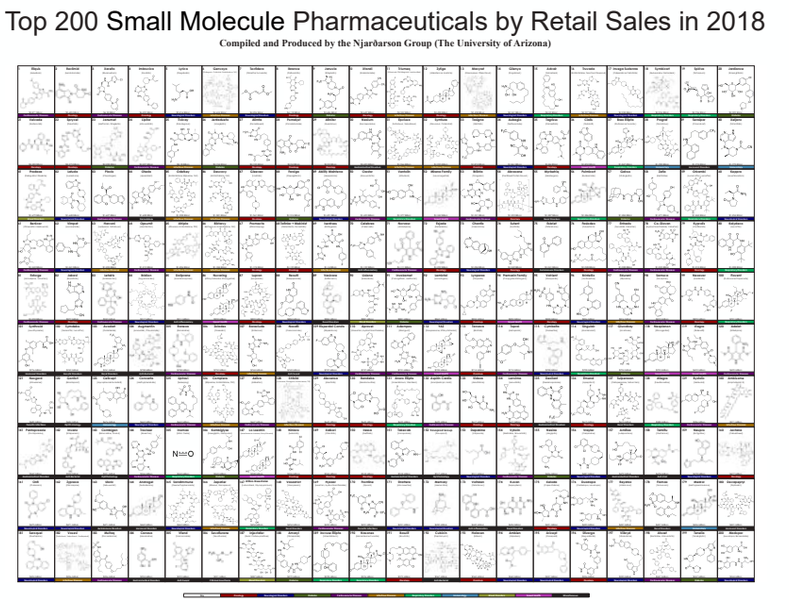
***Product of early stage reactions such as $S_NAr$, cross-coupling, amide coupling, etc.***
***(chiral axis arises downstream as functionality added)***




***Dabrafenib***

*oncology*

*2 chiral axes, no separable diastereomers*




- *estimated that ~15% of FDA approved drugs are Class I*

- *another ~10% of drugs are Class I-proatropisomeric (chiral axis readily interconverts under biological conditions)*

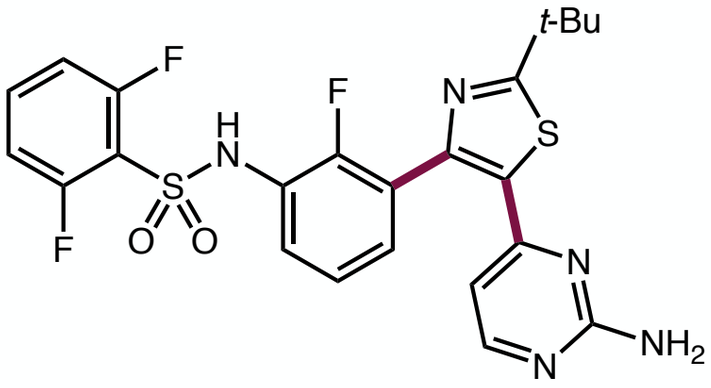

Toenjes, S.; Gustafson, J. *Future Med. Chem.* **2018**, *10*, 4109.
Laplante, S. et. al. *J. Med. Chem.* **2011**, *54*, 7005.

## *Class I Atropisomers*

$t_{1/2}$ < 1 min, $\Delta G^{‡}$ < ~20 kcal/mol

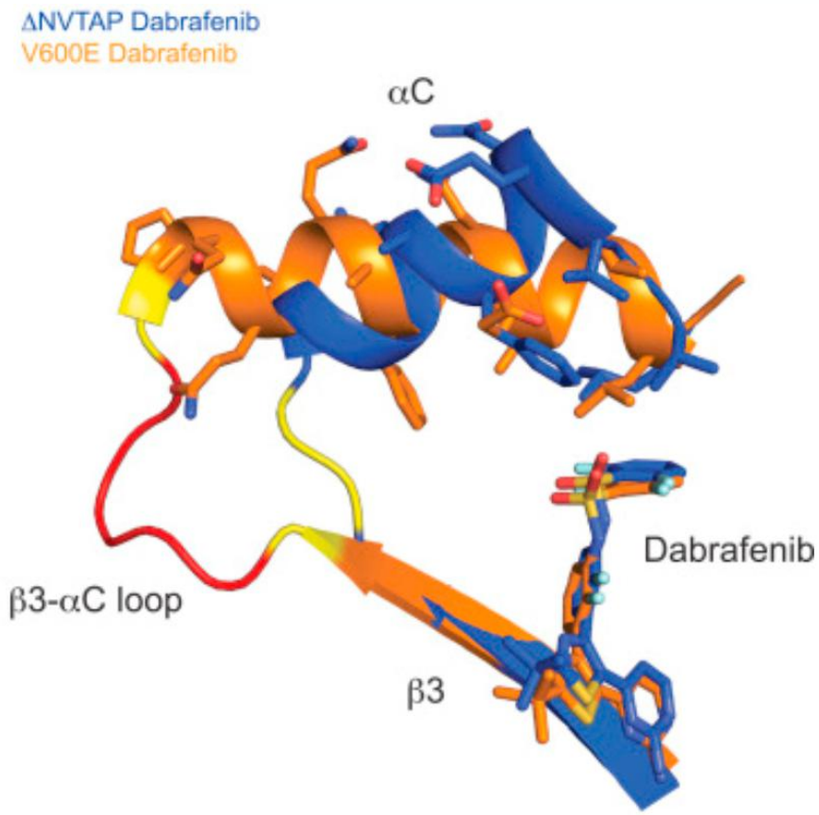
***Class I compounds can exhibit heightened binding/potency from one axial orientation***

***Overlooked aspect in design of higher performance analogs***




*BRAF target*

*binding*



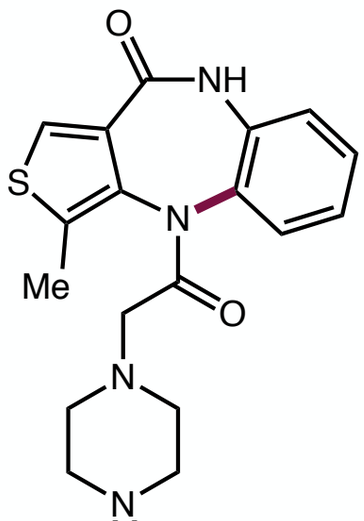

*atroposelective binding observed*

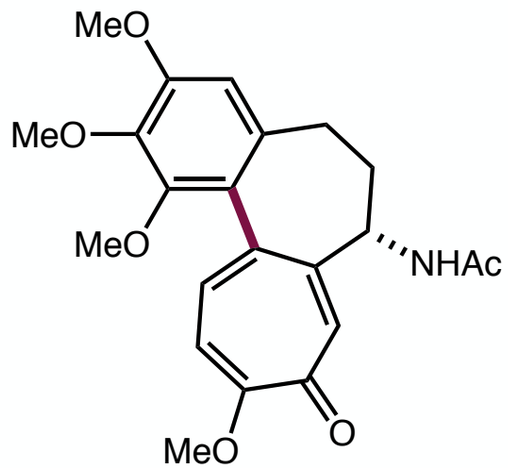
*despite rapid axial racemization!*

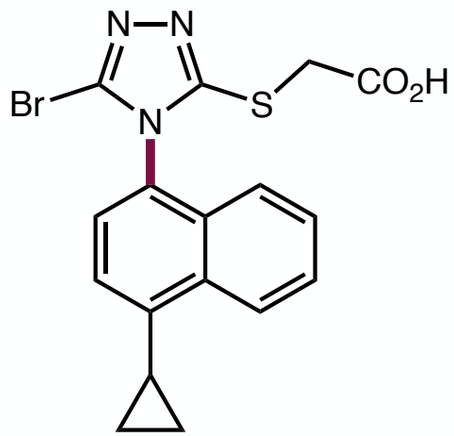
Foster, S. A. et al. *Cancer Cell* **2016**, *4*, 477.

# *Class III Atropisomers*

$t_{1/2} > 1$ year, $\Delta G^{\ddagger} > 30$ kcal/mol




***Telenzepine***

*treatment for peptic ulcers*

***Colchicine***

*Gout/anti-inflammatory*

***Lesinurad***

*urate transport inhibitor*

*Indefinitely stable, can be developed and applied like point chiral drugs*

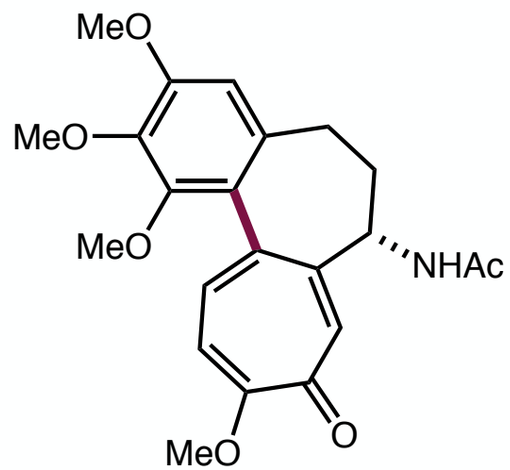
***Note: additional point chirality may be required to favor one diastereomer, stabilize chiral axis***

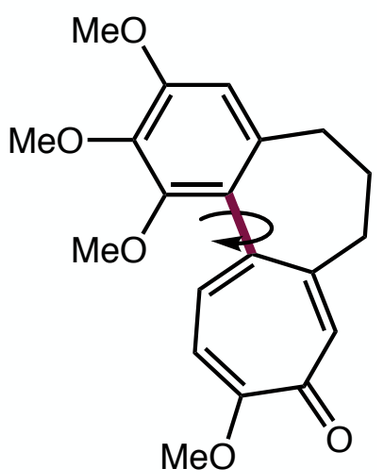

Toenjes, S.; Gustafson, J. *Future Med. Chem.* **2018**, *10*, 4109.

Laplante, S. et. al. *J. Med. Chem.* **2011**, *54*, 7005.

# *Class III Atropisomers*

$t_{1/2} > 1$ year, $\Delta G^{\ddagger} > 30$ kcal/mol




*$\Delta G^{\ddagger}_{(rac)} \sim 22$ kcal/mol*
*(racemizes in minutes)*

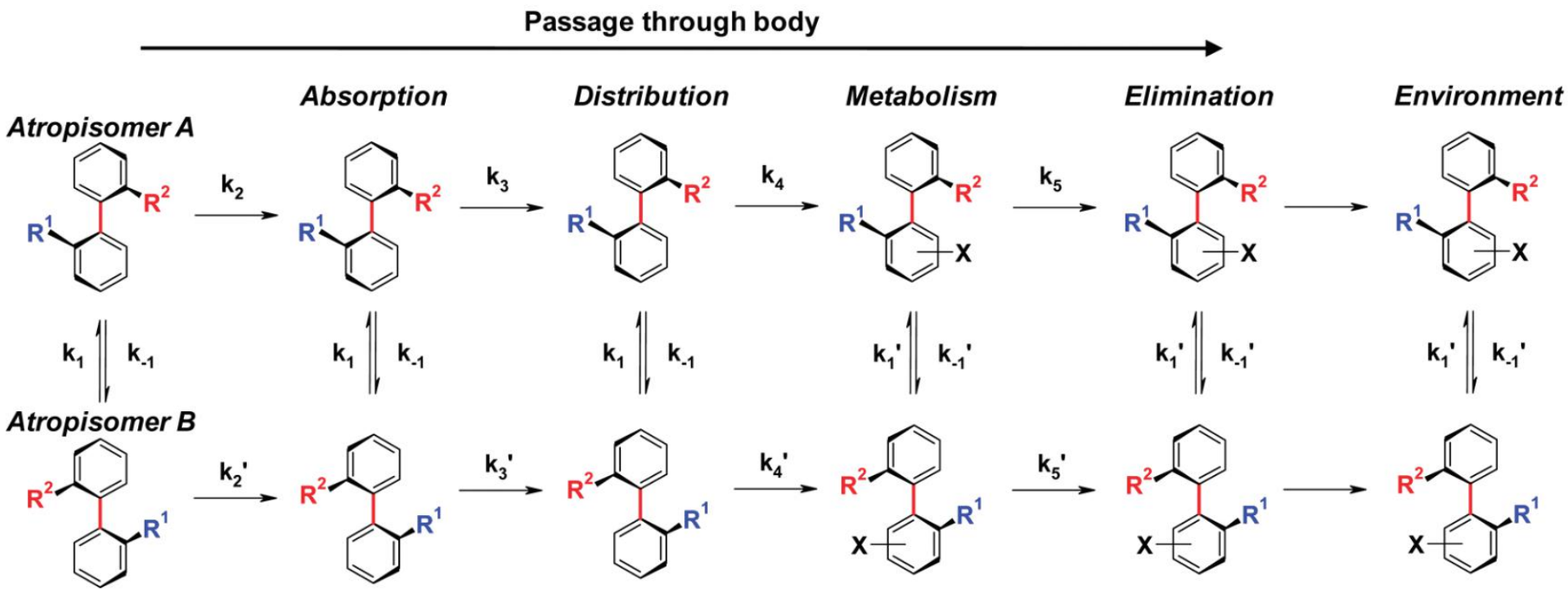
Toenjes, S.; Gustafson, J. *Future Med. Chem.* **2018**, *10*, 4109.

# *Class II Atropisomers*

$t_{1/2}$ ~ minutes–days, $\Delta G^{\ddagger}$ ~ 20–30 kcal/mol

***Most challenging class for pharmaceutical development (almost never clinically successful)***

- *Prior to widespread computational modeling, challenging to predict*
- *Difficult preparation and unconventional pharmacokinetic profiles*



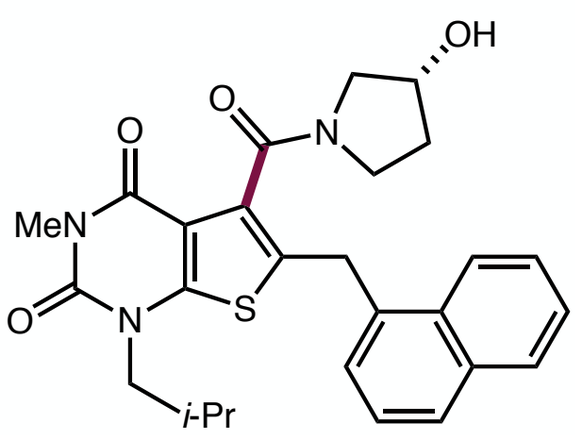

Toenjes, S.; Gustafson, J. *Future Med. Chem.* **2018**, *10*, 4109.
Laplante, S. et. al. *J. Med. Chem.* **2011**, *54*, 7005.

# *Class II Atropisomers*

$t_{1/2}$ ~ minutes–days, $\Delta G^{\ddagger}$ ~ 20–30 kcal/mol

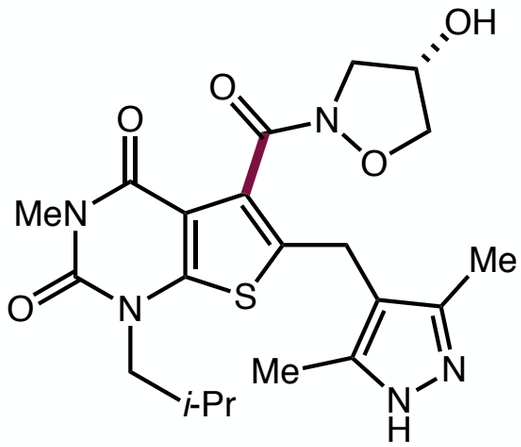
***Most challenging class for pharmaceutical development (almost never clinically successful)***

***Best strategy: redesign as either Class III (best case) or Class I***




*structural*

*overhaul*




*$\Delta G^{\ddagger}_{(rot)}$ = 24.6 kcal/mol*
*observable atropisomers*

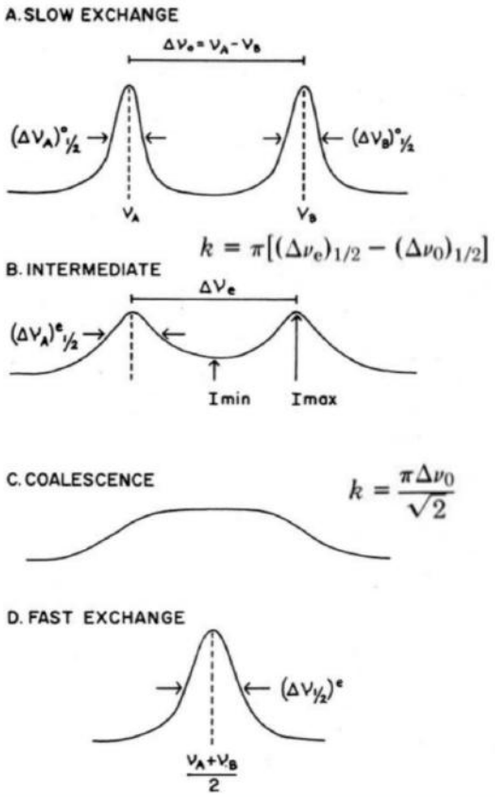
*$\Delta G^{\ddagger}_{(rot)}$ = 20.1 kcal/mol*
*no detected atropisomers (Class I)*
*enhanced ADMET properties*


Toenjes, S.; Gustafson, J. *Future Med. Chem.* **2018**, *10*, 4109.
Laplante, S. et. al. *J. Med. Chem.* **2011**, *54*, 7005.

# *Other Challenges: Detection and Purification*

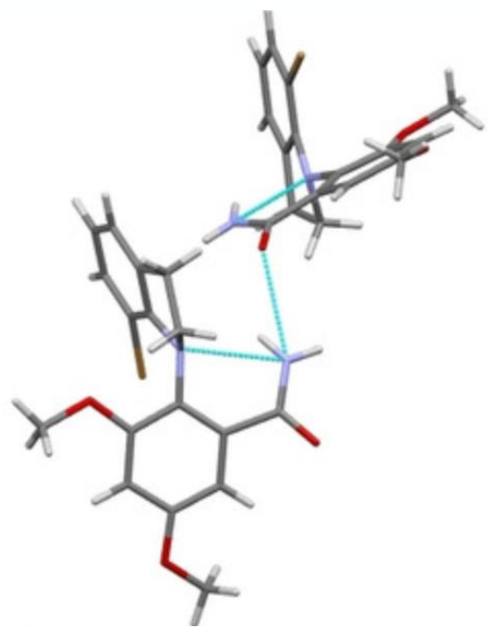
***Common methods:***

*NMR linewidth analysis*

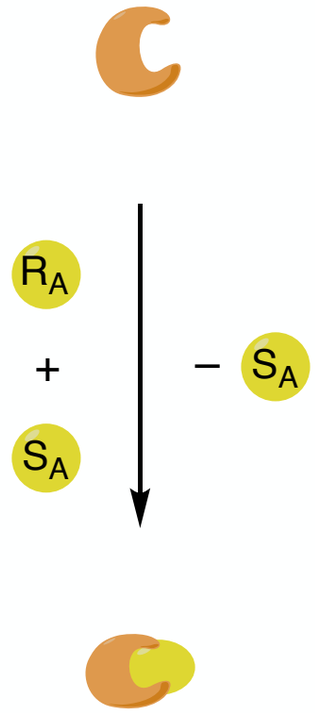



*Only useful for diastereomer equilibration rates*

*X-ray crystallography*



*Enzyme binding studies*



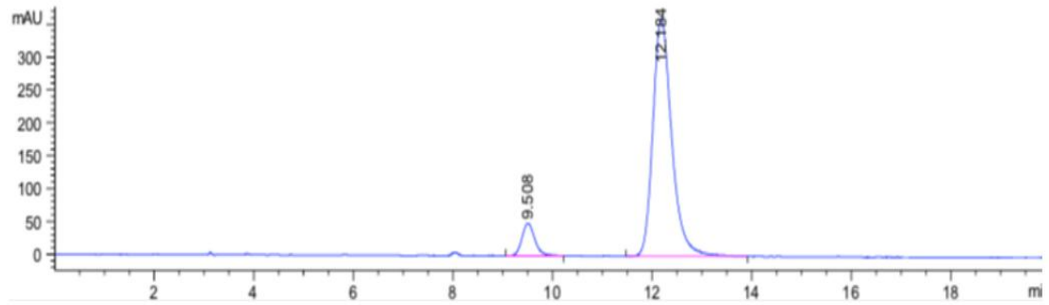

*Kinetic resolution, non-preparative*


Toenjes, S.; Gustafson, J. *Future Med. Chem.* **2018**, *10*, 4109.
Laplante, S. et. al. *J. Med. Chem.* **2011**, *54*, 7005.

# *Other Challenges: Detection and Purification*

***Common methods:***

*Chiral HPLC*




*Ideal for enantiotopic atropisomeric compounds*

***Considerable effort must be spent on screening conditions (frequently requires low-temperature operations)***

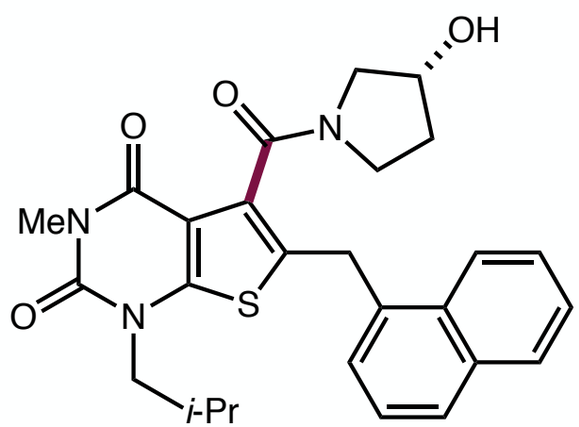
***May not translate to preparative or process-scale conditions***


Toenjes, S.; Gustafson, J. *Future Med. Chem.* **2018**, *10*, 4109.
Laplante, S. et. al. *J. Med. Chem.* **2011**, *54*, 7005.

# *Other Challenges: Synthesis*

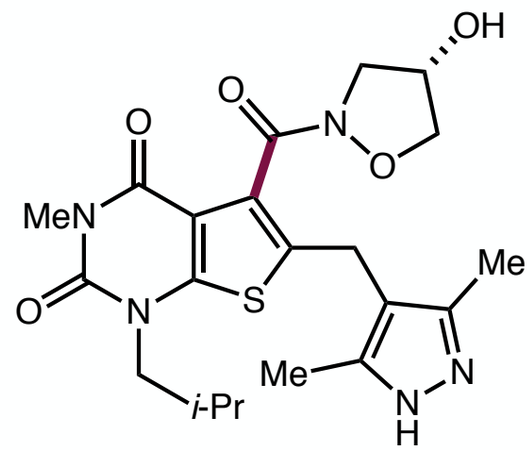
***To avoid setbacks from Class II compounds: simply increase ortho steric bulk → Class III!***

*Not so fast…*




*structural*

*overhaul*




$\Delta G^{\ddagger}_{(rot)}$ = 24.6 kcal/mol
observable atropisomers

$\Delta G^{\ddagger}_{(rot)}$ = 20.1 kcal/mol
no detected atropisomers (Class I)
enhanced ADMET properties

*Not always a simple retrosynthetic disconnection!*

*If bond constructed in early stage, must overhaul entire route*

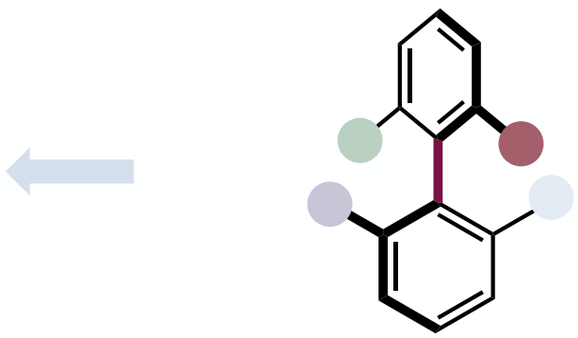

Toenjes, S.; Gustafson, J. *Future Med. Chem.* **2018**, *10*, 4109.
Laplante, S. et. al. *J. Med. Chem.* **2011**, *54*, 7005.

# *Other Challenges: Synthesis*

***To avoid setbacks from Class II compounds: simply increase ortho steric bulk → Class III!***

*Not so fast…*

*Greater hindrance limits axial rotation*



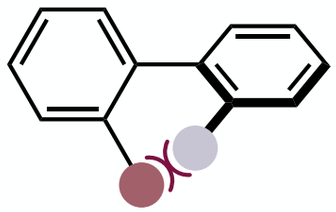
*Challenging formation of highly congested bond*

***New methods for late-stage, catalyst-controlled atroposelective synthesis are desirable***

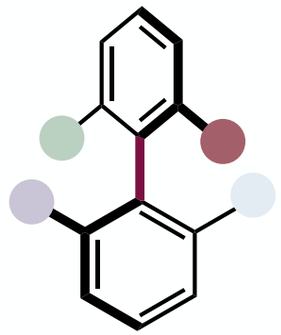

Toenjes, S.; Gustafson, J. *Future Med. Chem.* **2018**, *10*, 4109.
Laplante, S. et. al. *J. Med. Chem.* **2011**, *54*, 7005.

# *Outline*

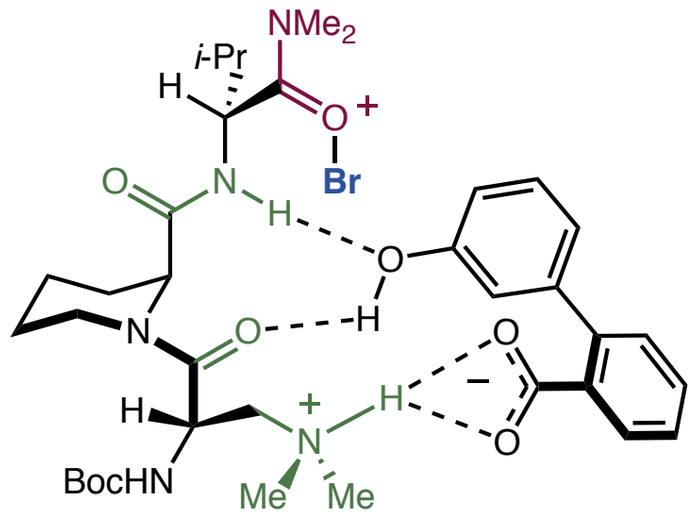
- Introduction and General Considerations
  - Discovery and fundamentals
  - Contributions to rotational barriers
  - Pharmaceutical considerations



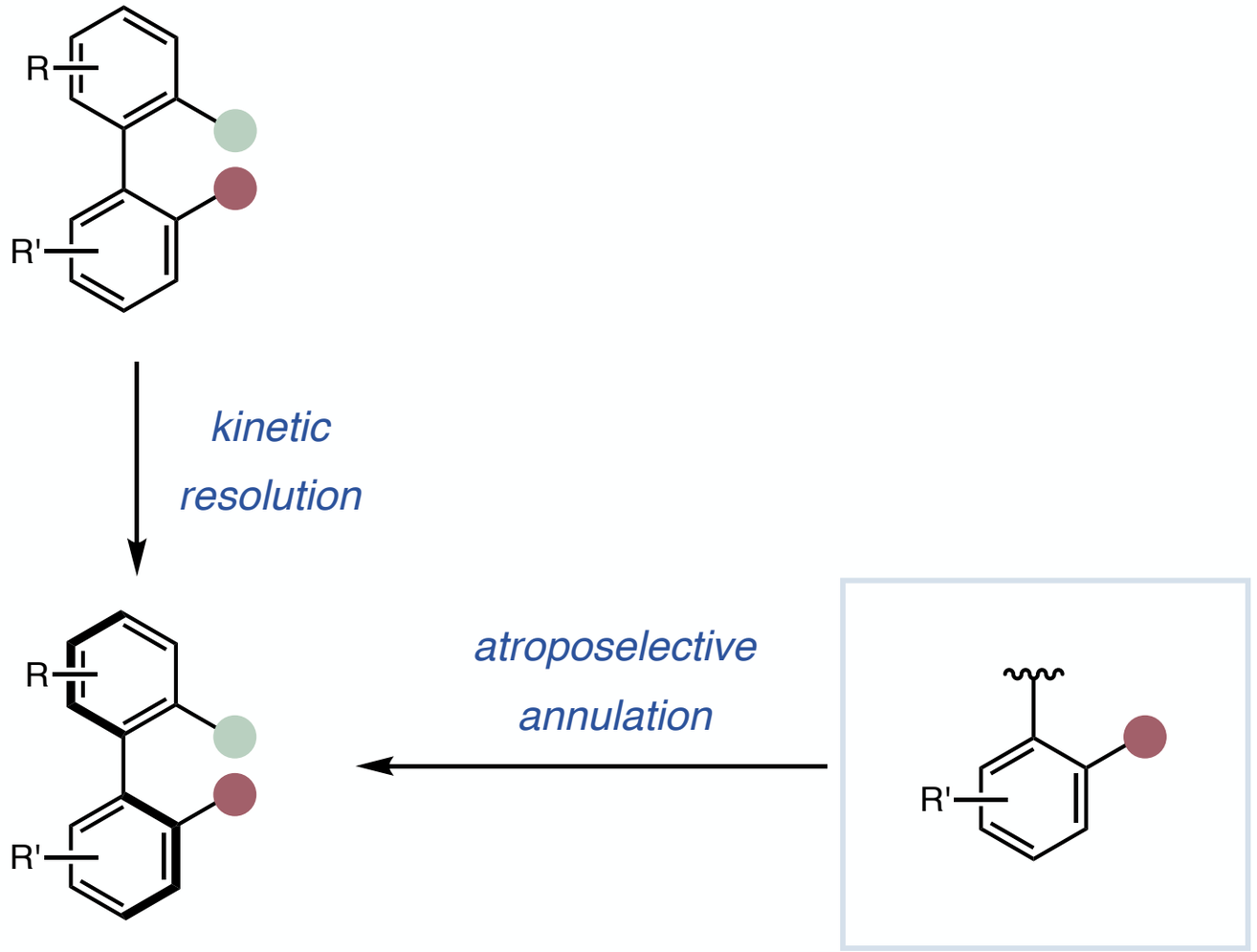
- Methods of (Catalytic) Synthesis
  - Diastereoselective methods
  - Dynamic kinetic resolutions and desymmetrization
  - Redox-neutral cross-oupling
  - Oxidative cross-oupling



- Applications
  - Case Study: Tryptorubin A



# *Common Strategies in Atropisomer Synthesis*

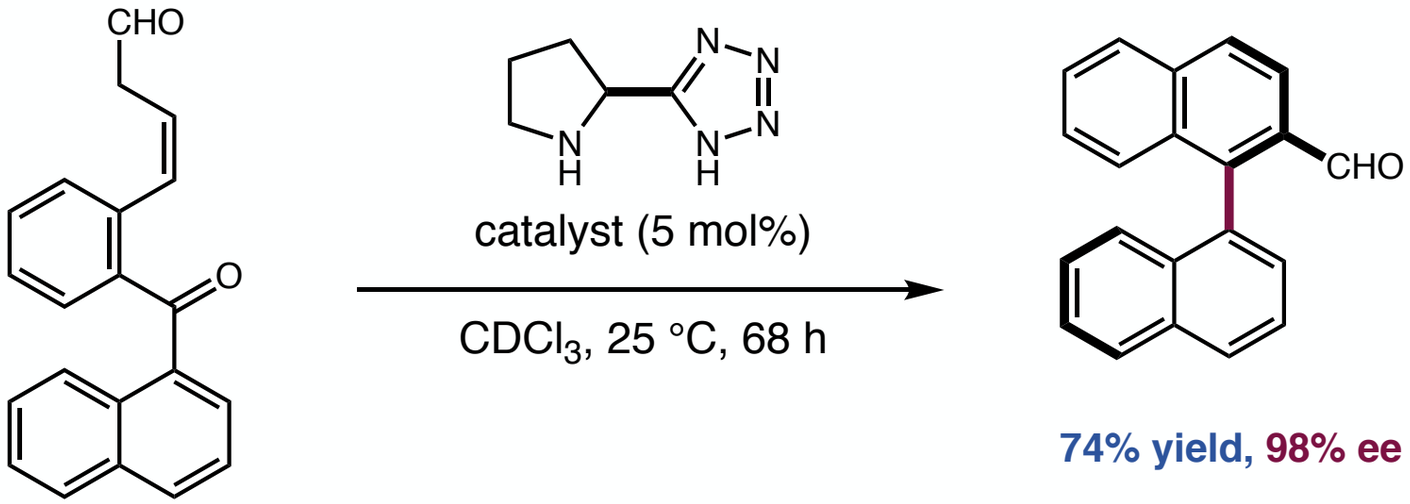


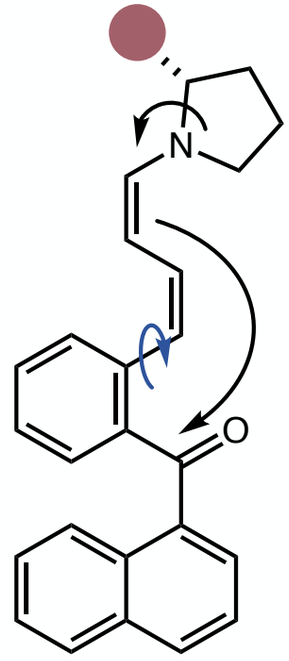


Zilate, B.; Castgrogiovanni, A.; Sparr, C. *ACS Catal.* **2018**, *8*, 2981.

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

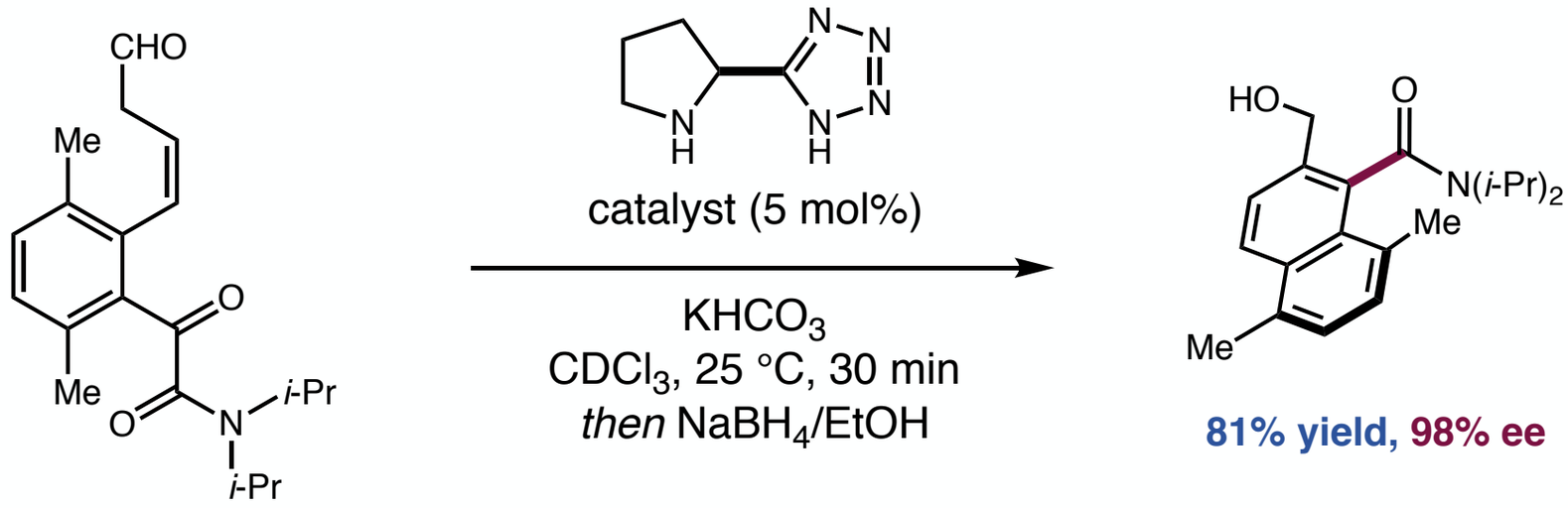
# *Organocatalytic Atroposelective Aldol Reactions*




*point-to-axial chirality transfer via Z-configured dienamine*

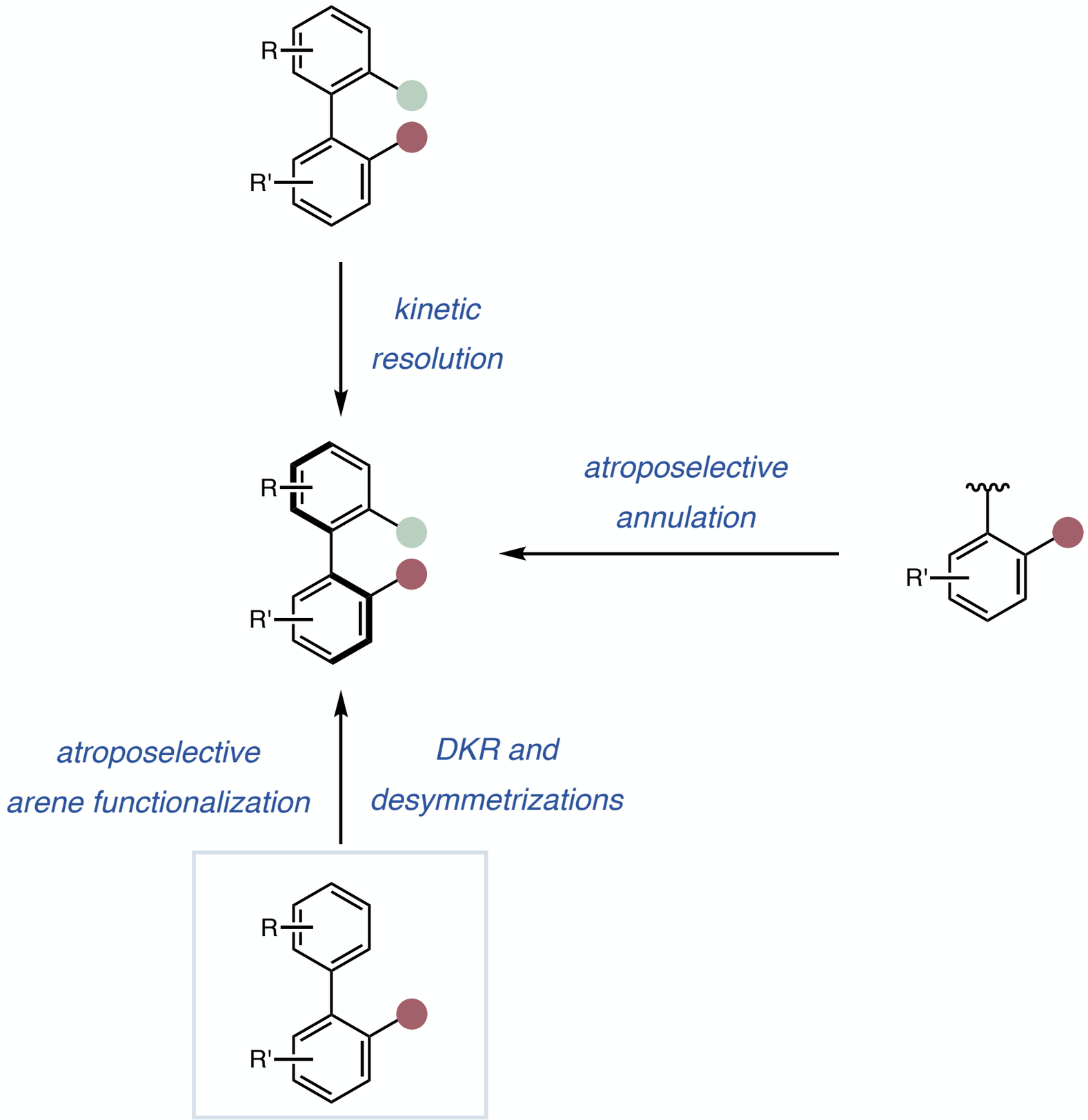
---




**81% yield, 98% ee**

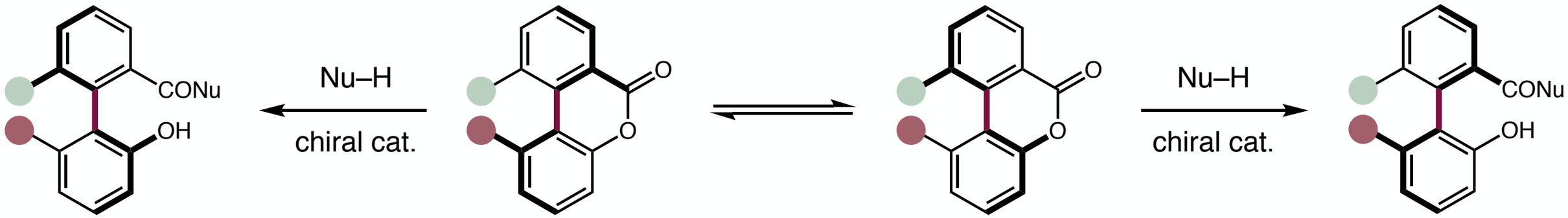

Faseke, V. C.; Sparr, C. *Angew. Chem. Int. Ed.* **2016**, *55*, 7261.
Link, A.; Sparr, C. *Angew. Chem. Int. Ed.* **2014**, *53*, 5458.

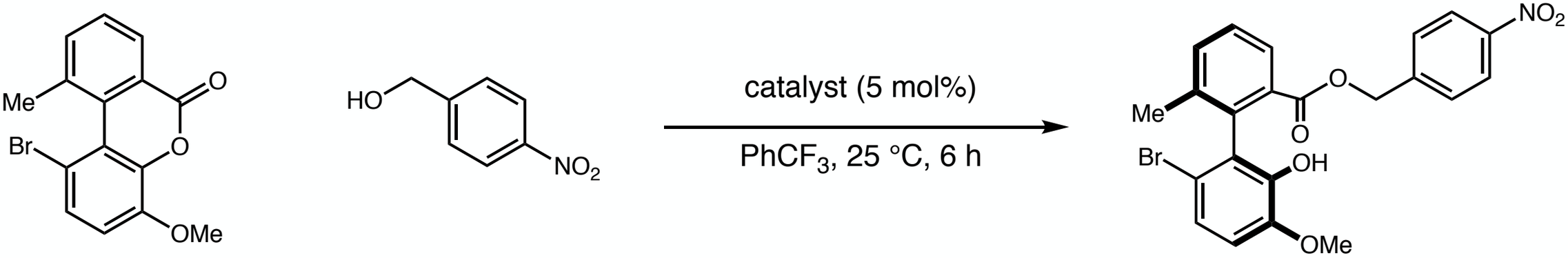
# *Common Strategies in Atropisomer Synthesis*



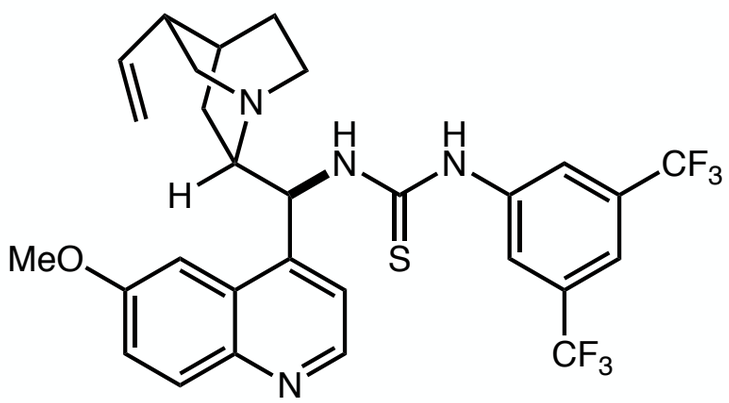

Bringmann, G.; Mortimer, A. J.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 5384.

# *The Bringmann Lactone Concept*




**99% yield, 96% ee**

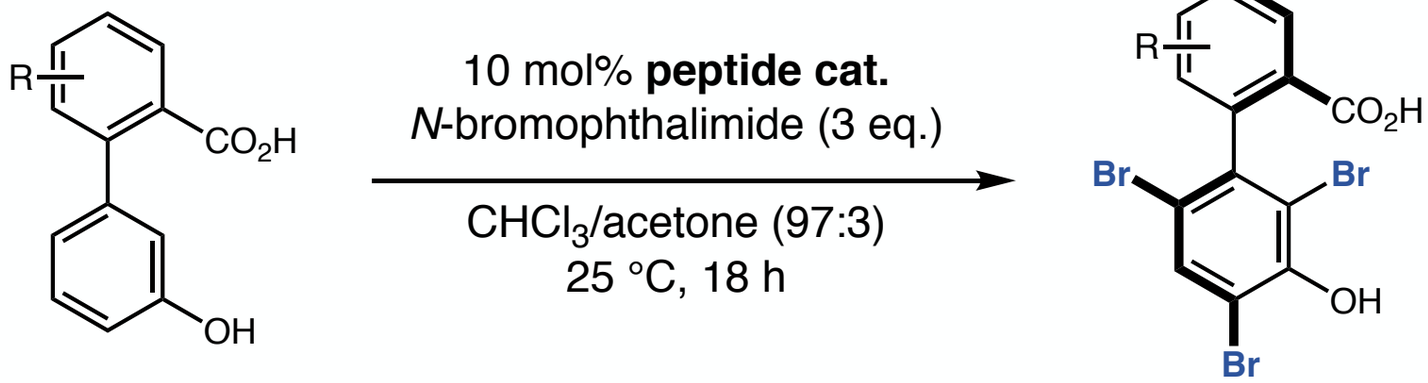


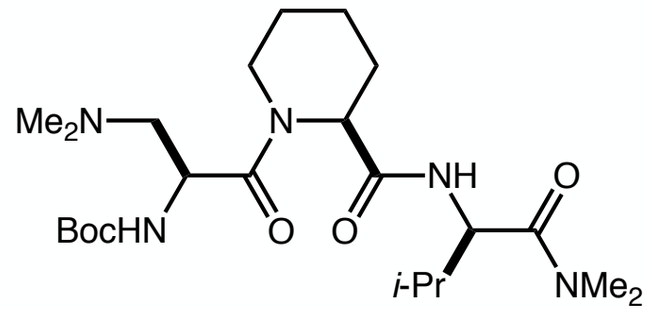

**thiourea catalyst**


Yu, C.; Huang, H.; Li, X.; Zhang, Y.; Wang, W. *J. Am. Chem. Soc.* **2016**, *138*, 6956.

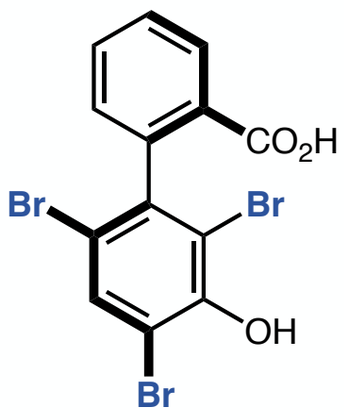
Bringmann, G.; Mortimer, A. J.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 5384.

# *Dynamtic Kinetic Resolution via Atroposelective Bromination*

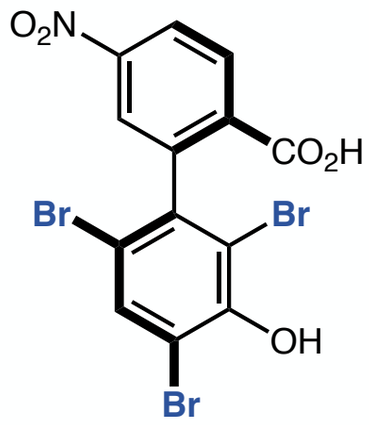


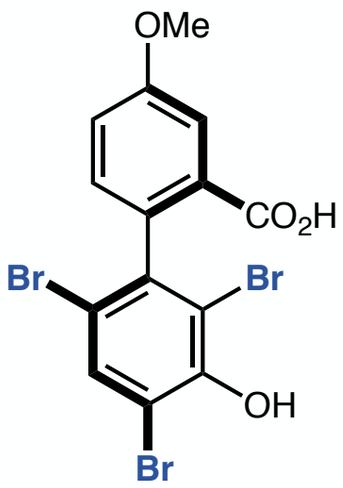

**peptide catalyst**



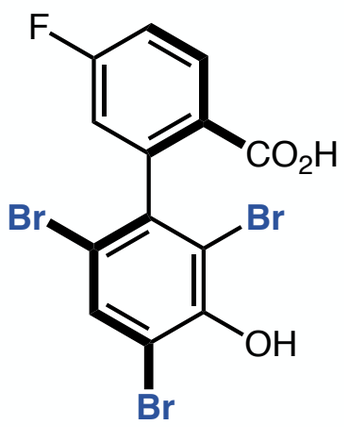

**80% yield, 97:3 er**



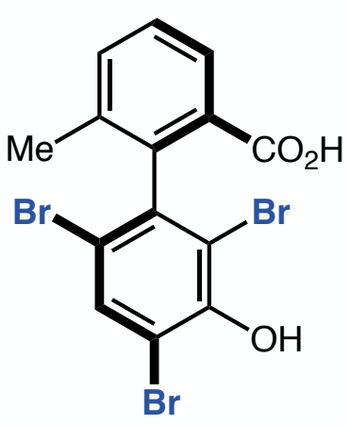

**85% yield, 97:3 er**



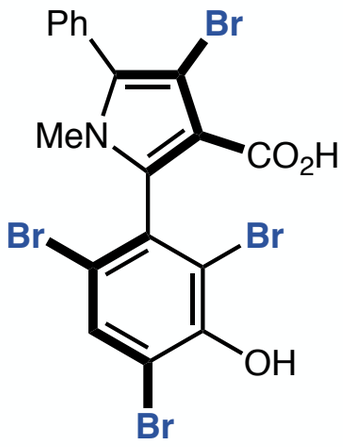

**70% yield, 96:4 er**




**65% yield, 96.5:3.5 er**



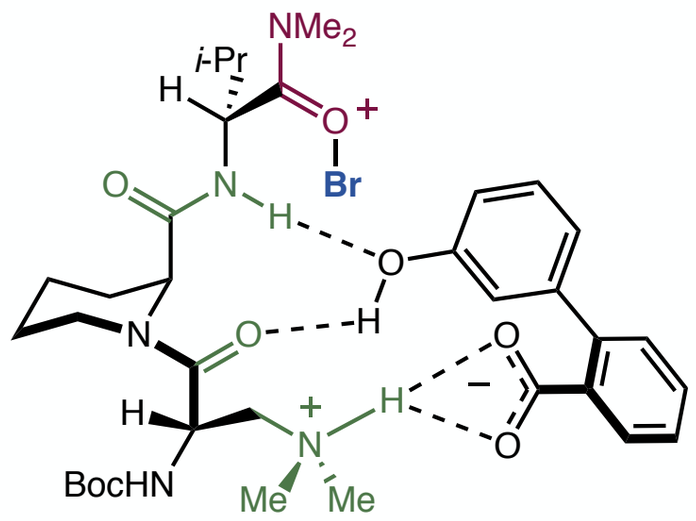

**85% yield, 87:13 er**




**77% yield, 85:15 er**

*amide-mediated*

*electrophilic bromination*



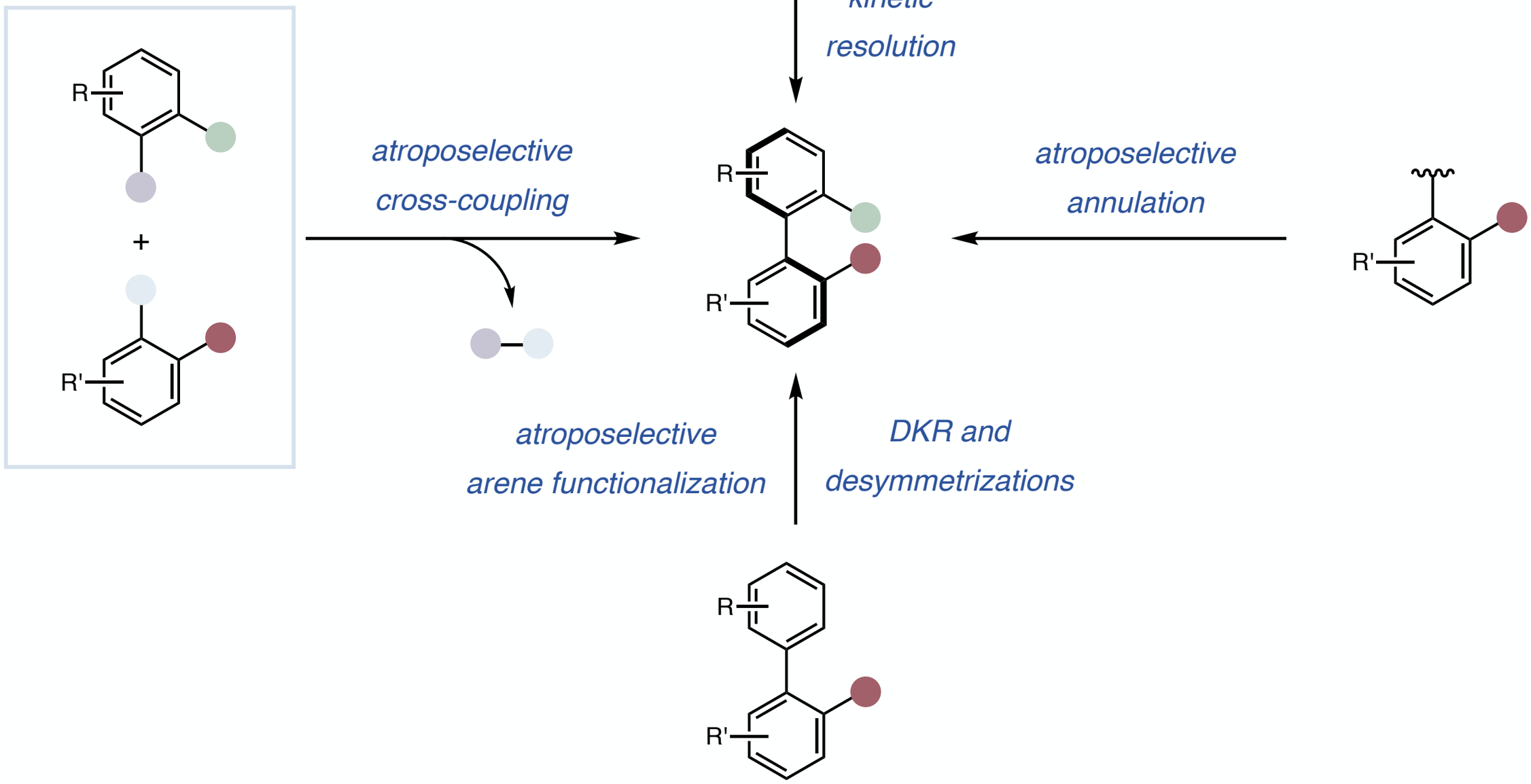

*pre-organization via*

*hydrogen bonding and*

*salt bridge stabilization*

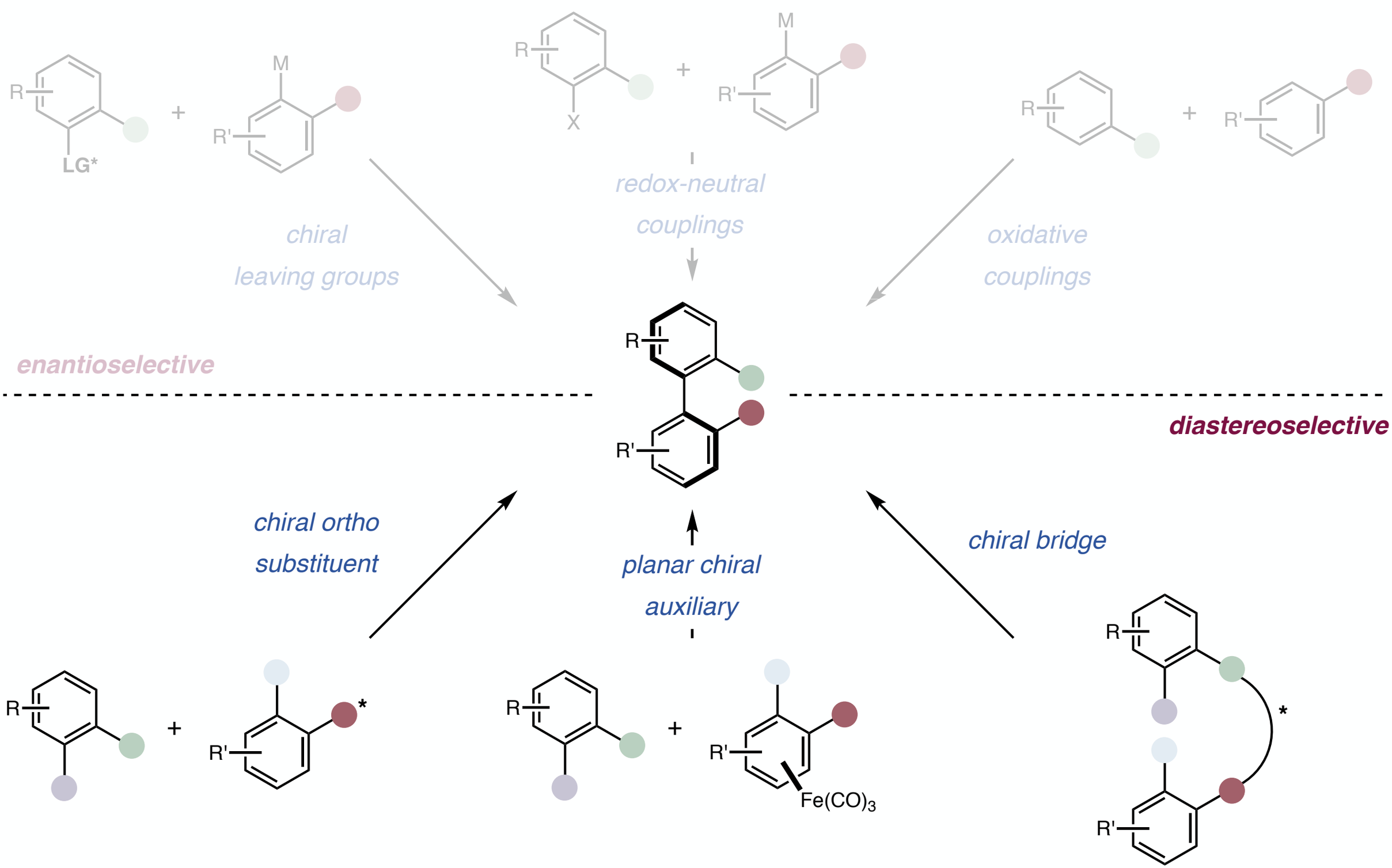
Gustafson, J. L.; Lim, D.; Miller, S. J. *Science* **2010**, *328*, 1251.

# *Common Strategies in Atropisomer Synthesis*




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

# *Common Strategies in Atropisomer Synthesis*



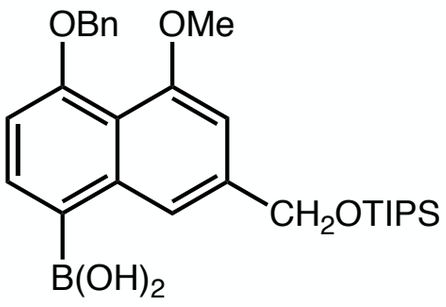


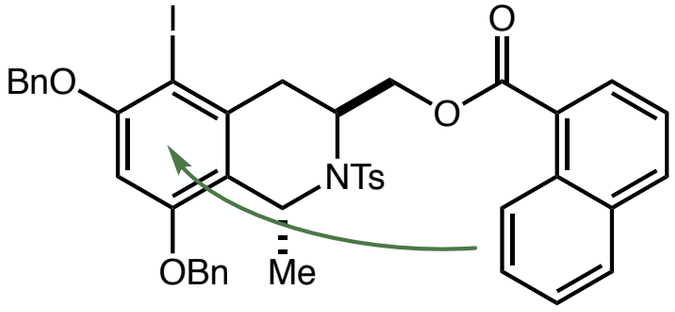
Zilate, B.; Castgrogiovanni, A.; Sparr, C. *ACS Catal.* **2018**, *8*, 2981.

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

# *Total Synthesis of (+)-korupensamine B*

*Lipshutz (2010):*




*intramolecular π-stacking*

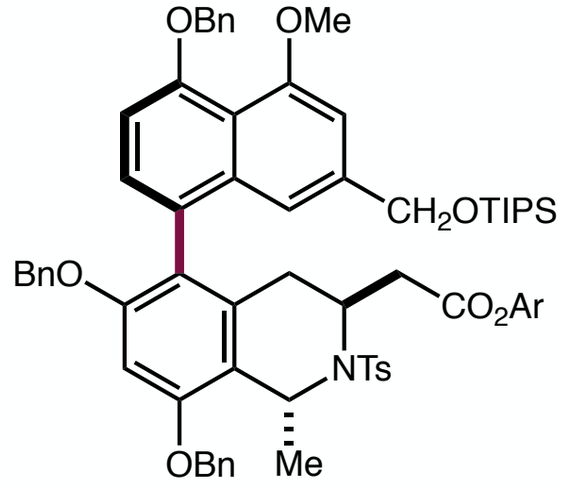
*distal chiral directing group*

$PdI_2$ (4 mol%)

**SPhos** (8 mol%)

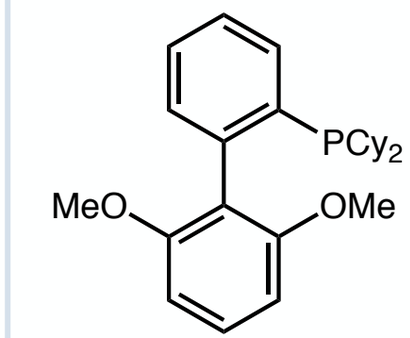
$K_3PO_4$ (3 equiv.)

*n*-BuOH, 25 °C, 24 h

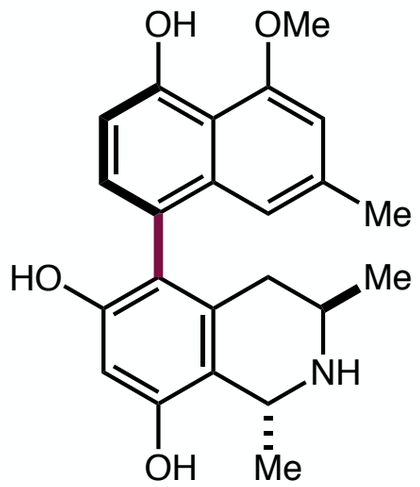



**72% yield, 11:1 dr**

**(Ar = 1-naphthyl)**




**SPhos**

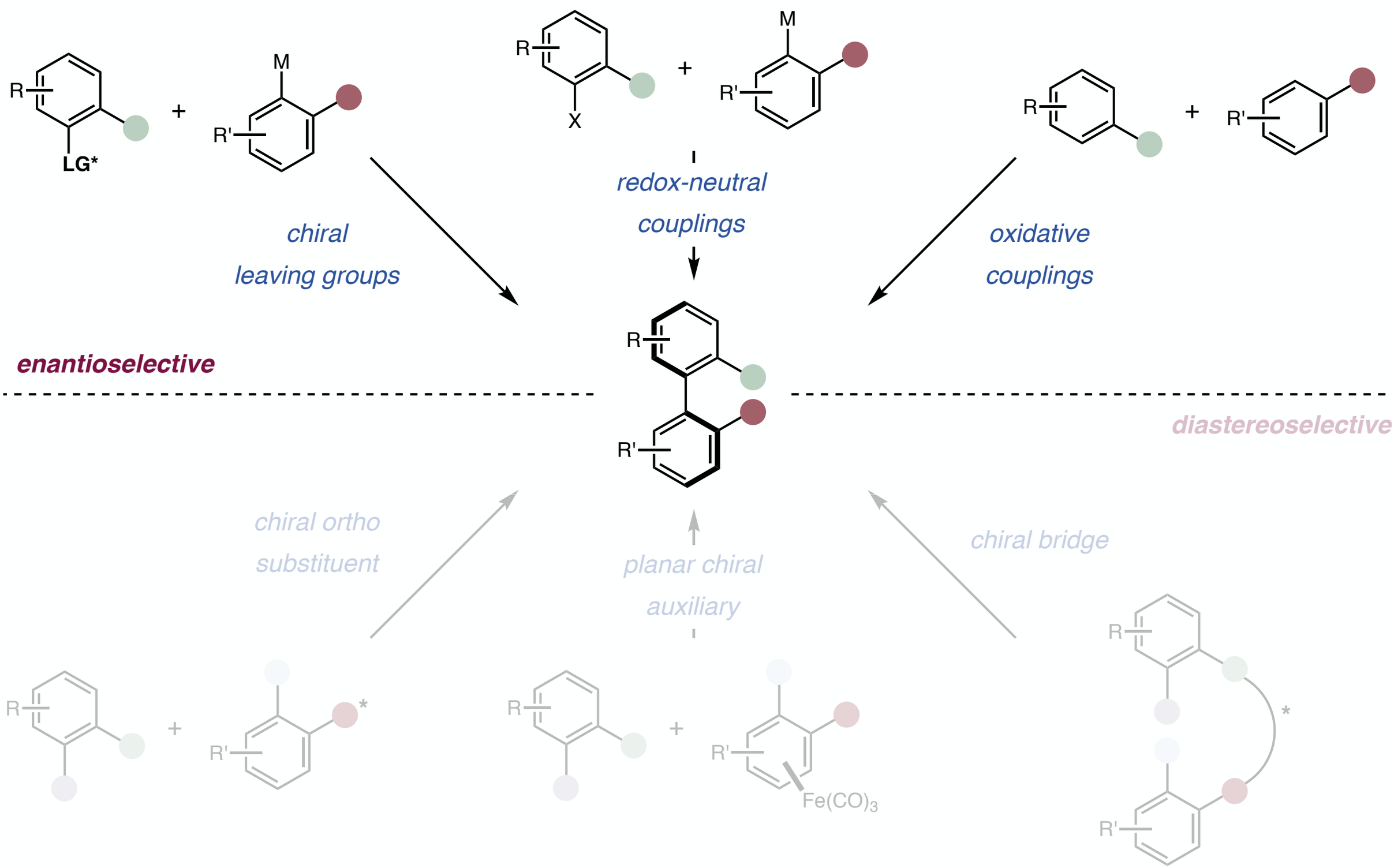



*(+)-korupensamine B*

*18 steps, 7% overall yield*

Huang, S.; Petersen, T. B.; Lipshutz, B. H. *J. Am. Chem. Soc.* **2010**, *132*, 14021.

# *Common Strategies in Atropisomer Synthesis*

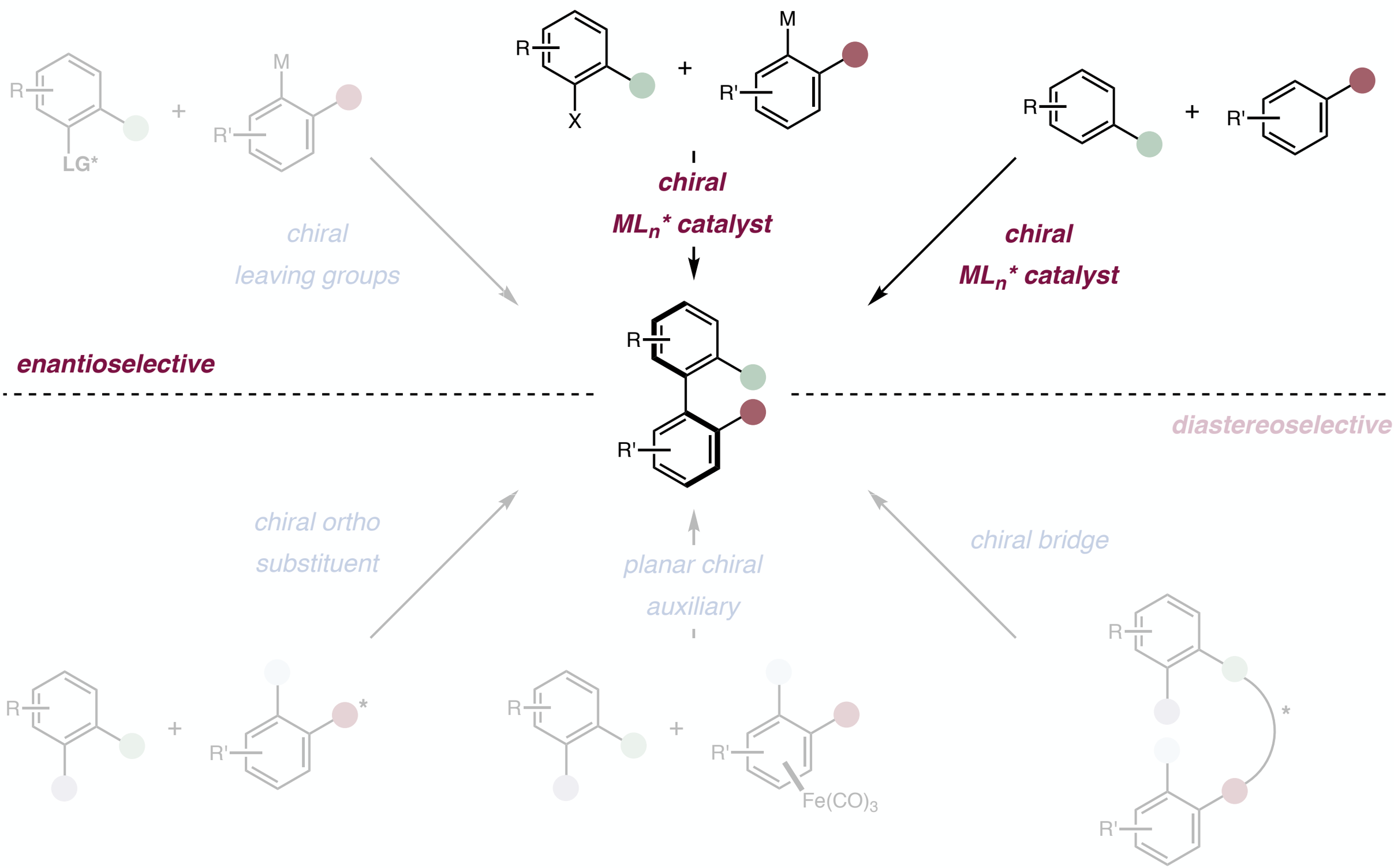




Zilate, B.; Castgrogiovanni, A.; Sparr, C. *ACS Catal.* **2018**, *8*, 2981.

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

# *Common Strategies in Atropisomer Synthesis*



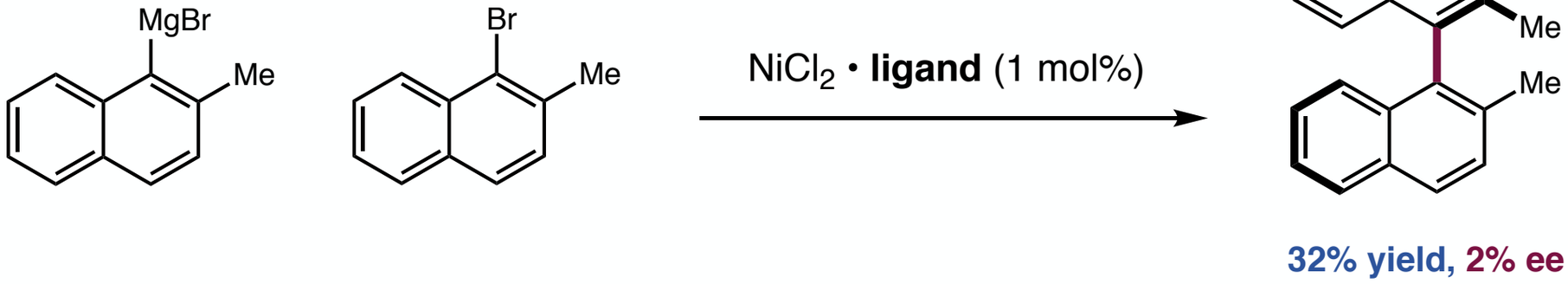


Zilate, B.; Castgrogiovanni, A.; Sparr, C. *ACS Catal.* **2018**, *8*, 2981.

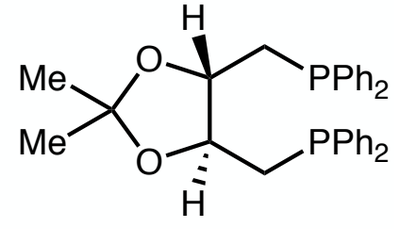
Bringmann, G.; Mortimer, A. J.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 5384.

# *Initial Success In Asymmetric Kumada Biaryl Synthesis*

*Three years after initial Kumada-Corriu reports (1975):*

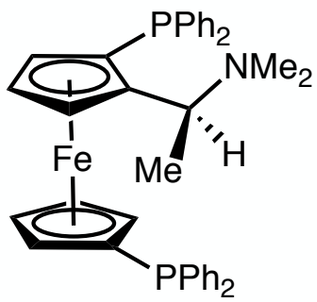



**32% yield, 2% ee**

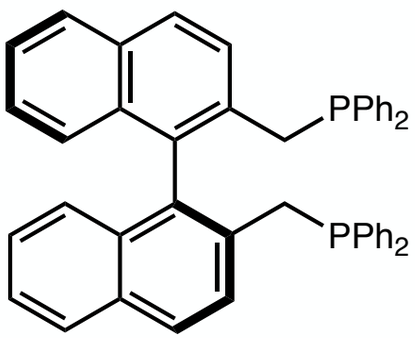



**DIOP**

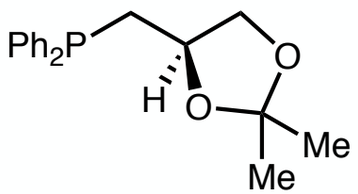
*Further ligand optimization was achieved over the next 14 years:*



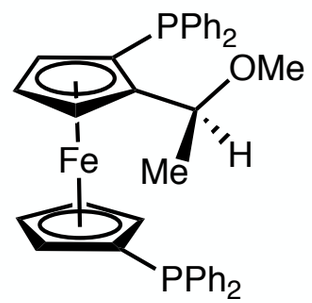

**5% ee**




**13% ee**




**40% yield, 50% ee**

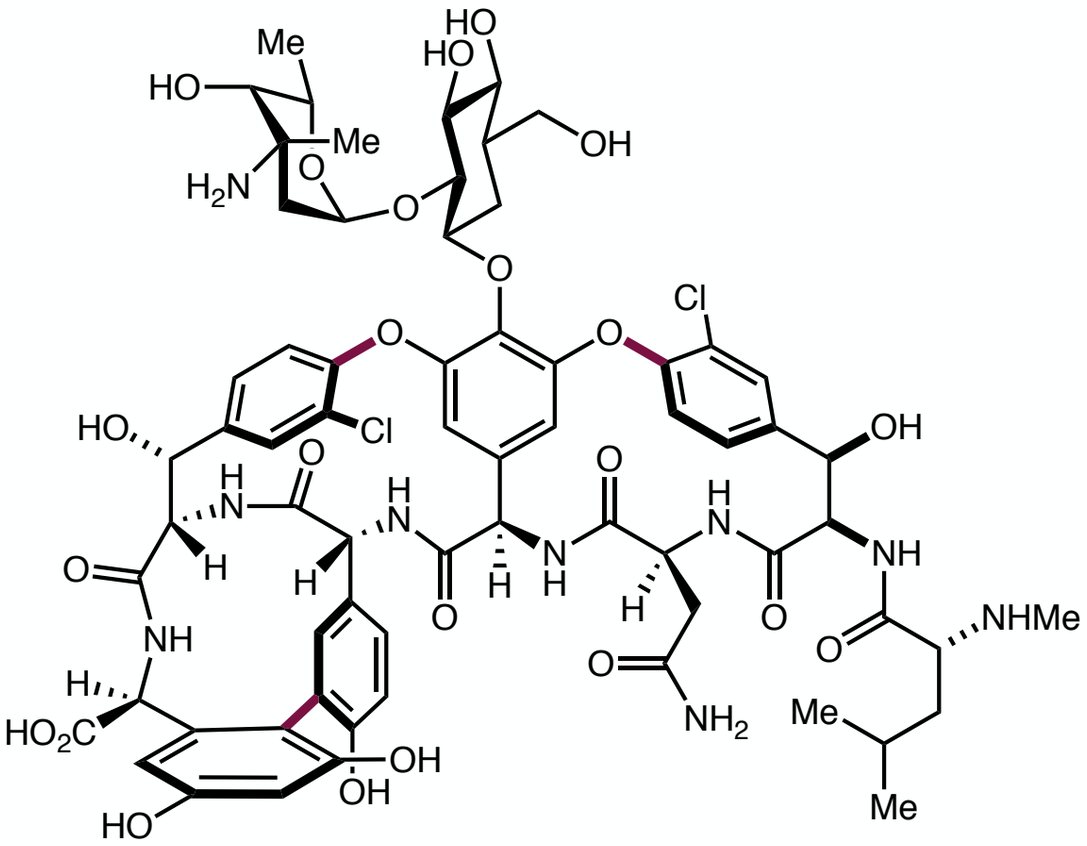



**69% yield, 95% ee**

***After these successes, no significant reports in redox-neutral cross-coupling over the next decade***

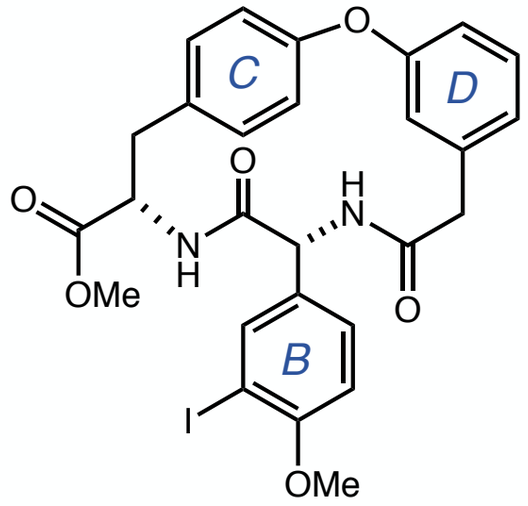

Tamao, K.; Minato, A.; Miyake, N.; Matsuda, T.; Kiso, Y. Kumada, M. *Chem. Lett.* **1975**, *4*, 133.
Hayashi, T.; Hayashizaki, K.; Kiyoi, T.; Ito, Y. *J. Am. Chem. Soc.* **1988**, *110*, 8153.
Hayashi, T.; Hayashizaki, K.; Ito, Y. *Tetrahedron Lett.* **1989**, *30*, 215.

# *Origins of Atroposelective Suzuki-Miyaura: Nicolau's Vancomycin Synthesis*

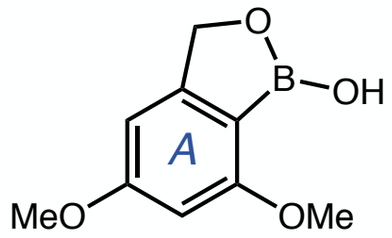


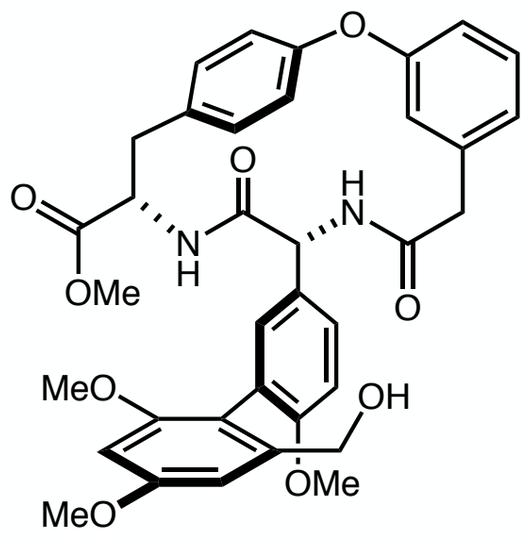
*Challenge - stereoselective synthesis of AB ring system in absence of bridging medium-sized ring*

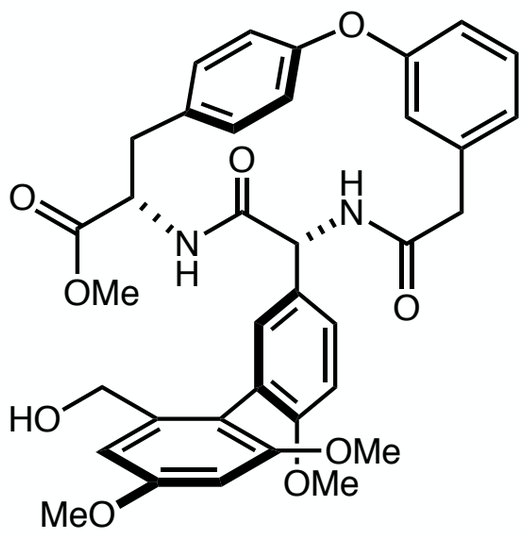
*Design plan for Suzuki-Miyaura:*



+



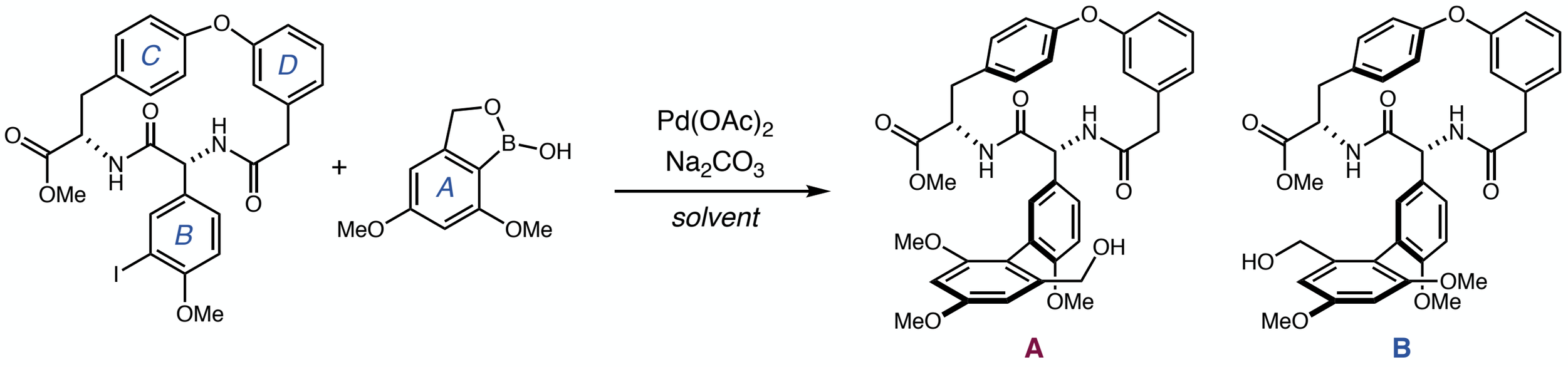




*Inherent bias for one atropisomer?*

Nicolaou, K. C.; Mitchell, H. J.; Jain, N. F.; Winssinger, N.; Hughes, R.; Bando, T. *Angew. Chem. Int. Ed.* **1999**, *1*, 240.

# *Origins of Atroposelective Suzuki-Miyaura: Nicolau's Vancomycin Synthesis*



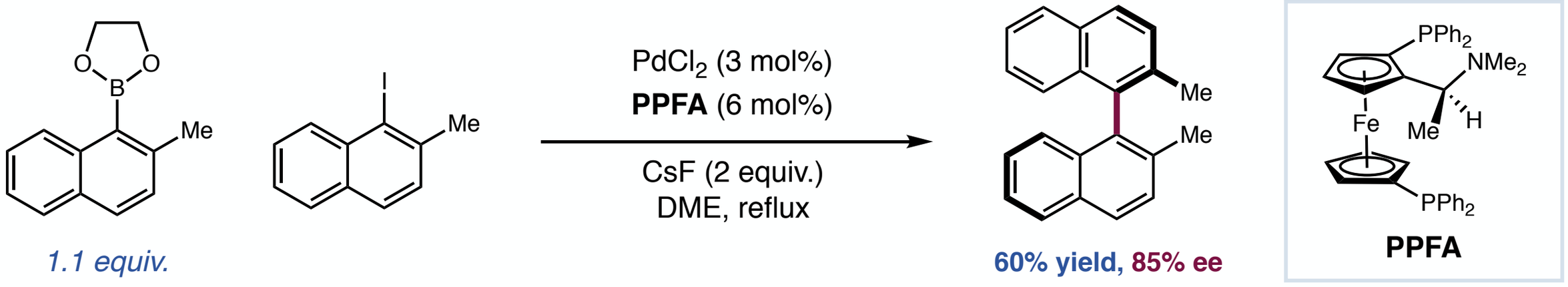

| entry | ligand | solvent | temp (°C) | time (h) | Yield (%) | Ratio (**A**:**B**) |
|---|---|---|---|---|---|---|
| 1 | $PPh_3$ | PhMe | 90 | 2 | 80 | 1:1 |
| 2 | BINAP | PhMe | 90 | 12 | trace | – |
| 3 | BINAP | THF | 65 | 12 | trace | – |
| 4 | (*S*)-BINAP | DMF | 80 | 8 | 60 | 2.3:1 |
| 5 | (*S*)-BINAP | PhMe:THF (1:1) | 70 | 5 | 40 | **>95:5** |
| 6 | (*R*)-BINAP | PhMe:THF (1:1) | 70 | 5 | 40 | **<5:95** |

*First report of catalyst-controlled stereoselective Suzuki-Miyaura biaryl coupling!*

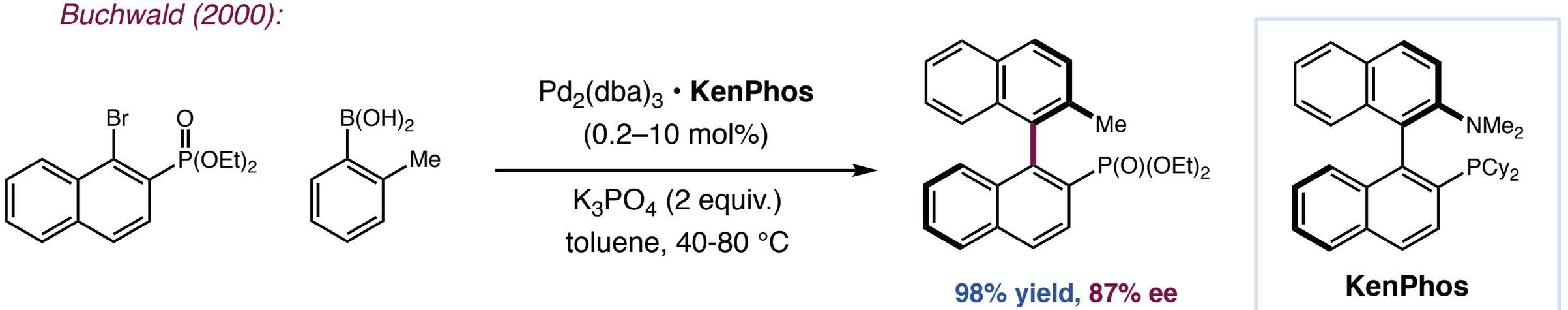
Nicolaou, K. C., et. al. *Chem. Eur. J.* **1999**, 5, 2584.

# *Expansion to Intermolecular Enantioselective Protocols*

*Cammidge (2000):*



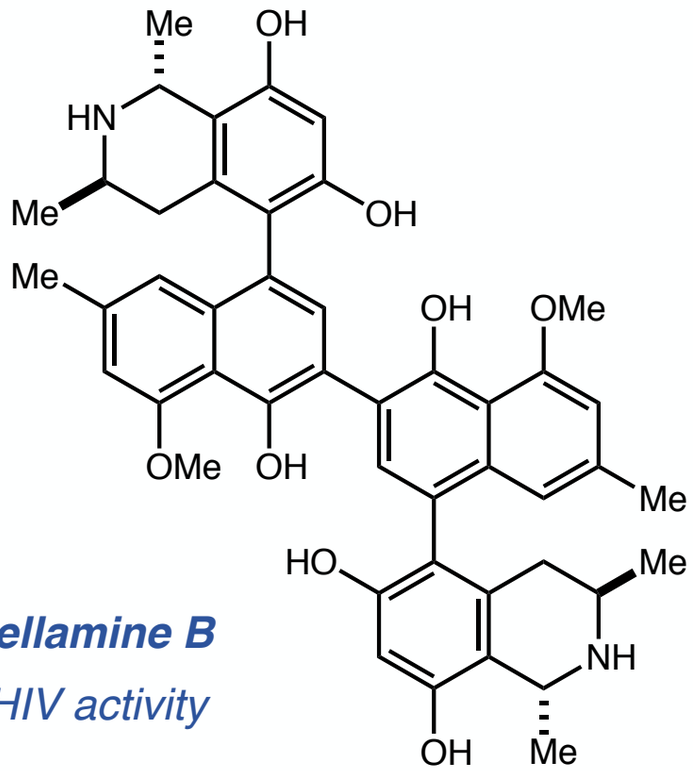

*Buchwald (2000):*





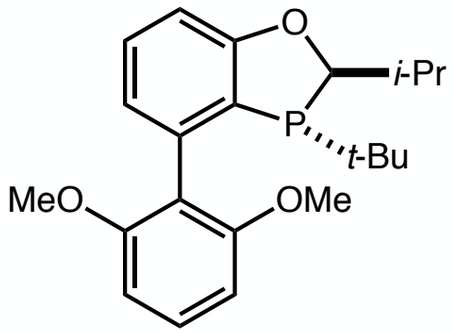
Cammidge, A. N.; Crépy, K. V. L. *Chem. Commun.* **2000**, 1723.
Yin, J. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 12051.

# *Application to Stereoselective Synthesis of Michellamine B (Tang, 2014)*

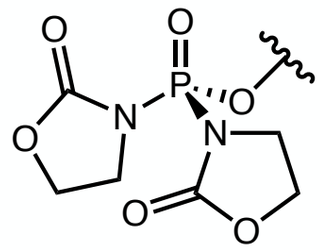



***Michellamine B***

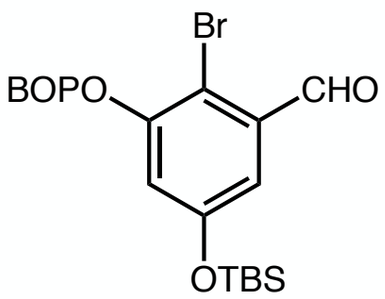
*anti-HIV activity*



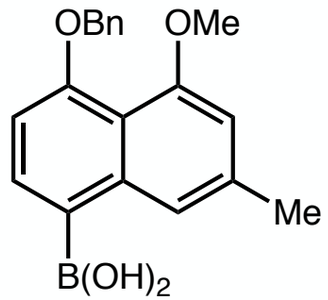

**ligand**




**BOPO–R**

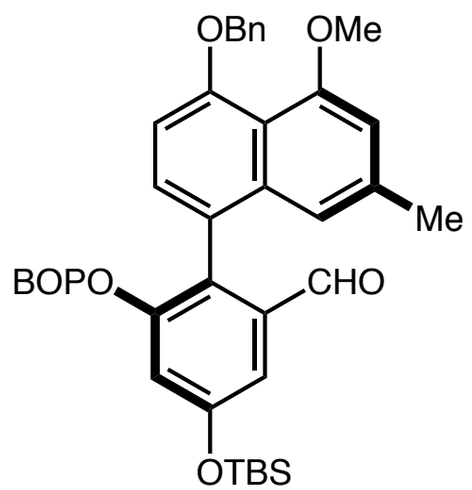



*1.1 equiv.*




$Pd(OAc)_2$ (1 mol%)
**ligand** (1.2 mol%)

$K_3PO_4$ (3 equiv.)
toluene/$H_2O$, 35 °C, 12 h



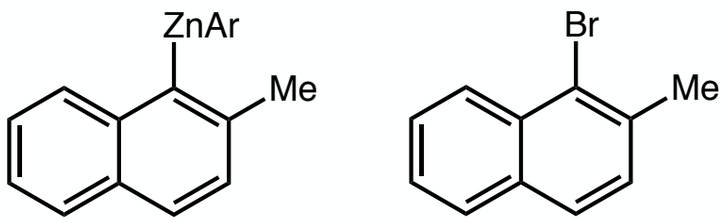

**96% yield, 93% ee**

*First asymmetric synthesis after 20+ years of investigation*

Xu, G.; Fu, W.; Liu, G. Senanayake, C. H.; Tang, W. *J. Am. Chem. Soc.* **2014**, *136*, 570.

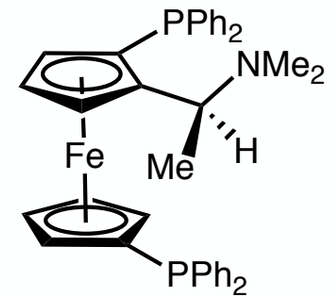
# *Expansion to Other Organometallic Nucleophiles*

*Espinet (2006):*



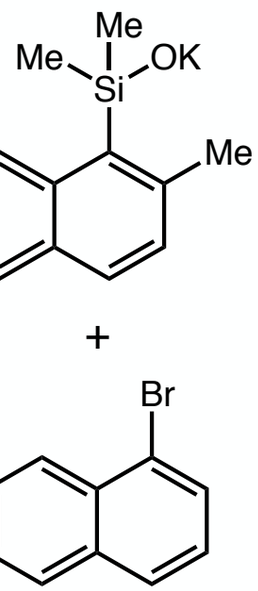

*1.5 equiv.*

**95% yield, 85% ee**



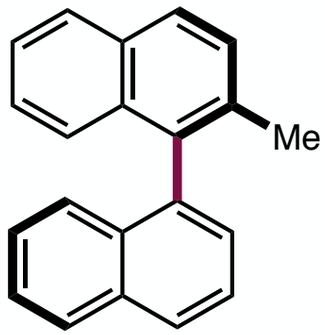

**PPFA**

*Denmark (2014):*

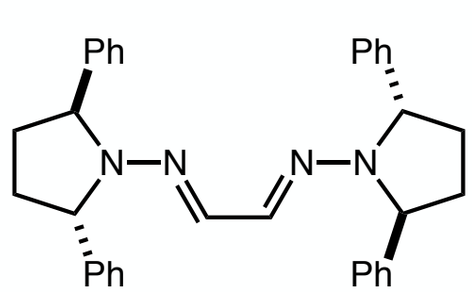



$Pd_2(dba)_3$ • **KenPhos**
(0.2–10 mol%)

$K_3PO_4$ (2 equiv.)
toluene, 40-80 °C




**98% yield, 87% ee**



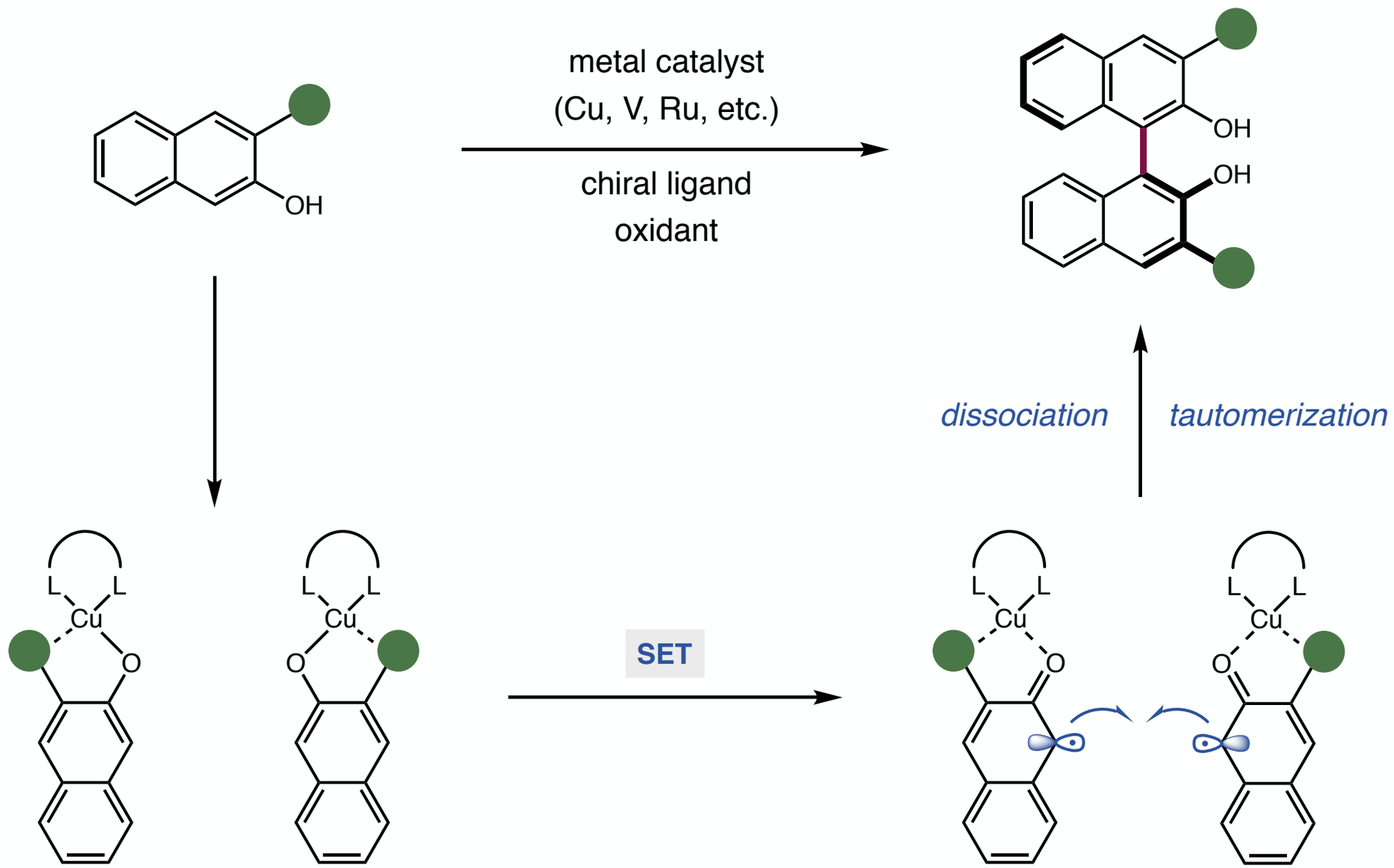

**ligand**

*Highly extensive investigation of mechanistic considerations in atroposelective redox-netural coupling*

***Swapping halide + silanol = identical ee, suggests stereodetermining reductive elimination (supported by DFT)***

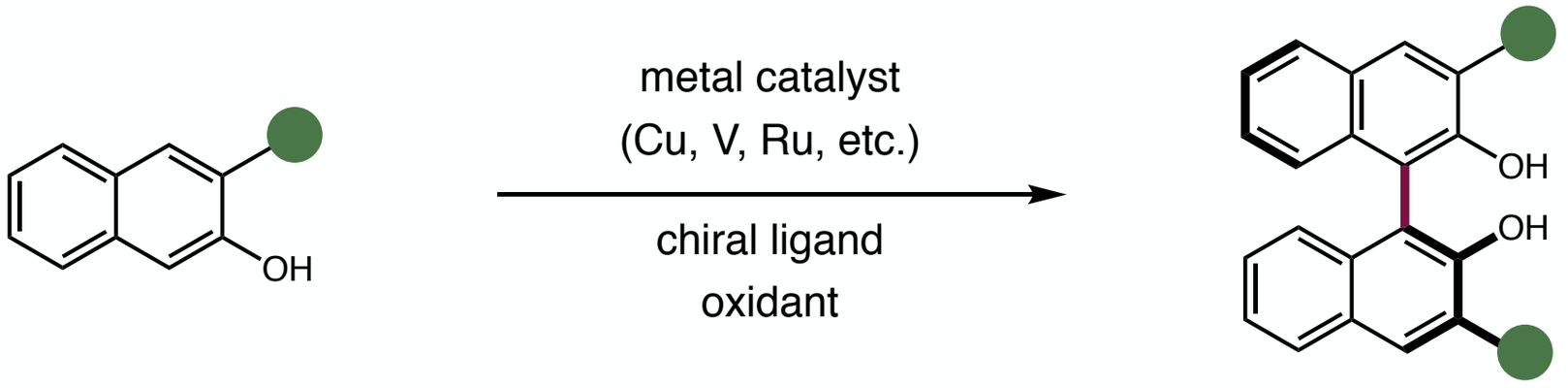

Genov, M.; Fuentes, B.; Espinet, P.; Pelaz, B. *Tetrahedron: Asymmetry* **2006**, *17*, 2593.
Denmark, S. E.; Chang, W-T. T.; Houk, K. N.; Liu, P. *J. Org. Chem.* **2015**, *80*, 313.

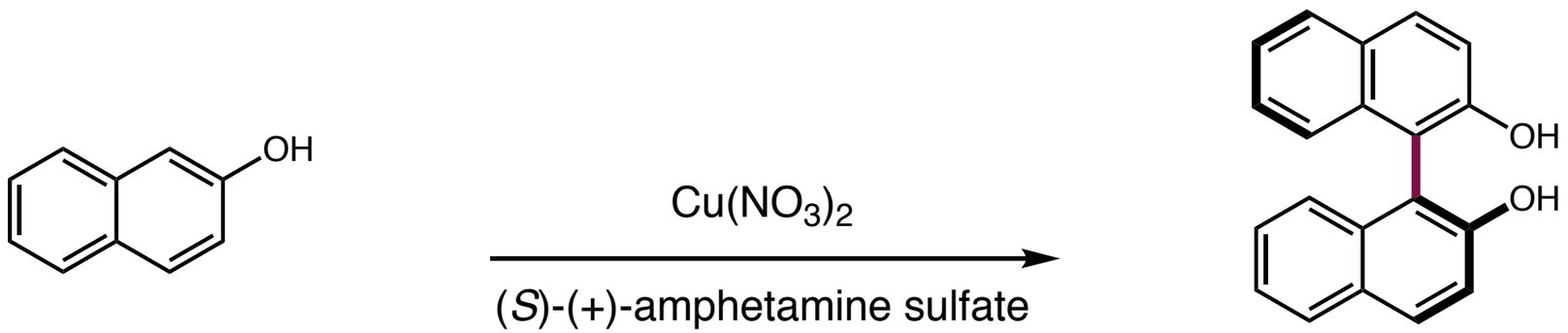
# *Oxidative Couplings: Fundamentals of Radical Approaches*




Zilate, B.; Castgrogiovanni, A.; Sparr, C. *ACS Catal.* **2018**, *8*, 2981.
Bringmann, G.; Mortimer, A. J.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 5384.

# *Oxidative Couplings: Fundamentals of Radical Approaches*



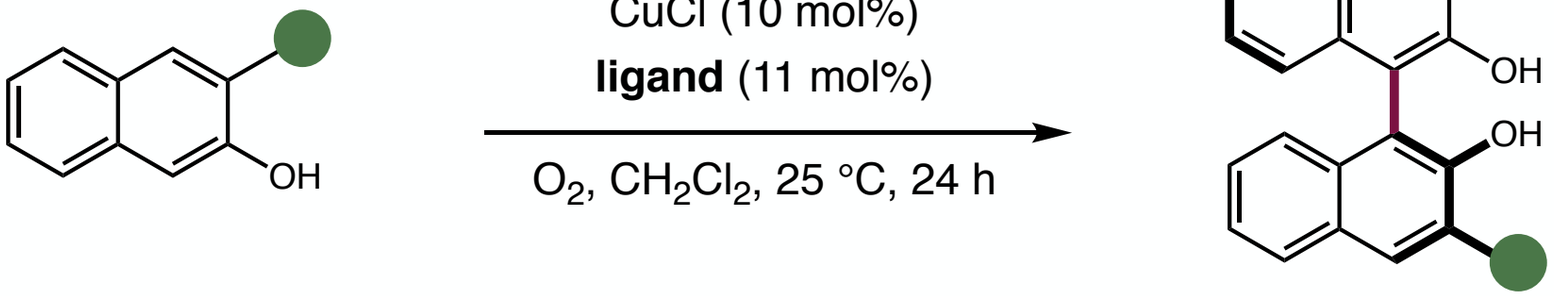

*2 equiv.*

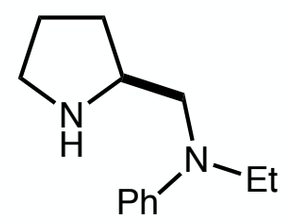
*(S)-BINOL*

**85% yield, 95% ee**

Brussee, J.; Jansen, A. C. A. *Tetrahedron Lett.* **1983**, *24*, 3261.

# *Directing Groups Enhance Efficiency of Oxidative Couplings*



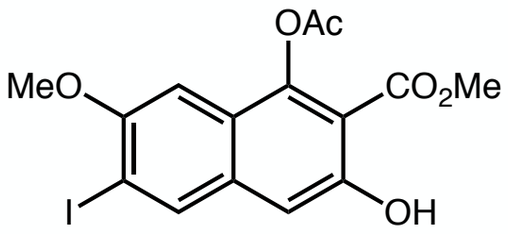




**ligand**

|  | yield (%) | ee (%) |
|---|---|---|
| $CO_2Me$ | 85 | 78 |
| $CO_2Et$ | 77 | 73 |
| $CO_2Bn$ | 77 | 76 |
| $CO_2$*t*-Bu | 69 | 58 |
| H | 89 | 17 |
| *i*-Pr | 58 | 5 |
| OBn | 95 | 24 |

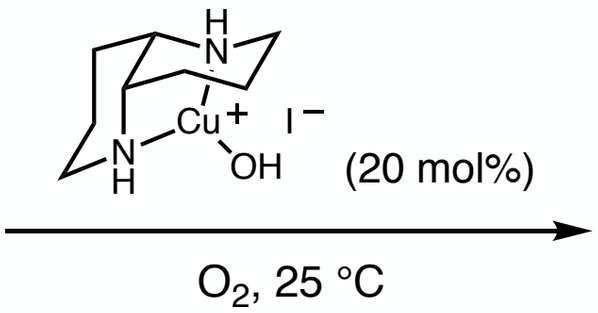
Nakajima, M.; Kanayama, K.; Miyoshi, I.; Hashimoto, S. *Tetrahedron* **1995**, *36*, 9519.

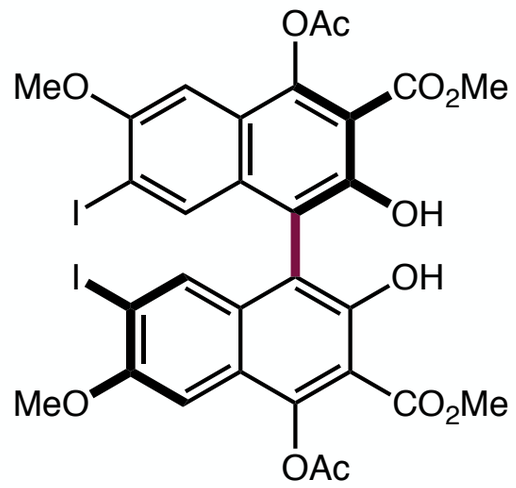
# *Kozlowski: Divergent Perylenequinone Syntheses*




*preparation:*

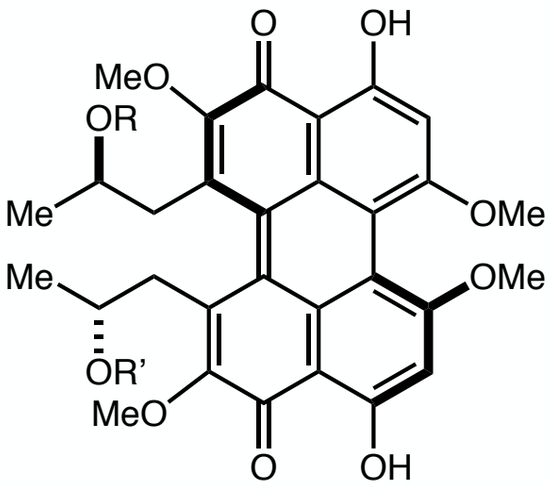
*33% over 5 steps*



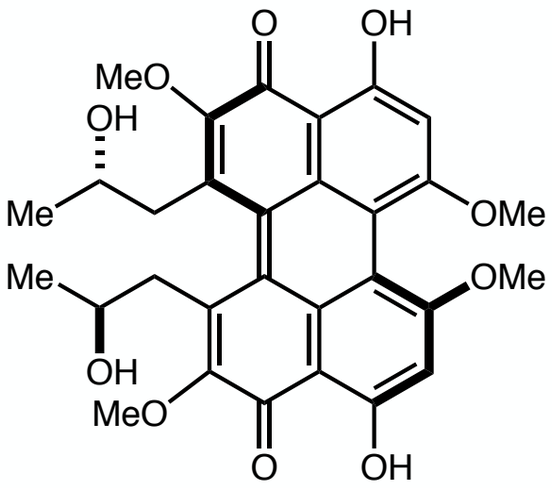




**80% yield, 81% ee**
**(>99% ee after trituration)**

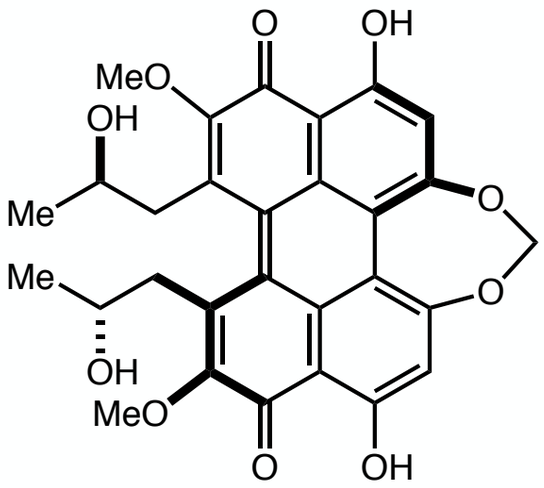
***Synthetic intermediate to:***



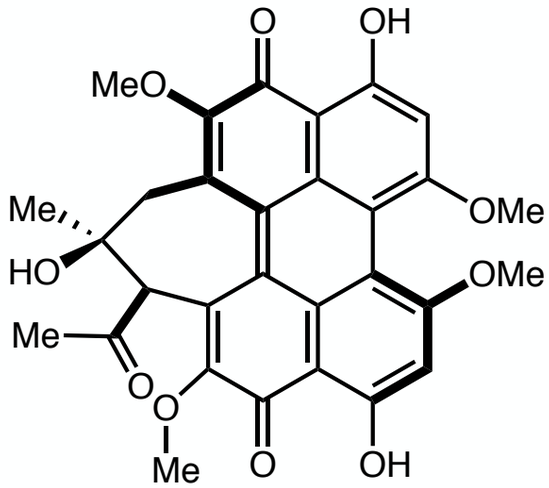

*(–)-Calphostins A-D*




*(–)-Phleichrome*



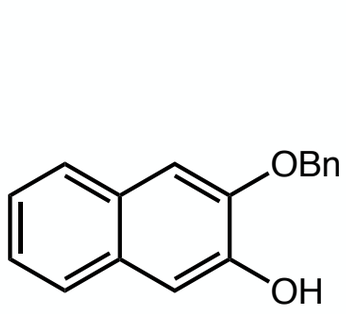

*Cercosporin*



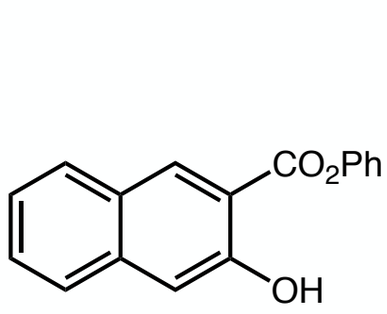

*Hypocrellin*

Morgan, B. J.; Dey, S.; Johnson, S. W.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2009**, *131*, 9413.

# *Achieving Cross-Selectivity in Oxidative Heterocouplings*



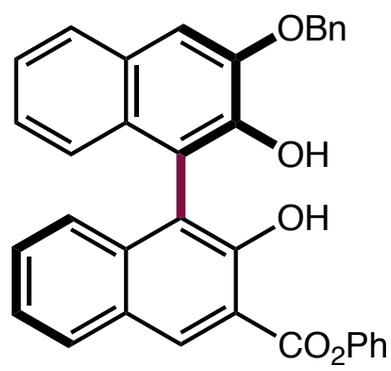

*more electron-rich*



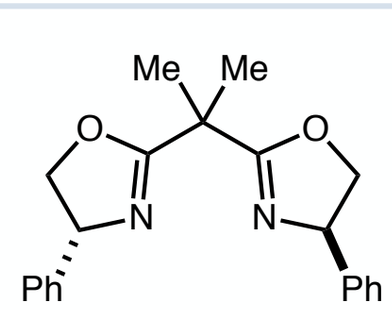

*better chelation*

CuCl (20 mol%)
**PhBOX** (6 mol%)

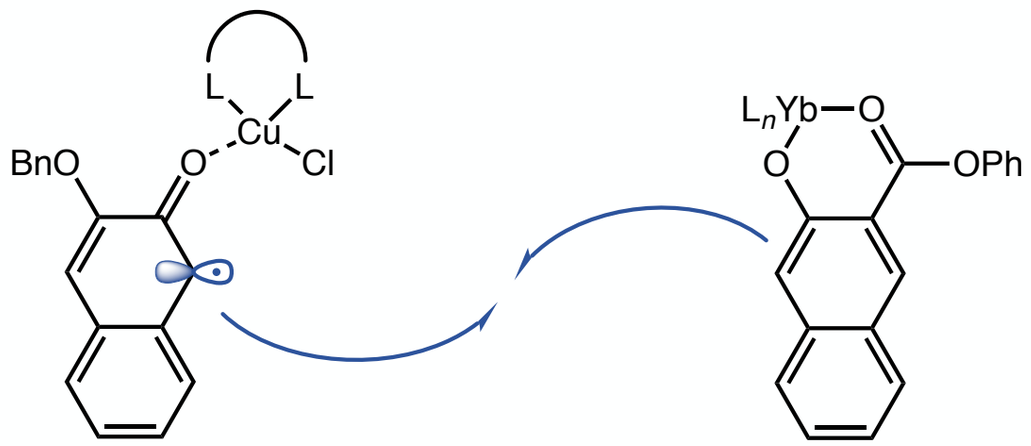
$Yb(OTf)_3$ (10 mol%)
$O_2$, THF, –20 °C




**95% yield, 85% ee**



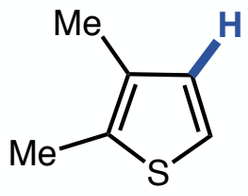

**PhBOX**

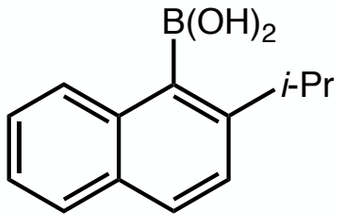



*Electronic differentiation required for cross-selectivity*

Habaue, S.; Temma, T.; Sugiyama, Y.; Yan, P. *Tetrahedron Lett.* **2007**, *48*, 8595.

# *Progress in Oxidative C–H Arylation*



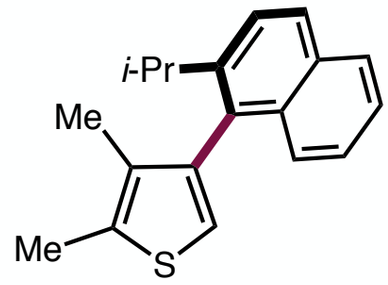




$Pd(OAc)_2$ (10 mol%)

**$L_1$ or $L_2$** (10 mol%)

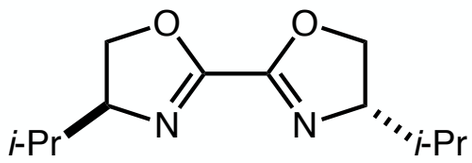
TEMPO (4 equiv.) or FePc (5 mol%)

*n*-PrOH or DMA, 70 °C

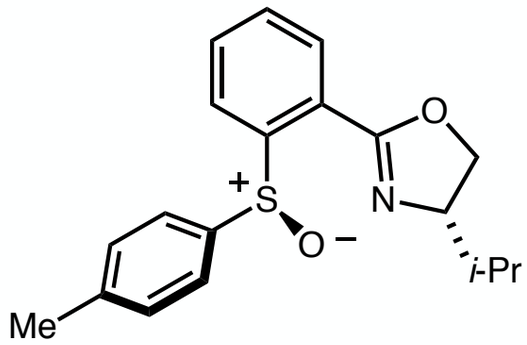



**$L_1$: 27% yield, 72% ee**

**$L_2$: 61% yield, 61% ee**




**$L_1$**

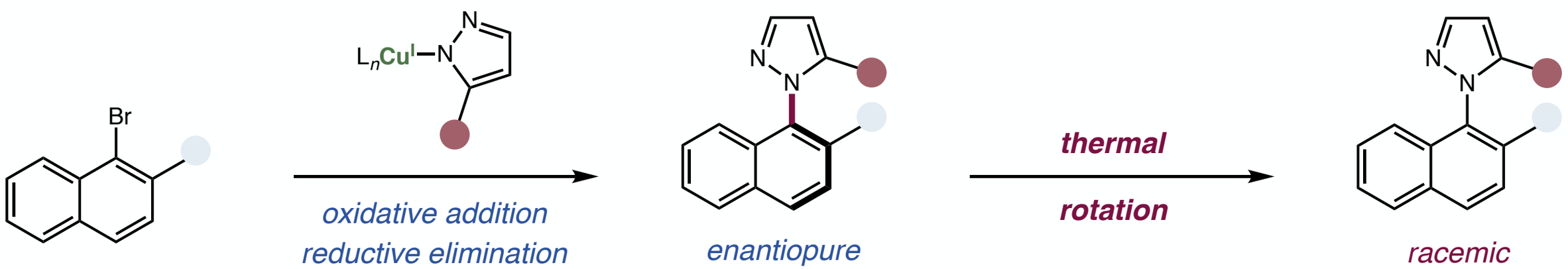



**$L_2$**

*Overall, underdeveloped strategy, requires substantial ligand development*

Yamaguchi, K.; Kondo, H.; Yamaguchi, J.; Itami, K. *Chem. Sci.* **2013**, *4*, 3753.

# *Ullmann-Goldberg: An Elusive Atroposelective Protocol*

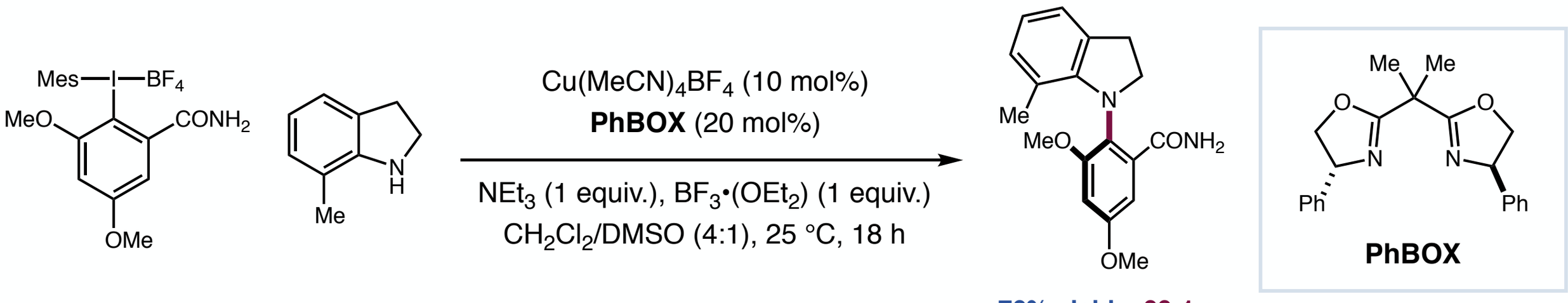



*More established than Buchwald-Hartwig for intramolecular, substrate-controlled cases (diastereoselective)*

***Forcing thermal conditions have prevented intermolecular utility***

Frey, J.; Malekafzali, A.; Delso, I.; Choppin, S.; Colobert, F.; Wencel-Delord, J. *Angew. Chem. Int. Ed.* **2020** *(pre-print)*.

# *The First Atroposelective Intermolcular Ullmann-Goldberg (2020)*




**76% yield, >99:1 er**

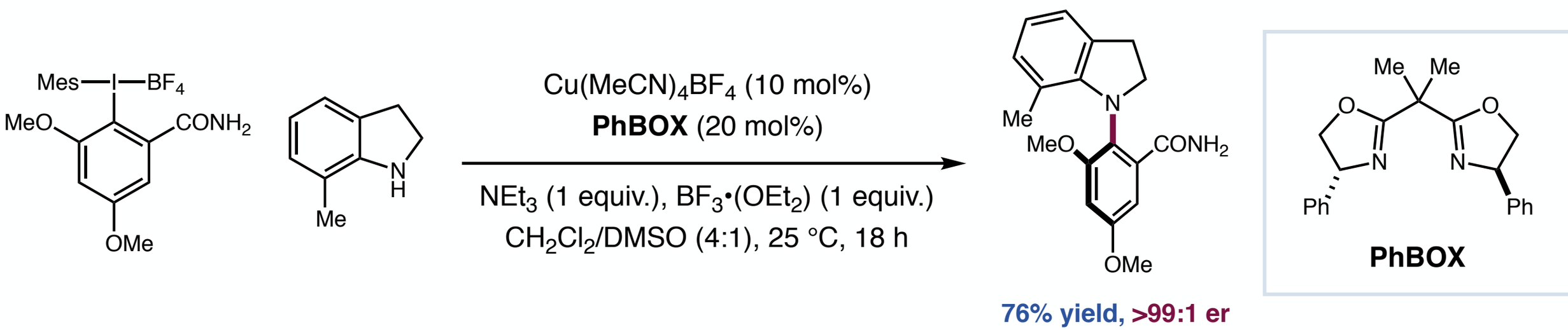
*Requirements:*

- *indoline nucleophiles*

- *iodonium must contain ortho-amide substituent*

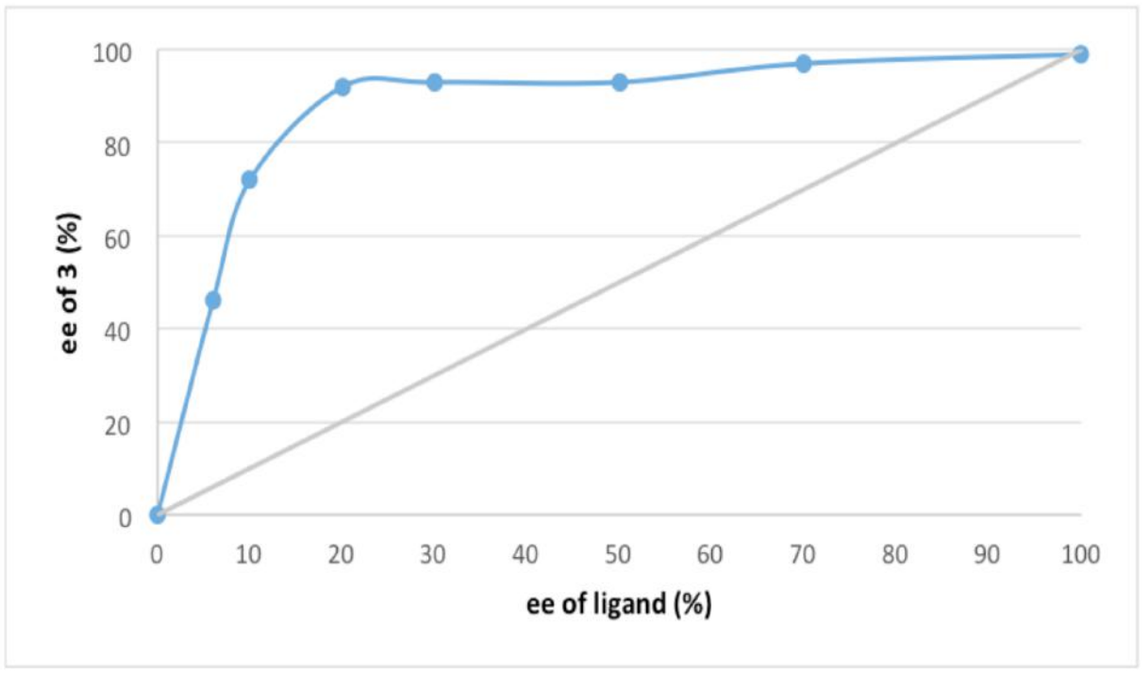
Frey, J.; Malekafzali, A.; Delso, I.; Choppin, S.; Colobert, F.; Wencel-Delord, J. *Angew. Chem. Int. Ed.* **2020** *(pre-print)*.

# *The First Atroposelective Intermolcular Ullmann-Goldberg (2020)*




**76% yield, >99:1 er**

***a full mechanistic investigation is still underway***

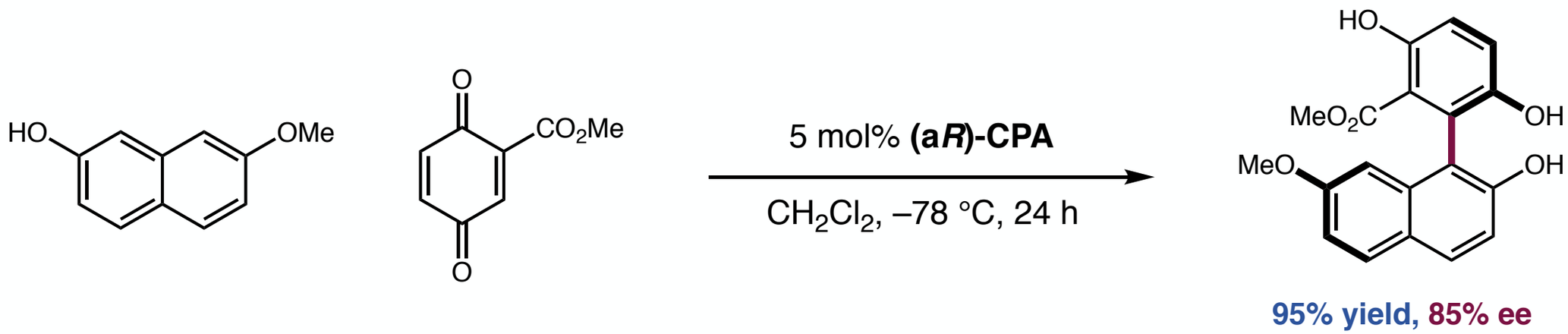


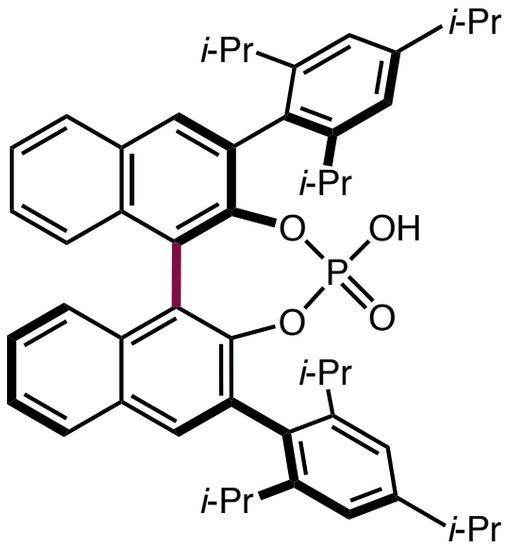

*Noteworthy that these Cu catalysts are exceptionally active for C–N coupling*

*Among strongest positive non-linear effects observed in asymmetric copper catalysis*

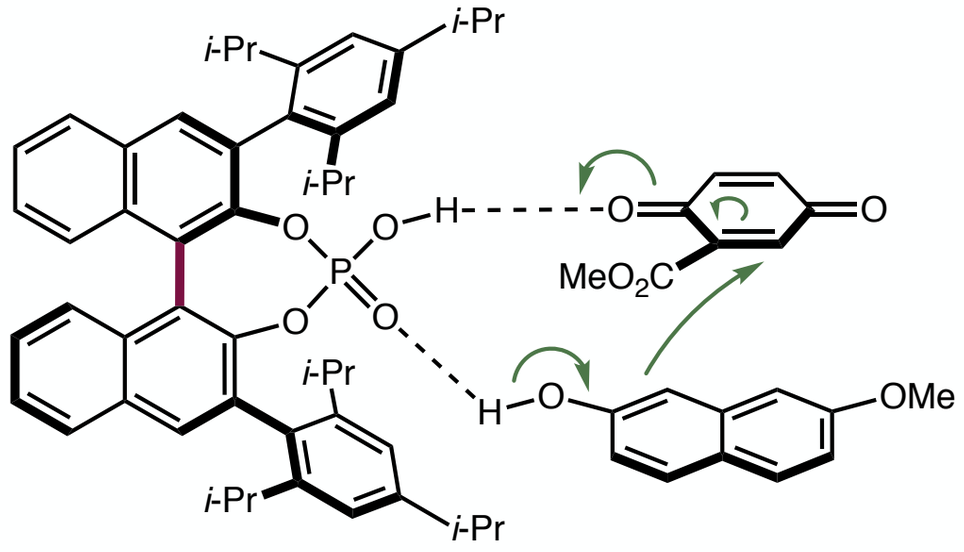
Frey, J.; Malekafzali, A.; Delso, I.; Choppin, S.; Colobert, F.; Wencel-Delord, J. *Angew. Chem. Int. Ed.* **2020** *(pre-print)*.

# *Organocatalytic Point-to-Axial Chirality Transfer in Oxidative Coupling*




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



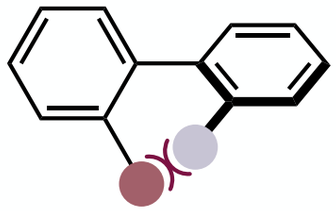


Chen, Y.-H.; Cheng, D.-J.; Zhang, J.; Wang, Y.; Liu, X.-Y.; Tan, B. *J. Am. Chem. Soc.* **2015**, *137*, 15062.

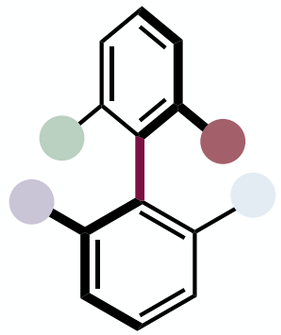
Wang, J.-Z.; Zhou, J.; Xu, C.; Sun, H.; Kürti, L. s.; Xu, Q.-L. *J. Am. Chem. Soc.* **2016**, *138*, 5202.

# *Outline*

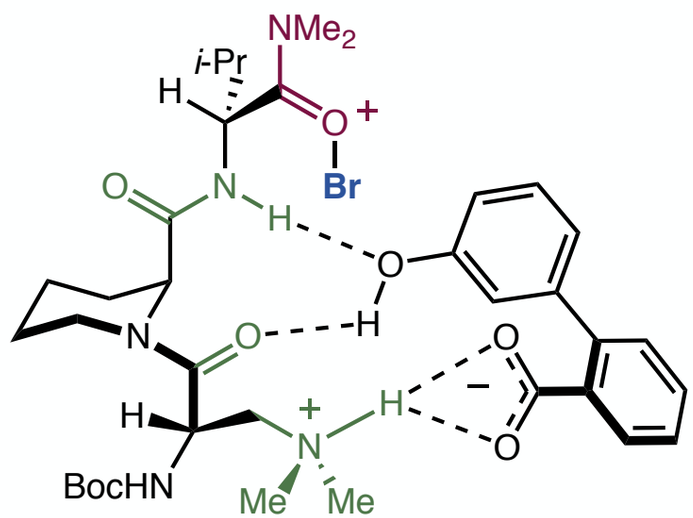
- Introduction and General Considerations
  - Discovery and fundamentals
  - Contributions to rotational barriers
  - Pharmaceutical considerations



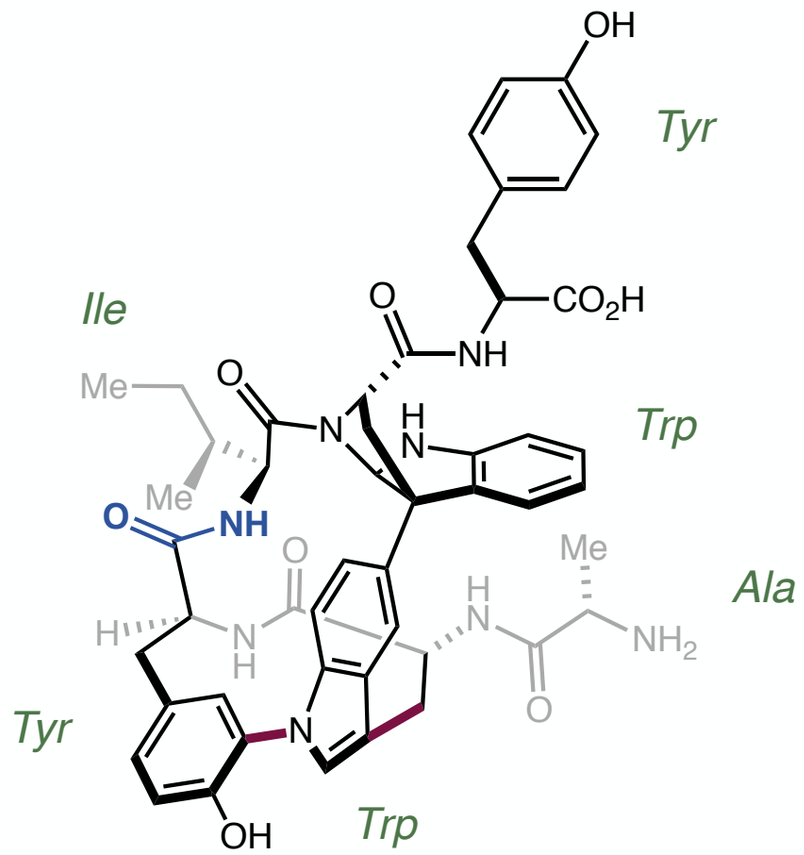
- Methods of (Catalytic) Synthesis
  - Diastereoselective methods
  - Dynamic kinetic resolutions and desymmetrization
  - Redox-neutral cross-oupling
  - Oxidative cross-oupling



- Applications
  - Case Study: Tryptorubin A



# *Atropospecific Total Synthesis of Tryptorubin A*




***Tryptorubin A***

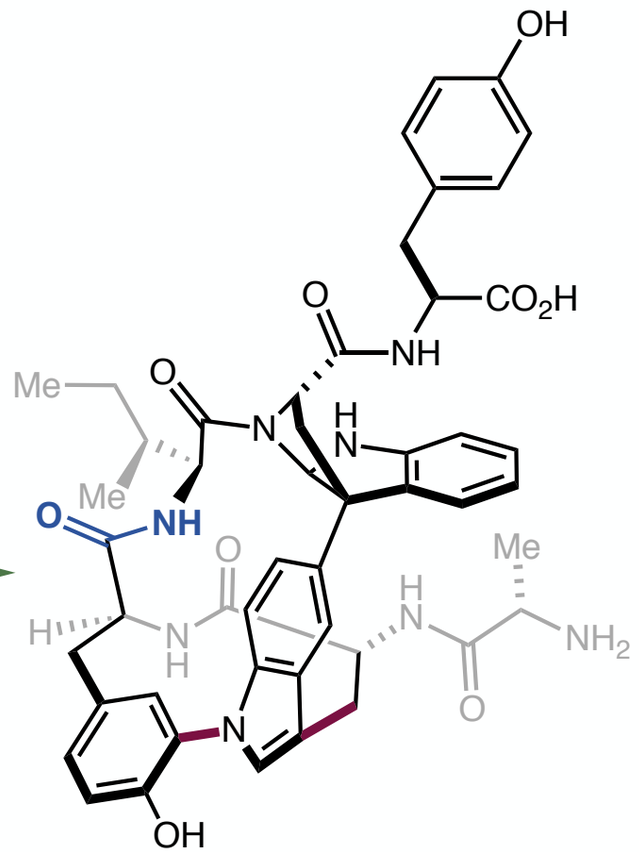
*peptidic indole alkaloid*

*unknown biological activity*

Reisberg, S. H.; Gao, Y.; Walker, A. S.; Helfrich, E. J. N.; Clardy, J.; Baran, P. S. *Science* **2020**, *367*, 458.

# *Atropospecific Total Synthesis of Tryptorubin A*

*First approach: late-stage amide coupling should enable diastereoselective macrocyclization*




***Tryptorubin A***

*peptidic indole alkaloid*

*unknown biological activity*

*Original structural disclosure: limited consideration of macrocyclic topology*

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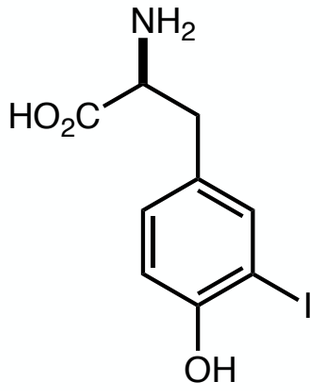
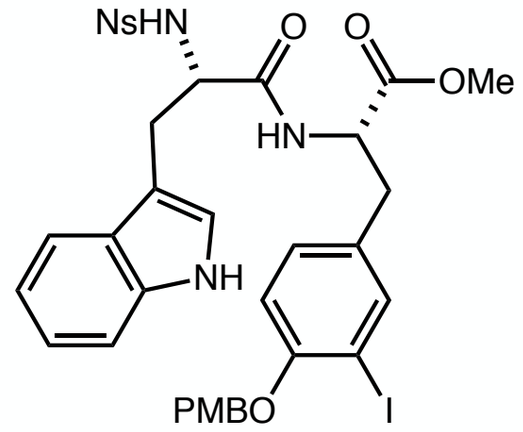



1. AcCl, MeOH *(quant.)*
2. PMBOH, DIAD, $PBu_3$ *(81%)*

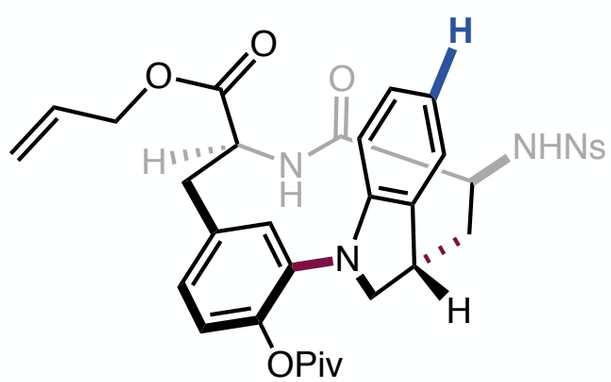
3. NsTrp-OH, HATU, DIPEA, DMF *(91%)*




*prepared in 5 steps*

4. CuI/L (cat.)
$Cs_2CO_3$, LiOH
THF/$H_2O$/dioxane;
then allyl-OH, HCl
*(61%)*

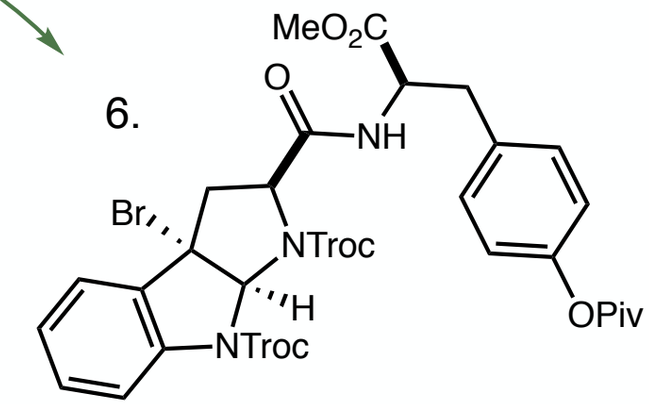
5. PivCl, $NEt_3$;
then TFA, $Et_3SiH$
DCM *(99%)*

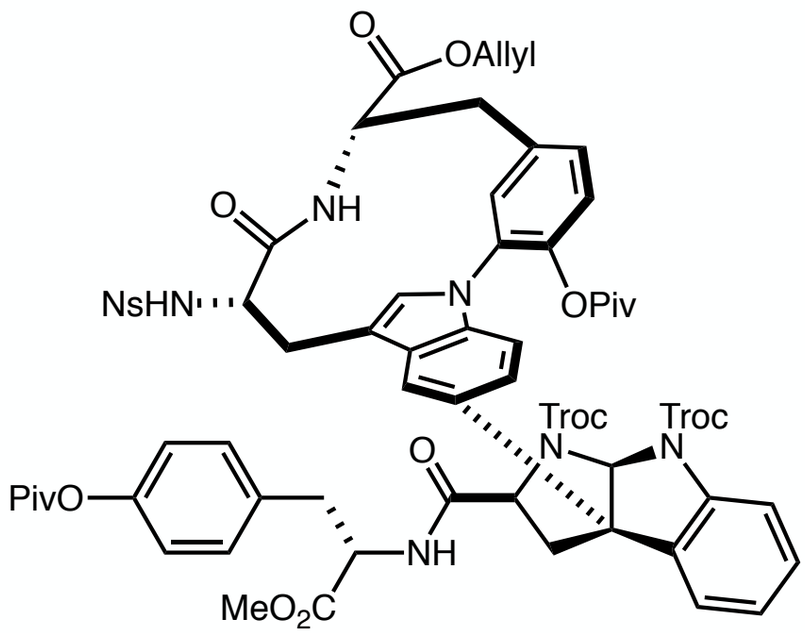



7. DDQ, EtOAc *(88%)*

$AgSbF_6$, DTBMP *(55%)*

6.

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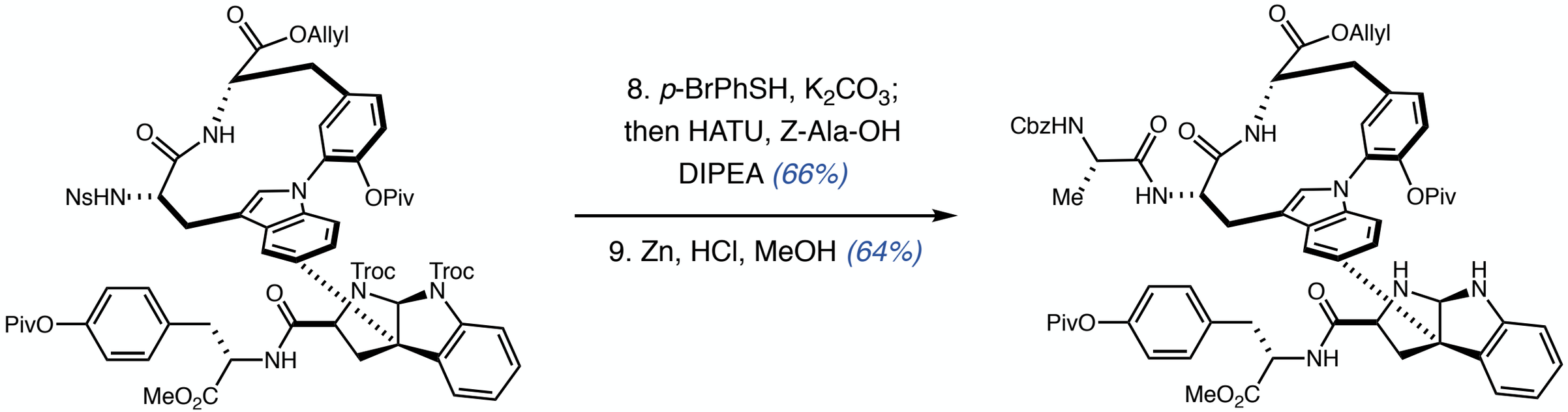


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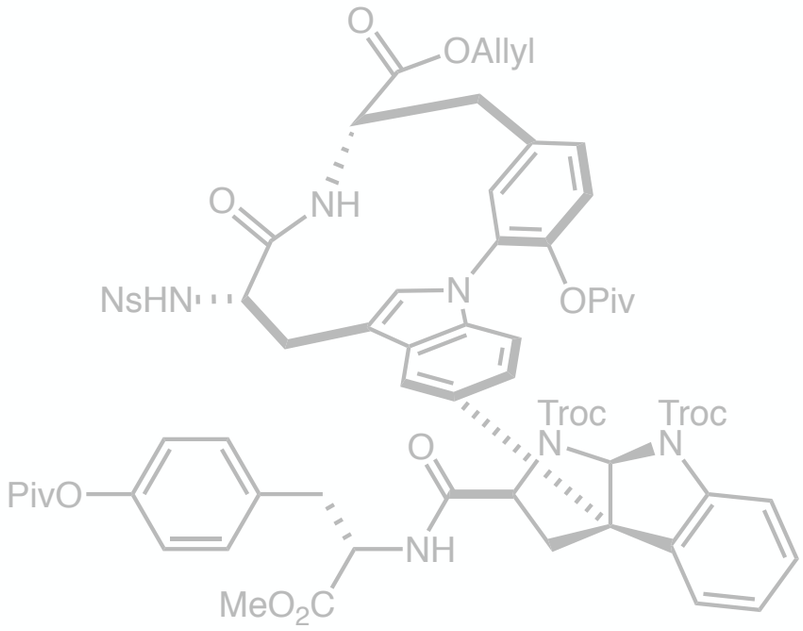
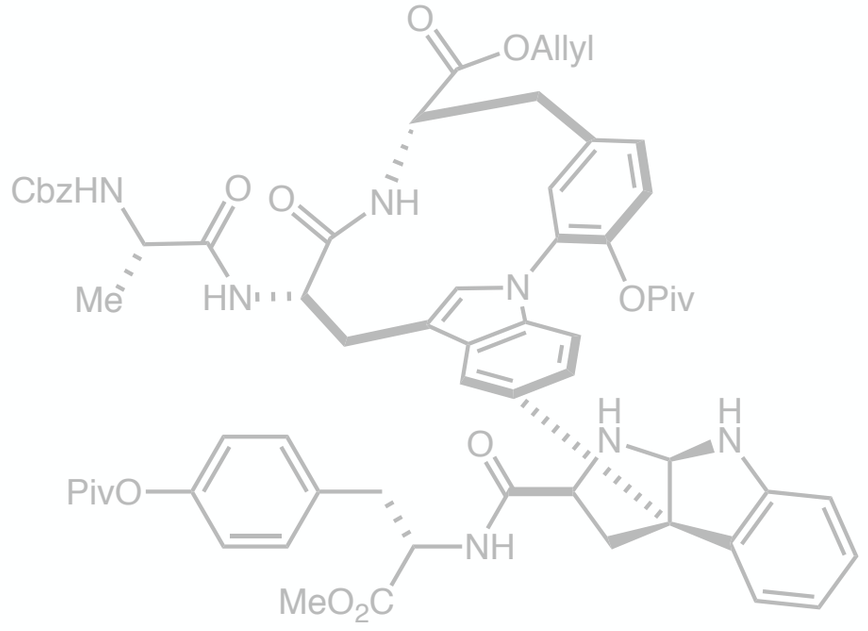


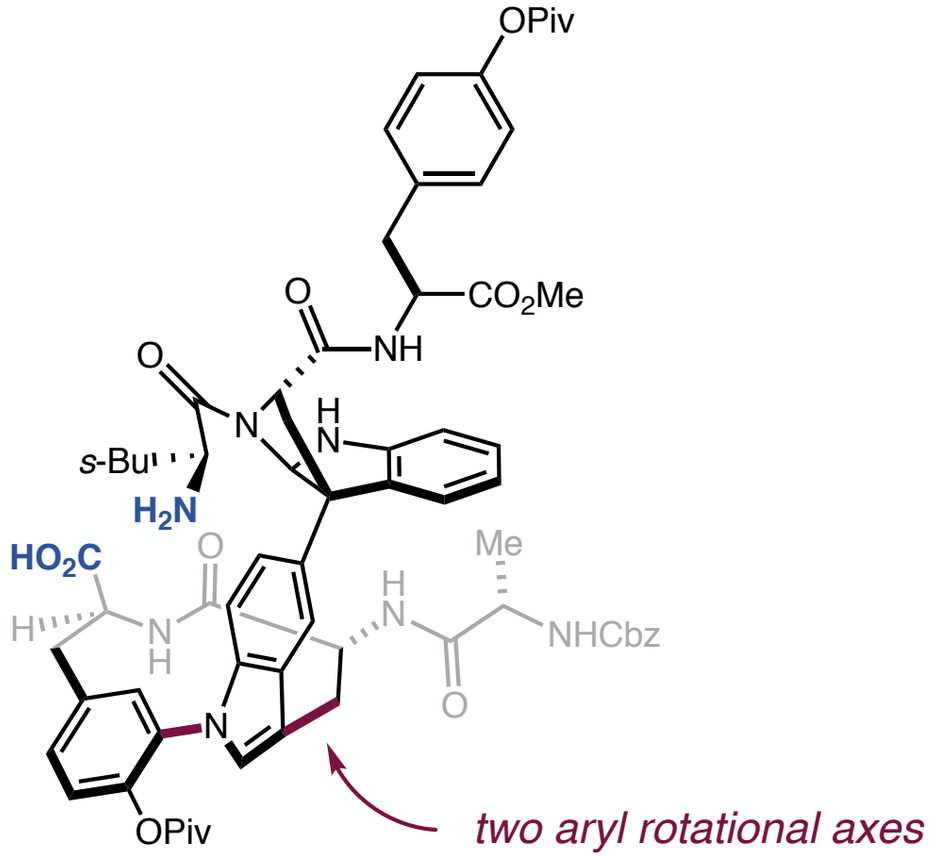

8. *p*-BrPhSH, $K_2CO_3$;
then HATU, Z-Ala-OH
DIPEA *(66%)*

9. Zn, HCl, MeOH *(64%)*




10. Boc-Ile-OH, HATU,
DIPEA, DCM;

then morpholine, $Pd(PPh_3)_4$;
then TFA *(30%)*




*macrocyclization disfavored*

*two aryl rotational axes*

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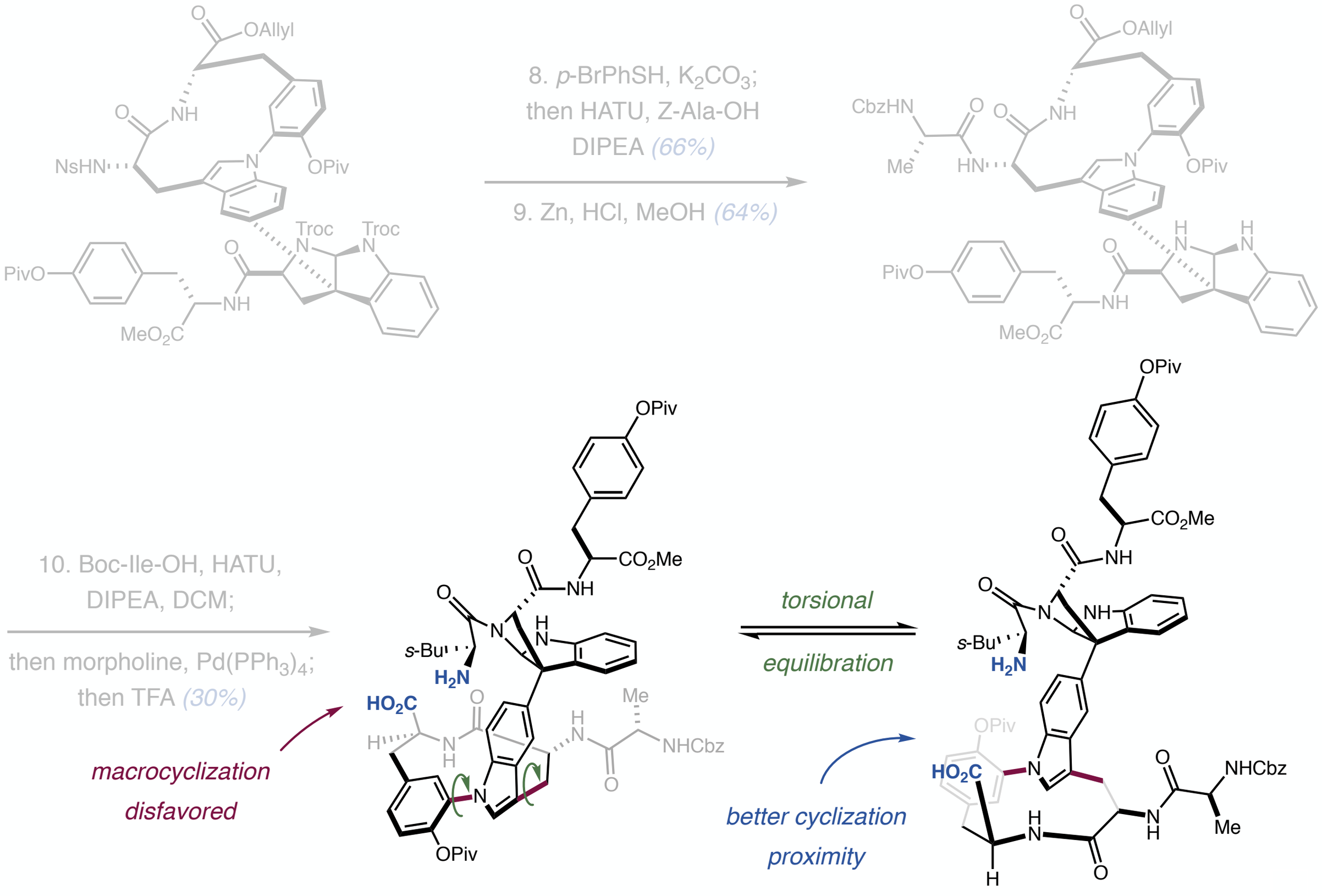


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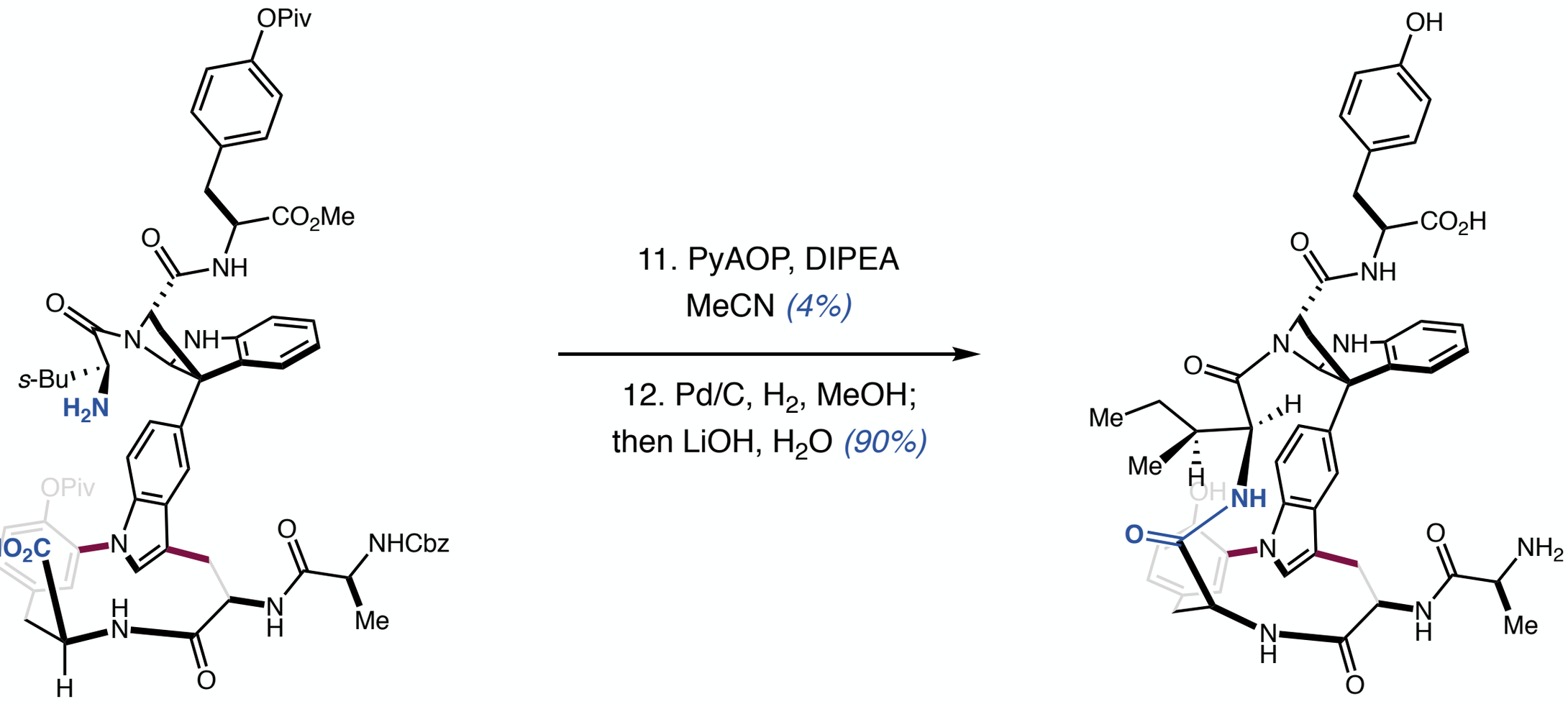


*characterization data inconsistent with reference - synthesis was atroposelective, but absolute stereochemistry wrong!*

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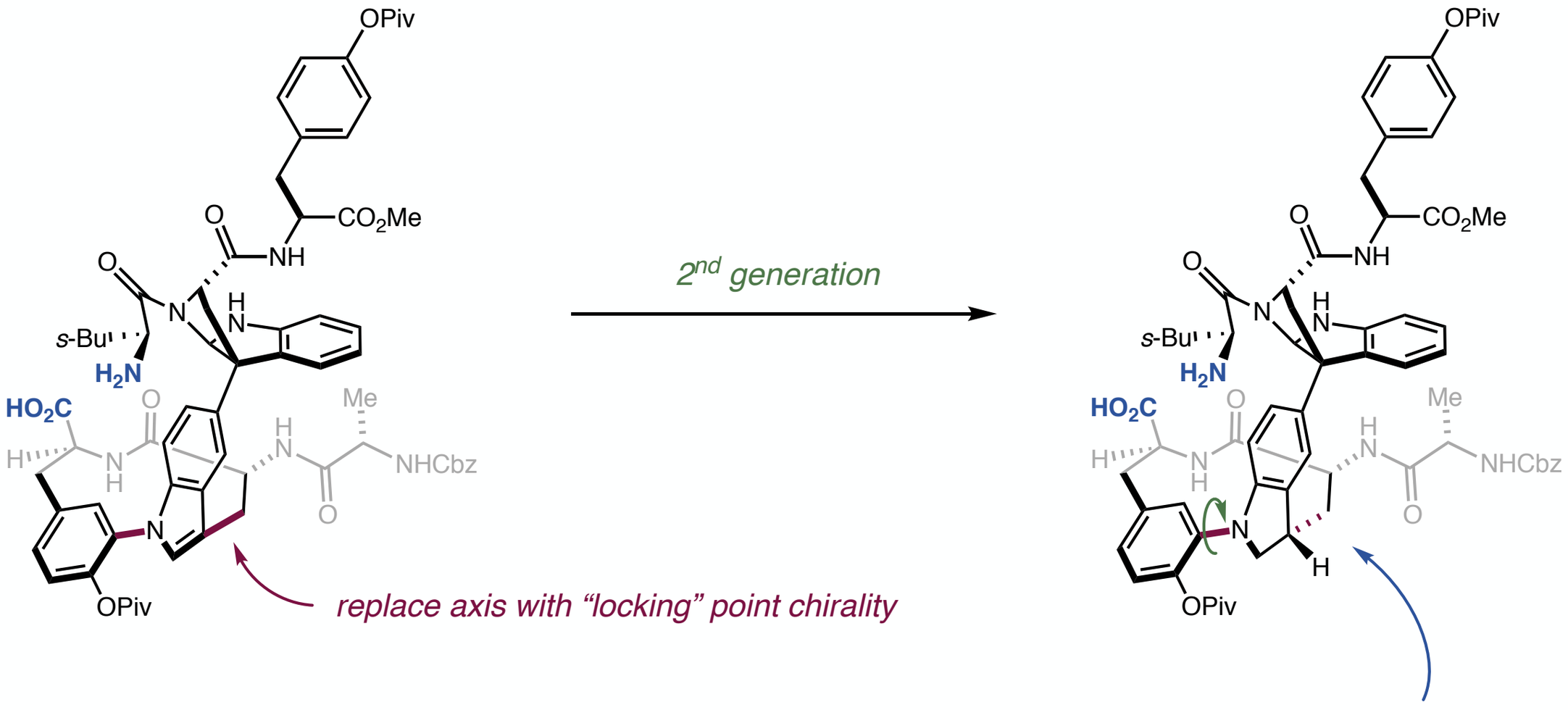


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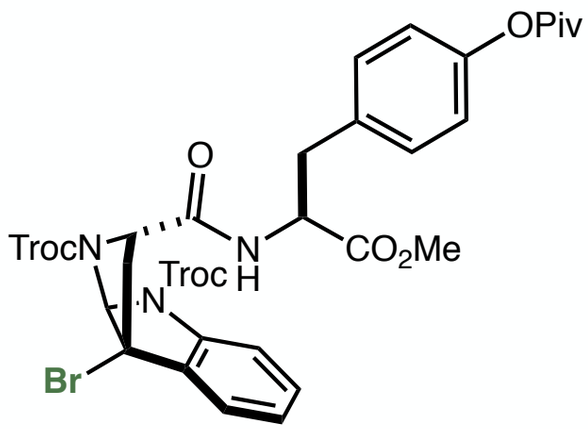
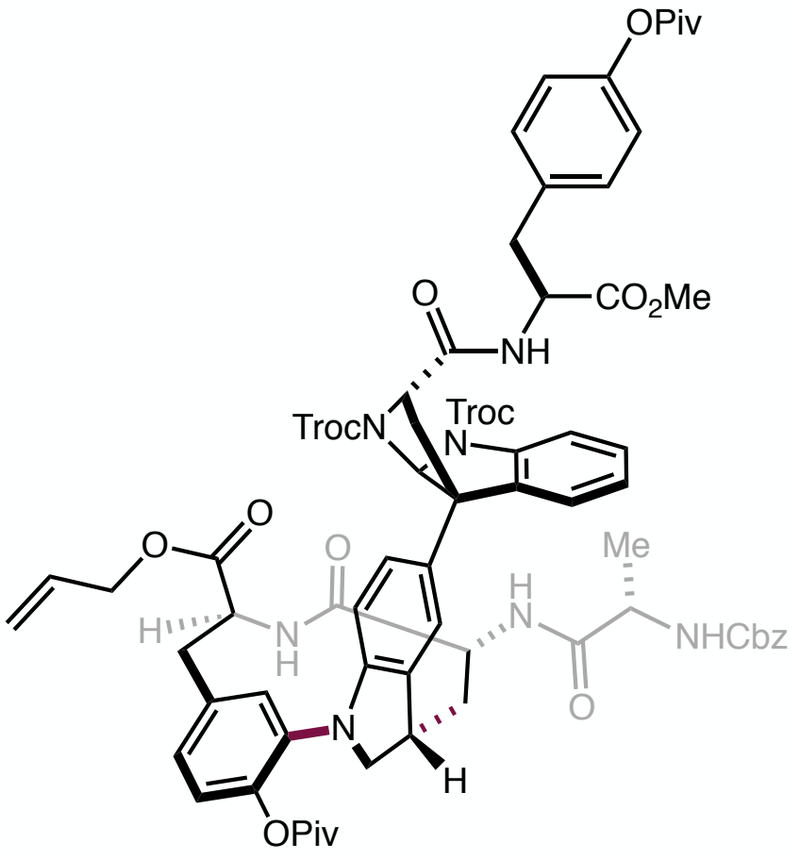
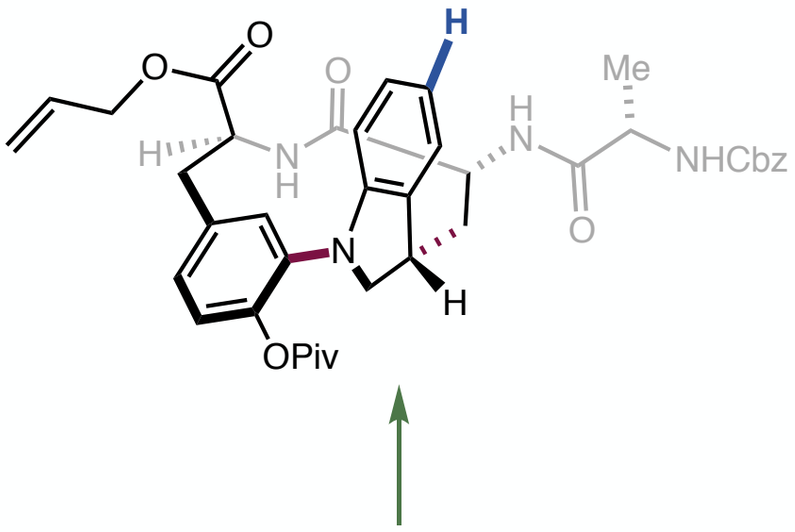



8. $AgSbF_6$, DTBMP, DCM *(62%)*

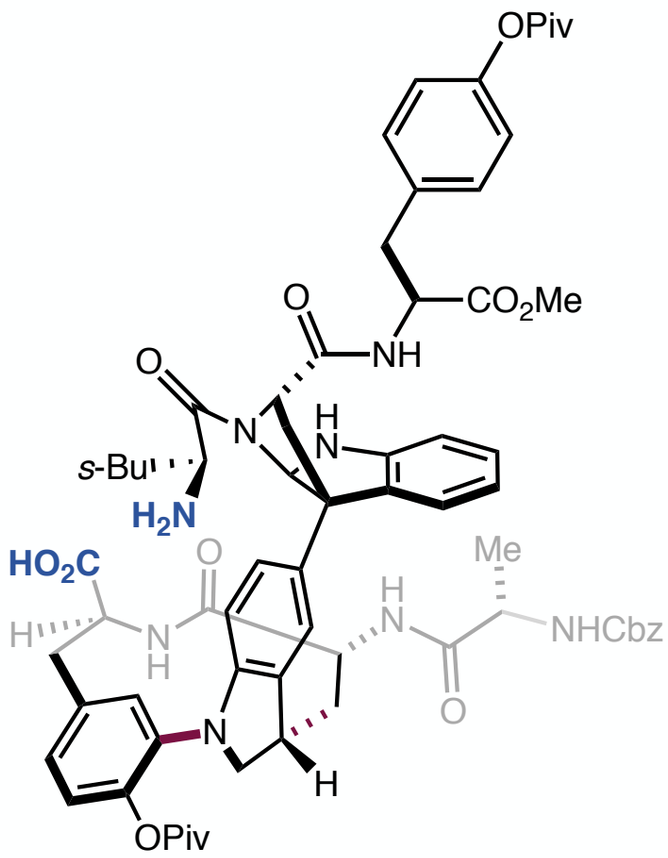



9. Zn, HCl, MeOH/THF/$H_2O$ *(84%)*

10. Boc-Ile-OH, HATU;
then morpholine, $Pd(PPh_3)_4$;
then TFA *(29%)*




*prepared in 7 steps*




*No torsional interconversion!*

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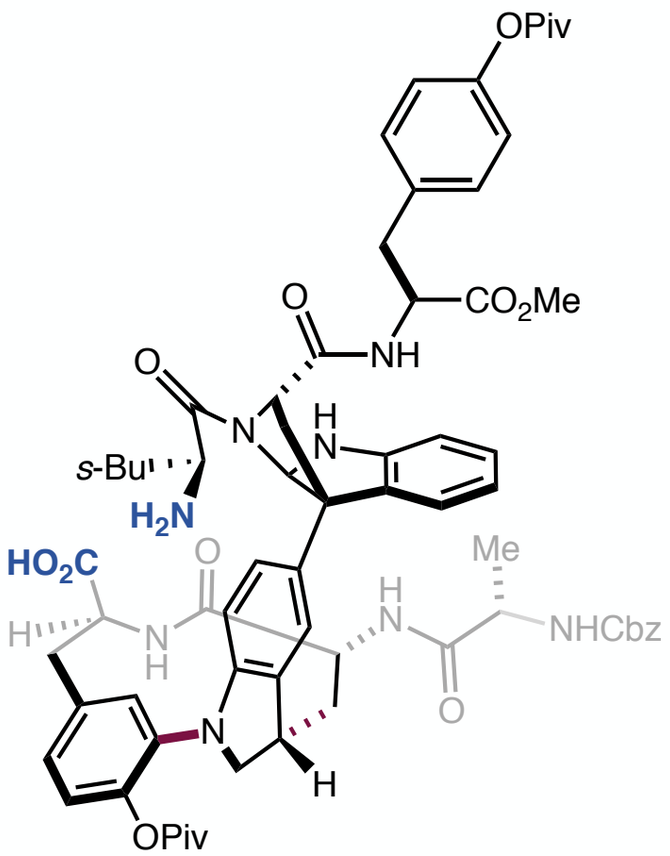
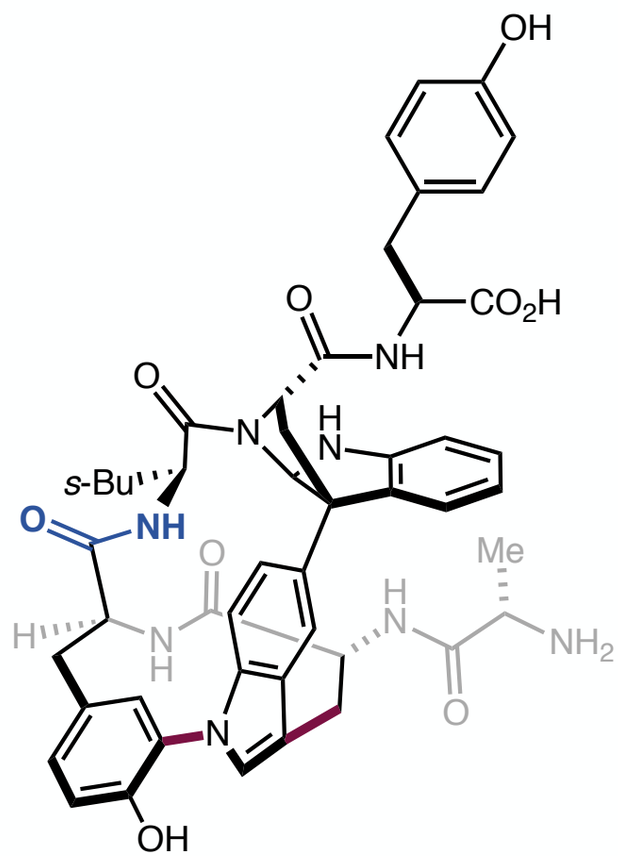



11. PyAOP, DIPEA
MeCN *(11%)*

12. DDQ, TFA/MeCN
microwave *(42%)*
13. Pd/C, $H_2$, MeOH;
then LiOH, $H_2O$ *(86%)*

*biomimetic?*




***Tryptorubin A***

*Subsequent genomics suggests 6-mer peptide synthesized ribosomally, downstream conversion is atroposelective*

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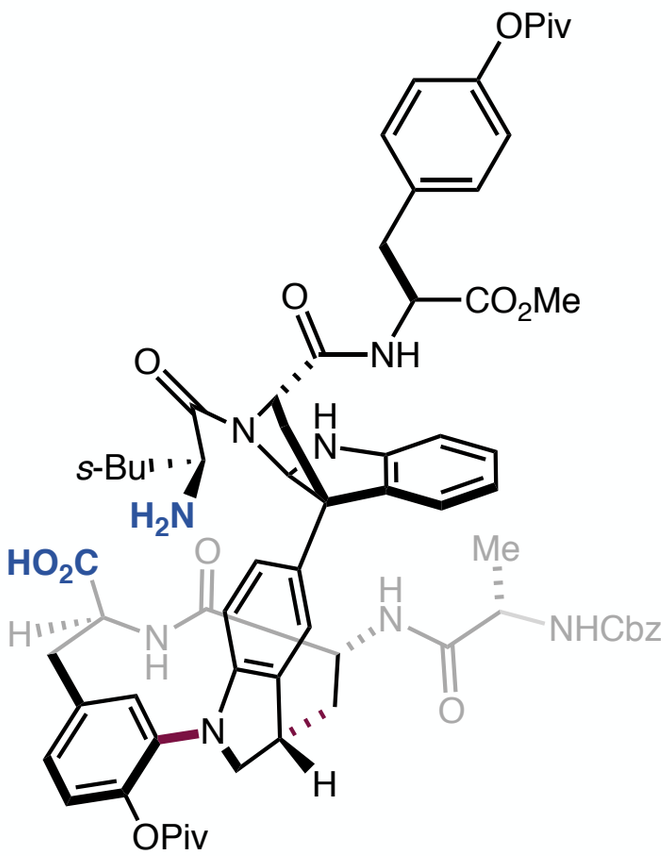


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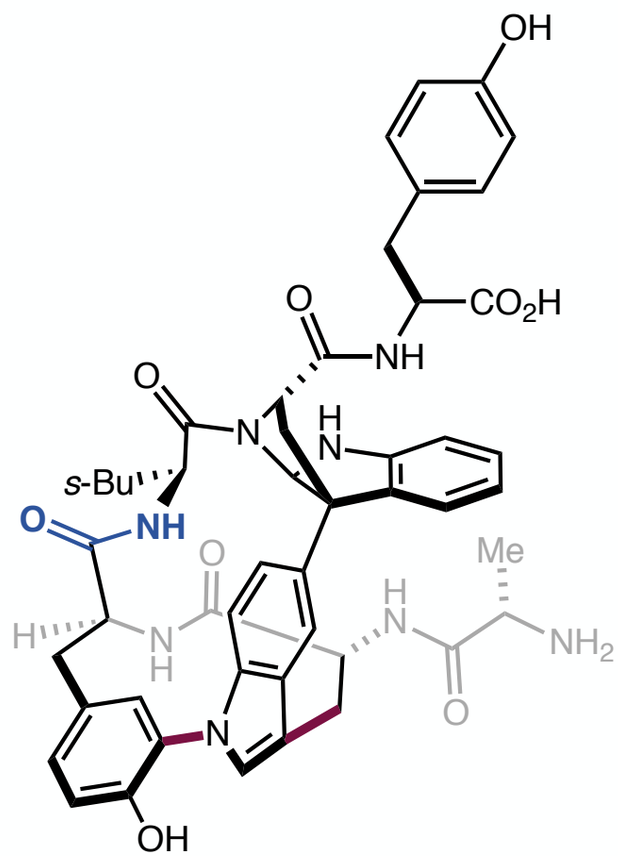


***Tryptorubin A***

***Axial chirality doesn't always resolve serendipitously!***

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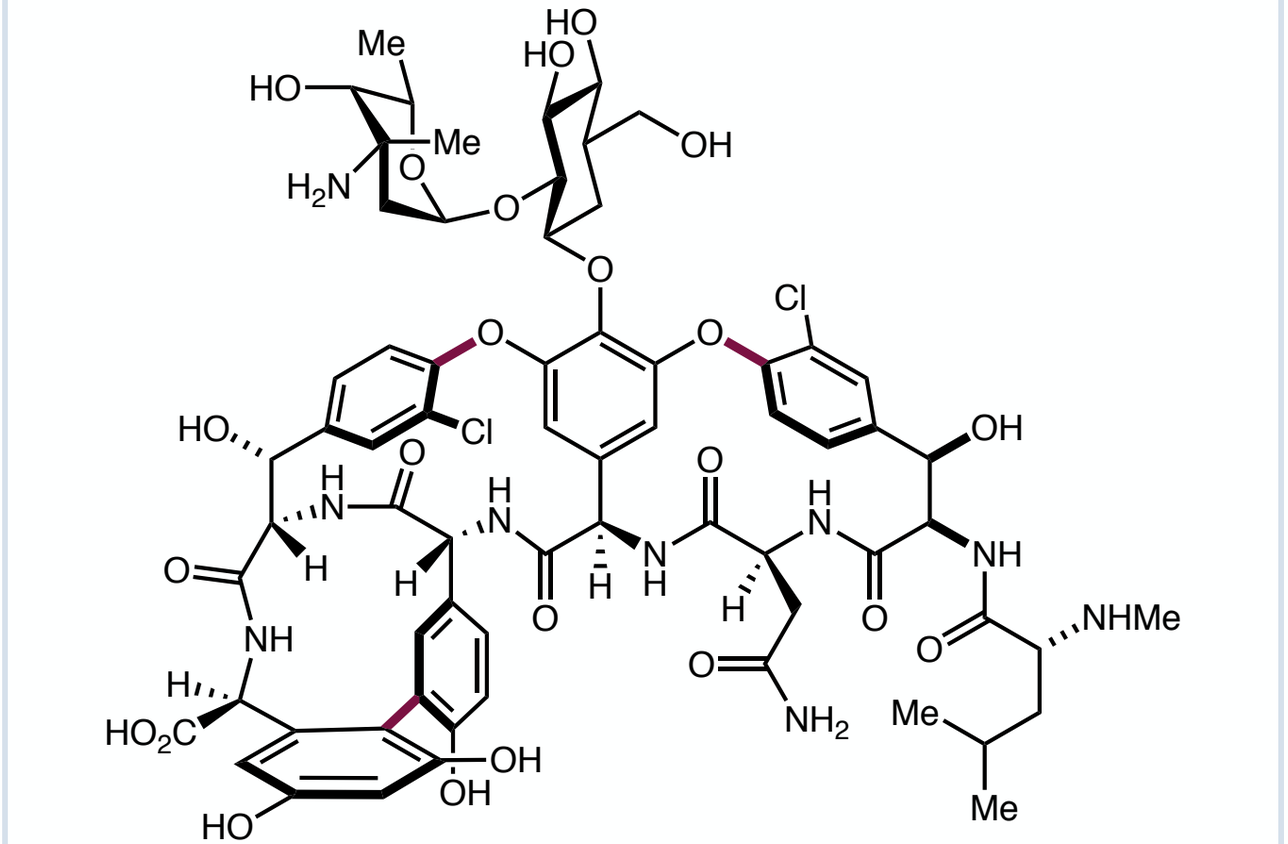
# *Methods and Applications in Atroposelective Chemistry*




*Nate Dow*
*Group Meeting Literature Talk*
*April 13, 2020*