# Atropisomerism

## Metal-mediated transformations to set biaryl chirality

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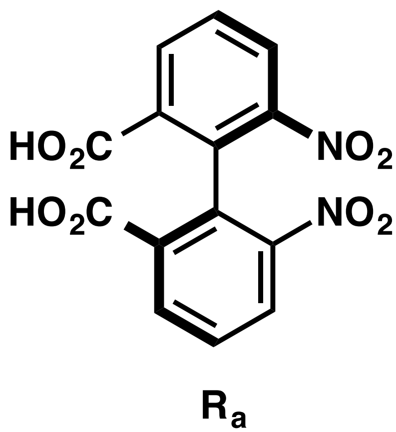
Literature Meeting

12 December 2014

# Atropisomerism

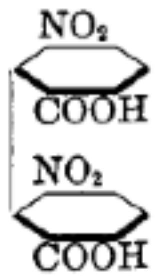
- *Atropos*- the "inflexible" or "without turn"
- Arise from hindered rotation about a single bond allowing for isolation of separate conformers




*6,6'-dinitro-2,2'-diphenic acid,*
the first experimentally described atropisomeric compound

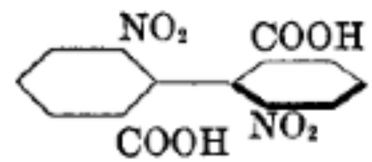
Journal of the Chemical Society, Transactions 121: 614

# First Evidence




XXIX


XXX

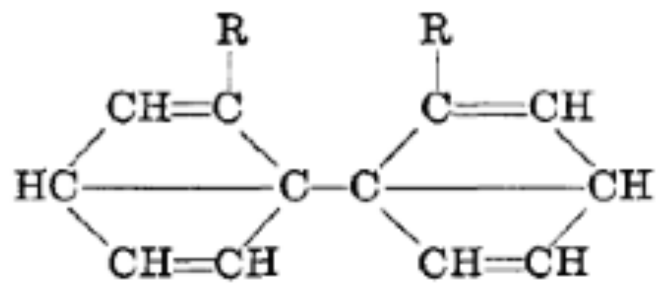



XXXI

- Kaufler Hypothesis: *cis* and *trans* isomers explain optical properties
- Supported by a series of misassignments in derivative studies
- "It has been suggested by Carothers and by Mascarrelli that an objection to the Kaufler formula which has never been emphasized is the necessity of bending a bond to an angle of 90°. With a Kekule nucleus such a formula cannot be constructed, and each time that chemists adobt assumptions that cannot be reconciled with the Kekule nucleus they encounter difficulties." –Adams, 1933

Rogers, A. and Yuan. H. C. *Chem. Rev.* **1933**, 12, 261.

# First Evidence




LV

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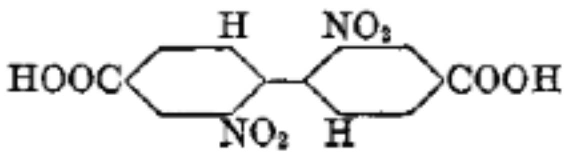
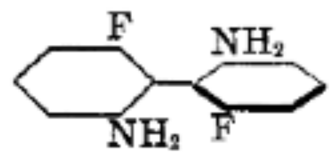
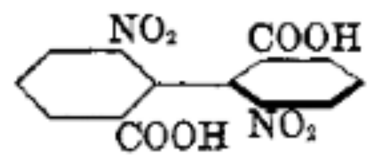
# Restricted Rotation




(nonresolvable)




(easily racemized)




(nonracemizable)

1926- The theory of restricted rotation (Turner, Le Fevre, Bell, and Kenyon)

- “Essentially, the theory states that substituents in 2, 2’, 6, 6’ positions in a diphenyl molecule can, by their interference, restrict the free rotation of the two nuclei around the common axis, thus preventing the rings from becoming coplanar and thereby producing in the molecule an asymmetric configuration.” –Adams, 1933

- Proven by resolution with alkaloids and subsequent racemization upon heating, studied extensively by dynamic NMR

Rogers, A. and Yuan. H. C. *Chem. Rev.* **1933**, 12, 261.

# Restricted Rotation

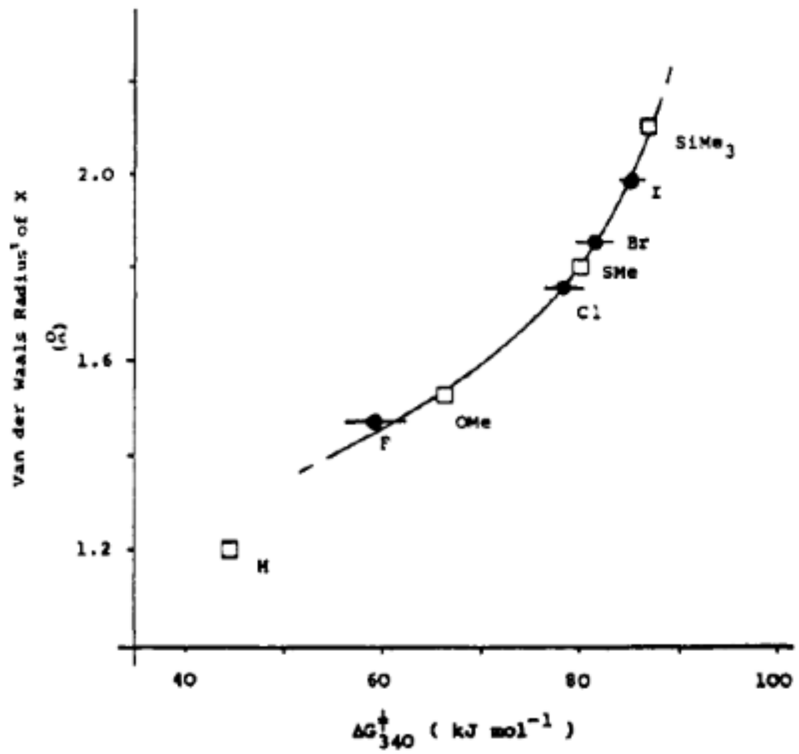
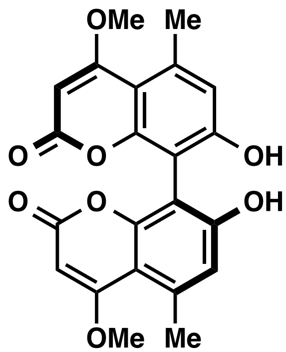



**Figure 3.** Plot of $\Delta G_{340}^{\ddagger}$ against the van der Waals radius[1] of X in some 6-(2-X-phenyl)-1,1,5-trimethylindans (**1**, Y = Me).

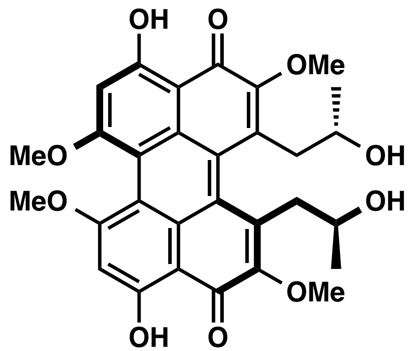
- Extensive dynamic NMR studies by Sternhell show direct correlation between van der Waals radii of substituents and energetic barrier to rotation.
- Increasing number of ortho-substituents and van der Waals radius of each decreases the rate of racemization
- Arbitrary definition of atropisomer is a half life of 1000 seconds at room temperature

Strenhell, S. J. Am. Chem. Soc., 1980, 102, 5618.

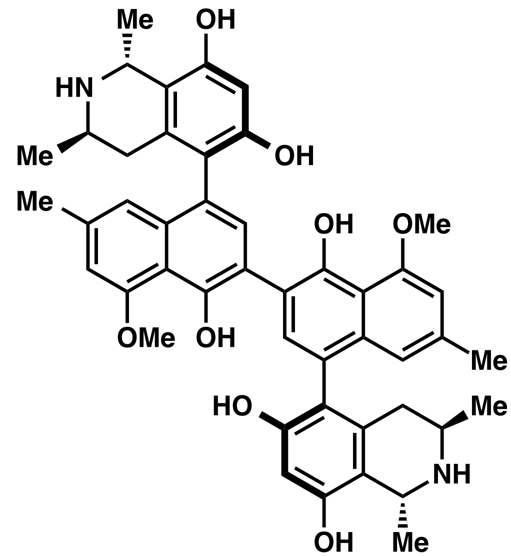
# In Nature



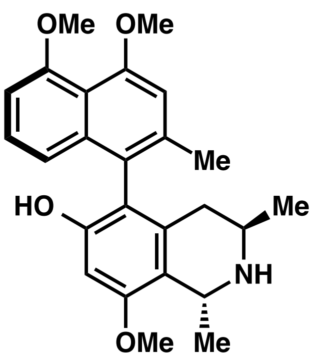

***(+)-orlandin***
*anti-plant growth*



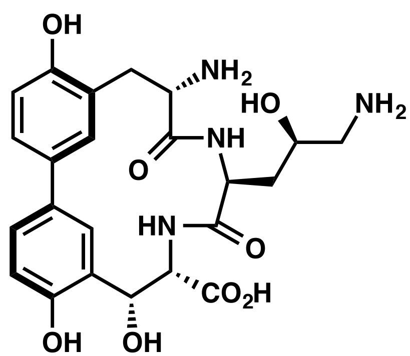

***(-)-phleichrome***
*photodynamic ROS generation*




***michellamine A***
*anti-HIV1 and HIV2*

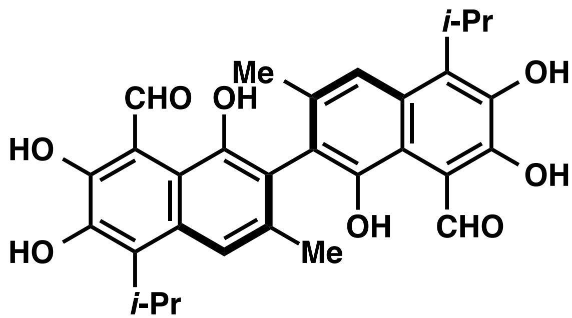



***ancistrocladine***
*anti-malarial*

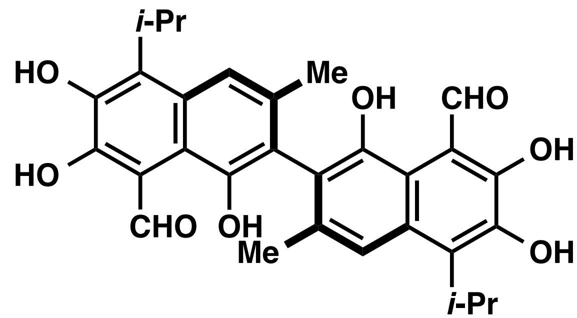



***biphenomycin A***
*antibiotic*

# Eudysmic Ratios

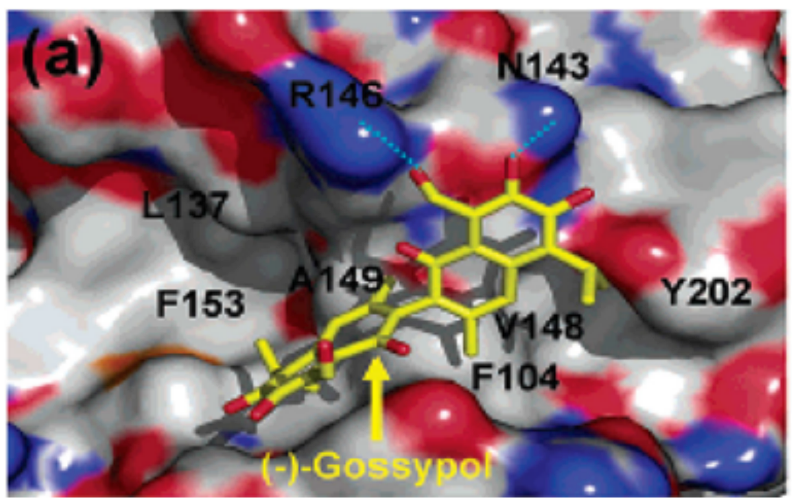


(–)-gossypol



(+)-gossypol

"A potent inhibitor of the antiapoptotic B-cell lymphoma/leukemia-2 (Bcl-2) family of proteins such as Bcl-XL and that the (M)-isomer is some tenfold more cytotoxic than the (P)-isomer."



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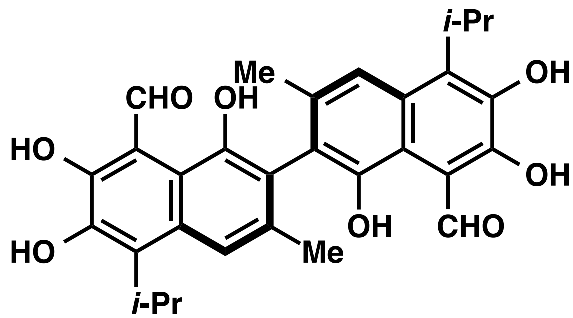
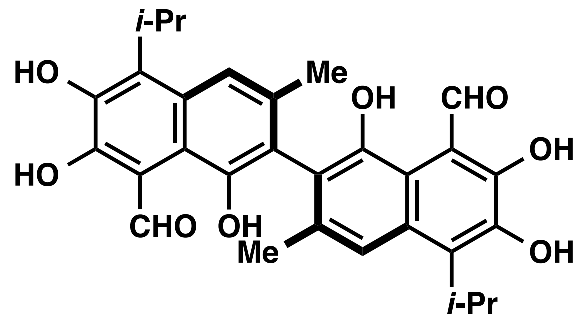
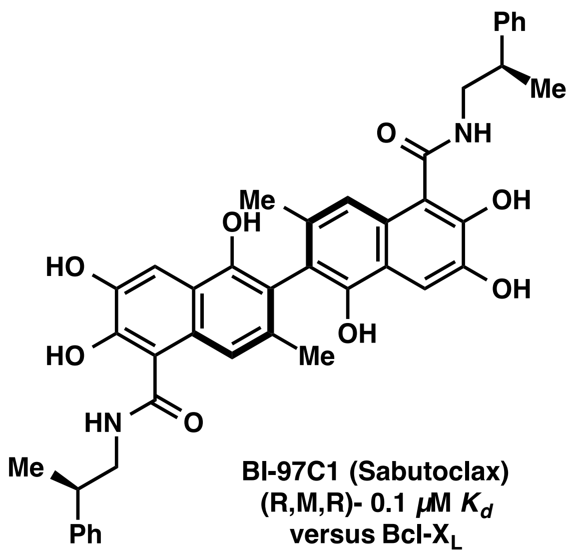


(–)-gossypol

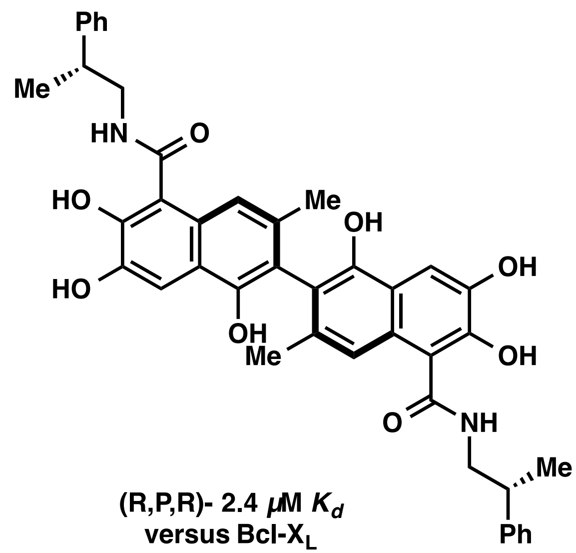


(+)-gossypol

-Derivatization led to increase in activity and in eudysmic ratio from 10 to 24.



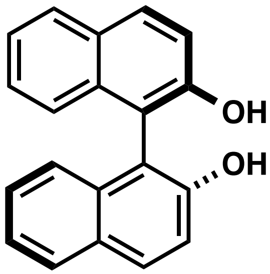
BI-97C1 (Sabutoclax)
(R,M,R)- 0.1 $\mu$M $K_d$
versus Bcl-$X_L$



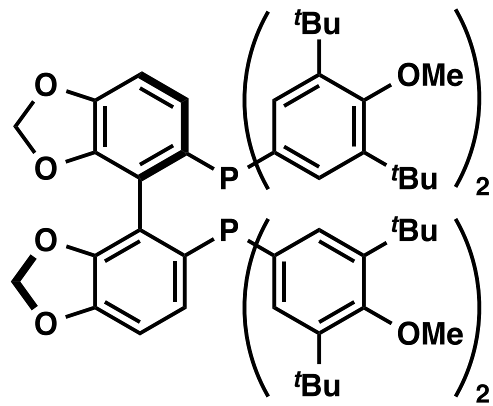
(R,P,R)- 2.4 $\mu$M $K_d$
versus Bcl-$X_L$

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

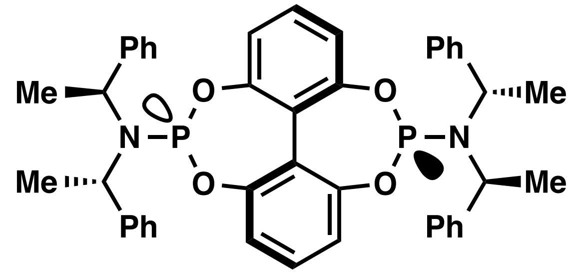
# Atropchiral Ligands and Catalysts



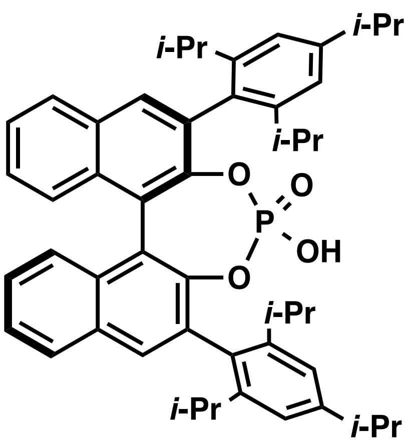
(R)-BINOL



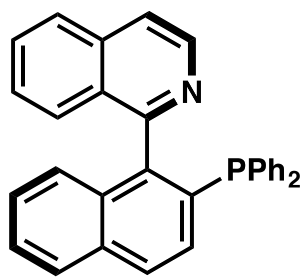
(R)-DTBM-SEGPHOS



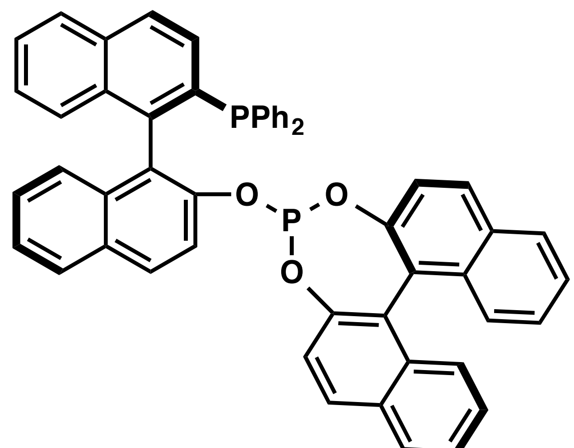
Zhang's D2-symmetric phosphoramidite



(R)-TRIP

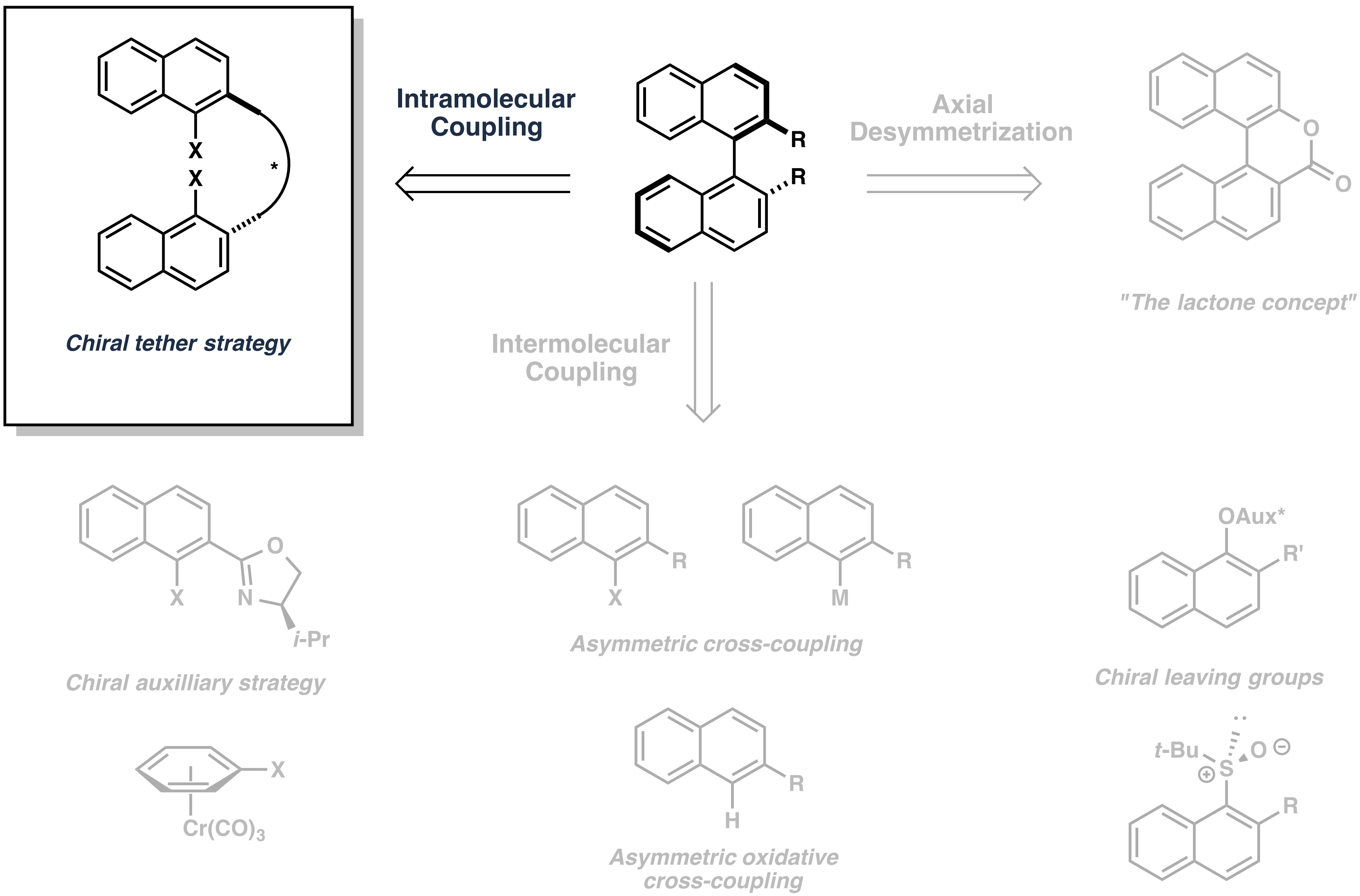


(R)-QUINAP



(R,S)-BINAPHOS

# Methods and Approaches



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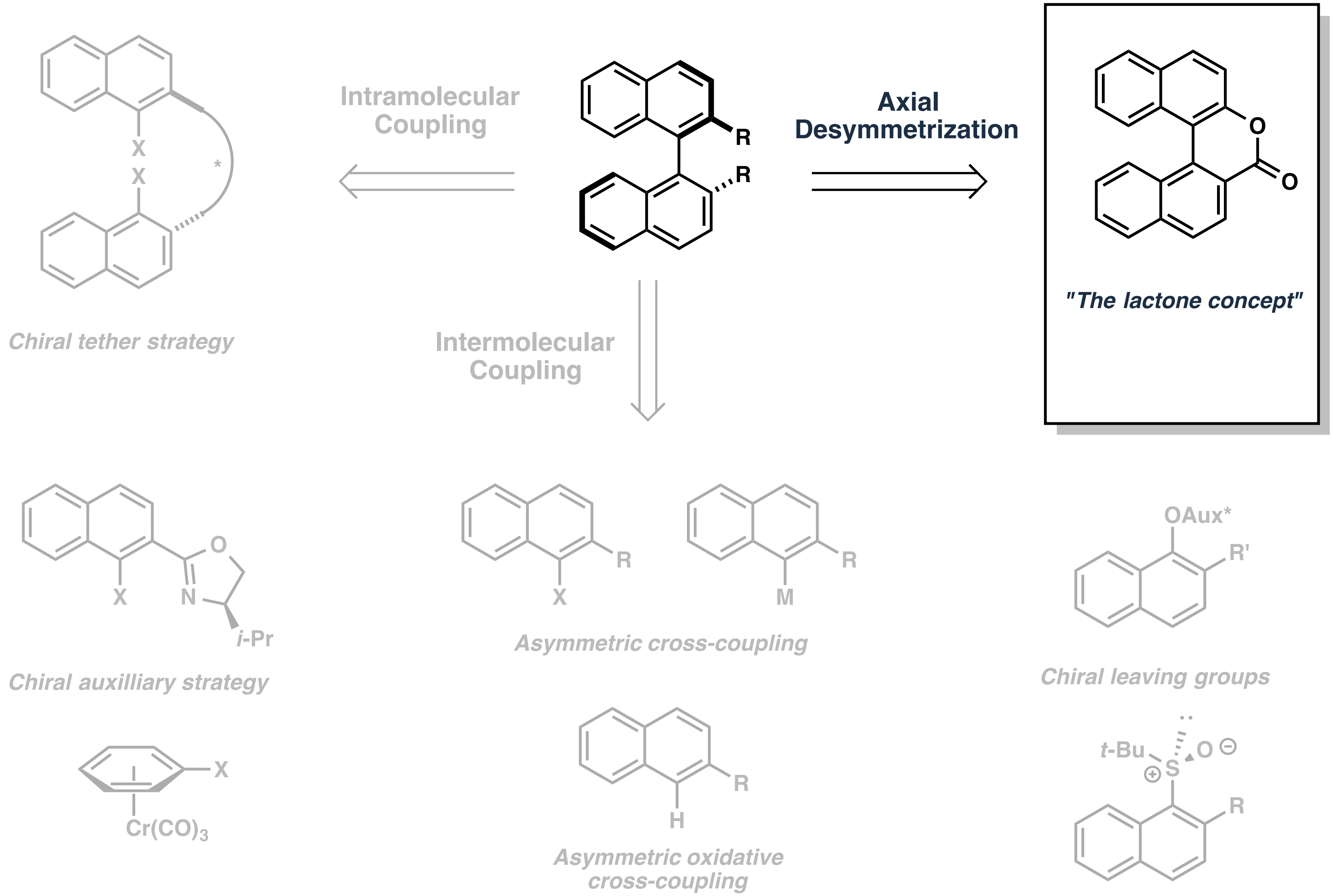

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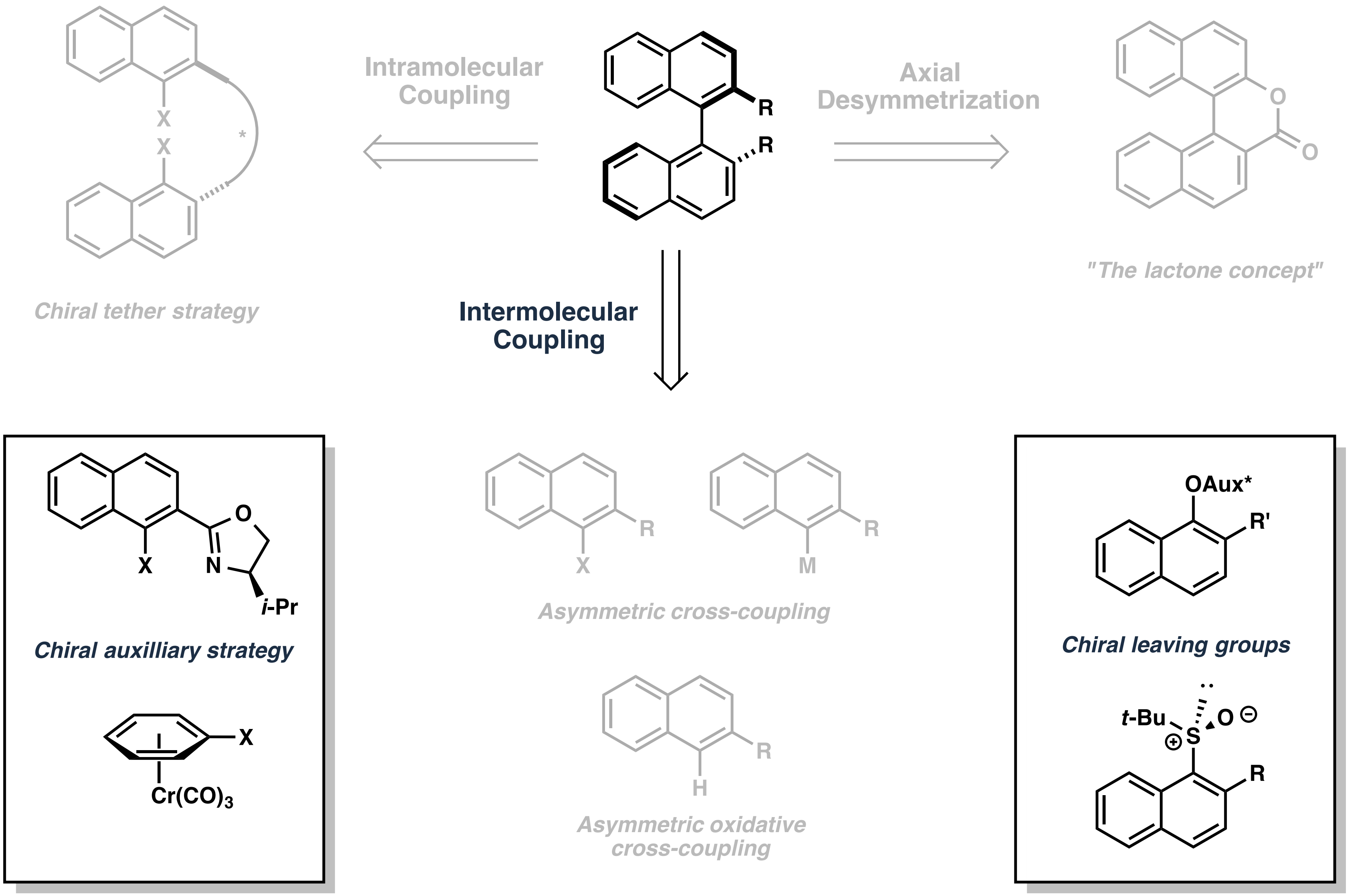

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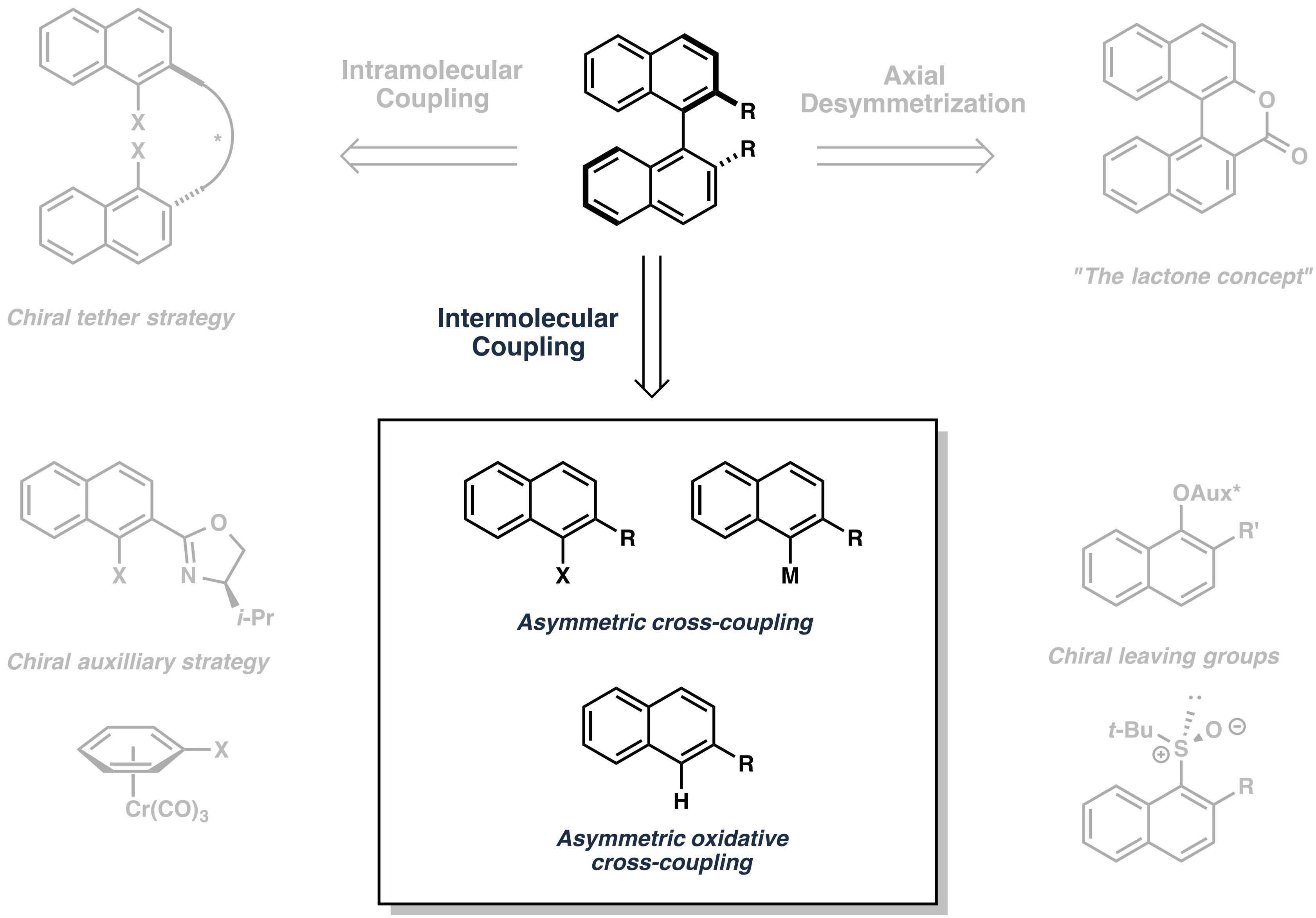


# Redox-Neutral Couplings

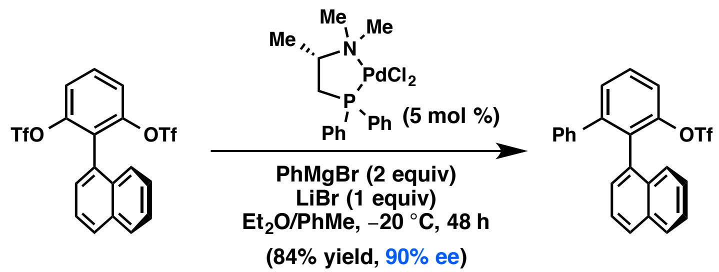
1. Enantioposition-selective cross-coupling of a difunctionalized achiral biaryl substrate

2. Dynamic kinetic asymmetric transformations via cross-coupling of a racemic substrate

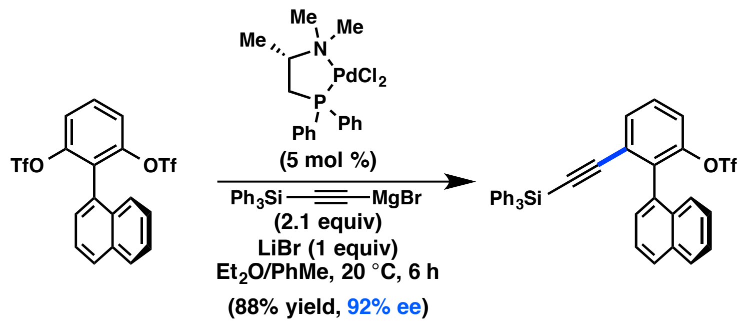
3. $sp^2$-$sp^2$ Cross-coupling producing axial chirality in the bond-forming event

# Enantioposition-selective

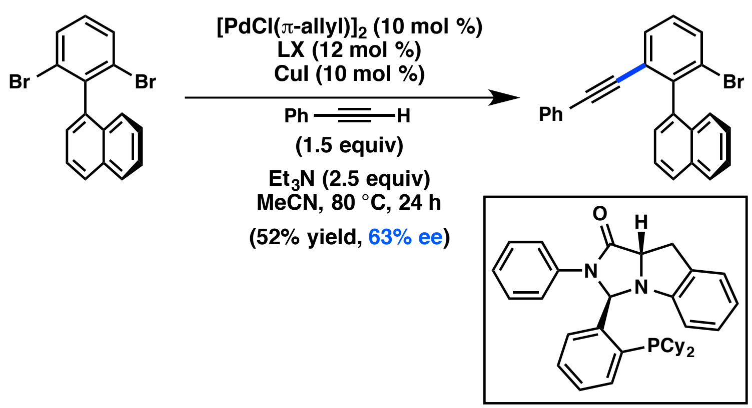
*a) Kumada-Corriu cross-coupling of aryl Grignard reagent*




*b) Kumada-Corriu cross-coupling of alkynyl Grignard reagent*




*c) Sonogashira cross-coupling of alkynes*




Uozumi, Y., *et al. J. Am. Chem. Soc.* **1995**, *117*, 9101
Kamikawa, T.; Hayashi, T. *Tetrahedron* **1999**, *55*, 3455.
Kamikawa, T.; Uozumi, Y.; Hayashi, T. *Tetrahedron Letters* **1996**, *37*, 3161.

# Enantioposition-selective

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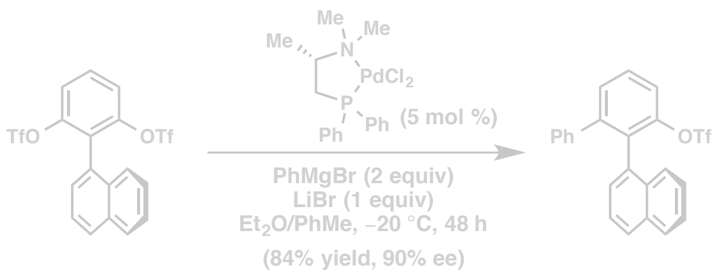
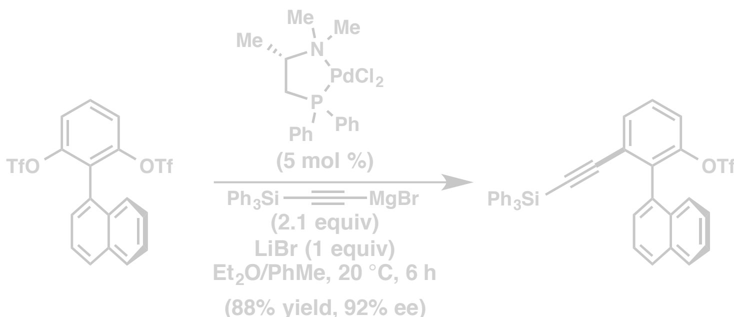



b) Kumada-Corriu cross-coupling of alkynyl Grignard reagent

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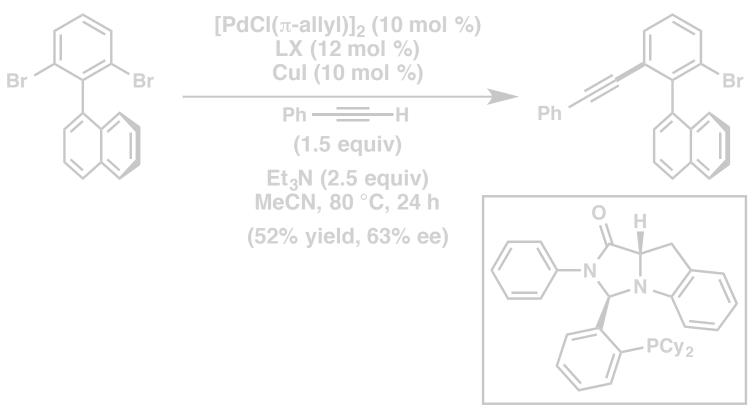


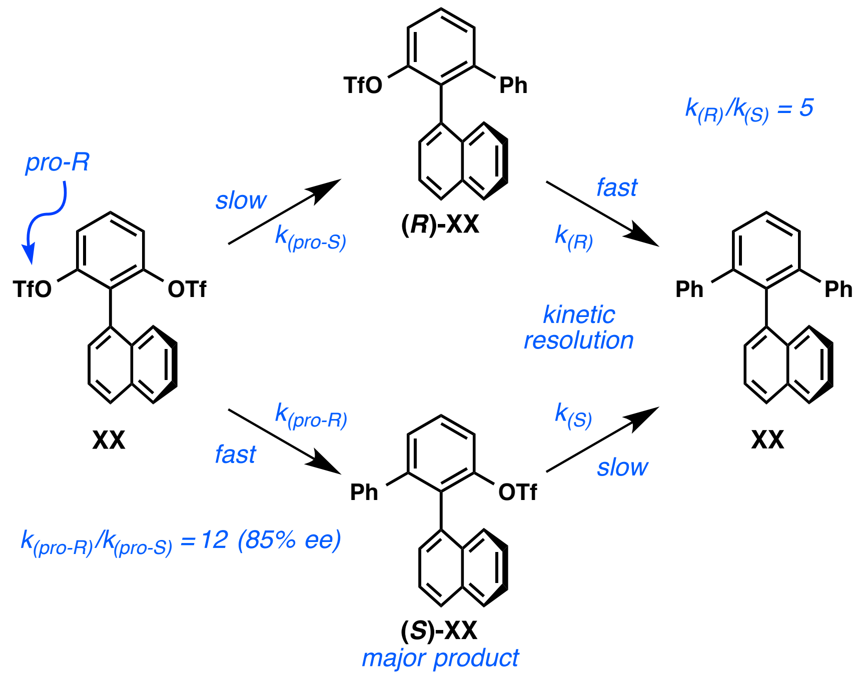



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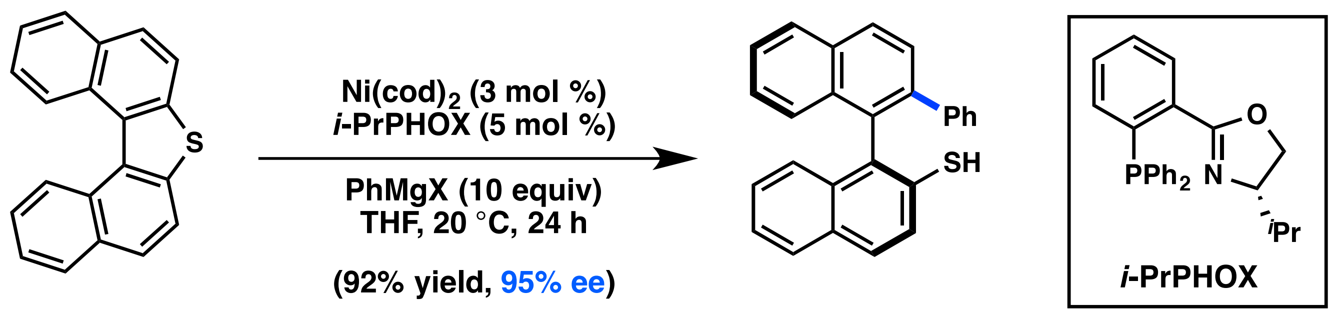
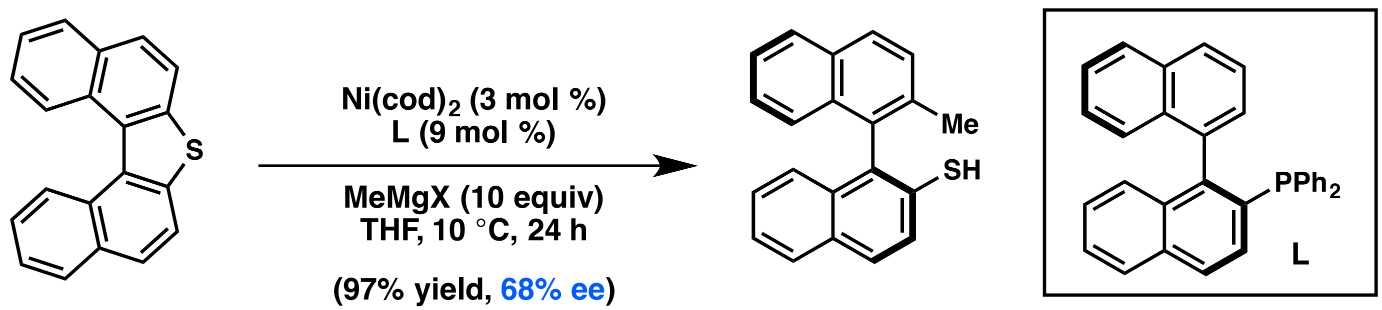
# DYKAT

*Hayashi, 2002 and 2004:*




Shimada, T.; Cho, Y. H.; Hayashi, T. *J. Am. Chem. Soc.* **2002**, *124*, 13396.
Cho, Y. H.; Kina, A.; Shimada, T.; Hayashi, T. *J. Org. Chem.* **2004**, *69*, 3811.

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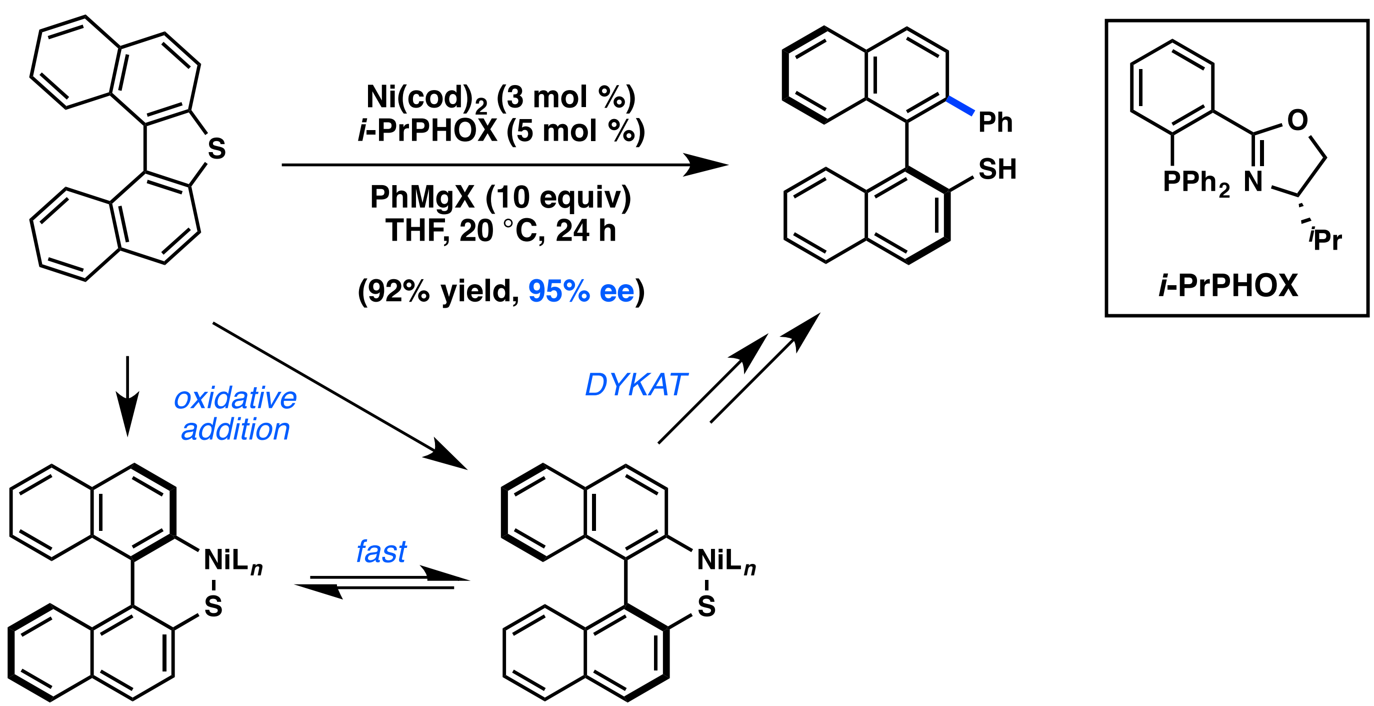



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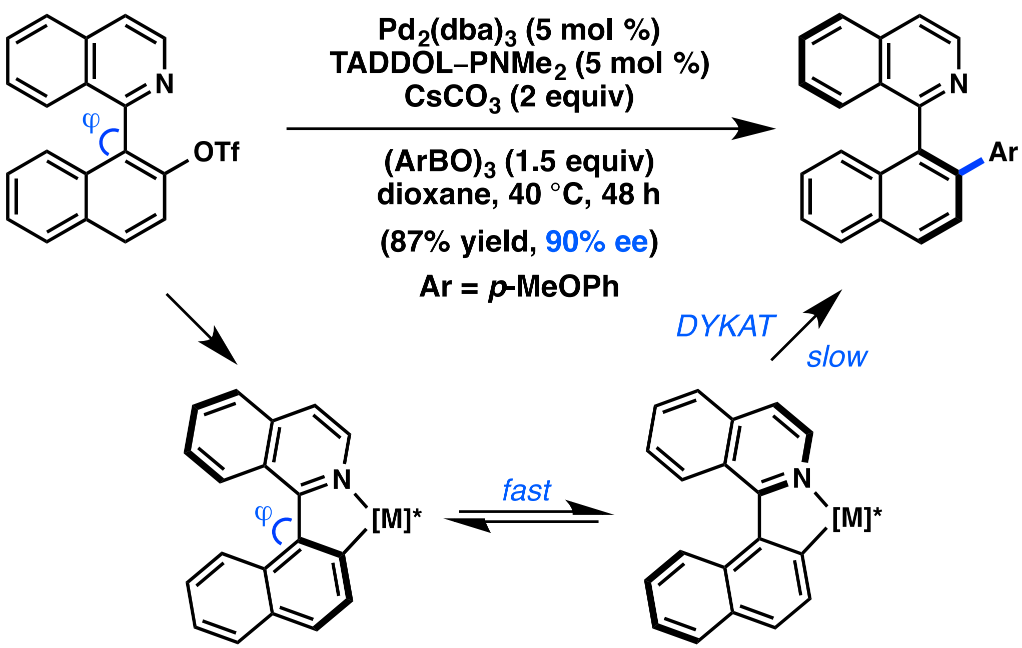
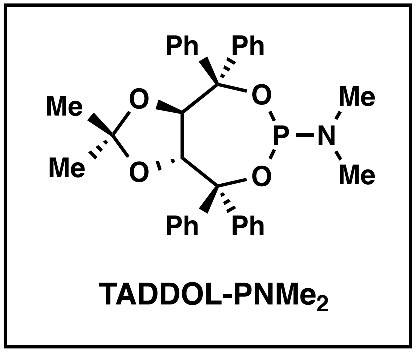
# DYKAT

*Lassaletta, 2013:*

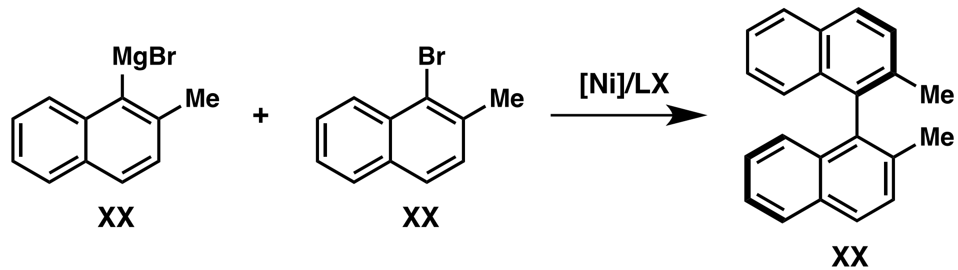


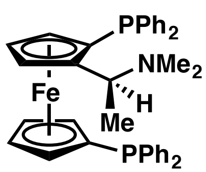




Lassaletta, J. M., *et al.* *J. Am. Chem. Soc.* **2013**, *135*, 15730.

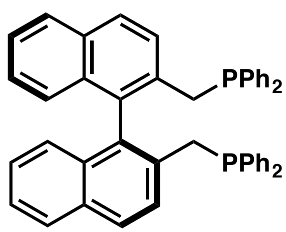
# Cross-Coupling

## -The 1980's: Asymmetric Kumada-Corriu coupling

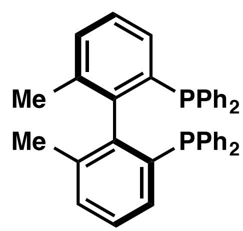


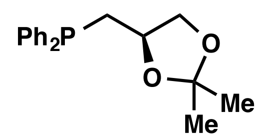

**BPPFA (LX)**
5% ee



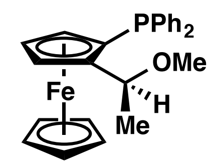

**NAPHOS (LX)**
13% ee




**BIPHEMP (LX) w/ Pd**
45% ee




**LX**
**40% yield,** 50% ee

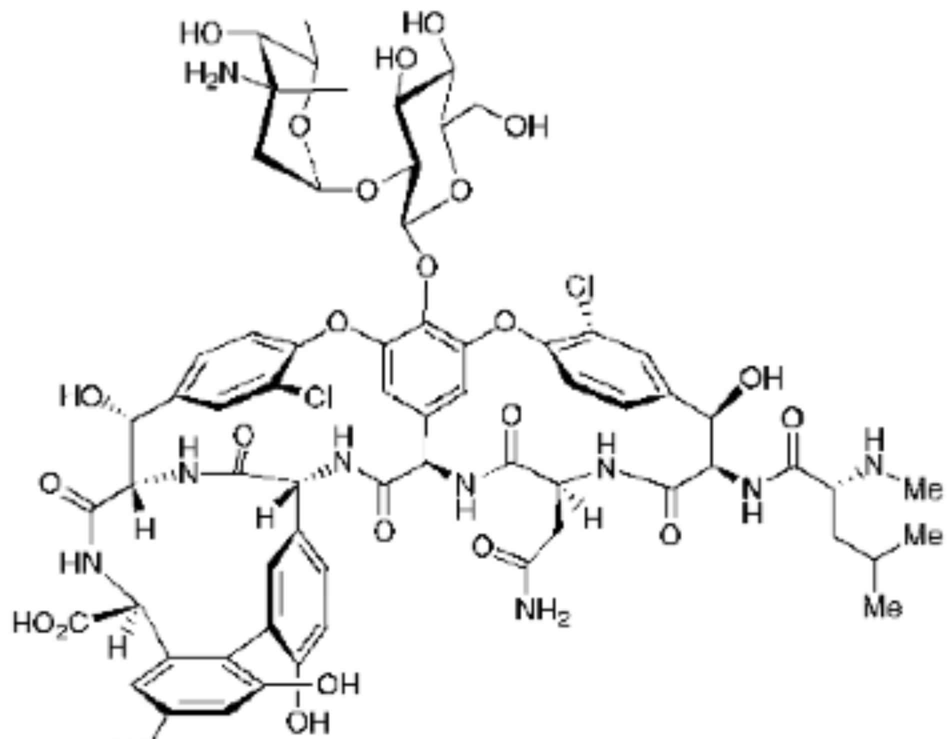



**LX**
**69% yield,** 95% ee

Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 4374
Corriu, J. P.; Masse, J. P. *J. Chem. Soc., Chem. Commun.* **1972**, 144.
Kumada, M., *et al. Chemistry Letters* **1975**, 133.
Kumada, M. *et al. Tetrahedron Letters* **1977**, *18*, 1389.
Frejd, T.; Klingstedt, T. *Acta Chemica Scandinavica* **1989**, *43*, 670.
Terfort, A.; Brunner, H. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1467.
Kumada, M. *et al. Tetrahedron Letters* **1977**, *18*, 1389.
Ito, Y. *et. al. J. Am. Chem. Soc.* **1988**, *110*, 8153
Hayashi, T.; Hayashizaki, K.; Ito, Y. *Tetrahedron Letters* **1989**, *30*, 215.

# Cross-Coupling

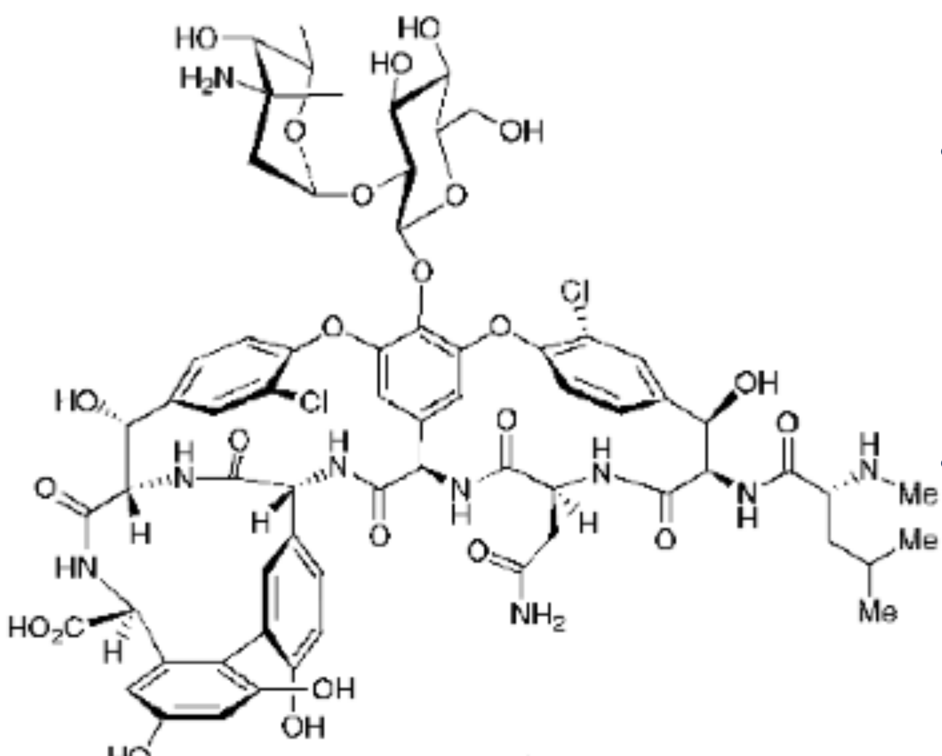
-Skipping ahead to 1999.



1: vancomycin

# Vancomycin

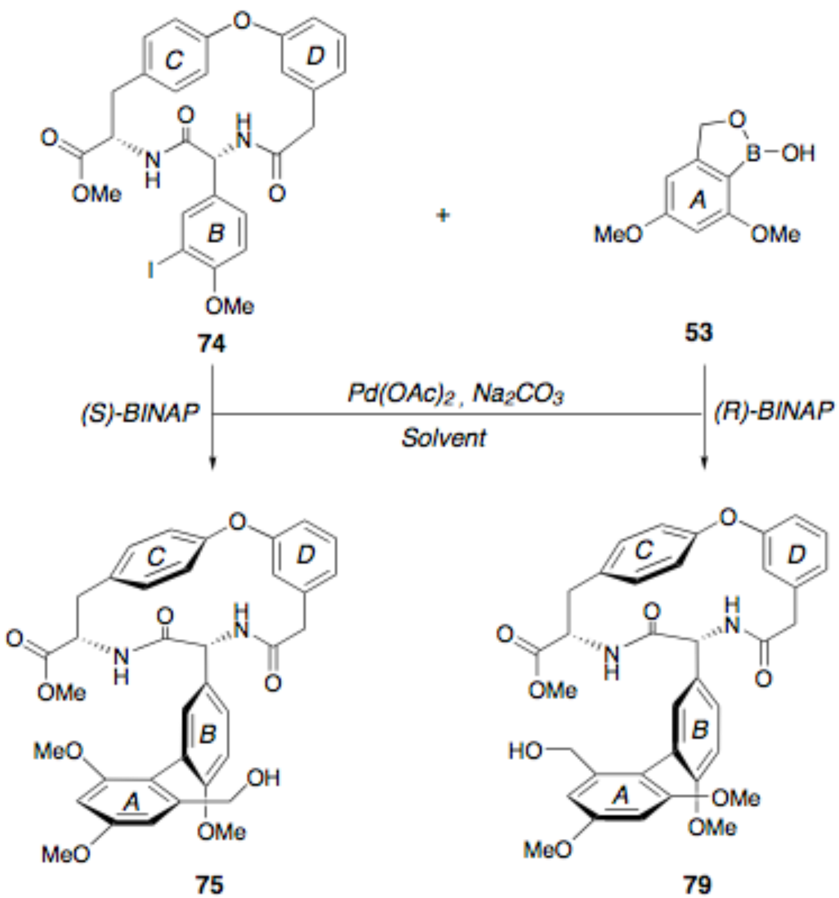
-Skipping ahead to 1999.



1: vancomycin

- Isolated in 1953 by Eli Lilly from soil bacterium *Amycolatopsis orientalis*.
- Antibiotic used for infections by Gram-(+) bacteria, especially those resistant to more common drugs (e.g. MRSA).
- Inhibits biosynthesis of Gram-(+) bacterial cell wall.

# Vancomycin




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

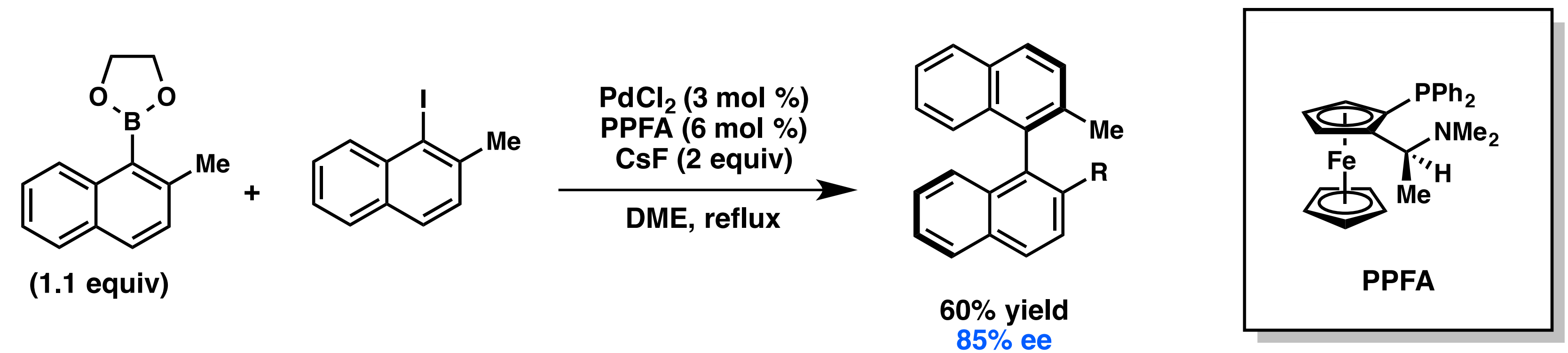
- No intrinsic substrate control in Suzuki reaction.
- Chiral ligand and condition screening identified BINAP as providing almost complete catalyst control.
- First catalyst-controlled enantioselective Suzuki coupling!

| Entry | Ligand | Solvent | Temp (°C) | Time (h) | Yield (%) | Ratio (**75**:**79**) |
|---|---|---|---|---|---|---|
| 1 | $Ph_3P$ | 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(70[a]) | >95:5[b] |
| 6 | (*R*)-BINAP | PhMe:THF(1:1) | 70 | 5 | 40(70[a]) | <5:95[b] |

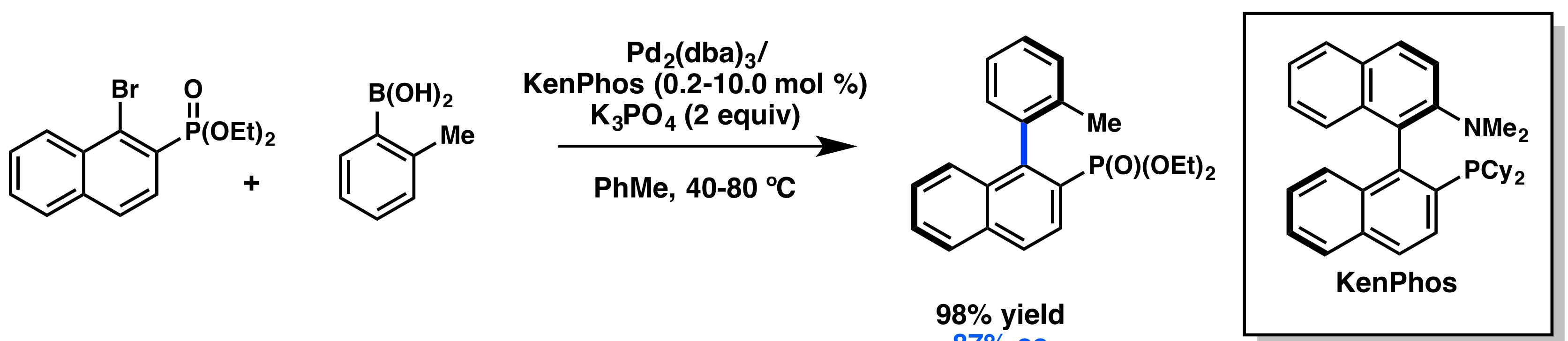
# Suzuki Coupling

## -The 2000's, the reign of Boron

*Cammidge, 2000:*



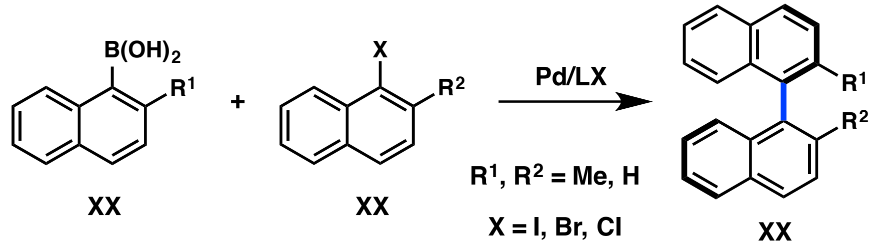

*Buchwald, 2000:*

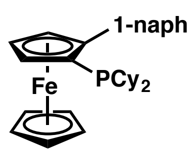




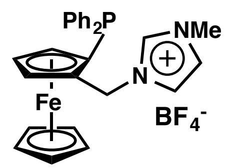
Cammidge, A. N.; Crépy, K. V. L. *Chemical Communications* **2000**, 1723.
Yin, J. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 12051

# Suzuki Coupling

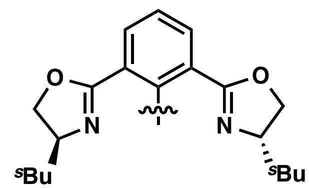


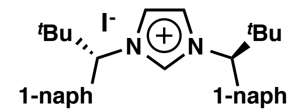

65% yield
54% ee
(Johannsen, 2003)



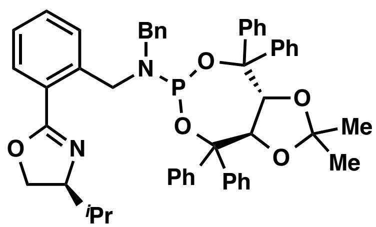

88% yield
42% ee
(Labande, 2010)



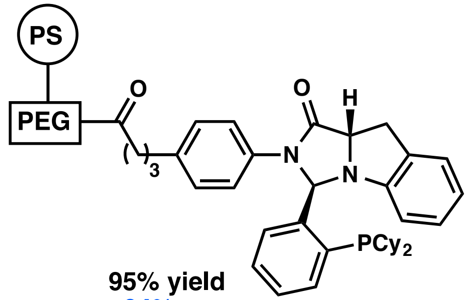

61% yield
49% ee
(Iwasa, 2007)



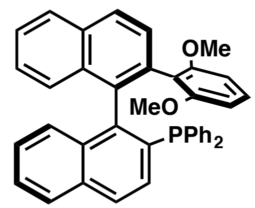

85% yield
80% ee
(Kündig, 2014)



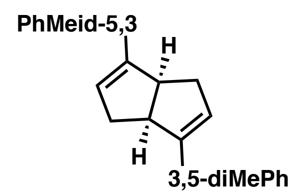

54% yield
46% ee
(Guiry, 2007)




95% yield
94% ee
(Uozumi, 2009)



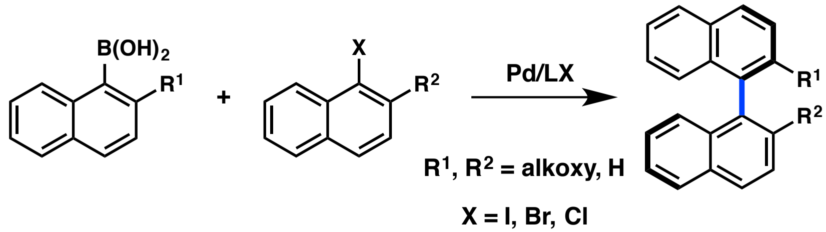

73% yield
62% ee
(Putala, 2013)

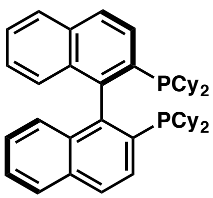



78% yield
90% ee
(Lin, 2010)

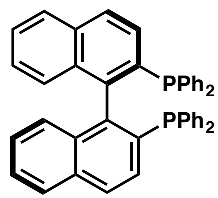

Jensen, J. F.; Johannsen, *Org. Lett.* **2003**, *5*, 3025.
Labande, A. *et al. New Journal of Chemistry* **2014**, *38*, 338.
Uozumi, Y., *et al. Angew. Chem. Int. Ed.* **2009**, *48*, 2708.
Lin, G. Q. *et al. Organic Letters* **2010**, *12*, 5546.
Benhamou, L.; Besnard, C.; Kundig, E. P. *Organometallics* **2014**, *33*, 260.
Iwasa, S. *et al. Tetrahedron Letters* **2007**, *48*, 3397.
Bronger, R. P. J.; Guiry, P. J. *Tetrahedron-Asymmetry* **2007**, *18*, 1094.
Meskova, M.; Putala, M. *Tetrahedron: Asymmetry* **2013**, *24*, 894.

# Suzuki Coupling

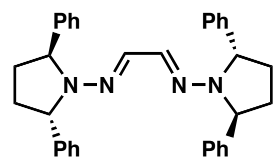


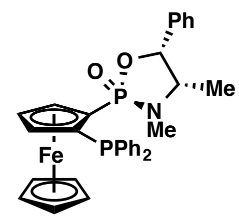
**CyBINAP**
**92% yield**
**70% ee**
**(Mikami, 2004)**



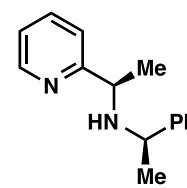
**BINAP**
**96% yield**
**69% ee**
**(Sawai, 2008)**



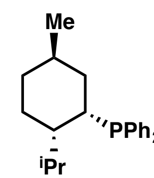
**61% yield**
**90% ee**
**(Lassaletta, 2008)**



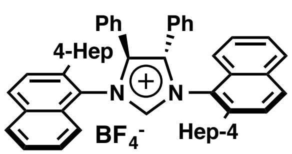
**26% ee**
**(Xiao, 2009)**



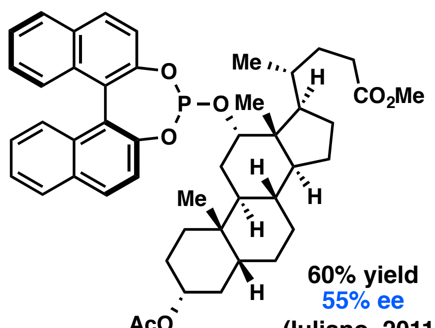
**75% yield**
**40% ee**
**(Prim, 2011)**



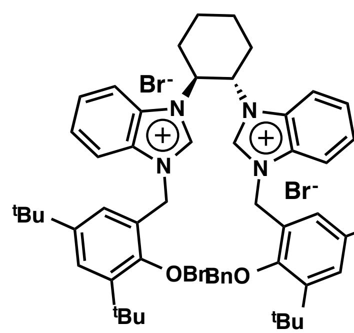
**35% ee**
**(Claver, 2013)**



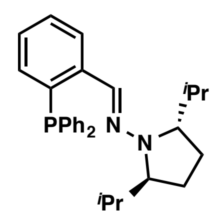
**91% yield**
**60% ee**
**(Dorta, 2013)**



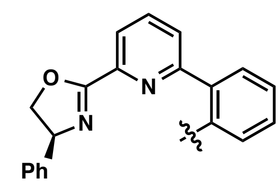
**60% yield**
**55% ee**
**(Iuliano, 2011)**



**73% yield**
**61% ee**
**(Zhang, 2012)**



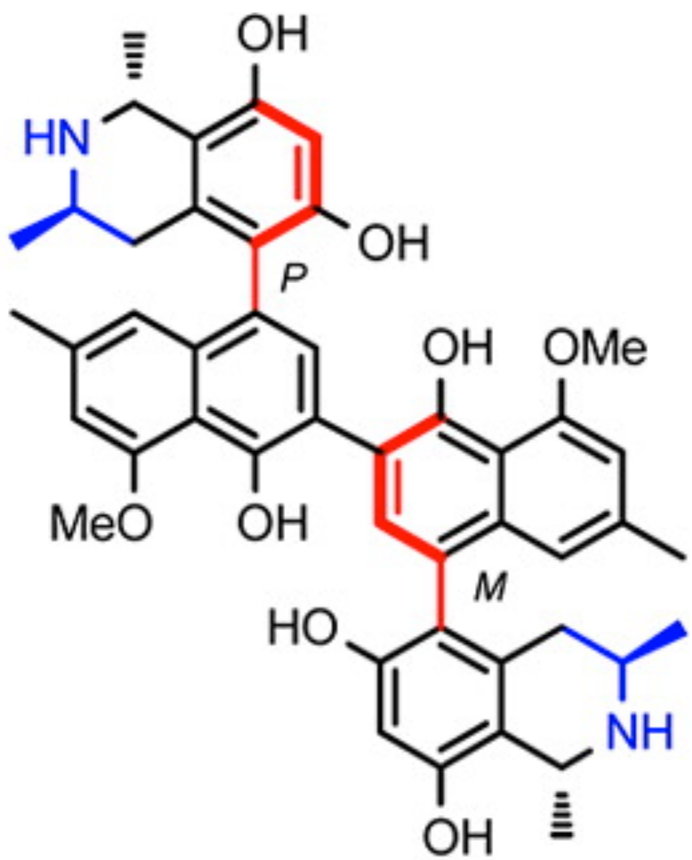
**90% yield**
**80% ee**
**(Lassaletta, 2012)**



**71% yield**
**50% ee**
**(Gong/Song, 2014)**

Mikami, K.; Miyamoto, T.; Hatano, M. *Chem. Commun.* **2004**, 2082.
Sawai, K. *et al. Angew. Chem. Int. Ed.* **2008**, *47*, 6917.
Lassaletta, J. M., *et al. J. Am. Chem. Soc.* **2008**, *130*, 15798
Lassaletta, J. M. *et al. J. Org. Chem.* **2012**, *77*, 4740.
Xiao, J. L., *et al. Can. J. Chem.* **2009**, *87*, 171.
Prim, D., *et al. Organometallics* **2011**, *30*, 4074.
Dorta, R. *et al. Synlett* **2013**, *24*, 1215.
Zhang, D. *et al. Organometallics* **2014**, *33*, 876.
Jumde, V. R.; Iuliano, A. *Tetrahedron-Asymmetry* **2011**, *22*, 2151.
Claver, C. *J. et al. Organomet. Chem.* **2013**, *743*, 31.
Gong, J. F.; Song, M. P., *et al. Organometallics* **2014**, *33*, 194.

# Michellamine B

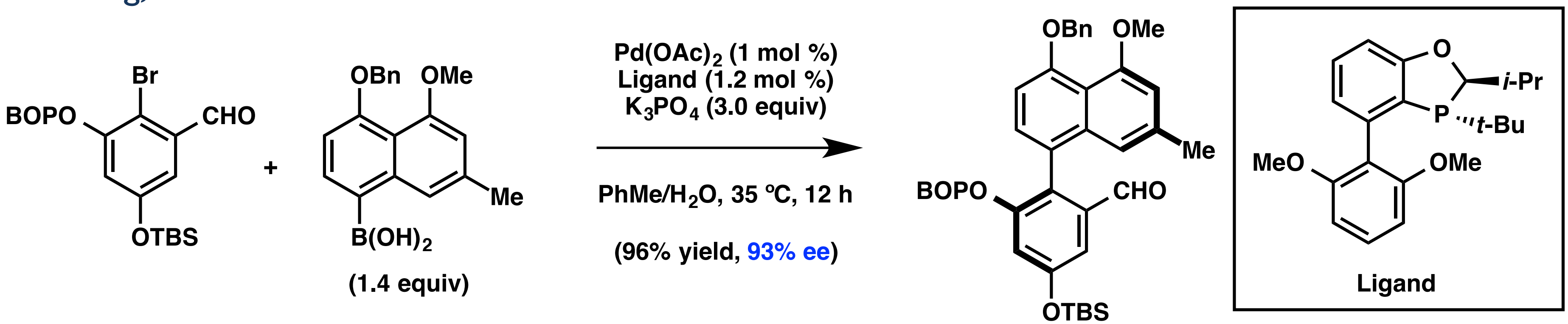



- Isolated in 1991 by Boyd and coworkers
- Anti- HIV-1 ($EC_{50}$ 10 μM) and HIV-2 ($EC_{50}$ 2 μM) activity including resistant strains as well.
- Configurationally labile at binaphthyl junction.
- Significant activity dependence on stereochemistry of naphthylisoquinoline axes.
- Previous approaches: diastereoselective biary coupling; chiral Cr-complexes, and asymmetric lactone cleavage.

Boyd. M. R., *et al. J. Med. Chem.*, **1991.** 34, 3402

# Michellamine B

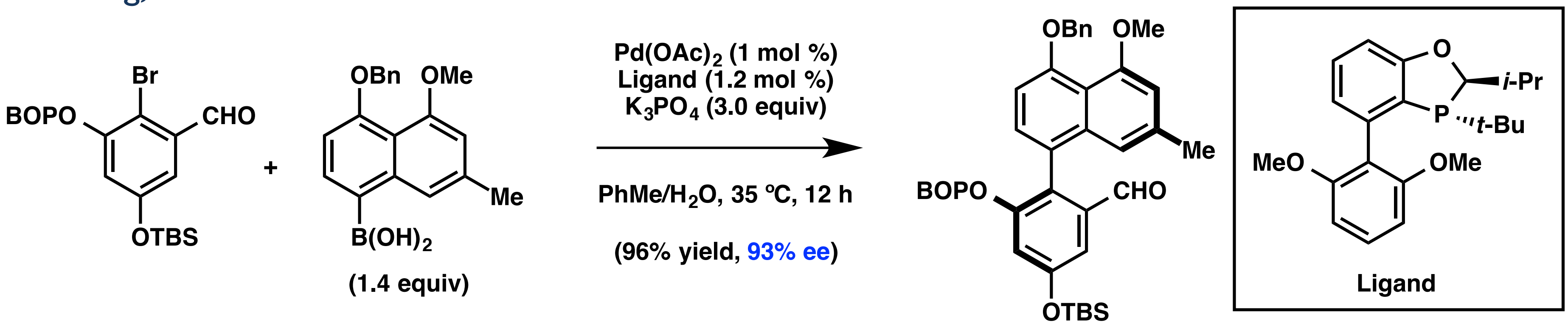
*Tang, 2014:*



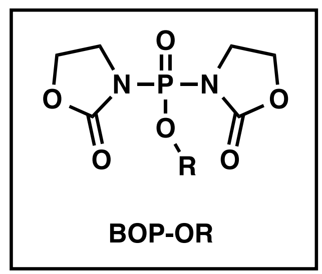

Tang, W., *et al. J. Am. Chem. Soc.* **2014**, 136, 570.

# Michellamine B

*Tang, 2014:*




- Building from Buchwald's work, screened a variety of ligands against various *ortho*-directing groups, arrived at BOP:

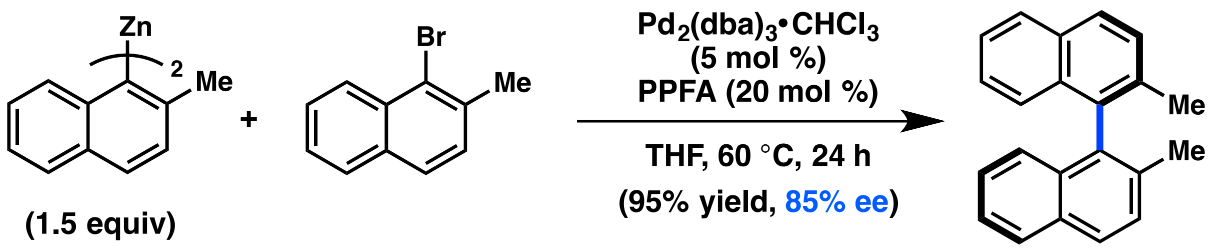


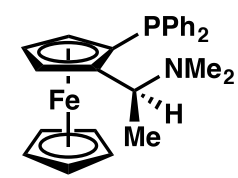

- First catalytic asymmetric preparation of Michellamine B in 20+ years of efforts.
- Very mild conditions employed for hindered Suzuki coupling.

Tang, W., *et al. J. Am. Chem. Soc.* **2014**, 136, 570.

# Cross-Coupling: Other Nucleophiles

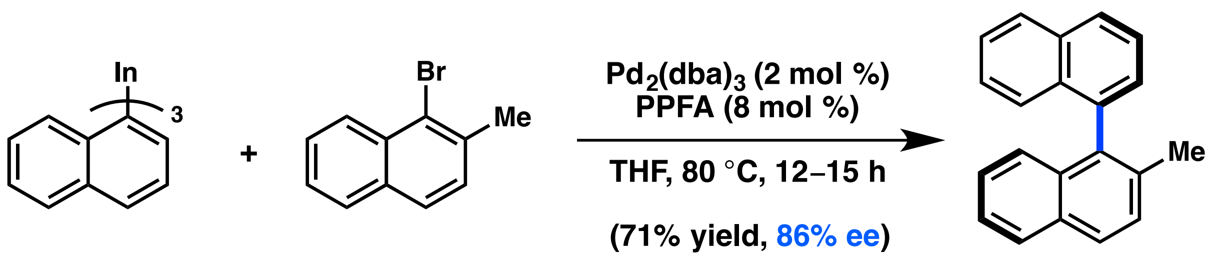
*Zinc: Espinet, 2006*




PPFA

*Indium: Sarandeses, 2013*

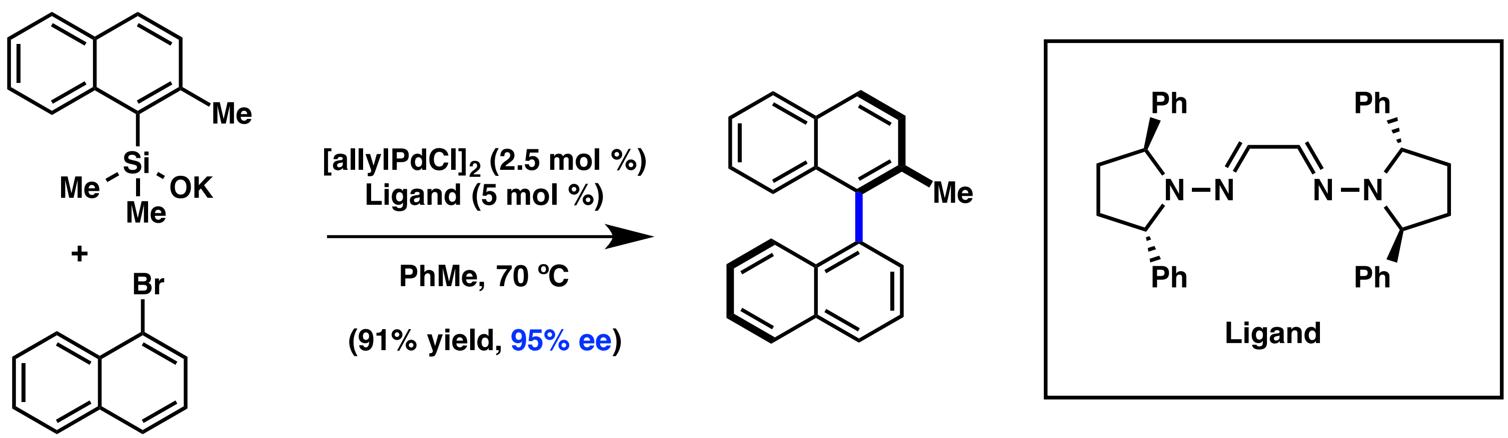




Espinet, P. *et al. Tetrahedron-Asymmetry* **2006**, *17*, 2593.
Sarandeses, L. A., *et al. Eur. J. Org. Chem.* **2013**, 2555.

# Cross-Coupling: Other Nucleophiles

*Silicon: Denmark, 2014*




-Coordinating substituents at 2-position decrease ee by competitive coordination with Pd.

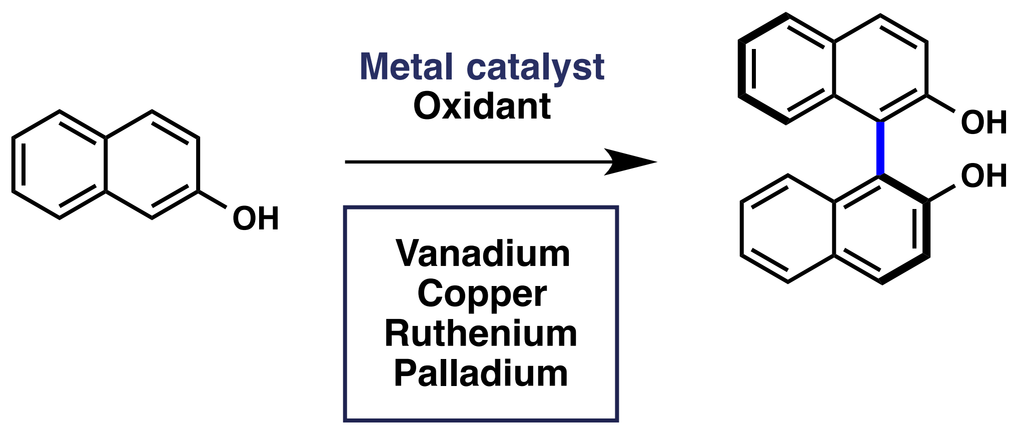
-Nucleophile/Electrophile swap gives identical ee. Combined with computational work indicates stereodetermining reductive elimination.

Denmark, S. E.; Chang, W.-T. T.; Houk, K. N.; Liu, P. *J. Org. Chem.* ASAP DOI: 10.1021/jo502388r

# Oxidative Coupling- Intro

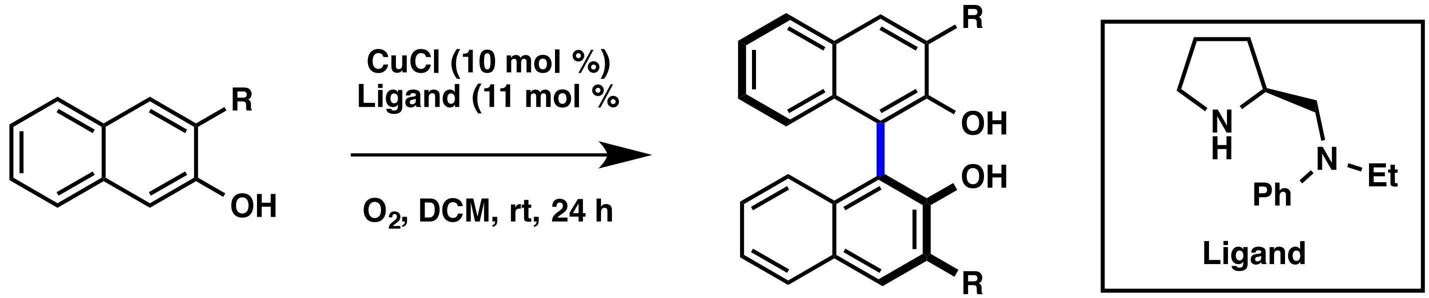
1. Catalytic asymmetric dimerization of activated phenols and naphthols

2. Oxidative cross-coupling of electronically differentiated arenes

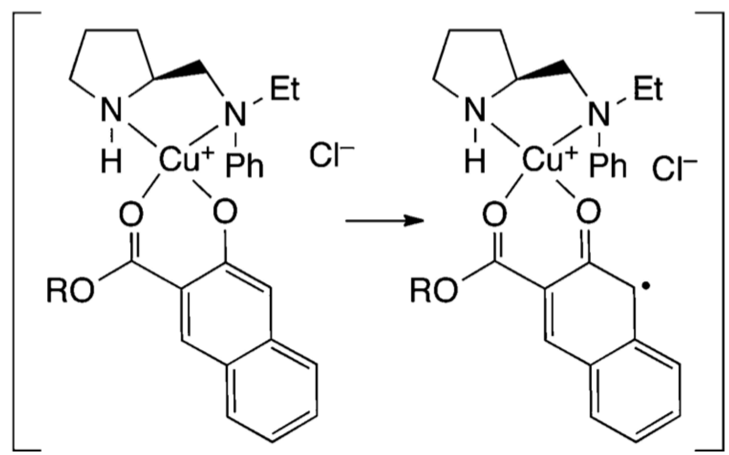


# Oxidative Coupling- Nakajima

*Nakajima, 1995*



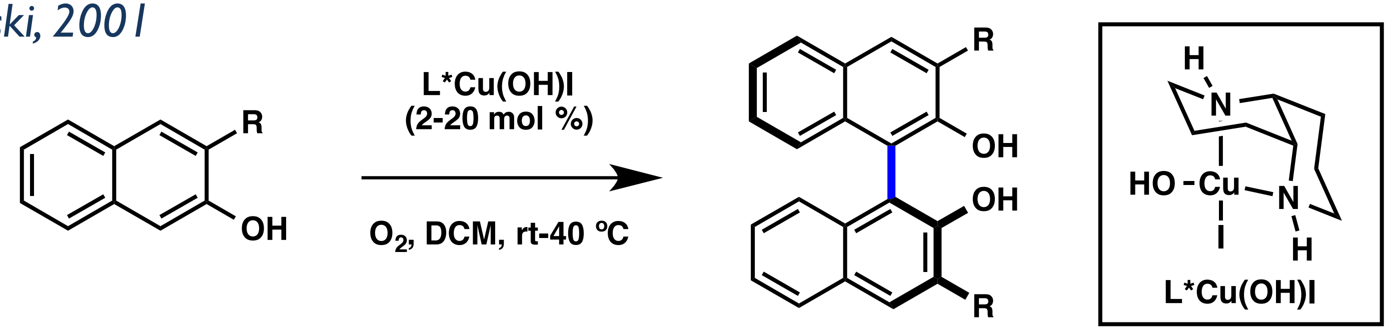

| R | yield (%) | ee (%) |
|---|---|---|
| $CO_2Me$ | 85 | 78 |
| $CO_2Et$ | 77 | 73 |
| $CO_2Bn$ | 77 | 76 |
| $CO_2$*t*-Bu | 69 | 58 |
| H | 89 | 17 |
| *i*-Pr | 58 | 5 |
| OBn | 95 | 24 |




Nakajima, M., *et al. Tetrahedron*. **1995**, 36, 9519.

# Oxidative Coupling- Kozlowski

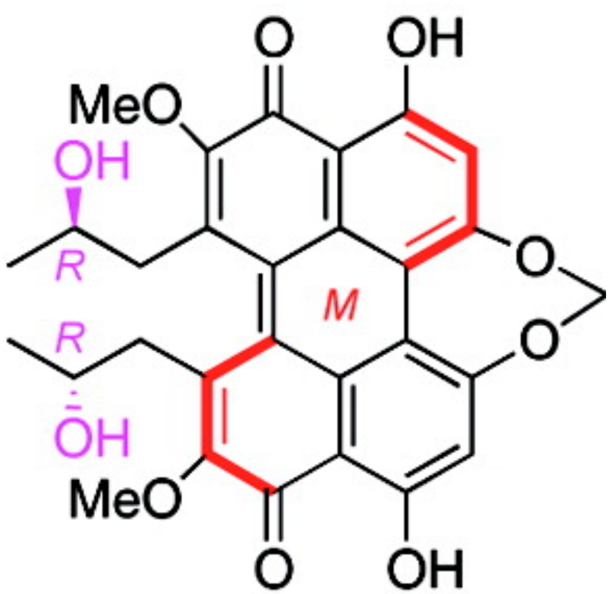
*Kozlowski, 2001*




| Entry | $R^1$ | Catalyst | Yield (%) | ee (%) |
|---|---|---|---|---|
| 1 | $CO_2Me$ | (*S*,*S*) | 85 | 93 (*R*) |
| 2 | $CO_2Me$ | (*R*,*R*) | 82 | 92 (*S*) |
| 3 | $CO_2Bn$ | (*S*,*S*) | 79 | 90 (*R*) |
| 4 | $CO_2$*n*-Hx | (*S*,*S*) | 70 | 87 (*R*) |
| 5 | $CON(CH_2CH_2)_2O$ | (*S*,*S*) | 61 | 75 (*R*) |
| 6 | COPh | (*S*,*S*) | 88 | 89 (*R*) |
| 7 | OBn | (*R*,*R*)-CuBr | 74 | 46 (*S*) |
| 8 | $P(O)(OMe)_2$ | (*S*,*S*) | 76 | 92 (*R*) |
| 9 | $SO_2C_6H_4$-*p*-OMe | (*S*,*S*) | 75 | 57 (*R*) (98, triturated) |

Li, X.; Yang, J.; Kozlowski, M. C. *Org. Lett.* **2001**, *3*, 1137.

# The Perylenequinones

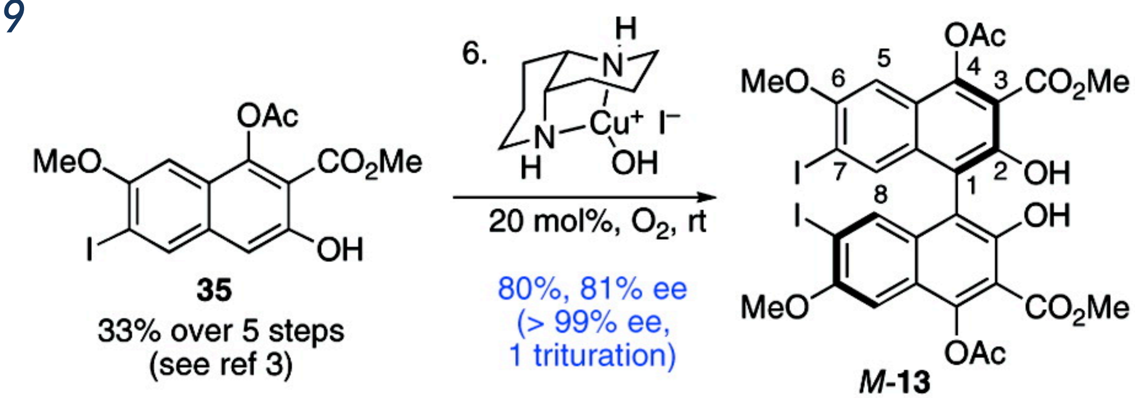



**Cercosporin (3)**

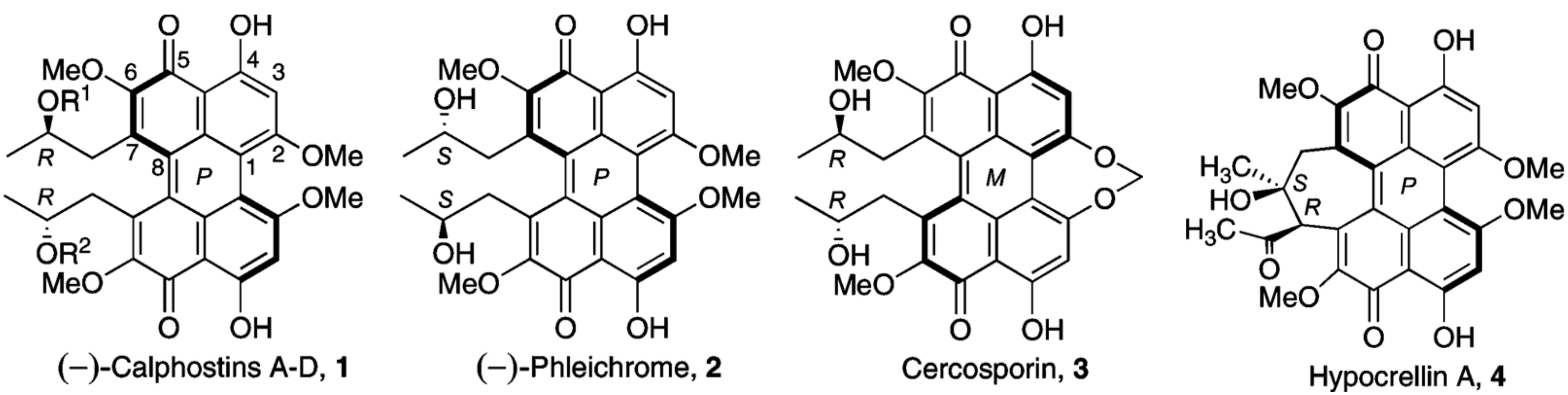
- Commonly isolated fungal natural products. Sources include *Cercospora kikuchii*, cause of soy bean "purple speck disease."
- Possess helical chirality about the core pentacycle. Atrop-stability varies among members of the family.
- Light-induced biological activity (singlet oxygen generation, ROS) makes them potential photodynamic therapeutics.

# Perylenequinone Syntheses

*Kozlowski, 2009*



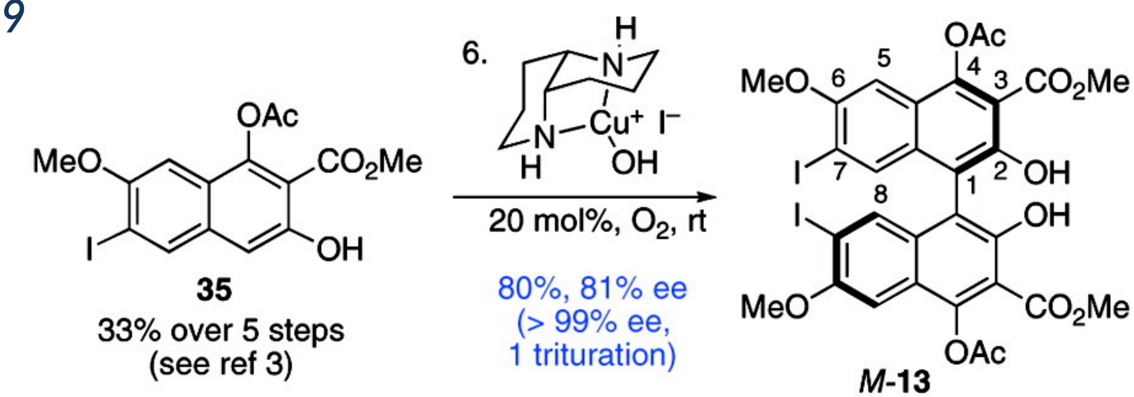

*Prepared from common intermediate:*



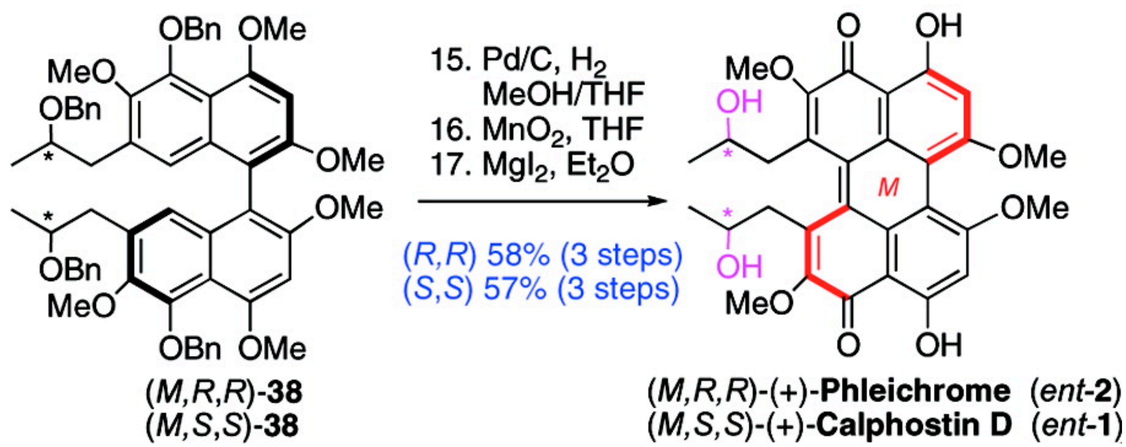

Kozlowski, M. C., *et al. J. Am. Chem. Soc.*, **2009**, 131, 9413.

# Perylenequinone Syntheses

*Kozlowski, 2009*



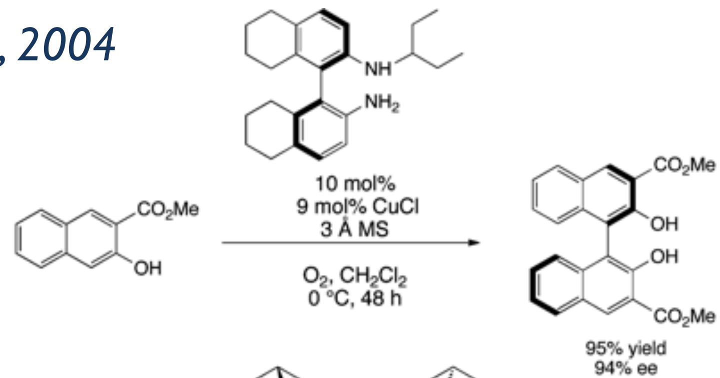

*Interesting bisquinone closure with $MnO_2$:*



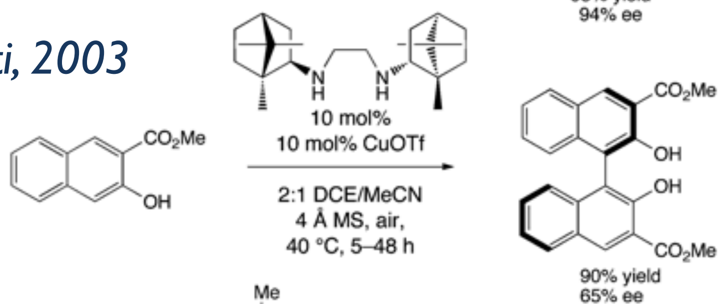

Kozlowski, M. C., *et al. J. Am. Chem. Soc.*, **2009**, 131, 9413.

# Oxidative Couplings

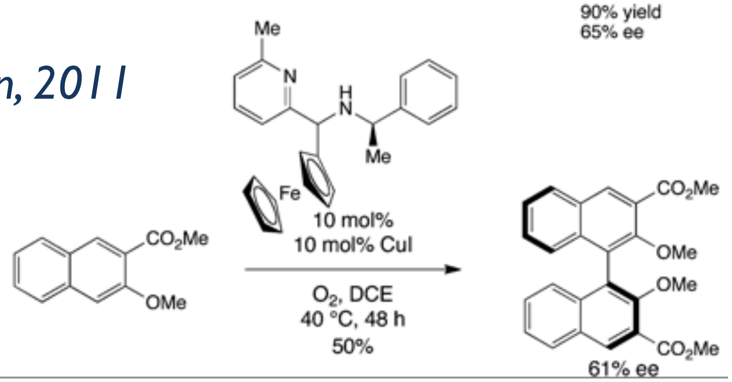
*Ha, 2004*



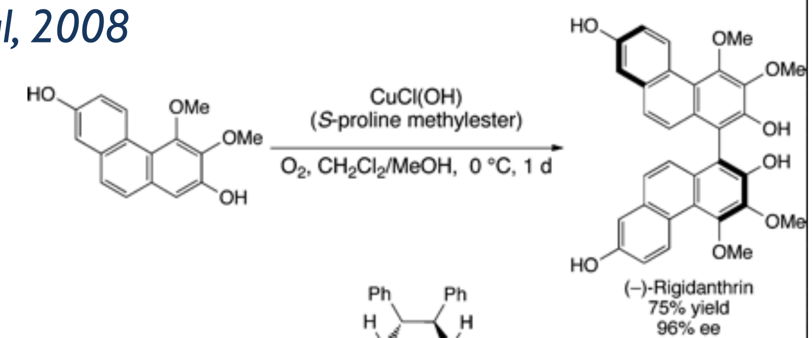

*Pilati, 2003*



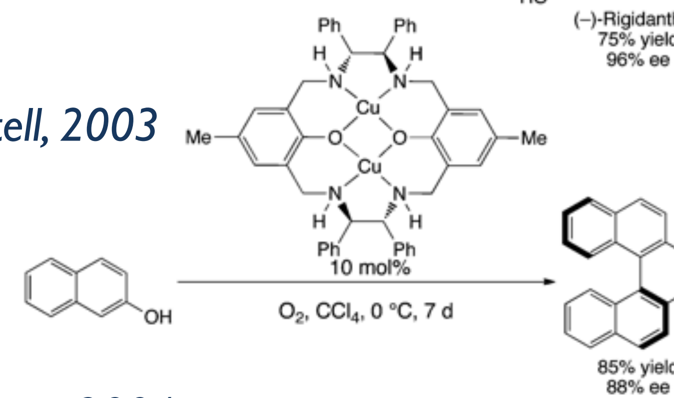

*Troin, 2011*



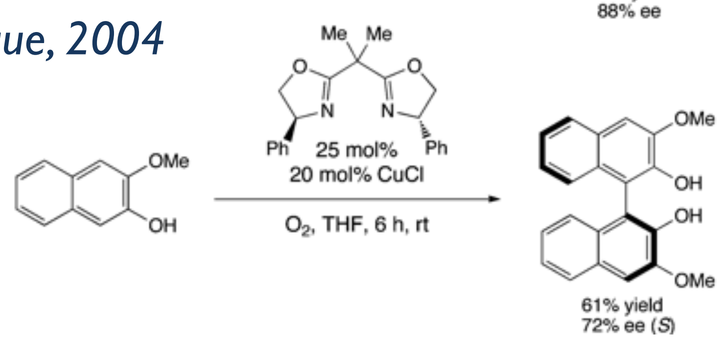

*Pal, 2008*




*Martell, 2003*

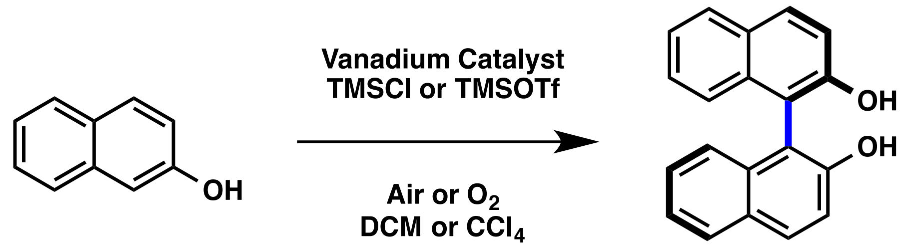


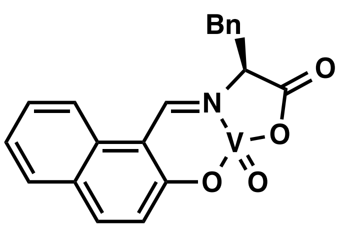

*Habaue, 2004*



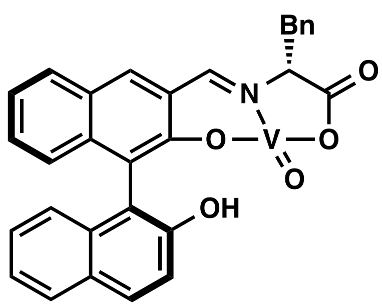

Ha, D.-C., *et al. Tetrahedron* **2004**, 60, 9037.
Pilati, T., *et al. Tetrahedron: Asymmetry* **2003**, 14, 1451.
Troin, Y. *et al. Organometallics* **2011**, 30, 4047.
Pal, S., *et al. J. Indian Chem. Soc.* **2008**, 85, 1116.
Martell, A. E., *et al. Angew. Chem., Int. Ed.* **2003**, 42, 6008.
Habaue, S., *et al. Polym. Sci., Part A: Polym. Chem.* **2004**, 42, 4528.

# Oxidative Coupling- Vanadium

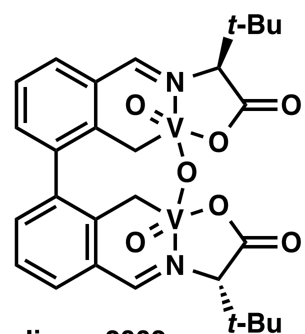


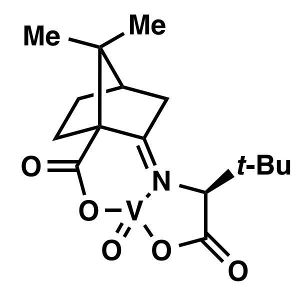

**Chen, 2001**
**(72% yield, 65% ee)**



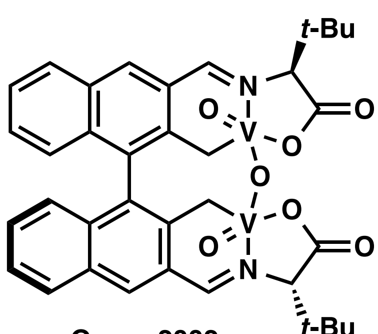

**Uang, 2002**
**(90% yield, 54% ee)**



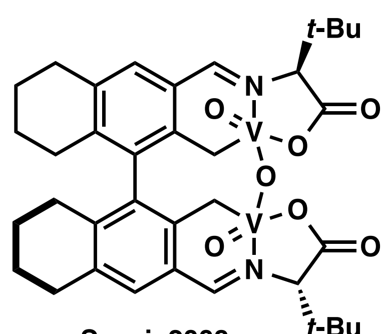

**Jiang, 2002**
**(62% yield, 90% ee)**




**Chen, 2002**
**(99% yield, 84% ee)**




**Gong, 2002**
**(95% yield, 83% ee)**




**Sasai, 2008**
**(76% yield, 91% ee)**


C.-T. Chen, *et al. Org. Lett.*, **2001**, 3, 869.
C.-Y. Chu and B.-J. Uang, *Tetrahedron: Asymmetry*, **2003**, 14, 53.
Y. Jiang, *et al. Chem. Commun.*, **2002**, 914.
N. B. Barhate and C.-T. Chen*, Org. Lett.*, **2002**, 4, 2529.
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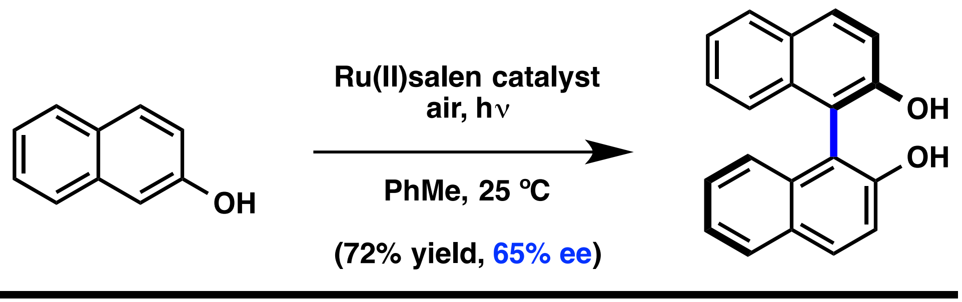
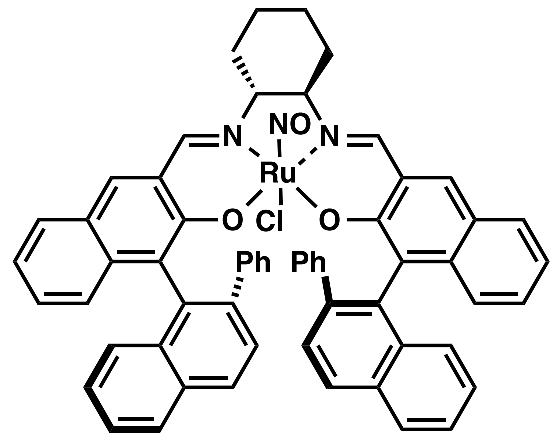
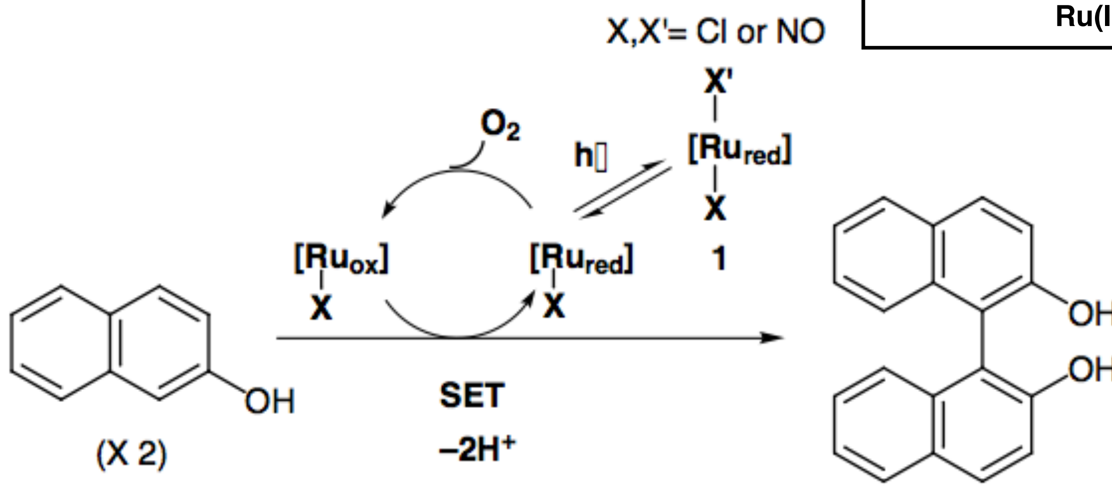
# Oxidative Coupling- Ruthenium

*Katsuki, 2000*




Ru(II)salen(NO)Cl

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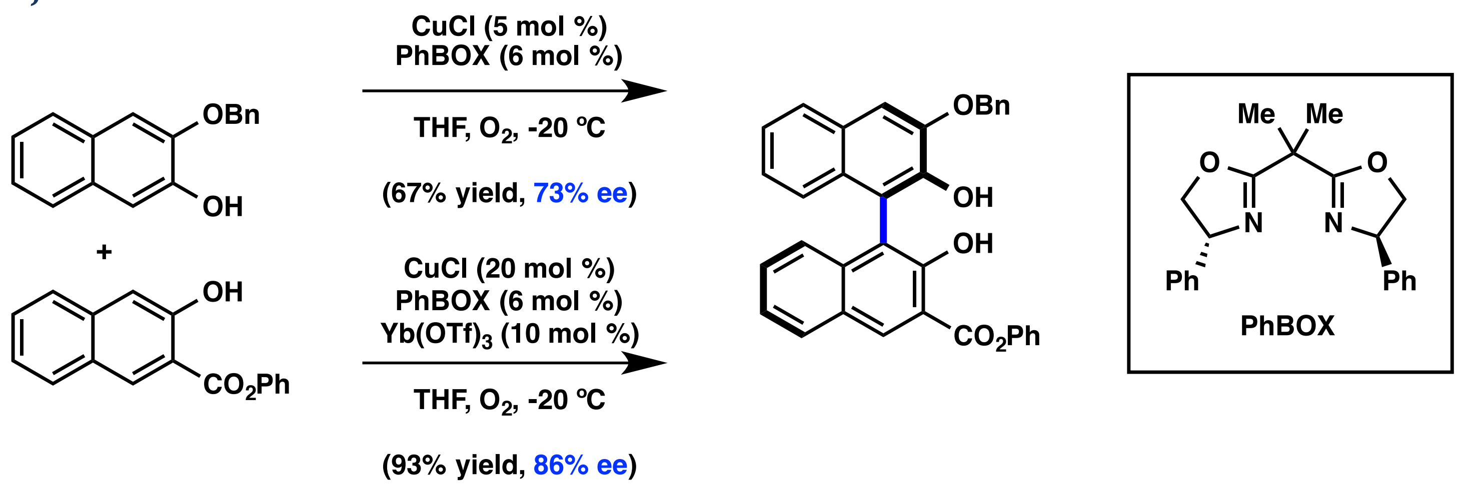
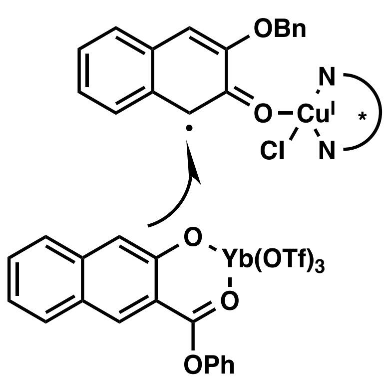
# Oxidative Heterocoupling

*Habaue, 2007*



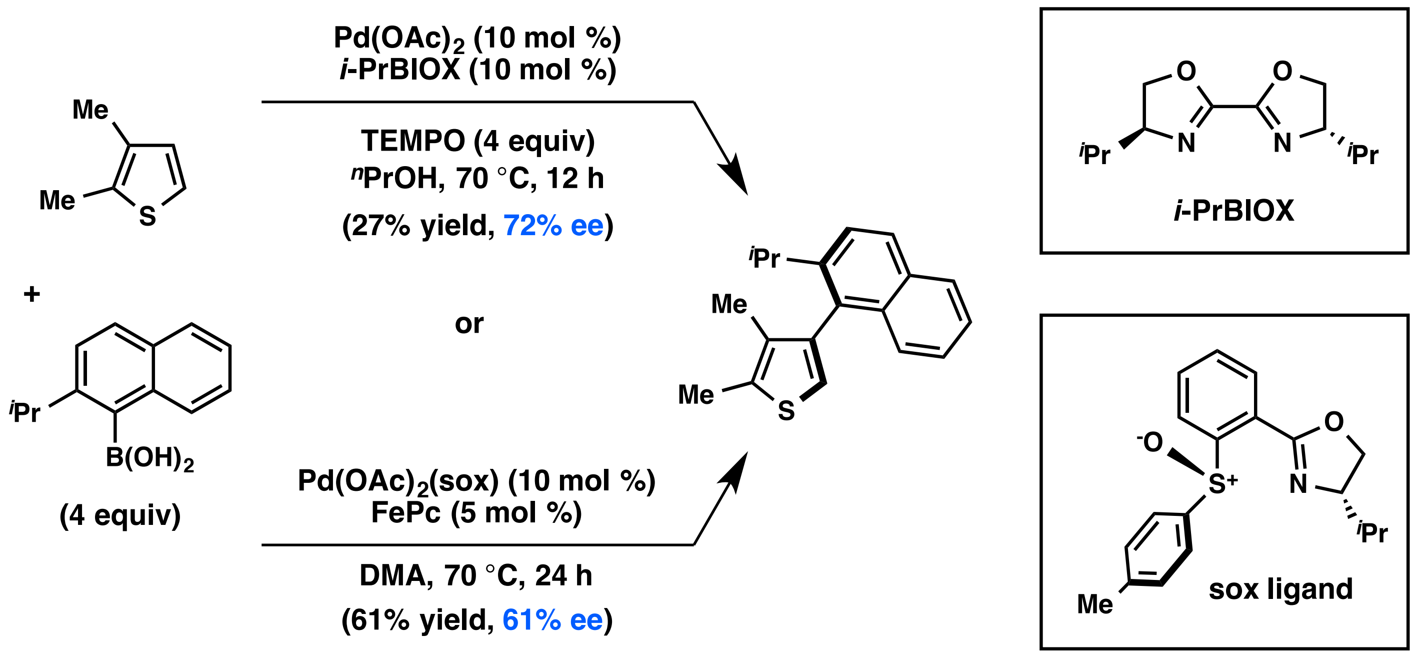




- Selective oxidation of more electron-rich naphthol
- Cross-selectivity achieved by activating chelating substrate with Lewis acid
- No mechanistic details reported

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

# Oxidative Heterocoupling

*Itami, 2012*

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# Conclusion

- Metal-catalyzed asymmetric biaryl cross-coupling has developed into a rich and synthetically useful field.
- Both redox-neutral and oxidative methods have been optimized and employed in complex settings.
- Oxidative cross-coupling and non-Mg, non-B redox neutral cross-coupling are underdeveloped emerging fields with significant potential.

# Resources

- Kevin Allen's group meeting, 2005:
  - Excellent coverage of diastereoselective methods and chiral leaving groups

    http://stoltz.caltech.edu/seminars/2005_Allan.pdf
- B. Collins (Denmark) group meeting, 2004:
  - Detailed descriptions of Vanadium oxidative reactions and aryl-Pb couplings

    http://www.scs.illinois.edu/denmark/presentations/2004/gm-2004-03_02.pdf
- M. Bruening review, 2011
  - Atropselective Total Synthesis of Axially Chiral Biaryl Natural Products

    *Chem. Rev.*, 2011, 111 (2), pp 563–639
- M. C. Kozlowski review, 2013
  - Aerobic Copper-Catalyzed Organic Reactions

    *Chem. Rev.*, 2013, 113 (8), pp 6234-6458