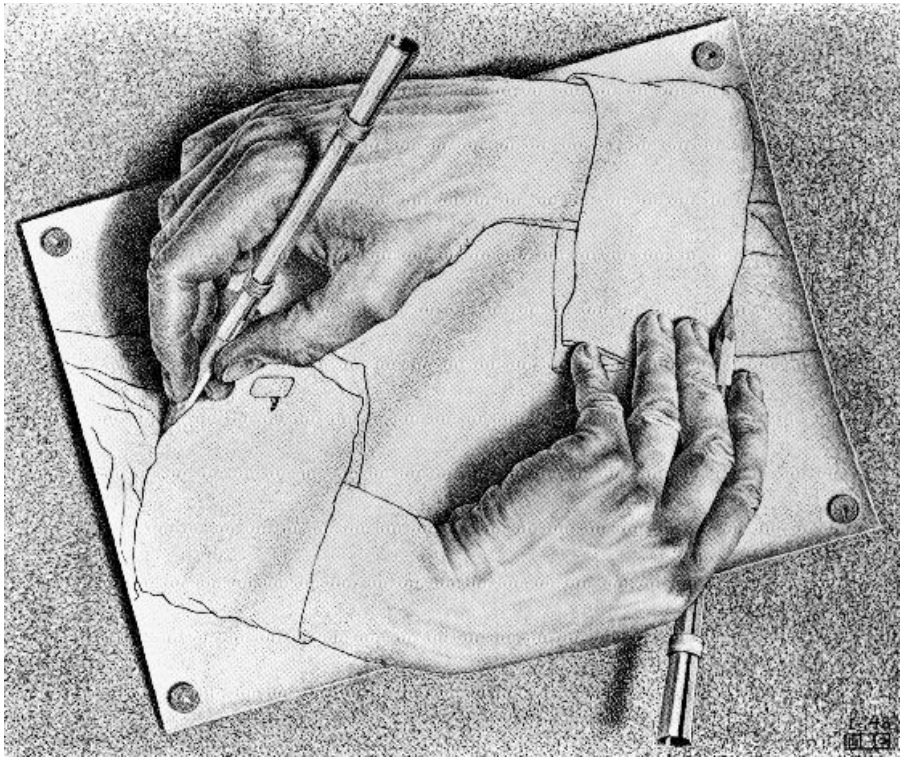
Biaryls in Nature and Synthetic Approaches to Axial Chirality

Frontiers of Chemistry
3/11/06
Erikah Englund



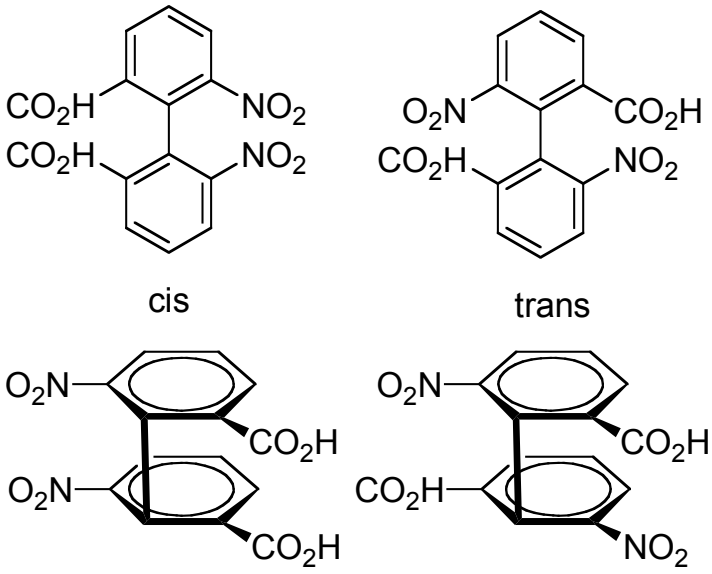
M.C.Escher's Drawing Hands

Outline

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

Timeline of Chirality

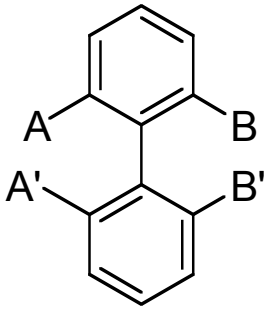
- **1848**: Louis Pasteur studied the enantiomers of tartaric acid while investigating the mechanism by which wine goes sour.
- **1874**: Van't Hoff proposed the tetrahedral carbon
- **1922**: Christie and Kenner first accurately described axial chirality (*J.Chem.Soc*. **1922**, *121*, 614)
- **1933**: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



Kaufler's explanation for axial chirality (*Ann*. **1907**, *151*, 351)

Features of Chiral Biaryl Atropisomers

- Stability/rotational barrier factors (a half life of 16.7 min (1,000 s) is considered physically separable):
  - Sterics (I>Br>Me>Cl>NO_2>CO_2H>OMe>F>H)
    - 3 or 4 ortho substituents generally form stable atropisomers
  - Existence, length and rigidity of bridges
    - 5 membered rings freely rotate at r.t.
  - Atropisomerization mechanisms
    - Physical (e.g. heat)
    - Photochemical
    - Chemically induced

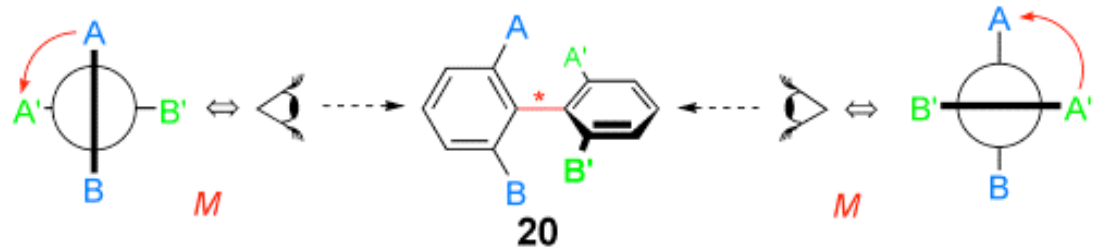


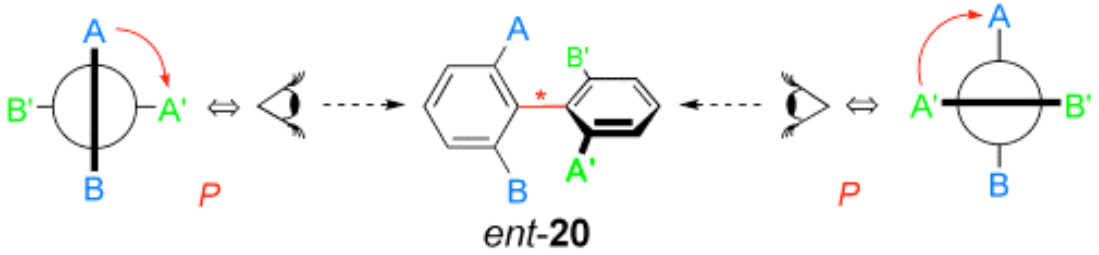
- Chirality criteria:
  - Different substituents on both sides of the axis (A≠B and A'≠B')
  - Presence and location of hetero-atoms
  - Different meta substituents

Angew.Chem.Int.Ed. **2005**, *44*, 5384

Assignment of Chirality

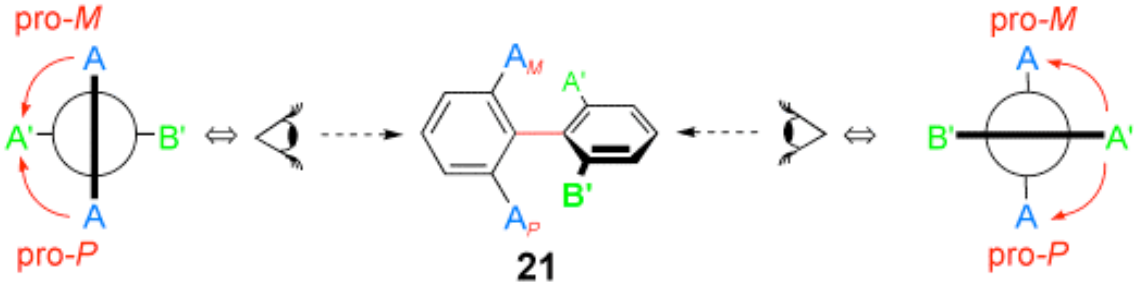
chirality in biaryl compounds (priority: A > B):





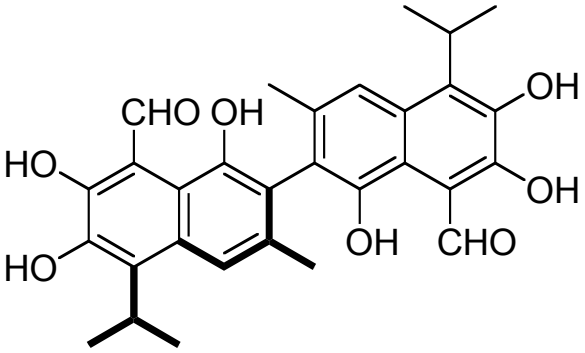
M=Minus
P=Plus

prochirality in biaryl compounds:



Angew.Chem.Int.Ed. **2005**, *44*, 5384

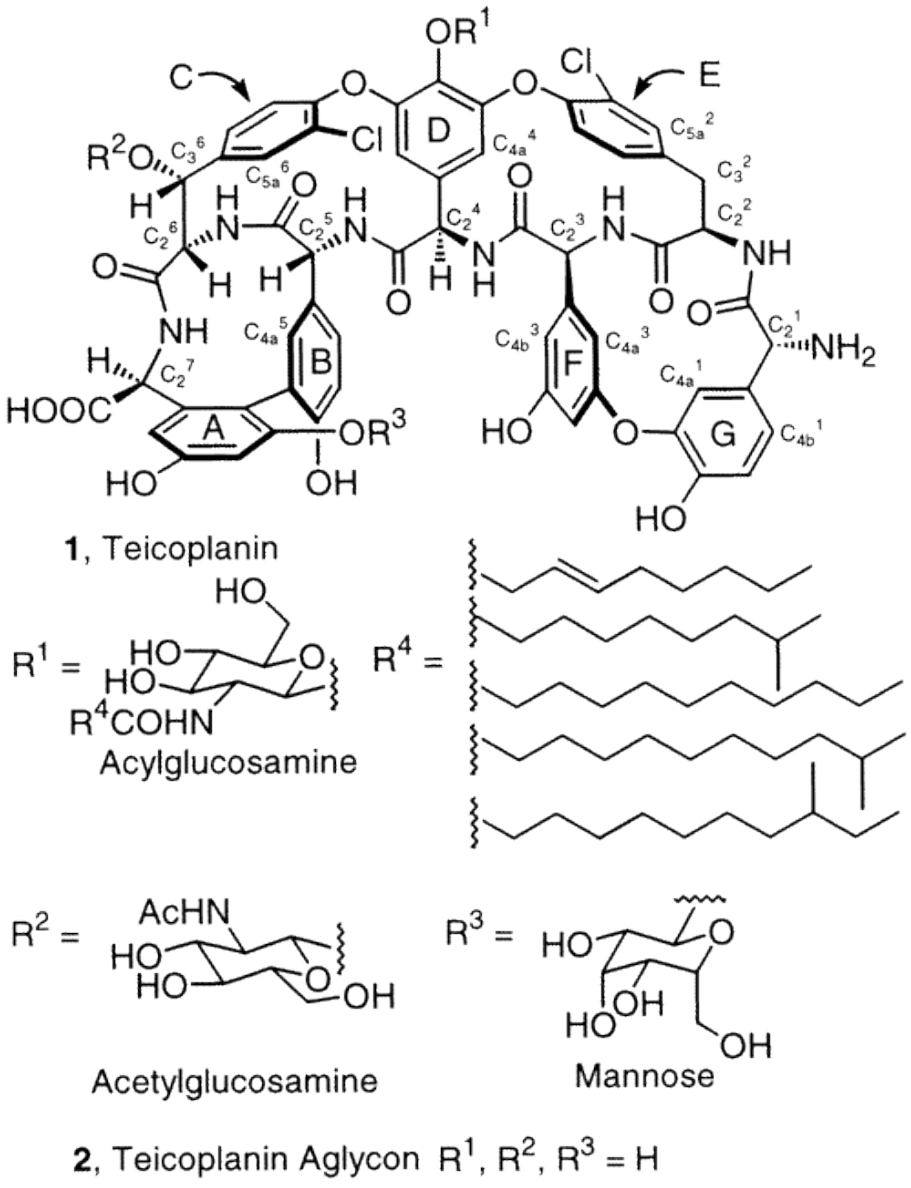
Biological Activity

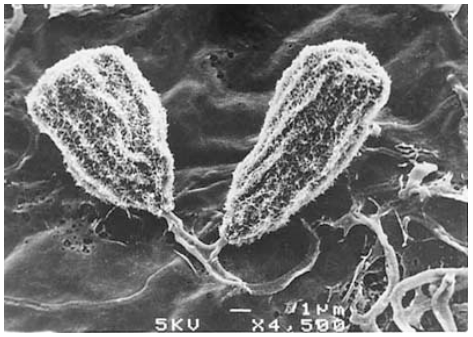


- Gossypol (from *gossypium hirsutum* seeds)
  - Discovered in 1899 (absolute stereochemistry determined in 1988)
  - The (-) enantiomer is either the major or sole possessor of the following biological activity:
    - Anti-fertility
    - Anti-tumor
    - Anti-amoebic
    - Anti-HIV

Phytochemistry,**1991**, *30*, 2655

Biological Activity (cont.)



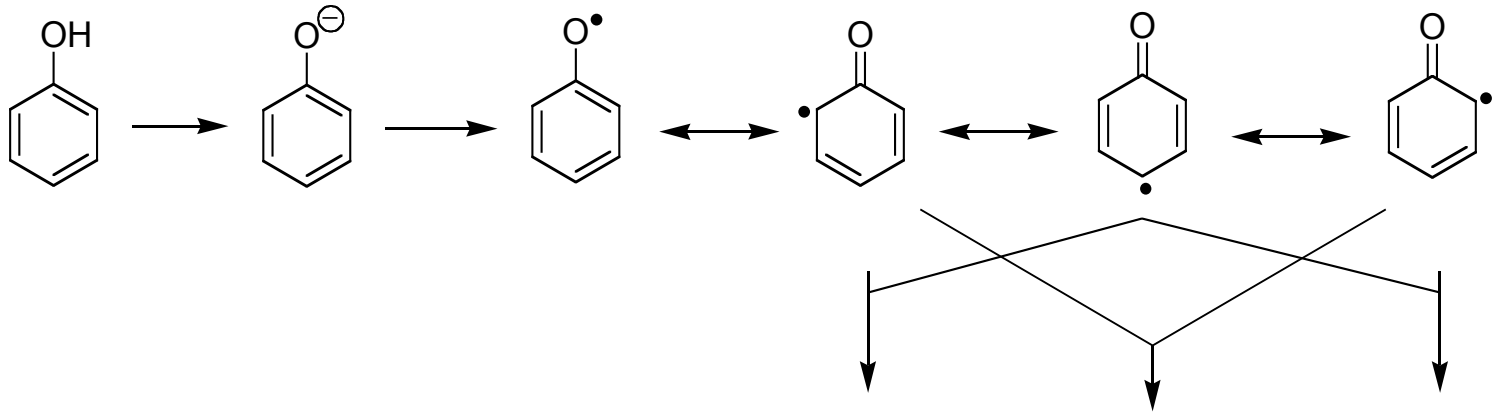


- Antimicrobial Teicoplanin (*actinoplanes teichomyceticus*)
  - 2-8 fold more potent than vancomycin and less cytotoxic
  - The biological activity of the DE ring atropisomer was 50 fold less active than the parent compound in antimicrobial and cell free binding assays

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

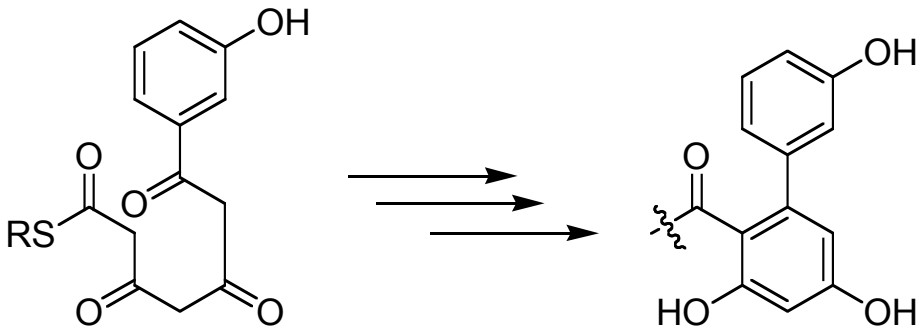
Biosynthetic Pathways

- **Oxidative phenolic coupling**



coupled biaryls

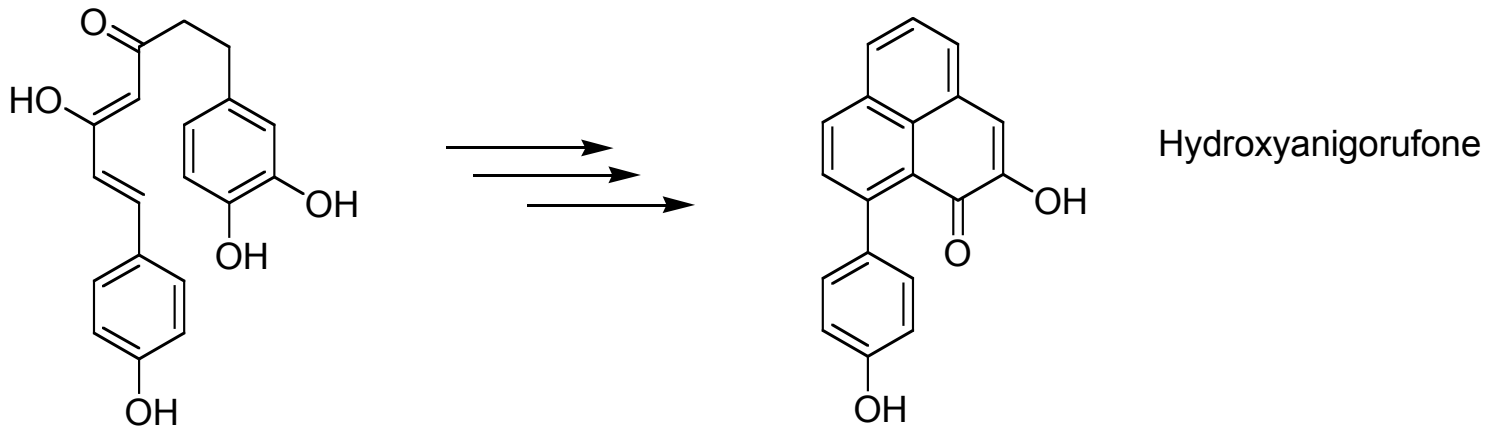
- **Polyketide cyclization**



Bringmann, *Progress in the Chemistry of Organic Natural Products* Vol. 82, **2001**, 1-249

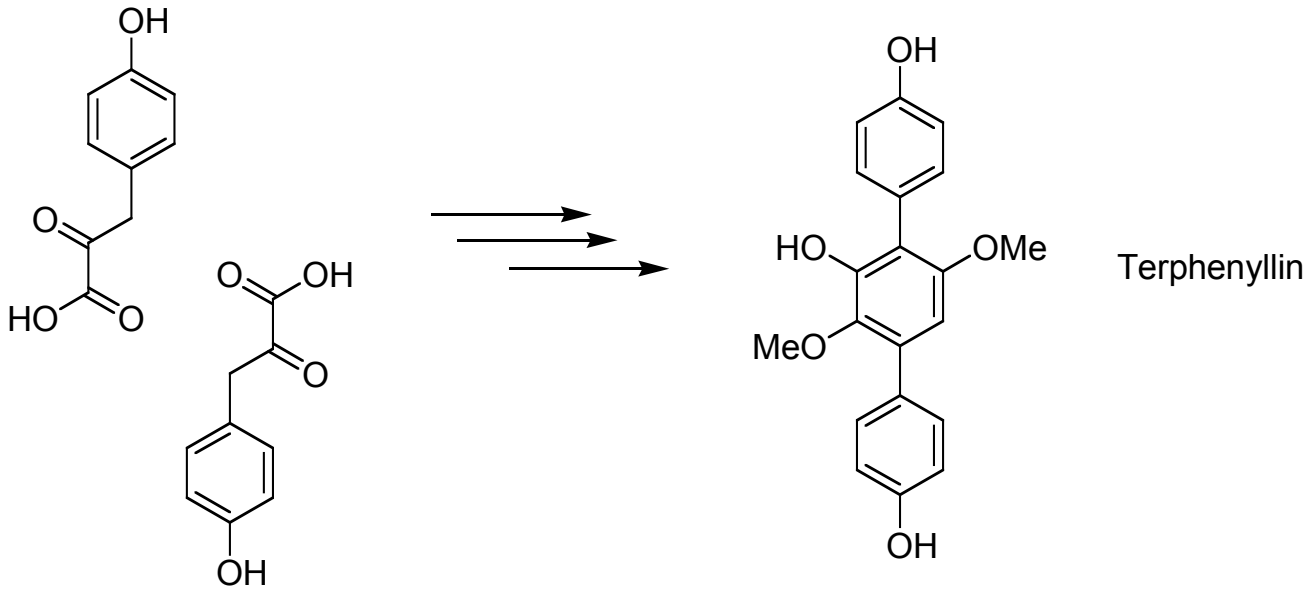
Biosynthetic Pathways (cont.)

- **Diels-Alder**



Hydroxyanigorufone

- **Aldol type cyclizations**



Terphenyllin

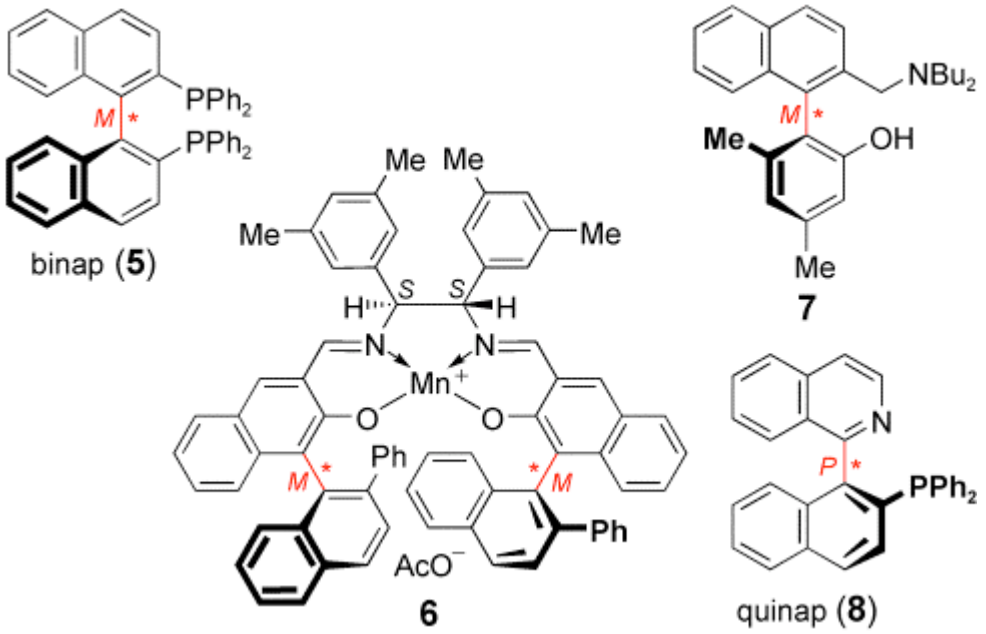
Biaryls in Nature

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

Bringmann

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

Biaryl Ligands



Ligand Review: *Tetrahedron* **2001**, *57*, 3809

Synthesis

- "Classic concept"
  - C-C bond formation between two aryl systems with simultaneous asymmetric induction
- Transformation of a "pro-chiral" biaryl system into a chiral system through chemical transformation
  - Desymmetrization
- Generation of second aromatic ring from nonaromatic precursor with simultaneous generation of desired chirality

I. Classical Approaches

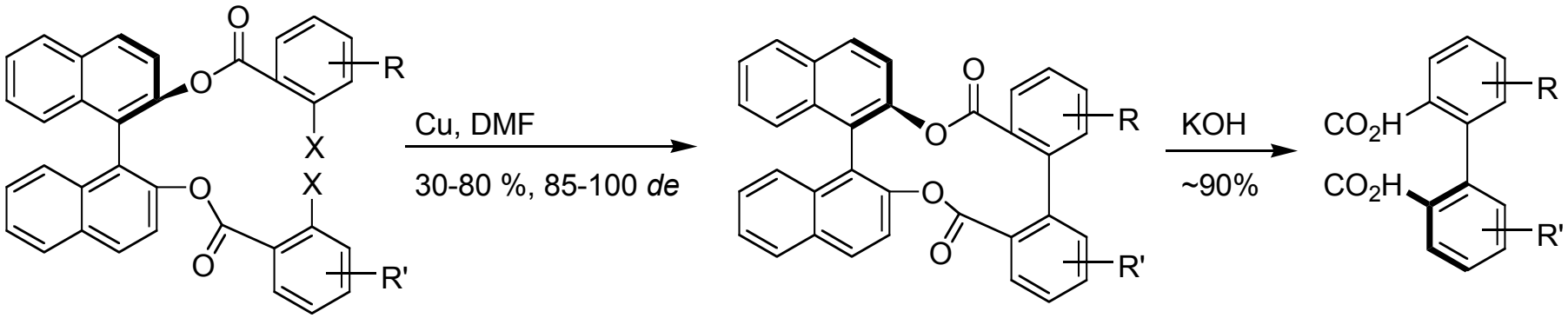
- Diastereoselective approaches:
  - Chiral bridge linking the two coupling partners
    - Bridge might or might not be present in final product
  - Chiral auxiliary on the arene (usually ortho position)
  - Incorporation of removable chiral unit (η^6 chromium complex)

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

Aryl-aryl bond formation review: Hassan, *Chem.Rev.***2002**, *102*, 1359

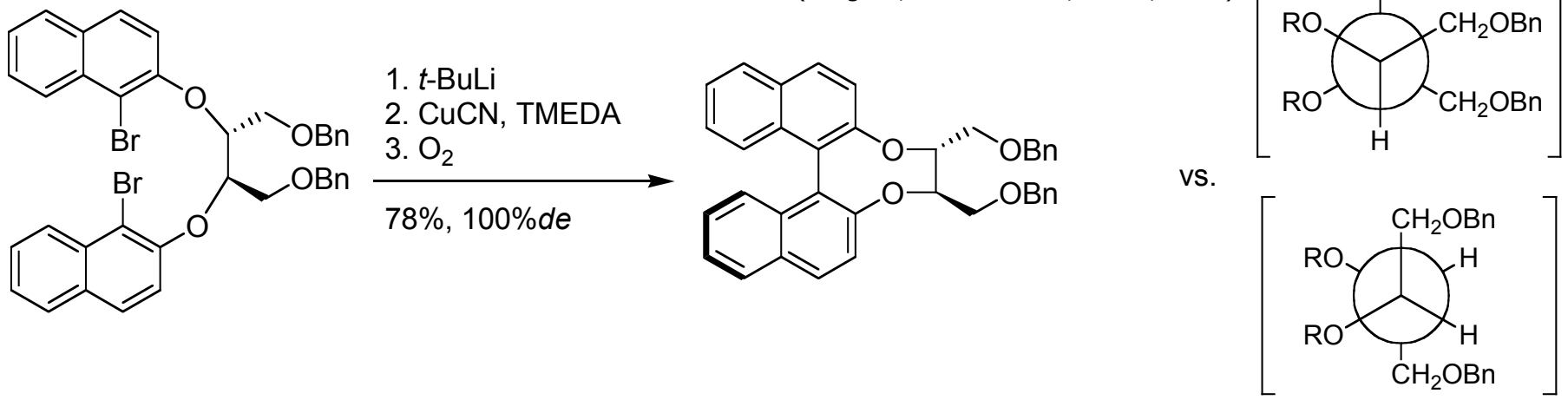
Classical Approach- chiral tethers

- Pioneering Work: (Miyano, *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3522)



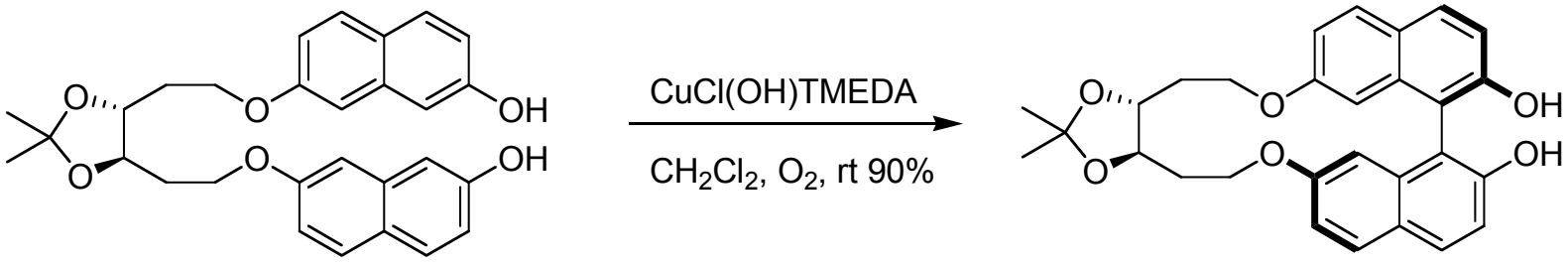
- Modifications: (Lipshutz, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1842)

Favored due to anomeric effect
(Sargent, *Chem.Comm*, **1998**, 2713)

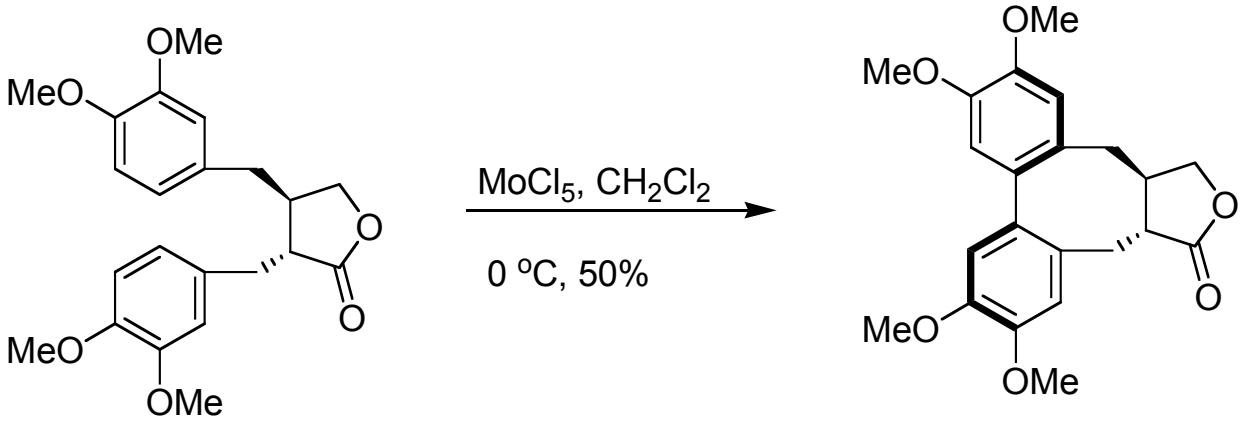


Additional Tethers

- **Acetonide** (Lipshutz, *Tetrahedron Lett.* **1997**, *38*, 753)
  - Designed to allow access to BINOL derivatives

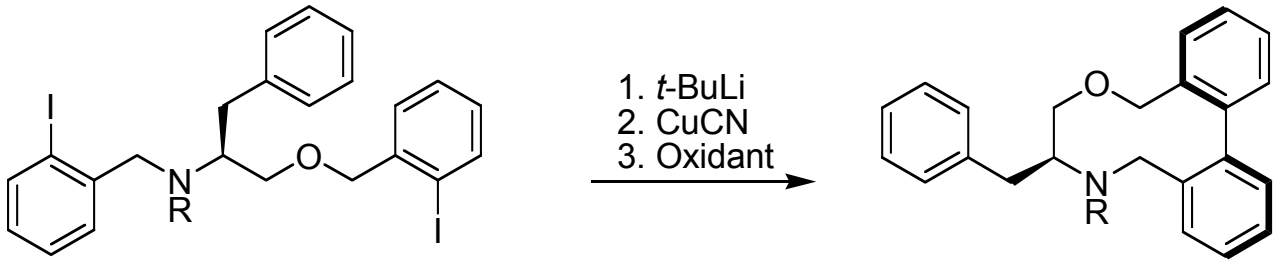


- **Lactone** (Waldvogel, *Angew. Chem. Int. Ed.* **2002**, *41*, 2981)
  - Structural motif in biologically active lignans (Charlton, *J.Nat.Prod*, **1998**, *61*, 1447)



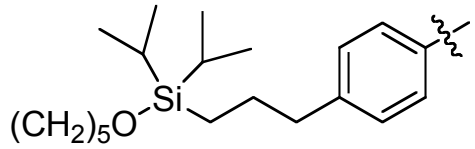
Schreiber's application to DOS

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



55%, 6:1 P:M

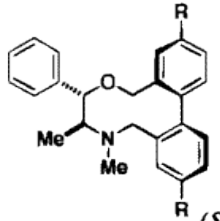
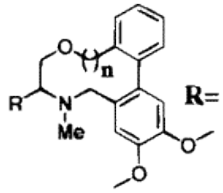
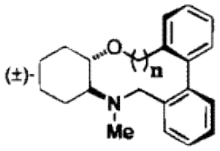
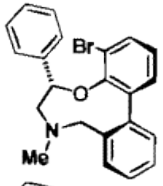
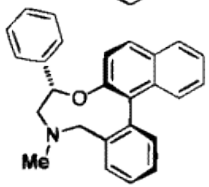
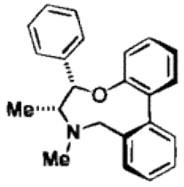
R=



500-560 micrometer polystyrene beads

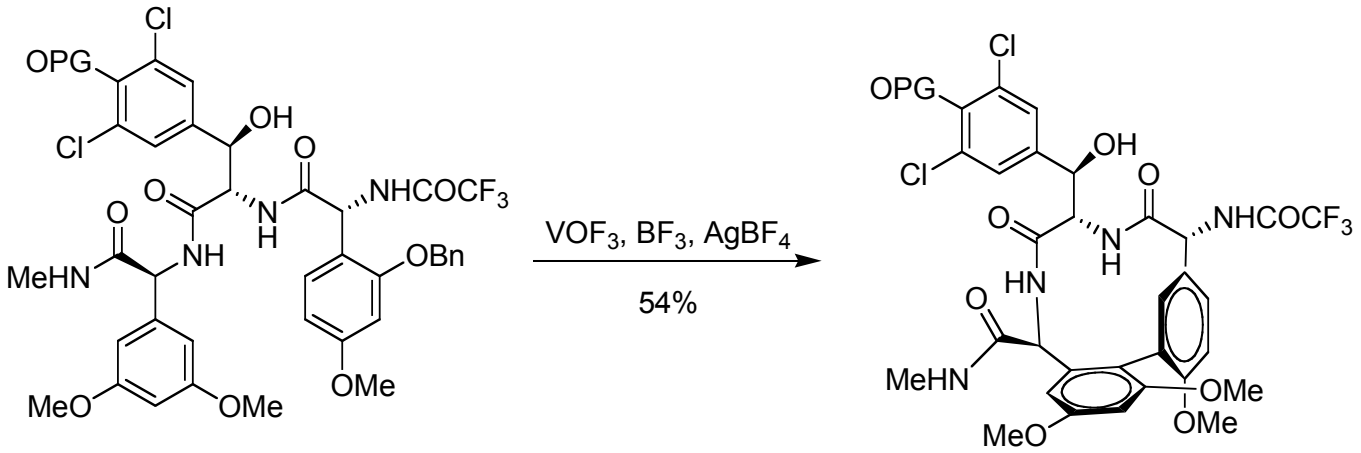
Schreiber's DOS results

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

Entry	Biaryl (3)[a]			% Yield[b]	Kinetic dr (*P*:*M*)[c]	Thermodynamic dr (*P*:*M*)[d]
h		R=H		94	17:1	1:1.5
i		Cl		94	6:1	1:2
j		(*S*)-Bn	1	92	16:1	1:11
k		(*R*)-Ph	1	84	1:23	2:1
l		(*S*)-*t*-Bu	1	83	4:1	1:2
m		(*S*)-CH_2Cy	1	88	22:1	1:11
n		R= (*S*)-*i*-Bu	n= 1	97	35:1	1:10
o		(*R*)-Et	1	91	1:25	9:1
p		(*R*)-Me	1	94	1:32	6:1
q		(*S*)-Bn	0	97	3:1	UD[g]
r		(*S*)-*i*-Bu	0	93	2:1	UD[g]
s		n=1		77	11:1[h]	1:3[h]
t		0		96	>50:1[i]	UD[g]
u				81[j]	1:>50	UD[g]
v				73	1.5:1	UD[g]
w				68	1:10	UD[g]

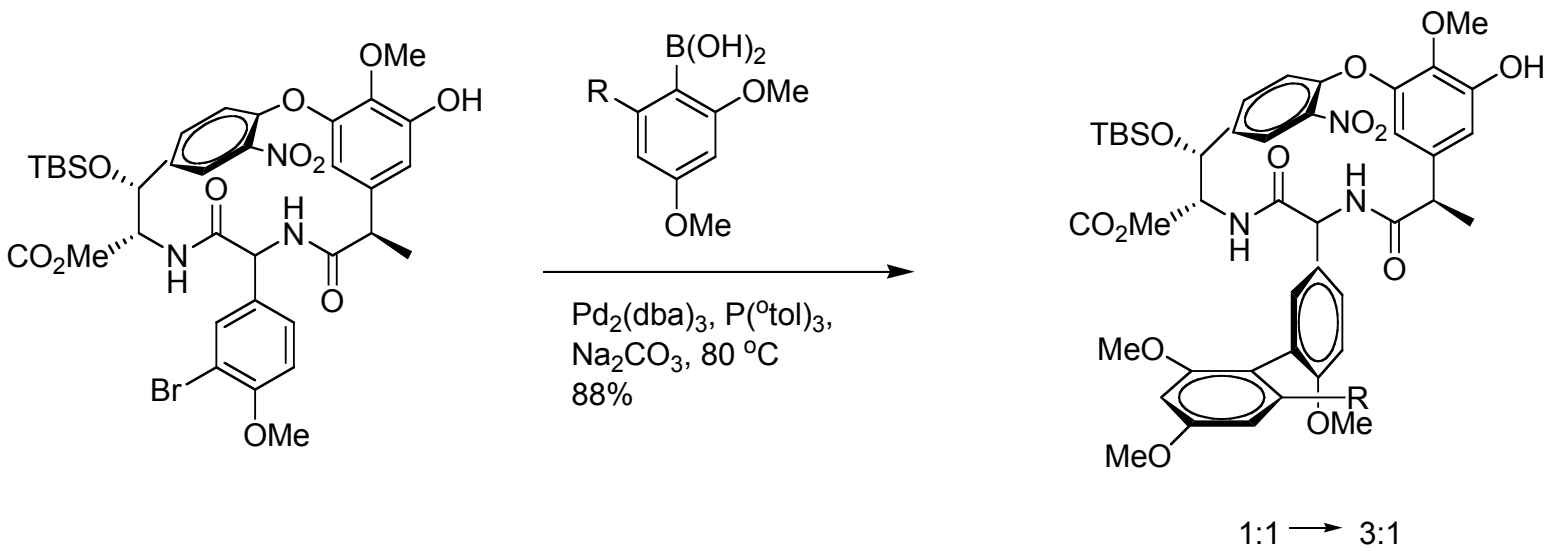
Total Synthesis Applications- Vancomycin

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



95:5

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



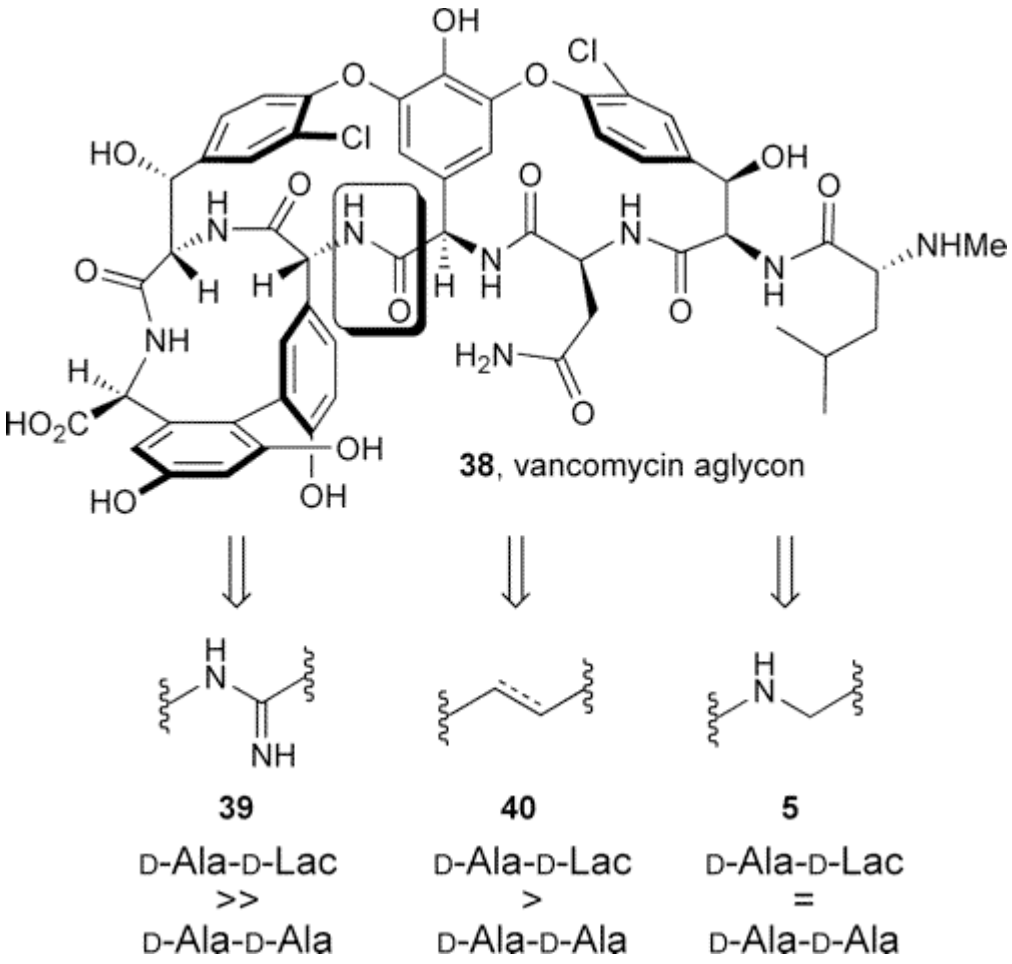
1:1 → 3:1

Vancomycin Derivatives

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

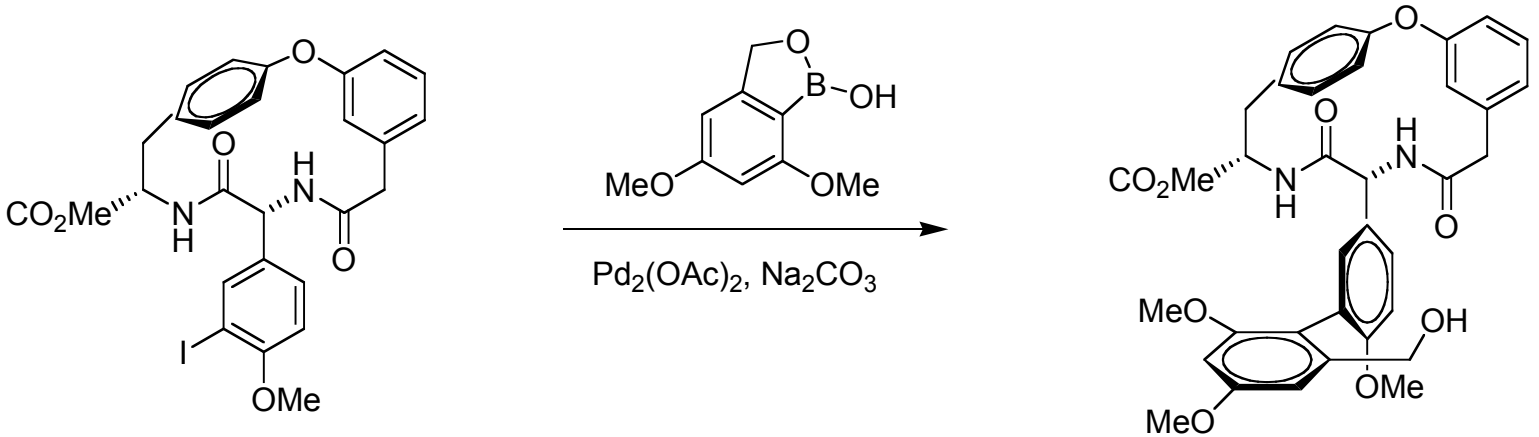
  - The A-B ring system was constructed in the same fashion as the parent compound (Suzuki coupling followed by thermal equilibration)

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



Vancomycin- Chiral Ligands

- Nicolaou (*Chem. Eur. J.* **1999**, *5*, 2584-2601)

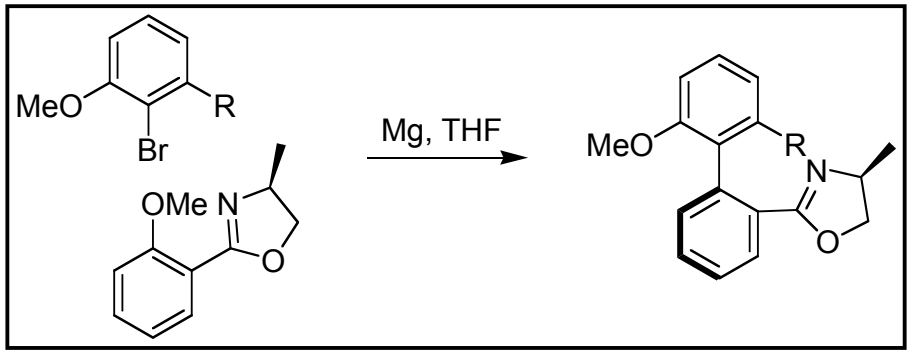


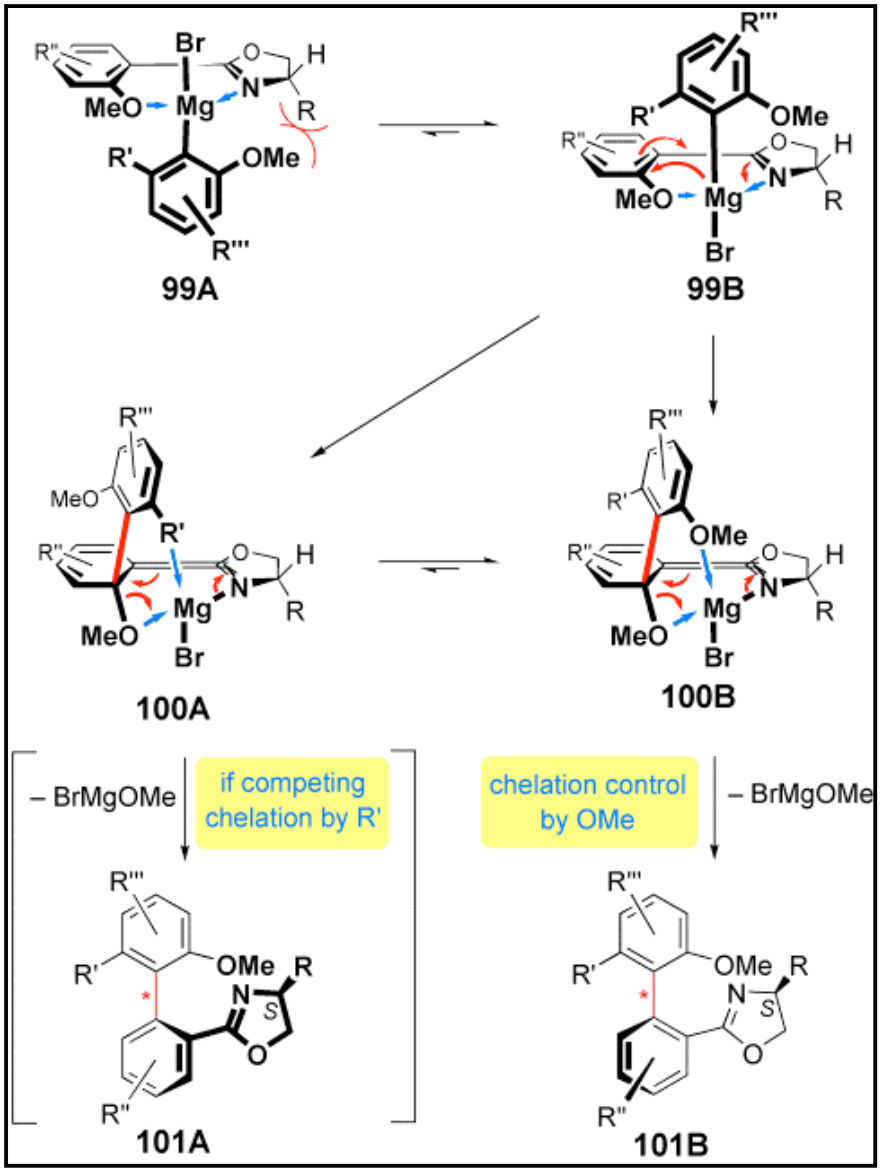
+ atropisomer

Entry	Ligand	Solvent	Temp	Time (h)	Yield	Ratio
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	95:5
6	R-BINAP	PhMe:THF(1:1)	70	5	40	5:95

Chiral Ortho Substituents

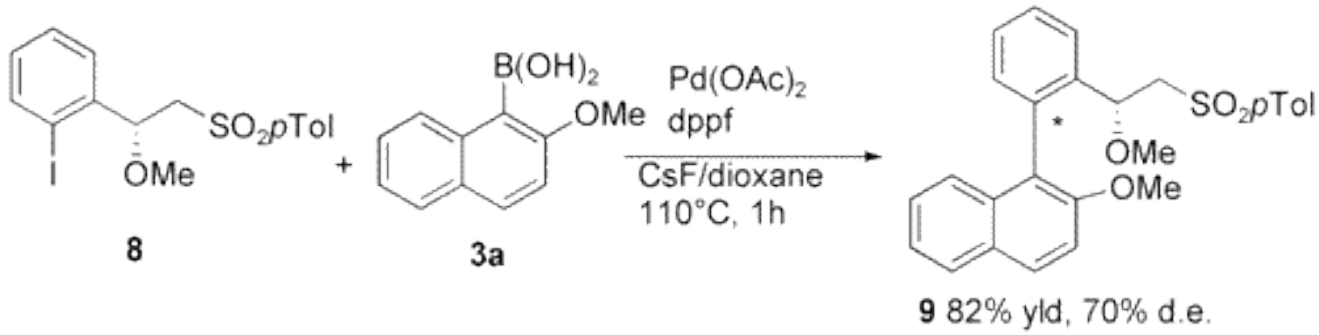
- Oxazoline and asymmetric Grignard addition (Meyers, *JACS,* **1985**, *107*, 682)
  - Grignard reagent essential
    - Low selectivity with aryllithium
    - Good yields of tri-ortho substituted products. Tetra-ortho substituted products are produced in low yields
  - R' and R''= Me, OMe, OMOM or OTBS,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



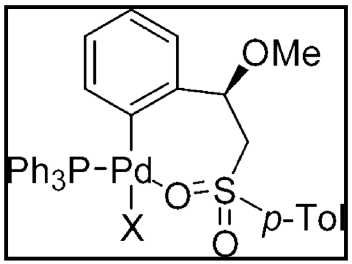


Chiral Ortho Substituents (cont.)

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

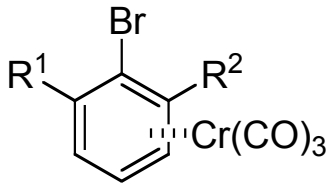


  - Mechanistic studies (Colobert, *Org.Lett*, **2005**, *7*, 3737)
    - Diastereoselectivity when SO_2pTol is replaced with:
      - H=60/40
      - OMe or OBn=70/30
      - NMe_2=<95/5
    - Proposed palladacycle intermediate:



Removable Chiral Unit

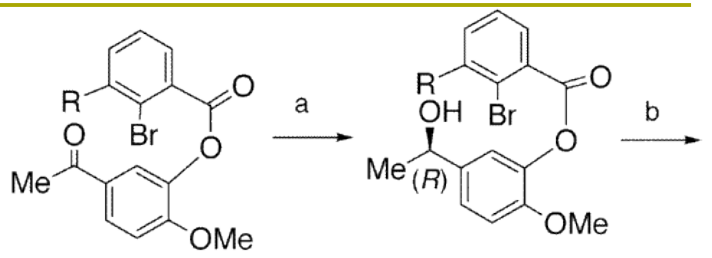
- Chromium complex (Uemura, *Synlett* **2000**, 938-949)



  - Used in:
    - Pinacol coupling with SmI_2 (*J.O.C.* **1996**, *61*, 6088)
    - Enantiotopic lithiation (*J.O.C.* **2002**, *67*, 1929)
    - Suzuki coupling (*Org. Lett.* **2001**, *3*, 2033)
      - Accelerates oxidative addition to aryl halide
      - Poor yields when chromium complexed to aryl boronic acid
  - Chromium removed through photooxidative demetalation
  - Disadvantages:
    - laborious to get to single enantiomer of chromium complex
    - toxic

Removable Chiral Unit

- Ruthenium complex (Uemura, *Org.Lett.* **2001**, *3*, 3667)
  - Single diastereomer
  - Reagents: (a) $BH_3 \cdot Me_2S$, (*S*)-oxazaborolidine b), (b) $Pd(OAc)_2$, (c) $[CpRu(CH_3CN)_3]PF6$, $(CH_2Cl)_2$, reflux, (51%), (d) NaOMe, MeOH, (98%), (e) *hv*, CH_3CN, (95%).

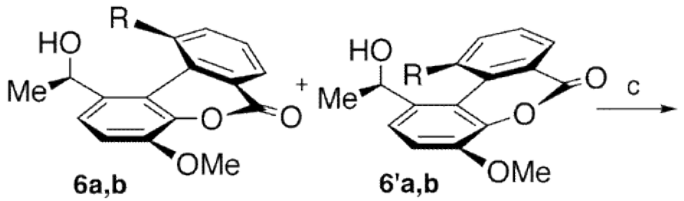


4a; R = Me

4b; R =OMe

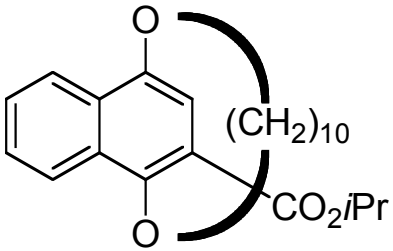
5a; $[\alpha]_D^{21}$ 9.3 (*c* 1.1, $CHCl_3$)

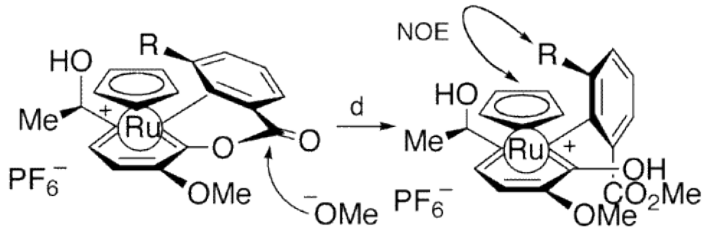
5b; $[\alpha]_D^{25}$ 19.5 (*c* 0.7, $CHCl_3$)



6a,b **6'a,b**

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



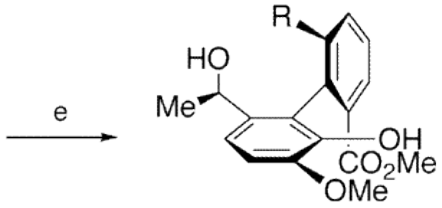


7a; $[\alpha]_D^{20}$ –24.2

7b; $[\alpha]_D^{24}$ –20.0

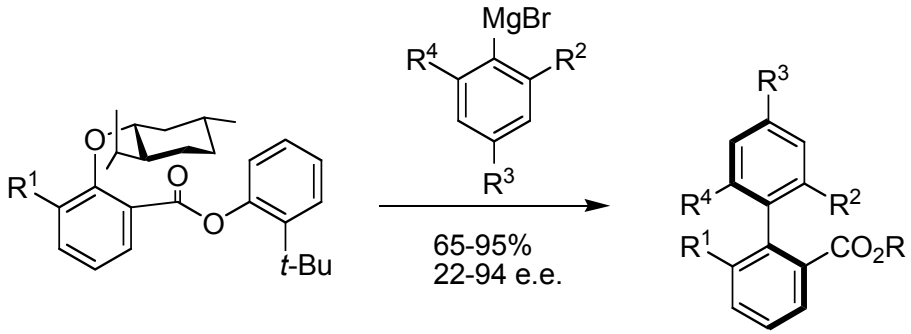
8a; $[\alpha]_D^{20}$ 67.3

8b; $[\alpha]_D^{25}$ 68.6

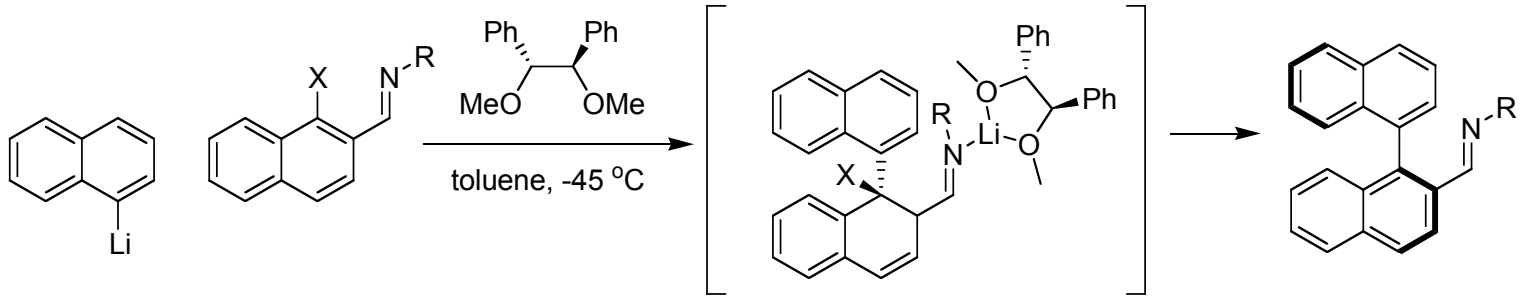


Enantioselective Approaches

- Chiral leaving group:
  - Initial studies found yields: 7-83% and optical purities: 10-95% (Wilson and Cram, *J. Am. Chem. Soc.* **1982**, *104*, 881-884)
  - Later work with menthyl:(Miyano, *J. Chem. Soc. Perkin Trans. 1* **1994**, 2273-2282)

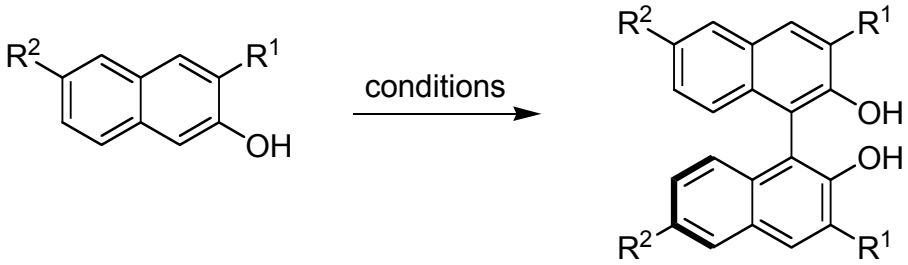


- Chiral Lithium (Tomioka, *J. Am. Chem. Soc.* **1992**, *114*, 8732-8733)
  - X=F, OMe, or OEt. Yield=81-99%, *ee*=82-90%



Oxidative Homocoupling

- Metal based with chiral ligand



  - **First report: $Cu(II)(NO_3)_2.3H_2O$ with chiral amine ligands** (Wynberg and Feringa, *Bioorganic Chemistry*, **1978**, *7*, 397-408)
    - **R¹**=H, 1-8% *ee*; **R¹**=ester, 6-16% *ee*
  - **Copper and 1,5, diazacis-decalin** (Kozlowski, *JOC*, **2003**, *68*, 5500)
    - **R¹**=H, 4-18% *ee*; **R¹**=ester, 56-94% *ee*
  - **Photochemical with chiral ruthenium salen catalyst** (Katsuki, *Synlett* **2000**, 1433-1436)
    - **R²**=H, 65% *ee*; **R²**=OMe, 33% *ee*, **R²**=methyl ester, 0% ee
  - **Vanadium catalyzed** (*Angew. Chem. Int. Ed.* **2002**, *41*, 4532-4535)
    - **R¹**=H, 89% *ee*; **R¹**=Br, 88% *ee*
  - **Electrochemical** (Osa, *J. Chem. Soc. Chem. Commun.* **1994**, 2535-2)
    - **R¹**=H, 99% *ee*
    - Works with both free alcohol and methyl ether

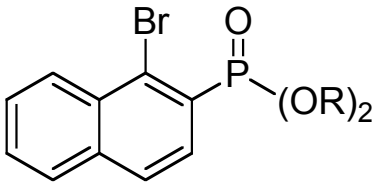
Redox Neutral Cross Coupling

- Enantioselective examples include:
  - Kumada coupling (Hayashi, *J. Am. Chem. Soc.* **1988**, *110*, 8153-8156)
    - Ni or Pd catalyzed with ferrocene derived ligand
    - 40-84 % yield and 16-83 % *ee*
    - Coupled naphthalenes with Me or Et substituents
  - Suzuki cross coupling (Buchwald, *J. Am. Chem. Soc.* **2000**, *122*, 12051)
    - 40-87% yield and 71-95 % *ee*
    - Conditions compatible with phosphonate and OMe substituents

- Currently, no examples of asymmetric:
  - Stille
  - Negishi

Buchwald Coupling Conditions

- 3a R=Et
- 3b R=Me
- 4a X=I
- 4b X=Br
- 4c X=Cl



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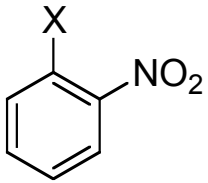
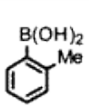
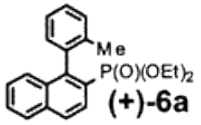
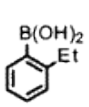
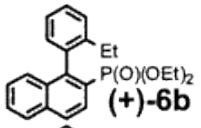
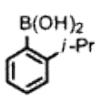
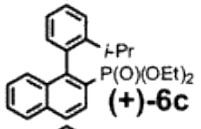
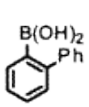
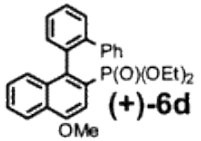
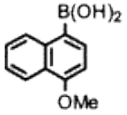
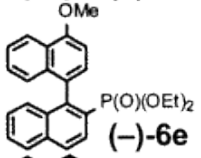
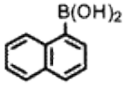
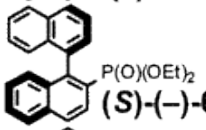
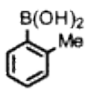
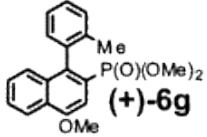
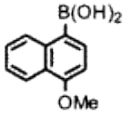
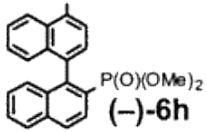
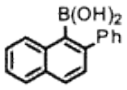
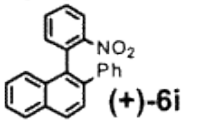


4

Entry	ArX	$ArB(OH)_2$	Product	mol% Pd	temp (°C)	time (h)	yld (%)	ee (%)
1	**3a**		 **(+)-6a**	4	70	88	98	87[b]
2				1	70	17	93	87[c,d]
3			 **(+)-6b**	8	70	88	90	92
4				2	70	24	96	92[c,d]
5				1	70	24	94	92[c]
6			 **(+)-6c**	10	80	140	83	85[b]
7				2	80	24	89	85[c,d]
8			 **(+)-6d**	3	60	48	74	74
9			 **(–)-6e**	4	40	92	97	71[b]
10			 **(*S*)-(–)-6f**	4	40	40	97	57[e]
11	**3b**		 **(+)-6g**	2	70	24	91	84
12				0.3	60	24	95	86[c,d]
13				0.2	60	24	95	86[c,f]
14			 **(–)-6h**	2	40	48	80	73
15	**4a**		 **(+)-6i**	3	70	48	86	73
16	**4b**			10	70	48	82	72
17	**4c**			4	70	48	83	72

Redox Neutral Cross Coupling (cont.)

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

- Disadvantages:
  - No standard protocol (time consuming optimization)
  - Long reaction times (sometimes up to 1 week)

II. Modification of Pro-stereogenic Biaryls

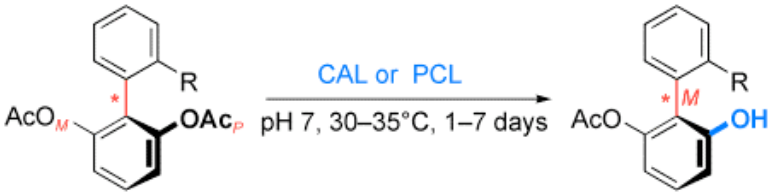
- Generation of axially chirality through reaction with "pro-chiral" biaryl unit
  - Biaryl axis formed, chirality introduced later

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

Desymmetrization of Biaryls

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

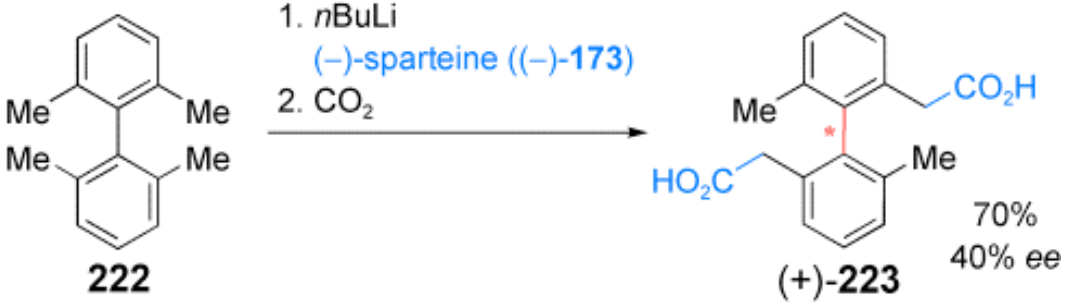
Review: *Chem. Rev.* **2005**, *105*, 313



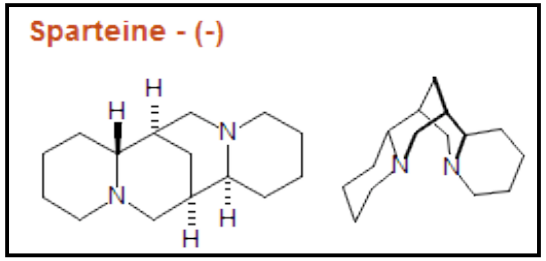
224 **(*M*)-225**

R	Me	Et	CH_2OBn	2,3-benzo
CAL: *ee* [%] (yield [%])	97 (80)	99 (57)	99 (68)	97 (72)
PCL: *ee* [%] (yield [%])	99 (86)	96 (67)	98 (51)	98 (94)

- Carbonylation (Raston, *J. Chem. Soc. Dalton Trans.* **1988**, 2403-2409)

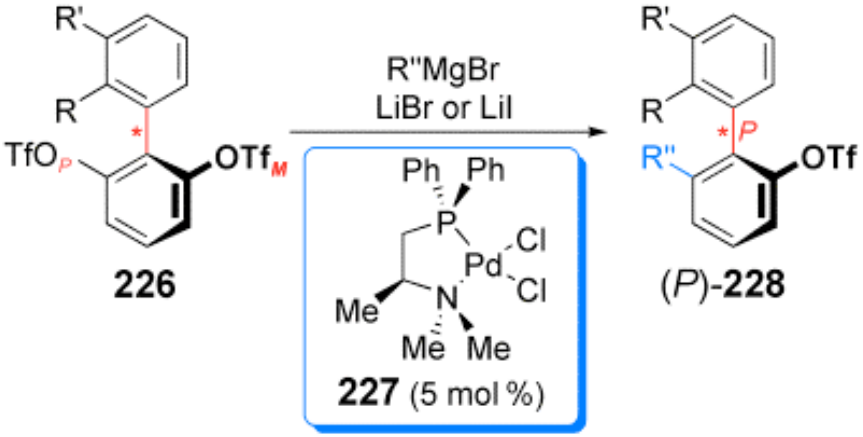


222 **(+)-223**

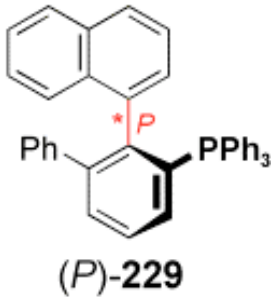


Desymmetrization in Cross Coupling

- Asymmetric Grignard cross coupling (Hayashi, *J. Am. Chem. Soc.* **1995**, *117*, 9101-9102)
  - Other triflate still available to react (converted to phosphonate (**229**) or ester)

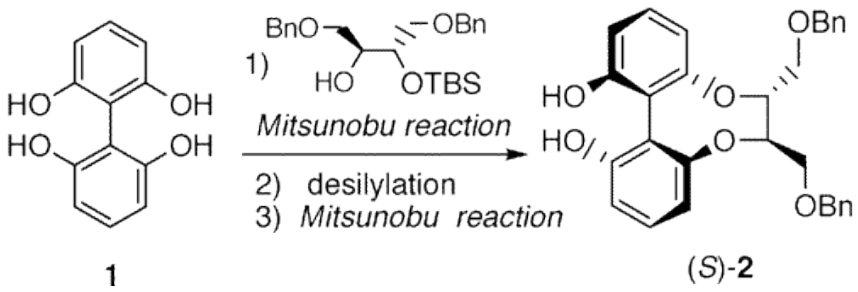


R	R'	R"	Yield [%]	*ee* [%]
benzo		Ph	92	94
benzo		*m*Tol	90	95
benzo		Ph_3Si—≡—	88	92
Ph	H	Ph	80	94
Ph	H	Ph_3Si—≡—	88	99
Me	H	Ph	85	95
Me	H	Ph_3Si—≡—	87	85

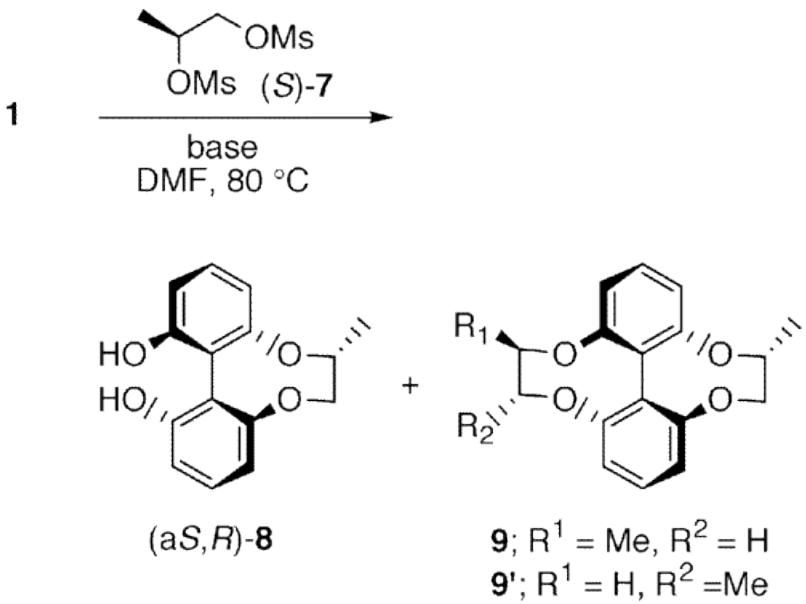


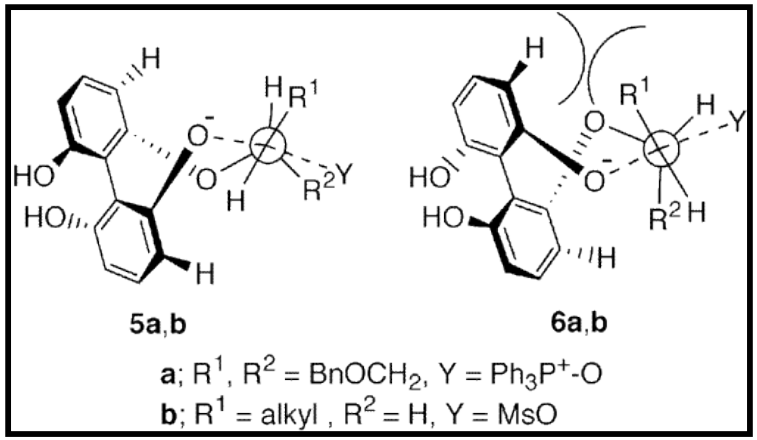
Desymmetrization through Bridge Formation

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



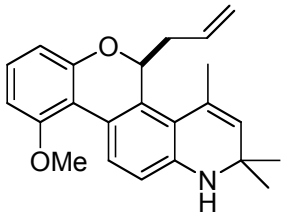
- Improvement: (*Org. Lett.* **2000**, *2*, 1319)
  - Using Cs_2CO_3, as the base, **8** could be obtained in 66% as a single diastereomer and **9** in only 7%.



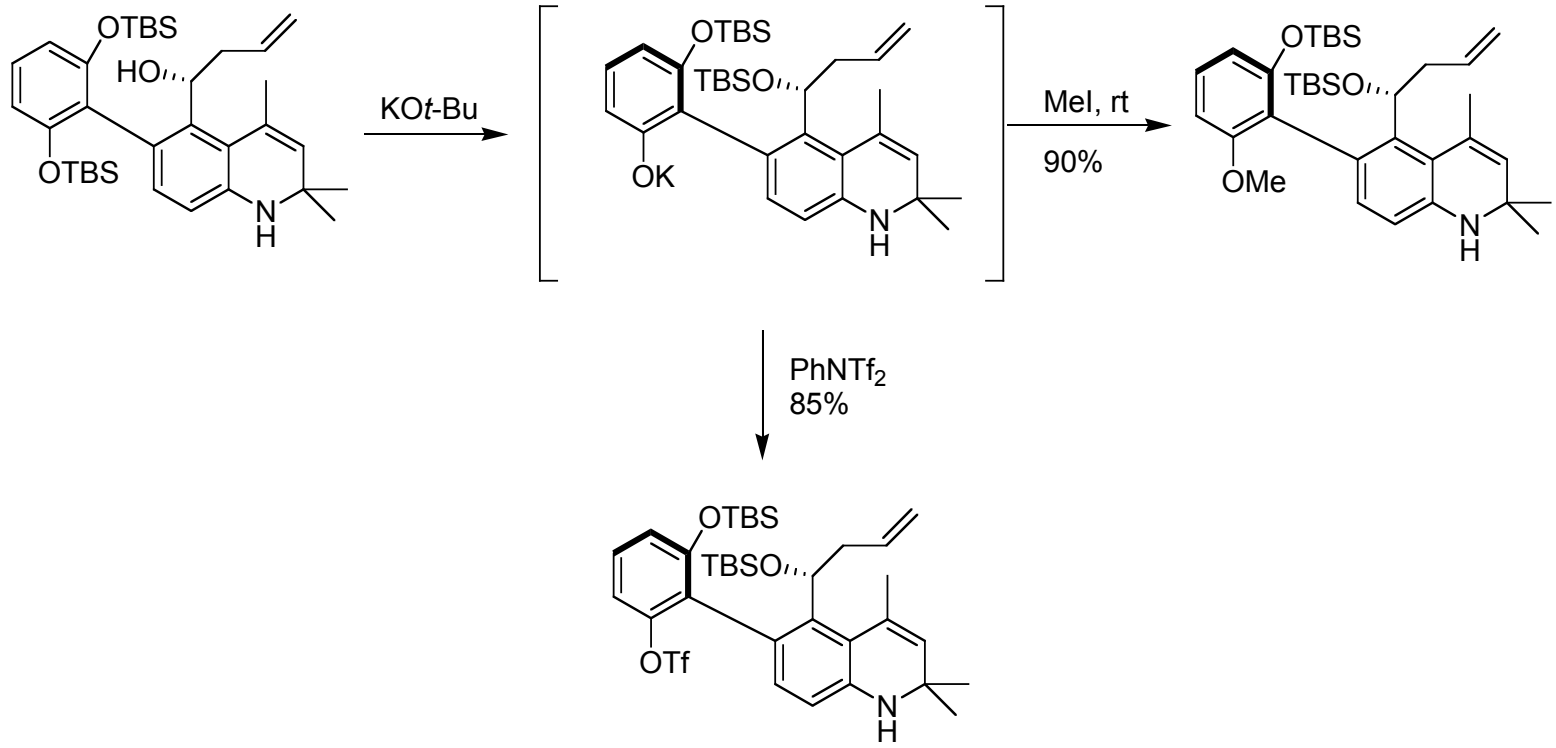


Desymmetrization in Total Synthesis

- Total synthesis of anti-inflammatory **A-240610.0,1** (Ku, *J. Am. Chem. Soc.* **2002**, *124*, 4282)

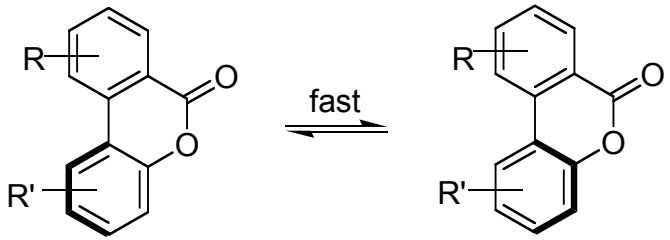


- Single atropisomer was needed for efficient etherification

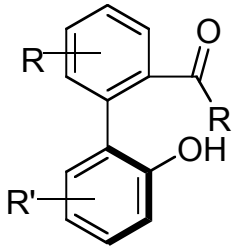


Axial Chirality through Ring Cleavage

- Lactones (Bringmann, *Acc. Chem. Res.* **2001**, *34*, 615)



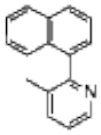
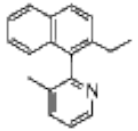
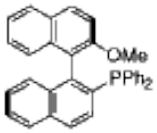
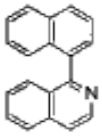
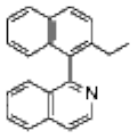
- The biaryl lactone is configurationally unstable
  - Opening the lactone with chiral nucleophiles can selectively provide the appropriate axial chirality
    - CBS (Brigmann, *Org. Synth.* **2002**, *79*, 72-83)
    - Sodium menthoxide (Bringmann, *Chem. Eur. J.* **1999**, *5*, 3029)
  - Drawback: Biaryls posessing a β-keto and β-hydroxy functionality readily racemize. β –ketosulfoxides and chiral c-nucleophiles can not be utilized



Configurationally unstable

Ortho Selective Reactions

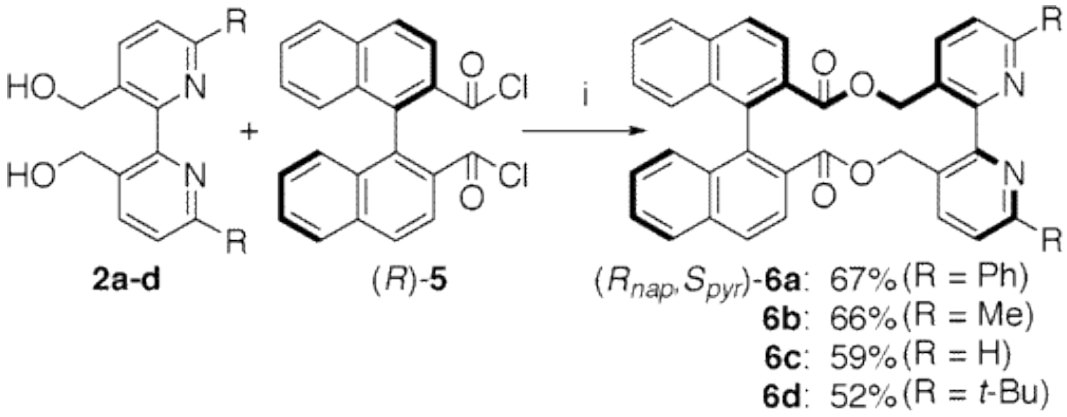
- C-H activation
  (Murai, *Tetrahedron: Asymmetry* **2000**, *11*, 2647)
- Starting material freely rotates. Alkylating the ortho position results in isolable atropisomers

run	biaryl compound	ligand	product	yield	ee [b]
1	 **1**	(*R*),(*S*)-PPFOMe	 **4**	37% [c]	49% ee
2	**1**	(*R*),(*S*)-PPFOMe	**4**	trace [d,e]	—
3 [f]	**1**	(*R*),(*S*)-PPFOMe	**4**	15% [g]	15% ee
4	**1**	(*R*)-BINAP	**4**	no reaction	
5	**1**	 (*R*)-MeO-MOP	**4**	49% [h]	0% ee
6	 **5**	(*R*),(*S*)-PPFOMe	 **6**	33%	22% ee
7	**5**	(*R*)-MeO-MOP	**6**	60%	3% ee

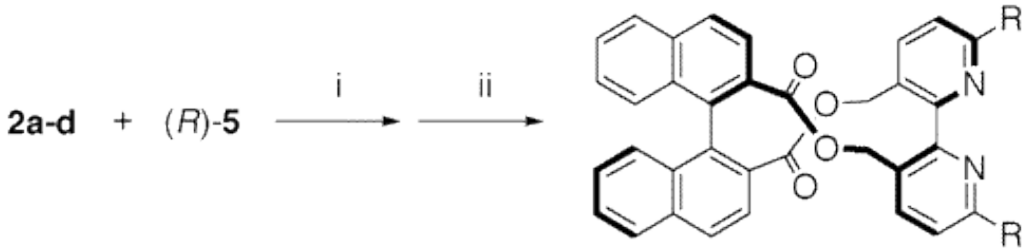
[a]Reaction conditions: biaryl compound (0.5 mmol), ethylene (7 kg/cm^2), $[RhCl(coe)_2]_2$ (0.025 mmol), ligand (0.15 mmol), toluene (2.5 mL), 120 °C, 20 h. [b]All enantioselectivities were determined by HPLC analysis on a Daicel OD-H column. [c]The biaryl compound **1** was recovered in 52% yield. [d]The reaction was carried out at 60 °C for 72 h. [e]The biaryl compound **1** was recovered in 90% yield. [f]Ru(cod)(cot) and (*R*),(*S*)-PPFOMe catalyst system was used. [g]The biaryl compound **1** was recovered in 67% yield. [h]The biaryl compound **1** was recovered in 45% yield.

Ortho Selective Reactions

- N-oxide formation (Hayashi, *J. Org. Chem.* **2003**, *68*, 6329)
  - The initially coupled product could be converted cleanly to the other atropisomer through heating in toluene for 48 h
  - N-oxide formation with MCPBA followed by chiral auxiliary removal affords the stable atropisomers



2a-d (*R*)-**5** (R_{nap},S_{pyr})-**6a**: 67% (R = Ph)
6b: 66% (R = Me)
6c: 59% (R = H)
6d: 52% (R = *t*-Bu)



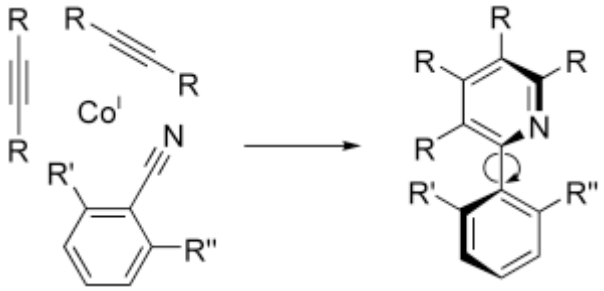
(R_{nap},R_{pyr})-**7a**: 75% (R = Ph)
7b: 83% (R = Me)
7c: 87% (R = H)
7d: 59% (R = *t*-Bu)

III. Second Aromatic Ring Generation

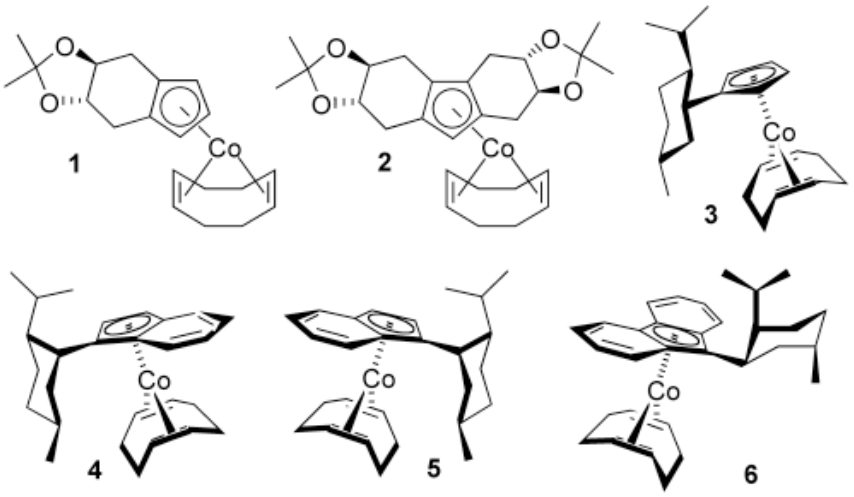
- Generation of chiral biaryls through formation of second aromatic ring
  - One of the newest methodologies to generate axial chirality
  - Chirality achieved through:
    - Metal catalyzed cyclization (chiral ligand source of chirality)
    - Central to axial chirality transfer

Chiral Pyridines

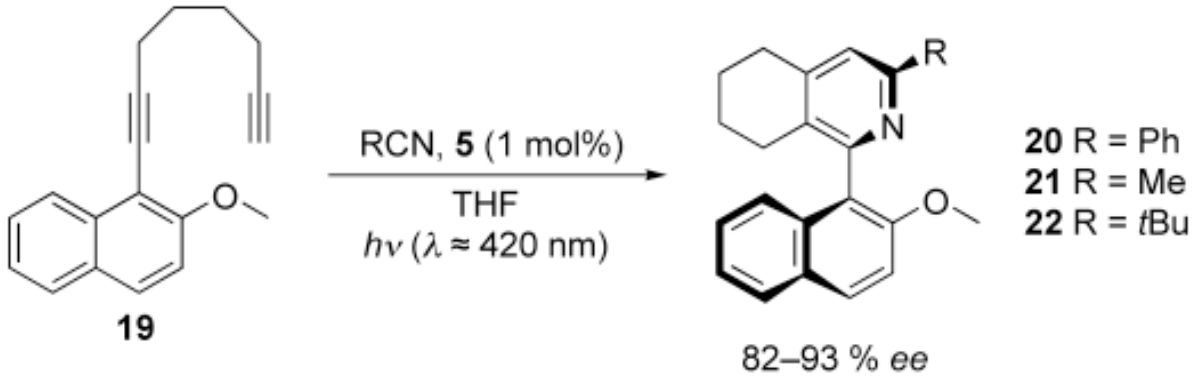
- [2+2+2] cyclization under photochemical conditions
  (Gutnov and Heller, *Angew. Chem. Int. Ed.* **2004**, *43*, 3795)



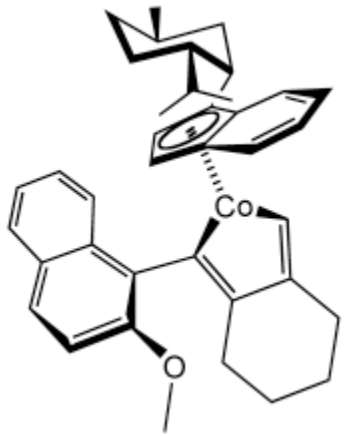
- A series of chiral cobal catalysts were screened. Catalyst **5** afforded the highest ee's



Chiral pyridines (cont.)

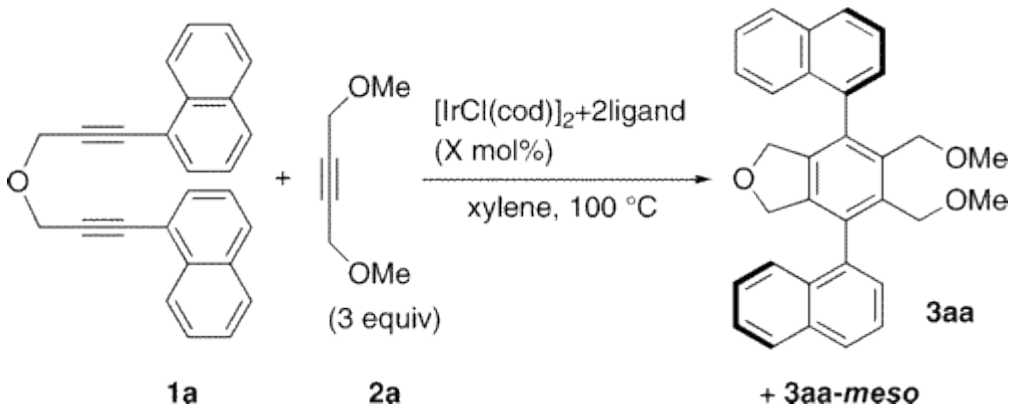


- Little temperature dependence (82% ee at 20 °C, 89% ee at 3 °C)
- No observed solvent dependence
- When alkyne not tethered, yields were 2-33% and ee's 32-63% (compared to 74-80%)
- Proposed source of selectivity:



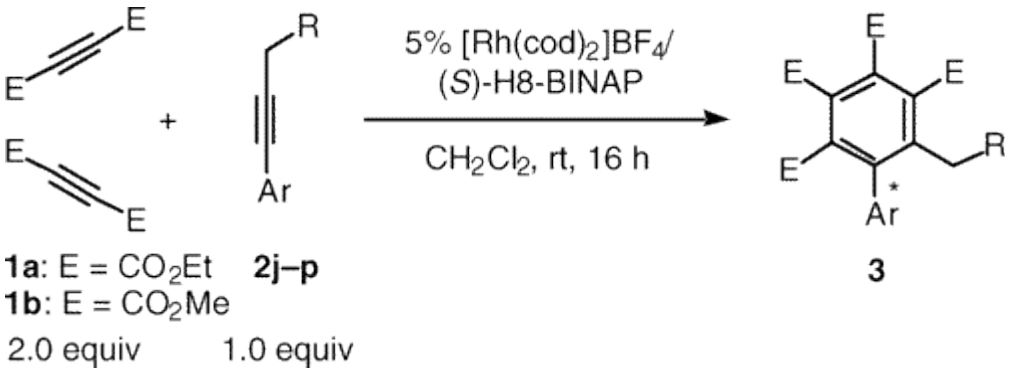
Cyclization

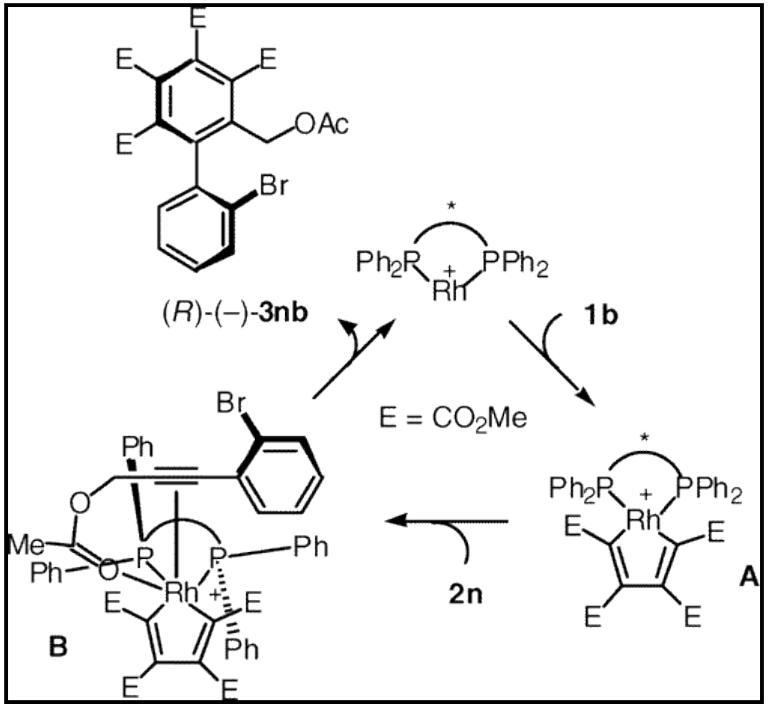
- Iridium catalyzed [2+2+2] cyclization (Shibata, *J. Am. Chem. Soc.*, **2004**, *126*, 8382)
  - 74-97% yield and *ee* s in the 90's
  - This methodology could also be applied to biaryls (81% *ee*)
  - Ether linkage was successfully replaced with:
    - Alkene
    - Methylene
    - Nitrogen



Cyclization (cont.)

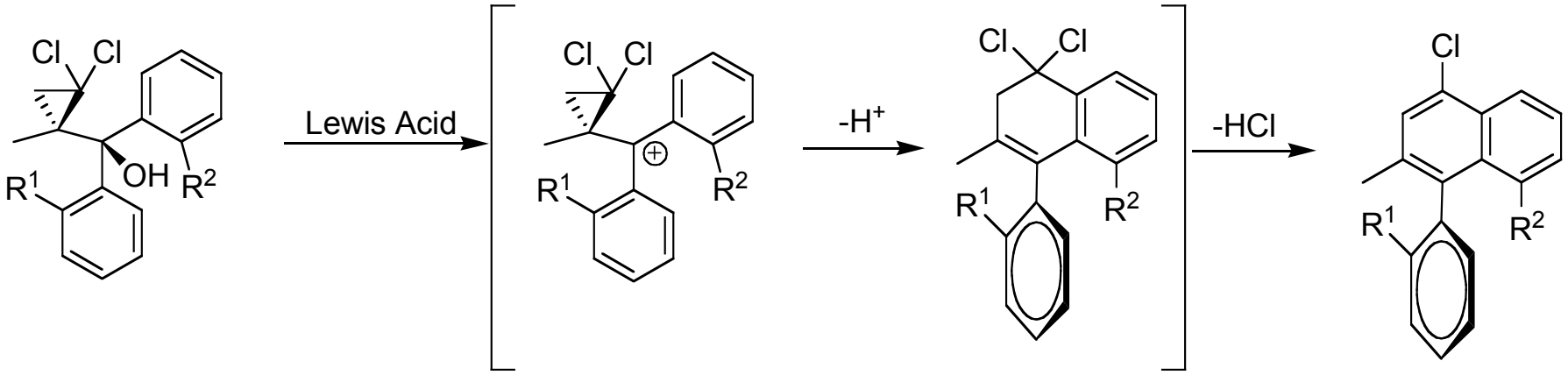
- Cross Cyclotrimerization
  (Tanaka*Org. Lett*, **2005**, *7*, 3119)
- 61-89% yield,
  84-96 % *ee*
- Br, Cl, Me, Et and naphtyl varieties were synthesized





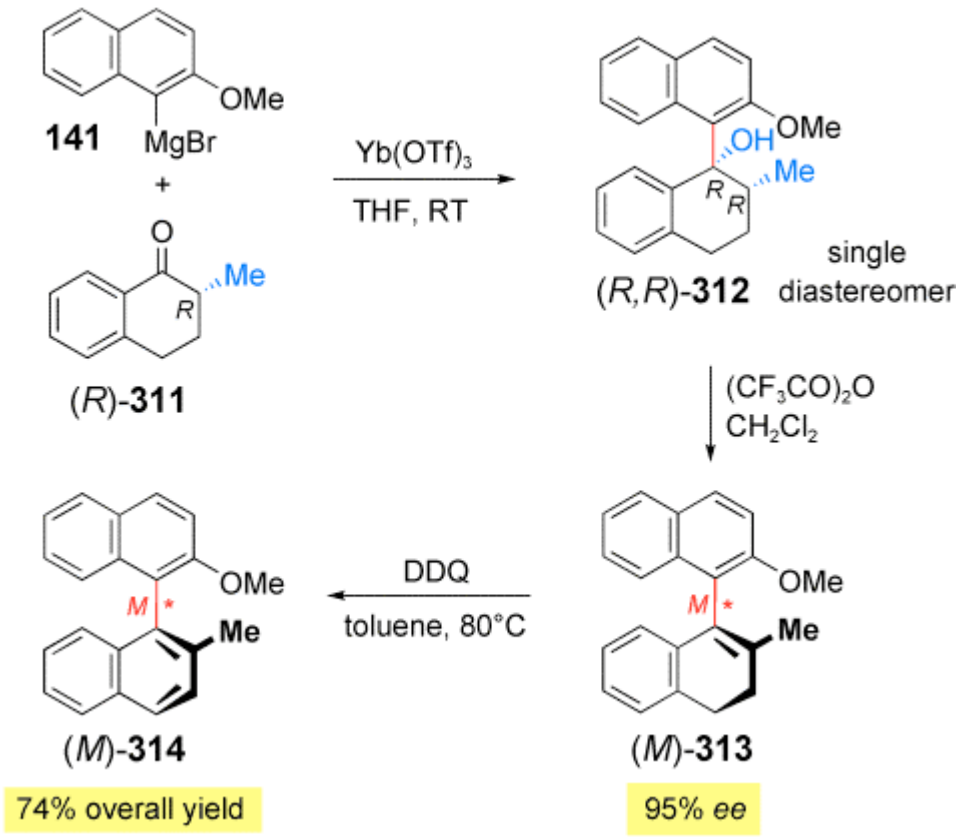
Chirality Exchange

- Chiral α-naphthalenes (Nishii and Tanabe, *J. Am. Chem. Soc.*, **2004**, *126*, 5358)
- 47-97% yield, >99% ee
- R1 = Cl, OMe, Me, R2 = H, Cl, Me



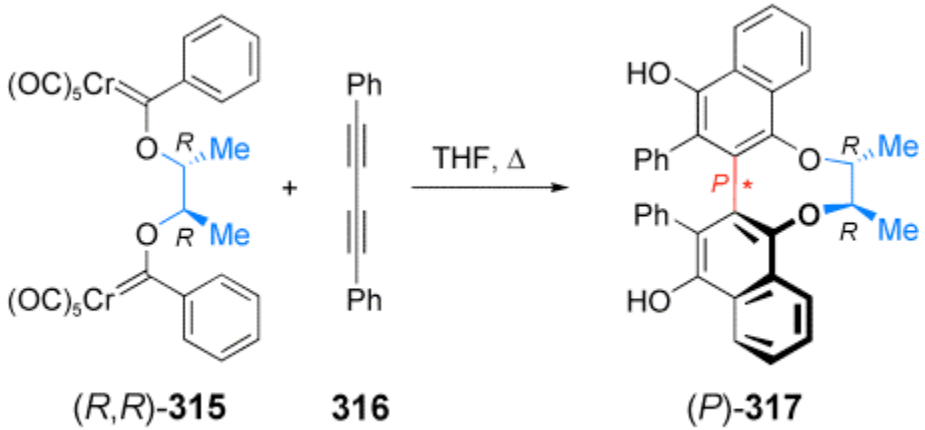
Chirality Exchange (cont.)

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



Carbenes

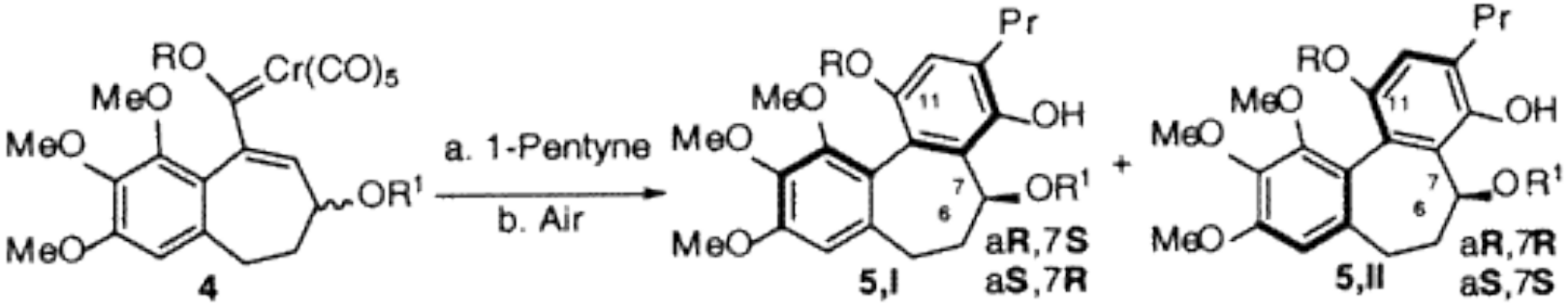
- Chirality controlled by:
  - Chiral bridges (Wulff, *J. Am. Chem. Soc.* 1996, **118**, 2166-2181)



(*R*,*R*)-**315** **316** (*P*)-**317**

23%, single stereoisomer

  - Stereogenic centers in the ortho position (Wulff, *J. Am. Chem. Soc.* 2002, **124**, 6512-6513) 47-73 %. Either only II detected or 13:1 (II:1)



Conclusion

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

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

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