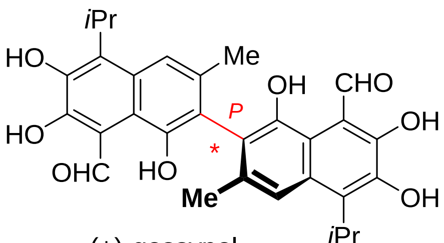
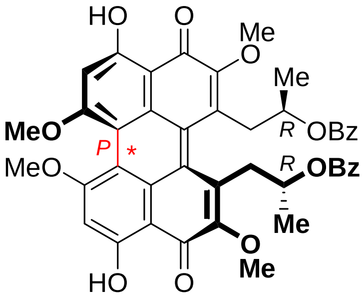
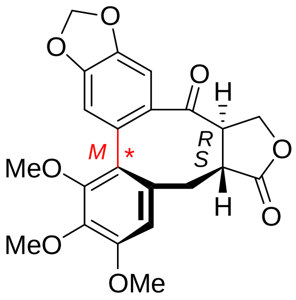
T. Gulder

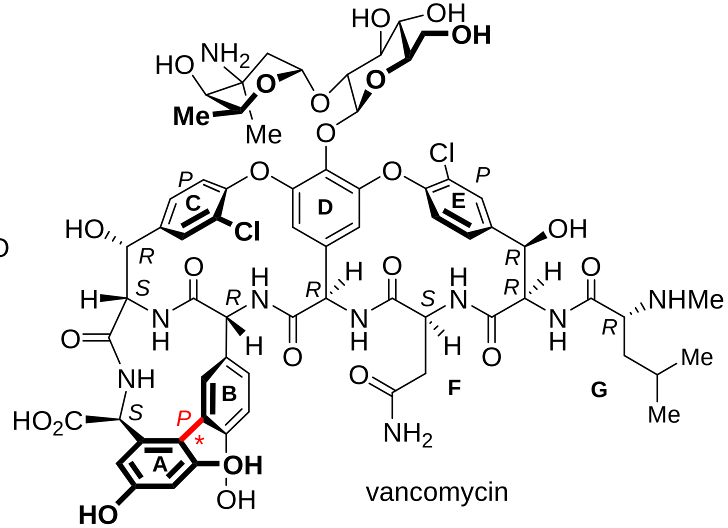
Atroposelective Biaryl Synthesis

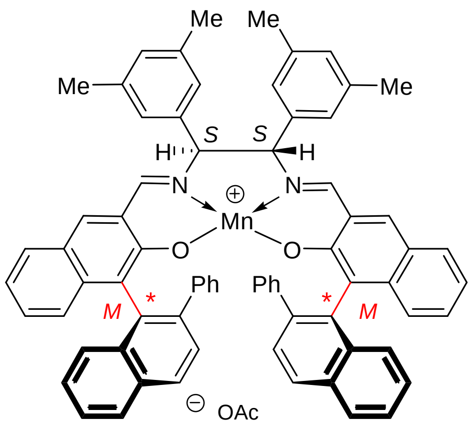
- the **atropisomerism phenomenon** arises from the hindered rotation around the biaryl bond
- at least two bulký substituents in *ortho* position to the biaryl axis are needed

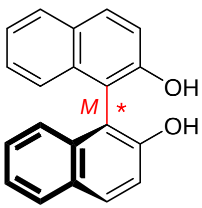

(+)-gossypol

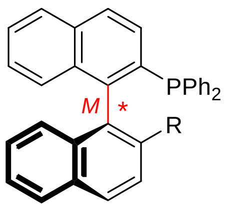

calphostine A


(-)-steganone


vancomycin

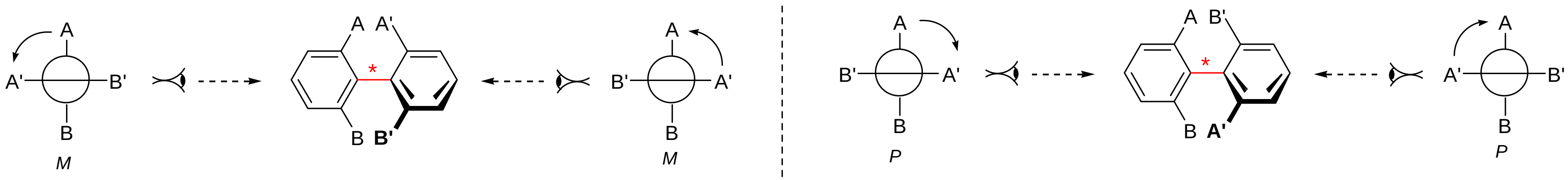



BINOL


R = PPh_2: BINOL
R = OMe: MOP

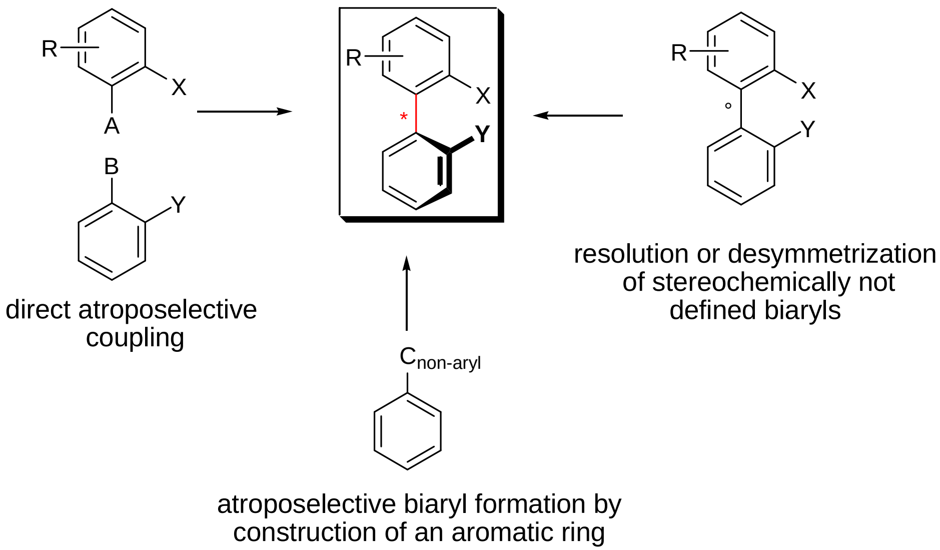
the configuration at a biaryl axis often plays an important role for pharmacological properties of bioactive compounds and is a fundamental basis for useful reagents and catalysts in asymmetric synthesis

assigment of the absolute configuration in chiral biaryls:



Atroposelective Biaryl Synthesis

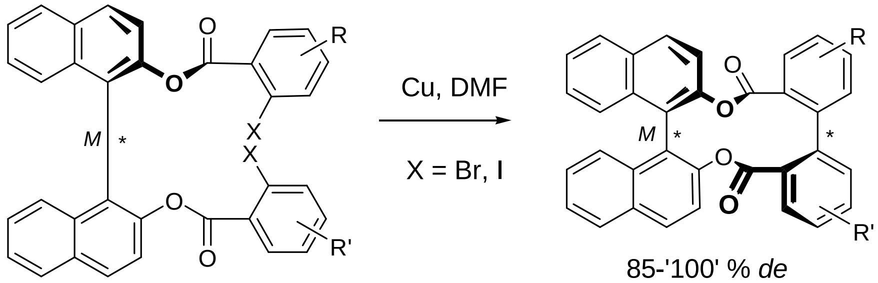
in principle, 3 different strategies are know



1. Asymmetric *C*,*C* coupling

- intramolecular coupling with chiral diesters

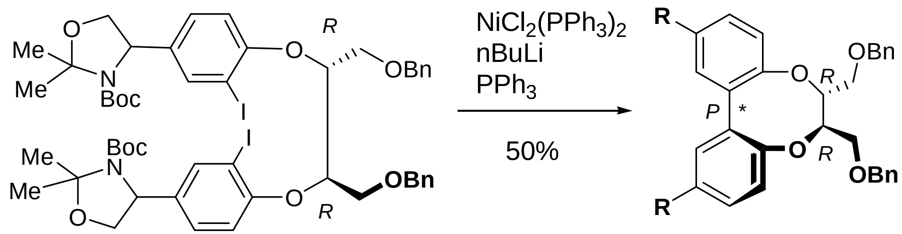
Miyano *et al.*



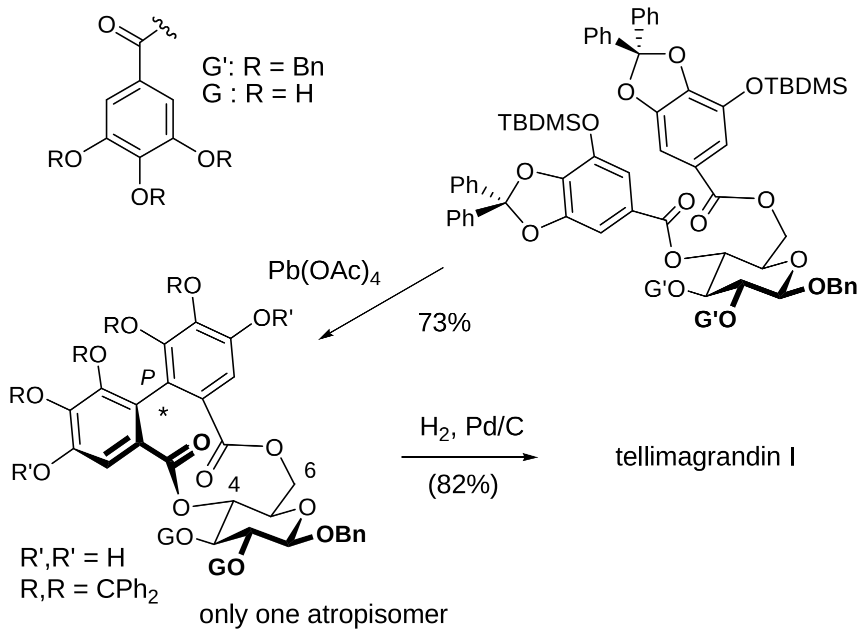
bad yields with bulky substituents *ortho* to the axis

- intramolecular coupling with chiral tethers

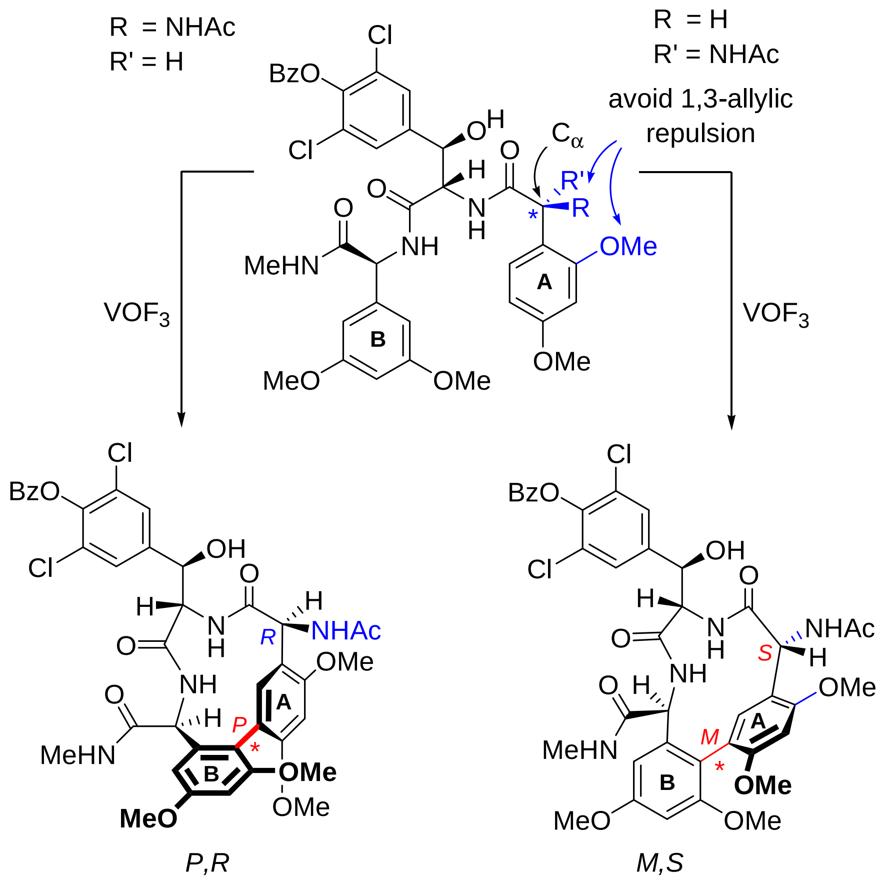
1,2-diols as tethers (Lipshutz *et al.)*



sugars as tethers (Feldman *et al.*)



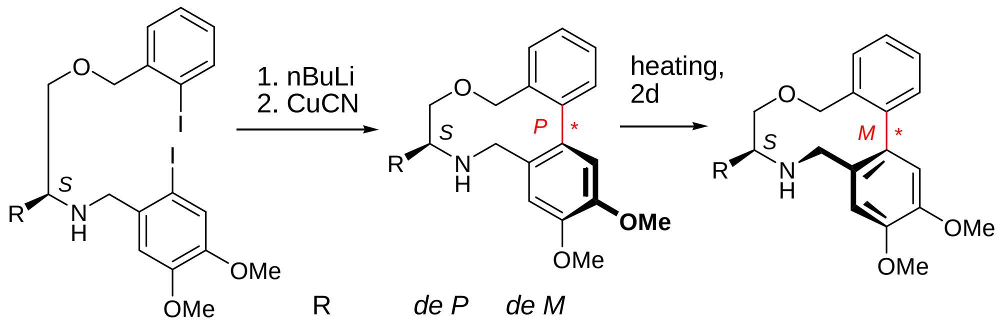
peptides as a chiral backbone



57%, >94% *de* natural *P*-atropisomer unnatural *R*-configuration at Ca	62%, >94% *de* unnatural *M*-atropisomer natural *S*-configuration at Ca

Evans *et al.*

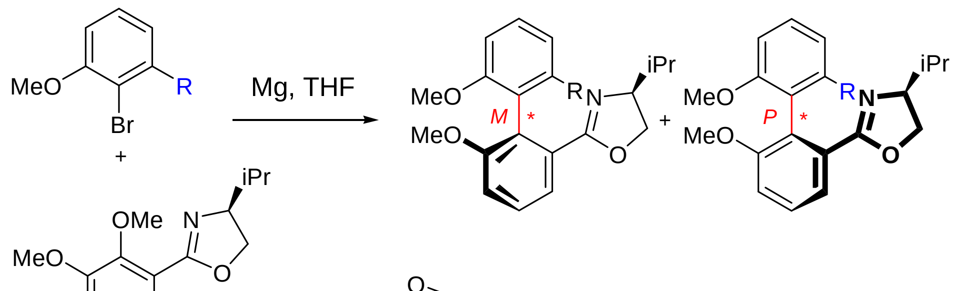
chiral amino alcohols as tethers (Schreiber *et al.*)

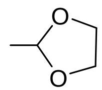


R	*de P*	*de M*
Me	94	71
Et	92	80
iBu	94	82
Bn	88	83
tBu	60	33

- intermolecular coupling with chiral *ortho* substituents

Grignard reactions (Meyers *et al.*)

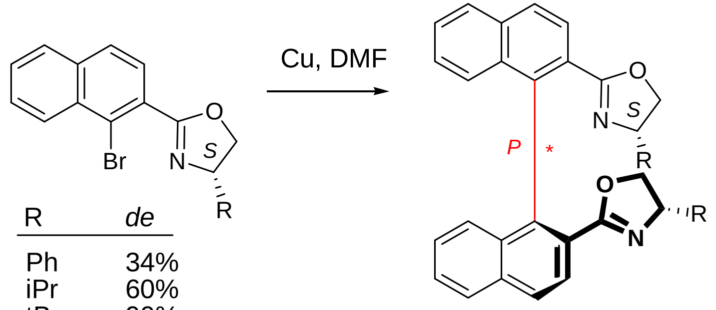


R		CH_2OMe	CHOBn	CH_3	OTBS
dr	80:20	60:40	58:42	10:90	7:93

← **electron-donating property of R**

Mechanism and stereochemical course of the S_N2 Ar reaction

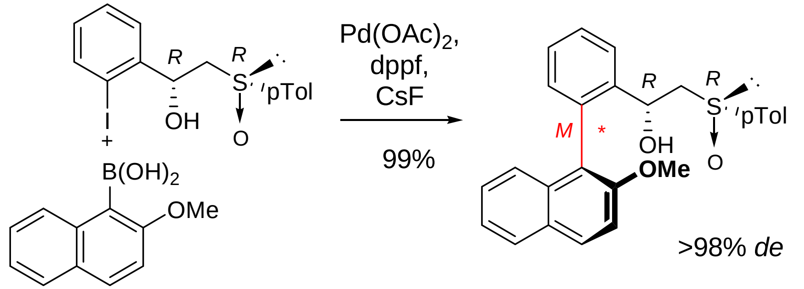
Ullman reaction (Meyers *et al.*)



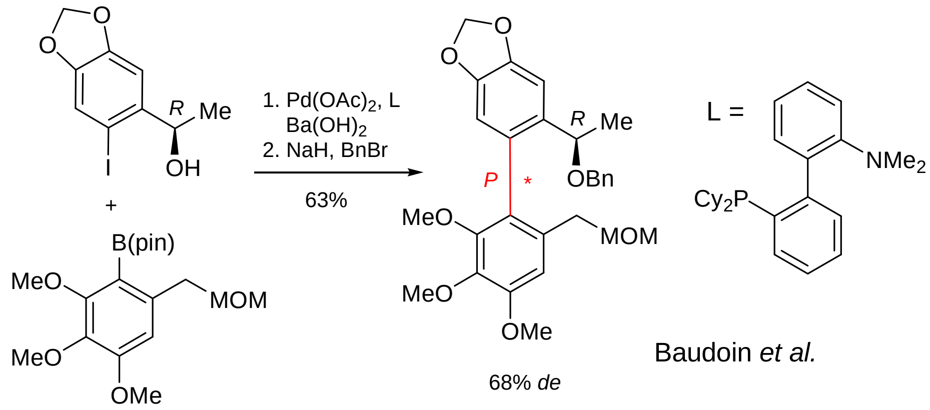
R	*de*
Ph	34%
iPr	60%
tBu	90%

only symmetric biaryls are accessible

Suzuki reaction (Colbort *et al.*)



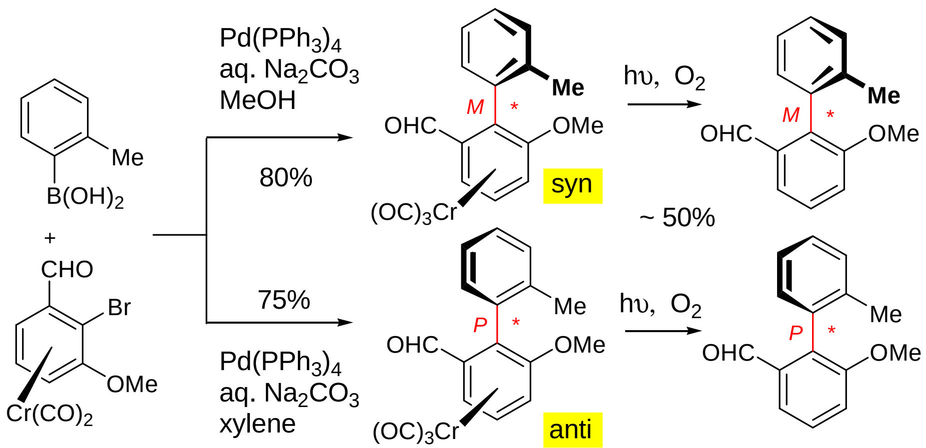
like configuration in the side chain necessary (matched case)



Baudoin *et al.*

- intermolecular coupling with planar-to-axial chirality transfer

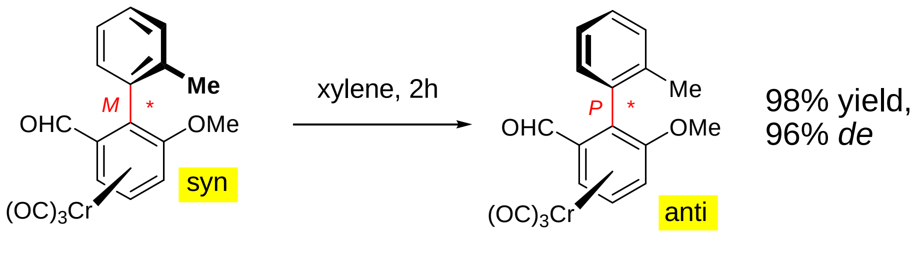
reaction with chiral chromium complexes (Uemura *et al.*)



if a carbonyl group is present *ortho* to the biaryl axis,
both atropisomers are accessible due to a lower rotational barrier

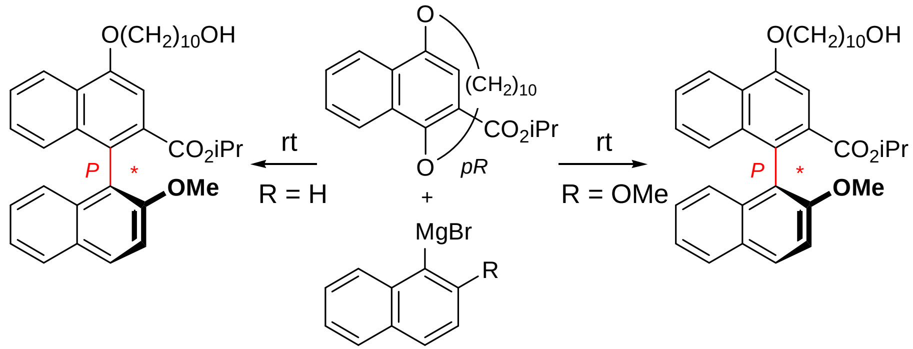
stereochemical inconsistent results

axial isomerization under thermal conditions



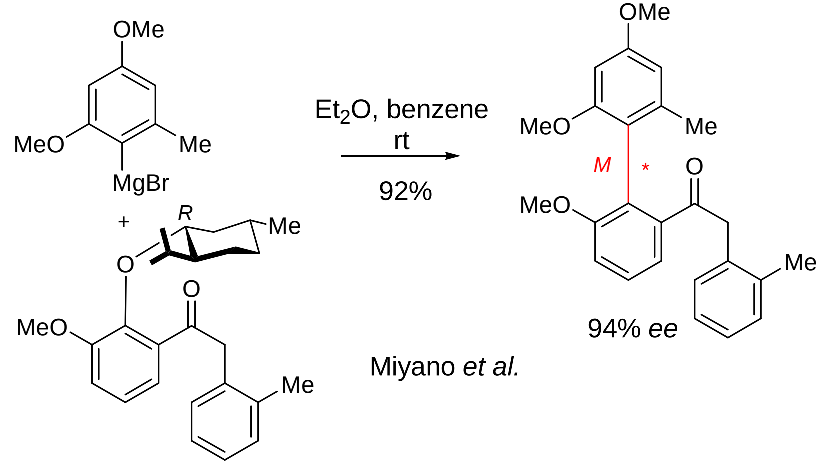
thermodynamic favored

reaction with chiral dioxocyclophanes (Miyano *et al.*)



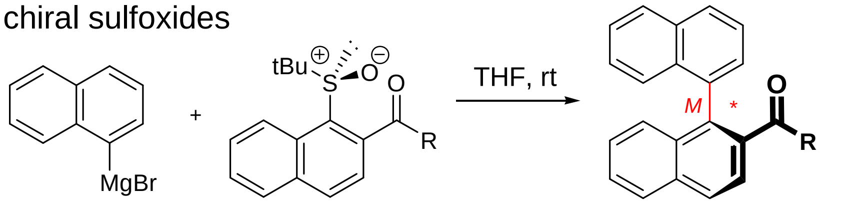
- intermolecular coupling with chiral leaving groups

chiral alcohols



Miyano *et al.*

chiral sulfoxides

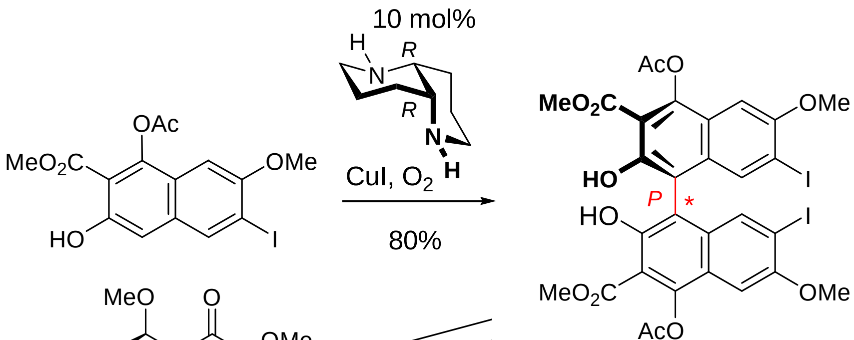


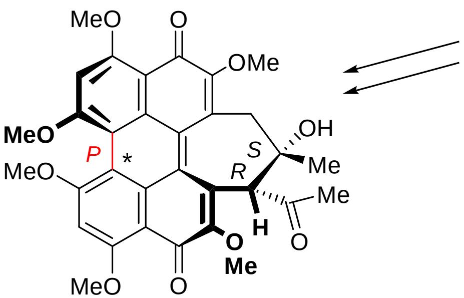
Baker and Sargent

R = O*i*Pr 90%, 95% *ee*
R = NMe_2 65%, 95% *ee*

- Oxidative Coupling with Chiral Additives

coupling with copper salts

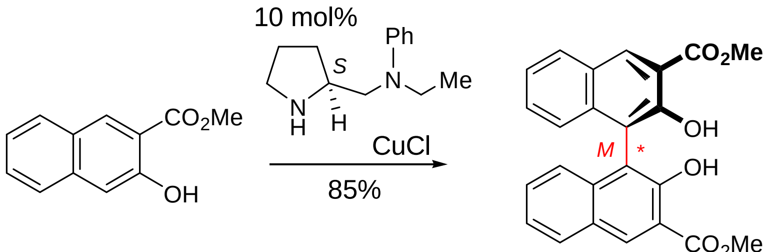




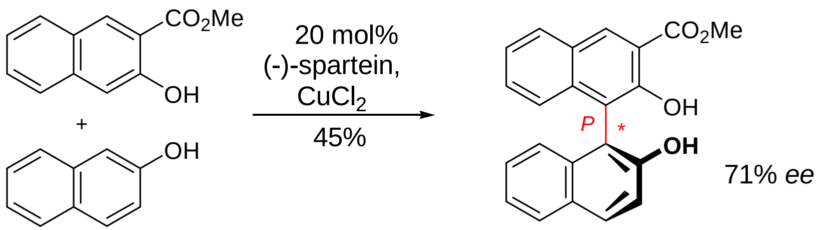
hypocrellin A

Kozlowski *et al.*

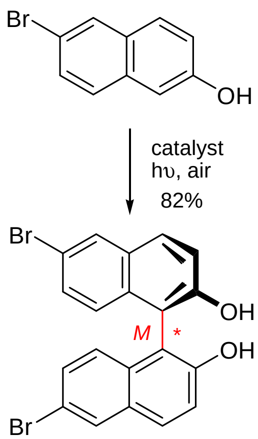
Mechanism of the homocoupling

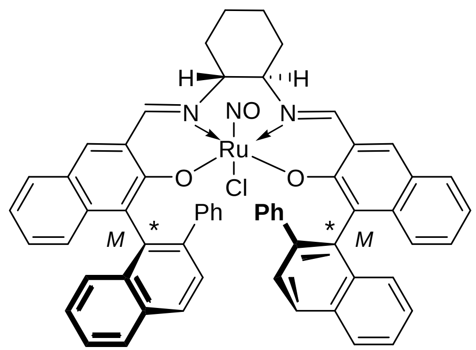


Nakajima *et al.*



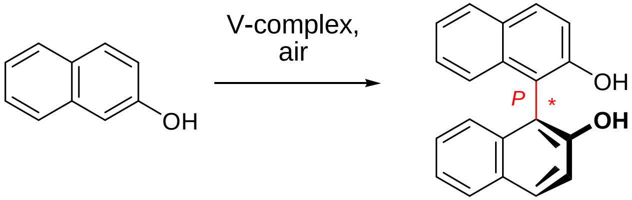
coupling with salen-Ru(II)-nitroso complexes

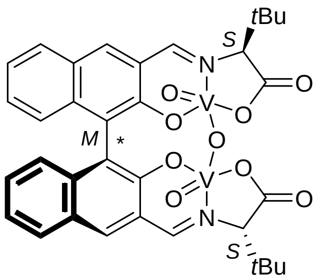




Katsuki *et al.*

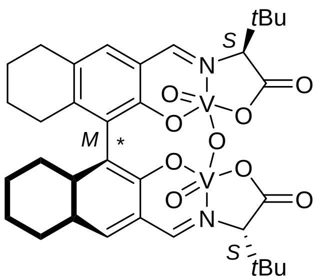
coupling with chiral dinuclear V(-complexes





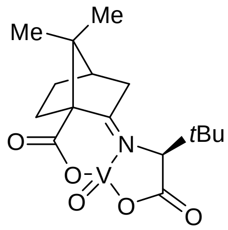
95% yield, 83% *ee*

Gong *et al.*



76% yield, 91% *ee*

Sasai *et al.*

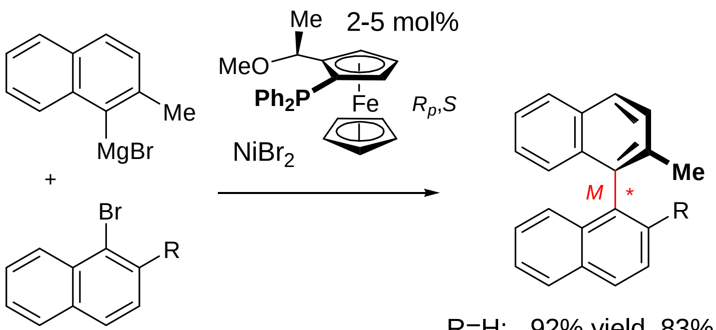


99% yield, 84% *ee*

Chen and Barhate

- cross coupling using chiral ligands

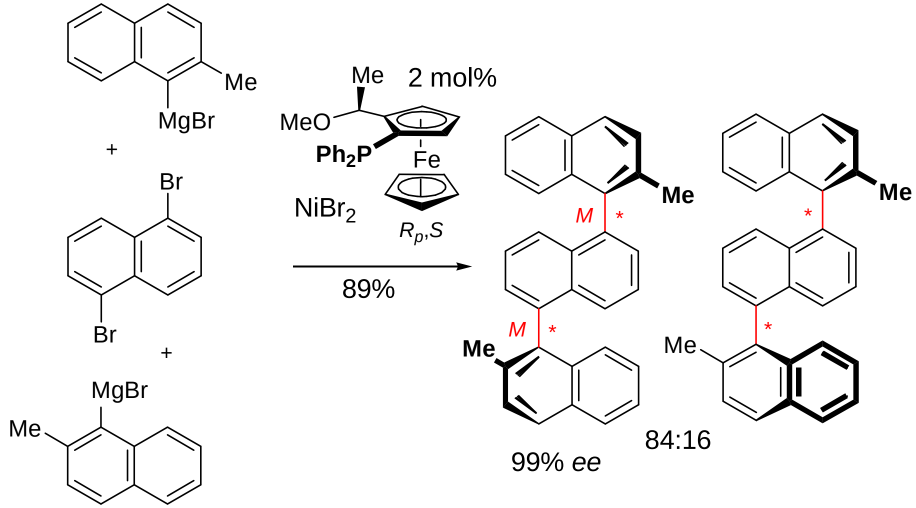
using a Kumada coupling



R=H, Me

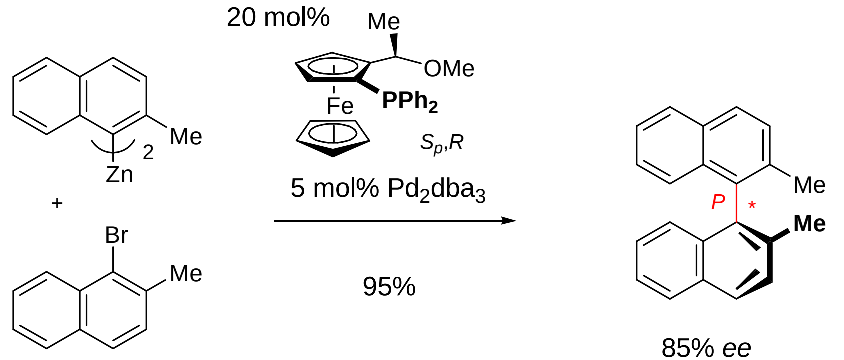
Hayashi and Itoh

R=H: 92% yield, 83% *ee*
R=Me: 69% yield, 95% *ee*



99% *ee*

using a Negishi coupling

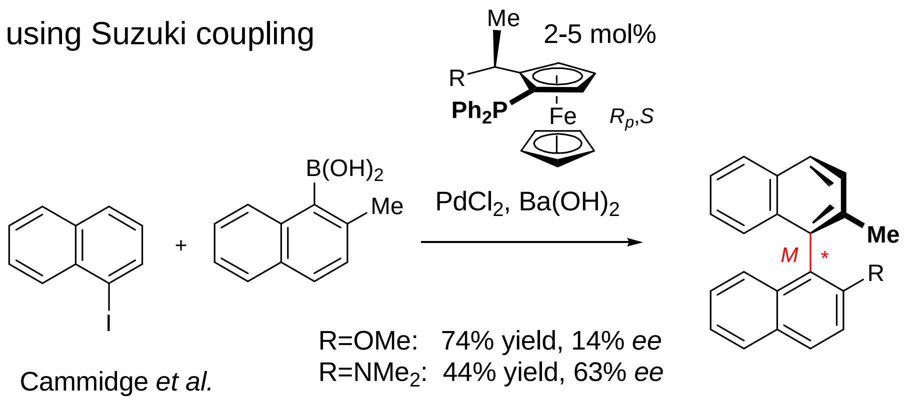


Espinet *et al.*

85% *ee*

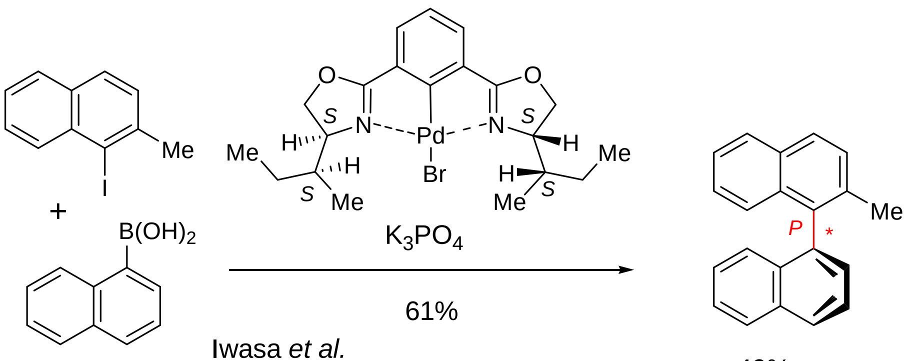
Atroposelective Biaryl Synthesis

using Suzuki coupling



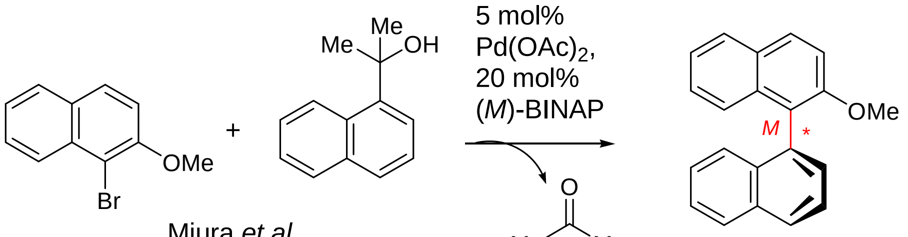
Cammidge *et al.*

stronger electron donor needed to precoordinate the less basic boronic acid in the same way as the methoxy substituent does with the magnesium cation of the aryl Grignard reagent in the Kumada coupling



Iwasa *et al.*

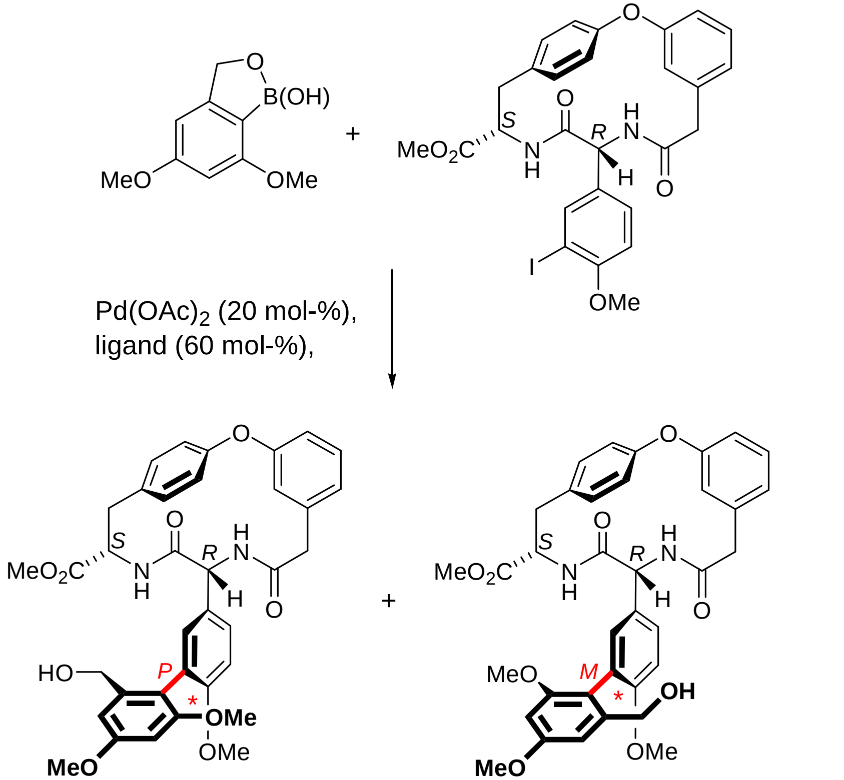
49% *ee*

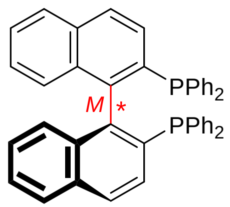


Miura *et al.*

83% yield, 63% *ee*

Studies on the Biaryl Fragment of Vancomycin



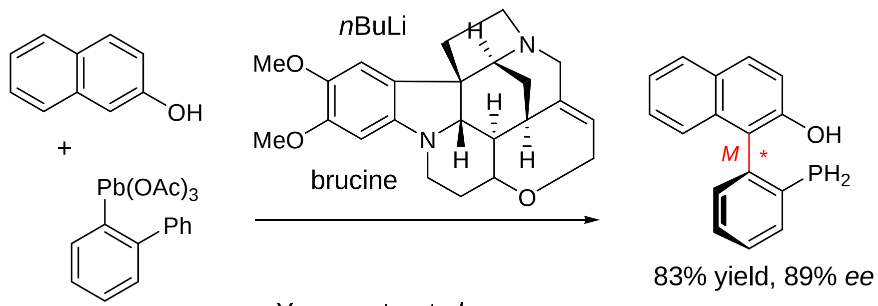


(*M*)-BINAP

Ligand	Yield [%]	(*P*):(*M*)
PPh_3	80	50:50
(*M*)-BINAP	40	>95: 5
(*P*)-BINAP	40	< 5:95

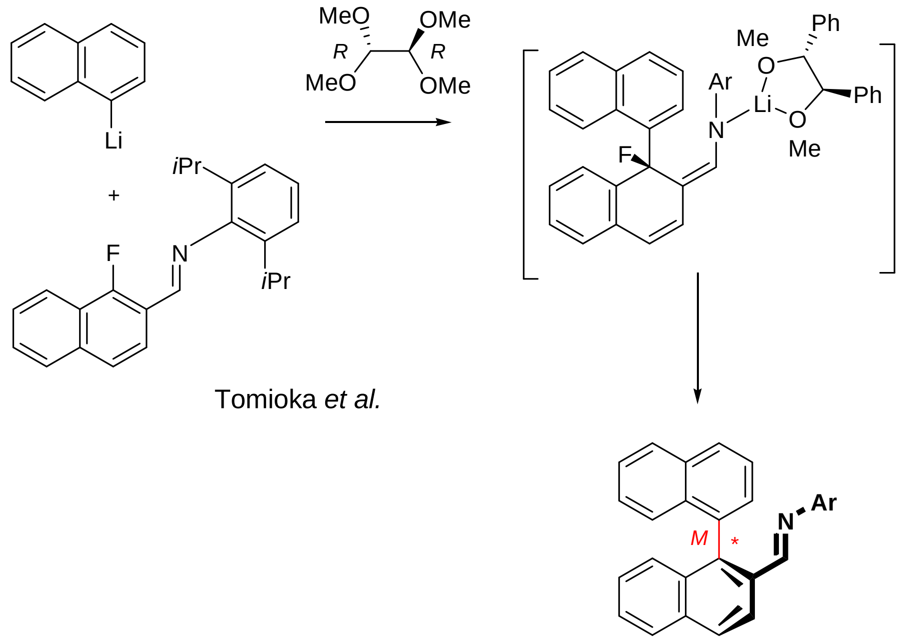
Nicolaou *et al.*

asymmetric coupling using lead reagents



Yamamoto *et al.*

asymmetric coupling using a organo lithium species



Tomioka *et al.*

2. Atroposelctive Transformation of prostereogenic Biaryls

1. nonstereoselective *C*,*C*-coupling reaction
2. establishing of the absolute configuration

precondition of the substrate:

either biaryl has to be

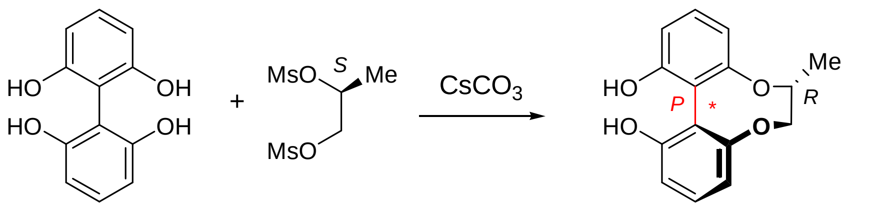
rotational hindered but achiral or **chiral but configurationally unstable**

⇩ enantiotopos-differentiating transformations

⇩ dynamic kinetic resolution

- Desymmetrization configurationally stable but achiral biaryls compounds

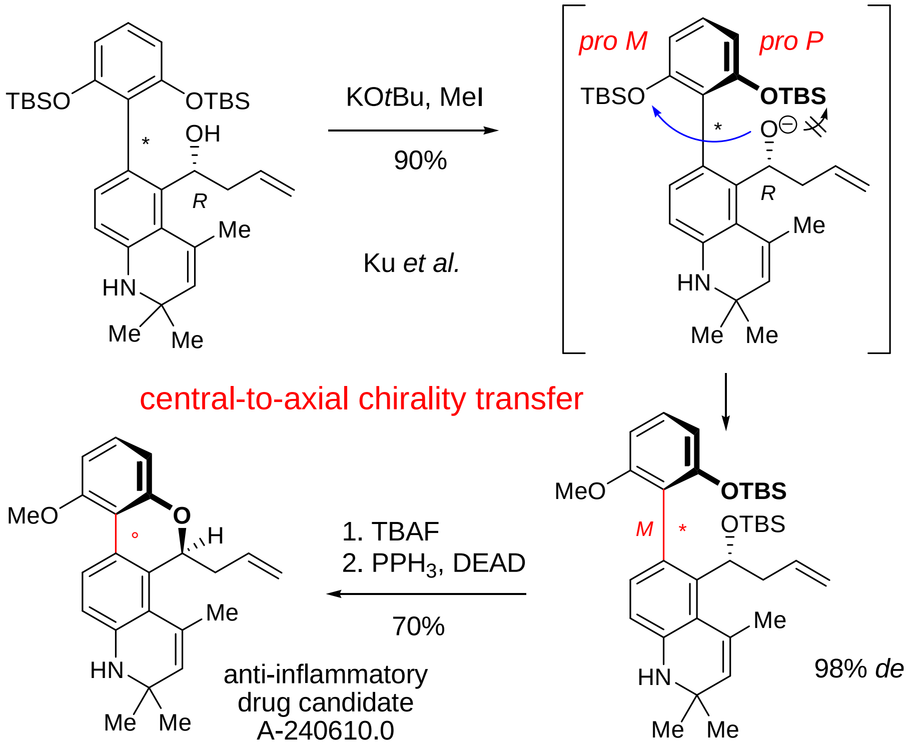
by an atropoenantiomer-differening bridge formation

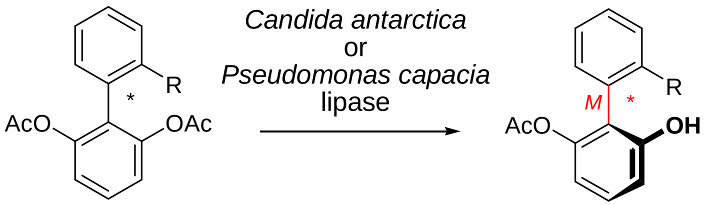


Harada *et al*.

single diastereomer

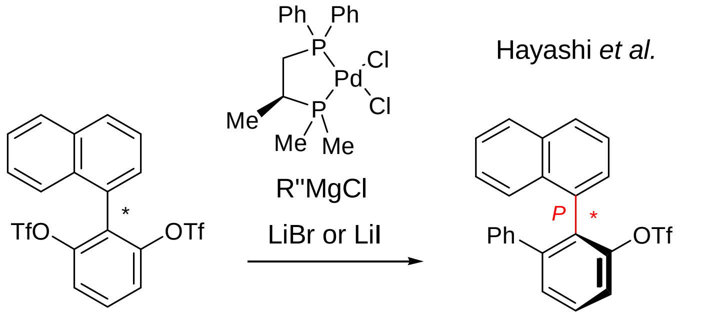
stereocontrol is achieved during the second S_N2 reaction atropoenantiomer-differentiating manipulation of *ortho* substituents





Matsumoto *et al.*

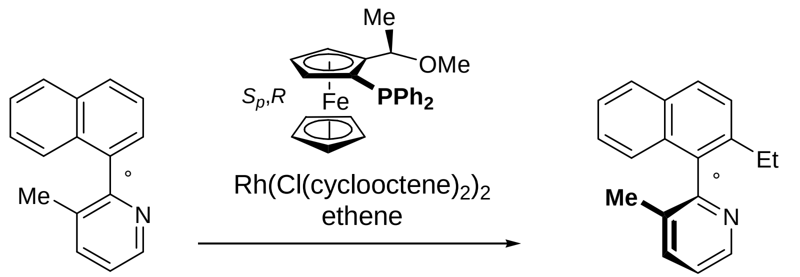
R	Me	Et	CH_2OBn
CAL:	80%, 97%*ee*	57%, 99%*ee*	68%, 99%*ee*
PCL:	86%, 99%*ee*	67%, 96%*ee*	94%, 98%*ee*



92% yield, 94%*ee*

- atropselective conversion of axially chiral but configurationally unstable biaryls

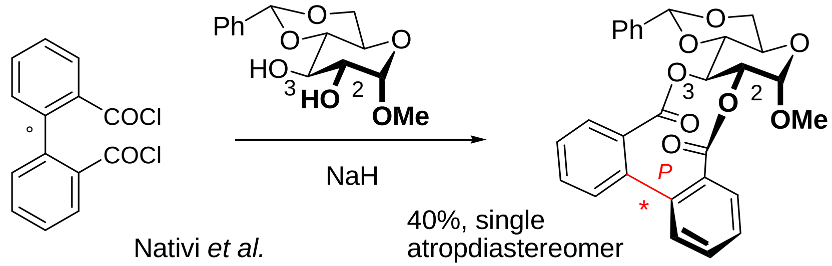
selective introdction of a *ortho* substituent



Murai *et al.*

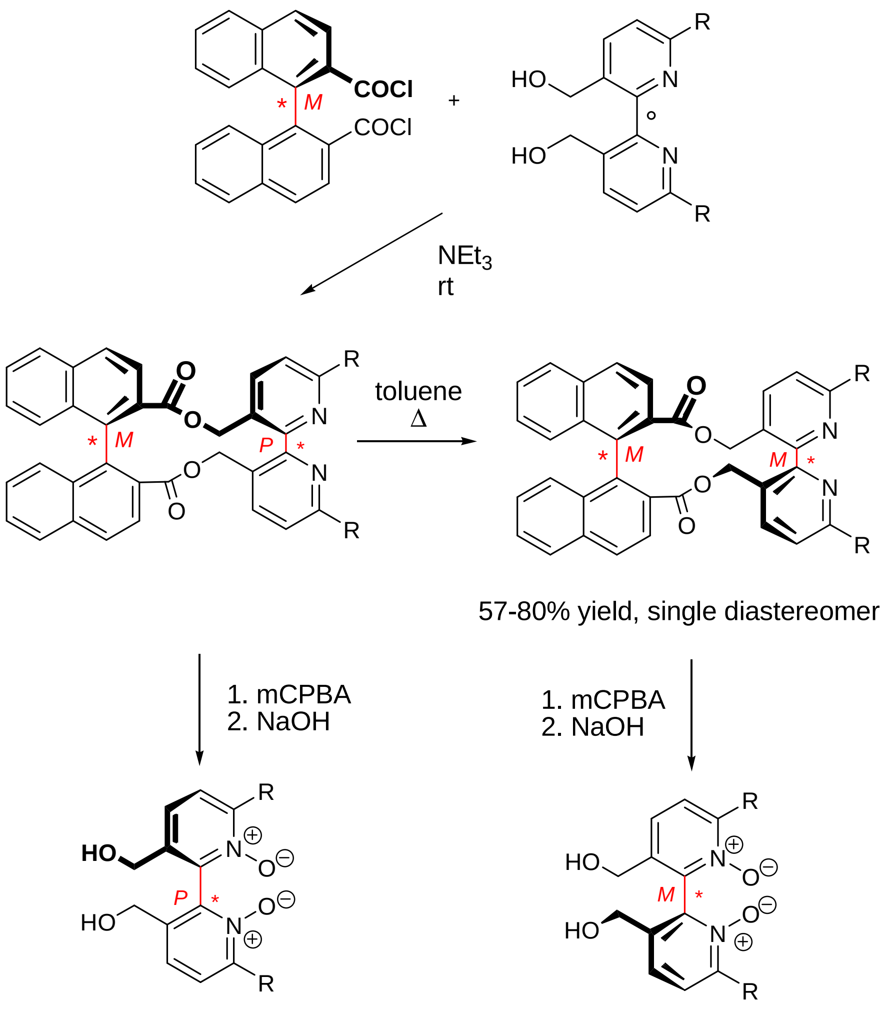
37% yield, 49%*ee*

atropodiastereoselective bridge formation



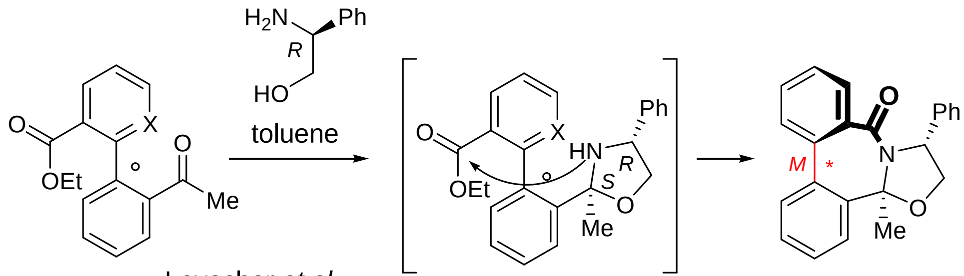
Nativi *et al.*

40%, single atropdiastereomer



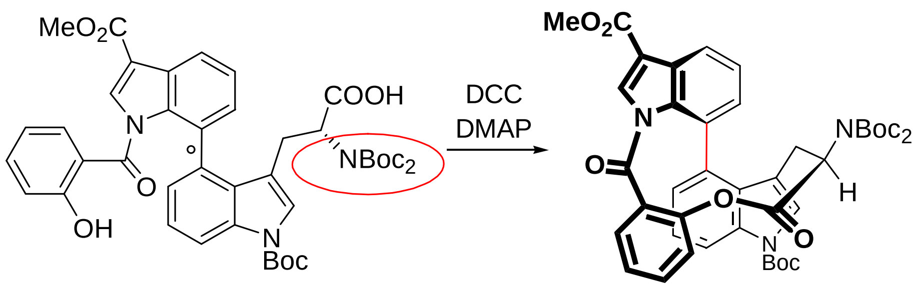
Hayashi *et al.*

R	Yield	*ee*
H	67%	89%
Me	66%	92%
Ph	67%	89%
*t*Bu	52%	67%



Levacher *et al.*

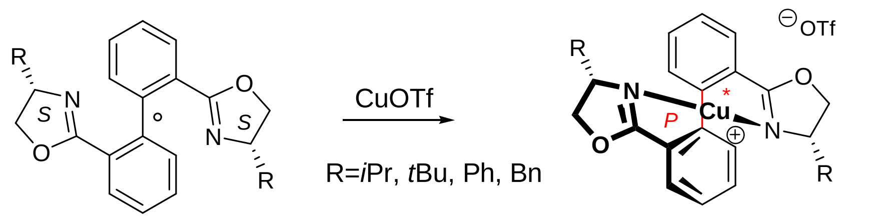
atroposelective macrolactonization of the diazonamide model



Feldman *et al.*

65%, single atropisomer

atropodiastereoselective metal bridge formation

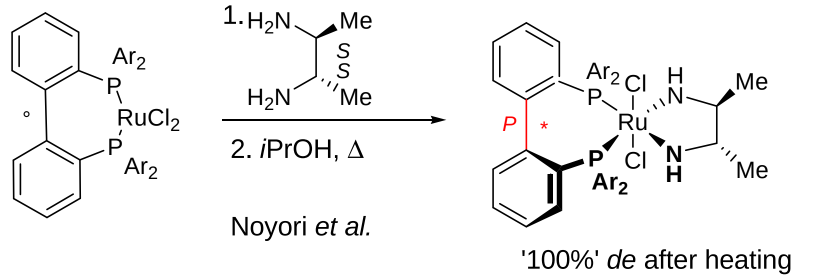


Ikeda *et al.*

single diastereomer
cyclopropanation catalyst

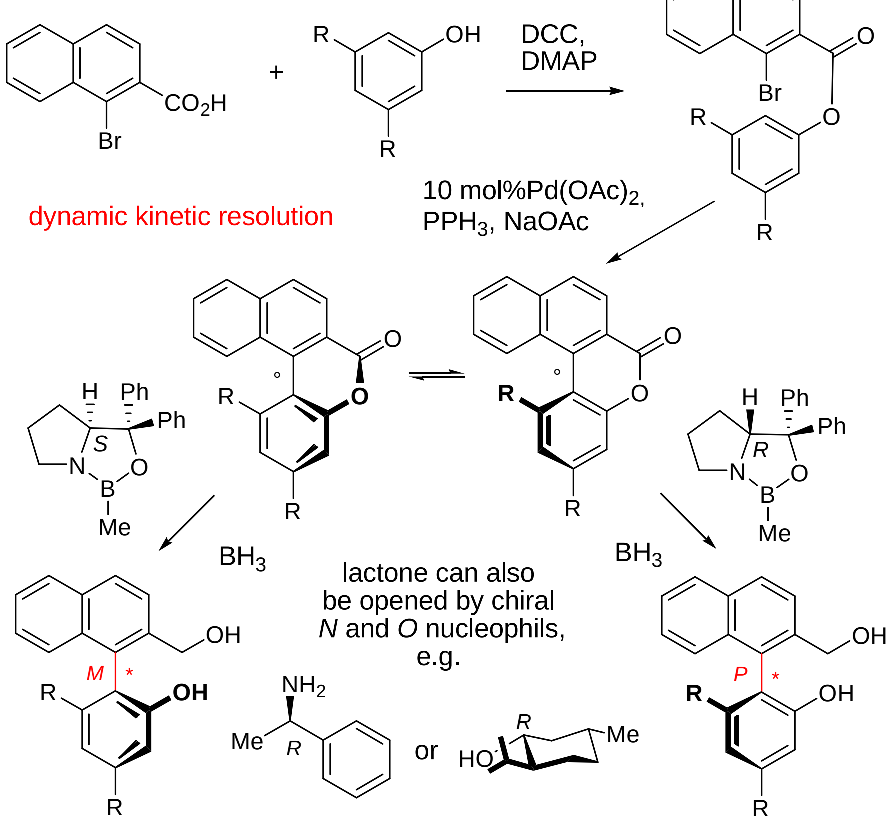
M atropoisomer disfavored due to severe steric interactions of Rs

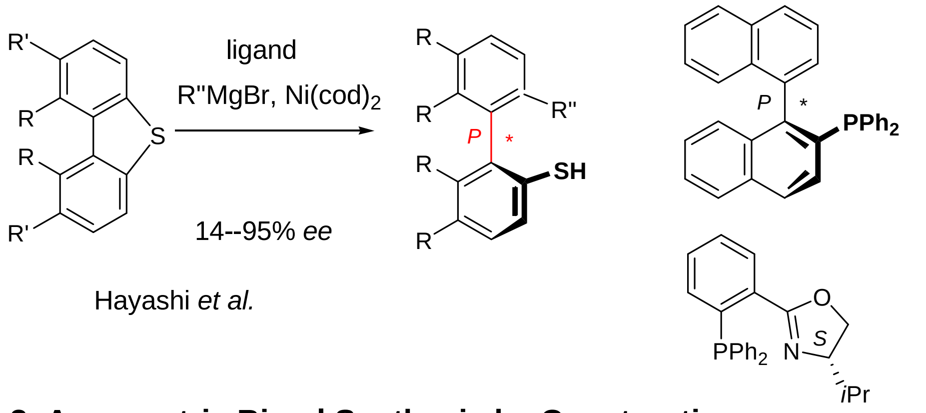
Atroposelective Biaryl Synthesis



- atroposelective cleavage of bridges

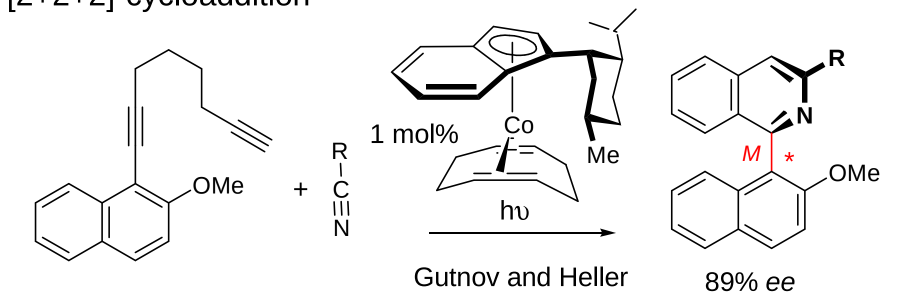
Lactone concept (Bringmann *et al.)*

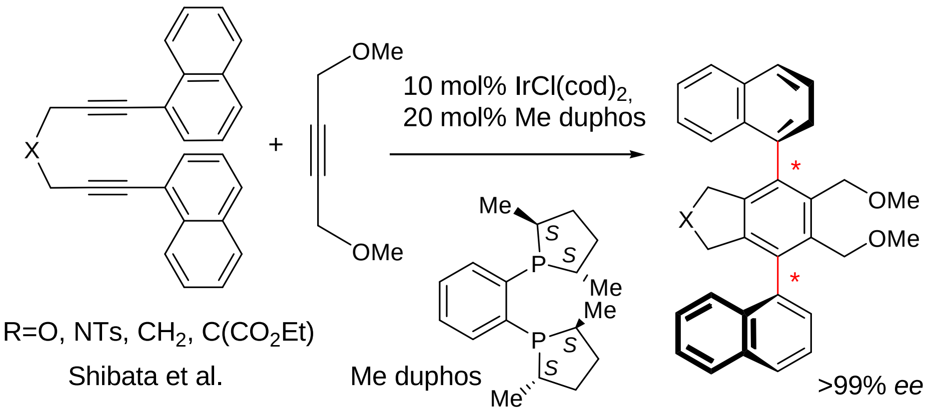




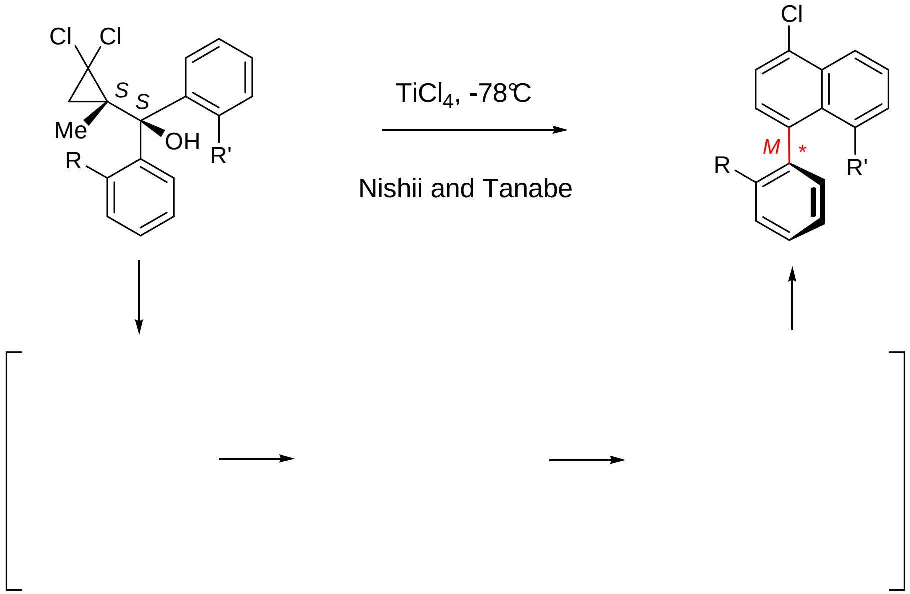
3. Asymmetric Biaryl Synthesis by Construction of an Aromatic Ring

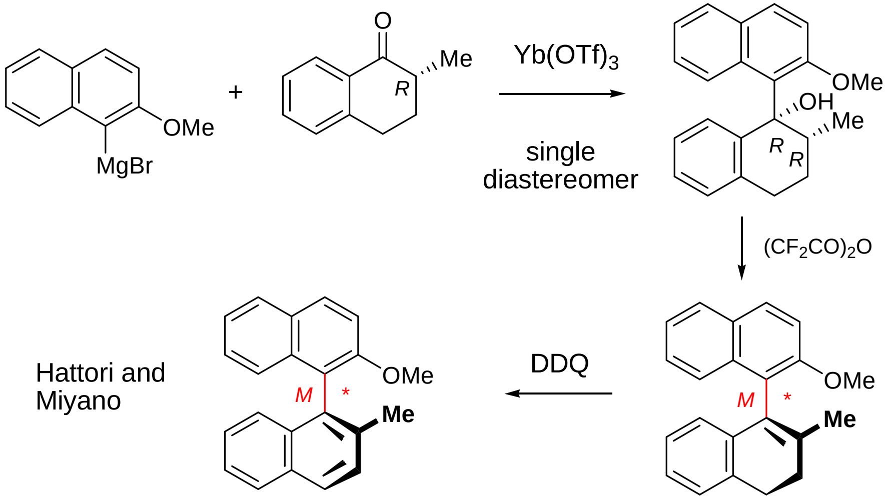
[2+2+2]-cycloaddition





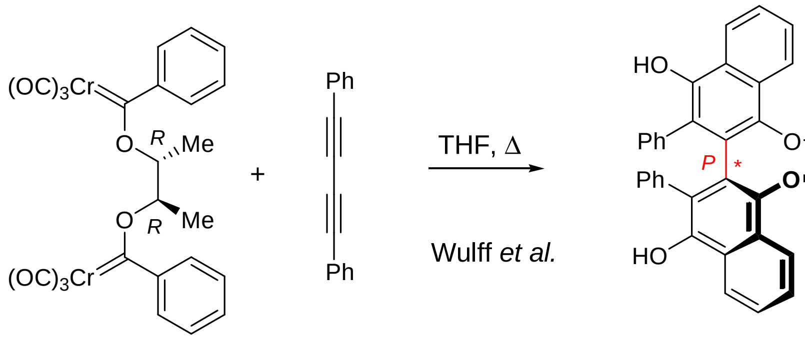
central-to-axial chirality transfer





Hattori and Miyano

Dötz benzannulation of Fischer carbenes



4. Literature

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