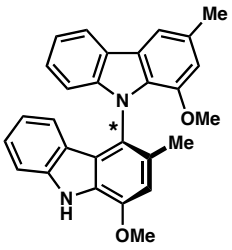
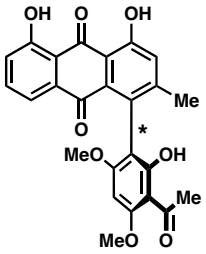
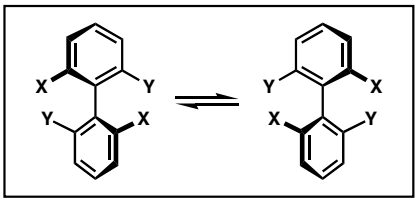


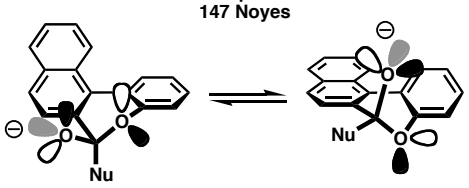


Atropisomerism

Axial Chirality in Nature and Synthesis



Kevin Allan
Stoltz Group Literature Meeting
Monday 11/14/2005
8 pm
147 Noyes



Outline

I. Introduction

a. History and Background
b. Conditions for Axial Chirality

II. Direct Atroposelective Aryl-Aryl Coupling

a. Diastereoselective Coupling
b. Enantioselective Coupling

III. Resolution/Desymmetrization of Prostereogenic Biaryls

a. Configurationally Stable, Axially Achiral
b. Configurationally Unstable, Axially Chiral
   i. Atropodiastereoselective Bridge Formation
   ii. Atroposelective Bridge Cleavage / The "Lactone Method"

IV. Atroposelective Construction of an Aromatic Ring

Albert I. Meyers
Colorado State University

Motokazu Uemura (right) and
Ken Kamikawa (left)
Osaka Prefecture University

Gerhard Bringmann
Universitat Wurzburg

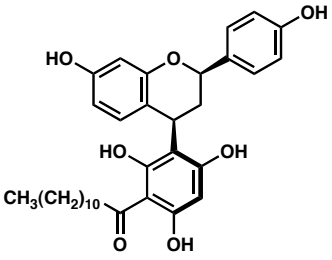
Matthias Breuning
Universitat Wurzburg

For a general review of biaryls in synthesis:
Bringmann, G.; Mortimer, A. J. P.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew. Chem. I. E.* **2005**, *44*, 5384-5427.

Biaryl cross-coupling:
Stanforth, S. P. *Tetrahedron.* **1998**, *54*, 263-303.
Lloyd-Williams, P.; Giralt, E. *Chem. Soc. Rev.* **2001**, *30*, 145-157.
Broutin, P.-E.; Colobert, F. *Eur. J. Org. Chem.* **2005**, 1113-1128.

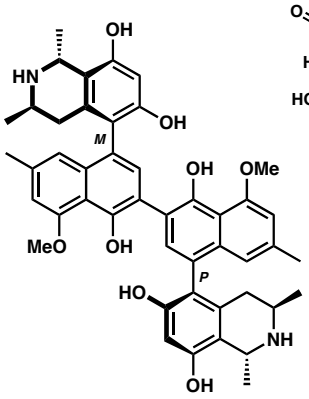
Lactone Methodology:
Bringmann, G.; Breuning, M.; Tasler, S. *Synthesis*, **1999**, *4*, 525-558.
Bringmann, G.; Tasler, S.; Pfeifer, R.-M.; Breuning, M. *J. Organomet. Chem.* **2002**, *661*, 49-65.

Atropisomerism is Everywhere



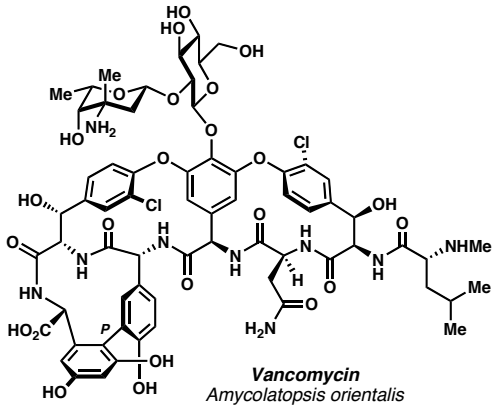
Myristinin B
Myristica cinnamomea

COX 2 inhibitor



Michellamine B
Ancistrocladus korupensis

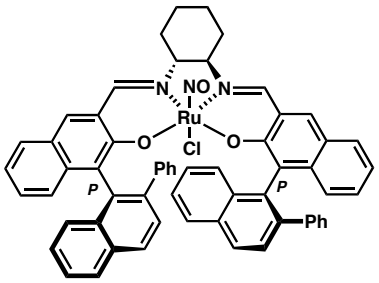
Protein kinase C inhibitor, anti-HIV-1,2



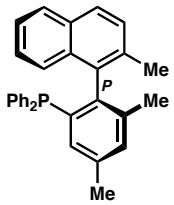
Vancomycin
Amycolatopsis orientalis

Antibiotic (Gram-positive)

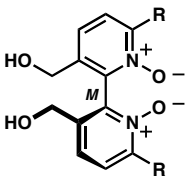
Atropisomerism is Everywhere



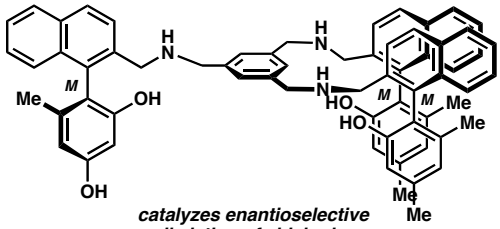
catalyzes asymmetric homo-coupling of 2-naphthols
Katsuki, T. *Synlett*, **2000**, 1433-1436.



catalyzes enantioselective hydrosilations
Bringmann, G. *Tetrahedron: Asymm.* **1999**, *10*, 3025-3031.



catalyzes enantioselective allylation of aldehydes
Hayashi, T. *J. Org. Chem.* **2003**, *68*, 6329-6337.



catalyzes enantioselective alkylation of aldehydes
Bringmann, G. *J. Org. Chem.* **2003**, *68*, 6859-6863.

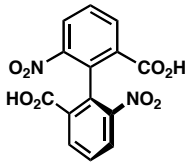
Atropisomerism

History & Background

Atropisomerism: a term coined by Richard Kuhn in 1933, it refers to stereoisomerism resulting from hindered rotation around a single bond such that the isolation of individual conformers is possible.

From Greek: *a* - not
tropos - to turn

- The first atropisomer was reported in 1922 by G. H. Christie and J. Kenner. A single enantiomer of **6,6'-dinitro-2,2'-diphenic acid** was isolated from the racemic mixture via diastereoselective crystallization with a chiral resolving agent:



Kuhn, R. "Molekulare Asymmetrie" in *Stereochemie.* Freudenberg, K. ed. Franz-Deutike: Leipzig-Wien, **1933**, p. 803.
Christie, G. H.; Kenner, J. *J. Chem. Soc.* **1922**, *121*, 614-620.

Atropisomerism

Conditions for Axial Chirality

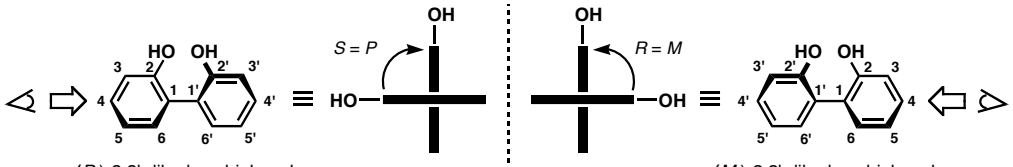
The Rules:

- A generally accepted--though arbitrary--rule states atropisomers are considered physically separable when they have a half-life at room temperature of ≥1000 s (16.7 min).
  - $\Delta G^{\ddagger}_{200\ K} = 61.6$ kJ mol^{-1}
  - $\Delta G^{\ddagger}_{300\ K} = 93.5$ kJ mol^{-1}

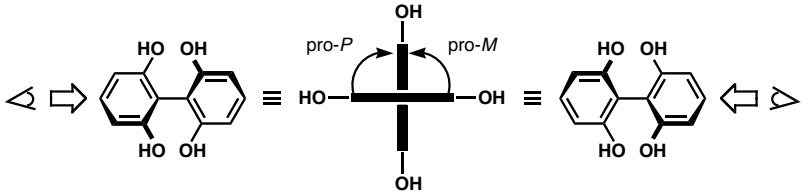
- Steric hindrance at the *ortho* positions (and to a lesser extent, electron donating/withdrawing character of each of the substituents around each aryl ring) determines the ability of a biaryl system to display atropisomeric behavior.

- When referring to axial (helical) chirality, *S* and *R* notation become *P* (plus) and *M* (minus), respectively.

- Hierarchy of functionality is identical to the determination of central (sp^3) chirality (highest atomic number, etc.).
  - Hierarchy of aryl substitution is as follows: endocyclic *ortho* --> *ortho* --> *meta* --> *para*



(*P*)-2,2'-dihydroxybiphenyl (*M*)-2,2'-dihydroxybiphenyl

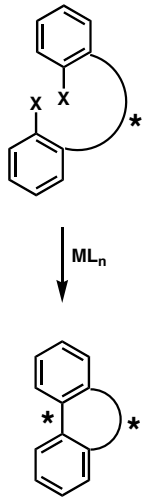


Bringmann, G. A*ngew. Chem. I. E.* 2**005,** *44,* 5384-5427.

Direct Atroposelective Aryl-Aryl Coupling

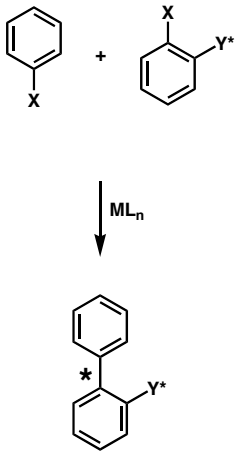
Diastereoselective Coupling

Chiral Tether Influences Configuration During Intramolecular Coupling



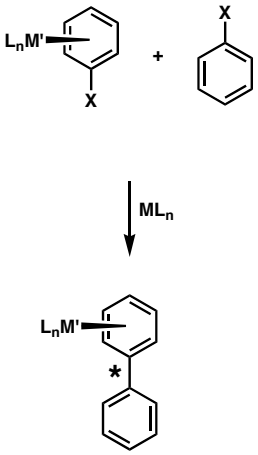
Central-to-axial transfer of chirality

Ortho Chiral Auxiliary Influences Configuration During Intermolecular Coupling



Central-to-axial transfer of chirality

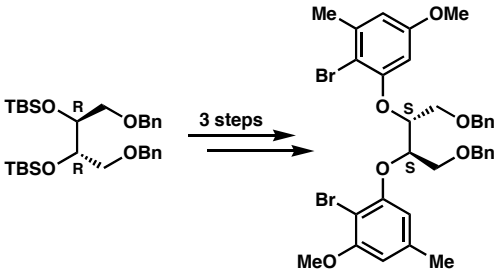
Planar Chiral Element Influences Configuration During Intermolecular Coupling



Planar-to-axial transfer of chirality

Diastereoselective Aryl-Aryl Coupling

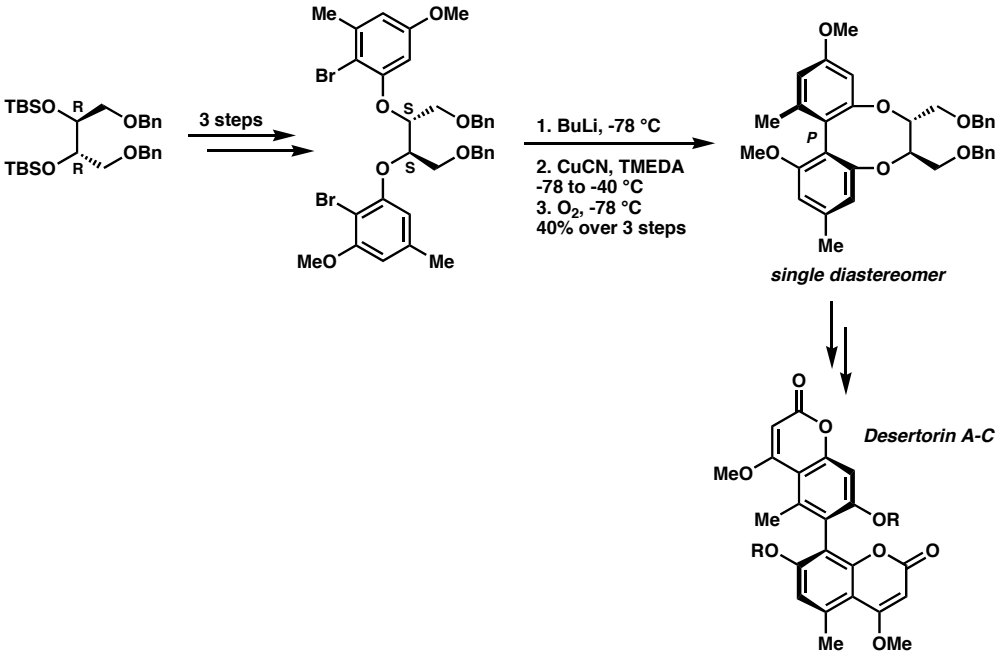
Intramolecular Coupling with Chiral Tethers - Toward Desertorin A-C



Lipshutz, B. H.; Kayser, F.; Lui, Z.-P. *Angew. Chem., I. E. Engl.* **1994**, *33*, 1842-1844.
Kyasnoor, R. V.; Sargent, M. V. *Chem. Commun.* **1998**, 2713-2714.

Diastereoselective Aryl-Aryl Coupling

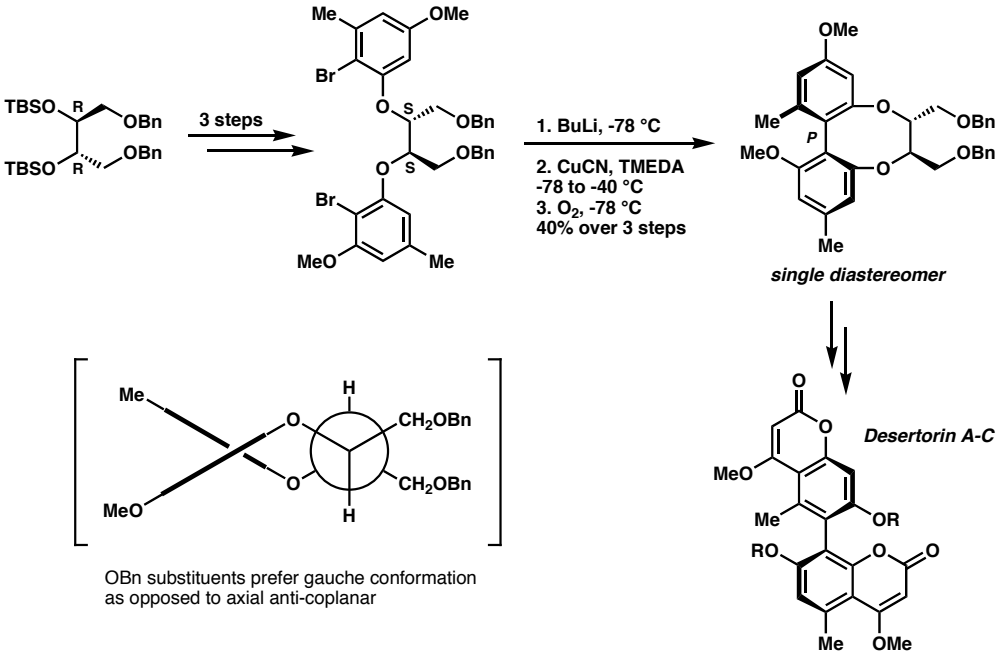
Intramolecular Coupling with Chiral Tethers - Toward Desertorin A-C



Lipshutz, B. H.; Kayser, F.; Lui, Z.-P. *Angew. Chem., I. E. Engl.* **1994**, *33*, 1842-1844.
Kyasnoor, R. V.; Sargent, M. V. *Chem. Commun.* **1998**, 2713-2714.

Diastereoselective Aryl-Aryl Coupling

Intramolecular Coupling with Chiral Tethers - Toward Desertorin A-C

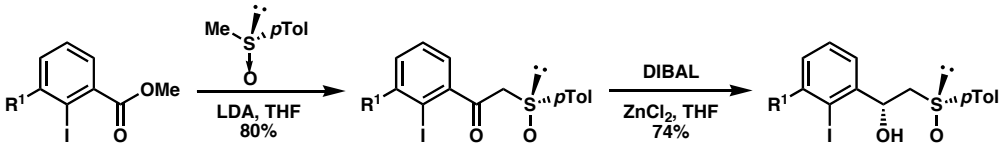


OBn substituents prefer gauche conformation as opposed to axial anti-coplanar

Lipshutz, B. H.; Kayser, F.; Lui, Z.-P. *Angew. Chem., I. E. Engl.* **1994**, *33*, 1842-1844.
Kyasnoor, R. V.; Sargent, M. V. *Chem. Commun.* **1998**, 2713-2714.

Diastereoselective Aryl-Aryl Coupling

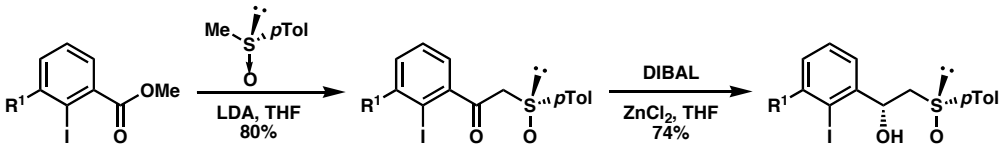
Ortho Chiral Auxiliaries - Asymmetric Suzuki Coupling

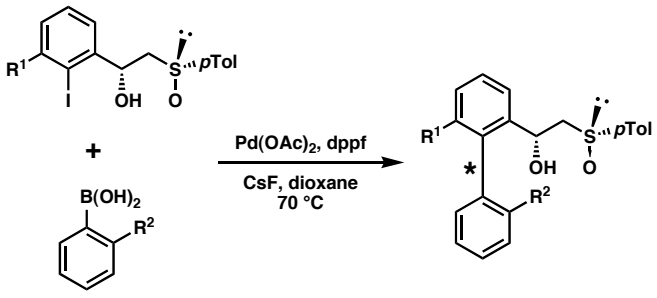


Broutin, P.-E.; Colobert, F. *Org. Lett.* **2003**, *5(18)*, 3281-3284.

Diastereoselective Aryl-Aryl Coupling

Ortho Chiral Auxiliaries - Asymmetric Suzuki Coupling





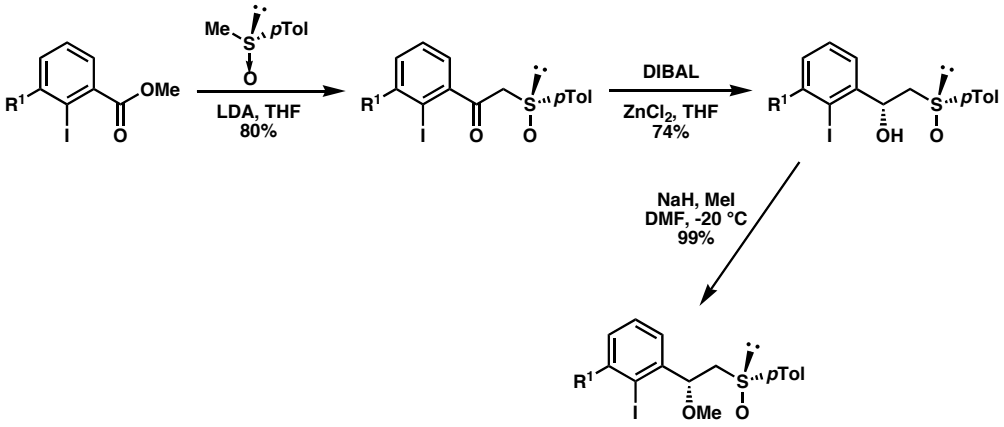
Entry	R^1	R^2	Yield (%)	dr*
1	Me	Me	60	70:30
2	Me	OMe	27	90:10
3	OMe	OMe	61	93:7

*determined by ^{1}H NMR
(absolute configuration unknown)

Broutin, P.-E.; Colobert, F. *Org. Lett.* **2003**, *5(18)*, 3281-3284.

Diastereoselective Aryl-Aryl Coupling

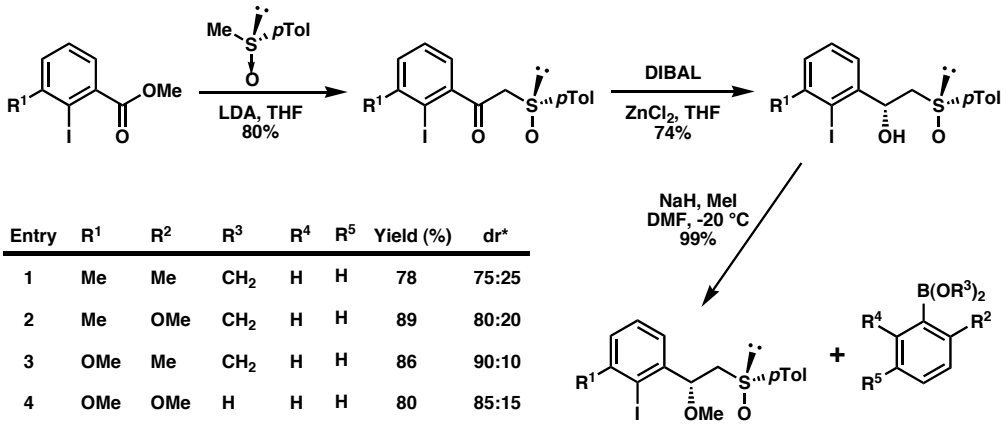
Ortho Chiral Auxiliaries - Asymmetric Suzuki Coupling



Broutin, P.-E.; Colobert, F. *Eur. J. Org. Chem.* **2005**, 1113-1128.

Diastereoselective Aryl-Aryl Coupling

Ortho Chiral Auxiliaries - Asymmetric Suzuki Coupling



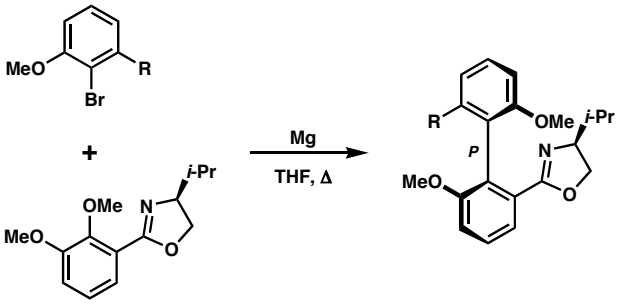
Entry	R^1	R^2	R^3	R^4	R^5	Yield (%)	dr*
1	Me	Me	CH_2	H	H	78	75:25
2	Me	OMe	CH_2	H	H	89	80:20
3	OMe	Me	CH_2	H	H	86	90:10
4	OMe	OMe	H	H	H	80	85:15
5	H	Me	H			99	>99:1
6	H	OMe	H			99	>99:1
7	Me	H	CH_2			88	90:10
8	OMe	H	CH_2			86	95:5

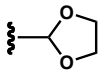
*determined by ^{1}H NMR (absolute configuration unknown)

Broutin, P.-E.; Colobert, F. *Eur. J. Org. Chem.* **2005**, 1113-1128.

Diastereoselective Aryl-Aryl Coupling

Ortho Chiral Auxiliaries - Aryl Grignard Coupling



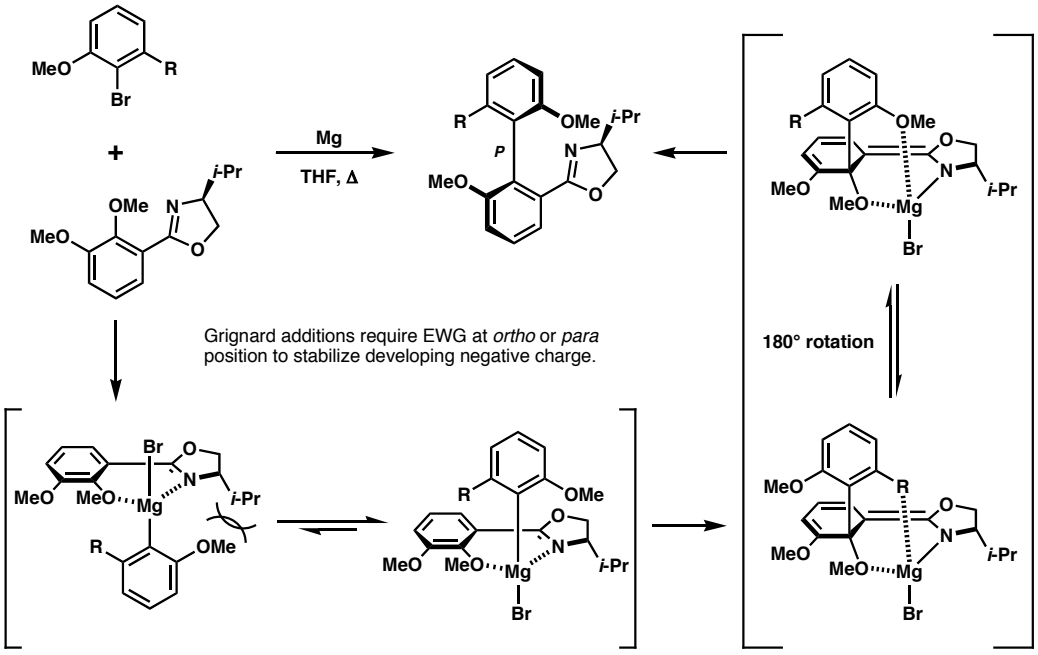
R	Yield (%)	dr (*P* :*M*)
	90	20:80
CH_2OMe	75	40:60
CH_2OBn	80	42:58
Me	79	90:10
CH_2OTBS	73	93:7

Grignard additions require EWG at *ortho* or *para* position to stabilize developing negative charge.

Meyers, A. I.; Nelson, T. D.; Moorlag, H.; Rawson, D. J.; Meier, A. *Tetrahedron*, **2004**, *60*, 4459-4473.

Diastereoselective Aryl-Aryl Coupling

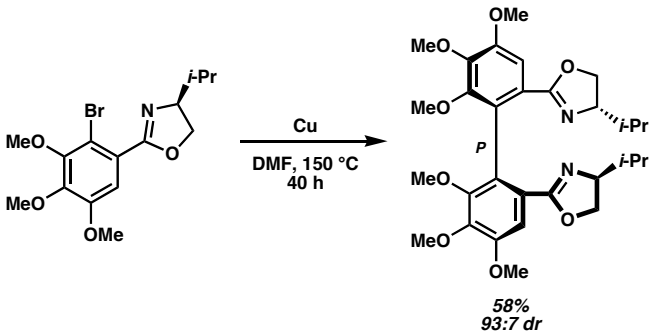
Ortho Chiral Auxiliaries - Aryl Grignard Coupling



Meyers, A. I.; Nelson, T. D.; Moorlag, H.; Rawson, D. J.; Meier, A. *Tetrahedron*, **2004**, *60*, 4459-4473.

Diastereoselective Aryl-Aryl Coupling

Ortho Chiral Auxiliaries - Ullmann Homocoupling

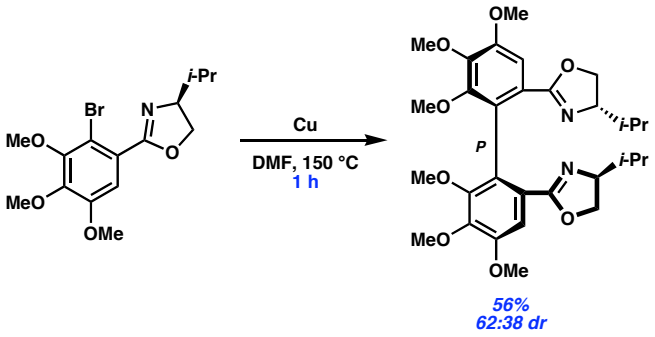


58%
93:7 dr

Nelson, T. D.; Meyers, A. I. *Tetrahedron Lett.* **1993**, *34*, 3061-3062.
Nelson, T. D.; Meyers, A. I. *Tetrahedron Lett.* **1994**, *35*, 3259-3262.

Diastereoselective Aryl-Aryl Coupling

Ortho Chiral Auxiliaries - Ullmann Homocoupling

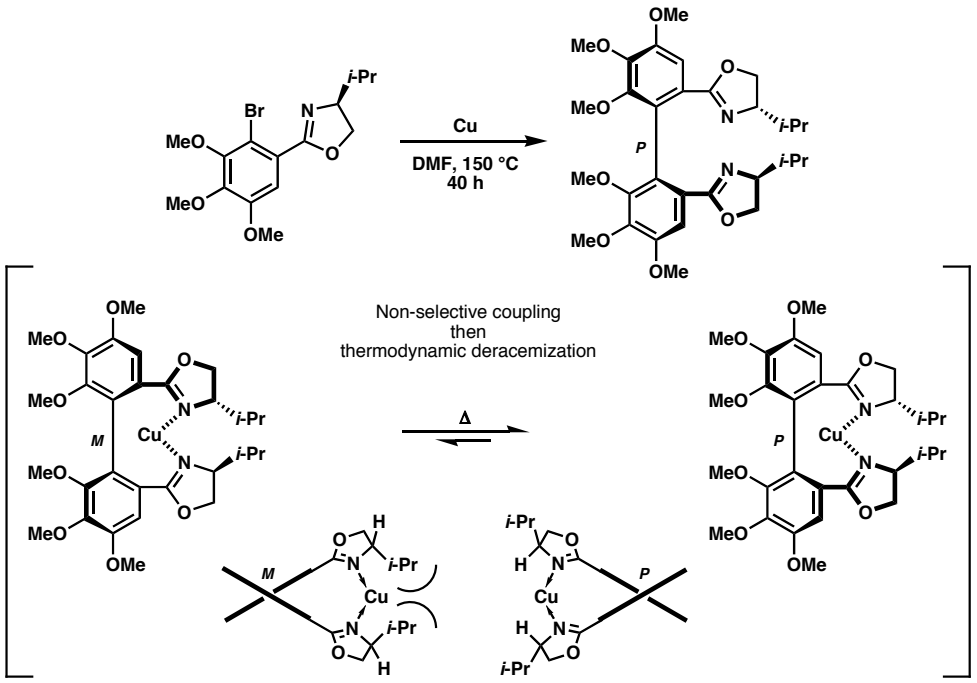


56%
62:38 dr

Nelson, T. D.; Meyers, A. I. *Tetrahedron Lett.* **1993**, *34*, 3061-3062.
Nelson, T. D.; Meyers, A. I. *Tetrahedron Lett.* **1994**, *35*, 3259-3262.

Diastereoselective Aryl-Aryl Coupling

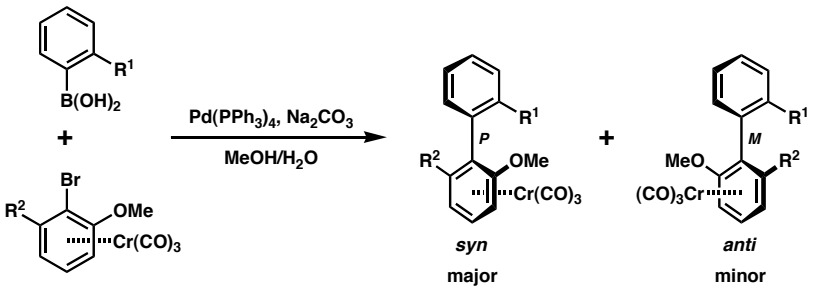
Ortho Chiral Auxiliaries - Ullmann Homocoupling



Nelson, T. D.; Meyers, A. I. *Tetrahedron Lett.* **1993**, *34*, 3061-3062.
Nelson, T. D.; Meyers, A. I. *Tetrahedron Lett.* **1994**, *35*, 3259-3262.

Diastereoselective Aryl-Aryl Coupling

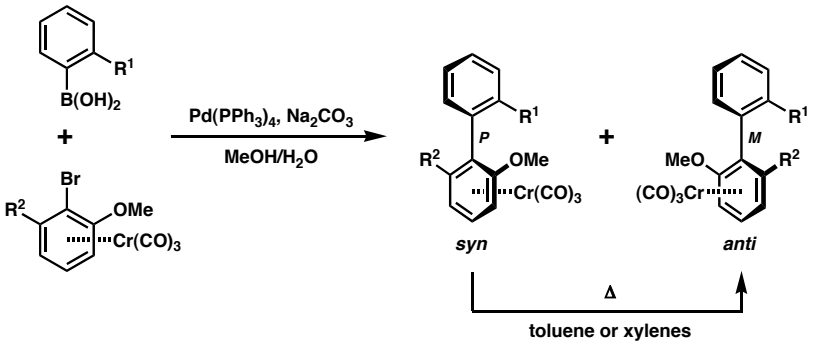
Planar Arene-Metal Complexes - Asymmetric Suzuki Coupling



Kamikawa, K.; Watanabe, T.; Uemura, M. *J. Org. Chem.* **1996**, *61*, 1375-1384.

Diastereoselective Aryl-Aryl Coupling

Planar Arene-Metal Complexes - Asymmetric Suzuki Coupling



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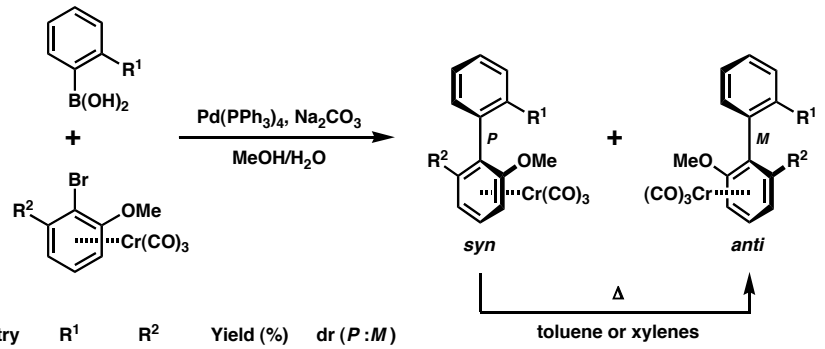
Diastereoselective Aryl-Aryl Coupling

Planar Arene-Metal Complexes - Asymmetric Suzuki Coupling

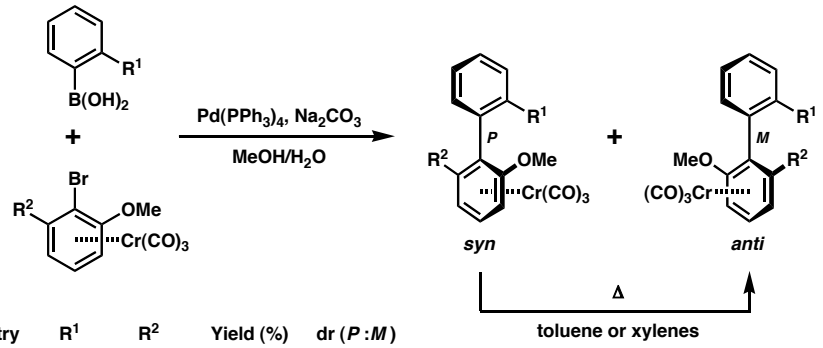


Entry	R^1	R^2	Yield (%)	dr (*P* : *M*)
1	Me	Me	96	100:0
2	Me	CH_2OH	77	100:0
3	OMe	Me	94	97:3
4	CHO	Me	95	0:100
5	CHO	CHO	43	0:100
6	OMe	CHO	85	4:96
7	Me	CHO	82	100:0

Kamikawa, K.; Watanabe, T.; Uemura, M. *J. Org. Chem.* **1996**, *61*, 1375-1384.

Diastereoselective Aryl-Aryl Coupling

Planar Arene-Metal Complexes - Asymmetric Suzuki Coupling



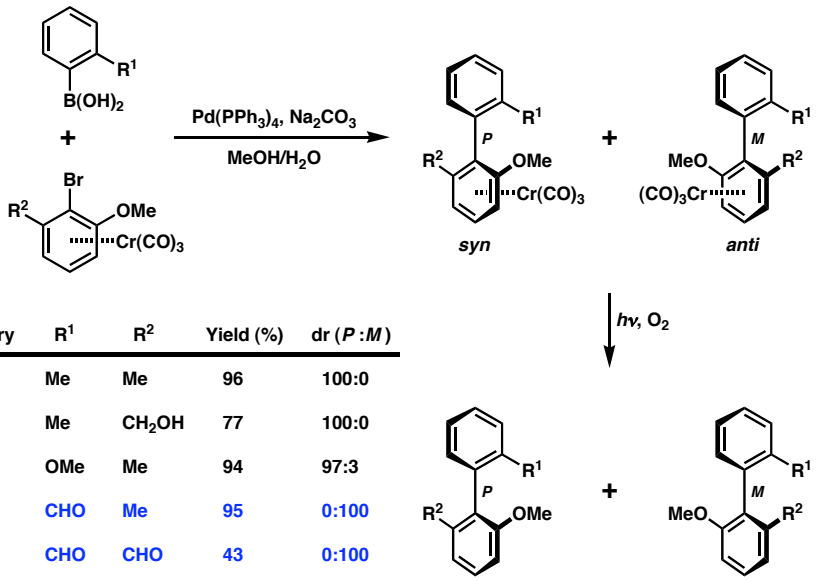
Entry	R^1	R^2	Yield (%)	dr (*P* : *M*)
1	Me	Me	96	100:0
2	Me	CH_2OH	77	100:0
3	OMe	Me	94	97:3
4	CHO	Me	95	0:100
5	CHO	CHO	43	0:100
6	OMe	CHO	85	4:96
7	Me	CHO	82	100:0

o-carbonyl substituents may result in chemical atropisomerization to the more thermodynamically stable (*anti*) product.

Kamikawa, K.; Watanabe, T.; Uemura, M. *J. Org. Chem.* **1996**, *61*, 1375-1384.

Diastereoselective Aryl-Aryl Coupling

Planar Arene-Metal Complexes - Asymmetric Suzuki Coupling

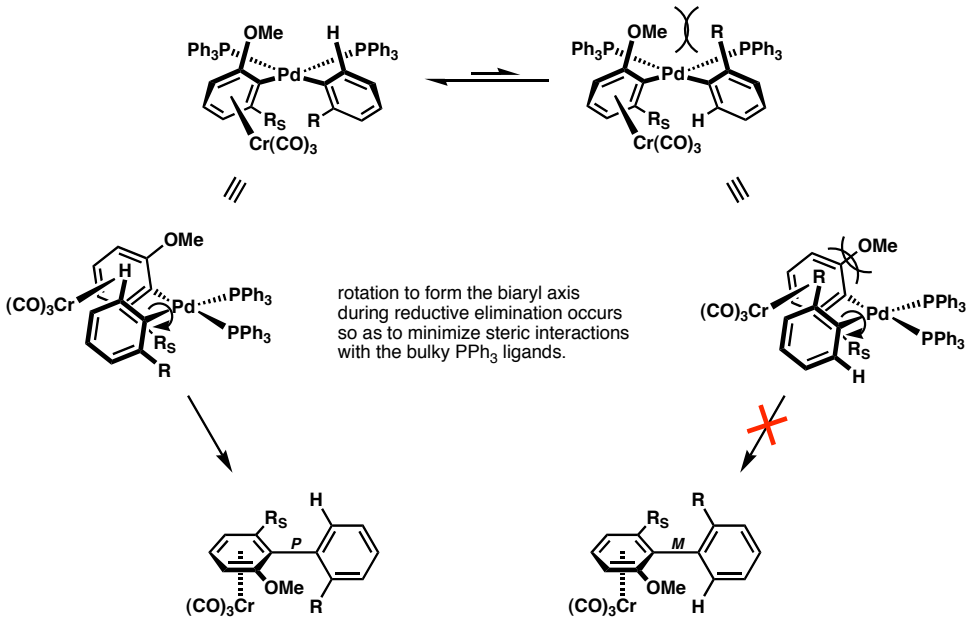


Entry	R^1	R^2	Yield (%)	dr (*P* : *M*)
1	Me	Me	96	100:0
2	Me	CH_2OH	77	100:0
3	OMe	Me	94	97:3
4	CHO	Me	95	0:100
5	CHO	CHO	43	0:100
6	OMe	CHO	85	4:96
7	Me	CHO	82	100:0

Kamikawa, K.; Watanabe, T.; Uemura, M. *J. Org. Chem.* **1996**, *61*, 1375-1384.

Diastereoselective Aryl-Aryl Coupling

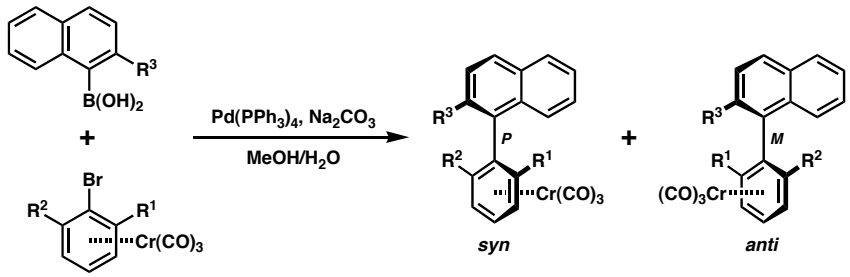
Planar Arene-Metal Complexes - Asymmetric Suzuki Coupling

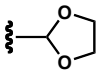


Kamikawa, K.; Uemura, M. *Synlett* **2000**, *7*, 938-949.

Diastereoselective Aryl-Aryl Coupling

Planar Arene-Metal Complexes - Asymmetric Suzuki Coupling



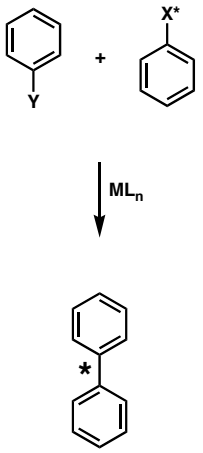
Entry	R^1	R^2	R^3	Yield (%)	dr (*P* :*M*)
1	OMe	Me	H	88	100:0
2	OMe	CHO	H	89	100:0
3	OMe	CH_2OH	H	86	100:0
4	OMe	Me		85	100:0
5	Me	H	Me	70	85:15
6	OMe	H	Me	71	71:29
7	Me	H	OMe	78	97:3

Kamikawa, K.; Uemura, M. *Synlett* **2000**, *7*, 938-949.

Direct Atroposelective Aryl-Aryl Coupling

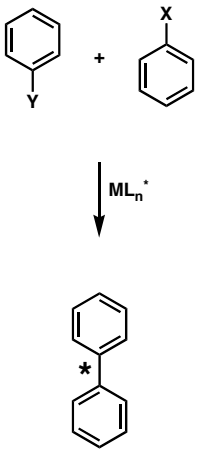
Enantioselective Coupling

Chiral Leaving Group Influences Configuration During Intermolecular Coupling



Central-to-axial transfer of chirality

Chiral Metal Complex Influences Configuration During Intermolecular Coupling



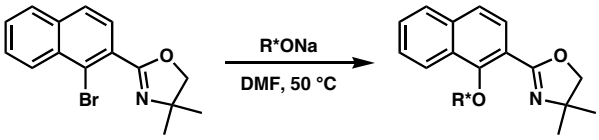
Oxidative:
- *Copper*
- *Vanadium*

Redox-Neutral:
- *Kumada*
- *Suzuki*
- *Aryl-Lead Species*

Central-to-axial transfer of chirality

Enantioselective Aryl-Aryl Coupling

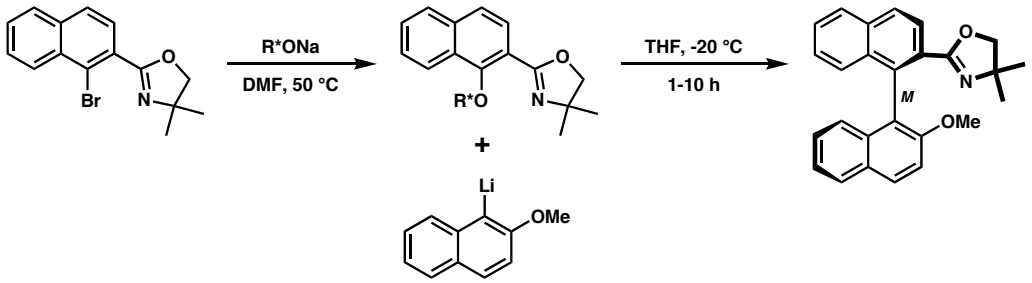
Chiral Leaving Groups



Wilson, J. A.; Cram, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 881-884.
Wilson, J. A.; Cram, D. J. *J. Org. Chem.* **1984**, *49*, 4930-4943.

Enantioselective Aryl-Aryl Coupling

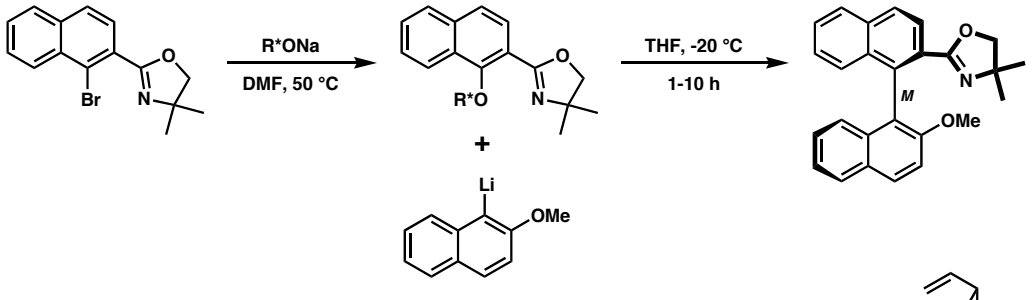
Chiral Leaving Groups



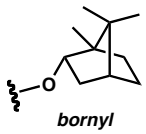
Wilson, J. A.; Cram, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 881-884.
Wilson, J. A.; Cram, D. J. *J. Org. Chem.* **1984**, *49*, 4930-4943.

Enantioselective Aryl-Aryl Coupling

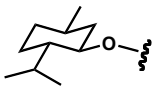
Chiral Leaving Groups



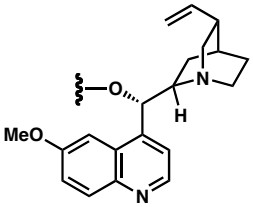
R* =



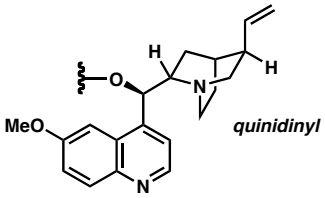
bornyl



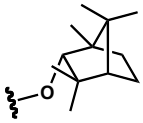
(*R*)-*menthyl*



quininyl



quinidinyl

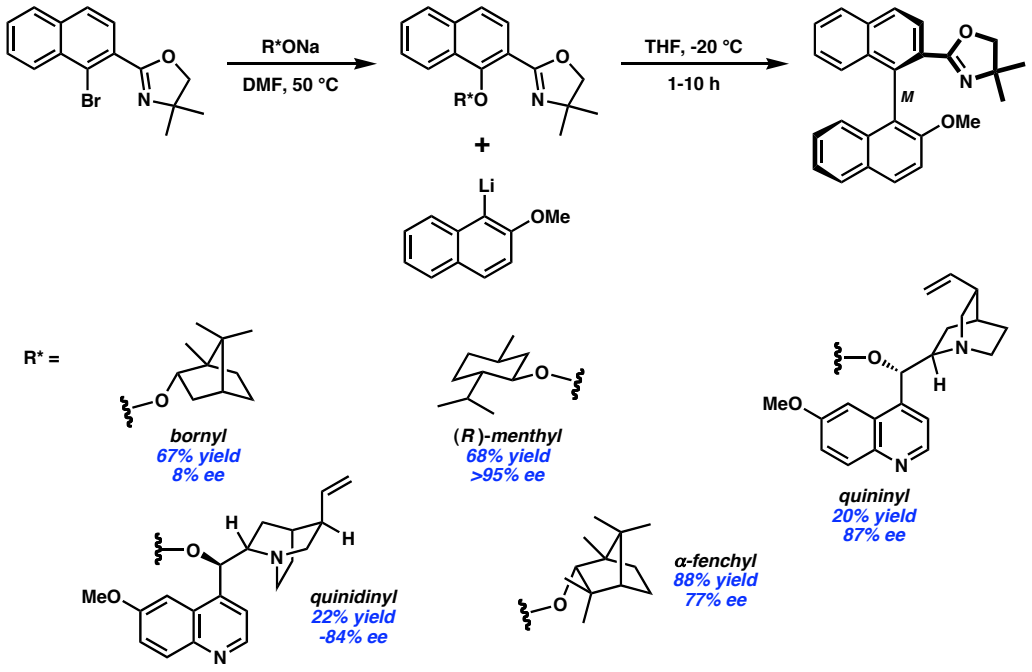


α-fenchyl

Wilson, J. A.; Cram, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 881-884.
Wilson, J. A.; Cram, D. J. *J. Org. Chem.* **1984**, *49*, 4930-4943.

Enantioselective Aryl-Aryl Coupling

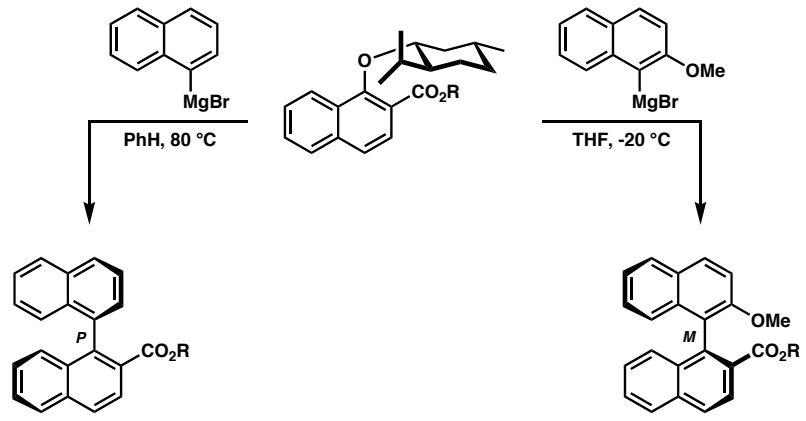
Chiral Leaving Groups



Wilson, J. A.; Cram, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 881-884.
Wilson, J. A.; Cram, D. J. *J. Org. Chem.* **1984**, *49*, 4930-4943.

Enantioselective Aryl-Aryl Coupling

Chiral Leaving Groups - Menthol

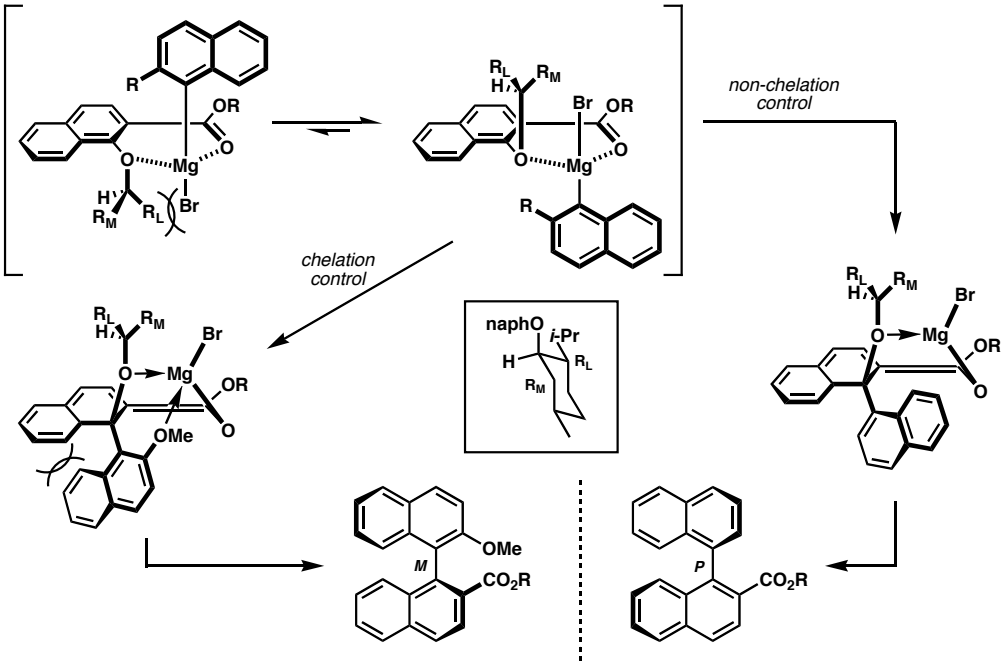


% Yield	% ee	R	% Yield	% ee
95	80	*i*-Pr	92	97
93	76	(*R*)-menthyl	81	98
74	91	(*R*)-phenylethyl	85	91

Wilson, J. A.; Cram, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 881-884.
Wilson, J. A.; Cram, D. J. *J. Org. Chem.* **1984**, *49*, 4930-4943.

Enantioselective Aryl-Aryl Coupling

Chiral Leaving Groups - Menthol

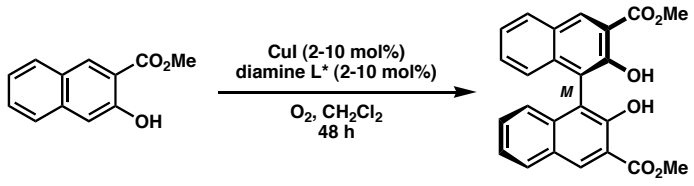


Wilson, J. A.; Cram, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 881-884.
Wilson, J. A.; Cram, D. J. *J. Org. Chem.* **1984**, *49*, 4930-4943.

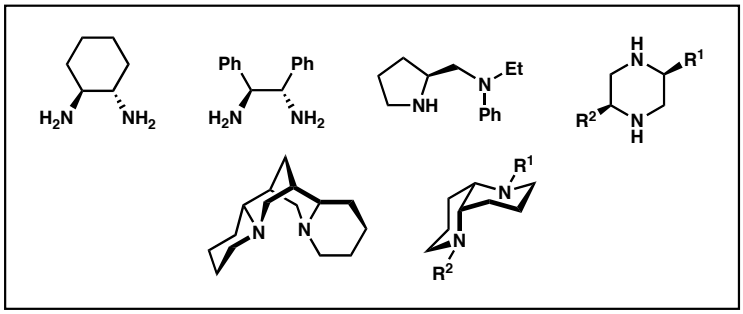
Enantioselective Aryl-Aryl Coupling

Oxidative Homocoupling - Copper

• Copper-amine complexes are the most widely investigated due to the ease of ligand screening.



Ligand Screen



Li, X.; Yang, J.; Kozlowski, M. *Org. Lett.* **2001**, *3(8)*, 1137-1140.

Enantioselective Aryl-Aryl Coupling

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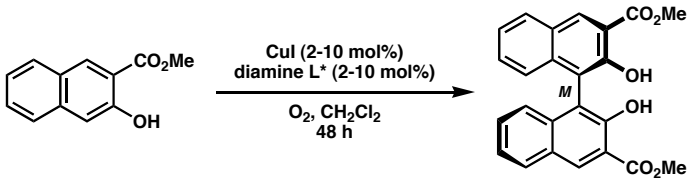
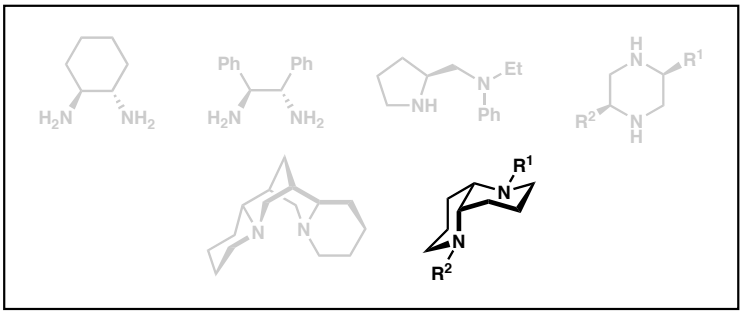


Ligand Screen



Li, X.; Yang, J.; Kozlowski, M. *Org. Lett.* **2001**, *3(8)*, 1137-1140.

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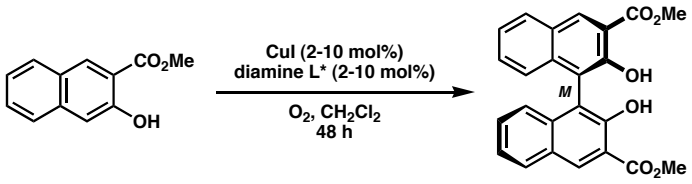
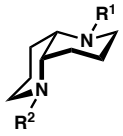


Ligand Screen



	% Yield	% ee
$R^1 = R^2 = H$	60	91
$R^1 = H, R^2 = Me$	53	79
$R^1 = R^2 = Me$	43	3
$R^1 = R^2 = Bn$	72	22
$R^1 = R^2 = CH_2CF_3$	NR	

Li, X.; Yang, J.; Kozlowski, M. *Org. Lett.* **2001**, *3(8)*, 1137-1140.

Enantioselective Aryl-Aryl Coupling

Oxidative Homocoupling - Copper

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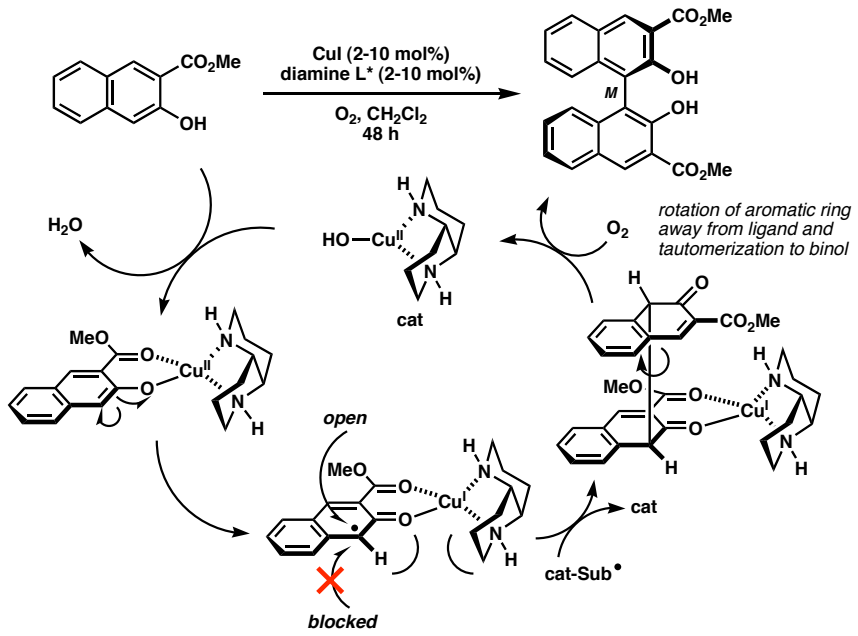
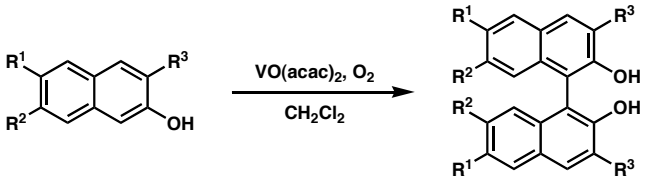


Li, X.; Yang, J.; Hewgley, B.; Mulrooney, C. A.; Yang, J.; Kozlowski, M. *J. Org. Chem.* **2003**, *68*, 5500-5511.

Enantioselective Aryl-Aryl Coupling

Oxidative Homocoupling - Vanadium



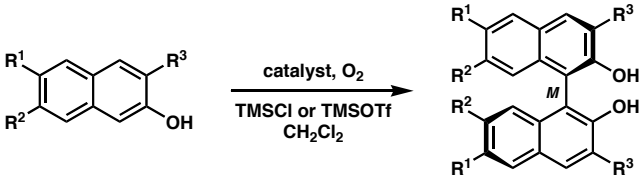
Entry	R^1	R^2	R^3	% Yield
1	H	H	H	92
2	Br	H	H	90
3	H	OMe	H	76
4	H	H	CO_2Me	35

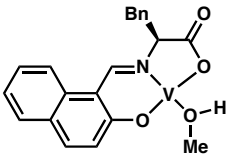
Mechanism unknown

Hwang, D.-R.; Chen, C.-P.; Uang, B.-J. *Chem. Commun.* **1999**, 1207-1208.
Chu, C.-Y.; Hwang, D.-R.; Wang, S.-K.; Uang, B.-J. *Chem. Commun.* **2001**, 980-981.
Chu, C.-Y.; Uang, B.-J. *Tetrahedron: Asymm.* **2003**, *14*, 53-55.

Enantioselective Aryl-Aryl Coupling

Oxidative Homocoupling - Vanadium





catalyst

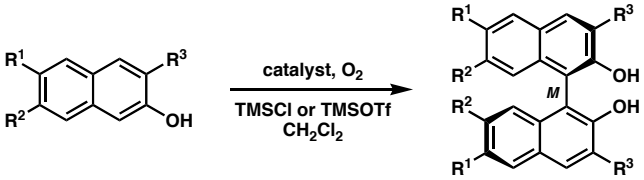
Entry	R^1	R^2	R^3	% Yield	% ee
1	H	H	H	82	51
2	Br	H	H	91	51
3	H	OMe	H	50	51
4	H	H	CO_2Me	trace	---

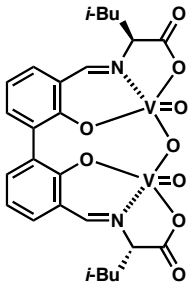
Mechanism unknown

Hwang, D.-R.; Chen, C.-P.; Uang, B.-J. *Chem. Commun.* **1999**, 1207-1208.
Chu, C.-Y.; Hwang, D.-R.; Wang, S.-K.; Uang, B.-J. *Chem. Commun.* **2001**, 980-981.
Chu, C.-Y.; Uang, B.-J. *Tetrahedron: Asymm.* **2003**, *14*, 53-55.

Enantioselective Aryl-Aryl Coupling

Oxidative Homocoupling - Vanadium





catalyst

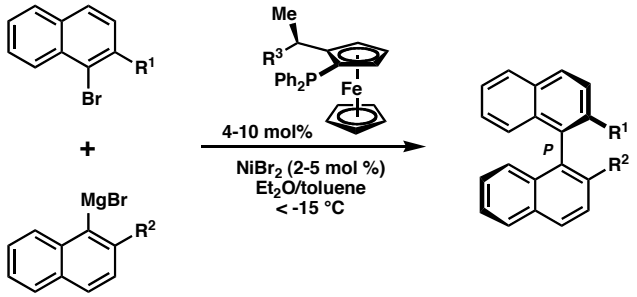
Entry	R^1	R^2	R^3	% Yield	% ee
1	H	H	H	62	90
2	Br	H	H	98	90
3	H	OMe	H	95	95
4	H	OEt	H	99	96
5	H	O*n*-Bu	H	99	94
6	H	OBn	H	80	95
7	H	H	OBn	trace	---

Mechanism unknown

Luo, Z.; Liu, Q.; Gong, L.; Cui, X.; Mi, A.; Jiang, Y. *Angew. Chem. I. E.* **2002**, *41(23)*, 4532-4535.

Enantioselective Aryl-Aryl Coupling

Redox-Neutral Coupling - Kumada Cross-Coupling

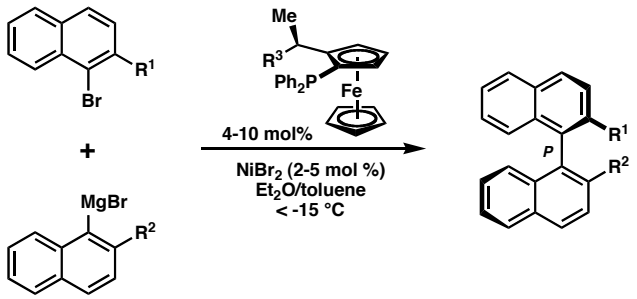


Entry	R^1	R^2	R^3	% Yield	% ee
1	Me	Me	OMe	69	95
2	Me	H	OMe	25	16
3	H	Me	OMe	92	83
4	H	Me	OEt	82	68
5	H	Me	H	81	1

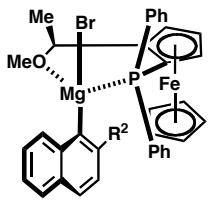
Hayashi, T.; Hayashizaki, K.; Kiyoi, T.; Ito, Y. *J. Am. Chem. Soc.* **1988**, *110*, 8153-8156.

Enantioselective Aryl-Aryl Coupling

Redox-Neutral Coupling - Kumada Cross-Coupling



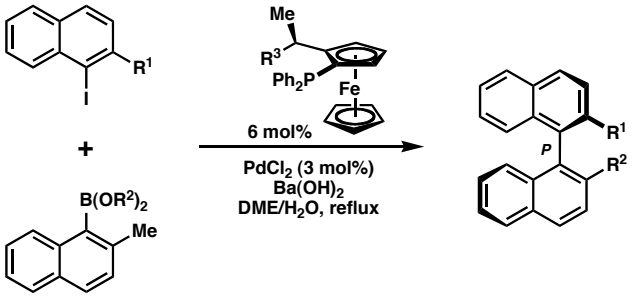
Entry	R^1	R^2	R^3	% Yield	% ee
1	Me	Me	OMe	69	95
2	Me	H	OMe	25	16
3	H	Me	OMe	92	83
4	H	Me	OEt	82	68
5	H	Me	H	81	1



Hayashi, T.; Hayashizaki, K.; Kiyoi, T.; Ito, Y. *J. Am. Chem. Soc.* **1988**, *110*, 8153-8156.

Enantioselective Aryl-Aryl Coupling

Redox-Neutral Coupling - Suzuki Cross-Coupling

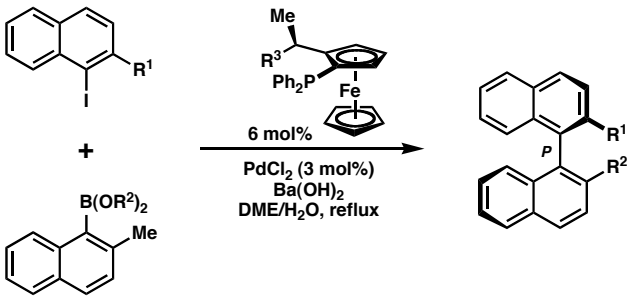


- Suzuki cross-coupling is a convenient, versatile method for the formation of atropisomeric biaryls with a wide range of functionality due to the mild nature of boronic acids/esters as nucleophilic arene species.

Cammidge, A. N.; Crepy, K. V. L. *Chem. Commun.* **2000**, 1723-1724.

Enantioselective Aryl-Aryl Coupling

Redox-Neutral Coupling - Suzuki Cross-Coupling



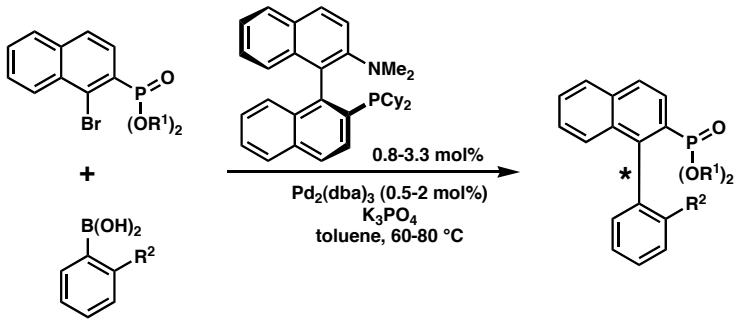
Entry	R^1	R^2	R^3	% Yield	% ee
1	H	H	OMe	74	14
2	H	H	NMe_2	44	63
3*	Me	CH_2	NMe_2	50	85

* used DME as solvent, CsF as additive, 6 days.

Cammidge, A. N.; Crepy, K. V. L. *Chem. Commun.* **2000**, 1723-1724.

Enantioselective Aryl-Aryl Coupling

Redox-Neutral Coupling - Suzuki Cross-Coupling



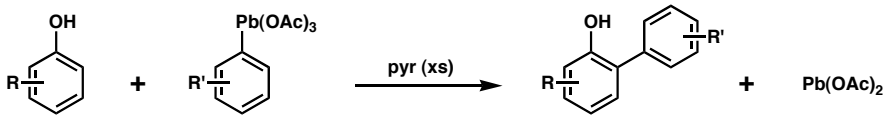
Entry	R^1	R^2	% Yield	% ee*
1	OEt	Me	98	87 (+)
2	OEt	Et	96	92 (+)
3	OEt	*i*-Pr	89	85 (+)
4	OEt	Ph	74	74 (+)
5	OMe	Me	91	84 (+)

* absolute configuration undetermined.

Buchwald, S. L.; Yin, J. *J. Am. Chem. Soc.* **2000**, *122*, 12051-12052.

Enantioselective Aryl-Aryl Coupling

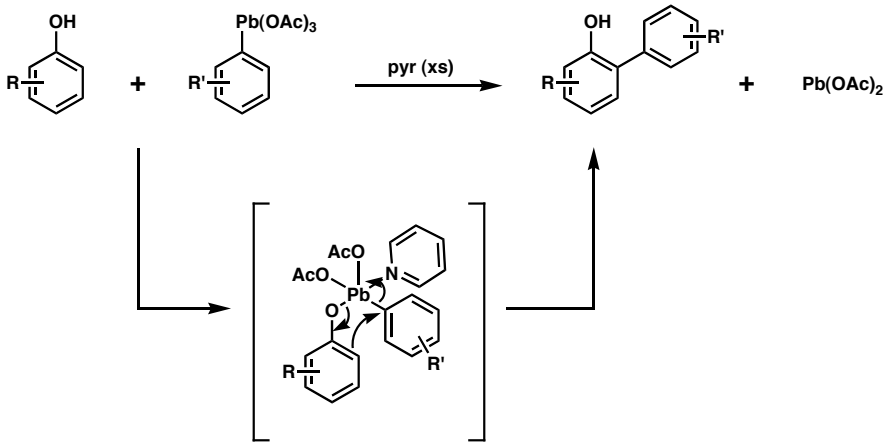
Redox-Neutral Coupling - Aryl-Lead Triacetate



Saito, S.; Kano, T.; Muto, H.; Nakadai, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1999**, *121*, 8943-8944.
Kano, T.; Ohyabu, Y.; Saito, S.; Yamamoto, H. *J. Am. Chem. Soc.* **2002**, *124*, 5365-5373.

Enantioselective Aryl-Aryl Coupling

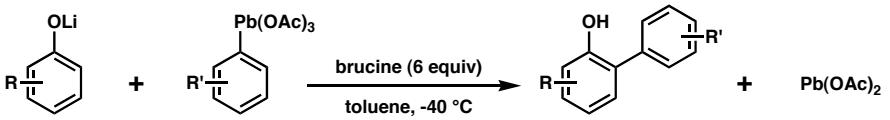
Redox-Neutral Coupling - Aryl-Lead Triacetate

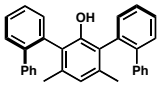
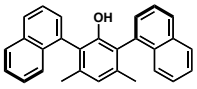
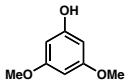
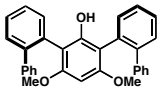
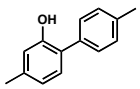
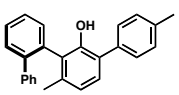
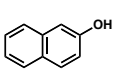
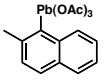
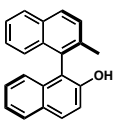


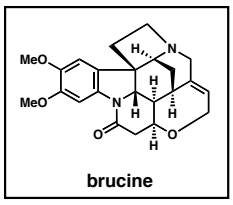
Saito, S.; Kano, T.; Muto, H.; Nakadai, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1999**, *121*, 8943-8944.
Kano, T.; Ohyabu, Y.; Saito, S.; Yamamoto, H. *J. Am. Chem. Soc.* **2002**, *124*, 5365-5373.

Enantioselective Aryl-Aryl Coupling

Redox-Neutral Coupling - Aryl-Lead Triacetate



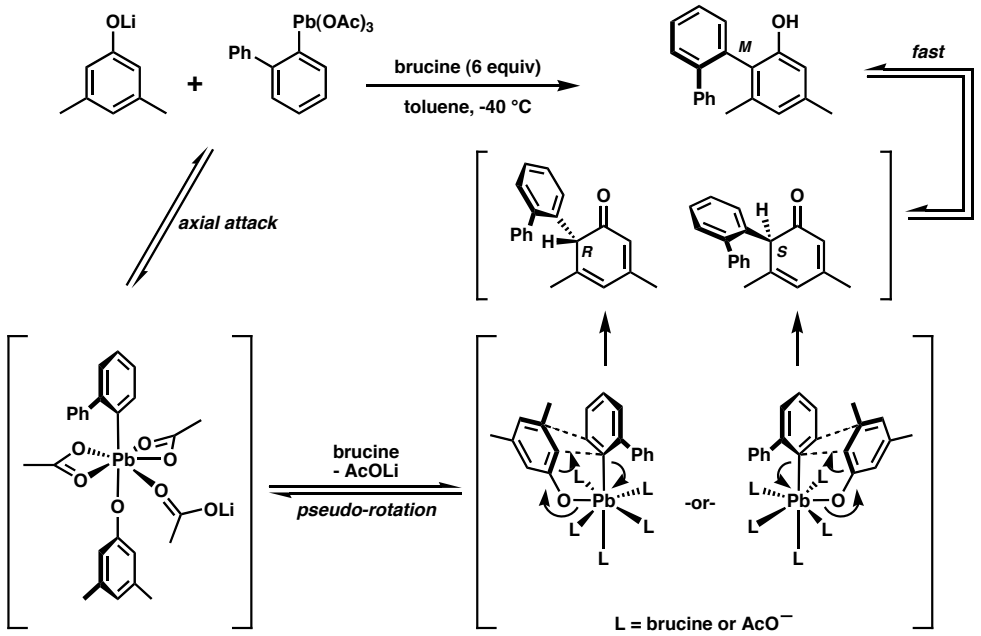
Entry	Phenol	Aryl-Lead	Product	% Yield (*dl:meso*)	% ee
1				68 (>99:1)	83
2				>99 (2:1)	51
3				55 (6.9:1)	93
4				99	85
5				99	20



Saito, S.; Kano, T.; Muto, H.; Nakadai, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1999**, *121*, 8943-8944.
Kano, T.; Ohyabu, Y.; Saito, S.; Yamamoto, H. *J. Am. Chem. Soc.* **2002**, *124*, 5365-5373.

Enantioselective Aryl-Aryl Coupling

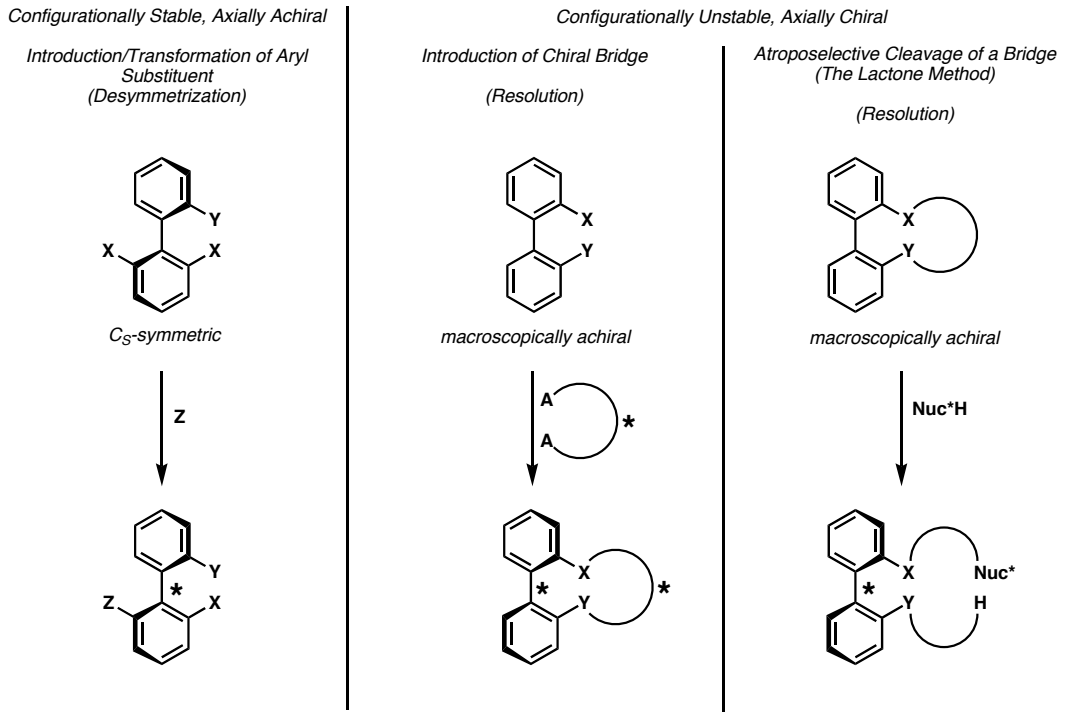
Redox-Neutral Coupling - Aryl-Lead Triacetate



Saito, S.; Kano, T.; Muto, H.; Nakadai, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1999**, *121*, 8943-8944.
Kano, T.; Ohyabu, Y.; Saito, S.; Yamamoto, H. *J. Am. Chem. Soc.* **2002**, *124*, 5365-5373.

Resolution/Desymmetrization of Prostereogenic Biaryls

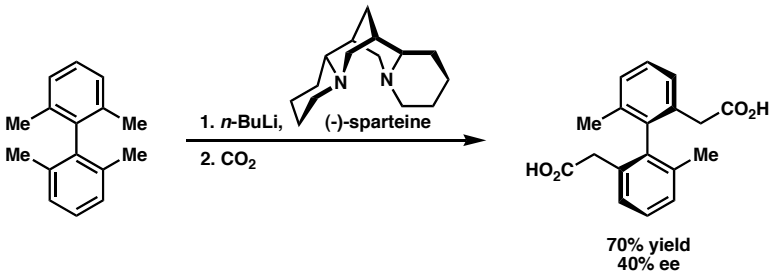
• Biaryl axis formed non-selectively prior to introduction of axial chirality.



Resolution/Desymmetrization of Prostereogenic Biaryls

Introduction/Transformation of an Ortho Substituent

- Very little investigation into this method.
- Usually no rationalization of stereochemistry.
- Most systems lack broad applicability due to substrate requirements or have low functional group tolerance.



70% yield
40% ee

Engelhardt, L. M.; Leung, W.-P.; Raston, C. L.; Salem, G.; Twiss, P.; White, A. H. *J. Chem. Soc. Dalton Trans.* **1988**, 2403-2409.

Resolution/Desymmetrization of Prostereogenic Biaryls

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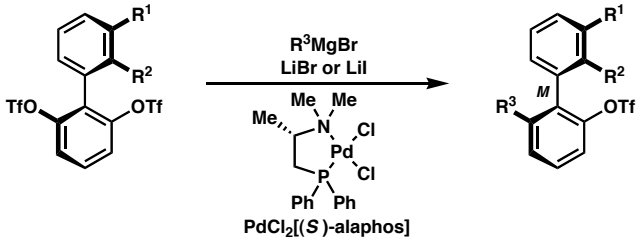


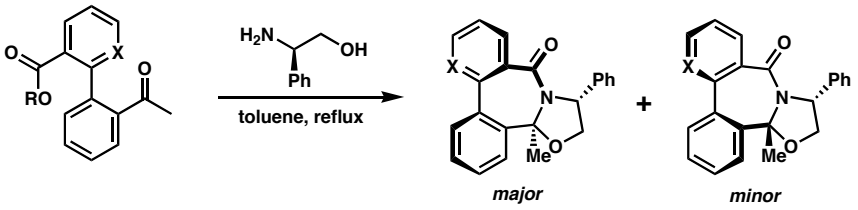
$PdCl_2$[(*S*)-alaphos]

Entry	R^1	R^2	R^3	Yield (%)	% ee
1	H	Me	Ph	85	95
2	H	Me	Ph_3Si–≡–	87	85
3	H	Ph	Ph	80	94
4	H	Ph	Ph_3Si–≡–	88	99
5			Ph	92	94
6			Ph_3Si–≡–	88	92

Hayashi, T.; Niizuma, S.; Kamikawa, T.; Suzuki, N.; Uozumi, Y. *J. Am. Chem. Soc.* **1995**, *117*, 9101-9102.
Kamikawa, T.; Hayashi, T. *Tetrahedron* **1999**, *55*, 3455-3466.

Resolution/Desymmetrization of Prostereogenic Biaryls

Introduction of a Chiral Bridge

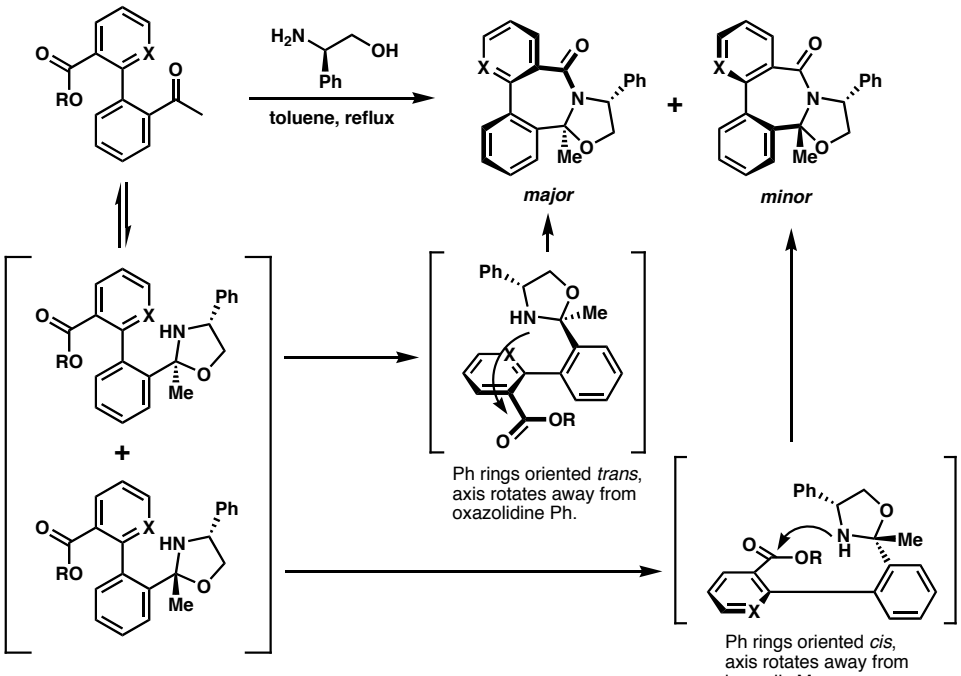


X = CH_2: 95%, >95% *de*
X = N: 72%, >95% *de*

Penhoat, M.; Levachet, V.; Dupas, G. *J. Org. Chem.* **2003**, *68*, 9517-9520.

Resolution/Desymmetrization of Prostereogenic Biaryls

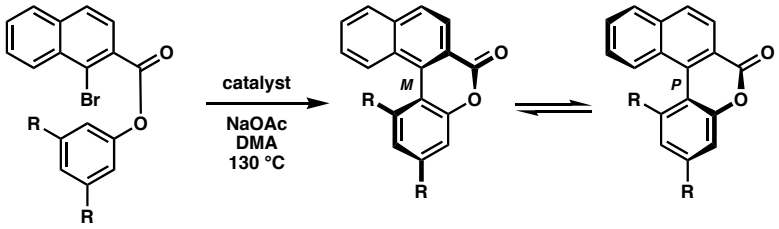
Introduction of a Chiral Bridge



Penhoat, M.; Levachet, V.; Dupas, G. *J. Org. Chem.* **2003**, *68*, 9517-9520.

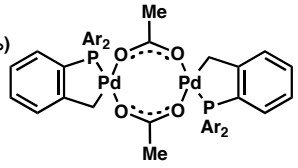
Resolution/Desymmetrization of Prostereogenic Biaryls

Atroposelective Cleavage of a Bridge - The Lactone Method



catalyst A: $Pd(OAc)_2$ (10 mol%)
PPh_3 (20 mol%)

catalyst B: (1 mol%)

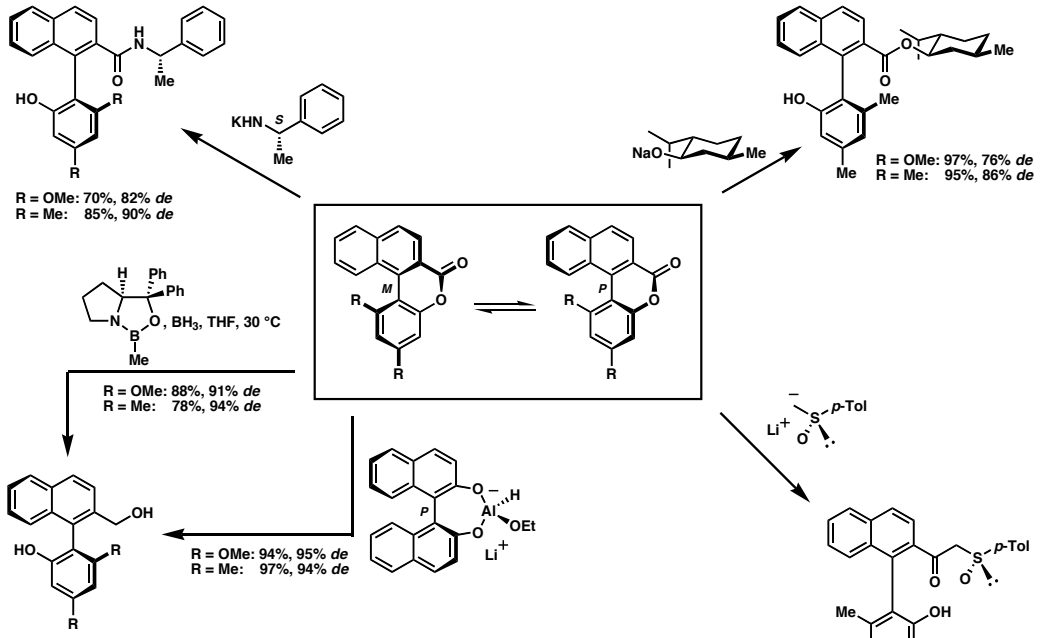


		Coupling Yields	
Entry	**R**	**A**	**B**
1	H	80	91
2	Me	75	87
3	OMe	77	90
4	Et	71	83
5	*i*-Pr	72	82
6	*t*-Bu	44	81

Bringmann, G.; Breuning, M.; Henschel, P.; Hinrichs, J. *Org. Synth.* **2002**, *79*, 72-83.

Resolution/Desymmetrization of Prostereogenic Biaryls

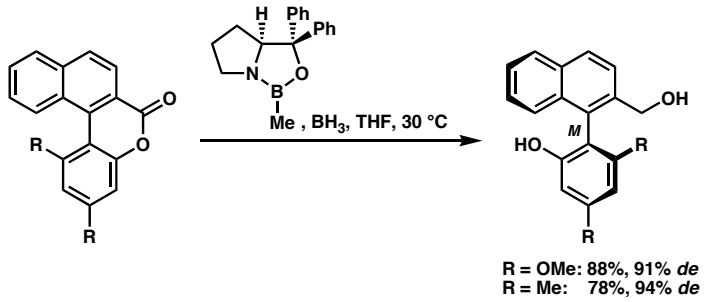
Atroposelective Cleavage of a Bridge - The Lactone Method



Bringmann, G. *Org. Synth.* **2002**, *79*, 72-83.
Bringmann, G. *Angew. Chem. I. E. Engl.* **1992**, *31*, 761-762.
Bringmann, G. *Synthesis* **1999**, 525-558.
Bringmann, G. *Eur. J. Org. Chem.* **1999**, 3047-3055.
Bringmann, G. *Chem. Eur. J.* **1999**, *5*, 3029-3038.

Resolution/Desymmetrization of Prostereogenic Biaryls

Atroposelective Cleavage of a Bridge - The Lactone Method

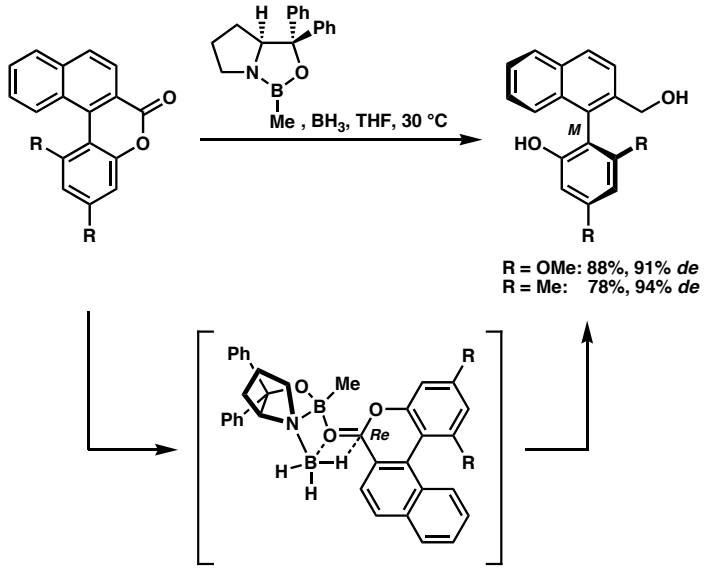


R = OMe: 88%, 91% *de*
R = Me: 78%, 94% *de*

Bringmann, G. *Synthesis* **1999**, *4*, 525-558.

Resolution/Desymmetrization of Prostereogenic Biaryls

Atroposelective Cleavage of a Bridge - The Lactone Method



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Resolution/Desymmetrization of Prostereogenic Biaryls

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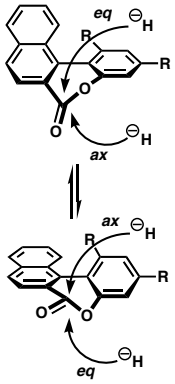

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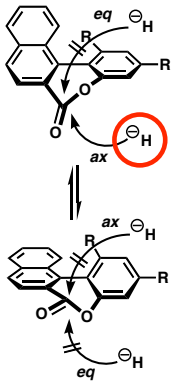

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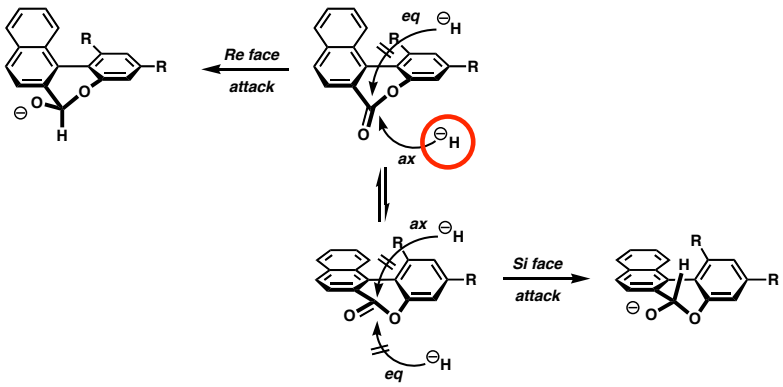

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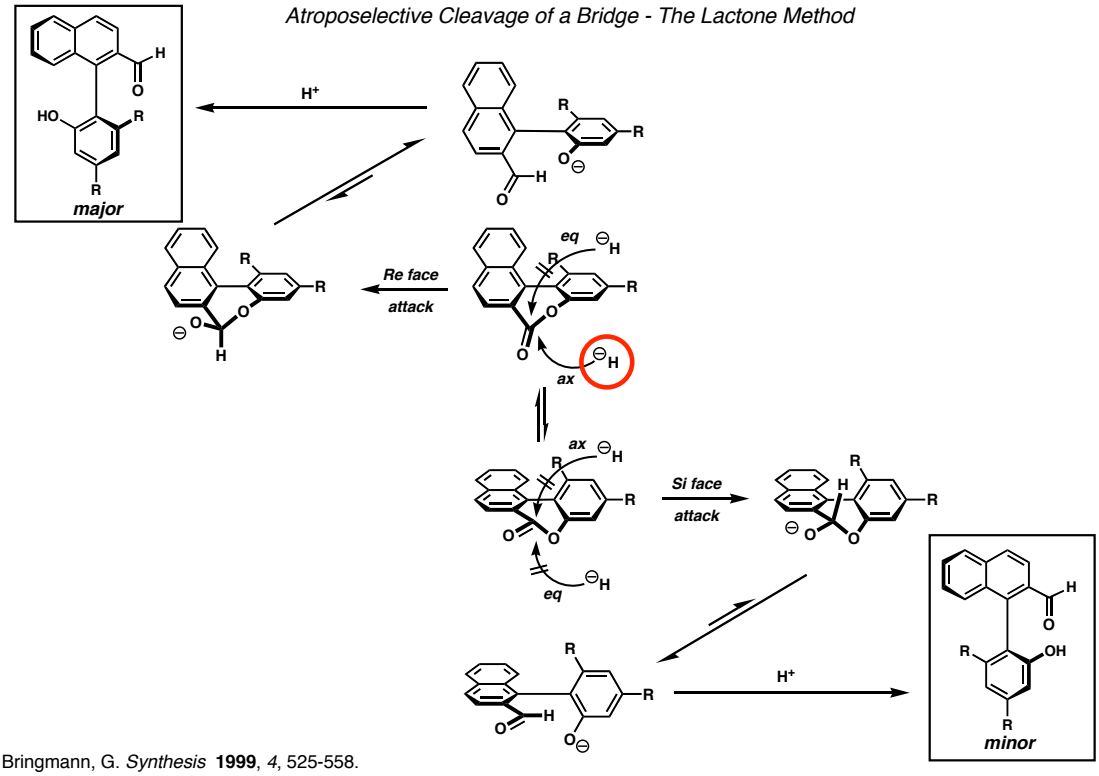

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Resolution/Desymmetrization of Prostereogenic Biaryls

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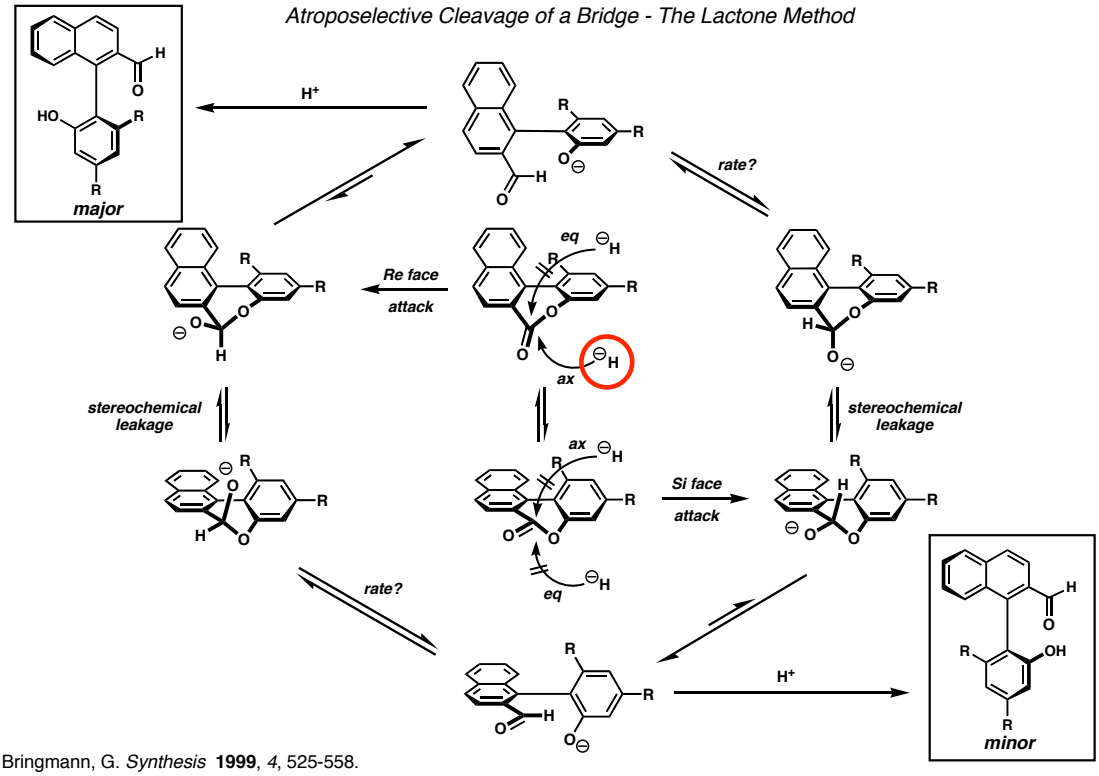

Bringmann, G. *Synthesis* **1999**, *4*, 525-558.

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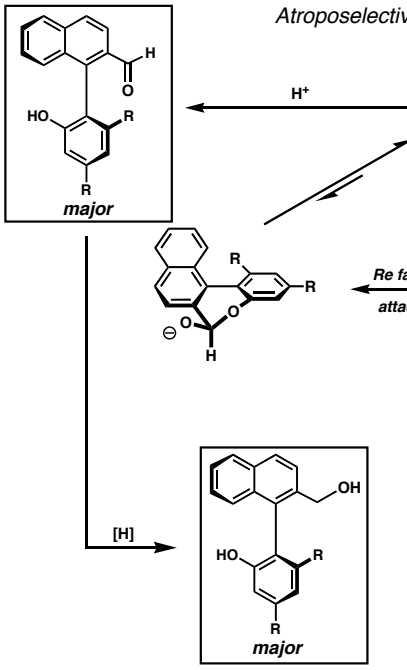
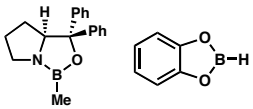


For optimal selectivity:

- use a reactive nucleophile in cases involving an intermediate ketone or aldehyde, in order to avoid "stereochemical leakage"
- use bulkier chiral nucleophiles for better facial selectivity.
- optimal reactivity/selectivity with Me-CBS and catechol borane.



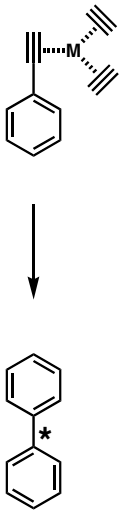
Bringmann, G. *Synthesis* **1999**, *4*, 525-558.

Atroposelective Construction of an Aromatic Ring

- Newest and least developed method for the formation of atropisomeric biaryls.
- Most intermediates/transition states unknown.

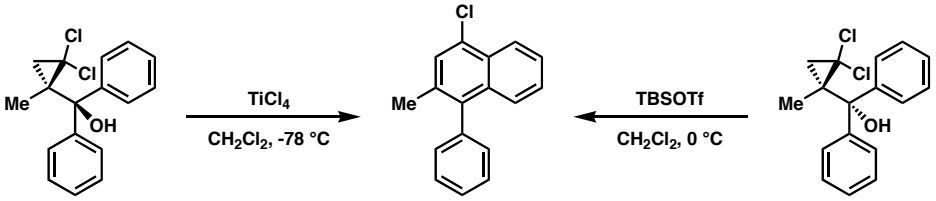
Transfer of Chirality from Benzylic sp^3 Center to Biaryl Axis

[2+2+2] Cycloaddition with Chiral Metal Complexes



Atroposelective Construction of an Aromatic Ring

Central-to-Axial Transfer of Chirality - Diaryl-2,2-dichlorocyclopropylmethanols



Nishii, Y.; Yoshida, T.; Tanabe, Y. *Tetrahedron Lett.* **1997**, *38(41)*, 7195-7198.
Nishii, Y.; Wakasugi, K.; Koga, K.; Tanabe, Y. *J. Am. Chem. Soc.* **2004**, *126*, 5358-5359.

Atroposelective Construction of an Aromatic Ring

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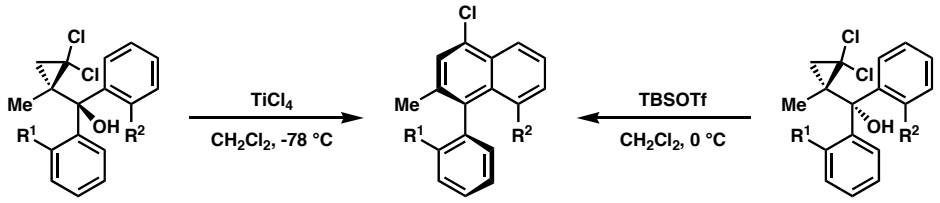

Entry	R^1	R^2	% Yield	% *ee*
1	Cl	H	97	>99
2	Cl	Cl	70	>99
3	OMe	Me	71	>99
4	OMe	Cl	65	>99
5	Me	Cl	47	>99

Entry	R^1	R^2	% Yield	% *ee*
1	Me	H	41	45

Nishii, Y.; Yoshida, T.; Tanabe, Y. *Tetrahedron Lett.* **1997**, *38(41)*, 7195-7198.
Nishii, Y.; Wakasugi, K.; Koga, K.; Tanabe, Y. *J. Am. Chem. Soc.* **2004**, *126*, 5358-5359.

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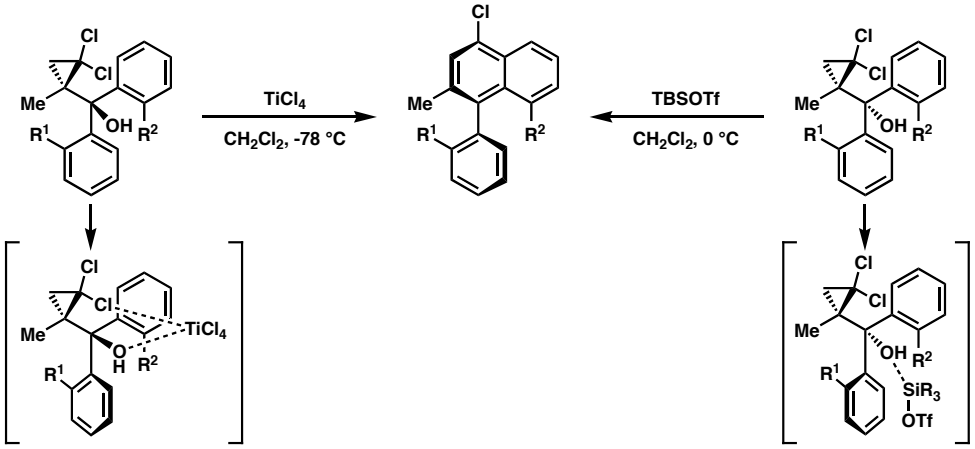

R^1 rotates away from chelated $TiCl_4$

R^1 rotates away from chelated TBSOTf

Nishii, Y.; Yoshida, T.; Tanabe, Y. *Tetrahedron Lett.* **1997**, *38(41)*, 7195-7198.
Nishii, Y.; Wakasugi, K.; Koga, K.; Tanabe, Y. *J. Am. Chem. Soc.* **2004**, *126*, 5358-5359.

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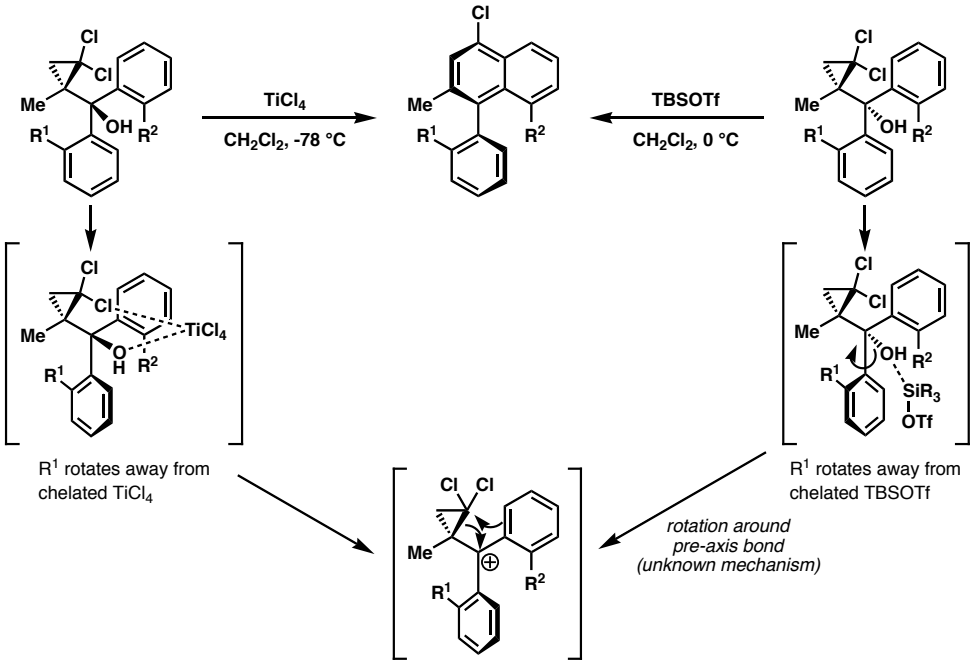

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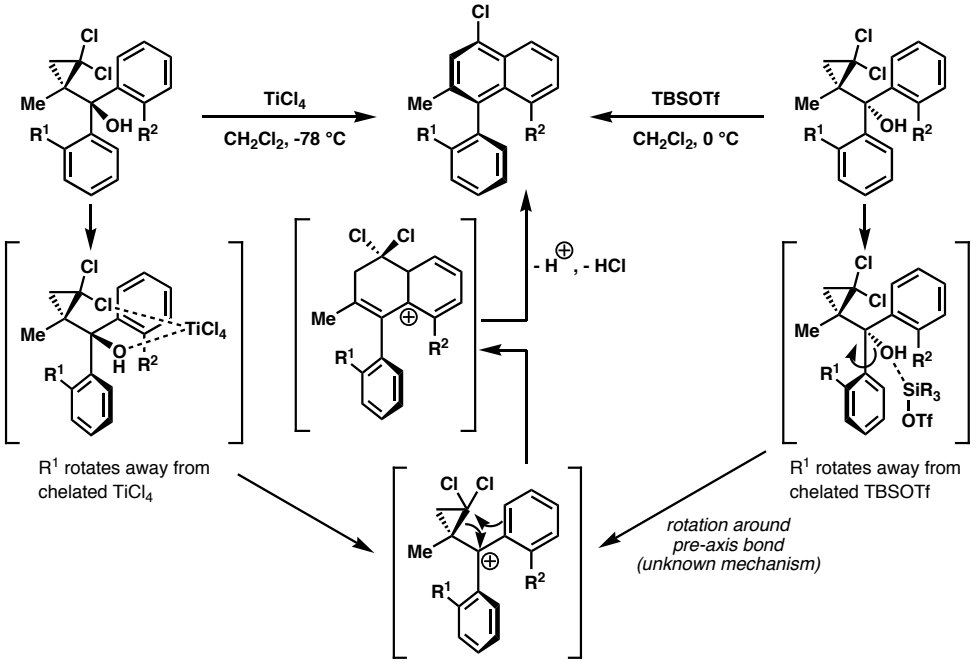

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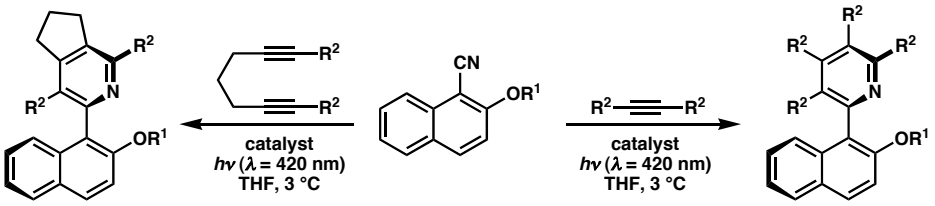
Nishii, Y.; Wakasugi, K.; Koga, K.; Tanabe, Y. *J. Am. Chem. Soc.* **2004**, *126*, 5358-5359.

Atroposelective Construction of an Aromatic Ring

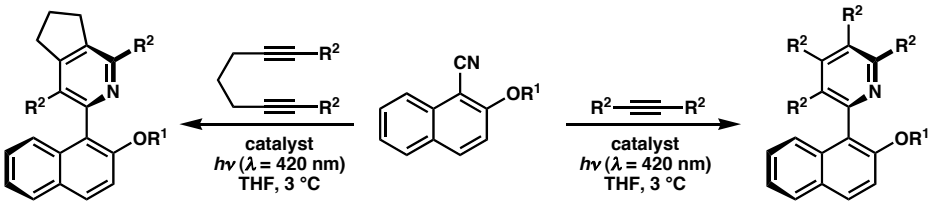
[2+2+2] Cycloadditions



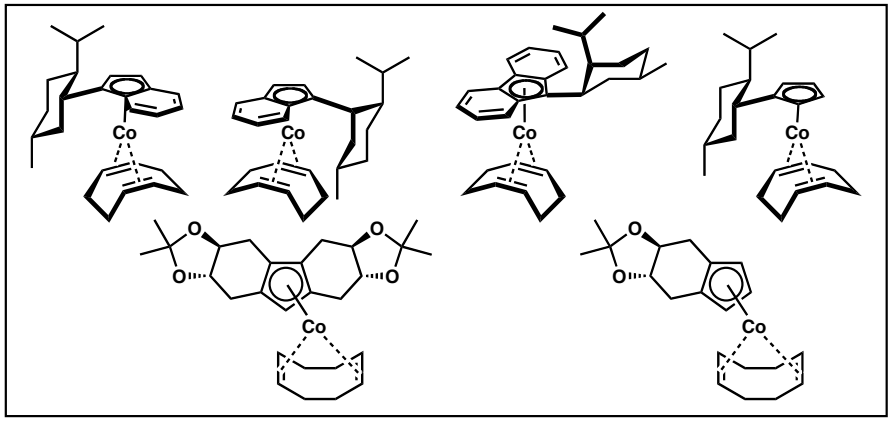
Gutnov, A. *Angew. Chem. I. E. Engl.* **2004**, *43*, 3795-3797.

Atroposelective Construction of an Aromatic Ring

[2+2+2] Cycloadditions



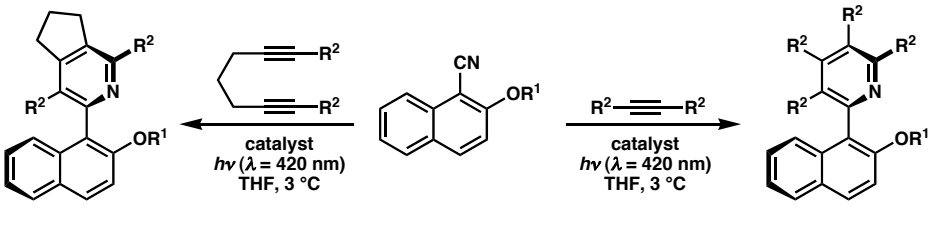
Catalyst Screen



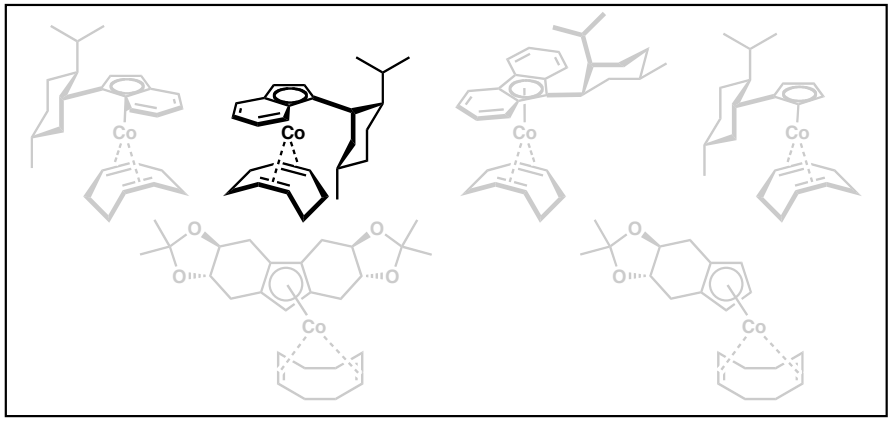
Gutnov, A. *Angew. Chem. I. E. Engl.* **2004**, *43*, 3795-3797.

Atroposelective Construction of an Aromatic Ring

[2+2+2] Cycloadditions



Catalyst Screen



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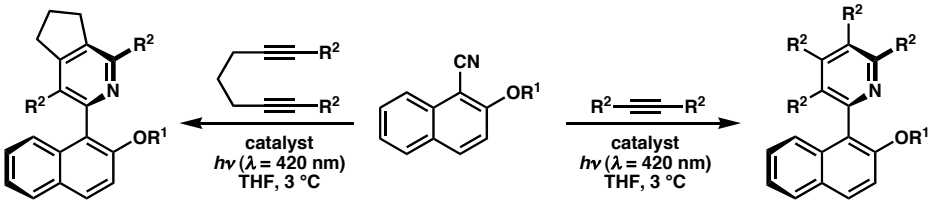
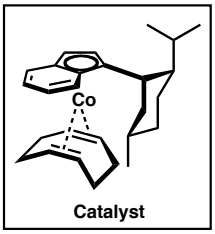
Atroposelective Construction of an Aromatic Ring

[2+2+2] Cycloadditions



Entry	R^1	R^2	% Yield	% *ee*
1	Me	*n*-pentyl	33	38
2	Me	*n*-Pr	8	32
3	Bn	*n*-pentyl	7	39



Catalyst

Entry	R^1	R^2	% Yield	% *ee*
1	Me	Et	10	64
2	Bn	Et	3	59
3	Me	*n*-pentyl	2	63

Gutnov, A. *Angew. Chem. I. E. Engl.* **2004**, *43*, 3795-3797.

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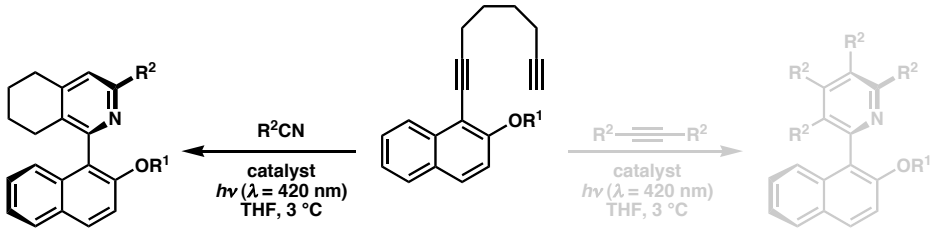
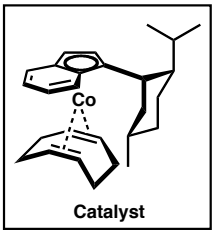


Entry	R^1	R^2	% Yield	% *ee*
1	Me	Me	88	88
2	Me	Ph	86	89
3	Me	*t*-Bu	74	88



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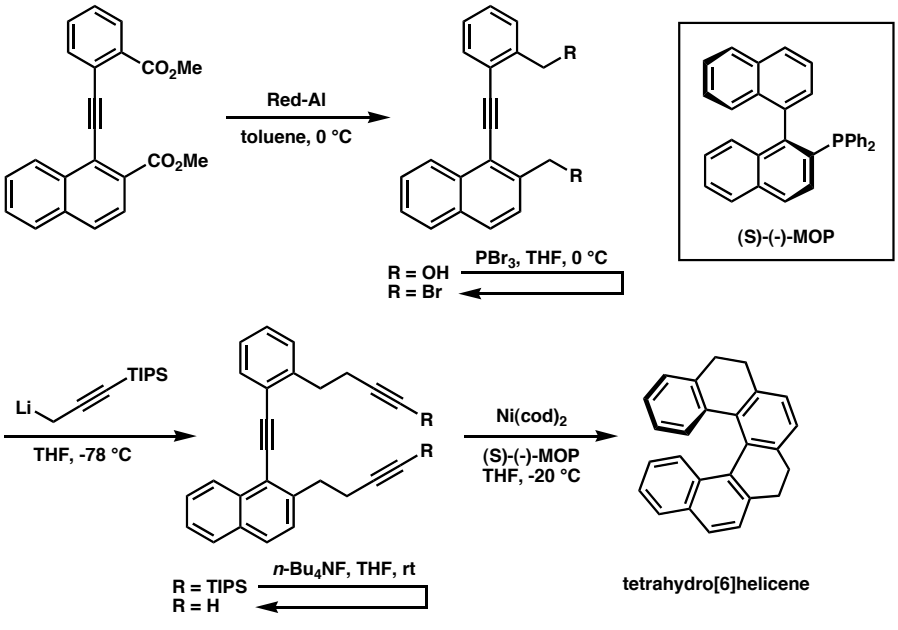
Atroposelective Construction of an Aromatic Ring

[2+2+2] Cycloadditions - Helicenes

- First reported asymmetric synthesis of a helicene derivative.



Stara, I. G. *Tetrahedron Lett.* **1999**, *40*, 1993-1996.

Atroposelective Construction of an Aromatic Ring

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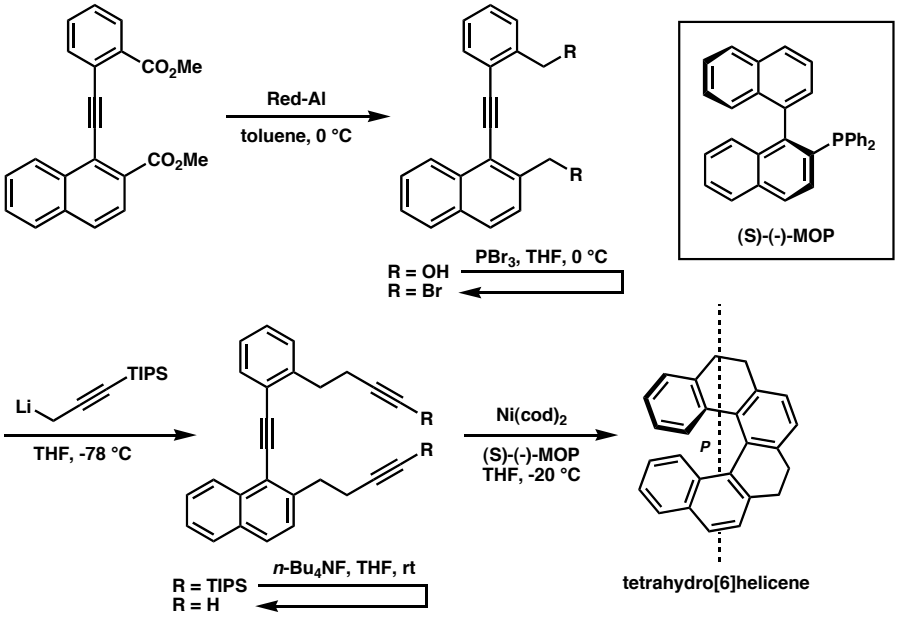

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