Enantioselective Construction of Biaryls

Outline

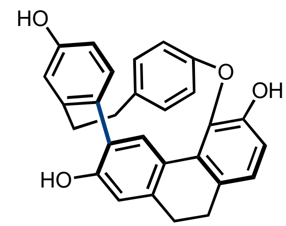
1) Definitions
2) Physical Organic considerations
3) Desymmeterization
4) C–C cross couplings
5) Aryl construction
6) Point-to-axial chirality transfer
7) Perylenequinones

Not Included

1) Diastereomeric biaryl constuction
2) Stoichiometric auxillary based construction

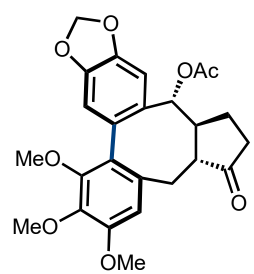
Major Reviews

1) Breuning, *ACIE* **2005**, 5384
2) Colobert, *Chem. Soc. Rev.* **2015**, 3418
3) Tanaka, *Chem. Asian. J.* **2009**, 508
4) Sparr, *ACS Catal.* **2018**, 2981



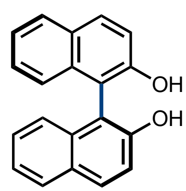
(*P*)–cavicularin

first isolated axially chiral natural product



(*P*)–steganacin

anticancer



(*P*)–BINOL

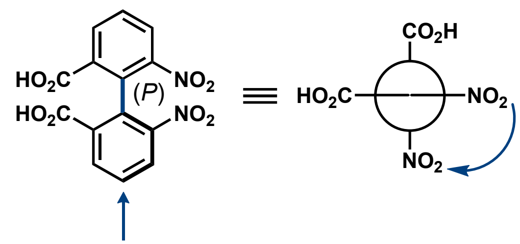
no introduction needed

Atropisomers

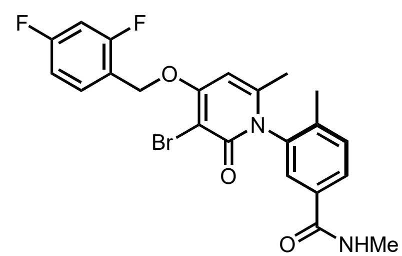
- Axially chiral when barrier to inversion around a single bond is high and allows for resolvable enatiomers
-$T_{1/2}$ is greater than 1000 seconds at room temperature (arbitrary, but reasonable condition)

Notation

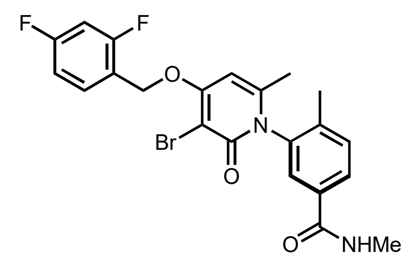
- Minus (*M*) and Plus (*P*)
  - Arrow from priority on front ring to priority on the back ring
  - Clockwise (*P*) and Counter-Clockwise (*M*)
  - Switching front ring and back ring still gives the same answer



Reason you shouldn't sleep for the next hour



PH-797804
p38 IC_{50} = 247 nM

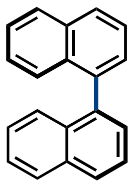


PH-797804
p38 IC_{50} = 2.3 nM

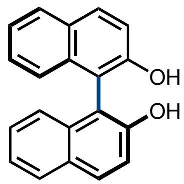
Got your attention, on to the Phys Org...

Enantioselective Construction of Biaryls

General Physical Organic Principles



$\Delta G^{\ddagger}_{317}$ = 101 kJ mol^{-1}

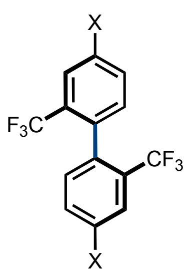


$\Delta G^{\ddagger}_{317}$ = 158 kJ mol^{-1}

ortho–substituents increase racemization barrier proportional to van der Waals radii

*tetra–ortho–substited biaryls are **almost** always rigid at ambient temperatures*

Substituent Effects

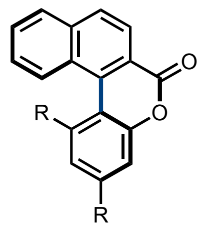


$\Delta G^{\ddagger}_{298}$

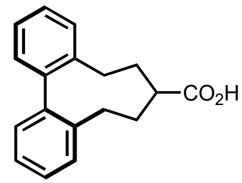
X = H, 109 kJ mol^{-1}
NO_2 110 kJ mol^{-1}
OMe, 102 kJ mol^{-1}

electron donation increases sp^3 character at biaryl junction; decreasing the barrier to rotation

1000 second $T_{1/2}$ requirement:
$\Delta G_{300\ K}$ = 93.5 kJ mol^{-1}
$\Delta G_{350\ K}$ = 109 kJ mol^{-1}



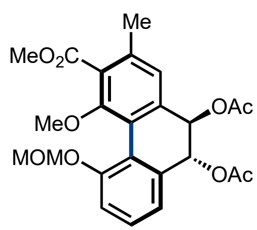
$\Delta G^{\ddagger}_{298}$
R = H, freely twisting
Me, freely rotating at rt
*t*Bu, 104 kJ mol^{-1}



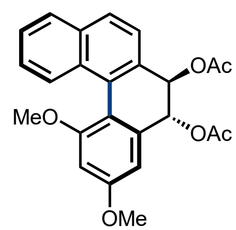
$\Delta G^{\ddagger}_{298}$ = 103 kJ mol^{-1}

macrocylic ring constraints may induce higher than expected barrier to inversion

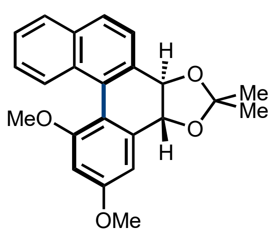
Bridging Effects



$\Delta G^{\ddagger}_{291}$ = 63 kJ mol^{-1}

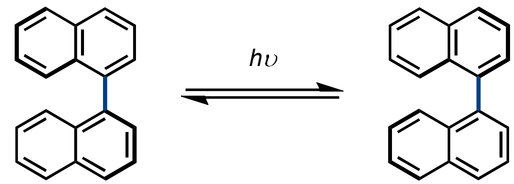


configurationally unstable

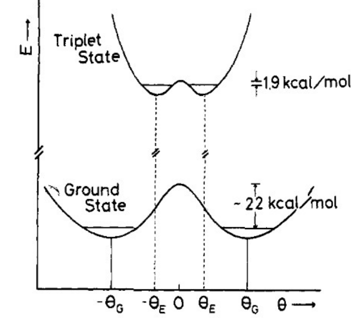


diastereomerically rigid

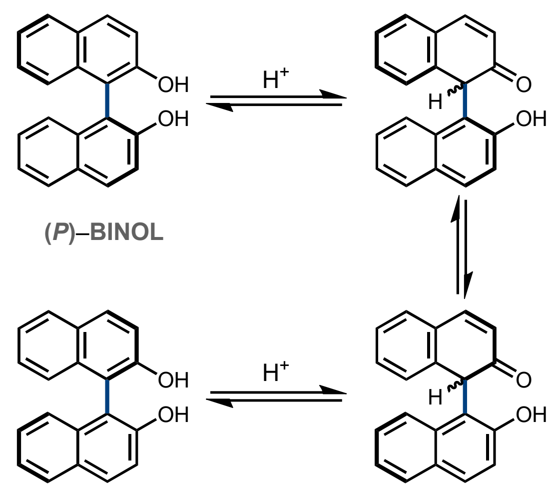
Breuning, *ACIE* **2005**, 5384
Hayashi, *J. Phys. Chem.* ***1977***, *973*



bond order of biaryl junction increases in triplet state, leading to a flattening of the TS an decrease in the torsion angle



Chemical Effects



(*P*)–BINOL

(*M*)–BINOL

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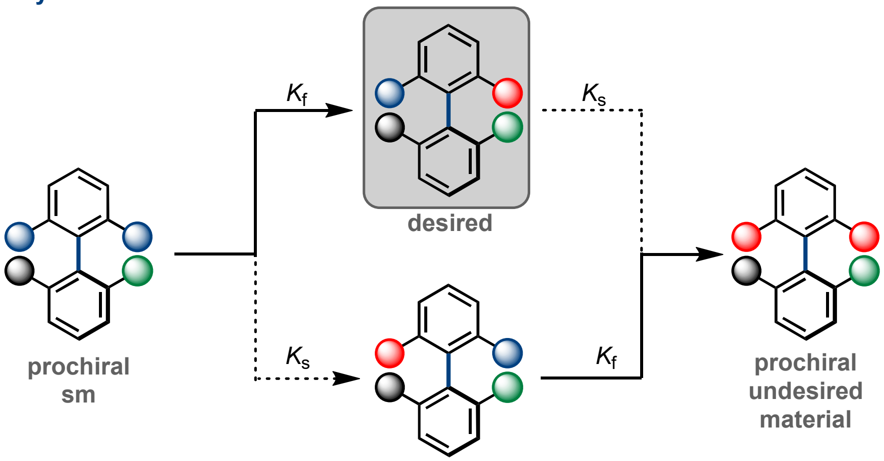
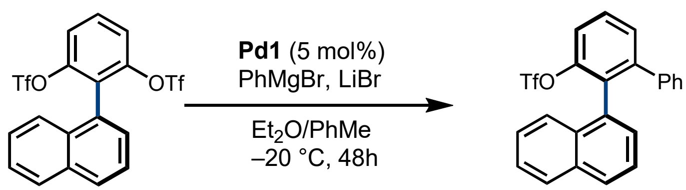
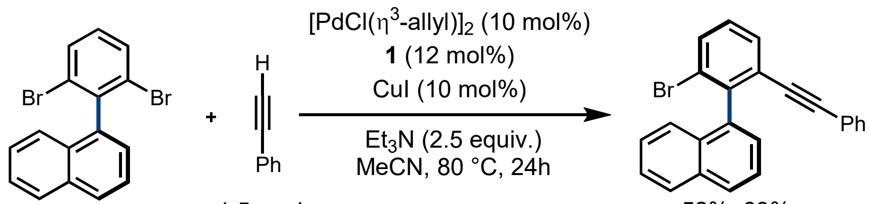
Desymmetrization



Seminal Results (Uozumi, Hayashi)

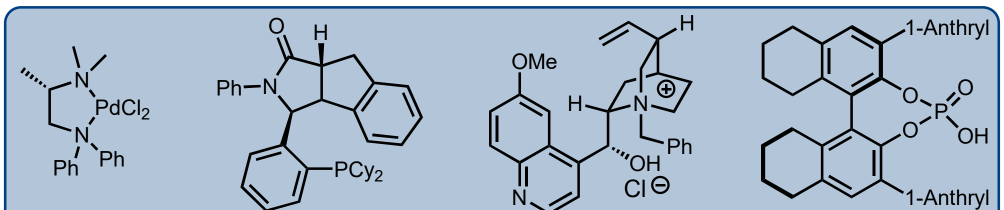


84%, 90% *ee*



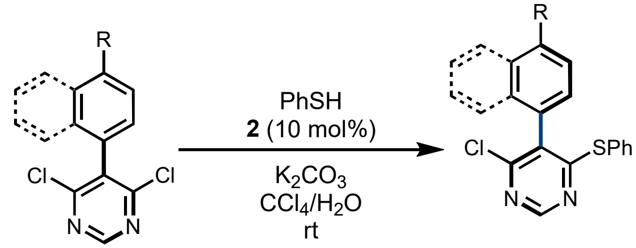
1.5 equiv.

52%, 63% *ee*



Pd1 **1** **2** **3**

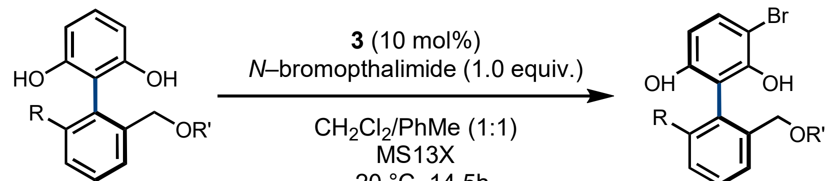
Cation–Directed Nucleophilic Substitution (Smith)



two ortho substitutients not tolerated

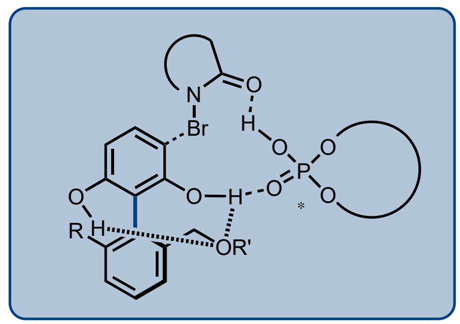
10 examples
85–97%
74–94 % *ee*

Chiral Phosphoric Acid Catalyzed Bromination (Akiyama)



hydroxyl groups and benzylic oxygen are required for high enantioselectivity

11 examples
90–97%
81–93% *ee*



highly ordered TS is responsible for high selectivities

Uozumi, *JACS* **1995**, 9101
Hayashi, *Tett. Lett.* **1996**, 3161
Smith, *ACIE* **2014**, 12822
Akiyama, *JACS* **2013**, 3964

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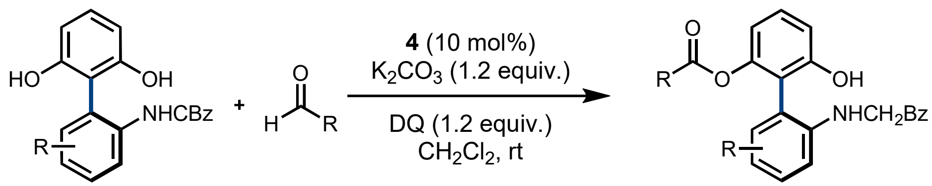
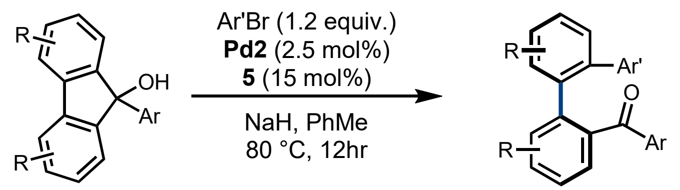
NHC Catalyzed Acylation (Wang)



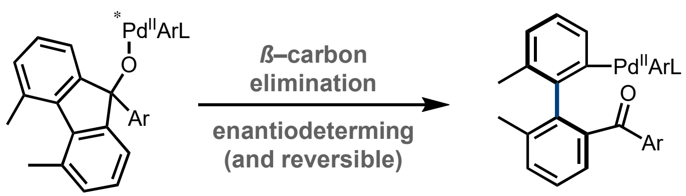
24 examples
82–94%
90–99% *ee*

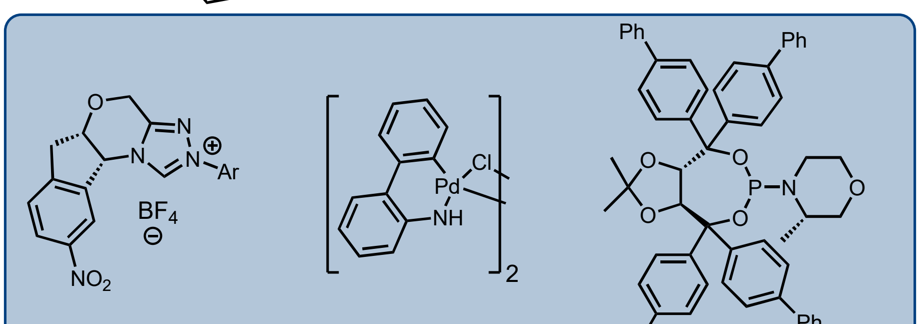
DYKAT (Gu)



43 examples
66–99%
80–96% *ee*

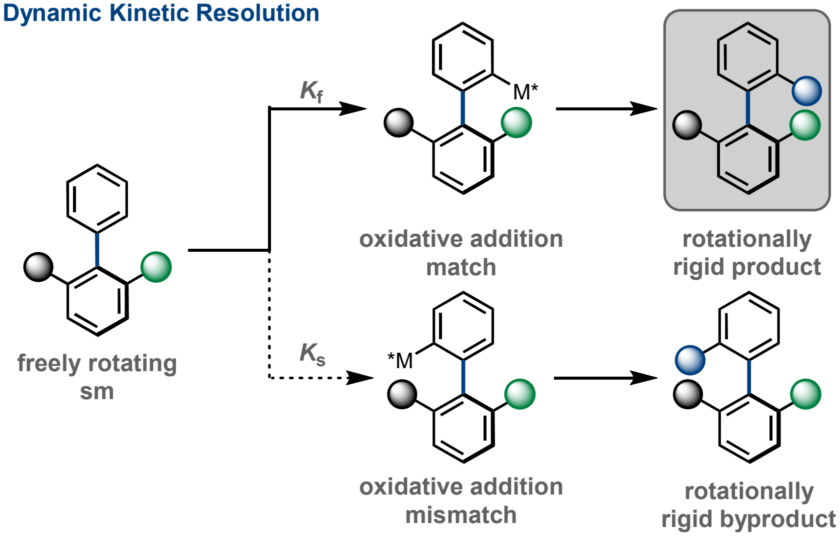
R-groups force palladium elimination pathway through strain release



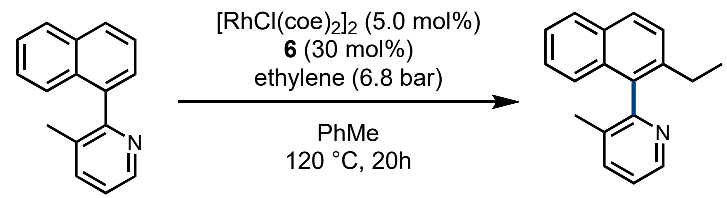


4 **Pd2** **5**

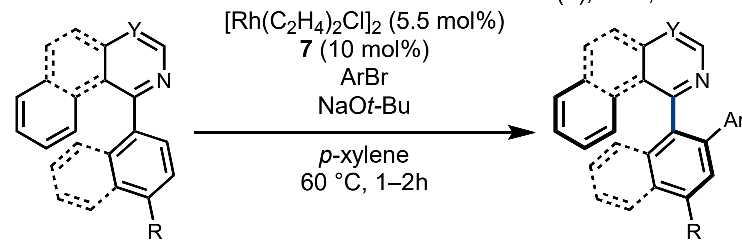
Dynamic Kinetic Resolution



Construction of Heterocyclic Biaryls (Murai, You)



(+), 37%, 49% *ee*



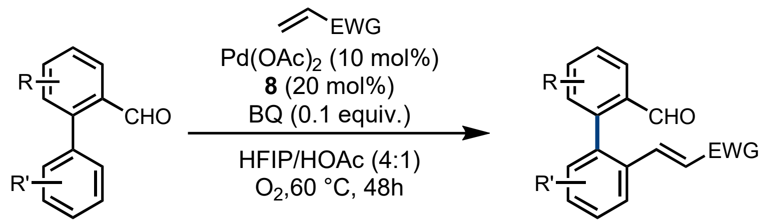
Y= C or N

37 examples
58–99%
79–99% ee

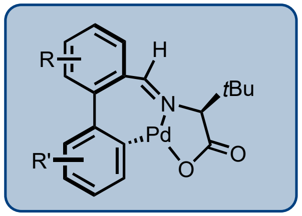
Wang, *Nat. Comm.* **2019**, 3062
Gu, *Chem* **2019**, 1834
Murai, *Tetrahedron Asymmetry* **2000**, 2647
You, *JACS* **2019**, 9504

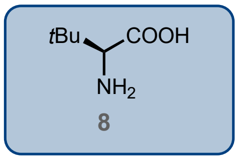
Enantioselective Construction of Biaryls

Transient Auxillary Approach (Shi)



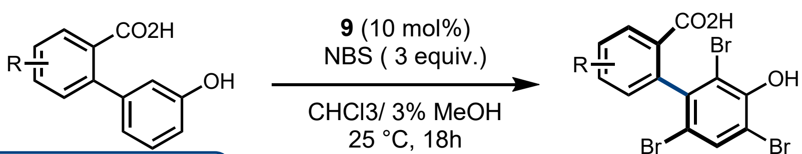
17 examples
60–98%
97–99% *ee*



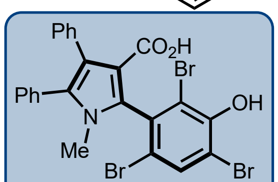


Shi, *ACIE* **2017**, 6617
Miller, *Science*, **2010**, 1251
Hartung, *Tetrahedron*, **1993**, 7891
Akiyama, *ACIE* **2016**, 11642
Wang, *ACIE* **2018**, 474

Peptide Catalyzed Bromination (Miller)

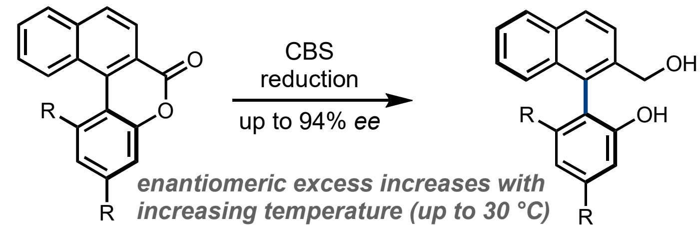


9 examples
65–85%
74–94% *ee*

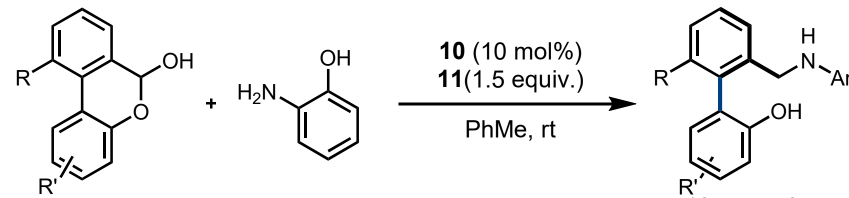


77%, 70% *ee*

Bridging Biaryl



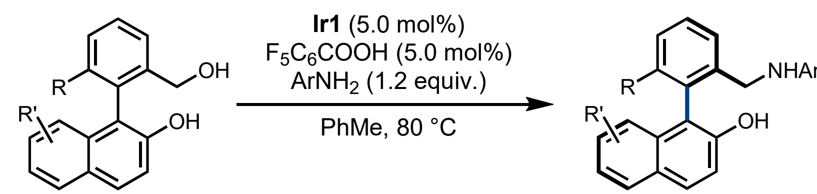
Asymmetric Hydrogenation (Akiyama)



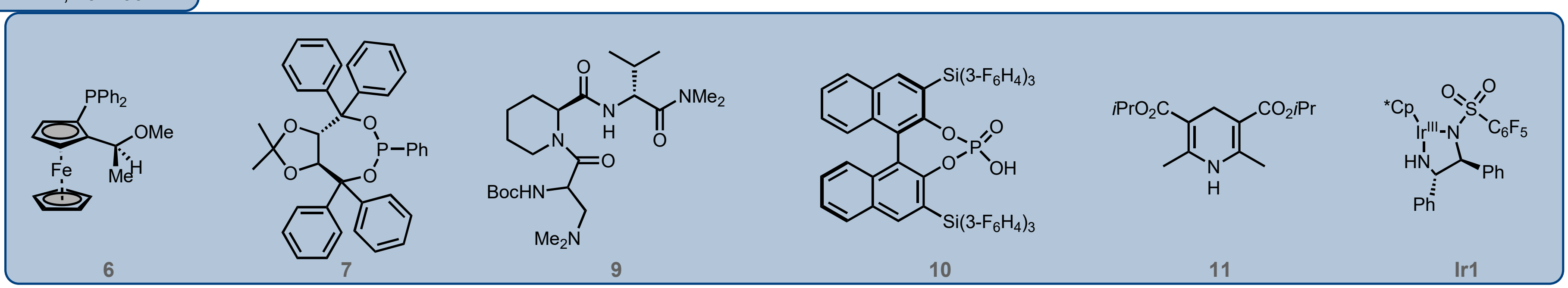
subjection of the hydroxy aldehyde leads to very low ee's (4%)

10 examples
79–99%
89–94% *ee*

Hydrogen Borrowing (Wang)



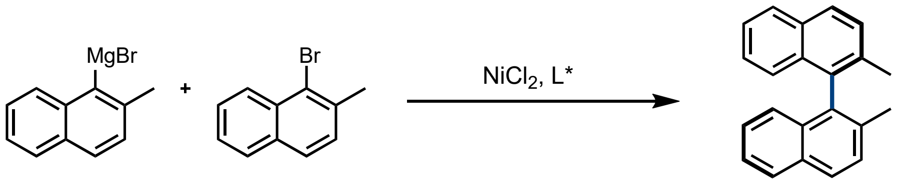
24 examples
64–88%
82–98% *ee*



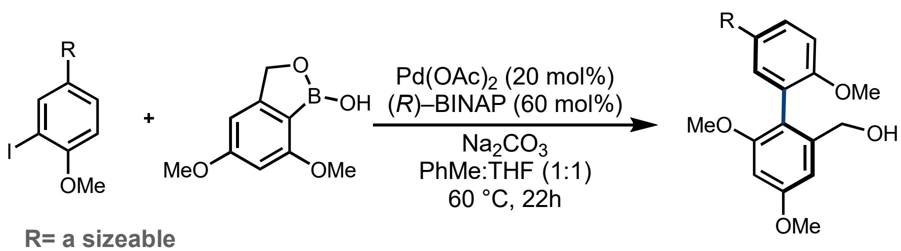
Enantioselective Construction of Biaryls

Enantioselective Cross Couplings

Kumada Coupling (Kumada, Ito)



12.5% *ee* with **12**
69%, 95% *ee* with **6**



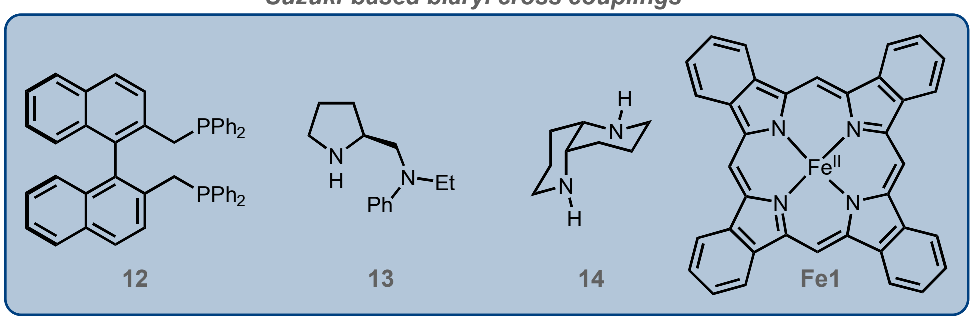
R= a sizeable portion of vancomycin

no substrate control observed

40%, 90:10 *dr*

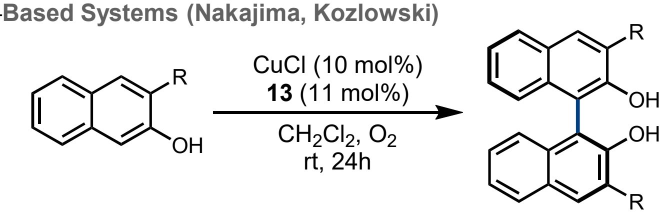
"It is expected that new ligands capable of effecting higher asymmetric induction at lower temperature could improve even further the current state of affairs in this important area of synthesis" – K.C. Nicolaou

recently, more than 20 ligands have been discovered to induce asymmetry in Suzuki-based biaryl cross couplings



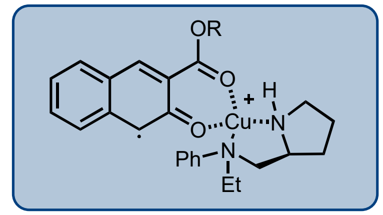
Oxidative C–C cross couplings

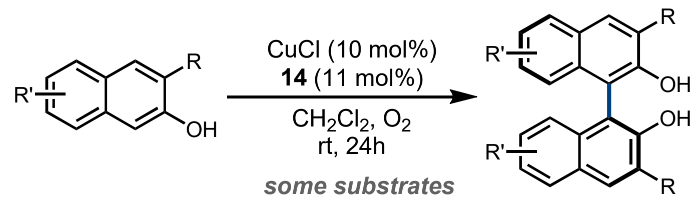
Copper–Based Systems (Nakajima, Kozlowski)



R must be able to coordinate and template copper for high ee's

7 examples
58–95%
5–78% *ee*

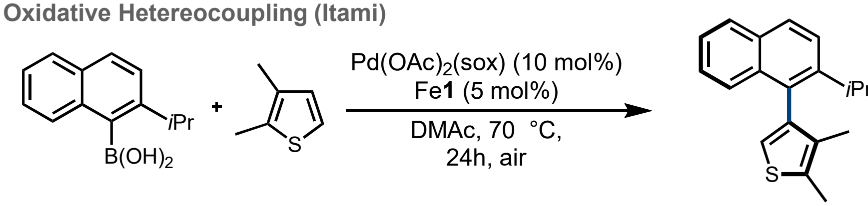




some substrates switch chirality

20 examples
27–93%
53–94% *ee*

Oxidative Hetereocoupling (Itami)

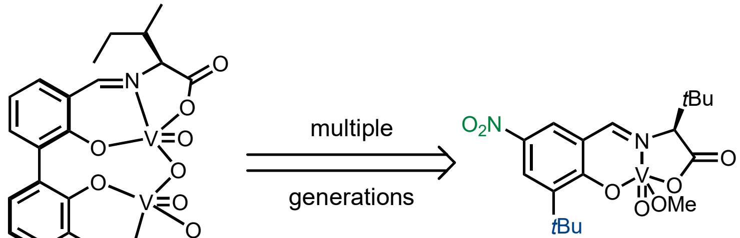


61%, 61% *ee*

Kumada, *Tett. Lett.* **1977**, 1389
Ito, *JACS* **1988**, 8153
Nicolaou, *Chem. Eur. J.* **1999**, 2584
Nakajima, *Tetrahedron* **1995**, 9519
Kozlowski, *Org. Lett.* **2001**, 1137
Itami, *Chem. Sci.* **2013**, 3753

Enantioselective Construction of Biaryls

Oxovanadium (Gong, Kozlowski)



originally demonstrated for enantioselective coupling of napthols

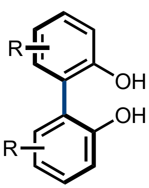
SAR studies

Bulky groups *ortho* to oxygen increase selectivity

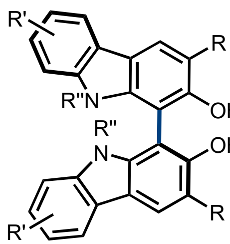
Monomer is sufficient

Electron withdrawing ligands destabilize the high valent V, leading to higher oxidation potentials

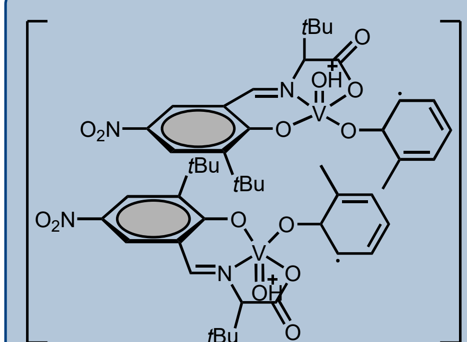
Lewis or Brønsted acid additives allow for comparable reactivity to dimeric systems



16 examples
AcOH as additive
0-89% *ee*



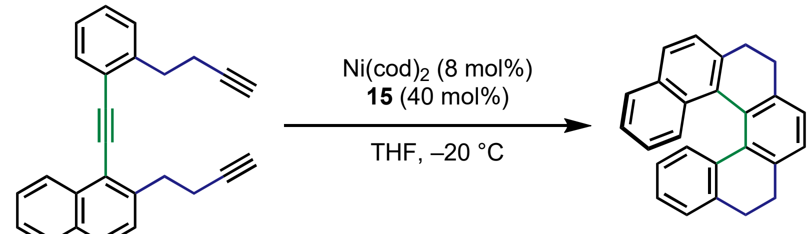
37–94% *ee*



Gong, *JACS* **2007**, 13927
Kozlowski, *Org. Lett.* **2018**, 14362
Saman, *Tett. Lett.* **1999**, 1993
Sundermann, *Chem. Eur. J.* **2007**, 1117
Shibata, *JACS* **2004**, 8382
Shibata, *Adv. Synth. Catal.* **2006**, 2475

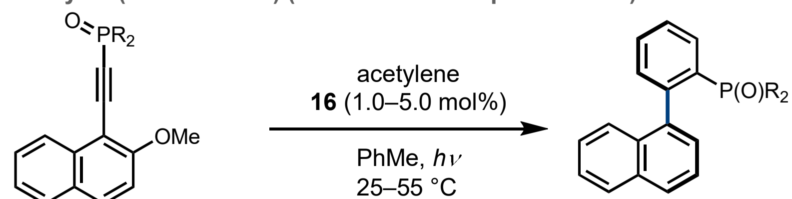
Arene Construction

Seminal Report for Helicene construction (Saman)



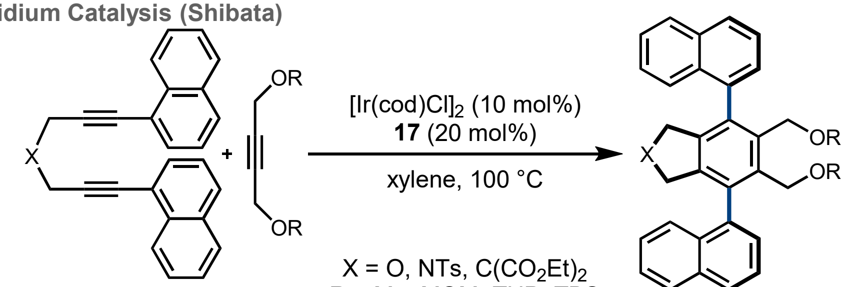
53%, 48% *ee*

Cobalt Catalysis (Sundermann) (see Yaroslav's topic for more)



24-80%
56-83% *ee*

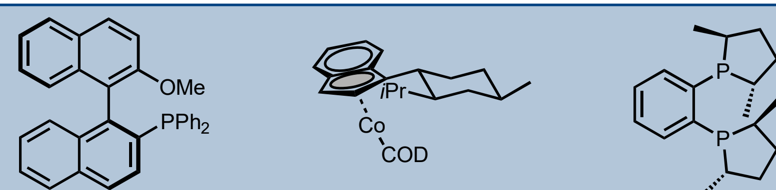
Iridium Catalysis (Shibata)



X = O, NTs, $C(CO_2Et)_2$
R = Me, MOM, THP, TBS

11 examples
72–96%
98.5–99.8% *ee*
91:9–99:1 *dr*

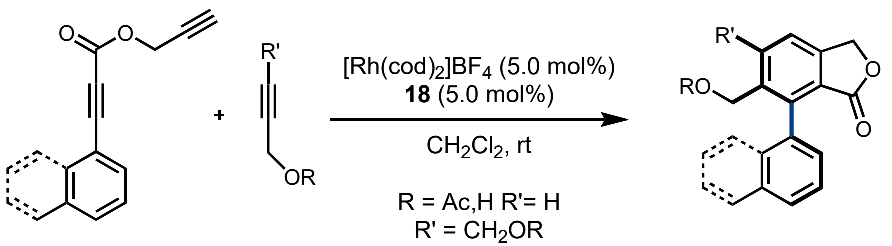
relatively high temperatures, but long chains of optically pure biaryls have been synthesized

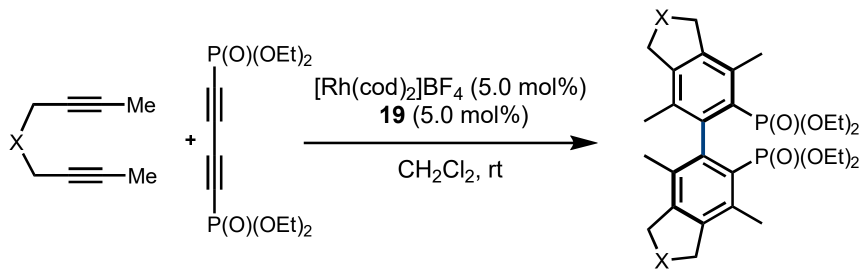


15 **16** **17**

Enantioselective Construction of Biaryls

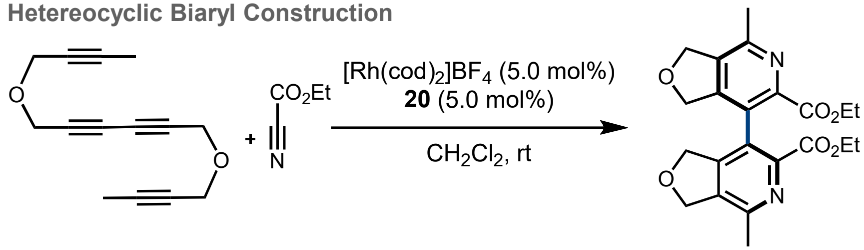
Cationic Rhodium (Tanaka)



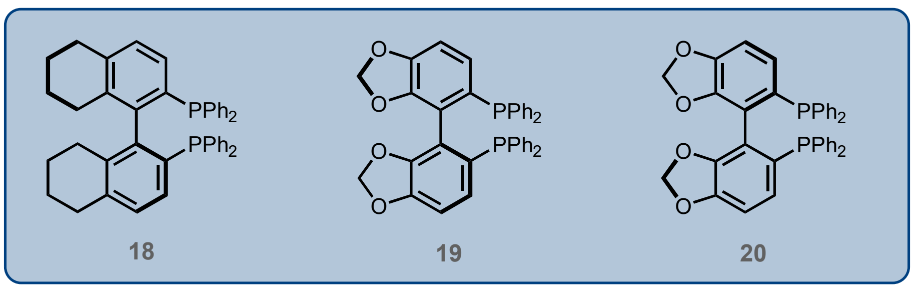


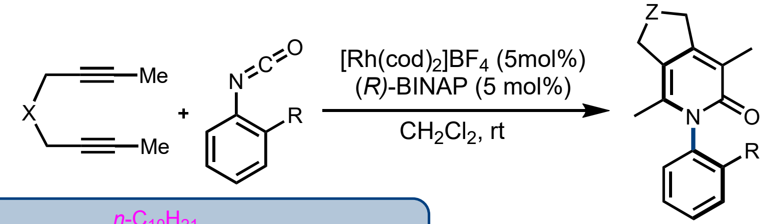
stepwise [2+2+2] cycloadditions can be performed with careful control of stoichiometry to generate asymmetric biaryls

Hetereocyclic Biaryl Construction

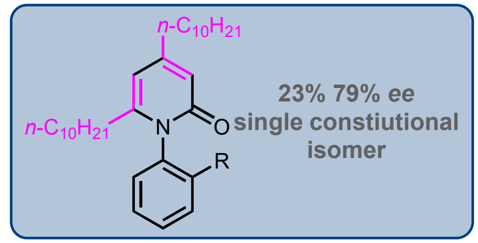


38%,98% *ee*

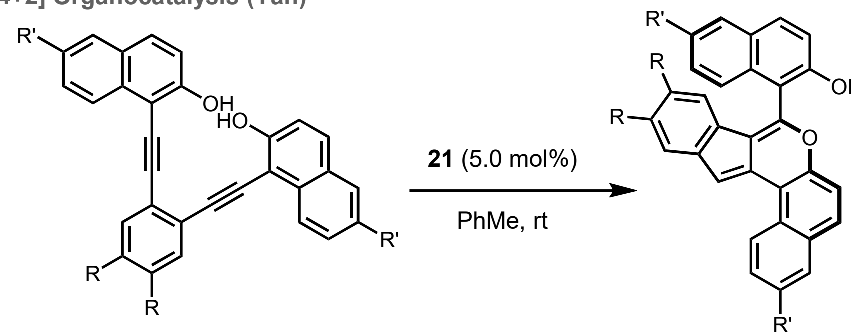




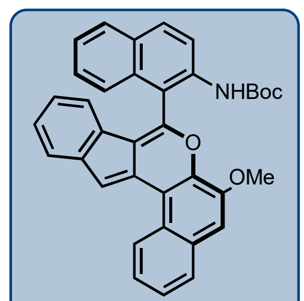
11 examples
27–92%
38–87% *ee*



[4+2] Organocatalysis (Yan)

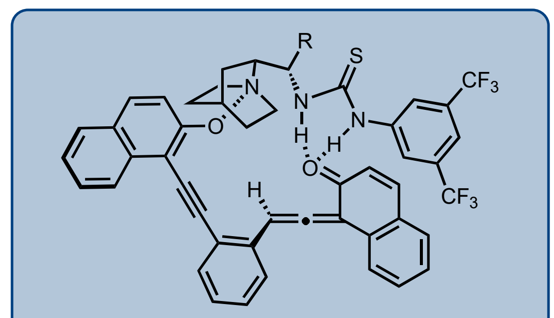


11 examples
80-97%
84-96% *ee*



80% 84% *ee*

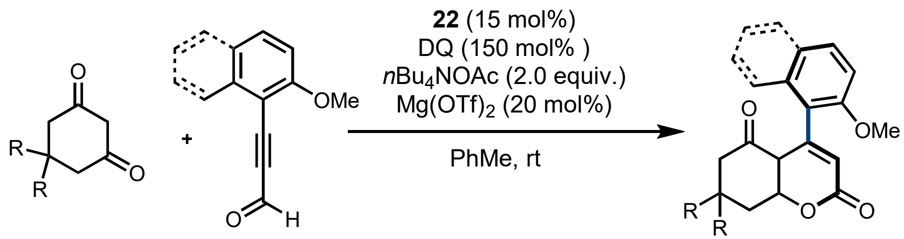
Tanaka, *ACIE* **2004**, 6672
Tanaka, *ACIE* **2007**, 3951
Tanaka, *Org. Lett.* **2006**, 3489
Tanaka, *Org. Lett.* **2005**, 4737
Yan, *ACIE* **2018**, 6491



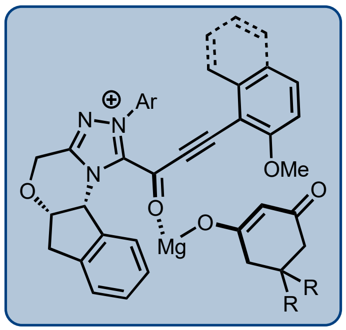
Docking model with 21

Enantioselective Construction of Biaryls

[3+3] Hantzsch Type Cylization (Wang)

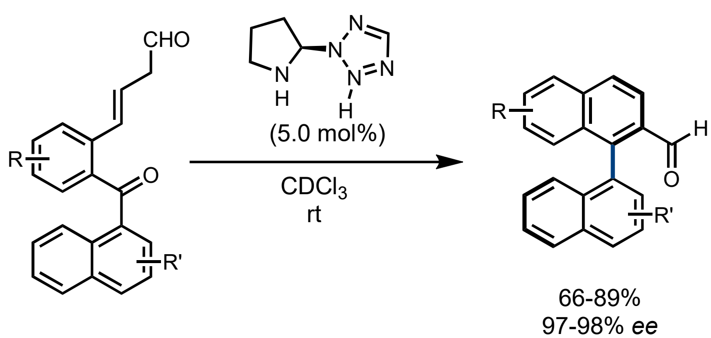


Wang, *Nat. Comm.* **2018**, 611
Sparr, *ACIE* **2014**, 5458
Zhu, *ACIE*, **2019**, 1494
Li *JACS* **2019**, 9527

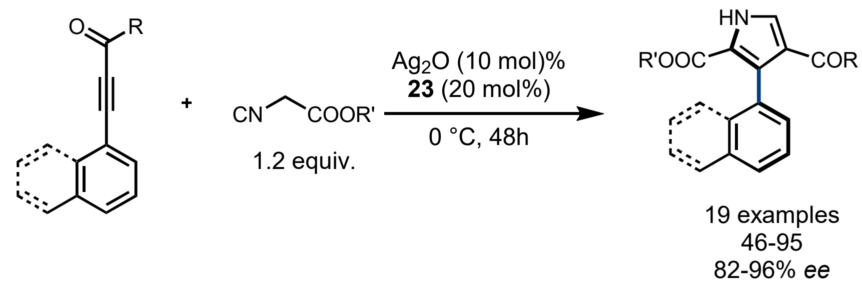


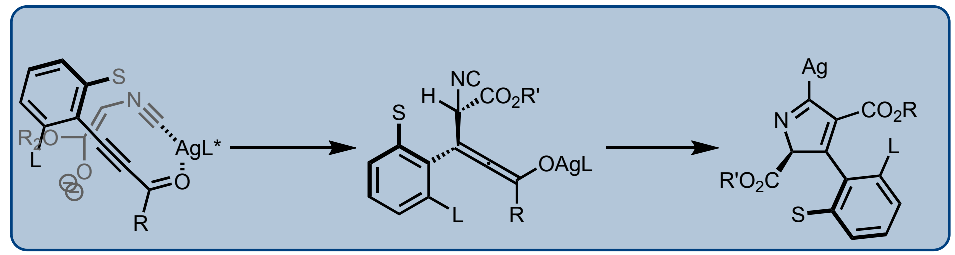
Michael addition into alkynl azolium is enantiodetermining

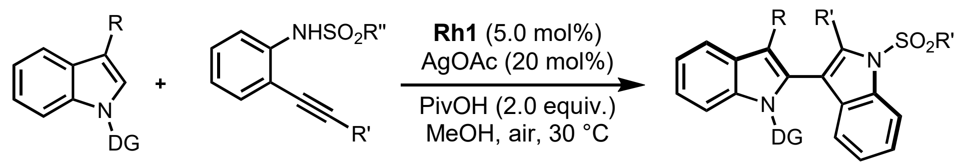
Old School (Sparr)

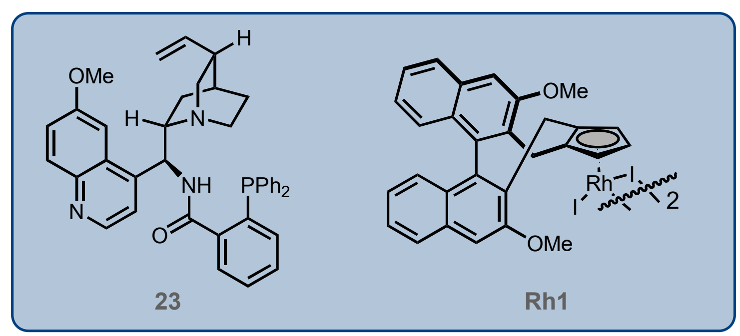


Construction of Pyrrole/Indole Biaryl Compounds (Zhu, Li)



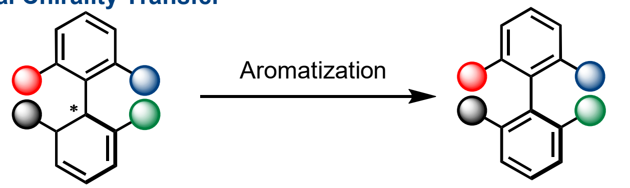




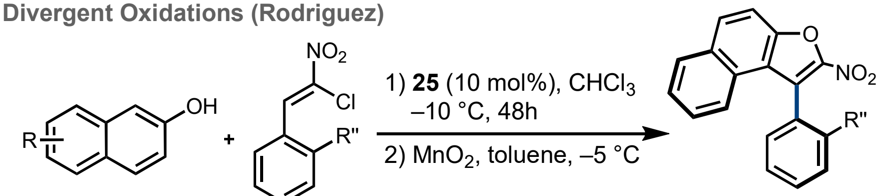


Enantioselective Construction of Biaryls

Point to Axial Chirality Transfer

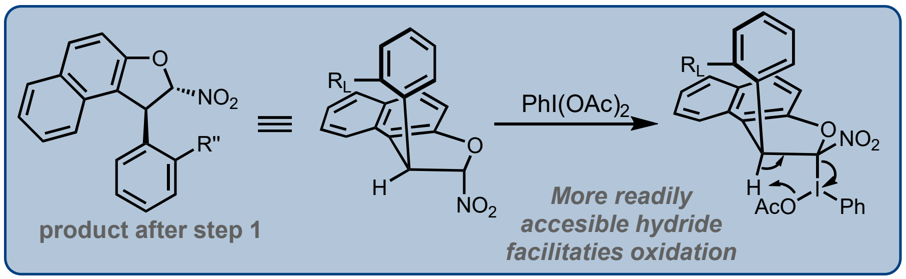


Divergent Oxidations (Rodriguez)

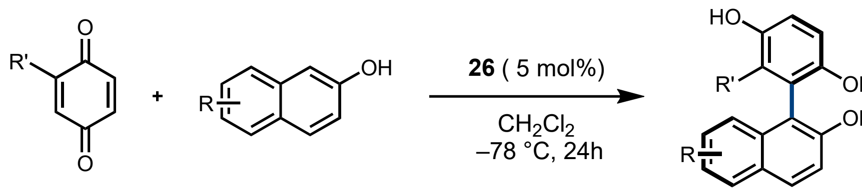


using $PhI(OAc)_2$, authors are able to switch position of R_L

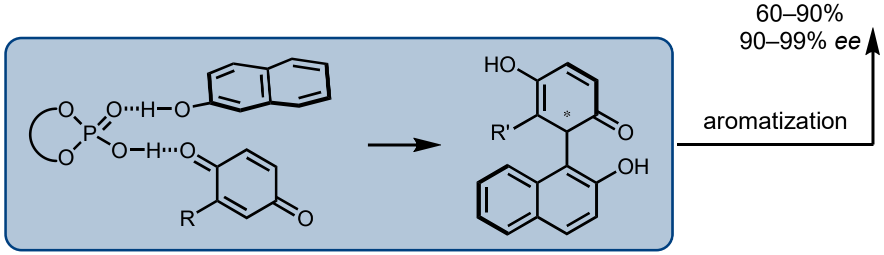
13 examples
42 – 93%
85–98% *ee*



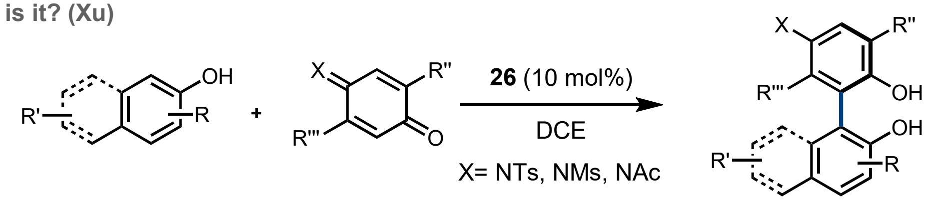
Chiral Phosphoric Acid Mediated Conjugate Addition (Bin Tan)



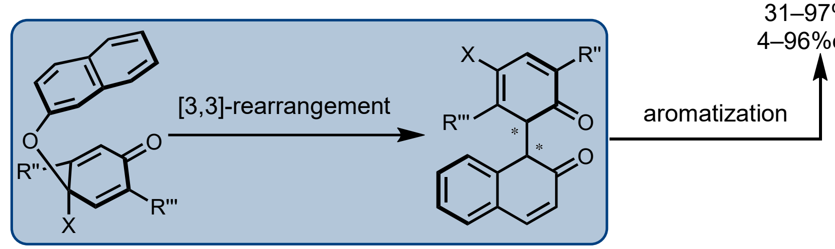
21 examples
60–90%
90–99% *ee*



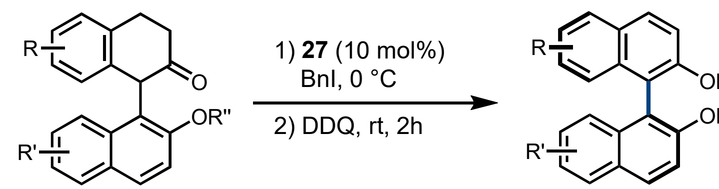
Or is it? (Xu)



25 examples
31–97%
4–96%ee

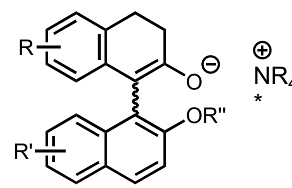


Counteranion Assisted Asymmetric Alkylation (Smith)



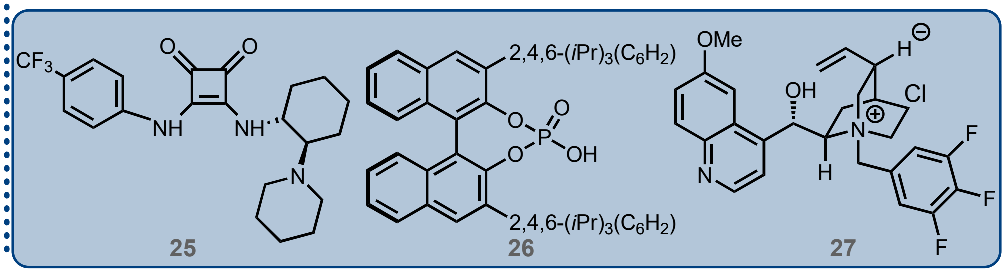
point chiral and racemic

17 examples
30– 99
50–96% *ee*



DKR to resolve both enatiomers

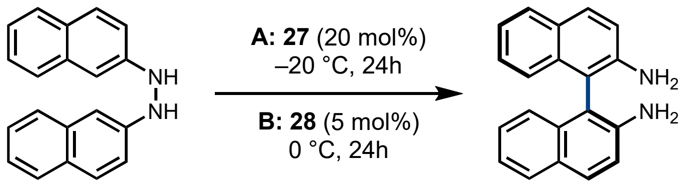
Rodriguez, *JACS* **2017**, 2140
Bin Tan, *JACS* **2015**, 15062
Xu *JACS* **2016**, 5202
Smith, *Nat. Chem.* **2017**, 558



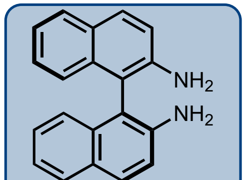
Enantioselective Construction of Biaryls

Honorable Mentions

[3,3]-Rearrangement (Kürti)

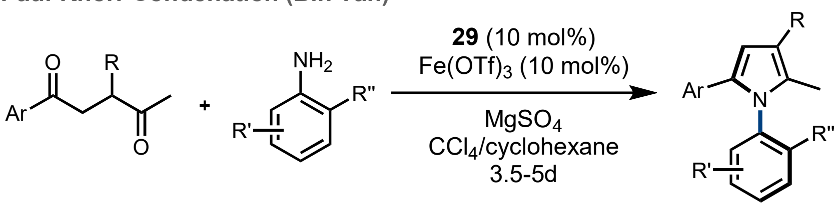


7 examples
A: 69-89%
31-86% *ee*
B: 67-90%
9-84% *ee*



89%, 86% *ee*

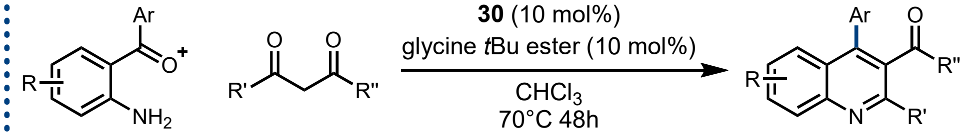
Paul-Knorr Condenation (Bin Tan)



running reaction in CCl_4/EtOH leads to the opposite enantiomer

35 examples
83 - 95 %
86 - 97% *ee*

Friedländer Annulation (Cheng)

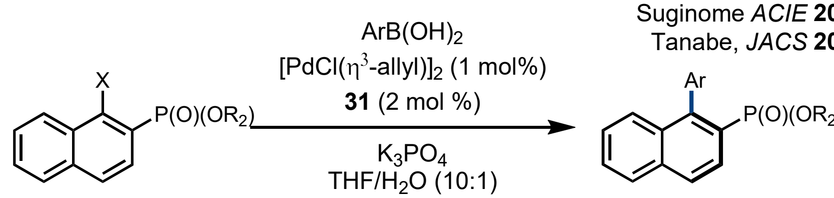


Keto esters symmetrical ketones aryl-alkyl ketones tolerated

26 examples
25-91%
37-97% *ee*

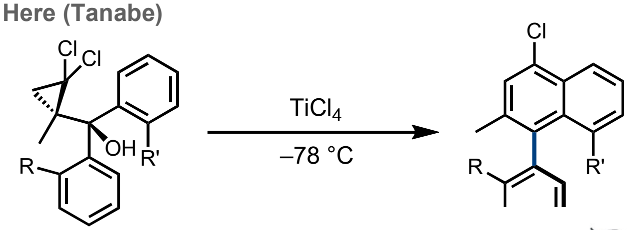
Kürti, *JACS* **2013**, 7414
Bin Tan, *JACS* **2017**, 1714
Cheng, *Org. Lett.* **2019**, 4831
Suginome *ACIE* **2011**, 8844
Tanabe, *JACS* **2004**, 5358

Suzuki Coupling Using a Helically Chiral Catalyst (Suginome)

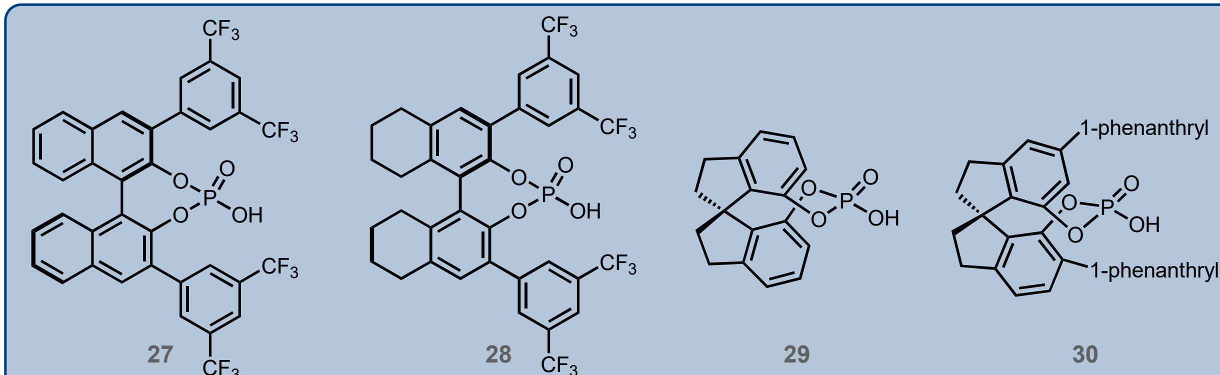


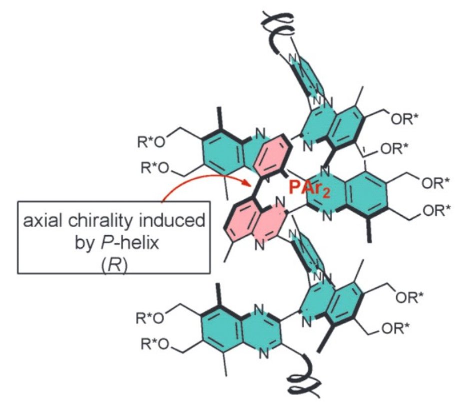
24-93%
78-95% *ee*

Just Leaving This Here (Tanabe)



5 examples
47-97%
>99% *ee*

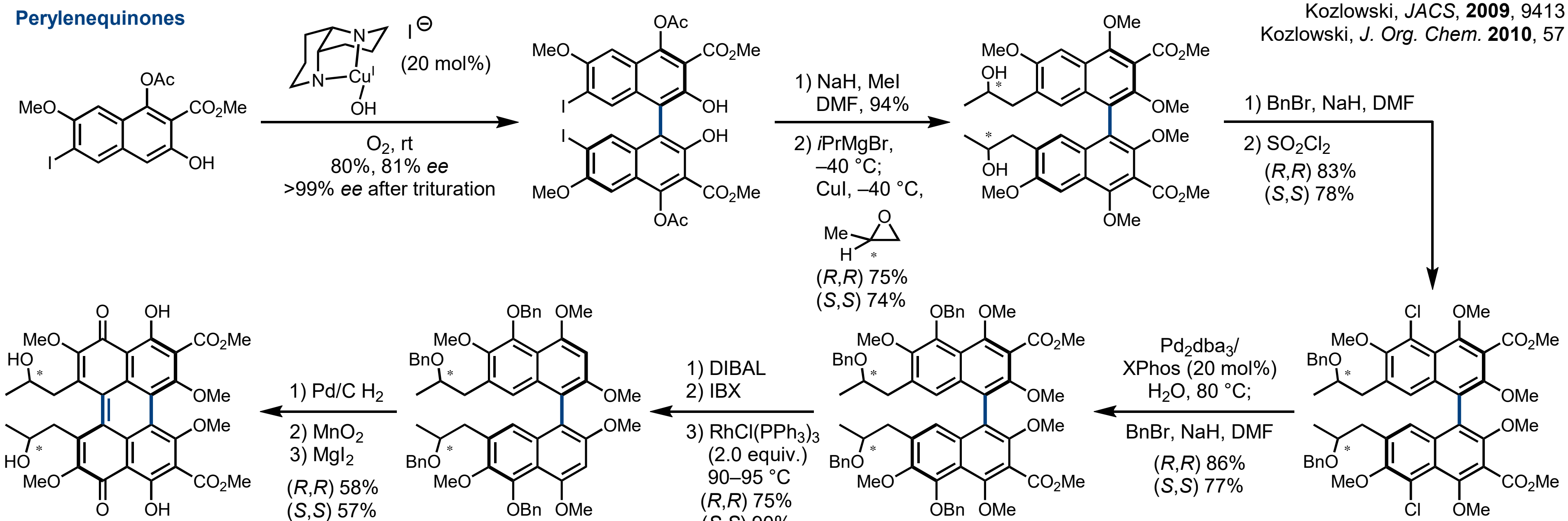




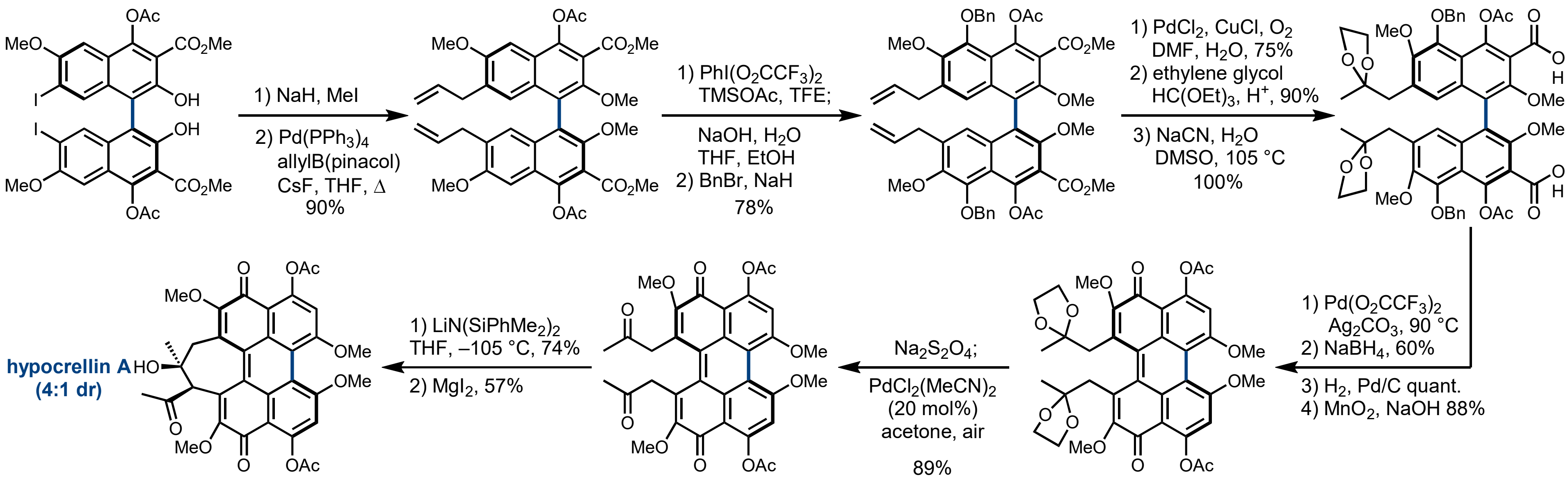
Enantioselective Construction of Biaryls

Perylenequinones

Kozlowski, *JACS*, **2009**, 9413
Kozlowski, *J. Org. Chem.* **2010**, 57



(M,*R*,*R*)-(+)-pheleichrome
(M,*S*,*S*)-(+)-calphostin D



hypocrellin A
(4:1 dr)