Literature Report IV

Organocatalytic Asymmetric Arylation of Indoles/2-Naphthols

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Checker: Ji Zhou
Date: 2017-12-25

Y.-H. Chen, D.-J. Cheng and B. Tan, *J. Am. Chem. Soc*. **2015**, *137*, 15062-15065.
L.-W. Qi, J.-H. Mao, J. Zhang and B. Tan, *Nat. Chem*. **2018**, *10*, 58-64.

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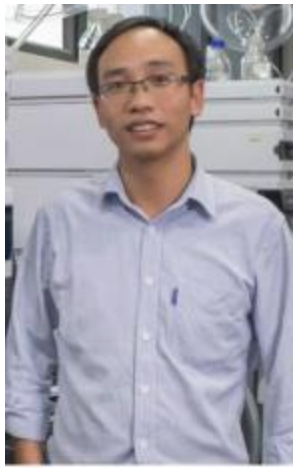
CV of B. Tan

Education and Professional Appointments:

1997-2001	B. S., Hunan University of Science and Technology
2002-2005	M. S., Xiamen University
2006-2010	Ph.D., Nanyang Technological University
2010-2012	Postdoctoral fellow, The Scripps Research Institute
2012-now	Associate professor, South University of Science and Technology of China

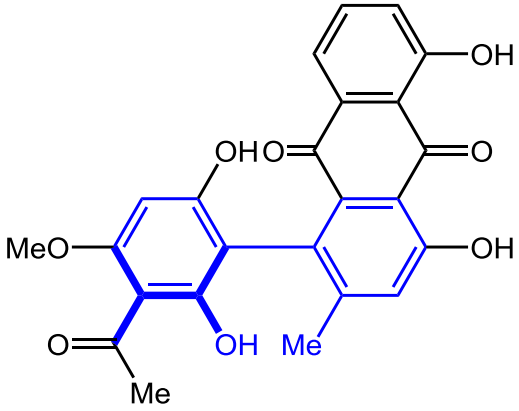


B. Tan

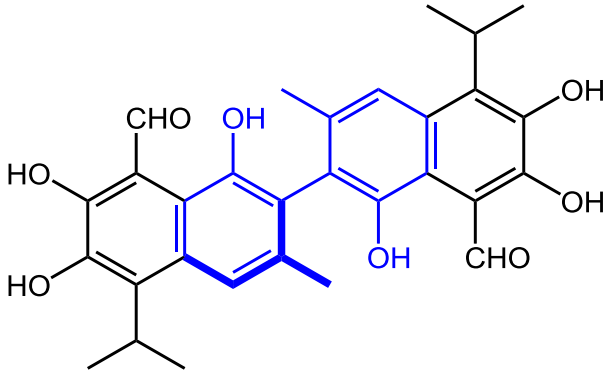
Research:

- Catalytic asymmetric multicomponent reactions (MCRs);
- Application of cooperative catalysis involving metal and organocatalyst;
- Synthesis of chiral drugs and natural products.

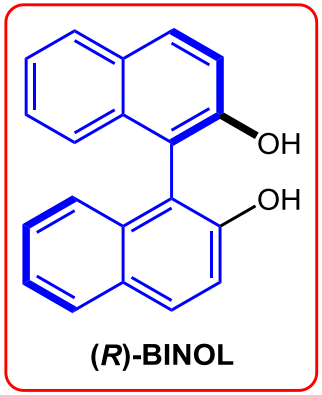
Axially chiral biaryldiols



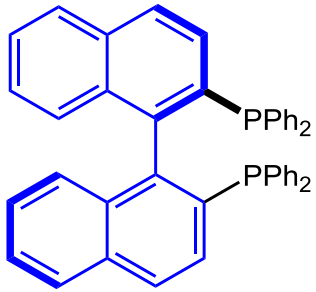
Knipholone



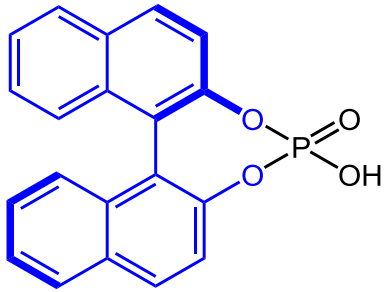
(-)-Gossypol



(*R*)-BINOL

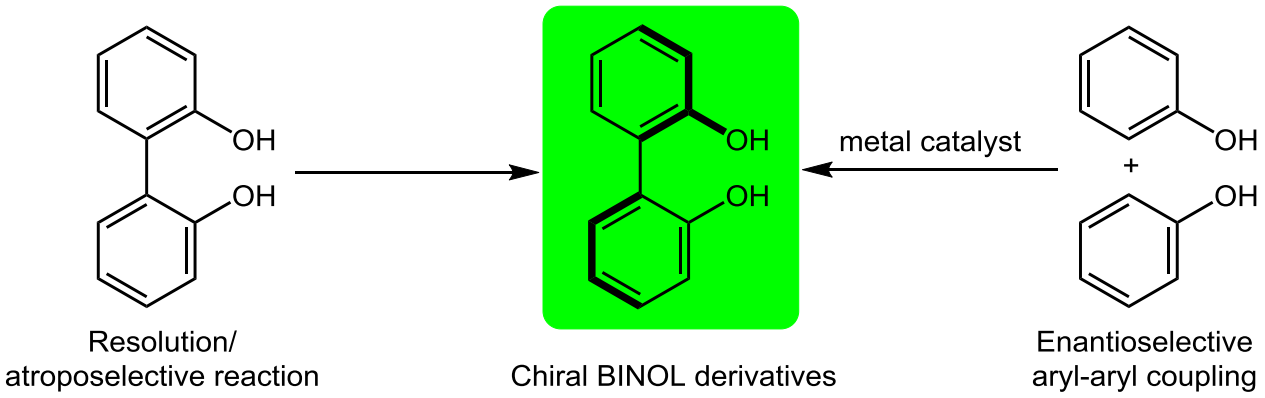


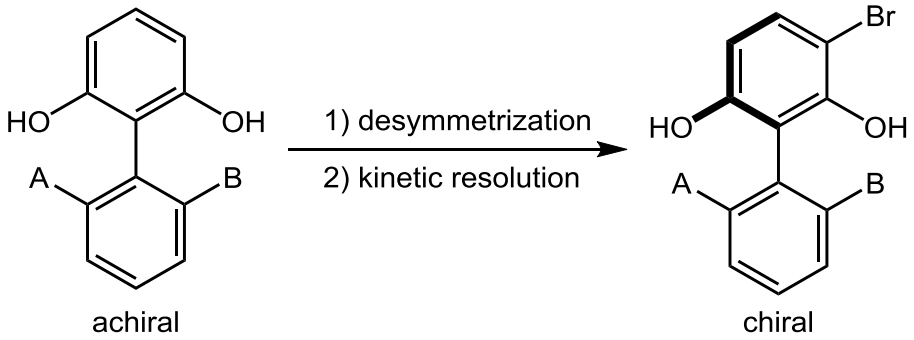
(*R*)-BINAP



(*R*)-Phosphoric acid

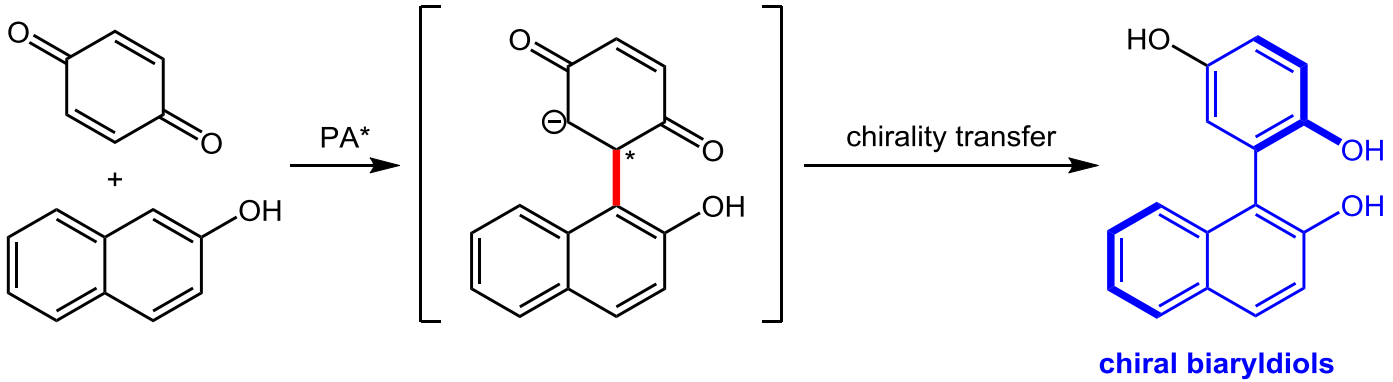
Axially chiral biaryldiols





K. Mori, Y. Ichikawa, T. Akiyama, *J. Am. Chem. Soc*. **2013**, *135*, 3964−3970.

Strategy for synthesis of axially chiral biaryldiols



Several challenges:

- the selection of a reasonable catalyst to increase the reactivity, to efficiently control C/O chemoselectivity of the 2-naphthols;
- the choice of a chiral catalyst to efficiently induce stereocontrol in the conjugated addition step;
- the use of mild reaction conditions to transfer the chirality and obviate the axial rotation.

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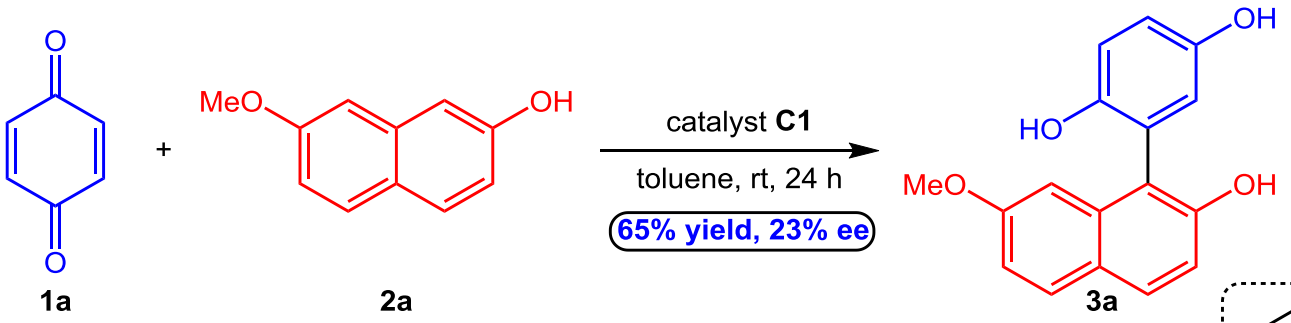
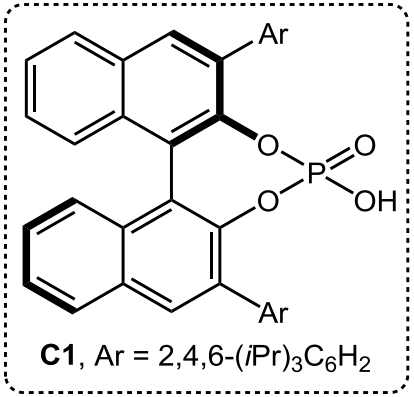
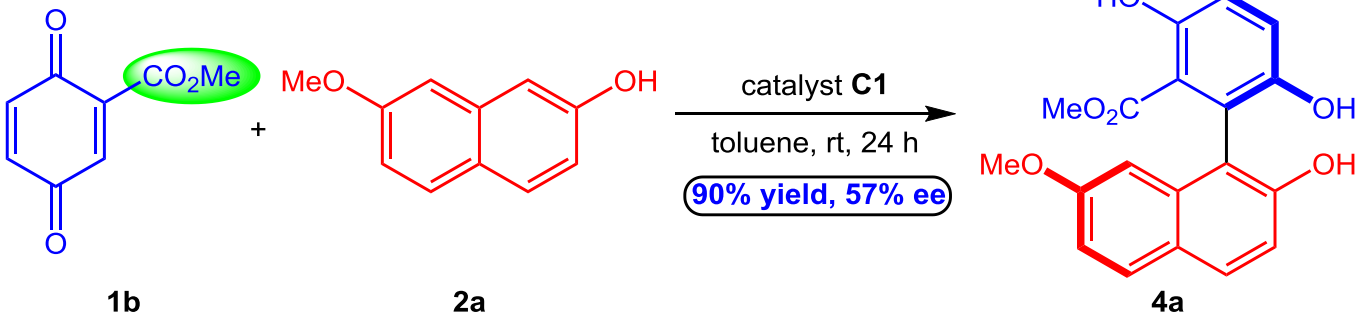
Initial results for direct synthesis of biaryldiols







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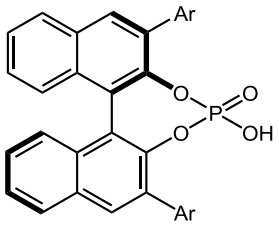
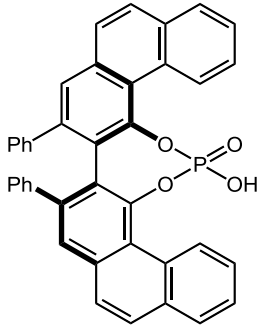
Optimization of the reaction conditions

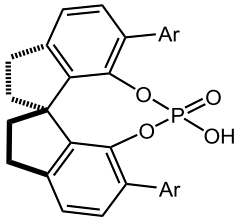
entry	catalyst	solvent	T (°C)	yield (%)	ee (%)
1	**C1**	toluene	25	90	57
2	**C2**	toluene	25	85	3
3	**C3**	toluene	25	85	3
4	**C4**	toluene	25	83	0
5	**C5**	toluene	25	88	-41
6	**C6**	toluene	25	81	-4
7	**C1**	DCM	25	92	72
8	**C1**	DCE	25	90	65
9	**C1**	DCM	0	92	80
10	**C1**	**DCM**	**-78**	**90**	**93**



C1, Ar = 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$
C2, Ar = 3,5-Ph$_2$C$_6$H$_3$
C3, Ar = 1-naphthyl

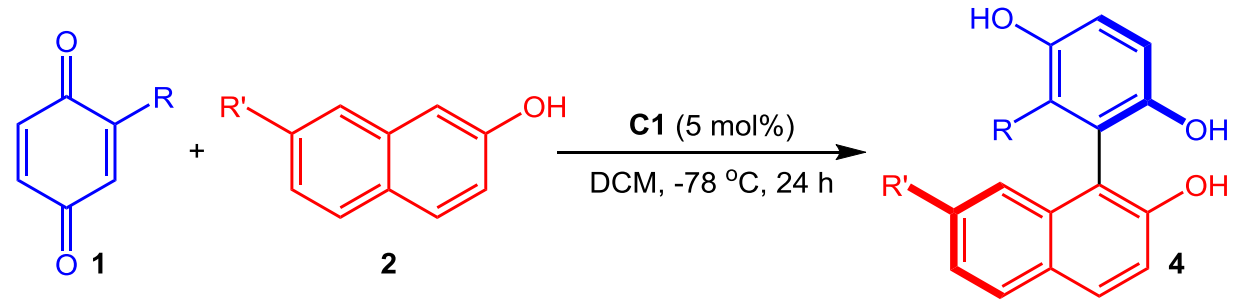


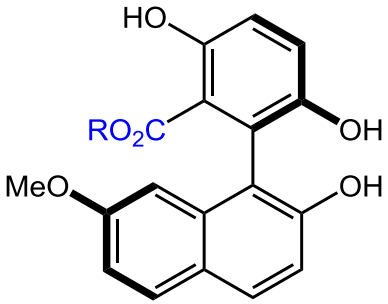
C4



C5, Ar = 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$
C6, Ar = Ph

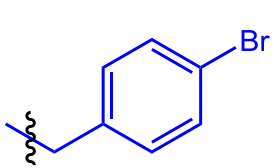
Substrate scope of direct arylation reaction

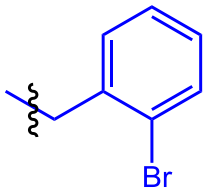


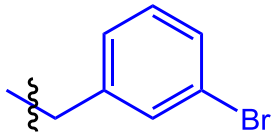


4a R = Me 90%, 93% ee
4b R = Et 90%, 96% ee
4c R = Pr 87%, 99% ee
4d R = *i*Pr 85%, 97% ee
4e R = Bu 82%, 95% ee
4f R = Bn 75%, 92% ee

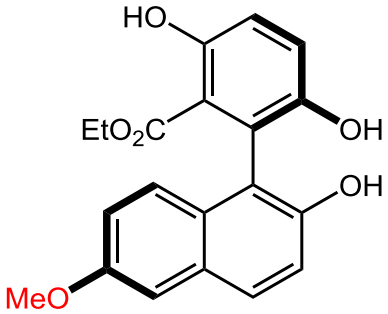
R =



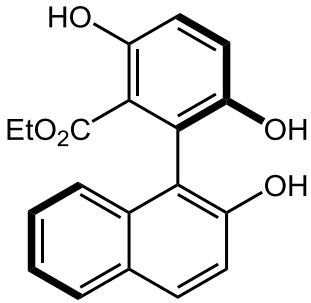




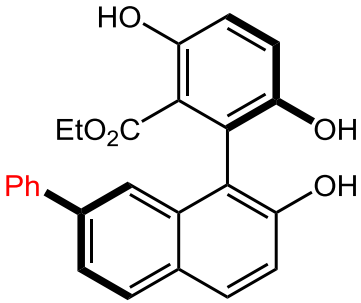
4g, 77%, 98% ee **4h**, 70%, 99% ee **4i**, 76%, 98% ee



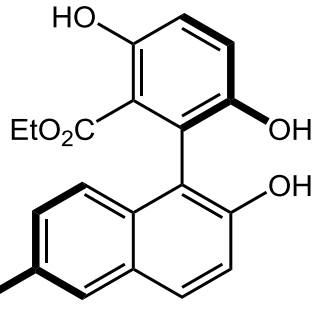
4j, 88%, 91% ee



4k, 88%, 99% ee

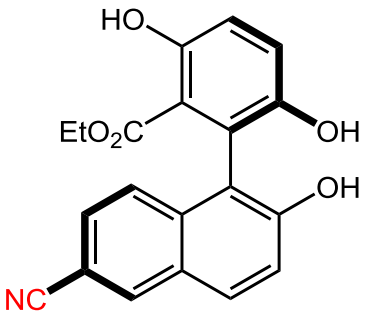


4l, 84%, 92% ee

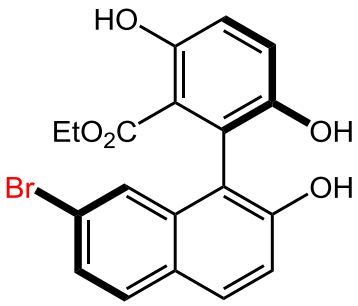


4m, 85%, 92% ee

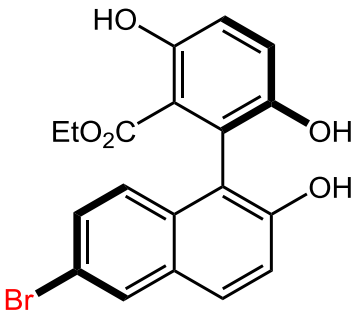
Substrate scope of direct arylation reaction



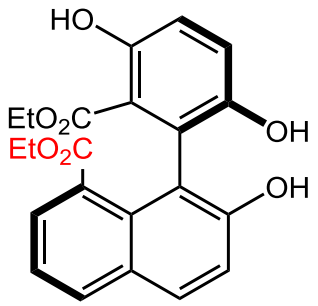
4n, 60%, 90% ee



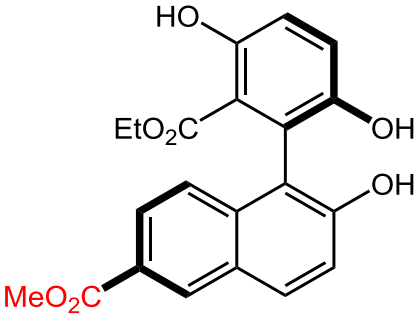
4o, 82%, 91% ee



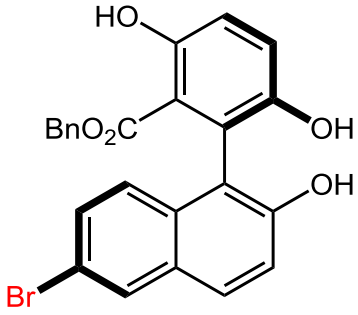
4p, 84%, 93% ee



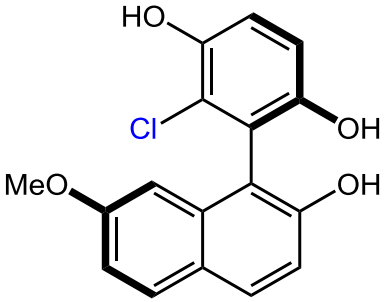
4q, 80%, 97% ee



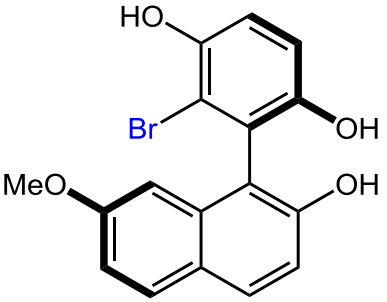
4r, 82%, 90% ee



4s, 71%, 90% ee

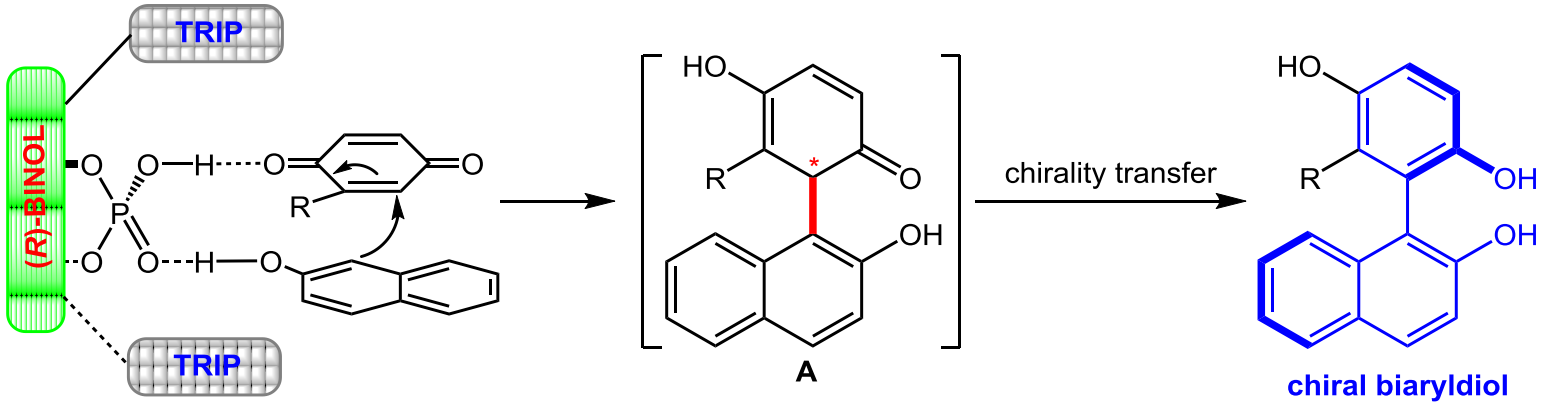


4t, 75%, 95% ee



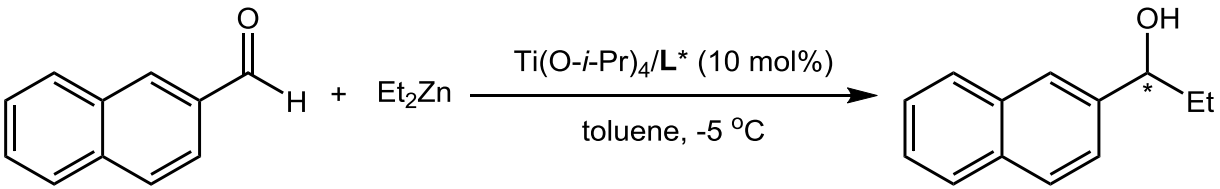
4u, 72%, 96% ee

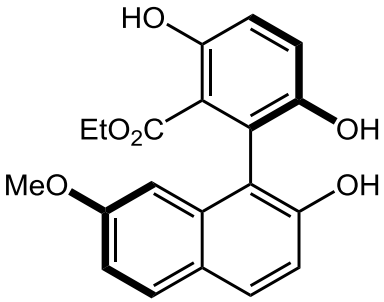
Proposed reaction process



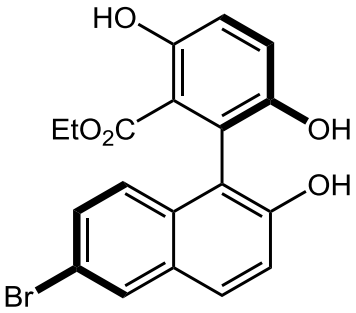
- Chiral phosphoric acid promote the first step of enantioselective conjugative addition to form intermediate **A**;
- The following step transfers its central chirality information to its axial chirality, affording the final chiral biaryldiol.

Preliminary application

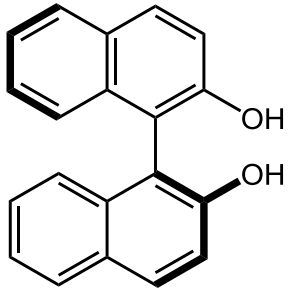




4p
88% yield
-96% ee

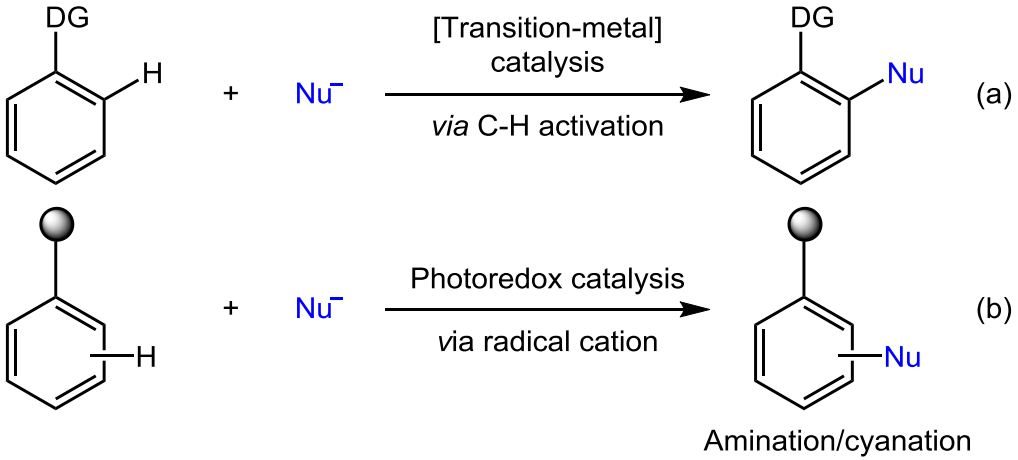


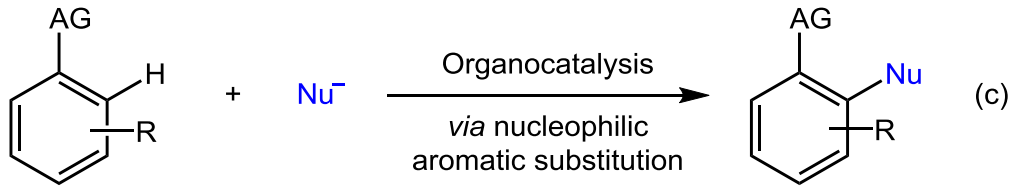
4p
90% yield
-98% ee

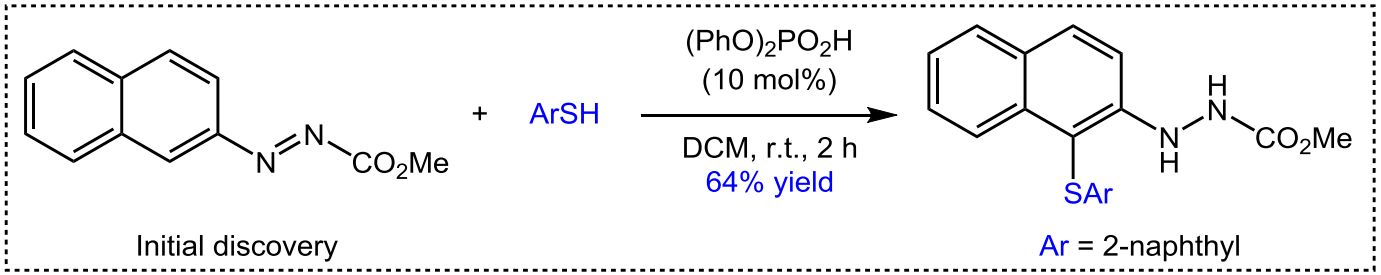


(*S*)-BINOL
86% yield
89% ee

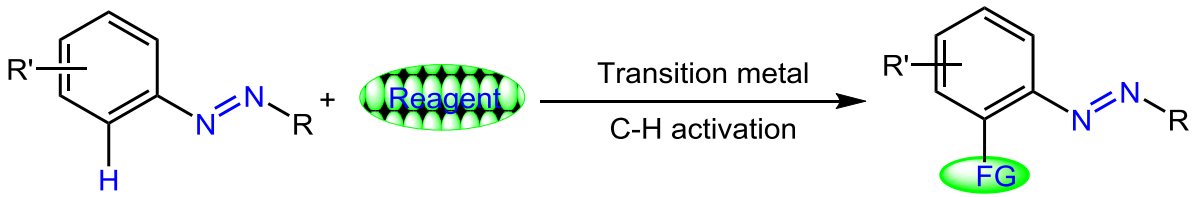
Nucleophilic aromatic substitution



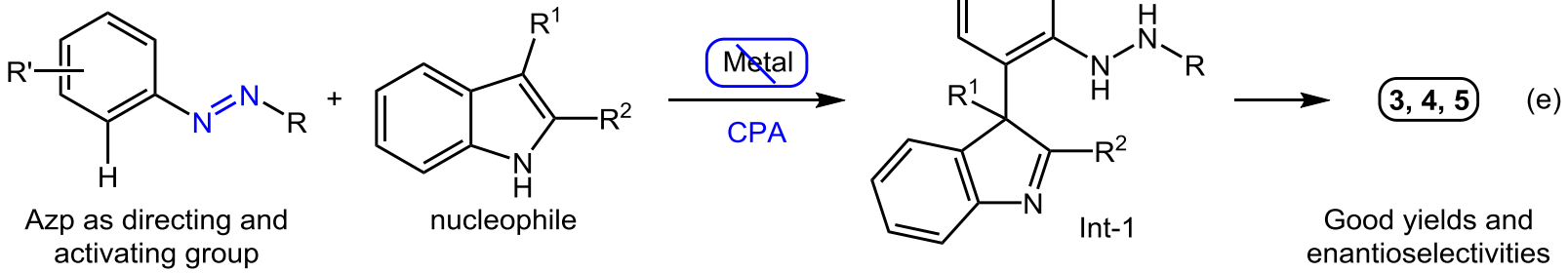




Nucleophilic aromatic substitution



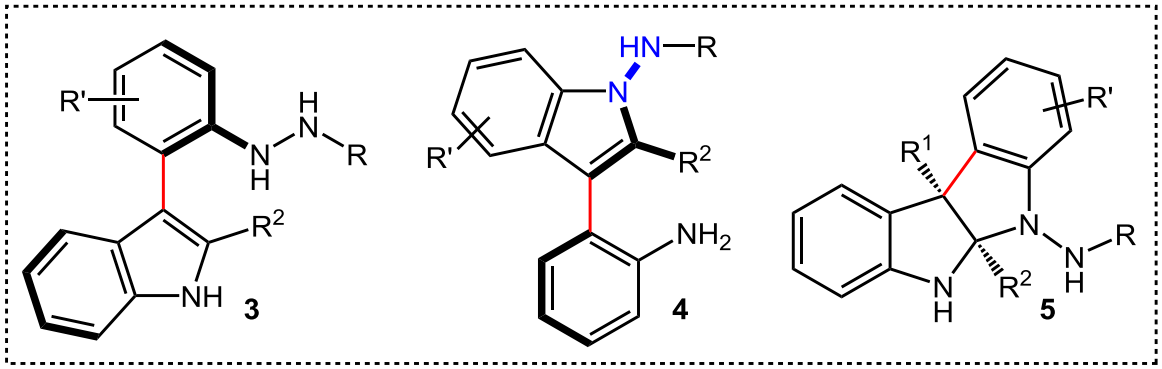
Azo as directing group



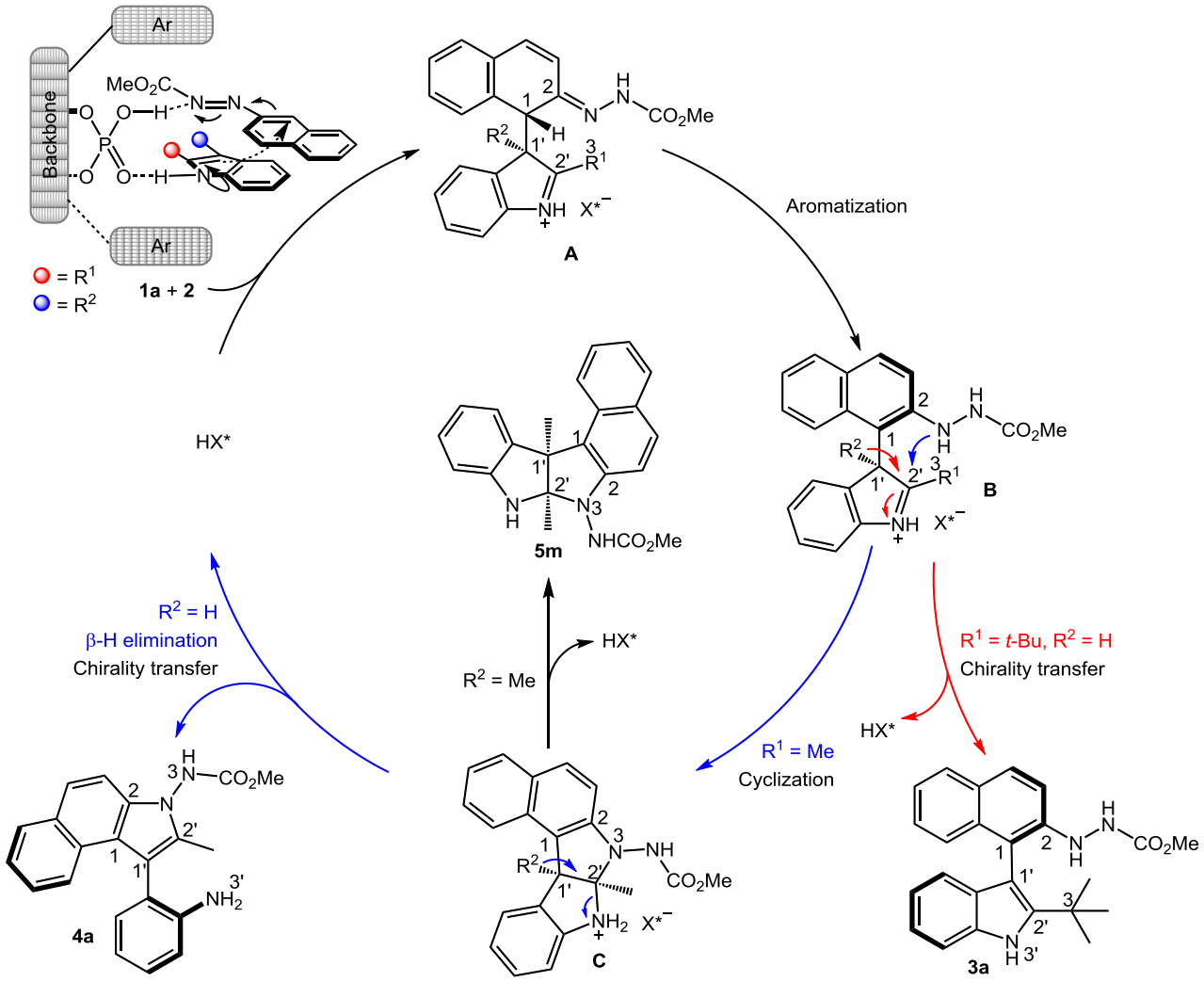
Azp as directing and activating group

nucleophile

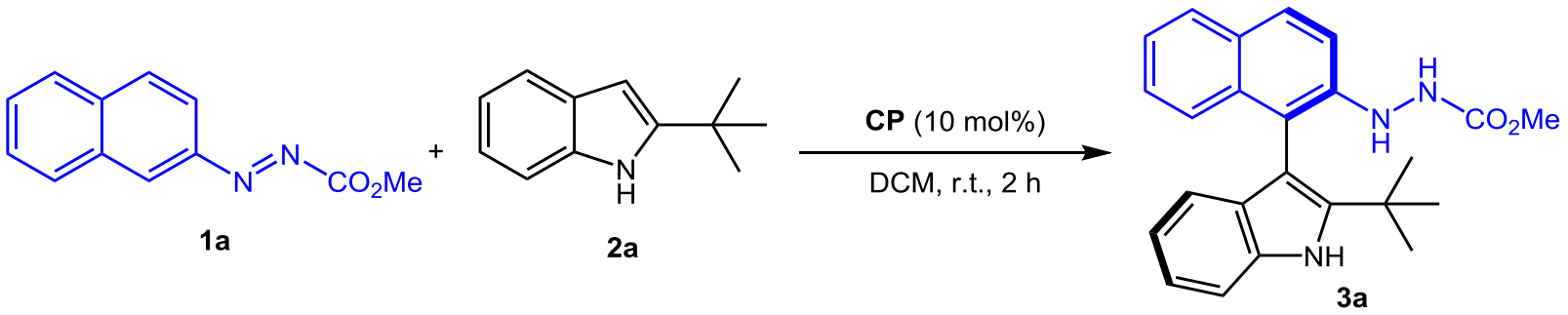
Good yields and enantioselectivities

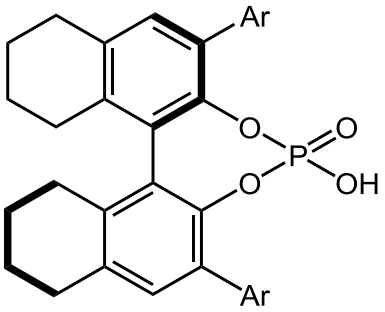


Proposed mechanism

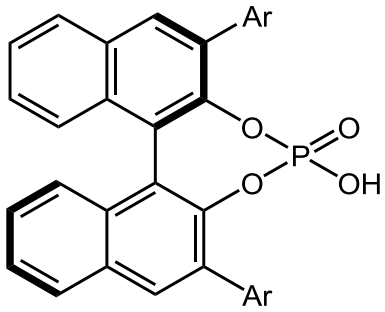


Optimization of the reaction conditions

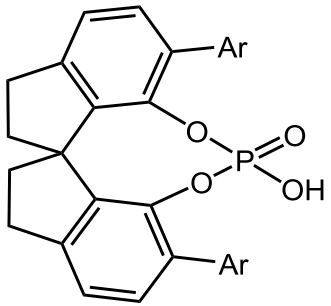




CP1: Ar = 3,5-Ph_2-C_6H_3
76% yield, 87% ee
CP2: Ar = 1-pyrenyl
82% yield, 78% ee

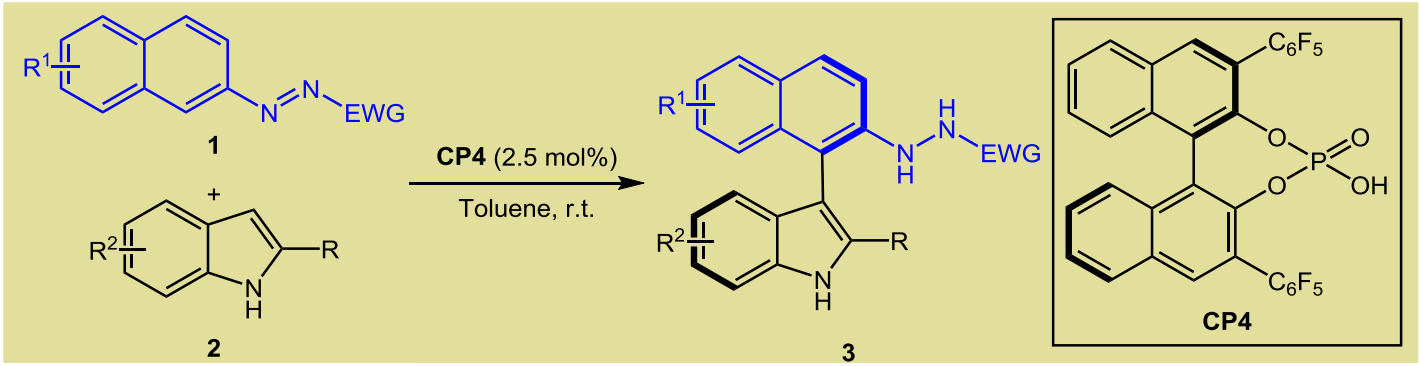


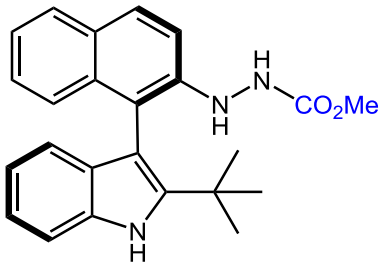
CP3: Ar = 9-anthryl
87% yield, 86% ee
CP4: Ar = C_6F_5
99% yield, 92% ee



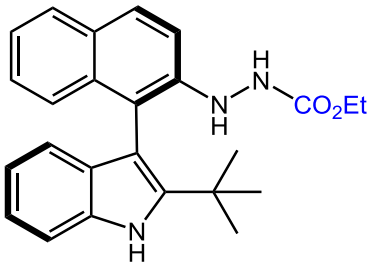
(*S*)-**CP5**: Ar = 1-pyrenyl
46% yield, 63% ee
(*R*)-**CP6**: Ar = 9-phenanthryl
33% yield, -90% ee

Substrate scope——axially chiral arylindoles

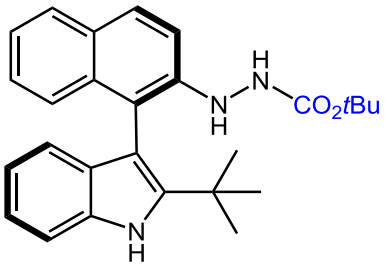




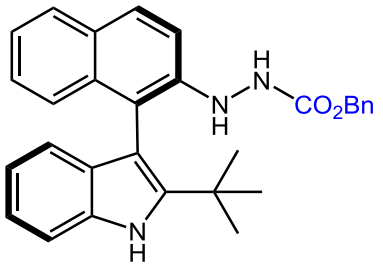
3a, 2 h, 94%, 97% ee



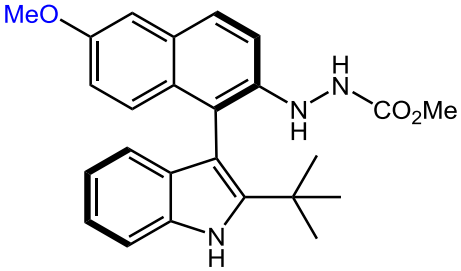
3b, 2 h, 95%, 97% ee



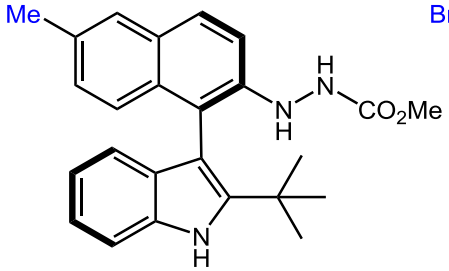
3c, 4 h, 92%, 98% ee



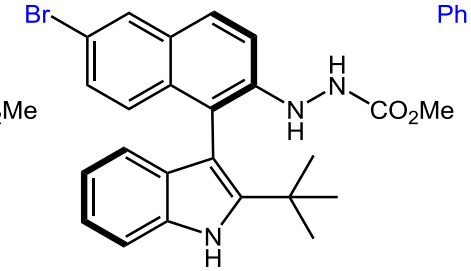
3d, 2 h, 93%, 99% ee



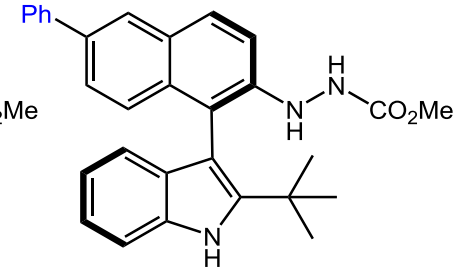
3e, 2 h, 94%, 94% ee



3f, 2 h, 94%, 98% ee

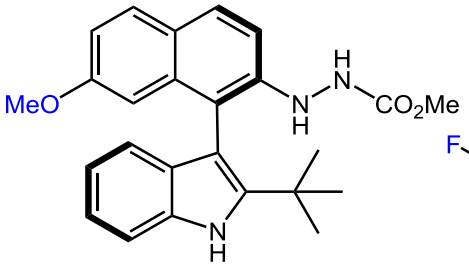


3g, 2 h, 90%, 98% ee

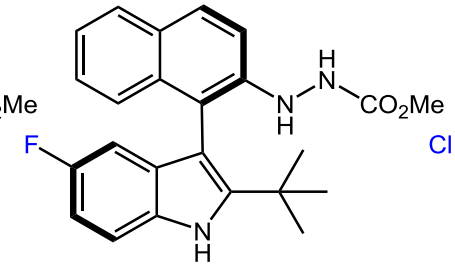


3h, 4 h, 96%, 98% ee

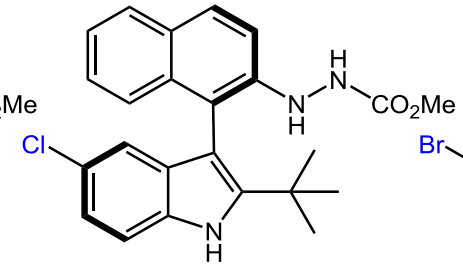
Substrate scope——axially chiral arylindoles



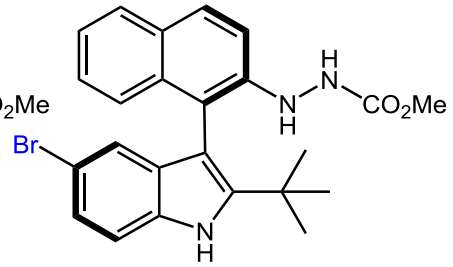
3i, 2 h, 93%, 98% ee



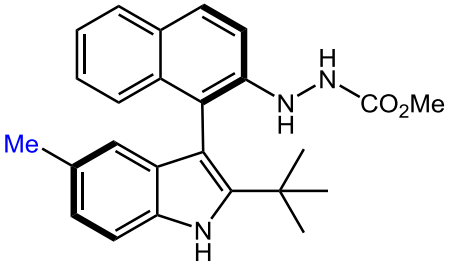
3j, 2 h, 96%, 97% ee



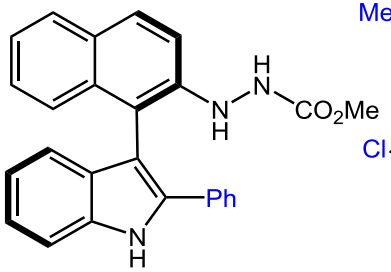
3k, 2 h, 98%, >99% ee



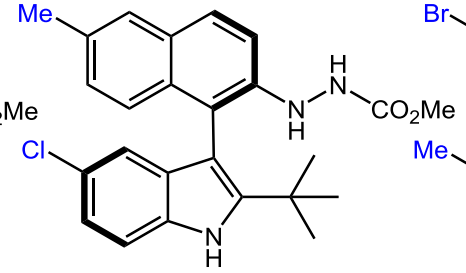
3l, 2 h, 98%, >99% ee



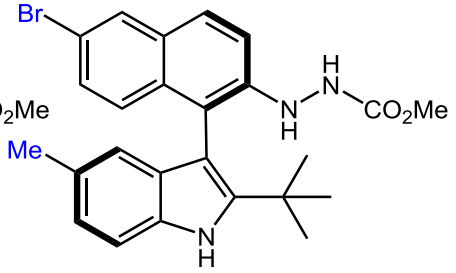
3m, 2 h, 90%, 98% ee



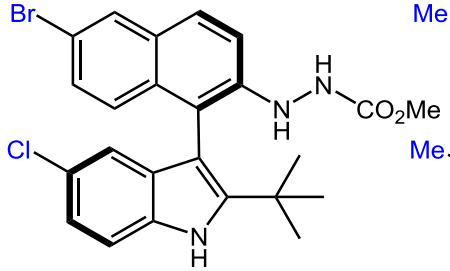
3n, 0.5 h, 84%, 80% ee



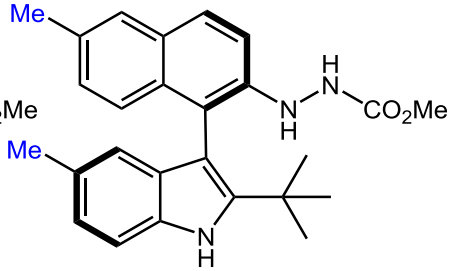
3o, 2 h, 97%, 99% ee



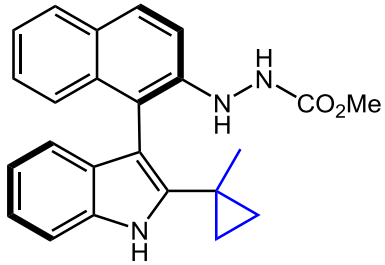
3p, 2 h, 87%, 98% ee



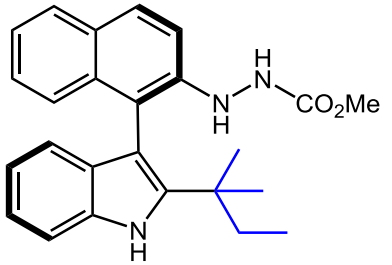
3q, 5 h, 93%, 98% ee



3r, 2 h, 92%, 98% ee

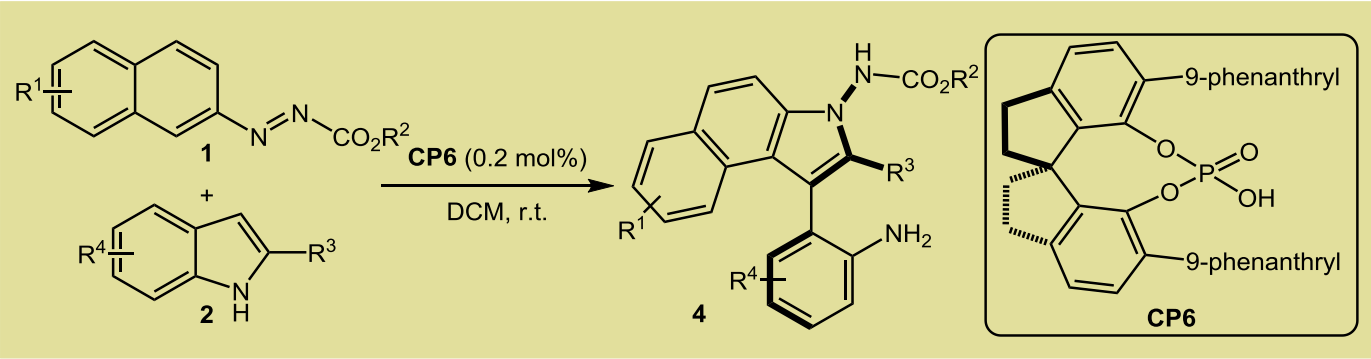


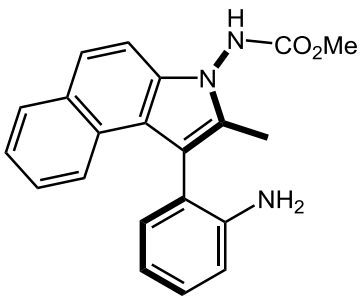
3s, 2 h, 90%, 88% ee



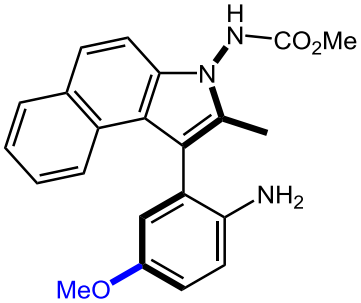
3t, 4 h, 95%, 92% ee

Substrate scope——aniline-indoles

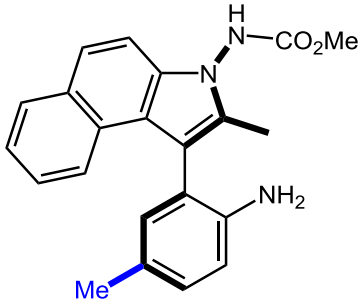




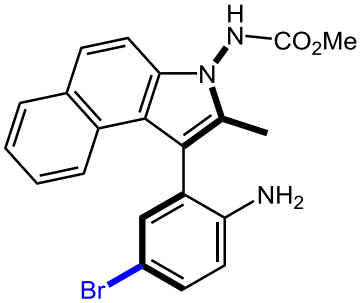
4a, 3 h, 87%, 99% ee



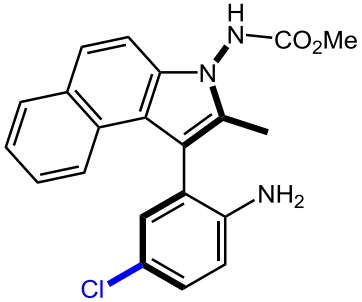
4b, 12 h, 45%, 99% ee



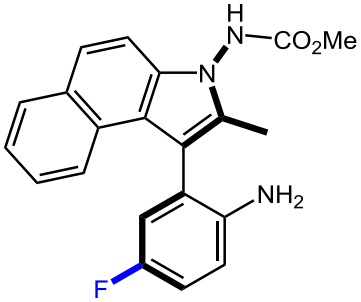
4c, 10 h, 74%, 99% ee



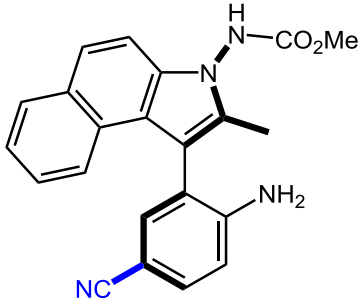
4d, 12 h, 69%, 99% ee



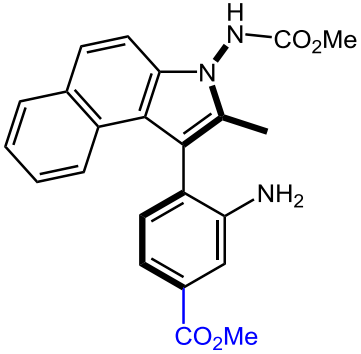
4e, 15 h, 78%, 99% ee



4F, 18 h, 72%, 99% ee

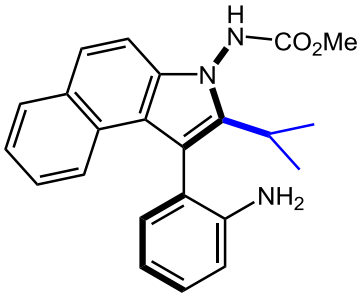


4g, 4 h, 84%, 99% ee

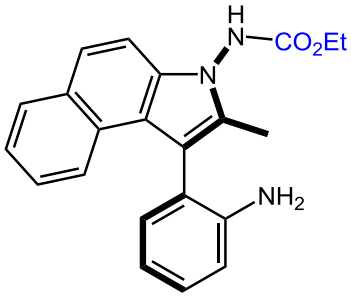


4h, 4 h, 78%, 98% ee

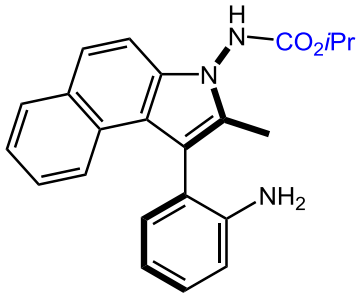
Substrate scope——aniline-indoles



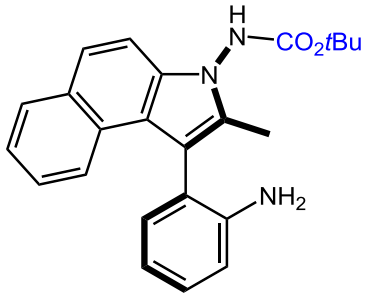
4i, 48 h, 76%, >99% ee



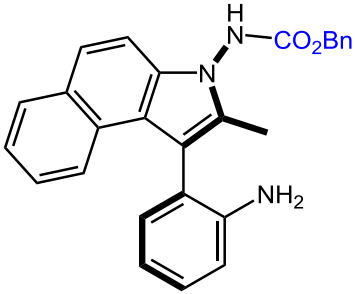
4j, 7 h, 86%, 99% ee



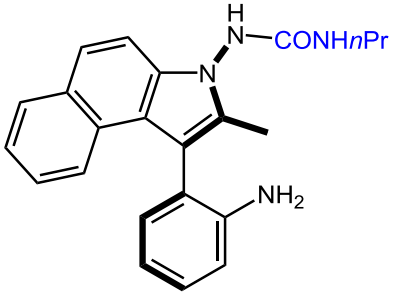
4k, 12 h, 78%, 99% ee



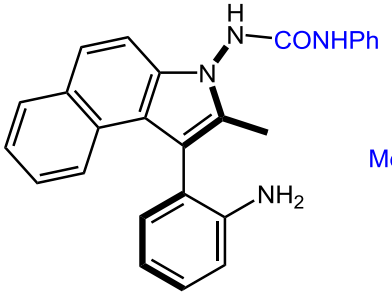
4l, 30 h, 83%, 99% ee



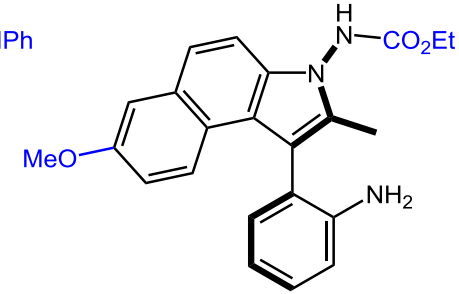
4m, 5 h, 81%, >99% ee



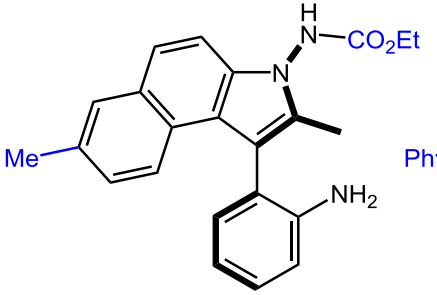
4n, 24 h, 81%, 98% ee



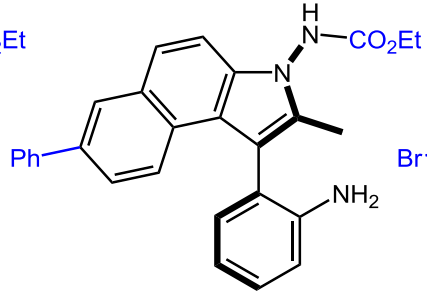
4o, 3 h, 87%, 99% ee



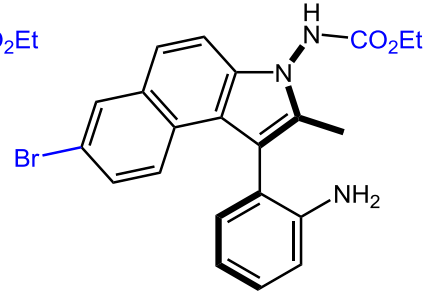
4p, 4 h, 72%, 99% ee



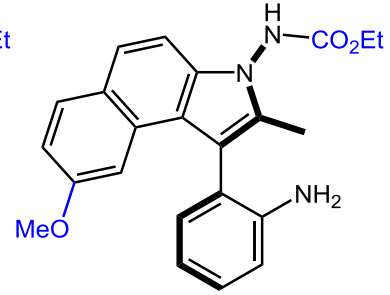
4q, 5 h, 86%, 99% ee



4r, 12 h, 84%, 99% ee

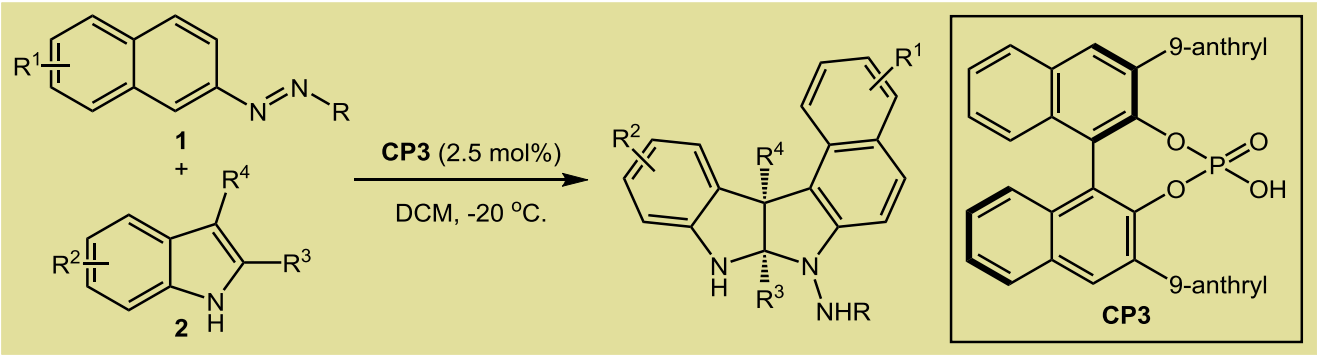


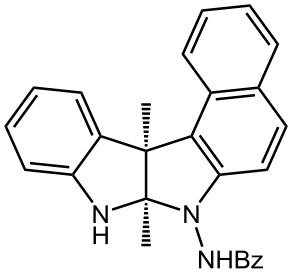
4s, 3 h, 88%, 99% ee



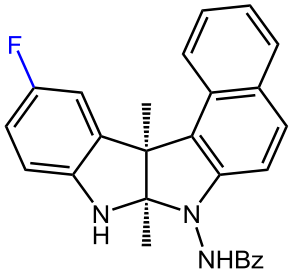
4t, 4 h, 83%, >99% ee

Substrate scope——pyrroloindolines

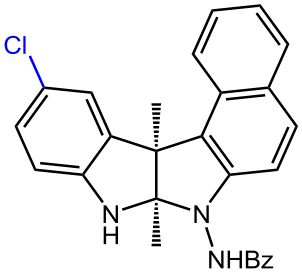




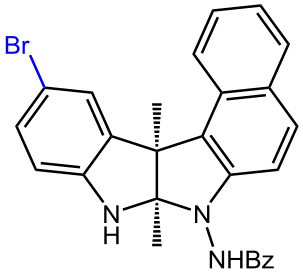
5a, 5 h, 99%, 97% ee



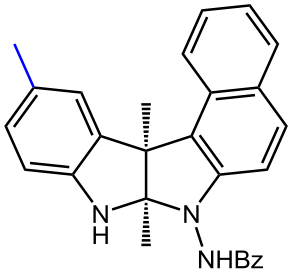
5b, 12 h, 99%, 95% ee



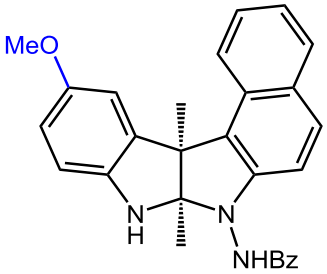
5c, 7 h, 99%, 95% ee



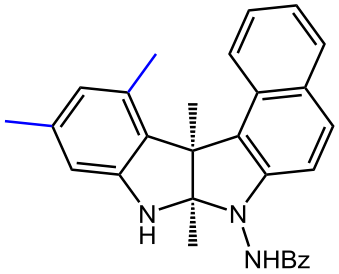
5d, 7 h, 97%, 95% ee



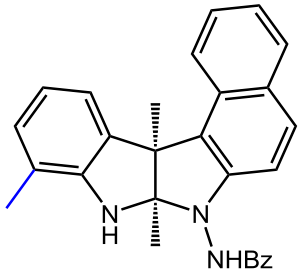
5e, 12 h, 99%, 96% ee



5f, 24 h, 99%, 93% ee

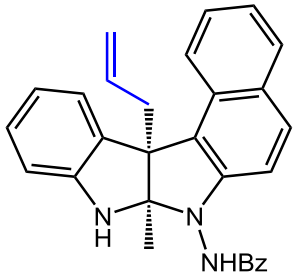


5g, 12 h, 99%, 94% ee

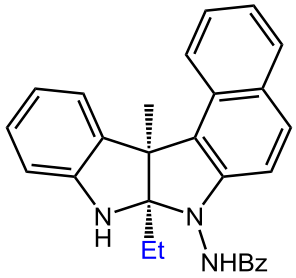


5h, 10 h, 94%, 96% ee

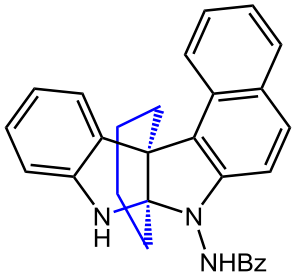
Substrate scope——pyrroloindolines



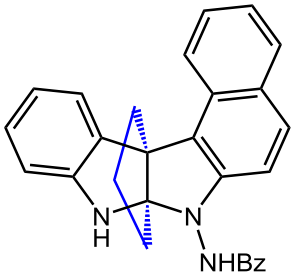
5i, 24 h, 85%, 89% ee



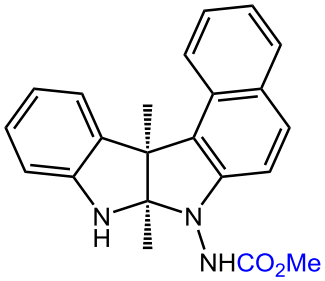
5j, 12 h, 99%, 91% ee



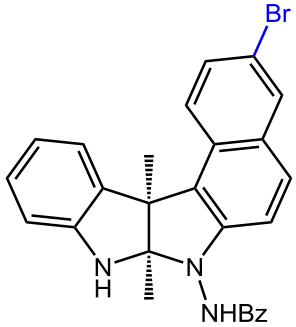
5k, 24 h, 95%, 92% ee



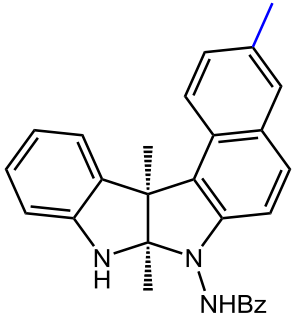
5l, 10 h, 98%, 96% ee



5m, 10 h, 98%, 86% ee

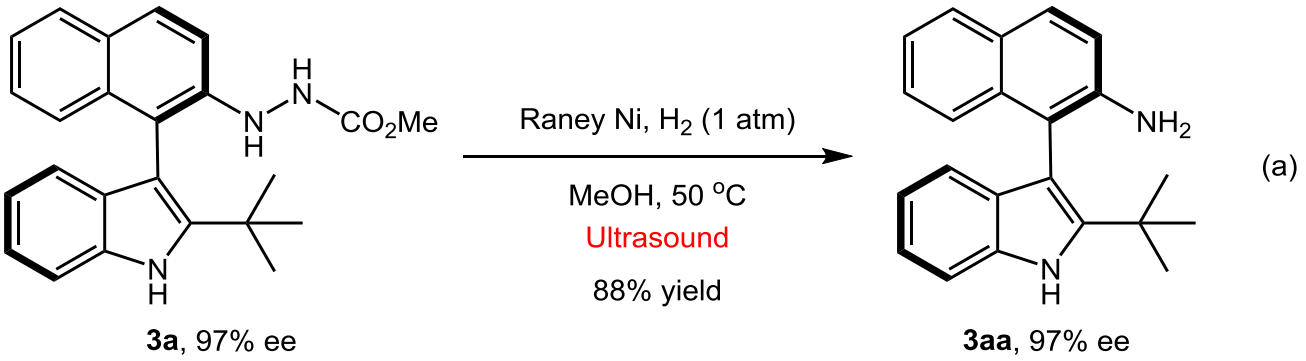


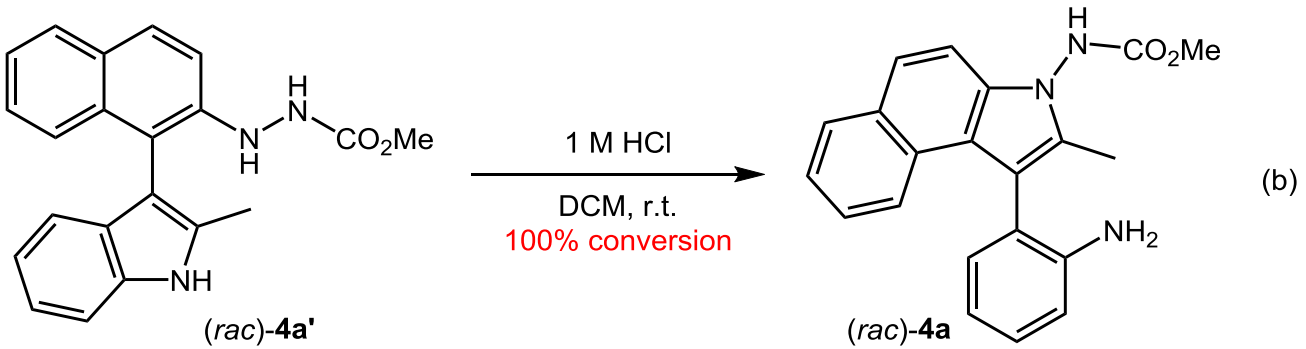
5n, 10 h, 96%, 97% ee



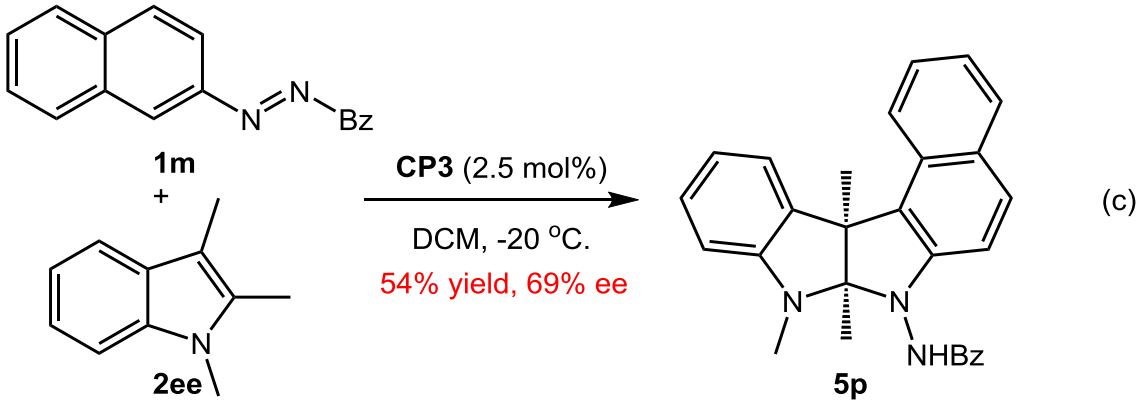
5o, 8 h, 99%, 94% ee

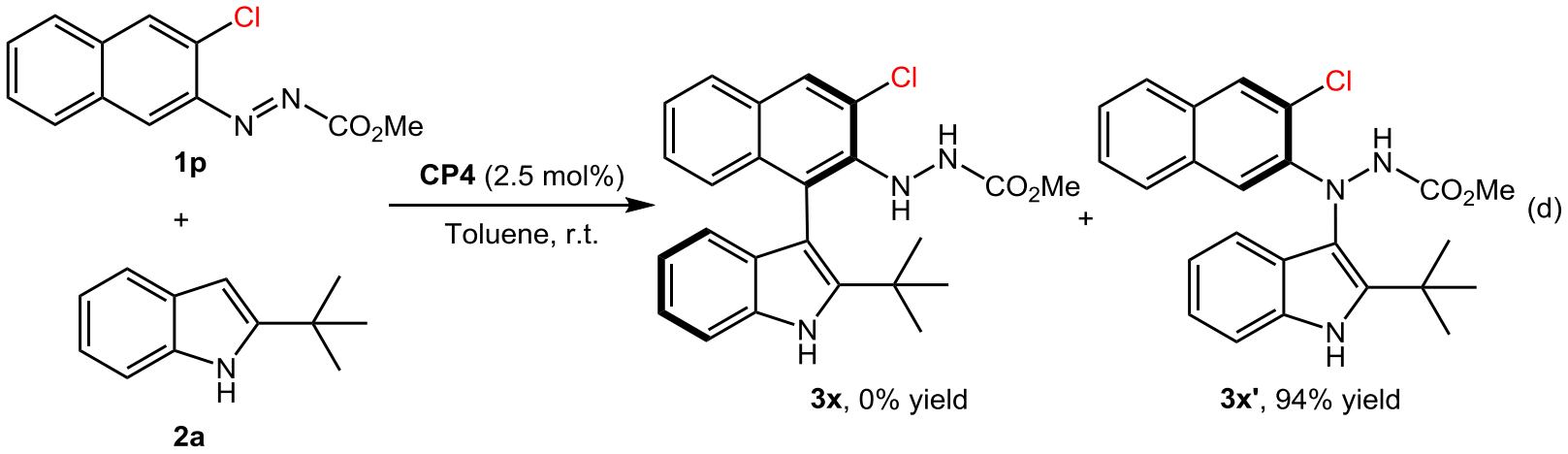
Transformation and control experiments



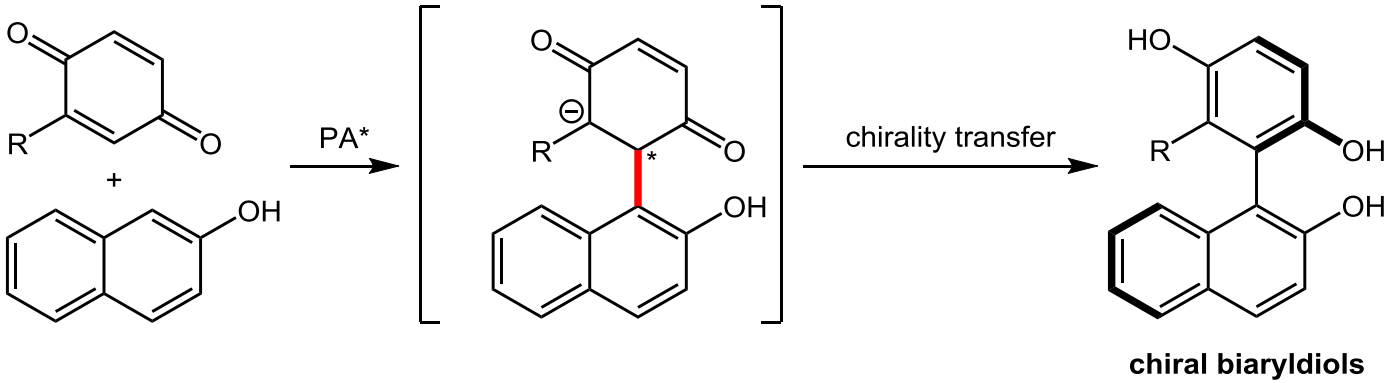


Control experiments

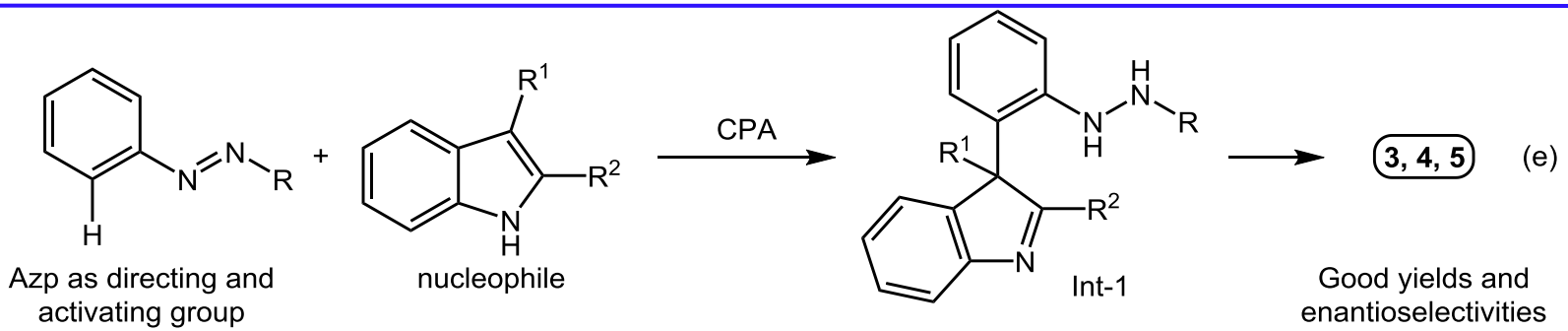


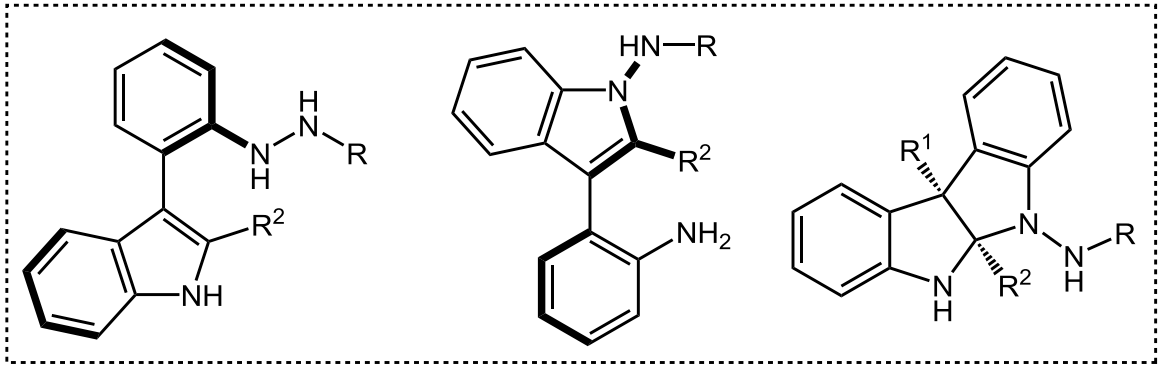


Summary



Y.-H. Chen, D.-J. Cheng and B. Tan, *J. Am. Chem. Soc*. **2015**, *137*, 15062-15065.





L.-W. Qi, J.-H. Mao, J. Zhang and B. Tan, *Nat. Chem*. **2018**, *10*, 58-64.

The First Paragraph

Electrophilic aromatic substitution is a textbook organic reaction, in which the aromatic ring acts as a nucleophile. Many important transformations, such as aromatic nitration, halogenation, sulfonation, acylation and alkylation, can be mediated by this type of reaction. In sharp contrast, nucleophilic aromatic substitution involving aryl C–H cleavage is rarely described. Although aromatic rings have been used as formal electrophiles to react with different nucleophiles in many useful transformations involving transition-metal catalysed aryl C–H activation, organocatalytic arylation involving formal nucleophilic aromatic substitution remains to be developed. Encouraged by these elegant works, we speculated that an electron-withdrawing group on an aromatic ring might interact with a Brønsted acid organocatalyst through hydrogen bonding, which might render the aromatic ring electrophilic enough for nucleophilic aromatic attack to take place.

The First Paragraph

As we all know, the azo group has served as an excellent directing group in a number of transition-metal-catalysed C–H activation transformations, including halogenation, oxygenation, arylation, acylation, amination, aminoalkylation, aminocarbonylation and cyclization. However, to the best of our knowledge, the organocatalytic arylation by azobenzene derivatives has never been documented. In this sense, using the azo group as both an activating group and a directing group together with an organocatalyst represents a novel and significant reaction modality and opens new avenues for the development of asymmetric organocatalysis.

The Last Paragraph

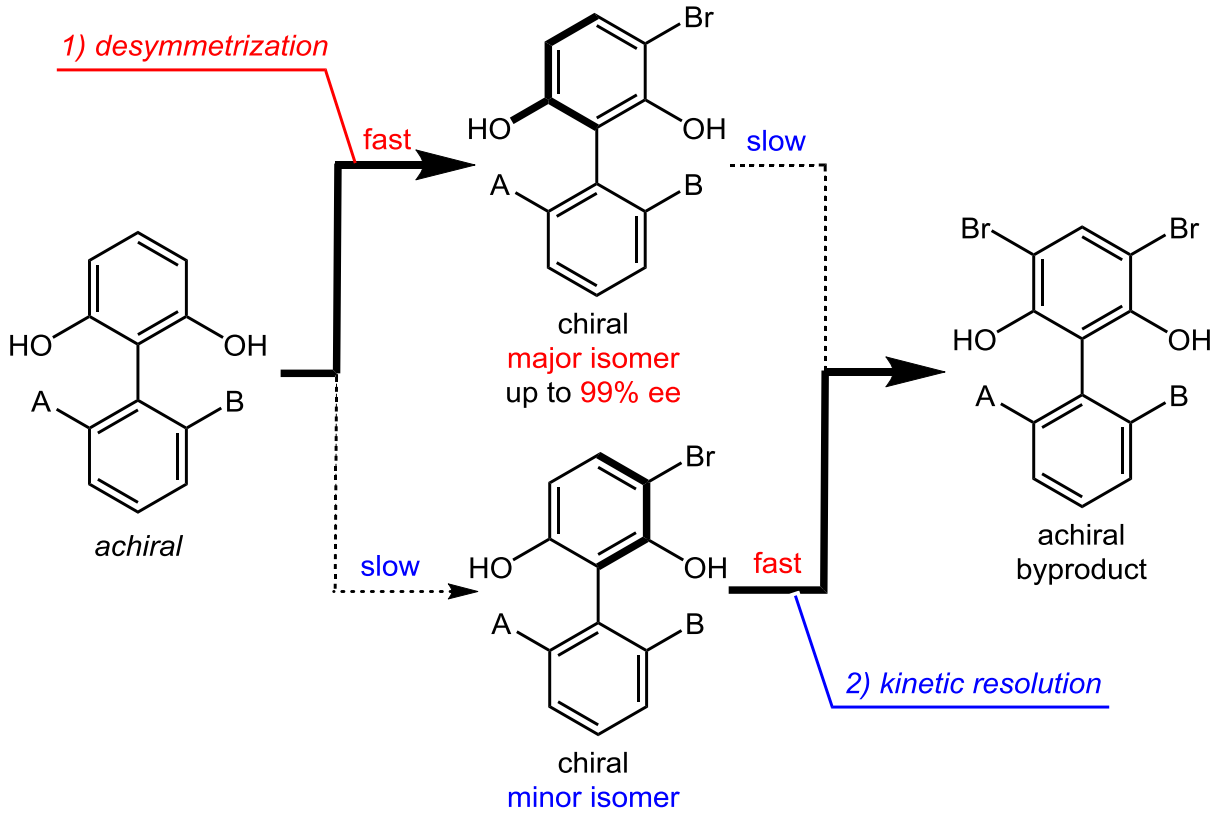
In summary, we have discovered that the azo group can not only effectively activate an aromatic ring for nucleophilic attack, but also efficiently directs the formal nucleophilic aromatic substitution, which allows for the successful development of unprecedented organocatalytic enantioselective arylation of indoles. The important features of these reactions are as follows: (1) organocatalytic formal nucleophilic aromatic substitution is realized, involving azobenzene derivatives as electrophiles; (2) the azo group acts as a directing and activating group for organocatalytic asymmetric arylation of indoles; (3) axially chiral arylindoles and aniline-indoles are accessed in good yields with excellent enantioselectivities by using chiral phosphoric acid as organocatalyst;

The Last Paragraph

(4) enantioenriched pyrroloindoles bearing two contiguous quaternary chiral centres are forged using a cascade approach with good results; and (5) catalyst loading can be reduced to 0.05 mol% for effective transformation under mild conditions. We anticipate that this strategy will foster the development of many other useful transformations and motivate new enthusiasm for organocatalytic asymmetric aryl functionalization.

Acknowledgment

Thanks for your attention


1) desymmetrization
fast
slow
HO
OH
A
B
Br
achiral
chiral
major isomer
up to 99% ee
slow
fast
chiral
minor isomer
achiral
byproduct
2) kinetic resolution