Dynamic Kinetic Resolution (DKR) and Dynamic Kinetic Asymmetric Transformation (DyKAT) of Atropisomeric Biaryls

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Supervisor: Can Zhu (朱灿 青年研究员)

2025.04.11

Content

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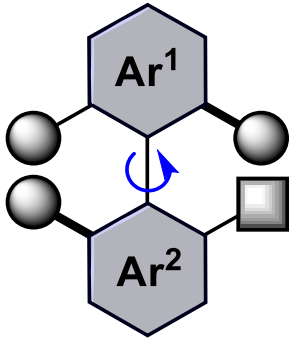
1. Introduction

➢ Axial Chirality and Atropisomeric Biaryls

(A)

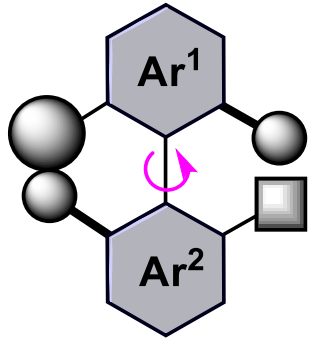


$\Delta G^{\ddagger} \leq 20$ kcal/mol

free axial rotation

25 °C: $t_{1/2} \leq 25.9$ s

(B)

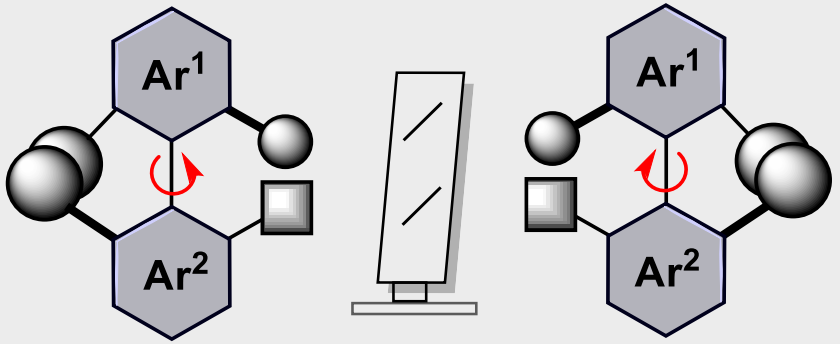


20 kcal/mol < $\Delta G^{\ddagger}$ < 30 kcal/mol

retarded axial rotation

25.9 s < $t_{1/2}$ < 17.7 y

(C) *atropisomeric biaryls* (**this topic**)



$\Delta G^{\ddagger} \geq 30$ kcal/mol

hindered axial rotation

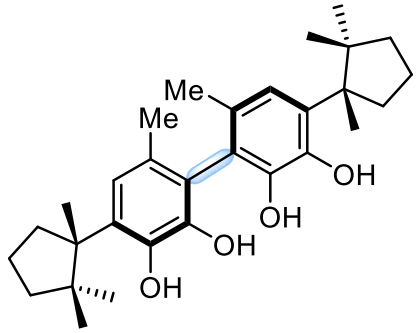
$t_{1/2} \geq 17.7$ y

Ōki, M. *Top. Stereochem.* **1983**, *14*, 1−81.
Hucke, O., et al. *ChemMedChem* **2011**, *6*, 505−513.
Edwards, P. J., et al. *J. Med. Chem.* **2011**, *54*, 7005−7022.
Piras, P., et al. *Adv. Heterocycl. Chem.* **2012**, *105*, 1−188.

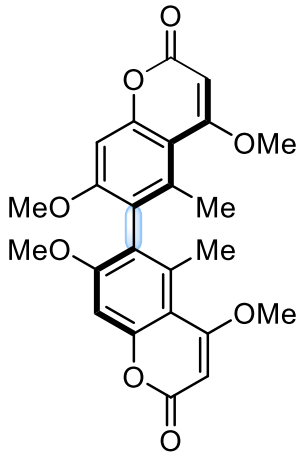
1. Introduction

➢ Axial Chirality and Atropisomeric Biaryls

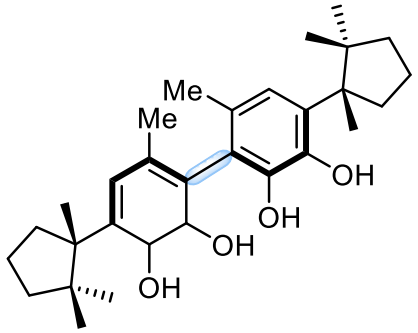
Natural products



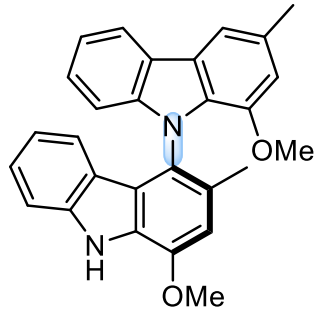
Mastigophorene A



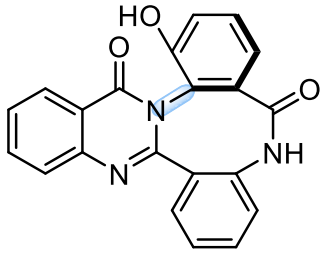
(+)-Isokotanin A



Mastigophorene B

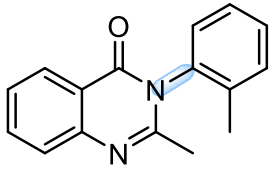


Murrastifoline-F

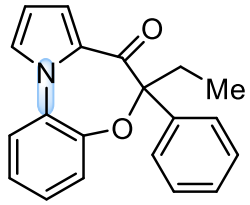


Eupolyphagin

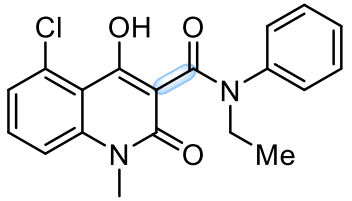
Drugs and bioactive molecules



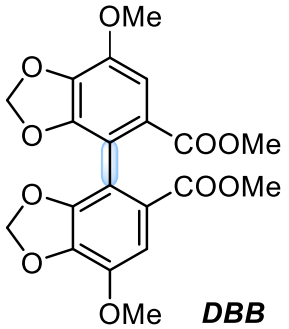
Methaqualone



PBO



Laquinimod



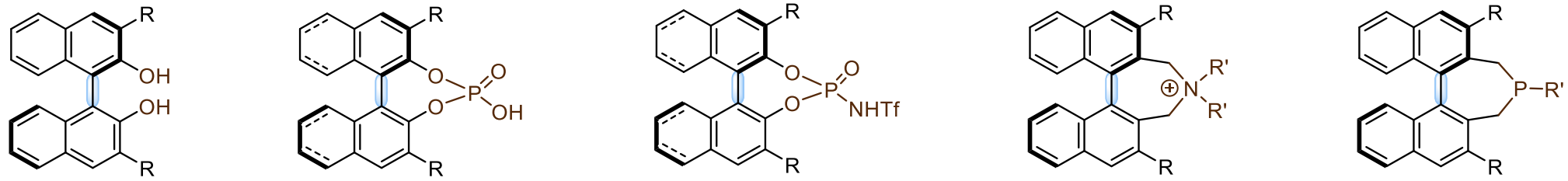
DBB

Yudin, A. K., et al. *Chem. Rev.* **2003**, *103*, 3155−3211. Keller, P. A., et al. *Nat. Prod. Rep.* **2015**, *32*, 1562−1583.
Gu, Z., et al. *Acc. Chem. Res.* **2022**, *55*, 1620−1633. Gustafson, J. L., et al. *Acc. Chem. Res.* **2022**, *55*, 2904−2919.

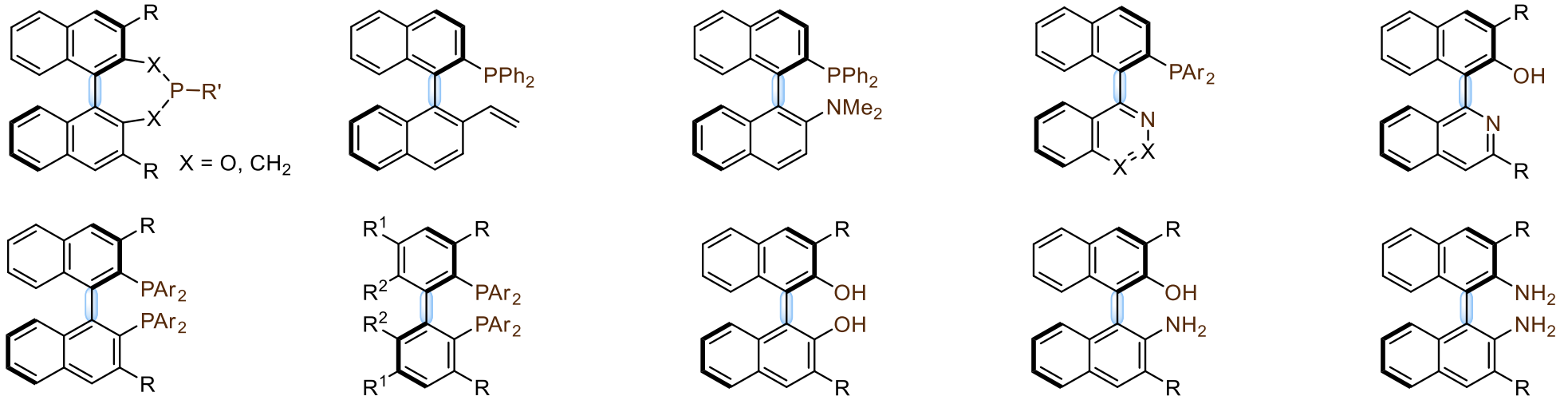
1. Introduction

➢ Axial Chirality and Atropisomeric Biaryls

Organocatalysts



Metal ligands

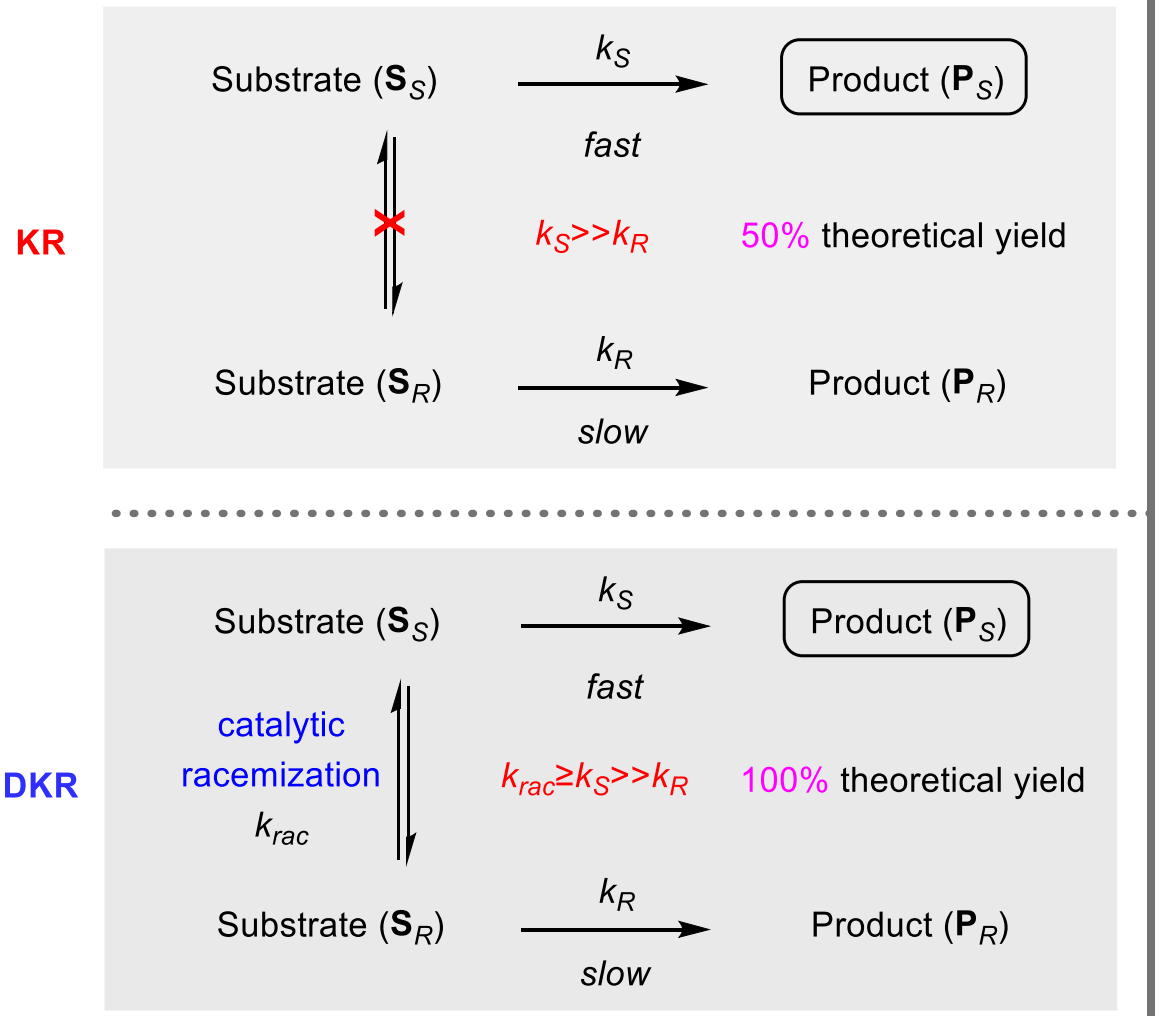


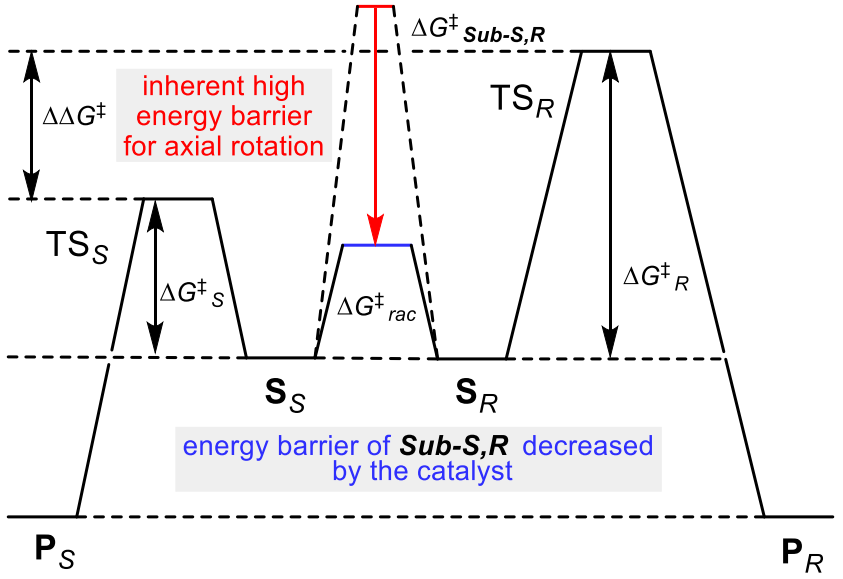
Yudin, A. K., et al. *Chem. Rev.* **2003**, *103*, 3155−3211. Keller, P. A., et al. *Nat. Prod. Rep.* **2015**, *32*, 1562−1583.
Gu, Z., et al. *Acc. Chem. Res.* **2022**, *55*, 1620−1633. Gustafson, J. L., et al. *Acc. Chem. Res.* **2022**, *55*, 2904−2919.

Content

2. DKR of Atropisomeric Biaryls

➢ Dynamic Kinetic Resolution (DKR)





- efficiently and reversibly racemize the substrates
- be inert over the chiral products
- be compatible with the KR system

Williams, J. M. J., et al. *Curr. Opin. Chem. Biol*. **1999**, *3*, 11−15. Bull, S. D., et al. *Tetrahedron: Asymmetry* **2003**, *14*, 1407−1446.
Park, J., et al. *Coord. Chem. Rev*. **2008**, *252*, 647−658. Zhu, C. et al. *Chin. Chem. Lett.* **2024**, *35*, 109160.

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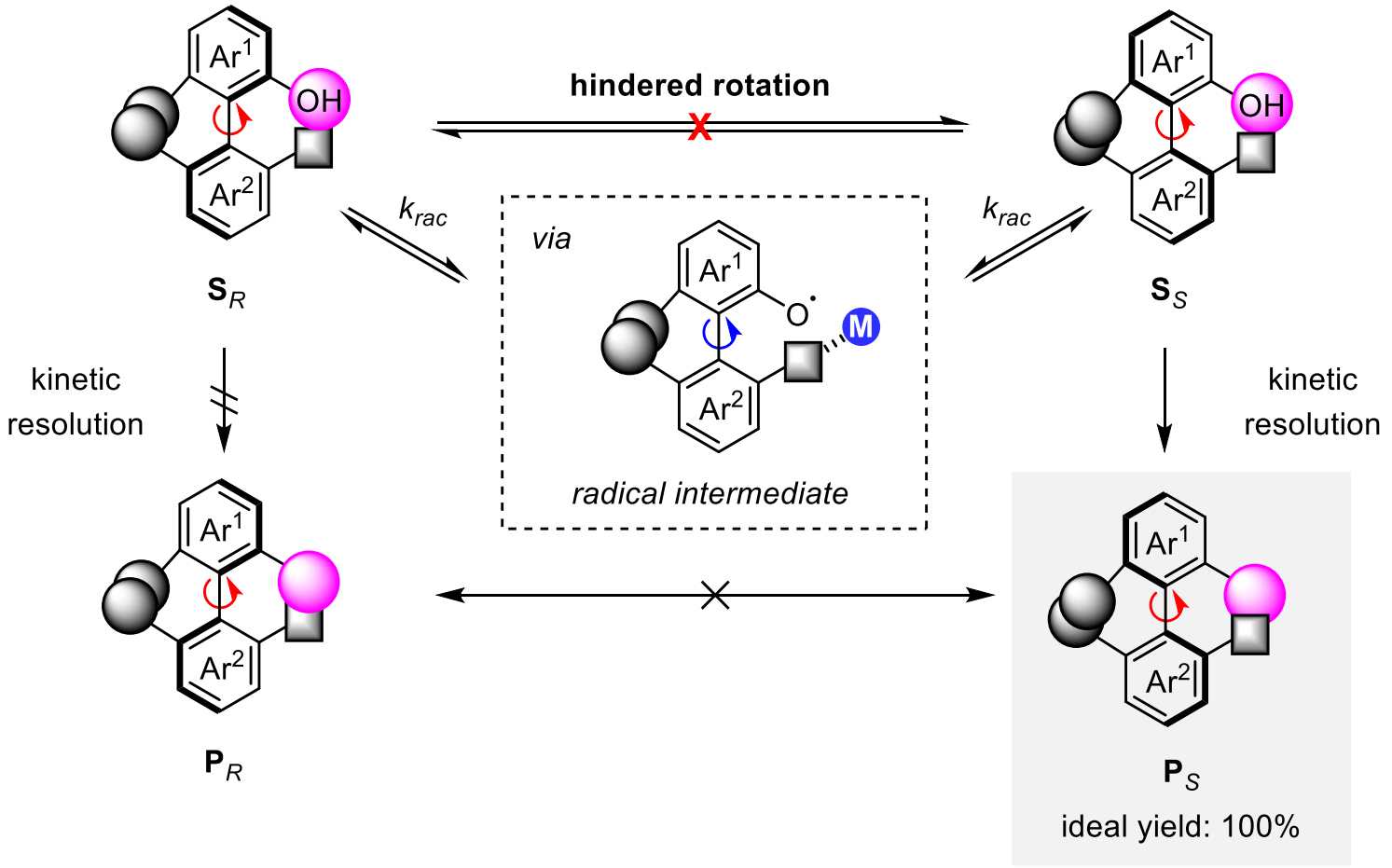
2.1 DKR of Atropisomeric Biarenols via a Radical Intermediate

➢ **Atropisomeric Biarenols**



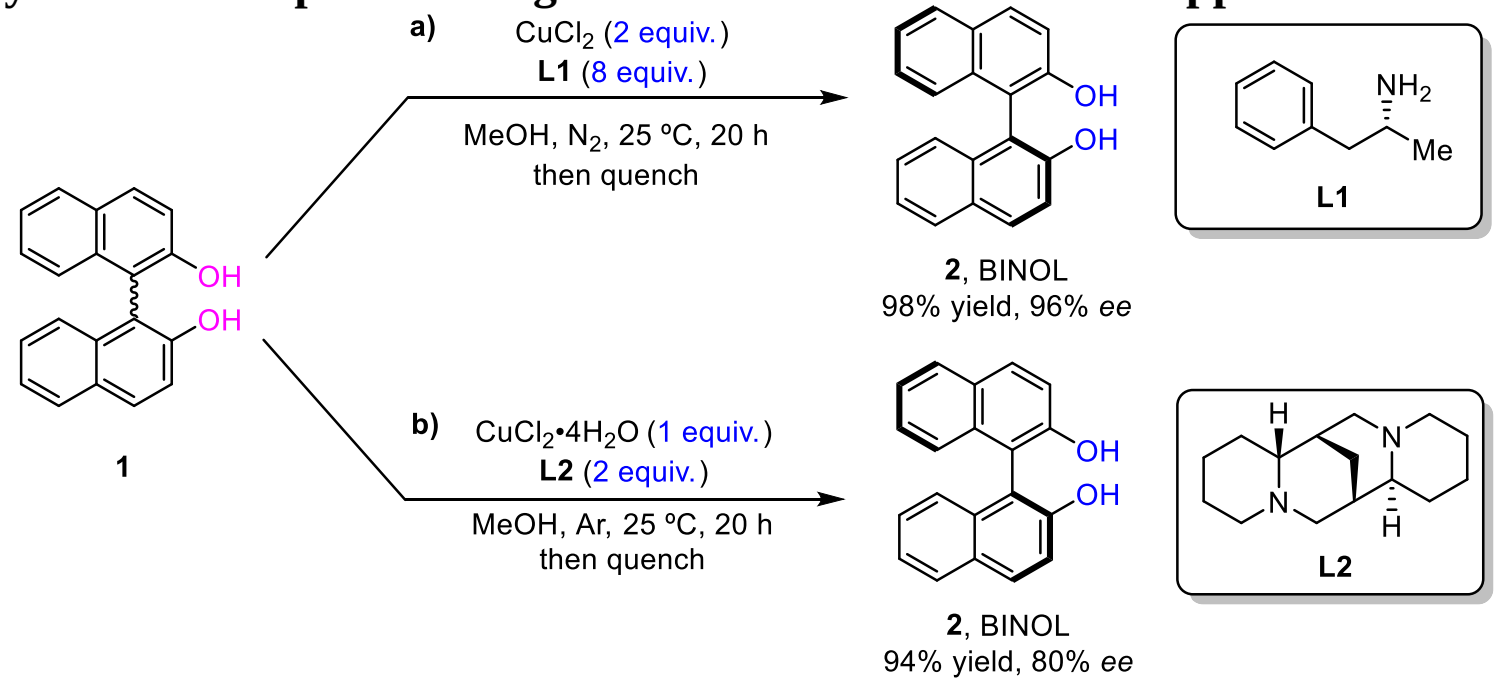
- ✓ chiral base
- ✓ chiral ammonium salt
- ✓ lipase

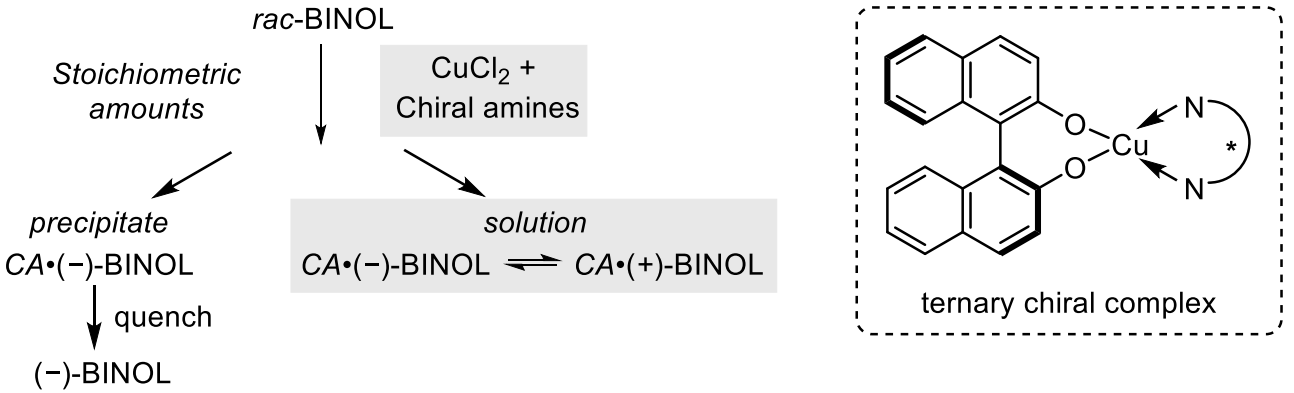
■ hindered axial rotation around the aryl-aryl bond ■ arenolic hydroxyl functionality

Lu, Y., et al. *Chem.* **2022**, *8*, 1855−1893. Debeli, D. K., et al. *J. Iran Chem. Soc.* **2022**, *19*, 1593−1611.

2.1 DKR of Atropisomeric Biarenols via a Radical Intermediate

➢ **Synthesis of Optically Active Bisnaphthol Using Stoichiometric Amounts of Copper and Chiral Amines**

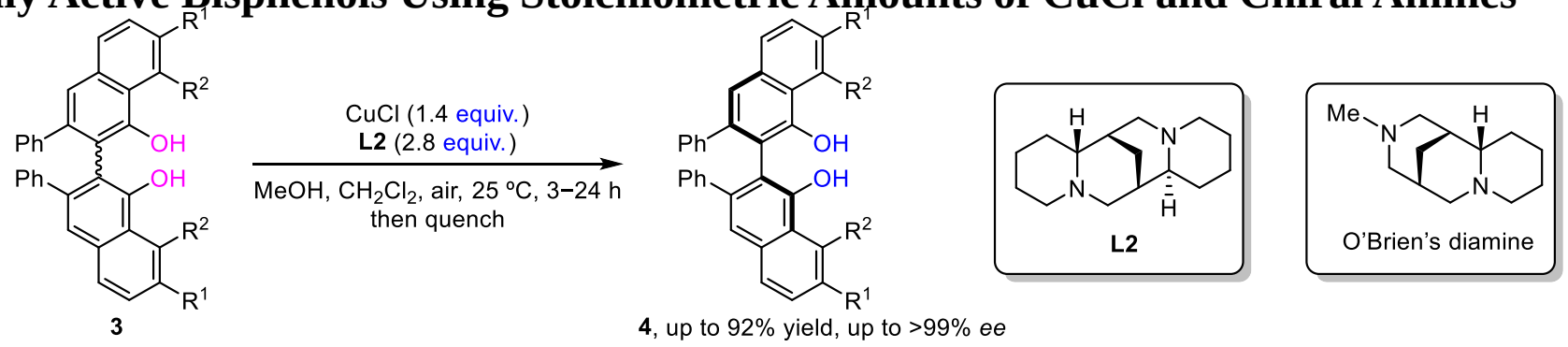


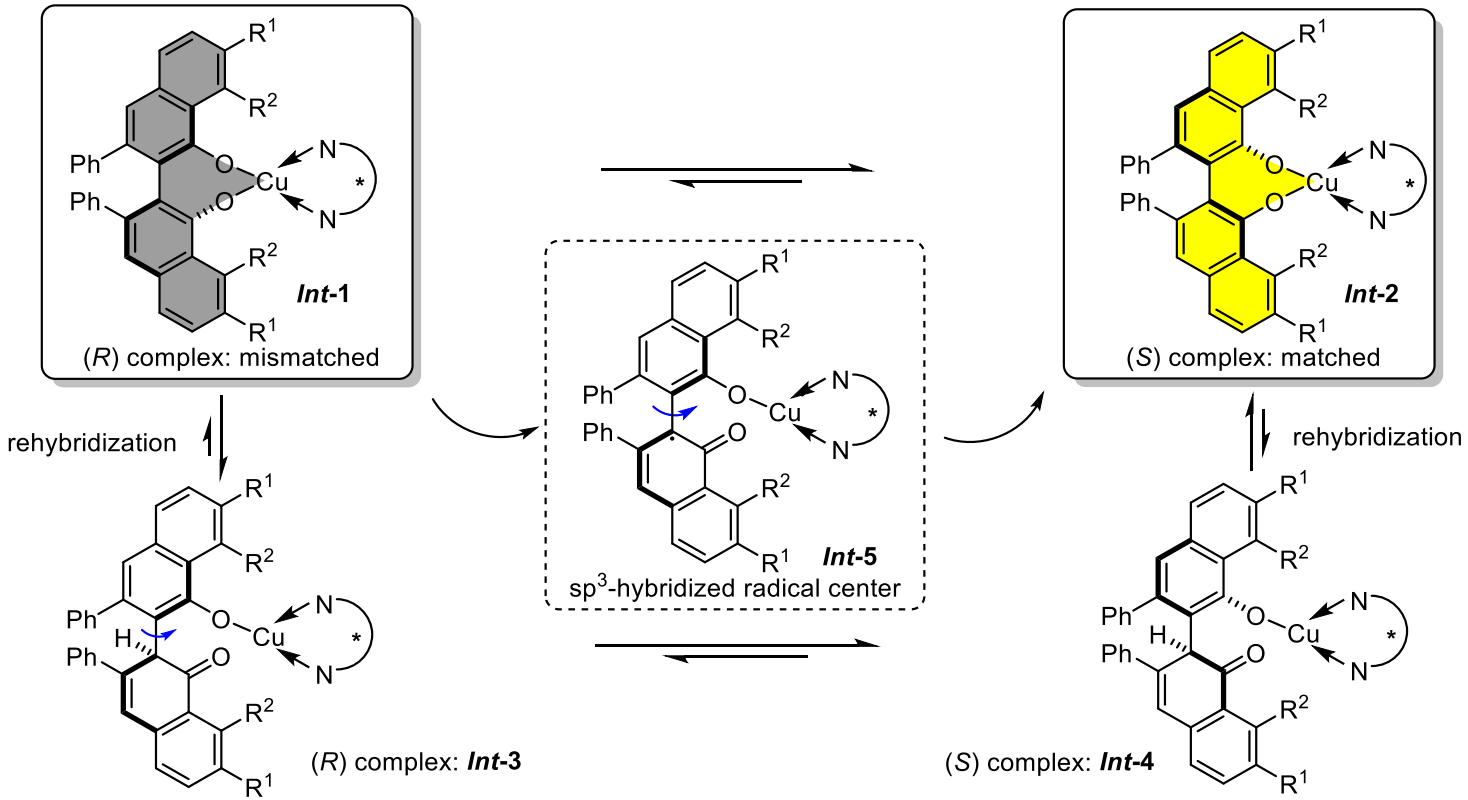


Jansen A. C. A., et al. *Tetrahedron* **1985**, *41*, 3313−3319. Kočovský, P., et al. *J. Org. Chem.* **1992**, *57*, 1917−1920. Kočovský, P., et al. *J. Org. Chem.* **1993**, *58*, 4534−4538.

2.1 DKR of Atropisomeric Biarenols via a Radical Intermediate

➢ Synthesis of Optically Active Bisphenols Using Stoichiometric Amounts of CuCl and Chiral Amines

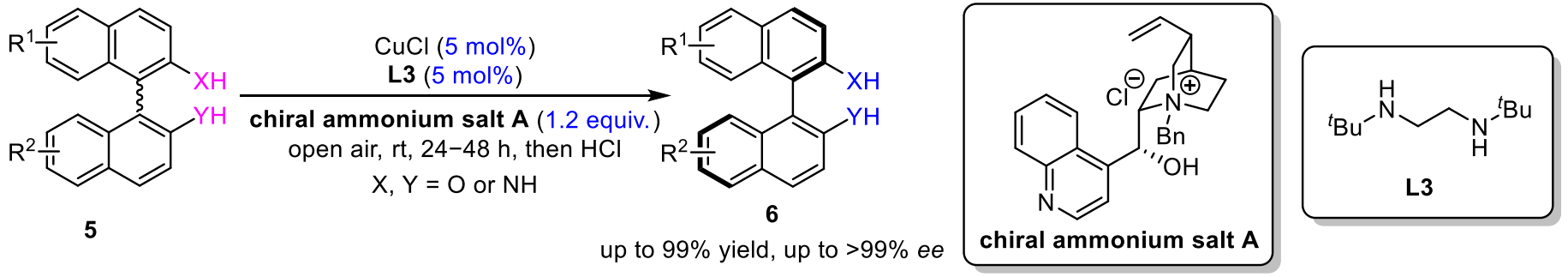


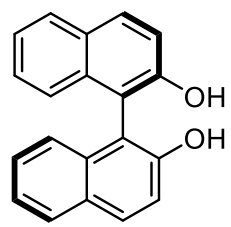


Wulff. W. D., et al. *Org. Lett.* **2003**, *5*, 1813−1816. Wulff, W. D., et al. *J. Am. Chem. Soc.* **2009**, *131*, 14355−14364.

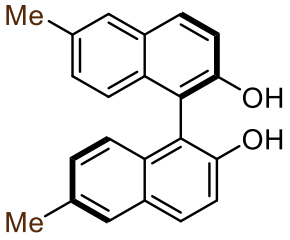
2.1 DKR of Atropisomeric Biarenols via a Radical Intermediate

➢ Copper-Catalyzed Crystallization Induced Deracemization of Atropisomeric Biaryls

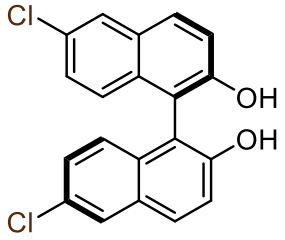




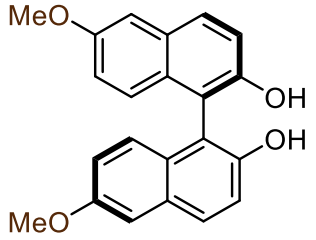
(*R*)-**6a**
86% yield, 99% *ee*



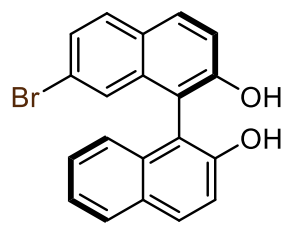
(*R*)-**6b**
92% yield, 95% *ee*



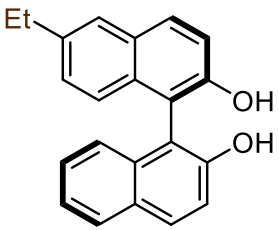
(*R*)-**6c**
99% yield, 99% *ee*



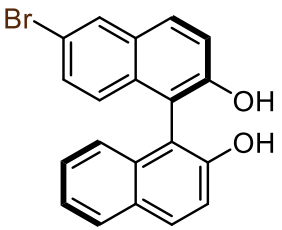
(*R*)-**6d**
86% yield, 95% *ee*



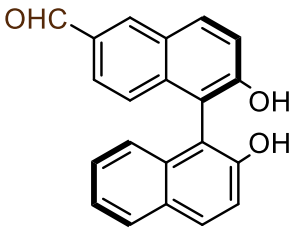
(*R*)-**6e**
74% yield, 99% *ee*



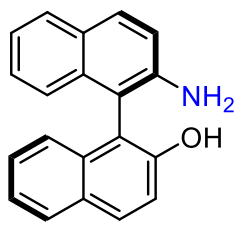
(*R*)-**6f**
83% yield, 99% *ee*



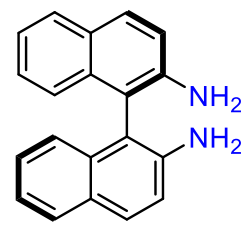
(*R*)-**6g**
90% yield, 97% *ee*



(*R*)-**6h**
74% yield, 99% *ee*



(*R*)-**6i**, NOBIN
71% yield, 98% *ee*



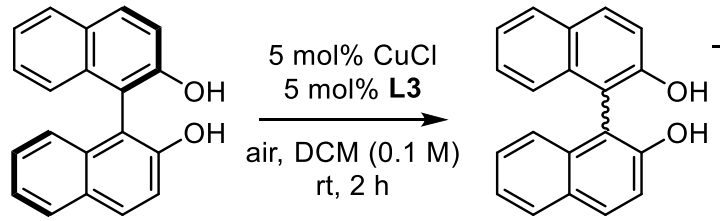
(*R*)-**6j**, BINAM
61% yield, >99% *ee*

Zhu, C., et al. *JACS Au*. **2024**, *4*, 502−511.

2.1 DKR of Atropisomeric Biarenols via a Radical Intermediate

➢ Copper-Catalyzed Crystallization Induced DKR of Atropisomeric Biaryls

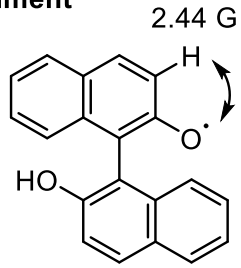
a) Control experiments



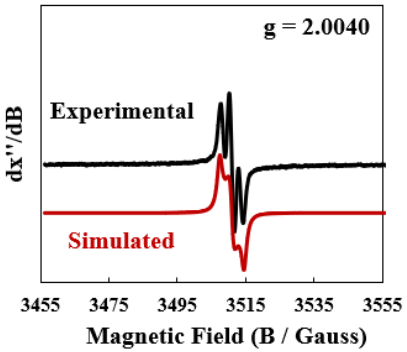
(*R*)-**6a**, >99% *ee* — **6a**

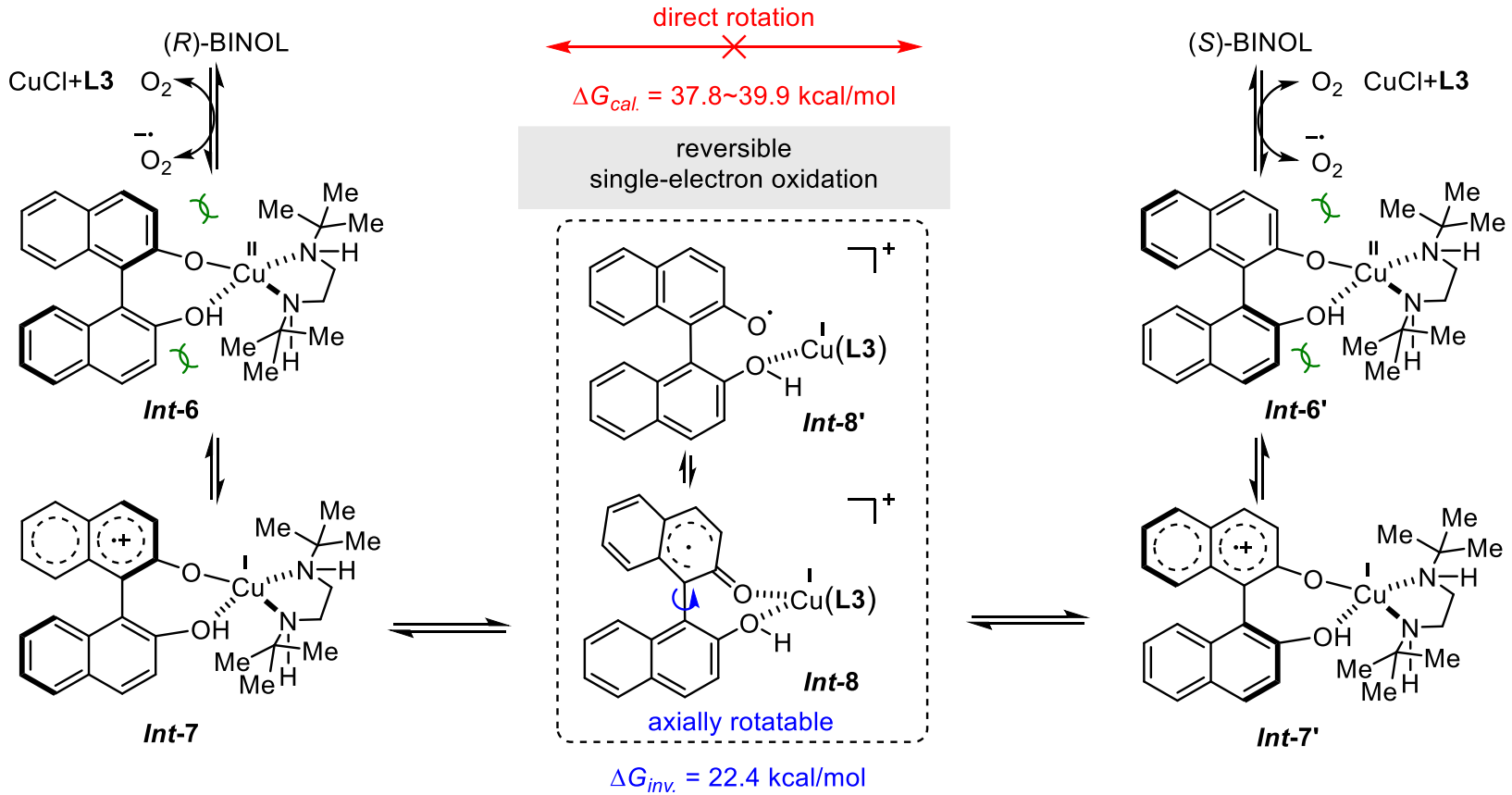
Deviations	*ee* (%) of **6a**
none	2
TEMPO (2 equiv)	90
BHT (2 equiv)	99
N_2	99
$CuCl_2$ instead of CuCl	0

b) EPR experiment



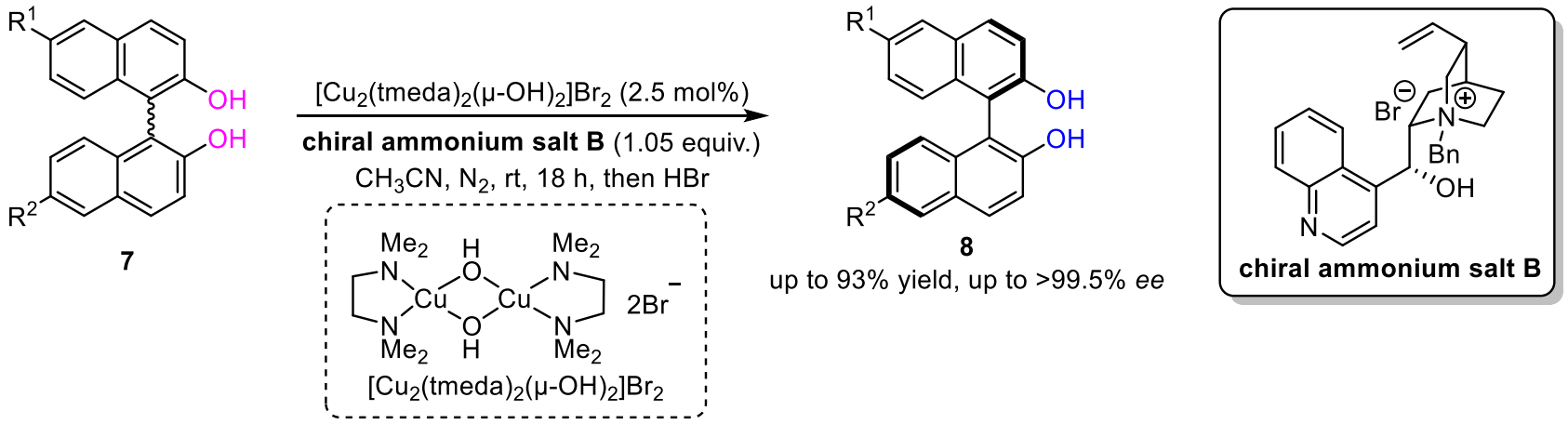
BINOL *O*-radical

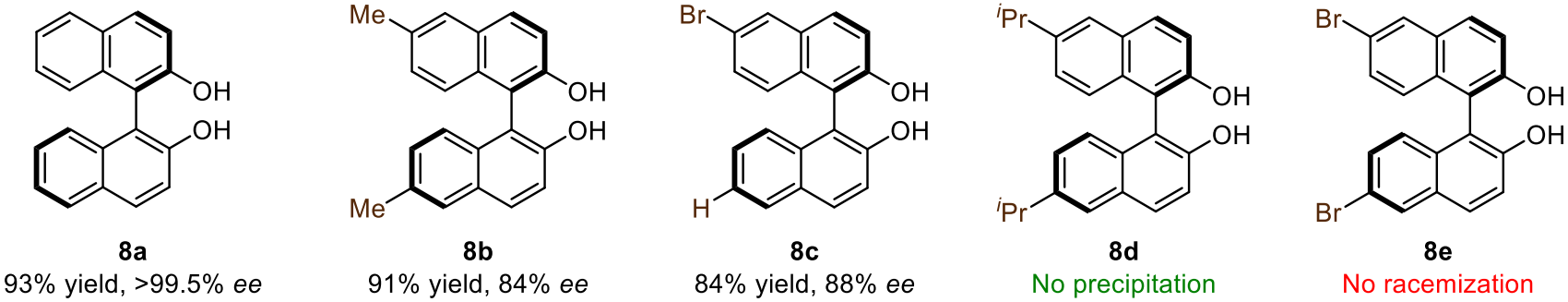




2.1 DKR of Atropisomeric Biarenols via a Radical Intermediate

➢ Copper-Catalyzed Dynamic Thermodynamic Resolution of Atropisomeric BINOLs

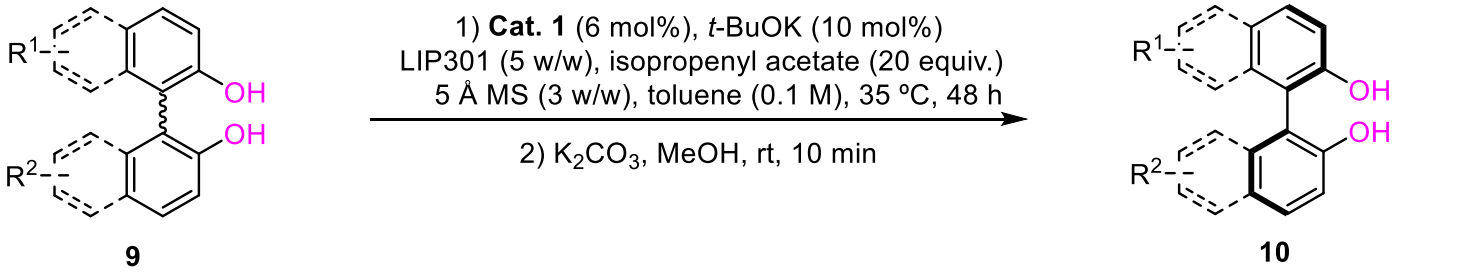


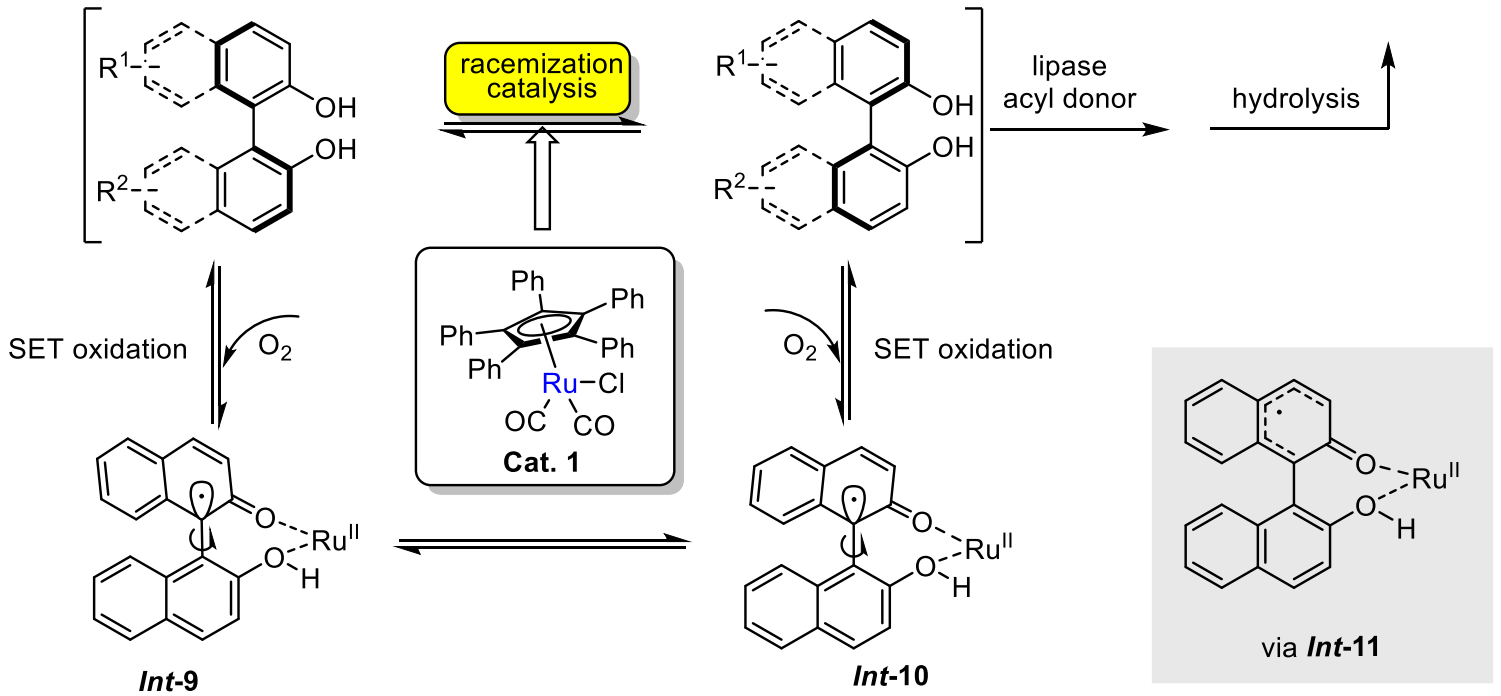


Pappo, D., et al. *Org. Lett.* **2024**, *26*, 2129−2134.

2.1 DKR of Atropisomeric Biarenols via a Radical Intermediate

➢ Chemoenzymatic DKR of Bisnaphthols by Dual Catalysis of Ruthenium and Lipase

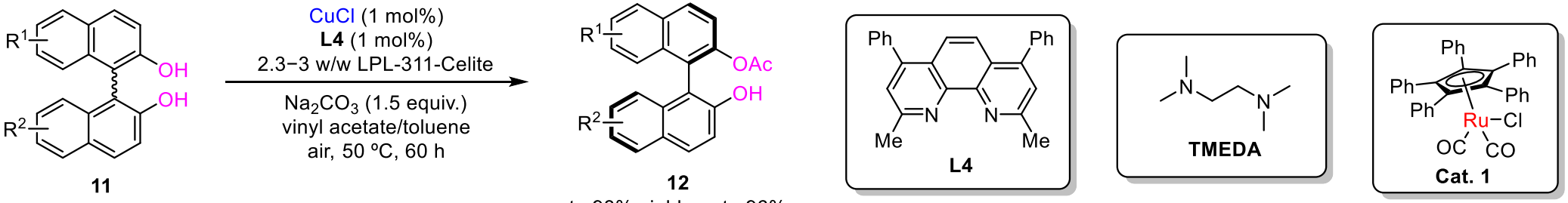


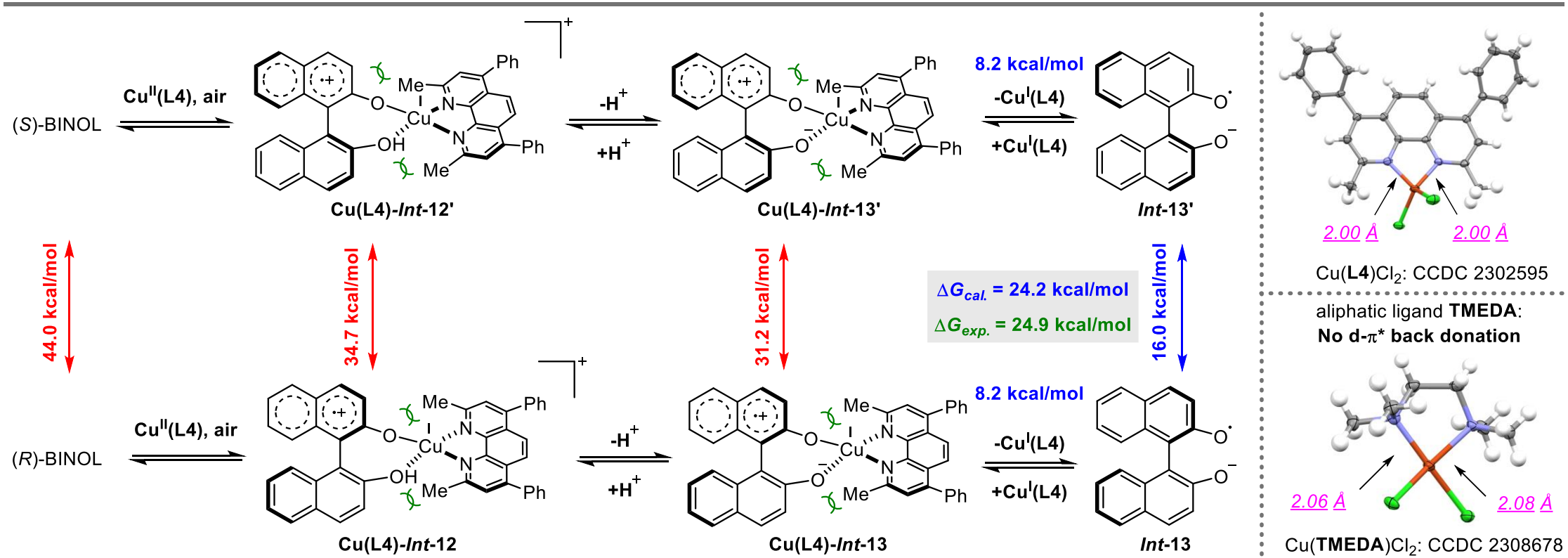


Akai, S., et al. *Angew. Chem. Int. Ed.* **2018**, *57*, 10278−10282.

2.1 DKR of Atropisomeric Biarenols via a Radical Intermediate

➢ Copper/Lipase-Cocatalyzed DKR of Atropisomeric Bisnaphthols Using a Neutral and Reliable Ligand





Cu(**L4**)Cl_2: CCDC 2302595

aliphatic ligand **TMEDA**:
No d-π* back donation

Cu(**TMEDA**)Cl_2: CCDC 2308678

L4 offers π* orbitals allowing additional metal-to-ligand d-π* back-donation to enhance coordination effects between the ligand and metal.

Zhu, C., et al. *ACS Cent. Sci.* **2024**, *10*, 2099−2110.

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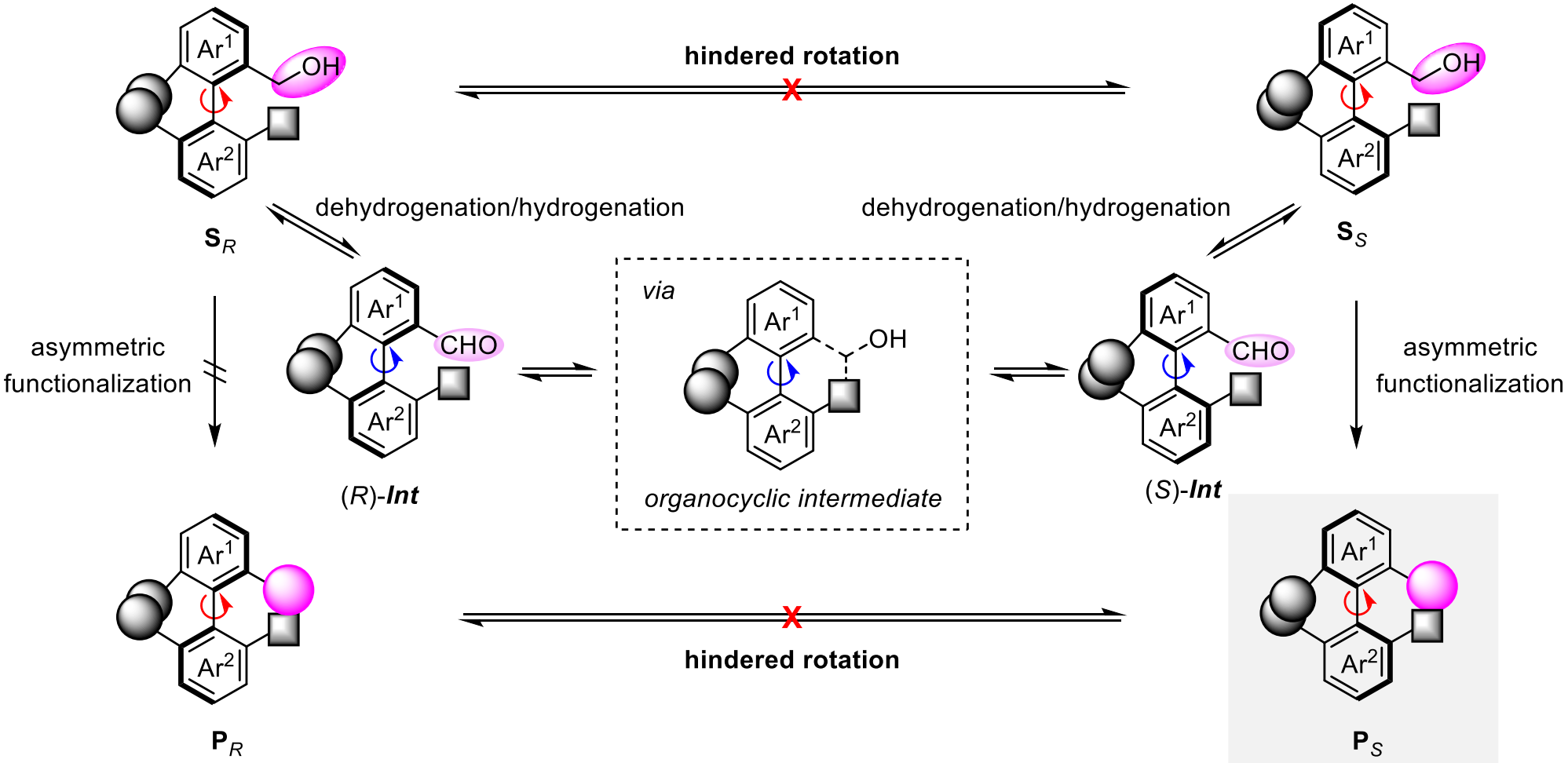
2.2 DKR of Atropisomeric Biaryls via a Transient Organocyclic Intermediate

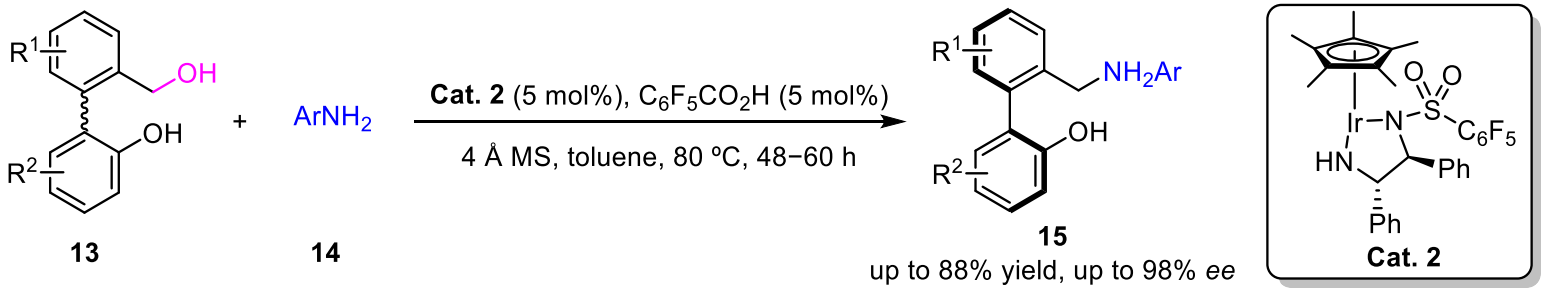
➢ **DKR of Benzylic Alcohols Bearing a Rotation-Hindered Aromatic Substituent at the *ortho* Position**

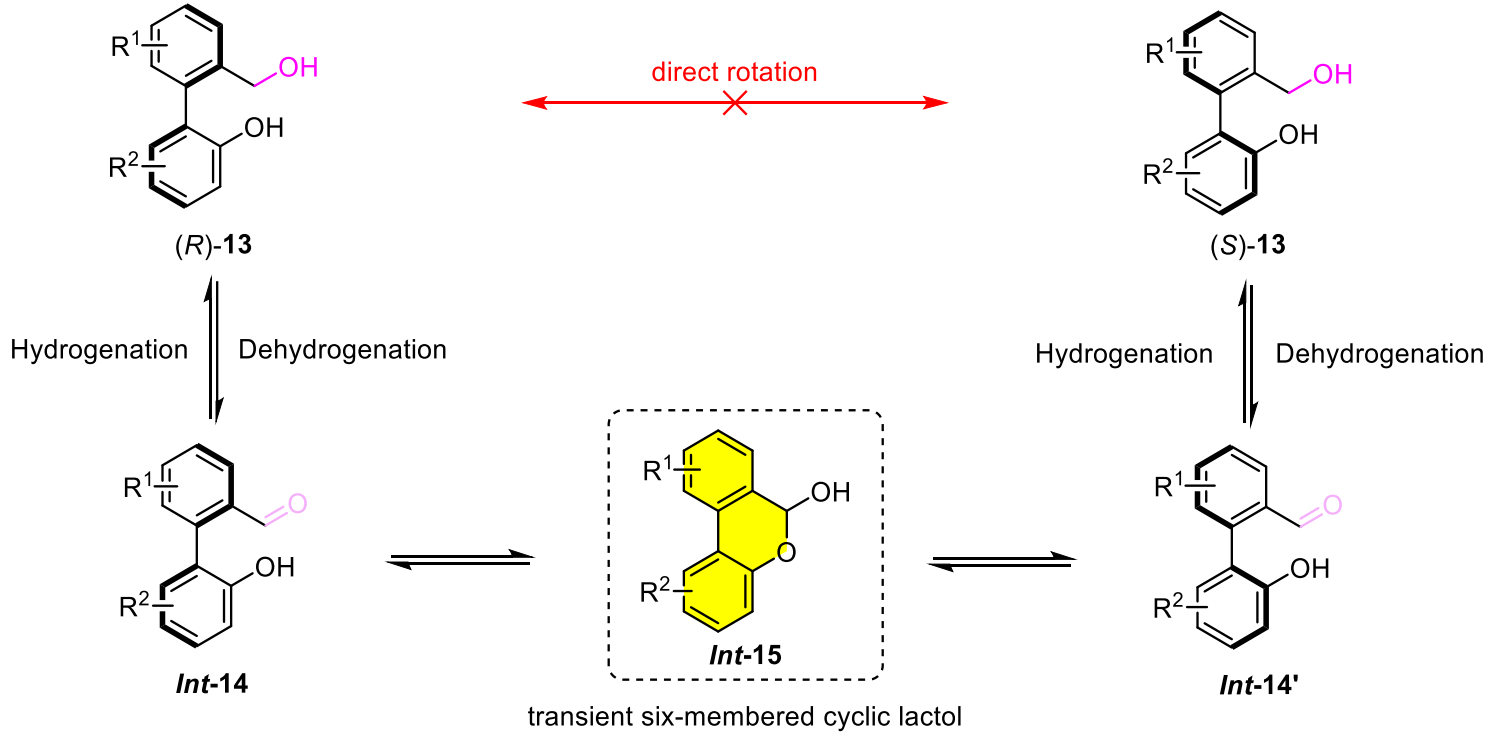


- By forming a fused transient cycle, the dihedral in a biaryl skeleton was able to be decreased facilitating its axial rotation.
- The locked cycle with torsional tension generated by the steric hindrance force can promote a ring-opening reaction.

2.2 DKR of Atropisomeric Biaryls via a Transient Organocyclic Intermediate

➢ DKR of Phenol-Benzylic Alcohols via a Transient Organocyclic Intermediate





Wang, J., et al. *Angew. Chem. Int. Ed.* **2018**, *57*, 465−469.

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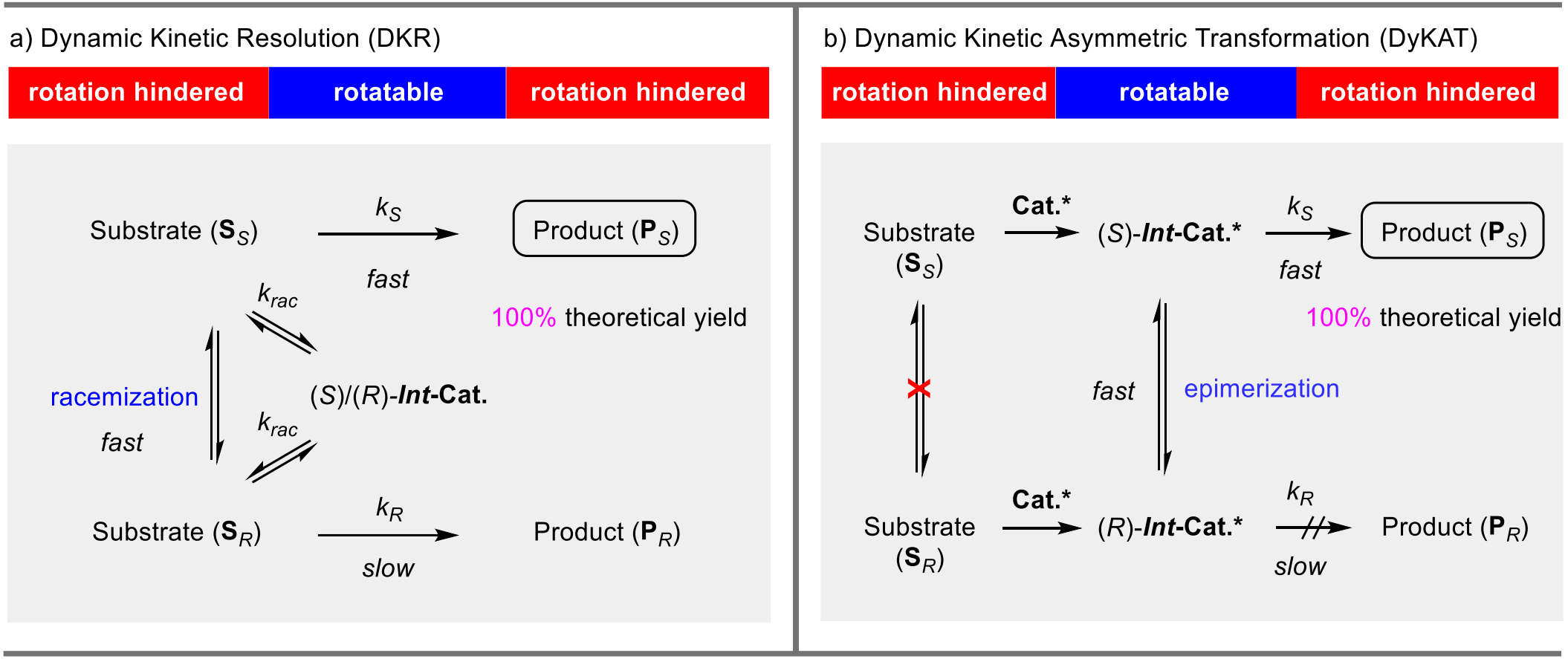
3. DyKAT of Atropisomeric Biaryls

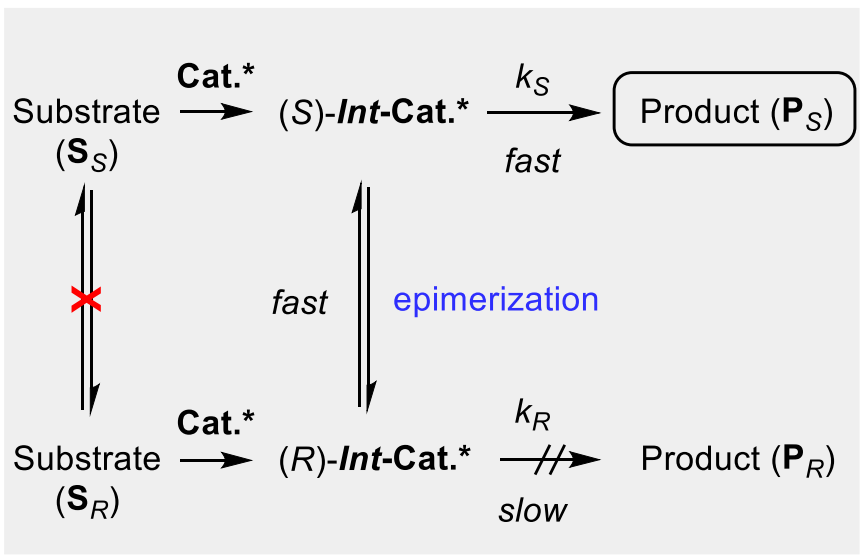
➢ Dynamic Kinetic Asymmetric Transformation (DyKAT)

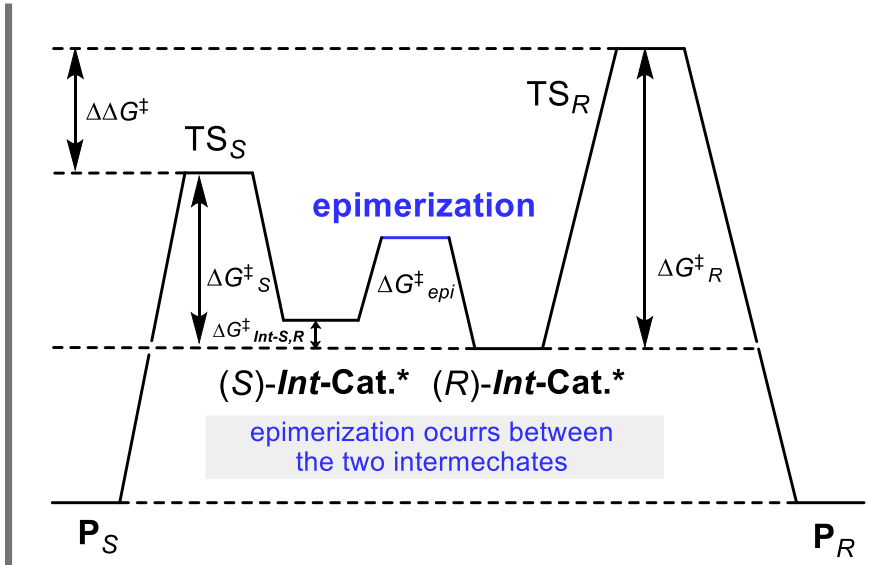


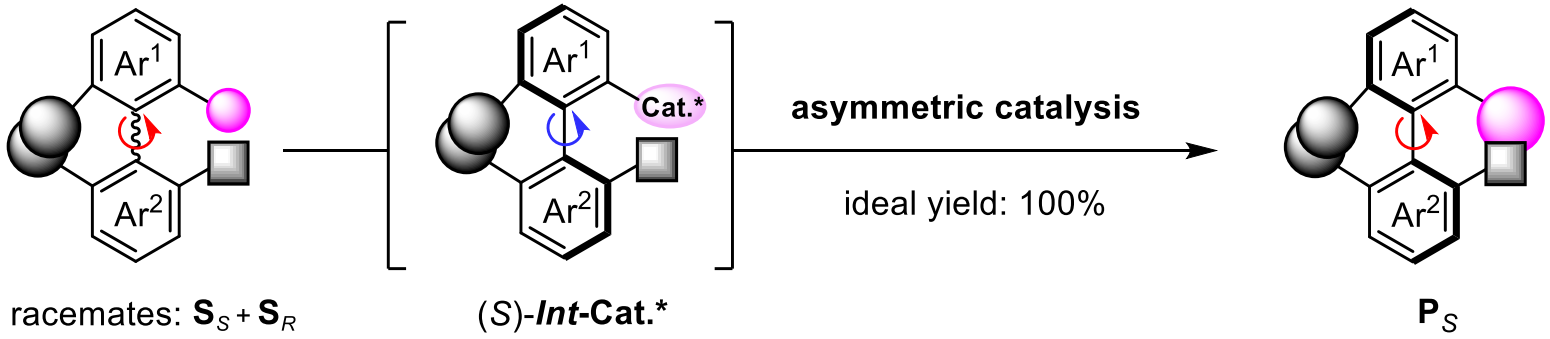
- DKR employs continuous racemization of the substrate in a mechanism that is independent of the asymmetric catalyst.
- DyKAT is generally realized by one catalytic system, which is not only responsible for erasing the original enantioenrichment, but also has to control the enantioselectivity in latter functionalization step.

Stoltz, B. M., et al. *Chem. Rev.* **2017**, *117*, 4528−4561. Narayan, A. R. H., et al. *Chem. Rev.* **2023**, *123*, 10641−10727.

3. DyKAT of Atropisomeric Biaryls



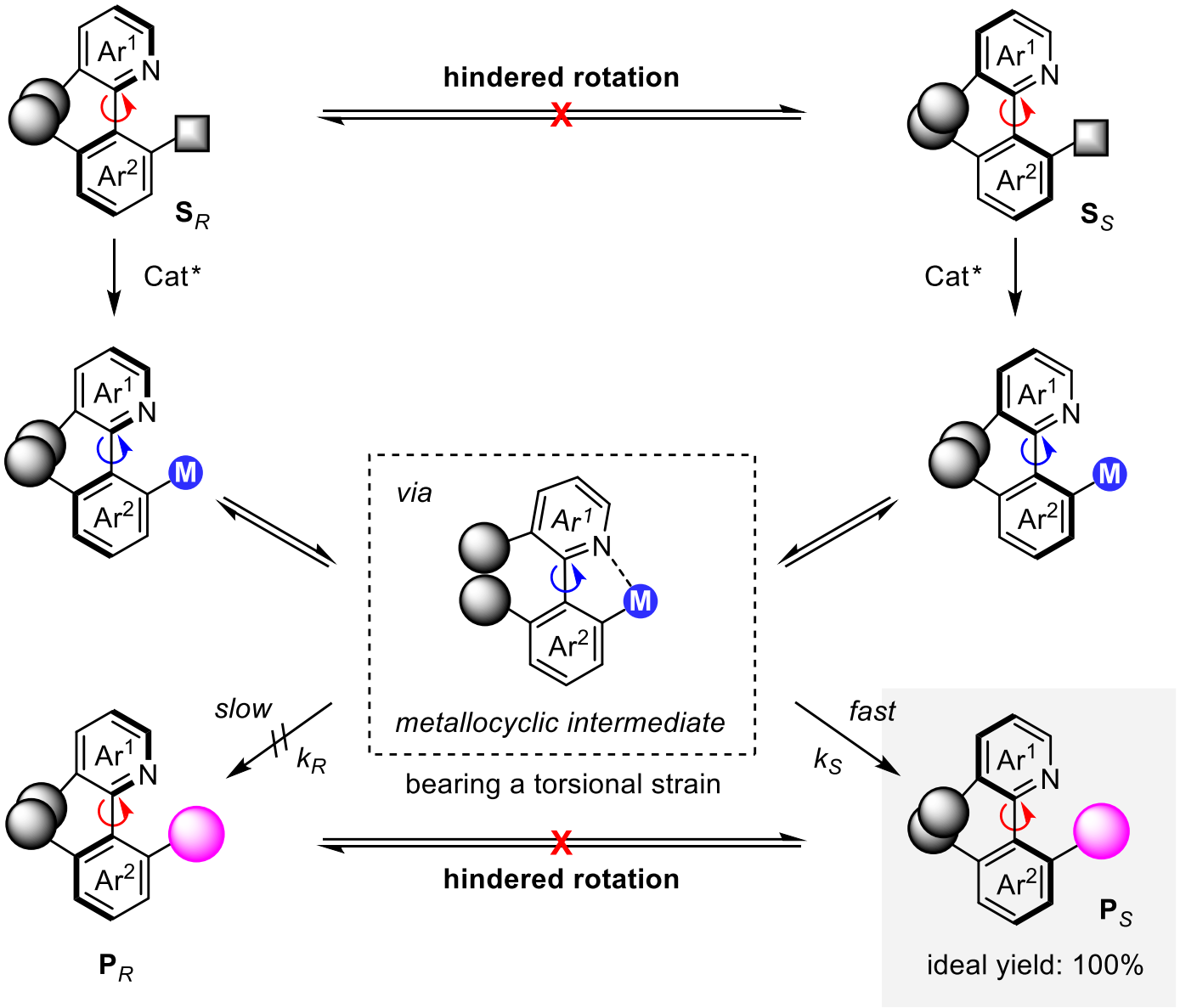




- Substrates react with the chiral catalyst to deliver two diastereomeric intermediates to trigger the epimerization;
- Matched intermediates can be enriched, and subsequently functionalized to deliver the chiral products.

Content

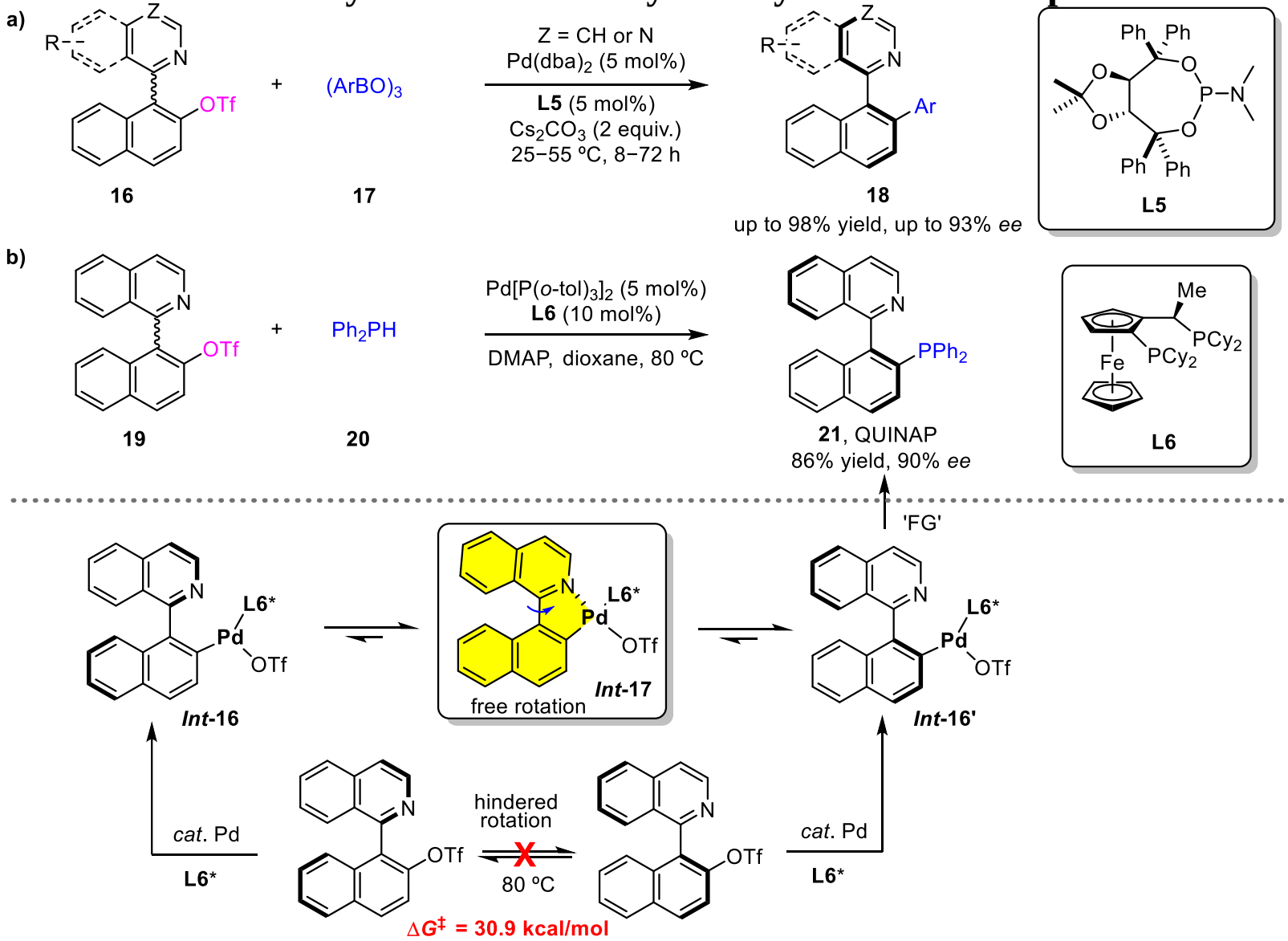
3.1 DyKAT of Atropisomeric Heterobiaryls via a Metallocyclic Intermediate



- Rely on the coordination of a nitrogen atom from the substrate to the transition metal

3.1 DyKAT of Atropisomeric Heterobiaryls via a Metallocyclic Intermediate

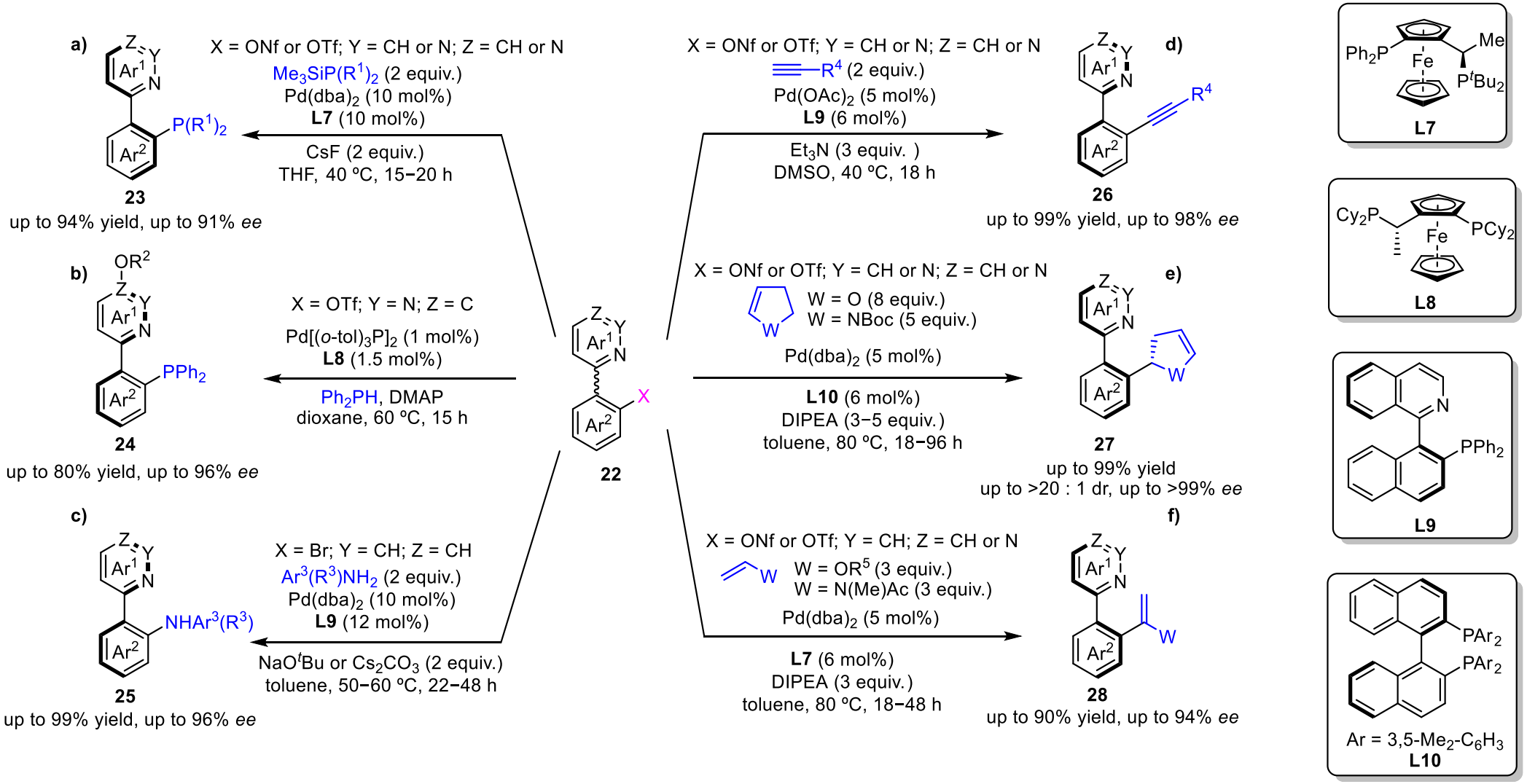
➢ DyKAT of QUINOL Triflates Enabled by Palladium-Catalyzed Arylation and Phosphination



Lassaletta, J. M., et al. *J. Am. Chem. Soc.* **2013**, *135*, 15730−15733. Virgil, S. C., et al. *J. Am. Chem. Soc.* **2013**, *135*, 16829−16832.

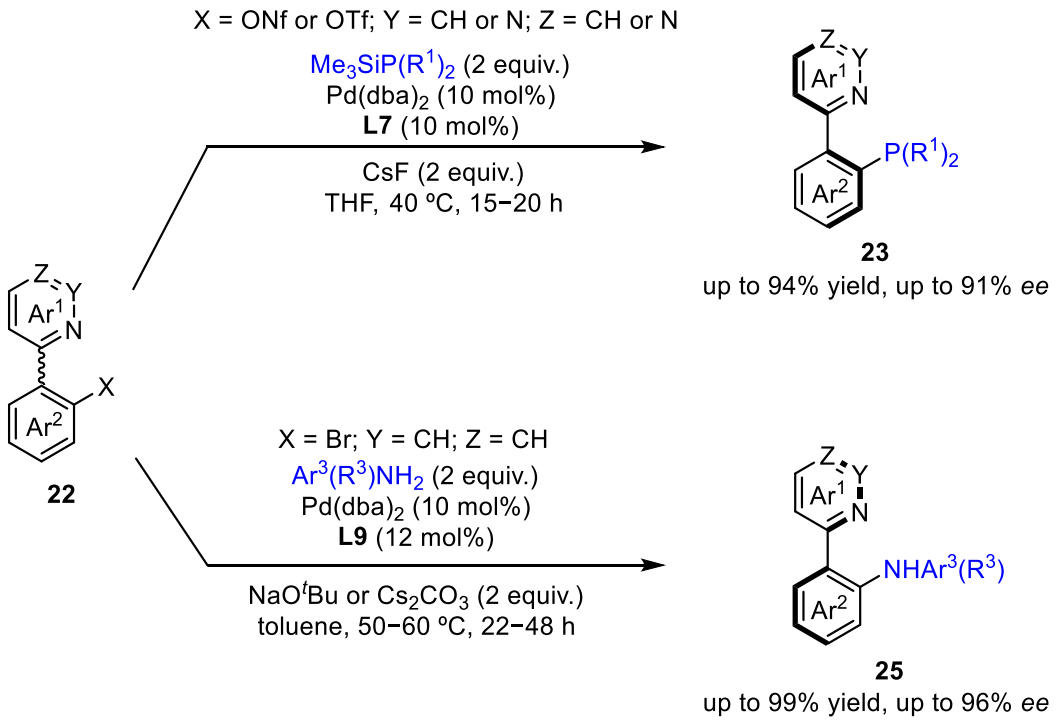
3.1 DyKAT of Atropisomeric Heterobiaryls via a Metallocyclic Intermediate

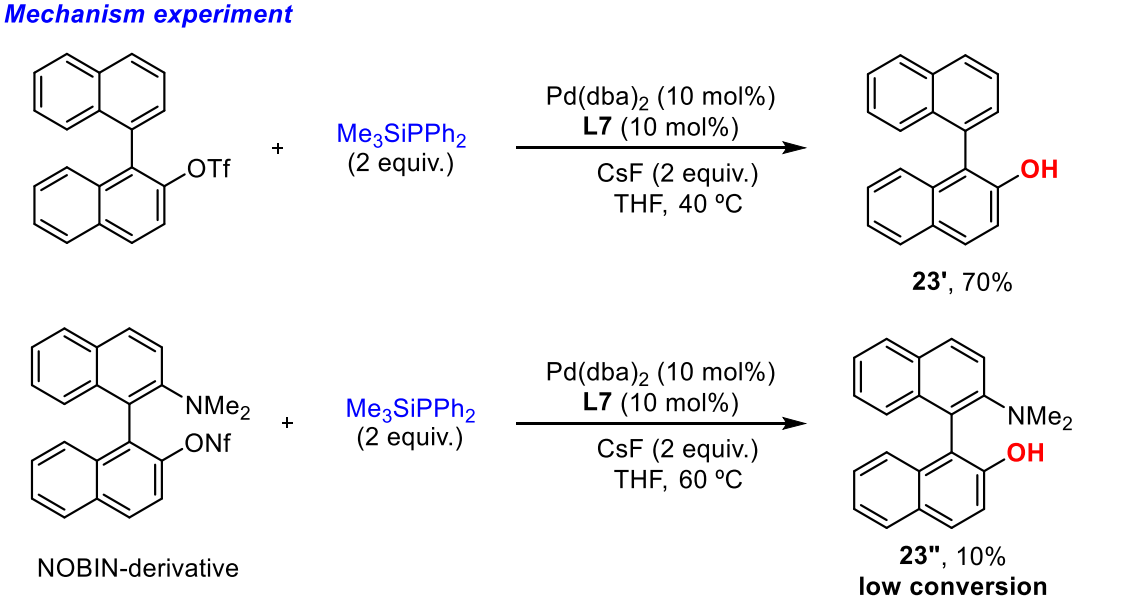
➢ Palladium-Catalyzed DyKAT Reactions for the Synthesis of Functionalized Axially Chiral Heterobiaryls

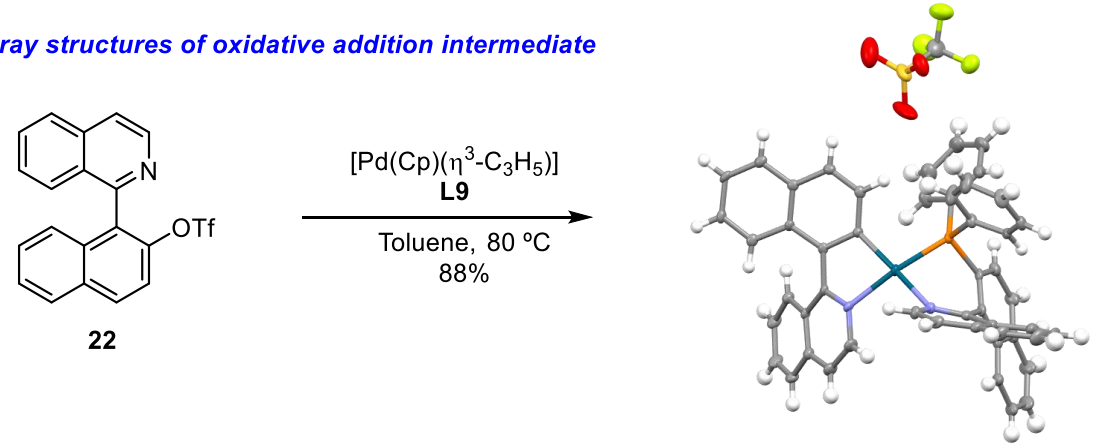


Lassaletta, J. M., et al. *ACS Catal.* **2016**, *6*, 3955−3964. Lassaletta, J. M., et al. *J. Am. Chem. Soc.* **2016**, *138*, 12053−12056.
Lassaletta, J. M., et al. *Chem. Commun.* **2016**, *52*, 14121−14124. Lassaletta, J. M., et al. *J. Am. Chem. Soc*. **2018**, *140*, 11067−11075.
Virgil, S. C., et al. *Adv. Synth. Catal.* **2019**, *361*, 441−444. Lassaletta, J. M., et al. *Org. Lett.* **2022**, *24*, 3812−3816.

3.1 DyKAT of Atropisomeric Heterobiaryls via a Metallocyclic Intermediate





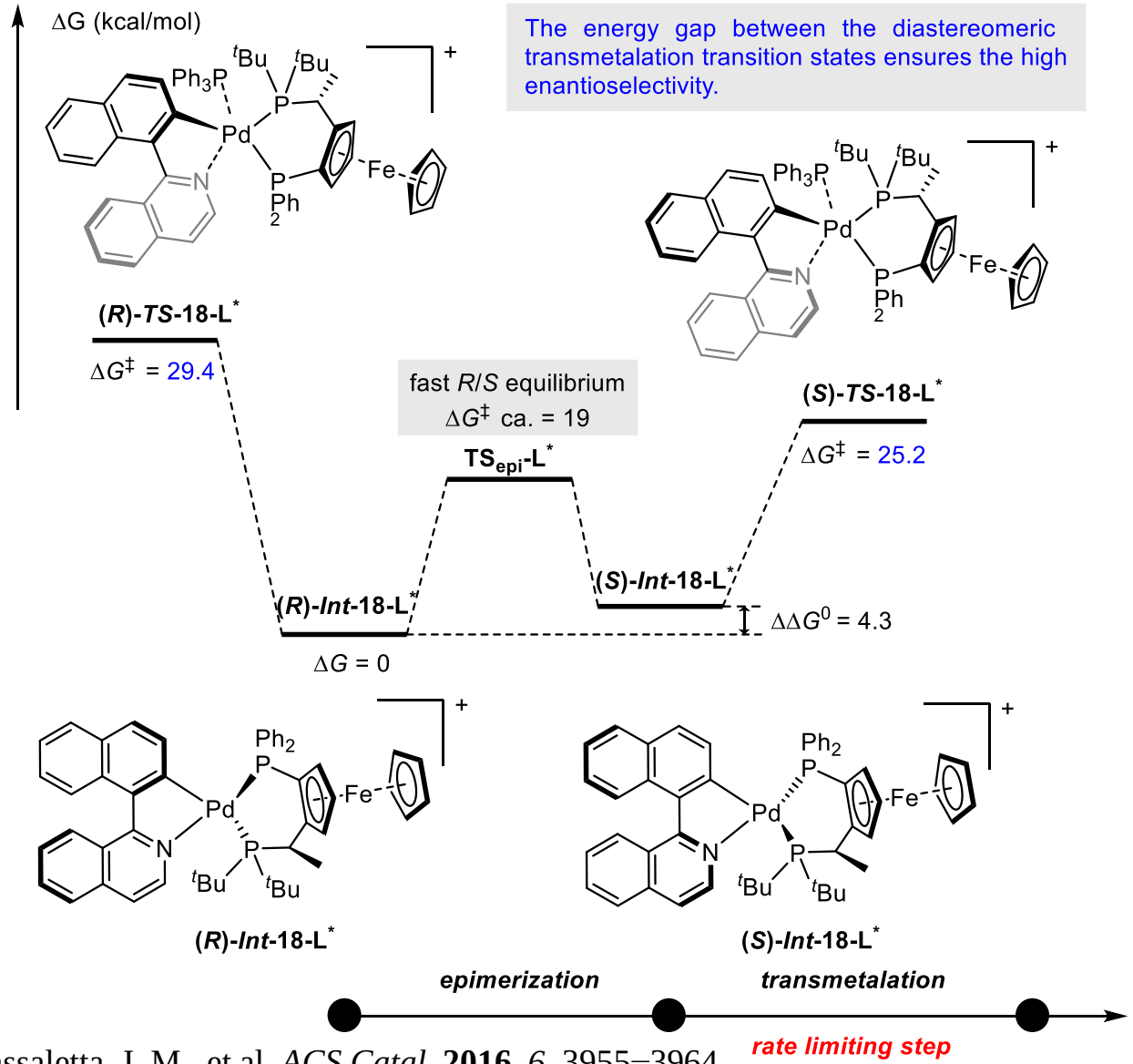


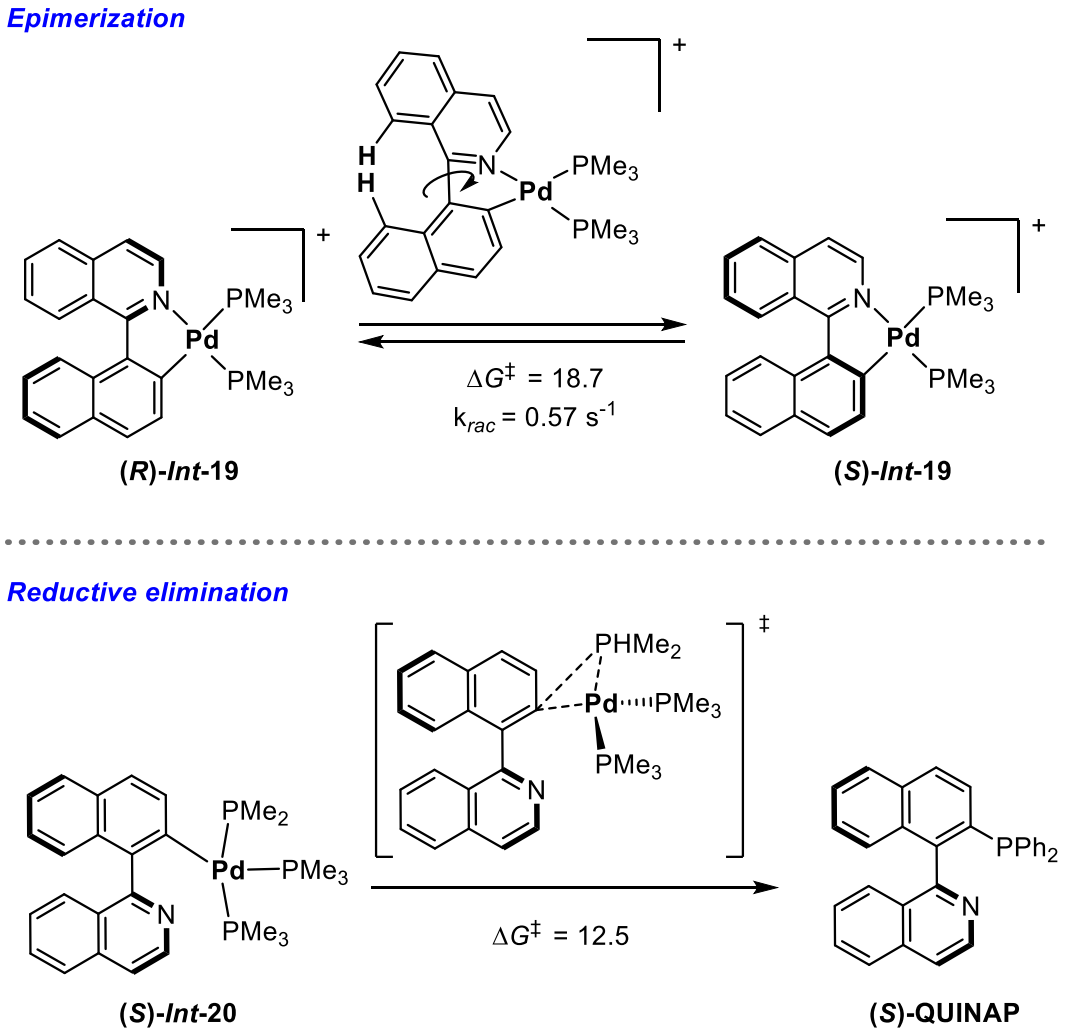
- The presence of a coordinating nitrogen is not only necessary to favor the formation of the cationic and configurationally labile palladacycle but also to facilitate the chelate-assisted oxidative addition of the racemic substrate to the Pd center.

Lassaletta, J. M., et al. *ACS Catal.* **2016**, *6*, 3955−3964. Lassaletta, J. M., et al. *J. Am. Chem. Soc.* **2016**, *138*, 12053−12056.

3.1 DyKAT of Atropisomeric Heterobiaryls via a Metallocyclic Intermediate

➢ DFT Calculations

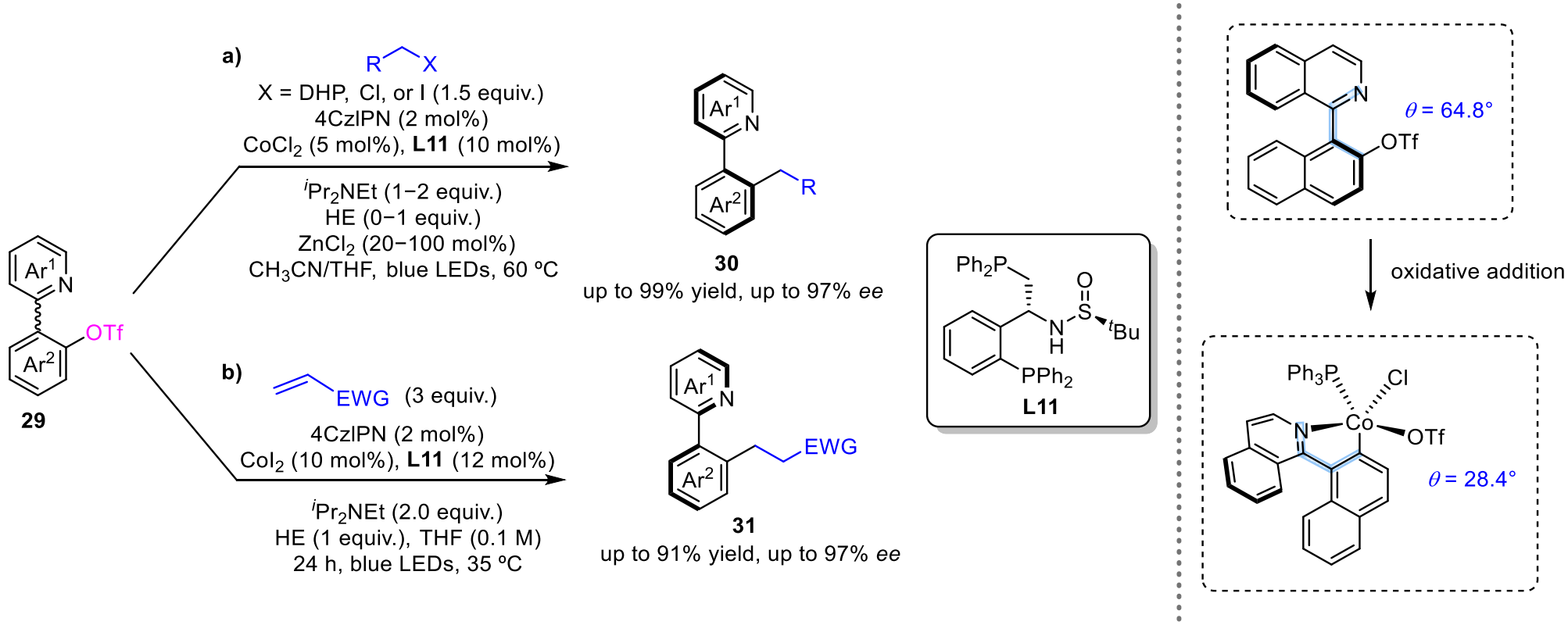




Lassaletta, J. M., et al. *ACS Catal.* **2016**, *6*, 3955−3964.

3.1 DyKAT of Atropisomeric Heterobiaryls via a Metallocyclic Intermediate

➢ Photoredox/Cobalt-Cocatalyzed Dynamic Kinetic Asymmetric Alkylation of Heterobiaryls

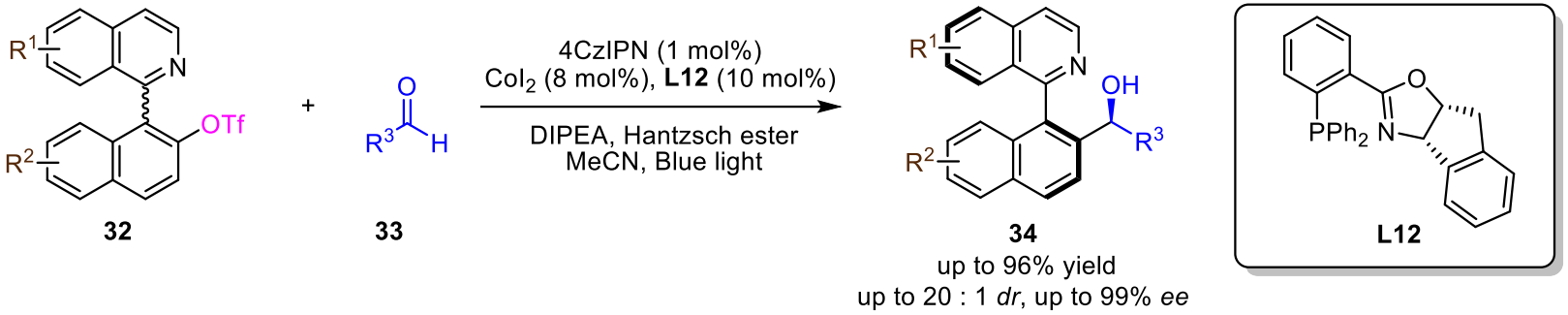


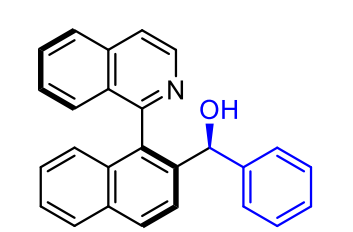
■ The significant geometric change reduces the group repulsion from the two aromatic rings during the C−C axis rotation process, thereby reducing the rotational energy barrier.

Xiao, W.-J., et al. *Nat. Catal.* **2022**, *5*, 788−797. Xiao, W.-J., et al. *J. Am. Chem. Soc.* **2023**, *145*, 7983−7991.

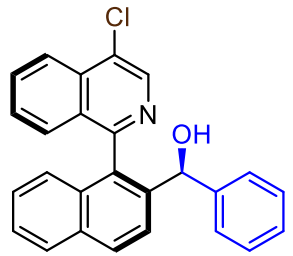
3.1 DyKAT of Atropisomeric Heterobiaryls via a Metallocyclic Intermediate

➢ Photoredox/Cobalt-Cocatalyzed Dynamic Kinetic Asymmetric Grignard-Type Addition Reaction

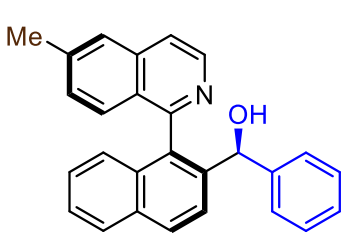




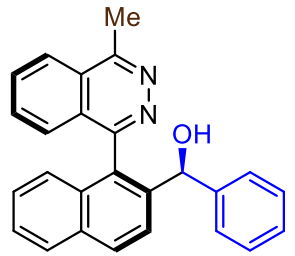
34a
94% yield, 95% *ee*



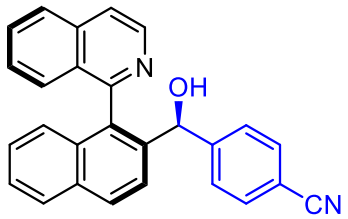
34b
90% yield, 86% *ee*



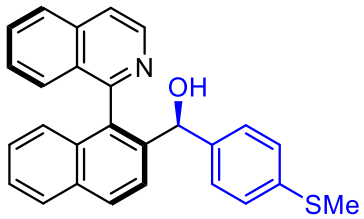
34c
82% yield, 94% *ee*



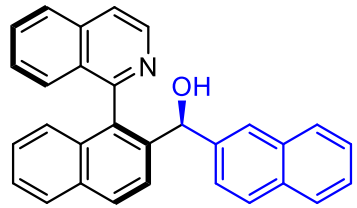
34d
94% yield, 99% *ee*



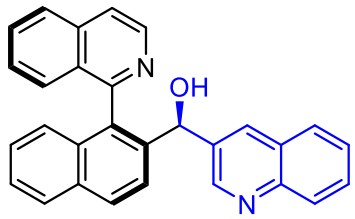
34e
94% yield, 96% *ee*



34f
96% yield, 96% *ee*



34g
94% yield, 95% *ee*

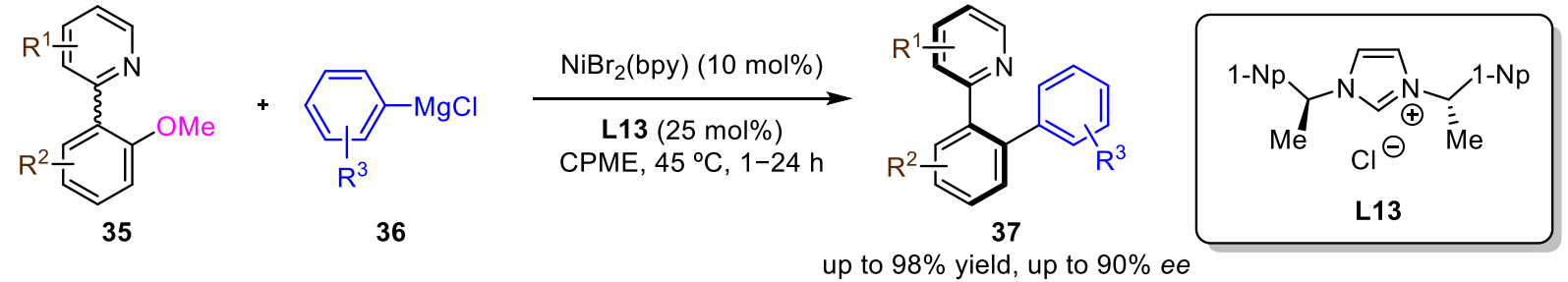


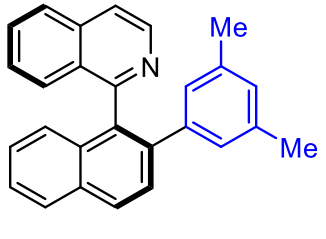
34h
75% yield, 94% *ee*

Liang, Y.-M., et al. *ACS Catal.* **2025**, *15*, 1147−1157. Wang, C., et al. *Org. Lett.* **2025**, *27*, 2897−2901.

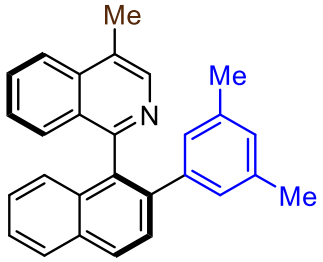
3.1 DyKAT of Atropisomeric Heterobiaryls via a Metallocyclic Intermediate

➢ Nickel-Catalyzed Dynamic Kinetic Asymmetric Arylation of Anisoles

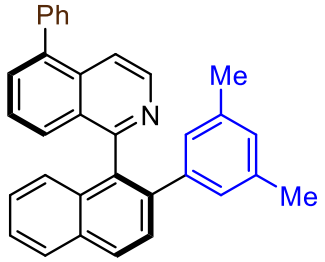




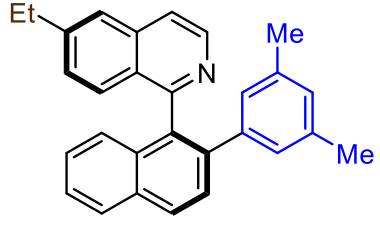
37a
88% yield, 88% *ee*



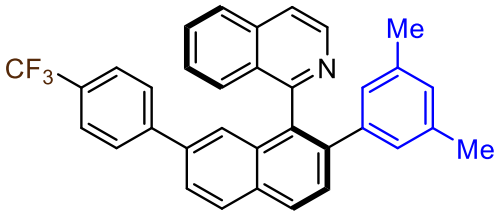
37b
98% yield, 84% *ee*



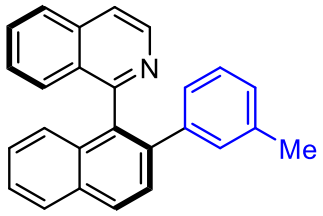
37c
83% yield, 85% *ee*



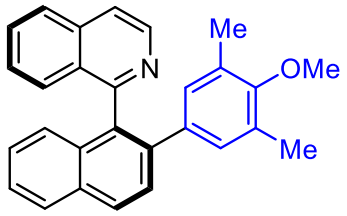
37d
98% yield, 88% *ee*



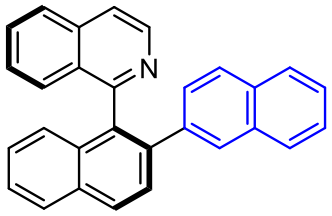
37e
74% yield, 90% *ee*



37f
88% yield, 80% *ee*



37g
81% yield, 81% *ee*

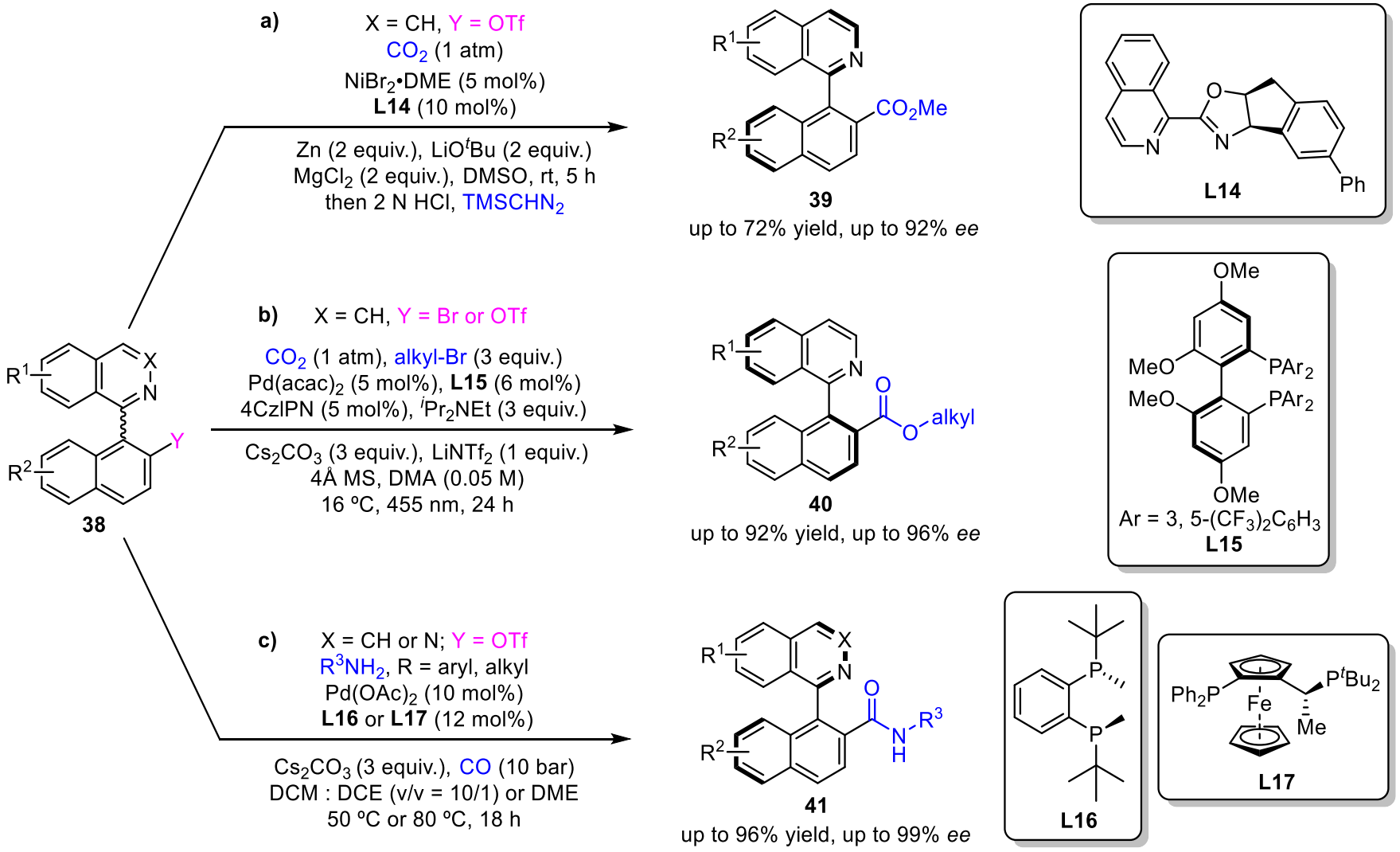


37h
54% yield, 78% *ee*

Cao, Z.-C., et al. *J. Am. Chem. Soc.* **2023**, *145*, 15721−15728.

3.1 DyKAT of Atropisomeric Heterobiaryls via a Metallocyclic Intermediate

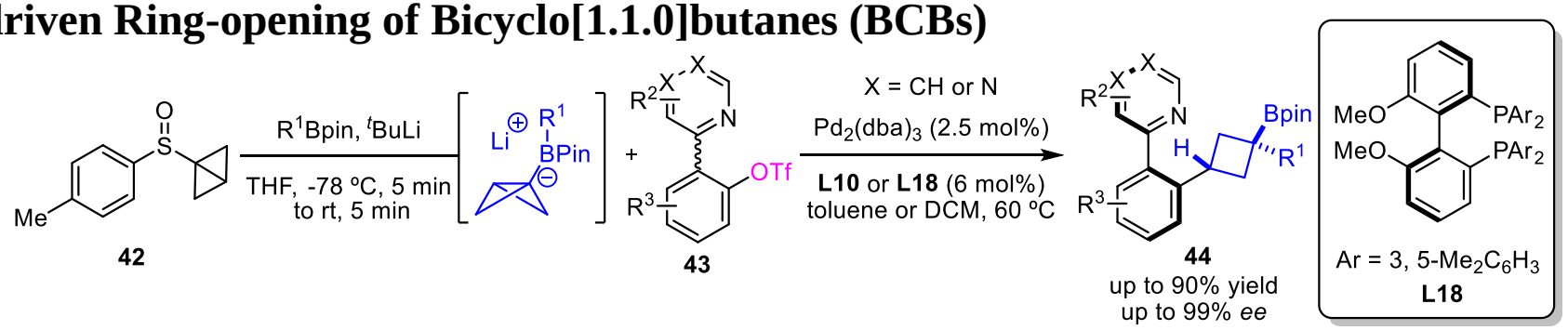
➢ Nickel/Palladium-Catalyzed Dynamic Kinetic Asymmetric Carboxylation and Aminocarbonylation

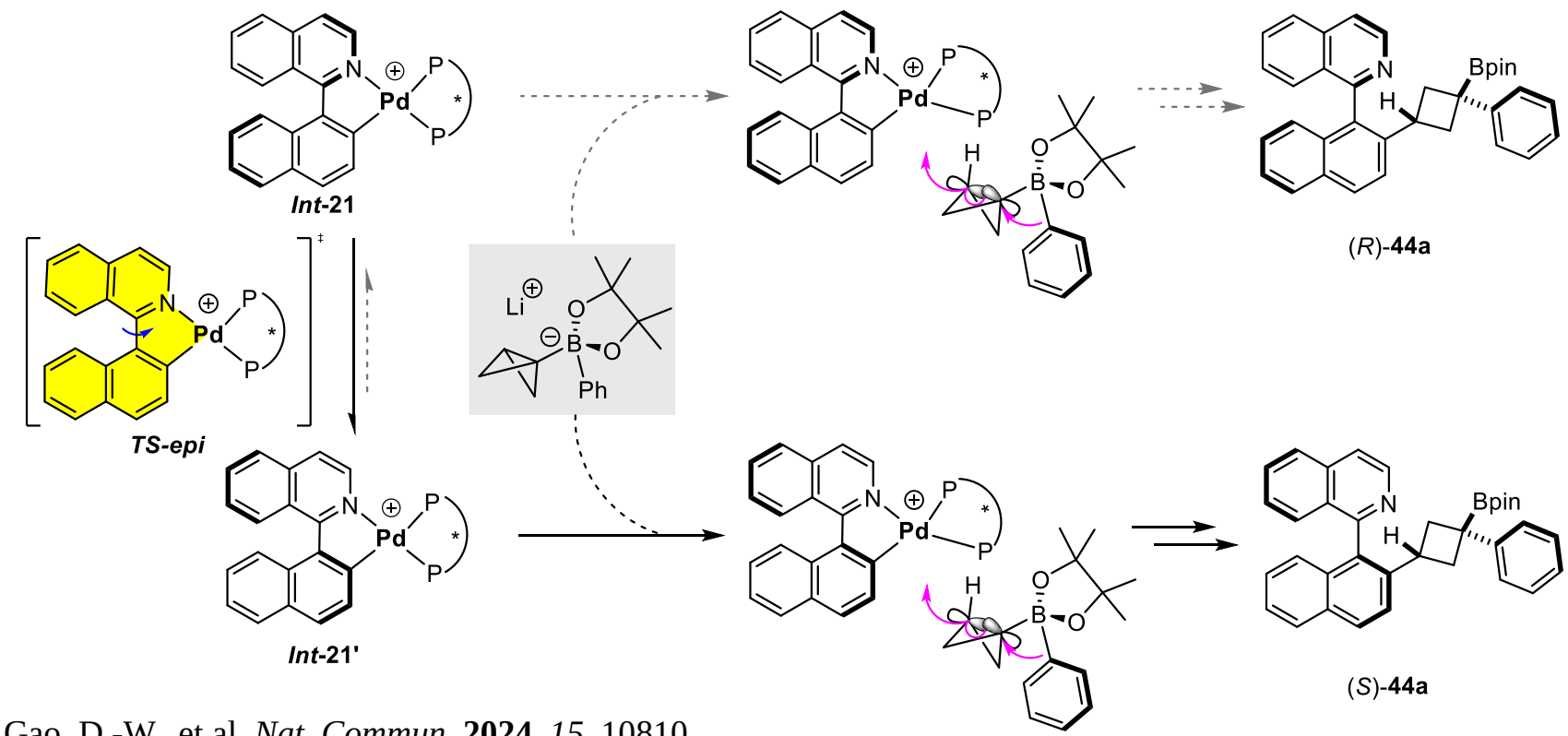


Yu, D.-G., et al. *Angew. Chem. Int. Ed.* **2024**, *63*, e202403401. Liu, J., et al. *Nat. Commun.* **2024**, *15*, 7248.
Liu, J., et al. *Angew. Chem. Int. Ed.* **2025**, *64*, e202413949.

3.1 DyKAT of Atropisomeric Heterobiaryls via a Metallocyclic Intermediate

➢ **Palladium-Catalyzed Construction of Atropisomers by Combining the DyKAT of *N*-Heterobiaryl Triflates with Strain-release-driven Ring-opening of Bicyclo[1.1.0]butanes (BCBs)**

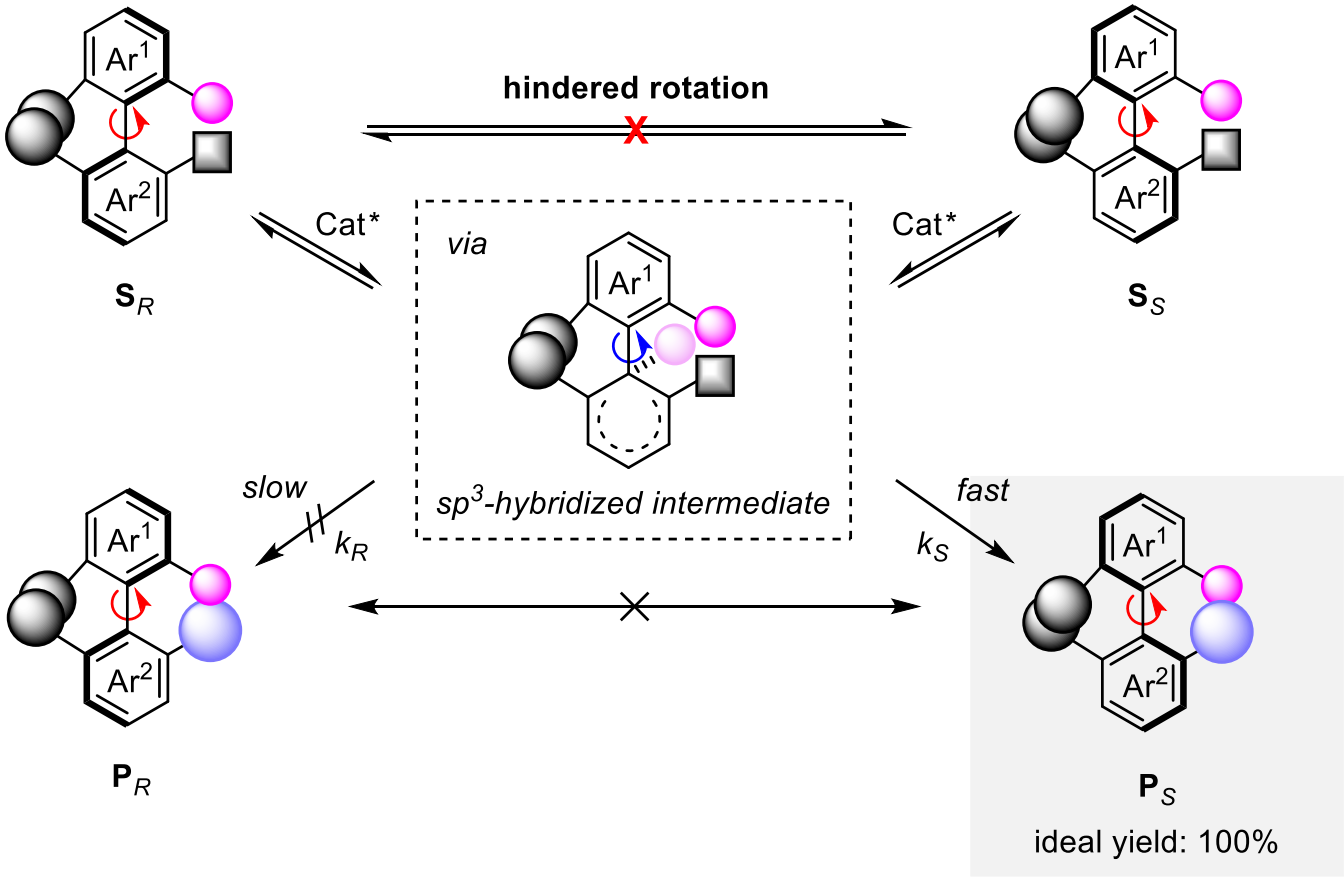




Gao, D.-W., et al. *Nat. Commun.* **2024**, *15*, 10810.

Content

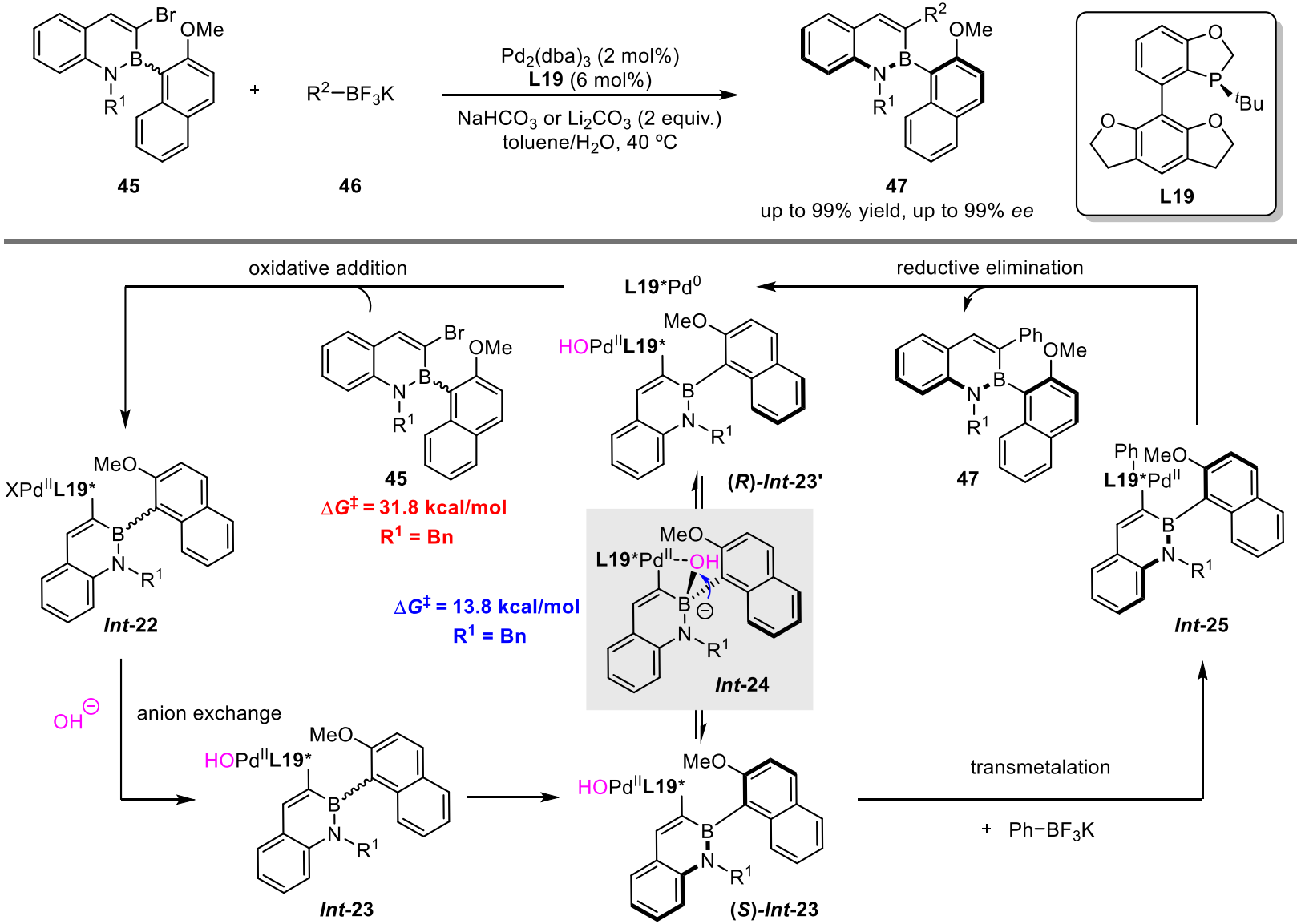
3.2 DyKAT of Atropisomeric Biaryls by Forming a sp^3-Hybridized Intermediate



- By reversibly changing the hybridization state of the axial atom in the diastereomeric intermediates from sp ²to sp ³, rapid interconversion of the diastereomeric intermediates is achieved.

3.2 DyKAT of Atropisomeric Biaryls by Forming a sp^3-Hybridized Intermediate

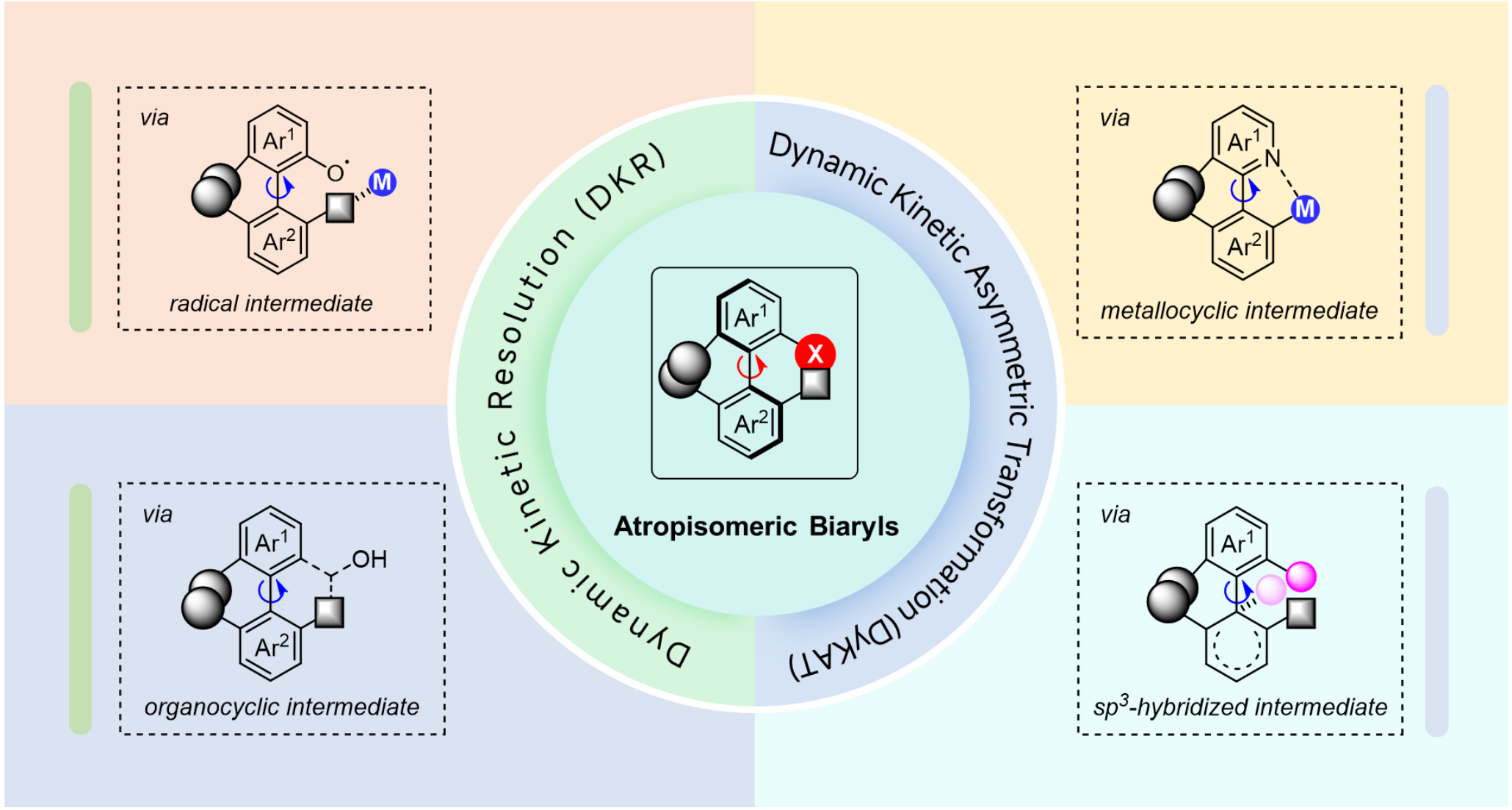
➢ Palladium-Catalyzed Dynamic Kinetic Asymmetric Suzuki-Miyaura Coupling Reactions of C–B Axially Chiral Biaryls



Song, Q., et al. *Nat. Commun.* **2023**, *14*, 4438.

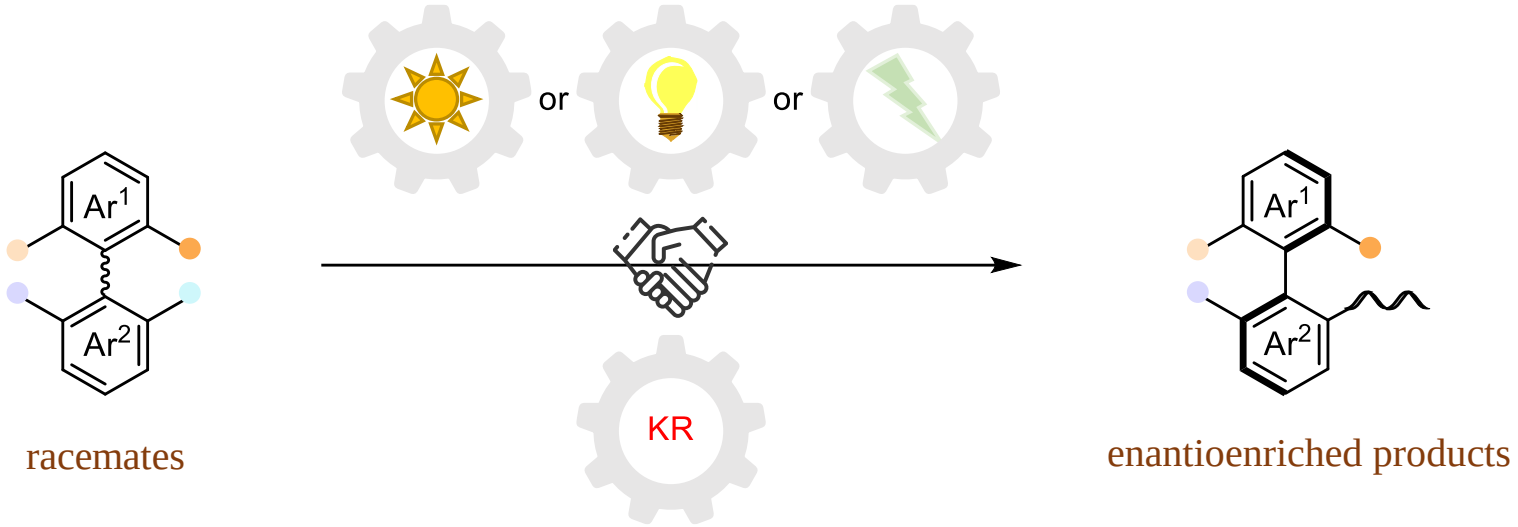
Content

4. Conclusions and Outlook

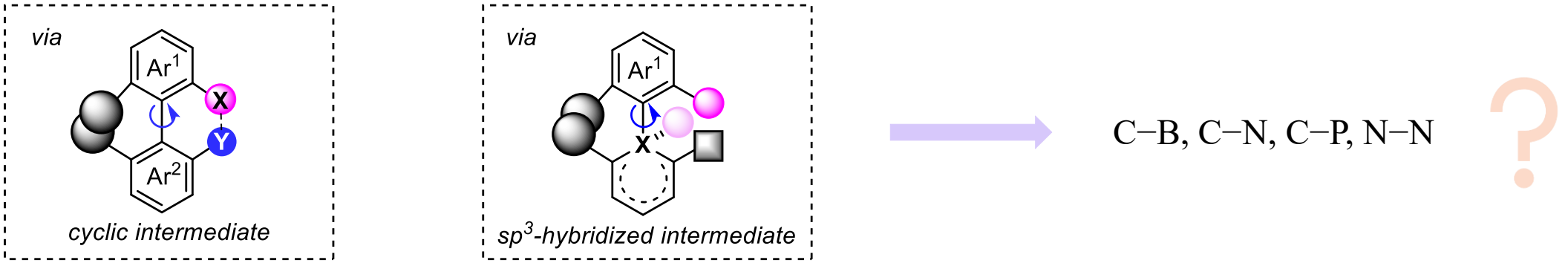


4. Conclusions and Outlook

➢ Developing New Racemization Strategies for DKR



➢ Designing New Intermediates for DyKAT



- Exploit covalent or non-covalent interactions
- Change the hybridization state

Thank you!