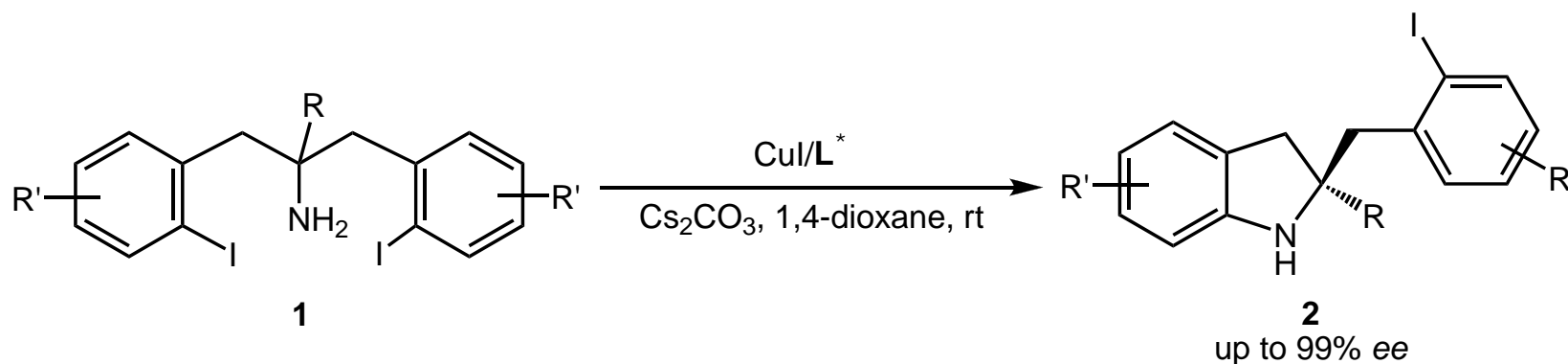


Literature Report

Copper-Catalyzed Desymmetric Intramolecular Ullmann C–N Coupling: An Enantioselective Preparation of Indolines

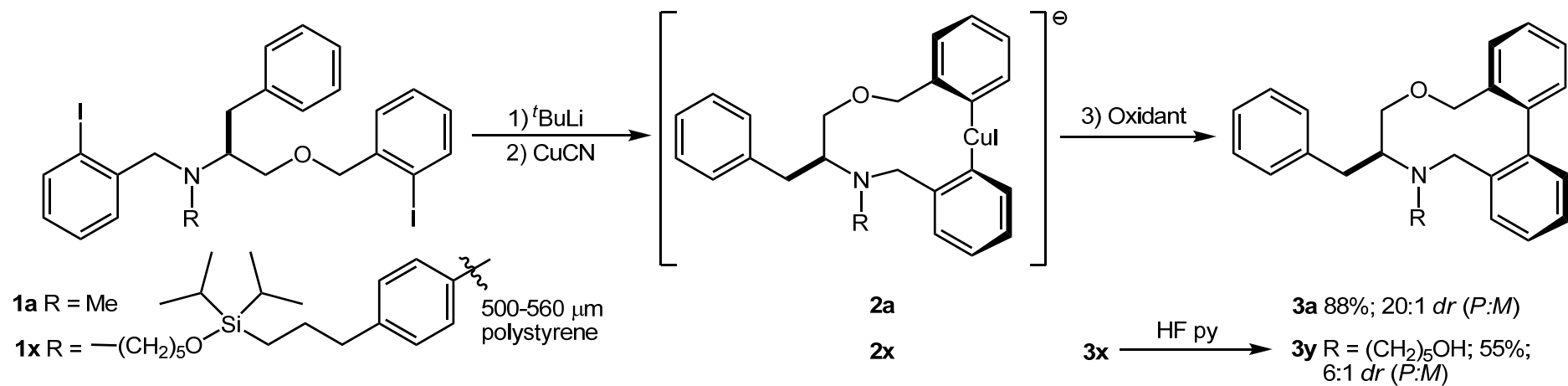


Cai, Q. *et al* *J. Am. Chem. Soc.* **2012**, *134*, 14326-14329.

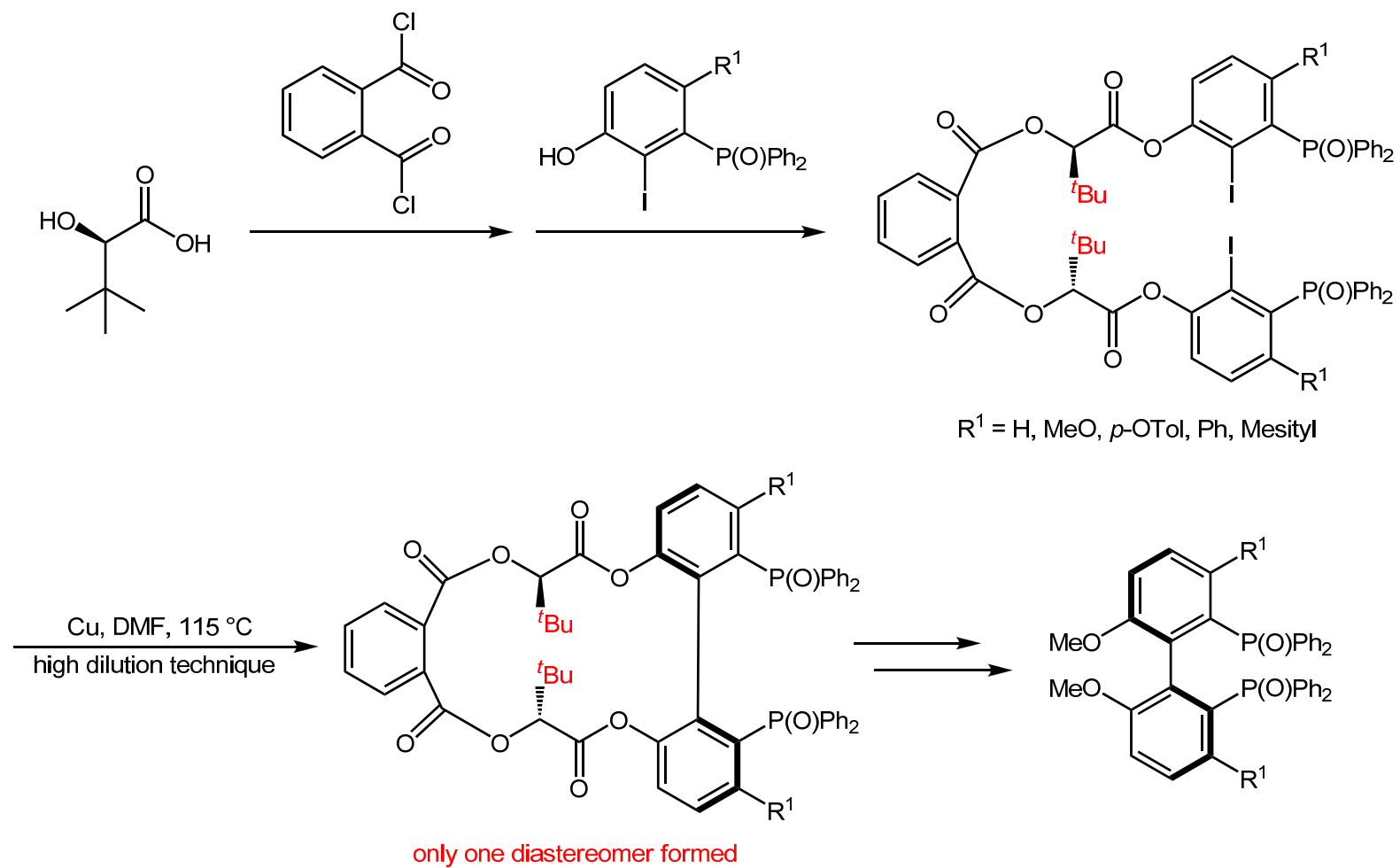
Reporter: Wen-Xue Huang

Checker: Ying Duan

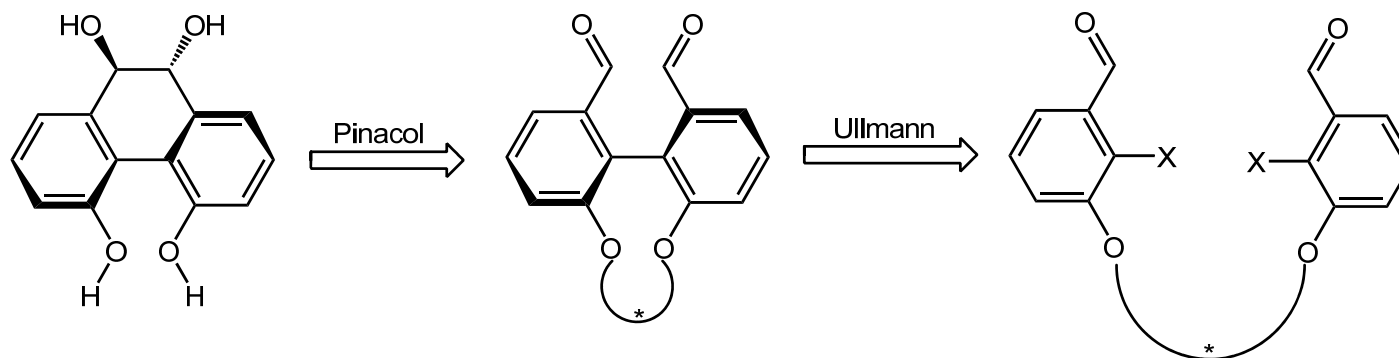
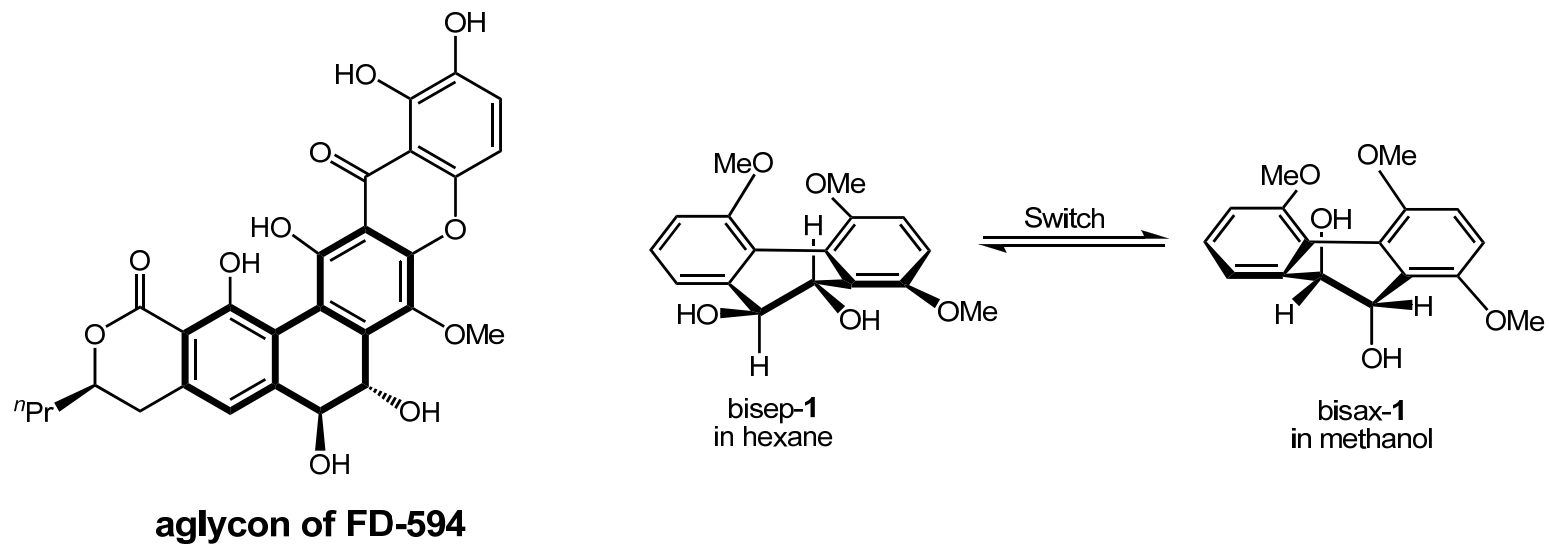
Asymmetric Ullmann-type Coupling Reactions



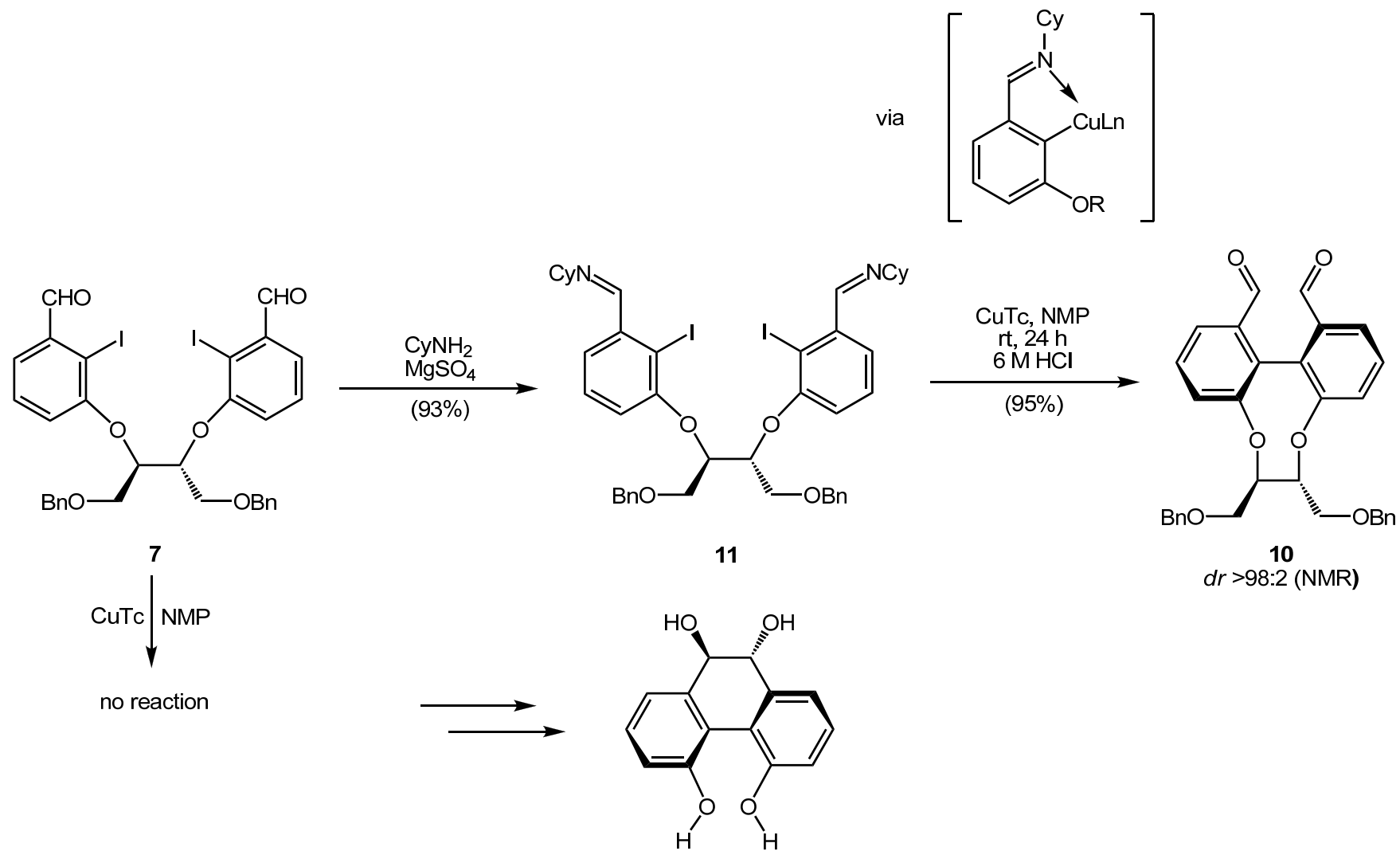
Schreiber, S. L. *et al* *J. Am. Chem. Soc.* **2000**, *122*, 5656-5657.



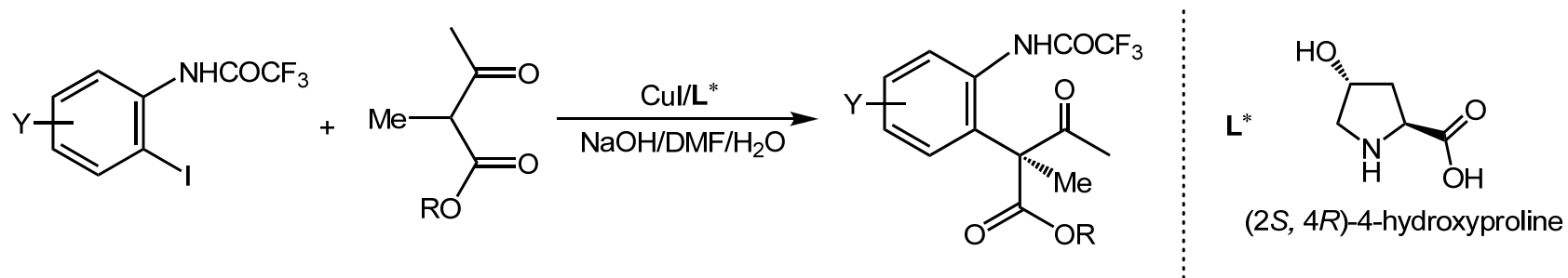
Keay, B. A. *et al Org. Lett.* **2006**, 8, 1483-1485.



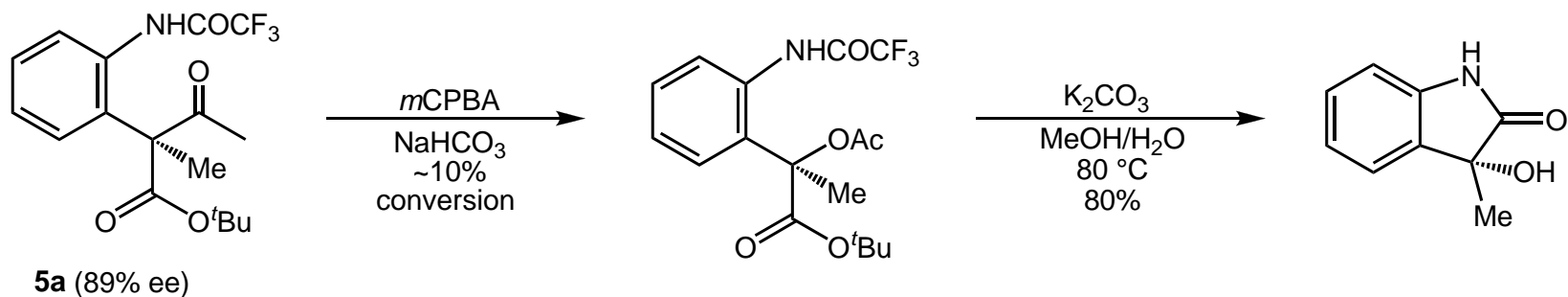
Breit, B. *et al Eur. J. Org. Chem.* **2007**, 5726-5733.



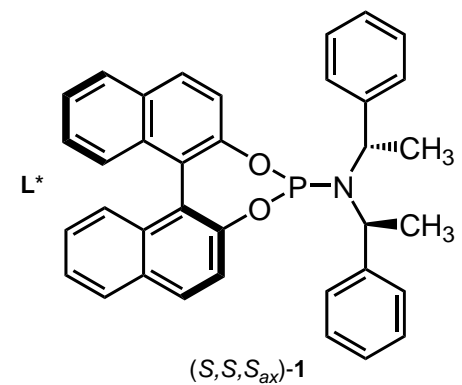
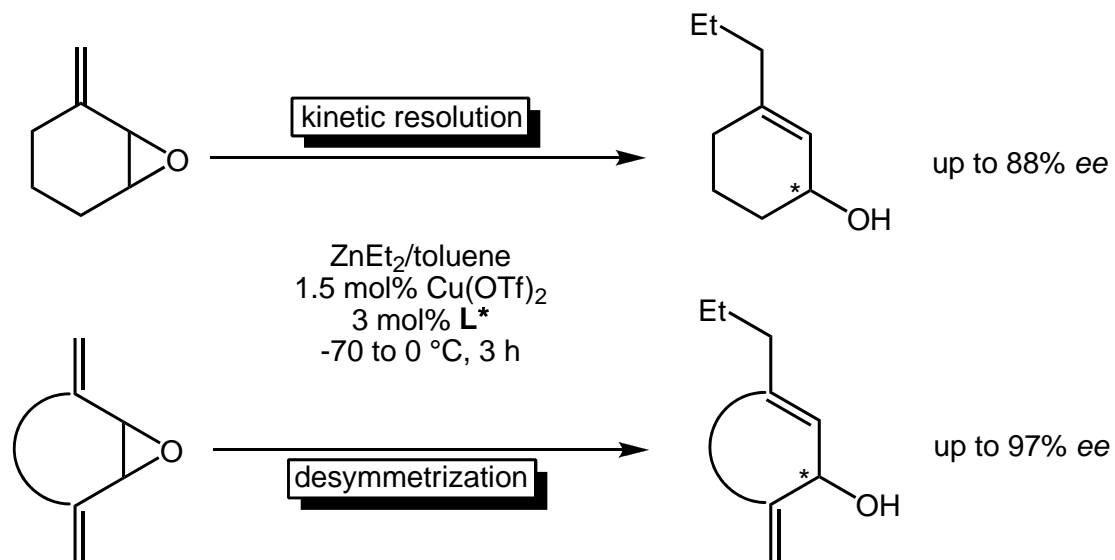
Breit, B. *et al Eur. J. Org. Chem.* **2007**, 5726-5733.



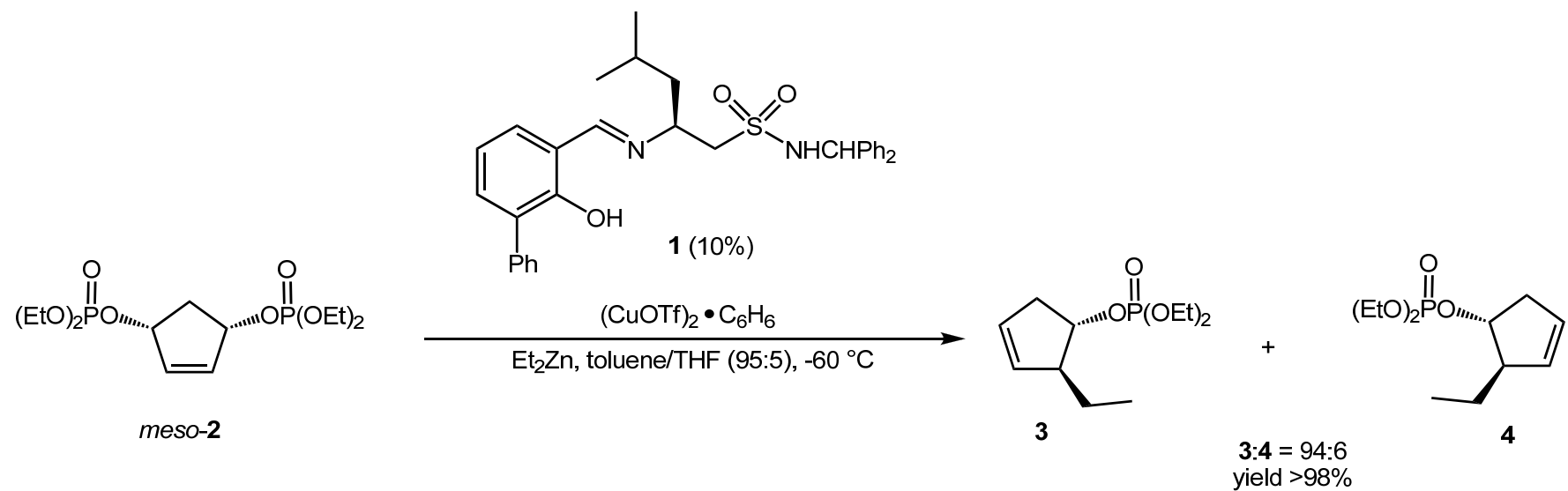
Coupling occurred smoothly at $-20\text{ }^\circ\text{C}$ or even at $-45\text{ }^\circ\text{C}$. This represents the lowest reaction temperature for Ullmann-type reactions so far.



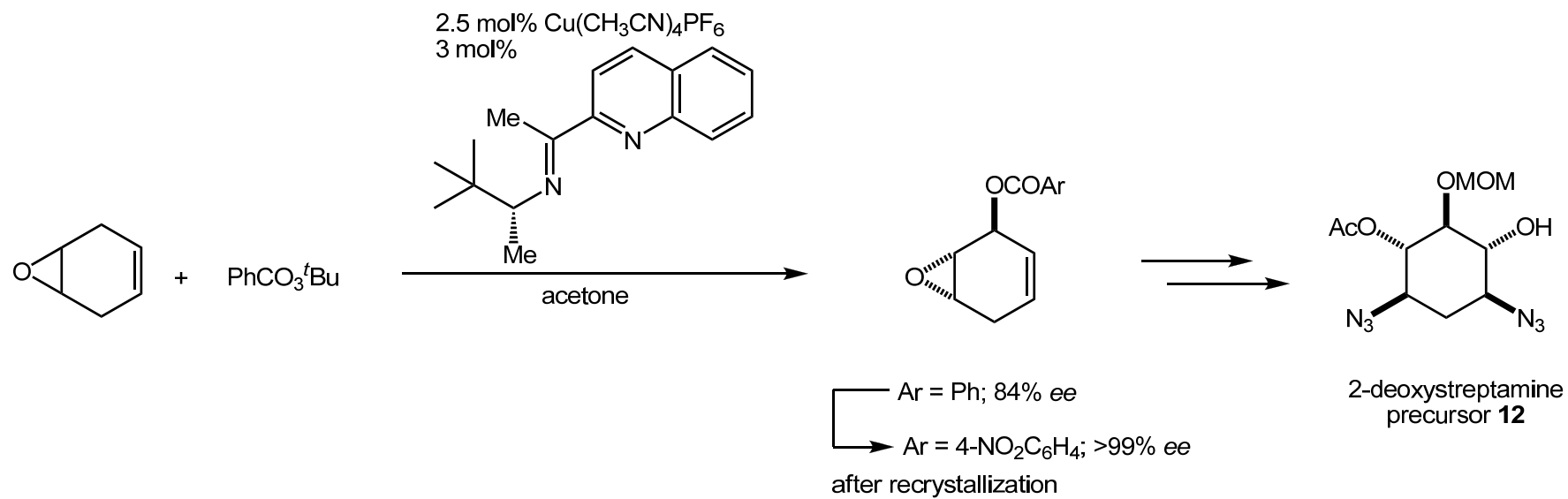
Examples of Copper-Catalyzed Asymmetric Desymmetrization Reactions



Pineschi, M. *et al Org. Lett.* **2000**, 2, 933-936.

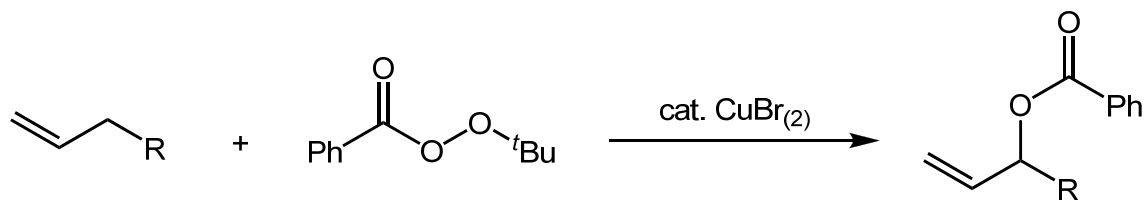


Piarulli, U. *et al* *Angew. Chem. Int. Ed.* **2003**, 42, 234-236.



Hayashi, M. *et al Org. Lett.* **2009**, *11*, 3314-3317.

The Kharasch-Sosnovsky Reaction



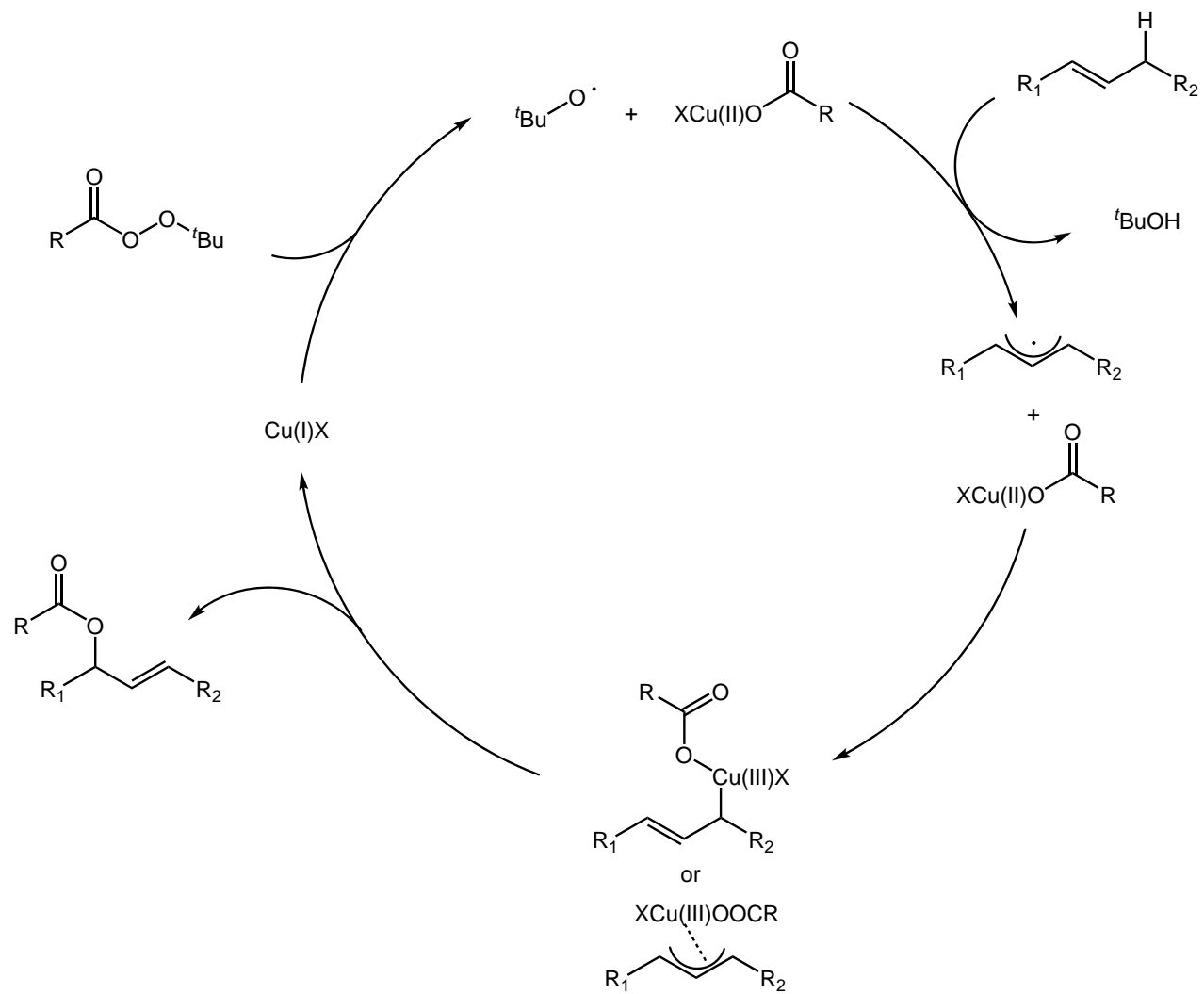
Either Cu(I) or Cu(II) may be used

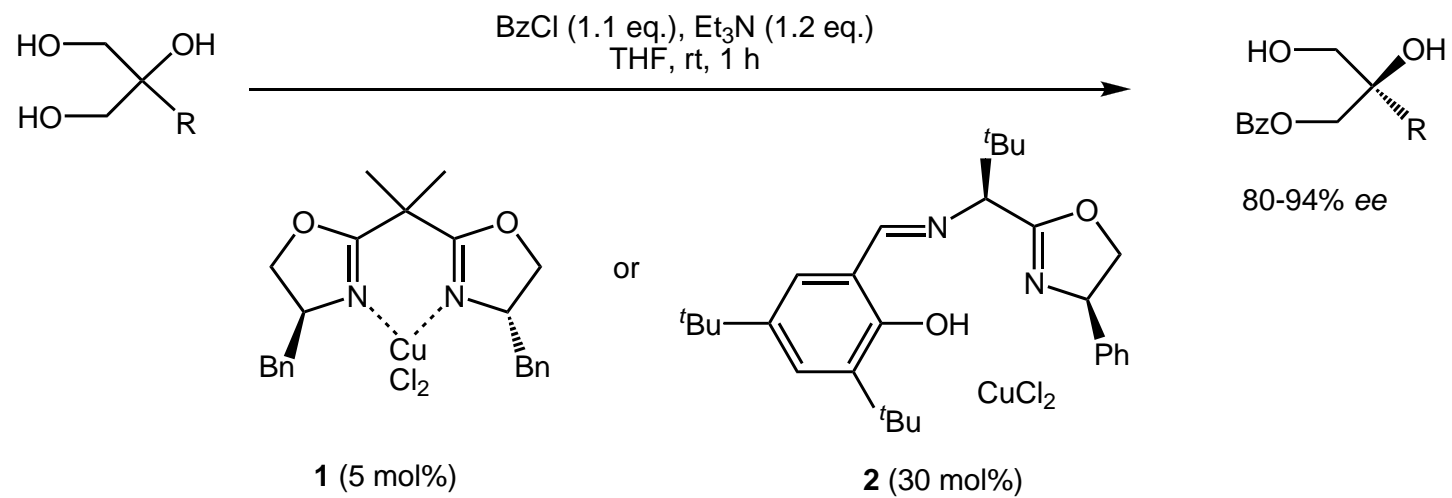
Terminal olefin products predominate from terminal or internal olefin reactants

Peroxides may also be used as the oxidant

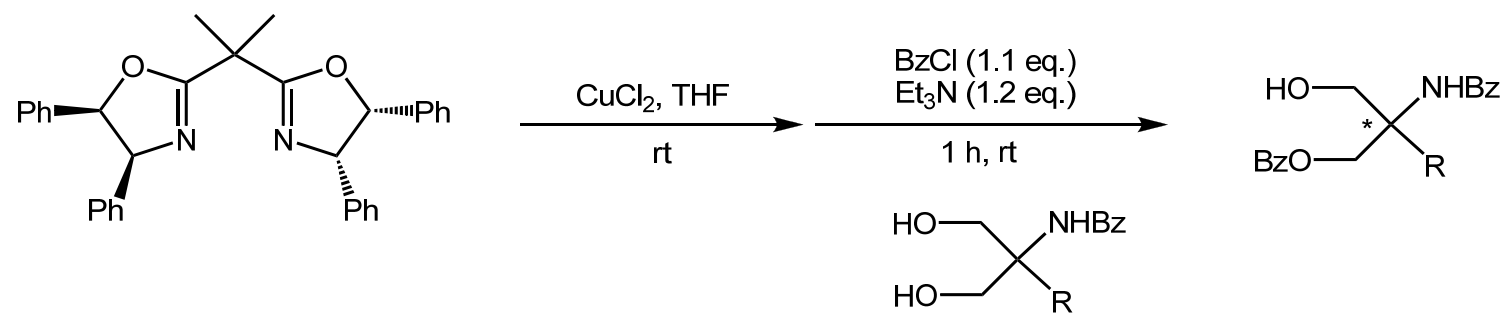
Reaction without copper salt leads to mixtures of substitution products

Reaction carried out with excess of olefin

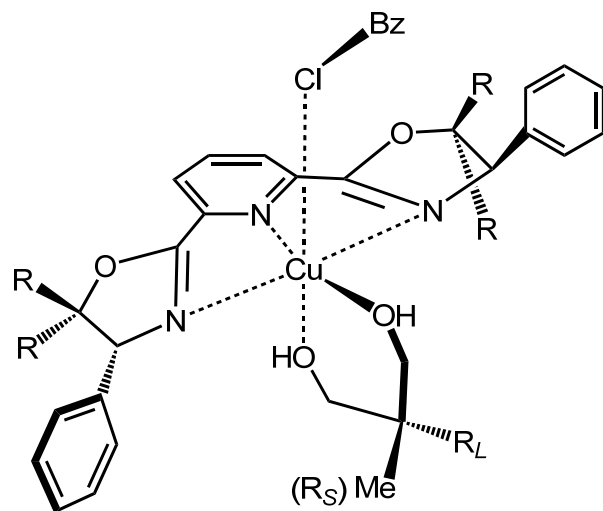
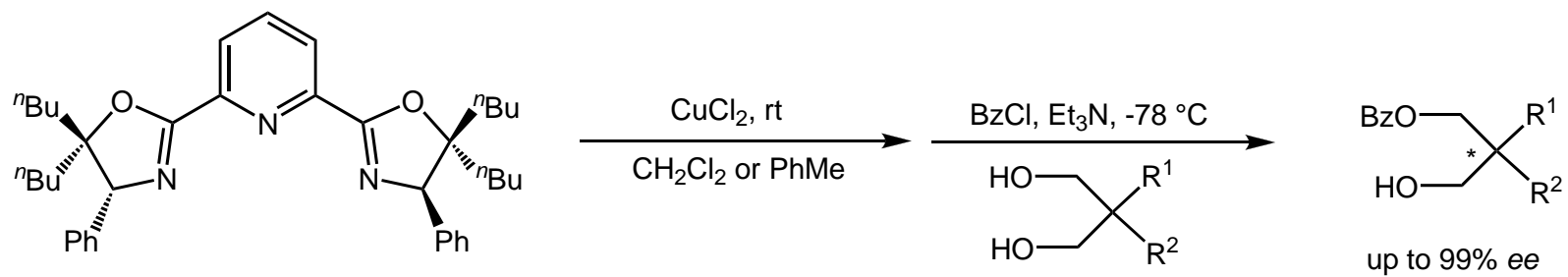




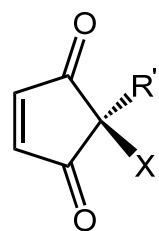
Kang, S. H. *et al* *Angew. Chem. Int. Ed.* **2007**, *46*, 2616-2618.



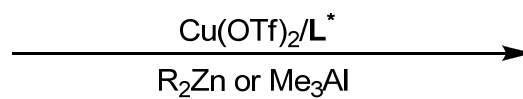
Kang, S. H. *et al* *Chem. Eur. J.* **2008**, *14*, 3290-3296.



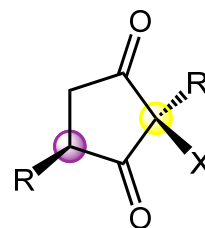
Kang, S. H. *et al* *J. Am. Chem. Soc.* **2011**, 133, 1772-1774.



achiral

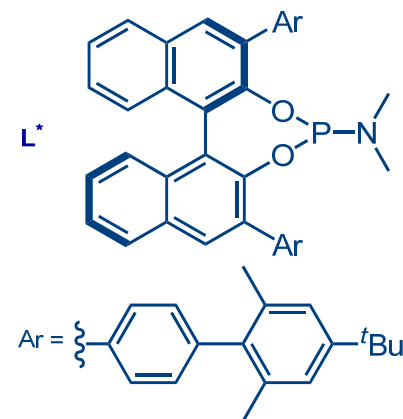


"desymmetrization"



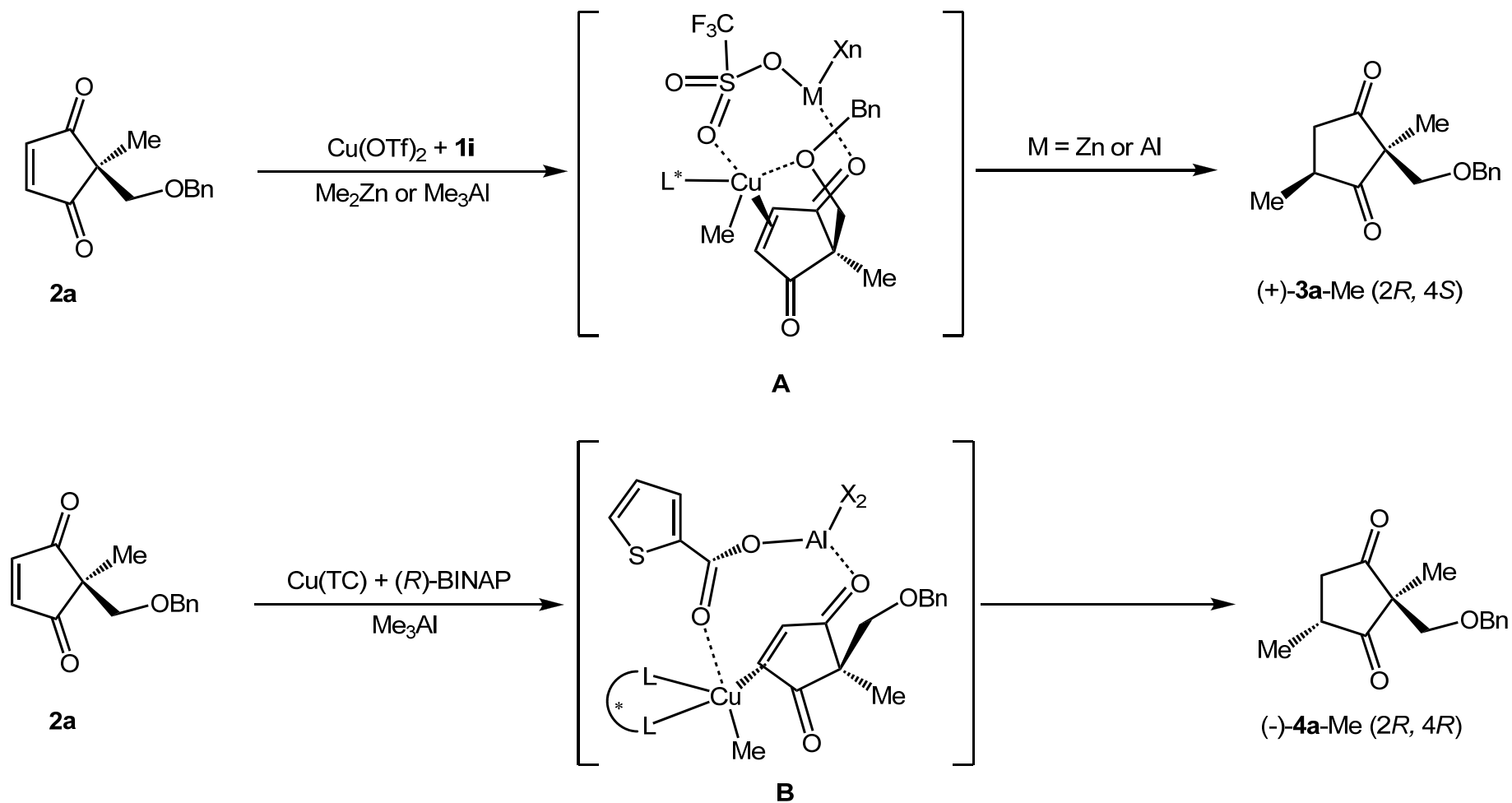
up to >99% yield
>90% *dr*
>99% *ee*

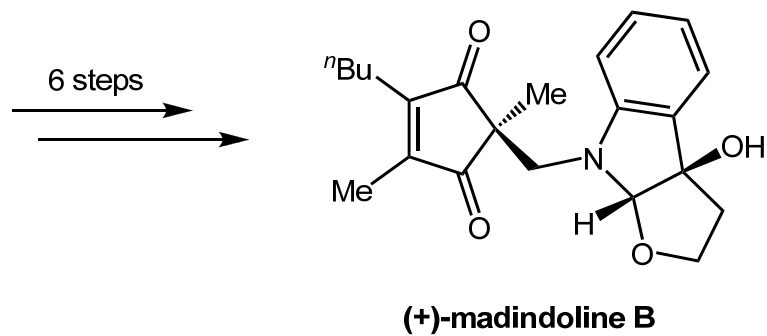
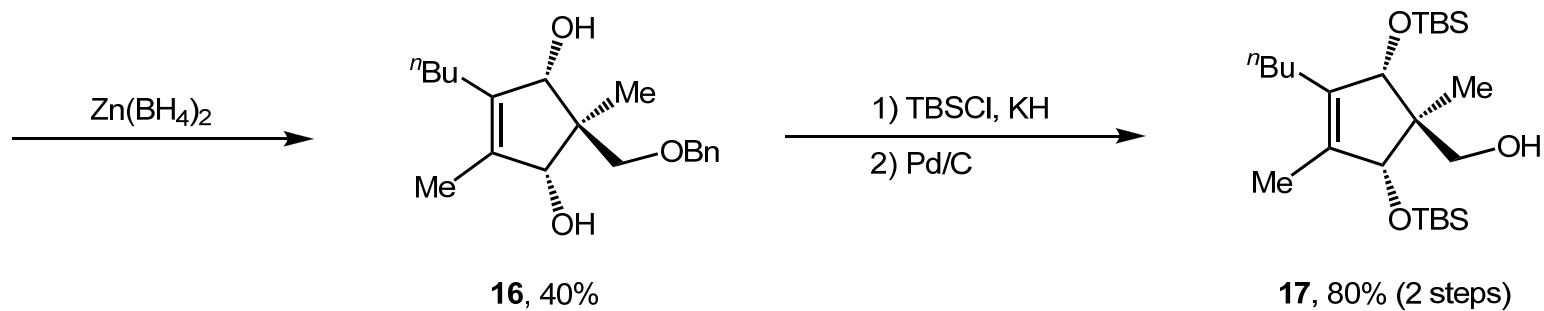
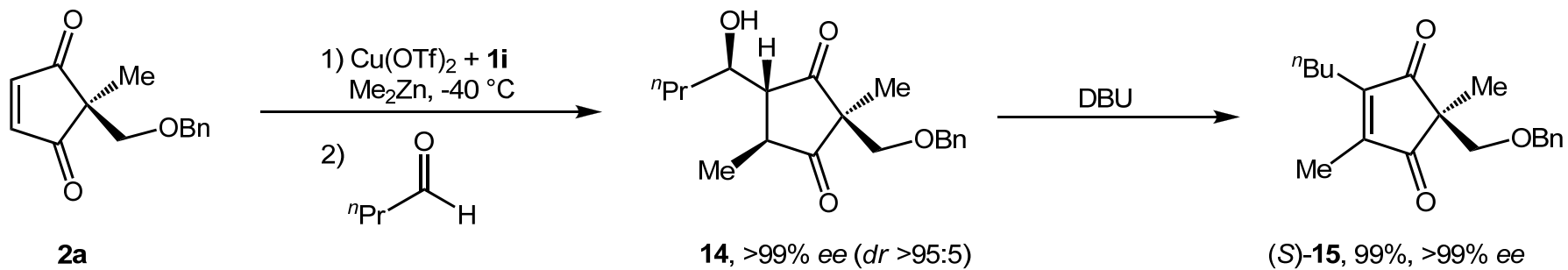
R = Me, Et, ⁿBu;
R' = Me, Et, ⁱPr, Ph;
X = CH₂OBn, CH₂COOMe, Ph.



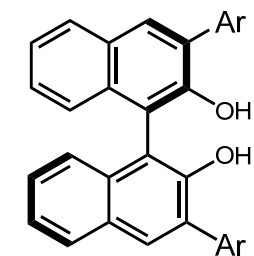
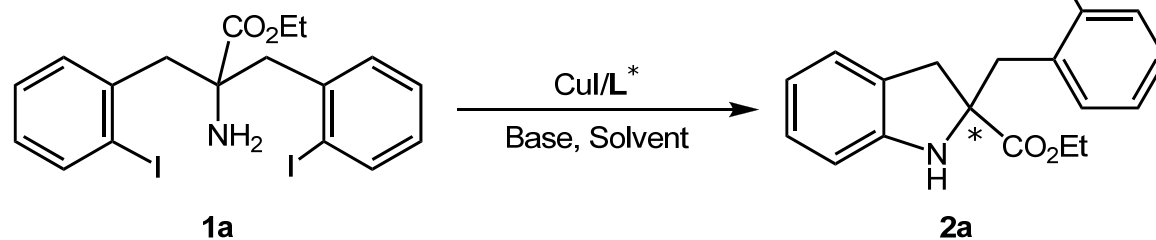
Mikami, K. *et al J. Am. Chem. Soc.* **2012**, *134*, 10329-10332.

Proposal for the Sense of the Diastereoselectivity:





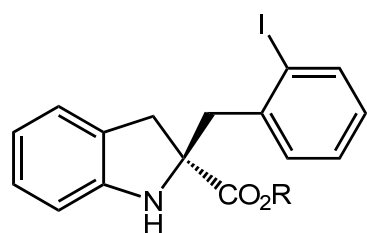
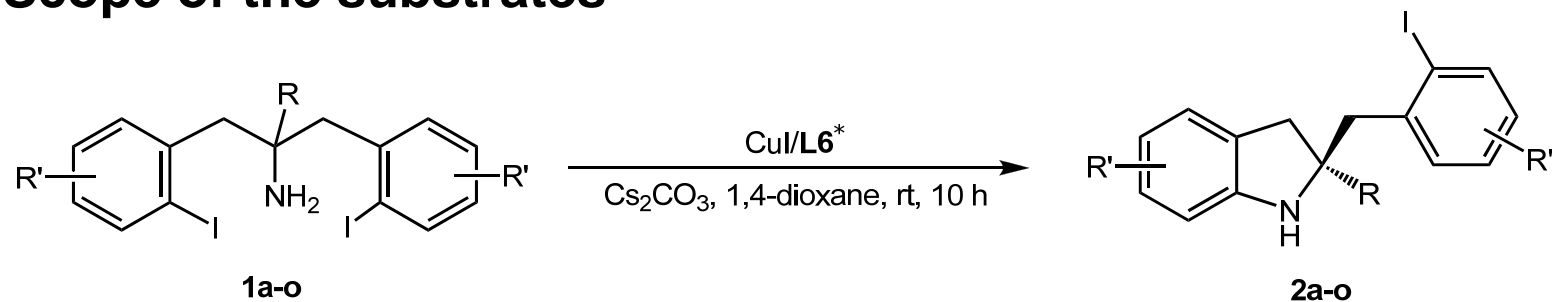
Screening Reaction Conditions



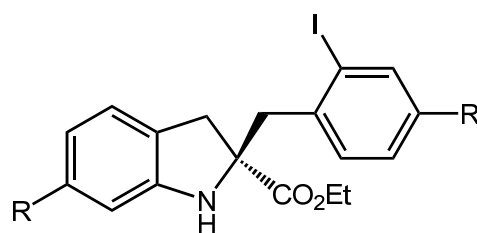
(R)-L1, *(R)*-BINOL
(R)-L2, Ar = Ph
(R)-L3, Ar = 4-MeOC₆H₅
(R)-L4, Ar = 4-CF₃C₆H₅
(R)-L5, Ar = 3,5-(CF₃)₂C₆H₄
(R)-L6, Ar = 9-Anthracene

entry	ligand	base	solvent	yield(%)	ee(%)
1	L1	K ₃ PO ₄	1,4-dioxane	51	40
2	L2	K ₃ PO ₄	1,4-dioxane	20	68
3	L3	K ₃ PO ₄	1,4-dioxane	16	70
4	L4	K ₃ PO ₄	1,4-dioxane	34	71
5	L5	K ₃ PO ₄	1,4-dioxane	78	89
6	L6	K ₃ PO ₄	1,4-dioxane	12	98
10	L5	K ₂ CO ₃	1,4-dioxane	53	87
11	L5	Cs ₂ CO ₃	1,4-dioxane	95	87
12	L6	Cs₂CO₃	1,4-dioxane	91	96

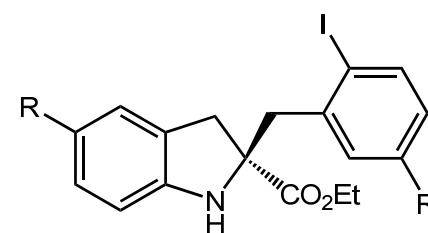
Scope of the substrates



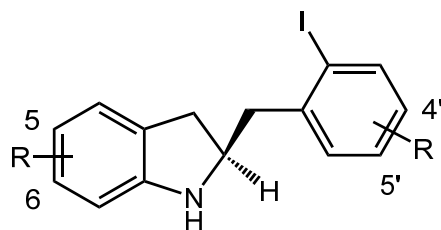
2a: R = Et, 91% yield, 96% ee
2b: R = ⁱPr, 93% yield, 98% ee
2c: R = ^tBu, 71% yield, 97% ee



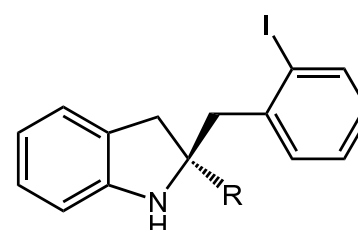
2d: R = F, 81% yield, 97% ee
2e: R = NO₂, 90% yield, >99% ee
2f: R = CO₂Me, 86% yield, 98% ee



2g: R = Br, 88% yield, >99% ee
2h: R = Me, 75% yield, 99% ee
2i: R = OMe, 64% yield, 96% ee

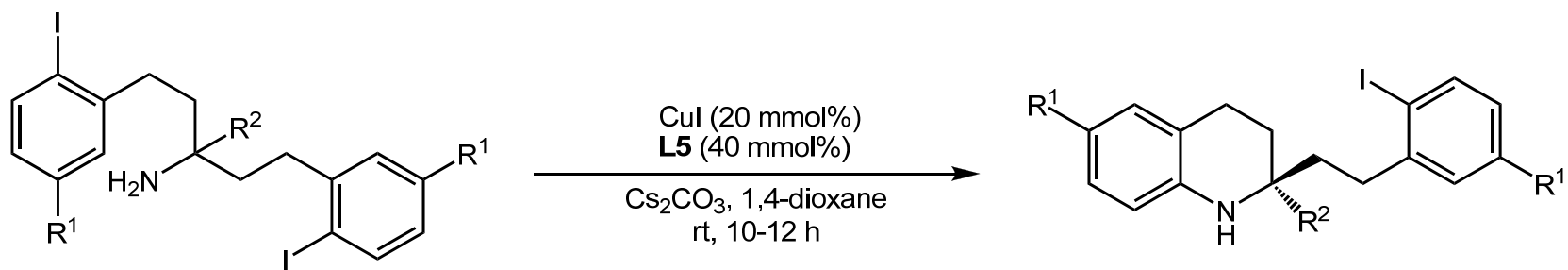


2j: R = H, 94% yield, 93% ee
2k: R = F (6, 4'), 94% yield, 95% ee
2l: R = Me (5, 5'), 93% yield, 92% ee



2m: R = Me, 89% yield, 83% ee
2n: R = CH=CH₂, 70% yield, 90% ee
2o: R = CH₂N₃, 75% yield, 75% ee

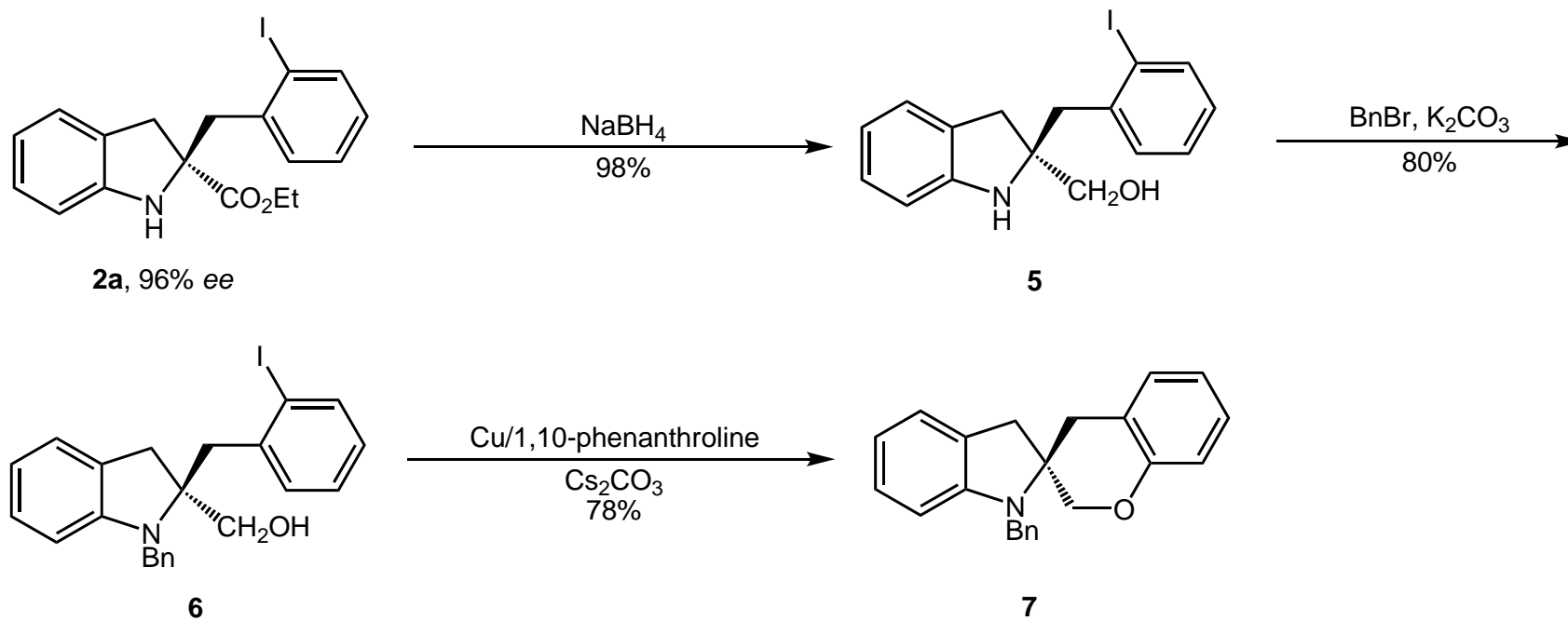
Enantioselective Formation of 1,2,3,4-Tetrahydroquinoline Derivatives via Intramolecular Desymmetric Ullmann C–N Coupling Reaction



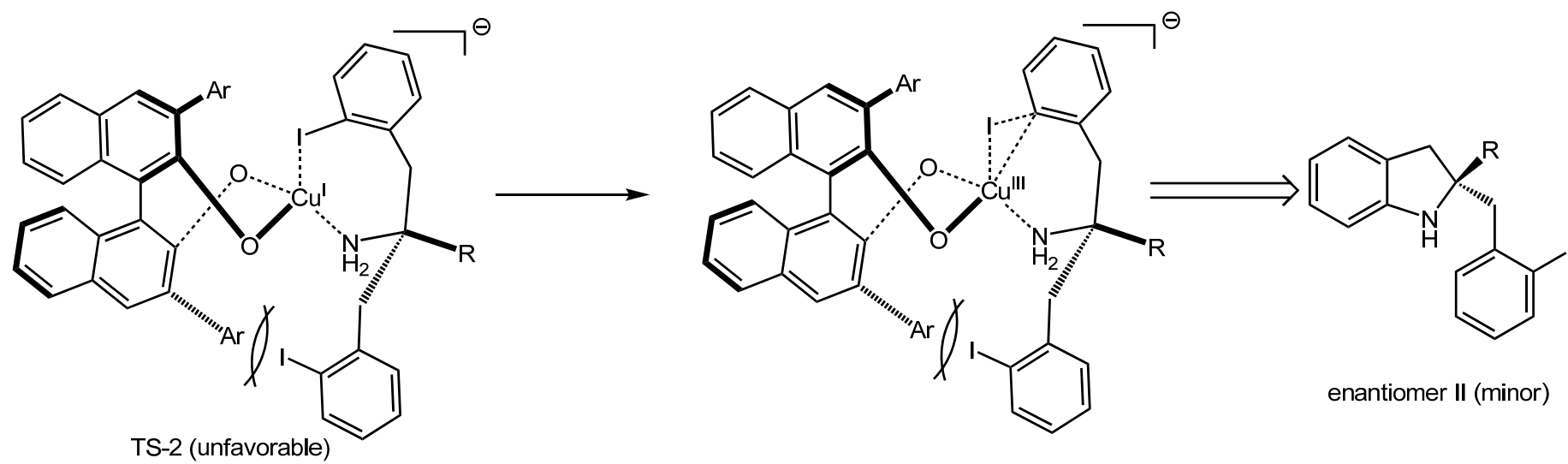
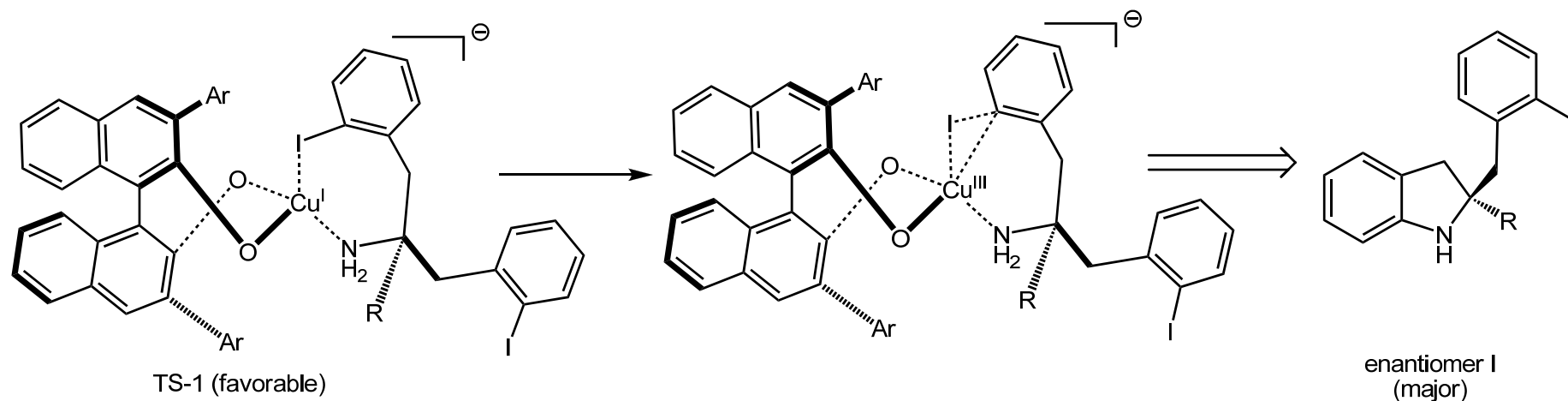
3a: R¹ = H, R² = CO₂Et
3b: R¹ = Me, R² = CO₂Et
3c: R¹ = R² = H

4a: 96% yield, >99% ee
4b: 85% yield, 99% ee
4c: 83% yield, 82% ee

Example for the Synthesis of Chiral Spirocyclic Compounds

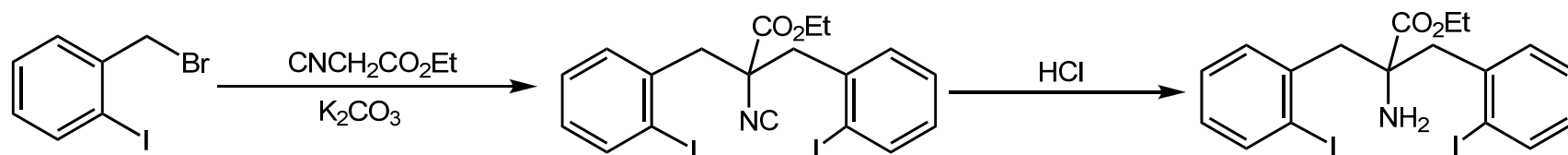


Plausible Intermediates for the Chirality Induction

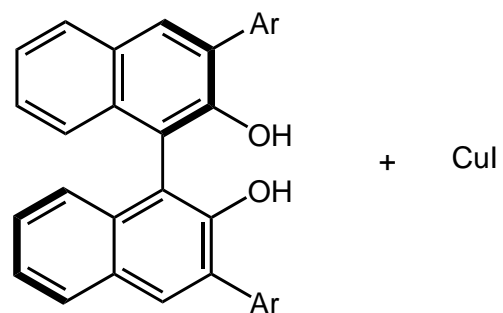


Summary

1. 巧妙的底物设计



2. 廉价的催化剂



3. 去对称化试剂 R_2Zn ; BzCl ; RCOOO^tBu .

Copper-catalyzed Ullmann-type coupling reactions have been extensively applied in both academia and industry, especially in recent years when great progress in the development of mild reaction conditions has been made. However, achieving enantioselectivity in copper-catalyzed Ullmann-type coupling reactions remains a significant challenge. So far, only one example for catalytic asymmetric Ullmann-type coupling reaction was reported by Ma *et al.* in 2006. In their reaction, a quaternary stereochemical center was directly formed by coupling 2-halotrifluoroacetanilides with 2-methylacetoacetates. Satisfactory yields and good enantioselectivity were achieved at $-45\text{ }^{\circ}\text{C}$. However, since other Ullmann-type couplings such as C–N, C–O, and C–S couplings did not involve direct formation of new stereochemical centers, little attention was focused on the asymmetric pattern of these copper-catalyzed coupling reactions.

In summary, we have developed the first enantioselective intramolecular Ullmann C–N coupling reaction by asymmetric copper catalysis through desymmetrization of the 1,3-bis(2-iodoaryl)propan-2-amines, which led to the formation of the chiral indolines in good yields and high ee values in 1,4-dioxane with Cs_2CO_3 as the base. This method was also applied to the enantioselective synthesis of 1,2,3,4-tetrahydroquinoline derivatives. Further exploration and application of this reaction in organic synthesis is underway in our laboratory.

谢谢大家!