

Literature Report 2

Enantioselective Dearomative [3+2] Umpolung Annulation of *N*-Heteroarenes with Alkynes

Reporter : Gaowei Wang

Checker : Xiang Li

Date : 2022-04-25

Yang, P.; Wang, Q.; Cui, B.; Liu, H.; Hang, W.-Y.; **Jia, Y.-X.**
J. Am. Chem. Soc. **2022**, *144*, 1087

CV of Prof. Yi-Xia Jia (贾义霞)

Education:

- ❑ **1994-1998** B.S., Zhejiang University of Technology
- ❑ **2000-2003** M.S., Zhejiang University of Technology
- ❑ **2003-2006** Ph.D., Nankai University (Prof. Qi-Lin Zhou)
- ❑ **2006-2009** Postdoc., University of Geneva (Prof. E. Peter Kündig)
- ❑ **2009-now** Full Professor, Zhejiang University of Technology



Research Interests :

- ❑ Chiral synthesis and asymmetric catalysis
- ❑ Green chemistry
- ❑ New processes for drug synthesis

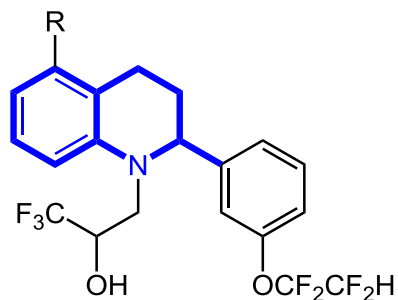
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1 Introduction

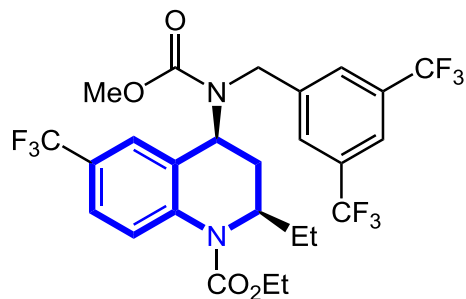
2 Enantioselective Dearomatization of *N*-Heteroarenes

3 Summary

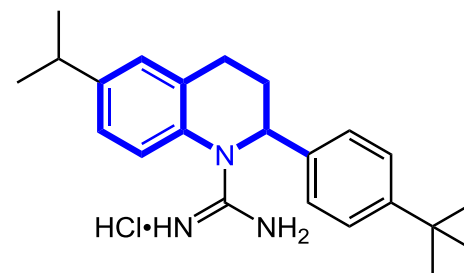
Introduction



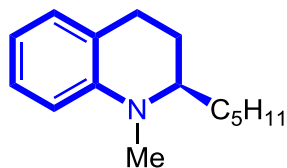
R = 3-OCF₃C₆H₄
Cholesteryl ester
 Transfer protein inhibitor



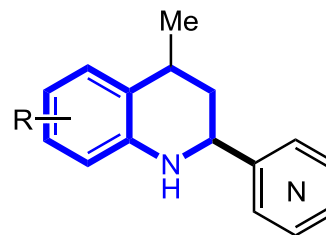
Torcetrapib
 Antihypercholesterolemia drug



Na⁺ Channel antagonist



(-)-Angustureine



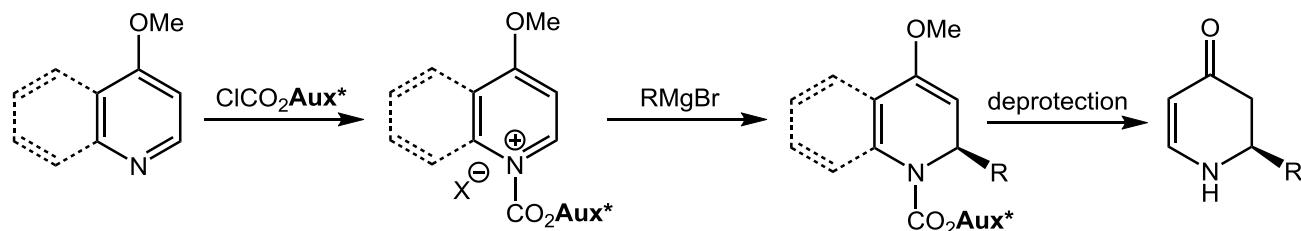
R = H, Me, OMe, etc.
Antifungal

Shi, M. *et al. Angew. Chem. Int. Ed.* **2016**, 55, 3776

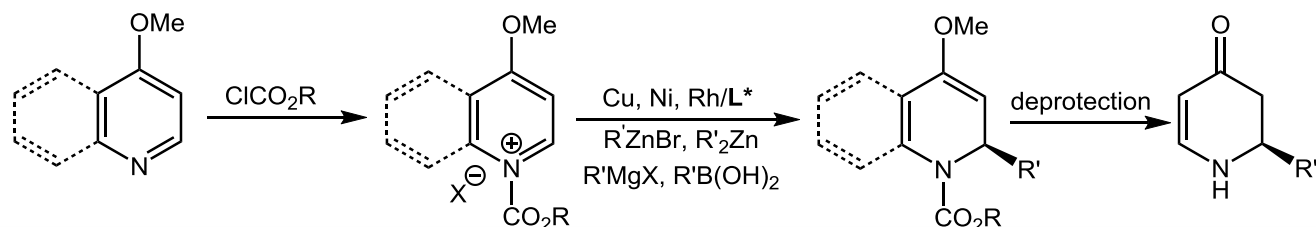
Introduction

State of the Art in Asymmetric Dearomatization of *N*-Heteroarenes

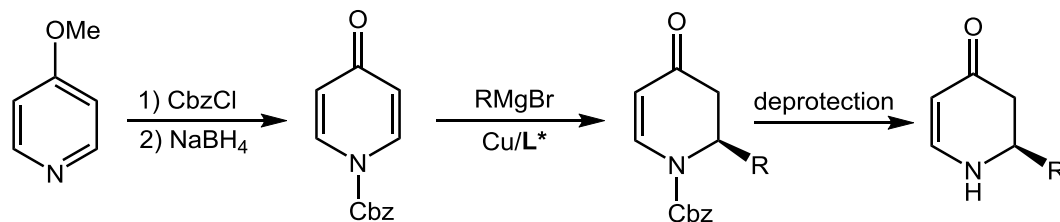
A) Stereoselective addition of Grignard reagents using chiral auxiliary



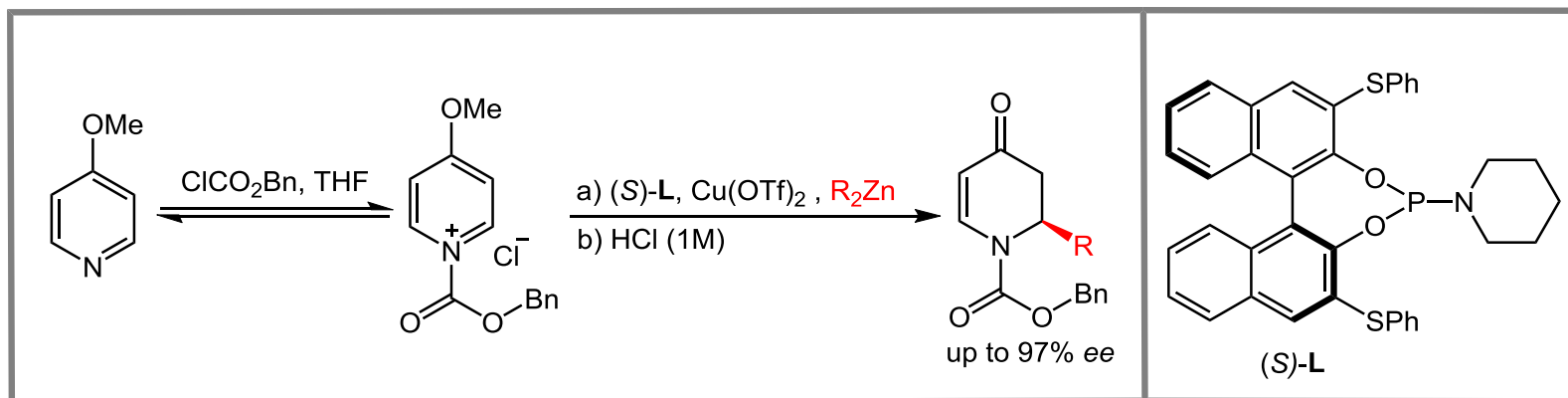
B) Transition metal-catalyzed enantioselective alkylation and arylation



C) Catalytic enantioselective additions to pyridones prepared from 4-Methoxypyridine

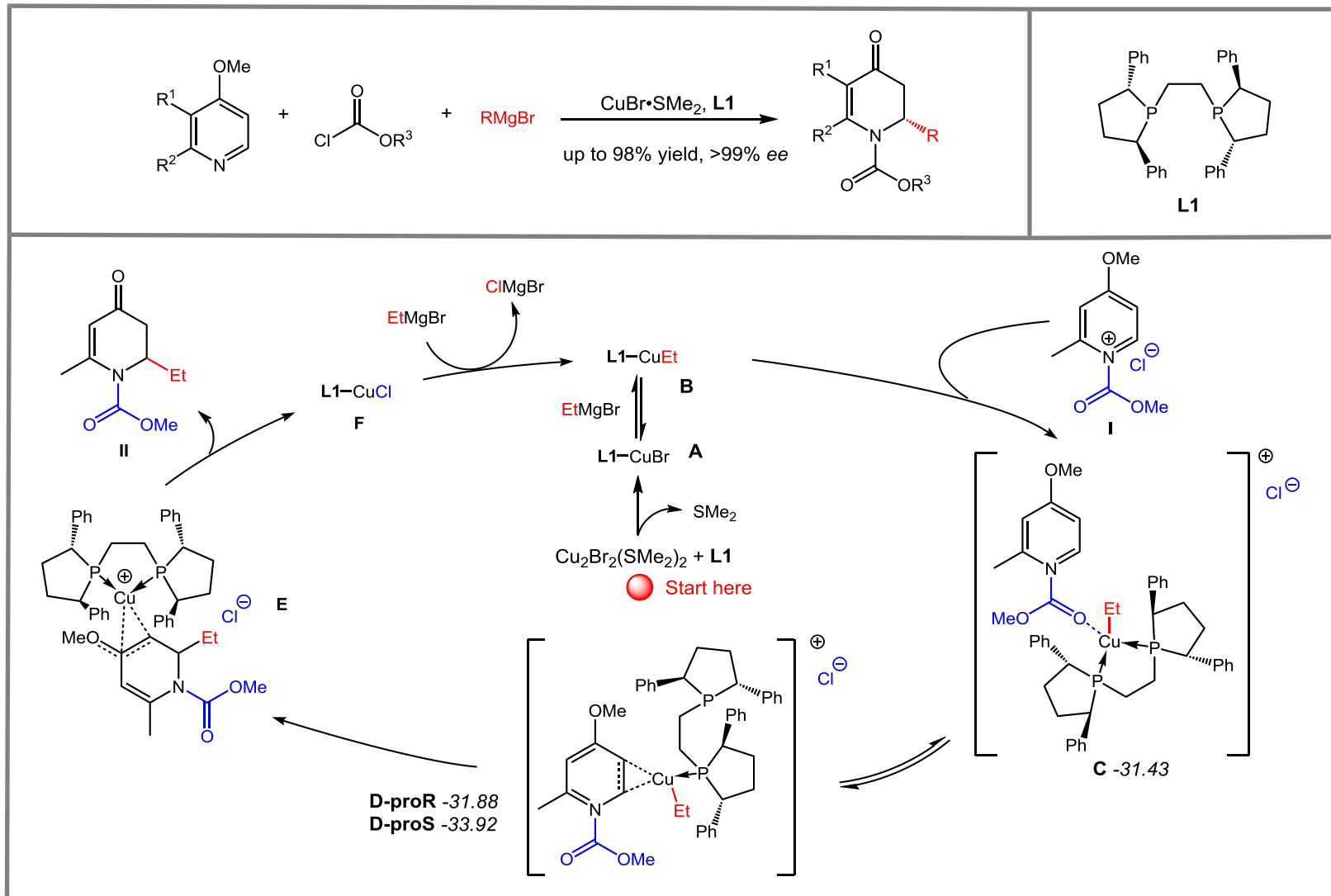


Copper-Catalyzed Dearomative Alkylation



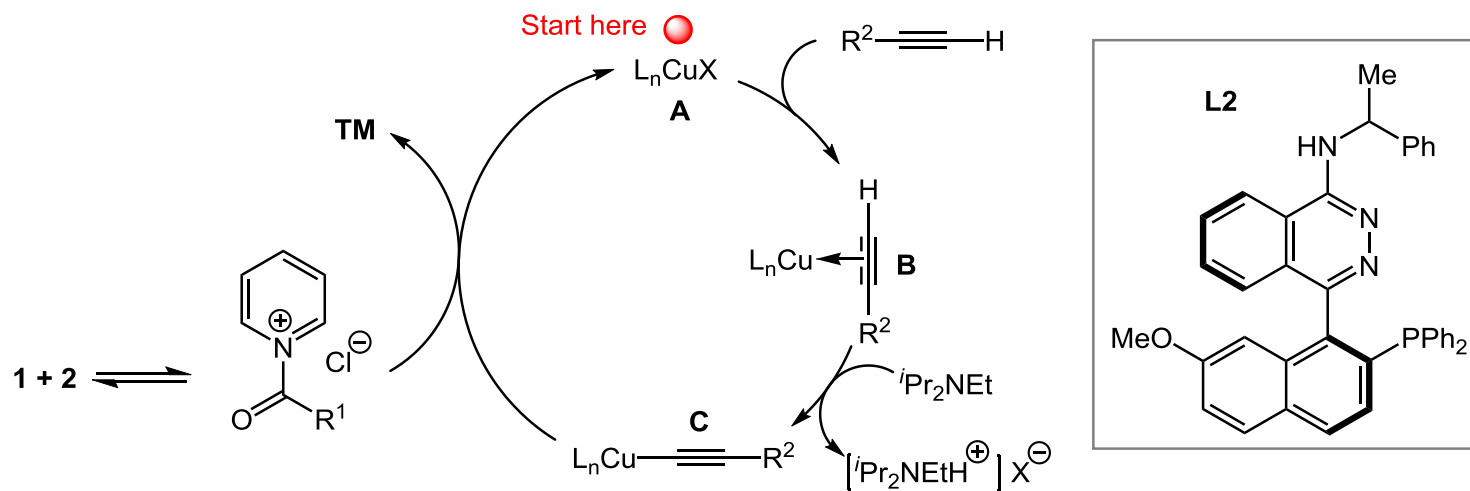
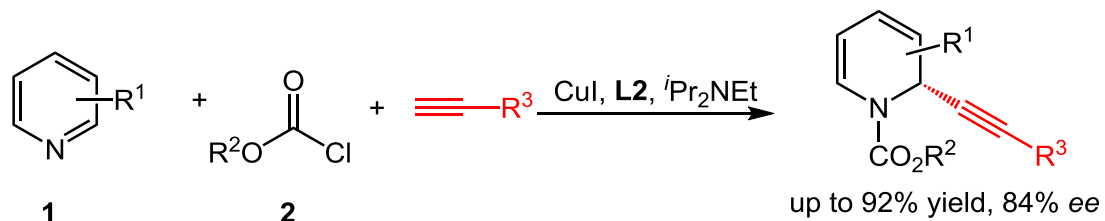
Feringa, B. L. *et al. Angew. Chem. Int. Ed.* **2009**, 48, 9339

Copper-Catalyzed Dearomative Alkylation



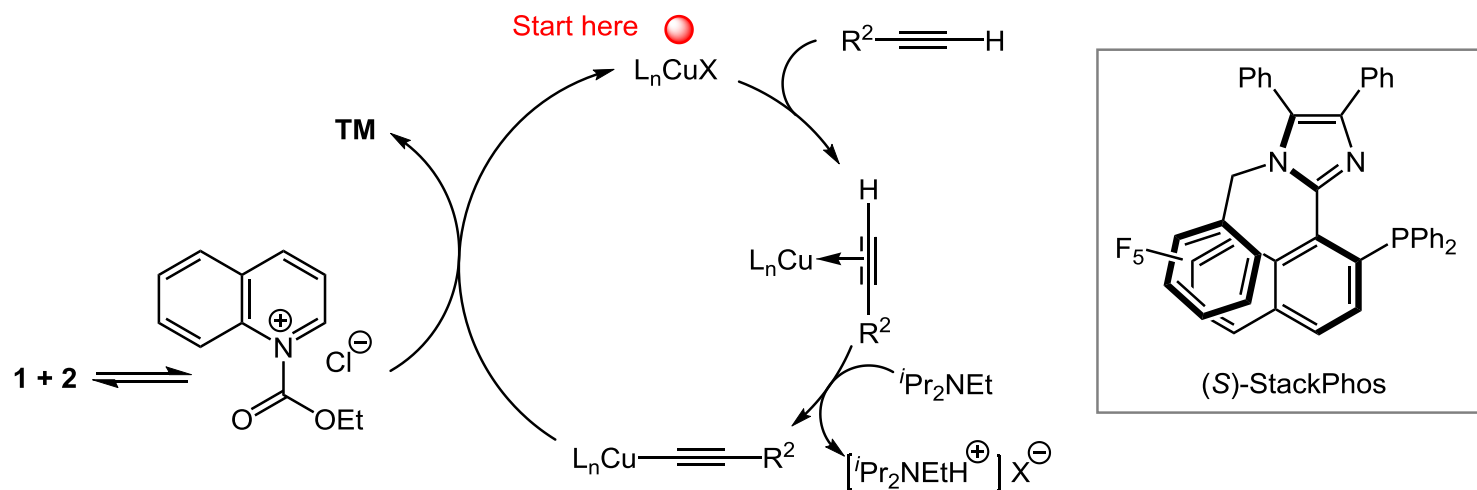
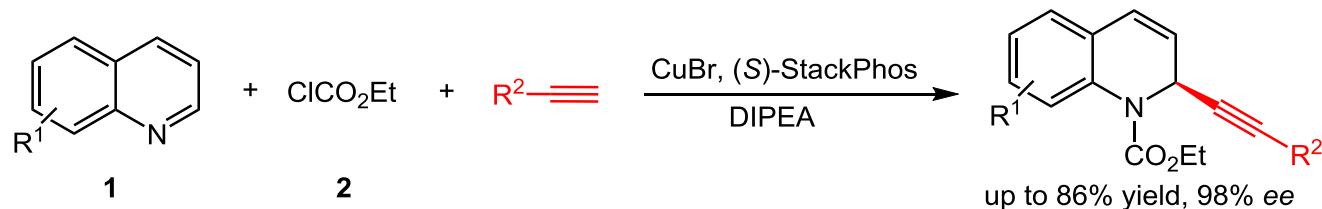
Harutyunyan, S. R. *et al. ACS Catal.* **2021**, 11, 8476

Copper-Catalyzed Dearomative Alkynylations



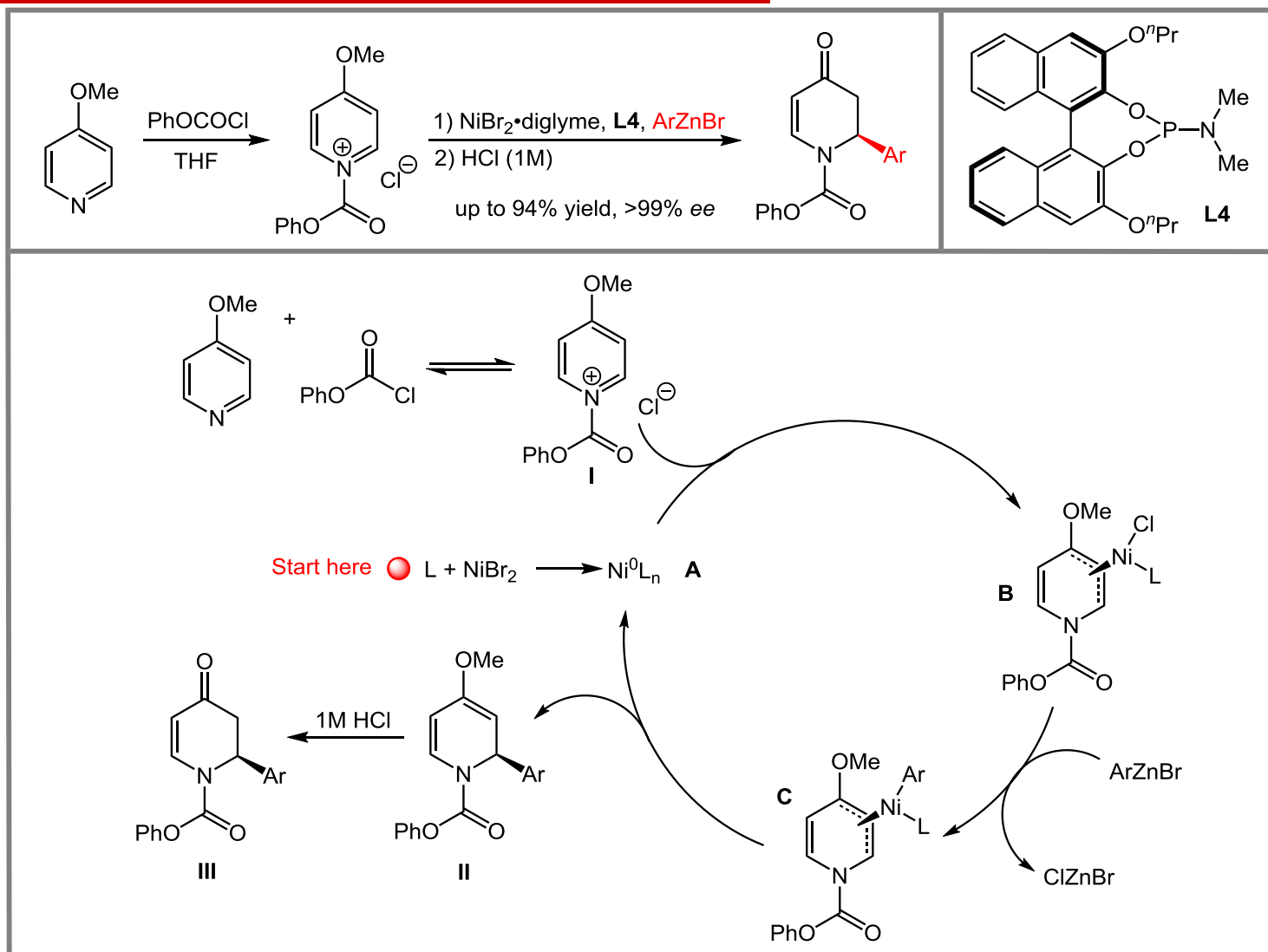
Arndtsen, B. A. *et al. J. Org. Chem.* **2008**, 73, 1906

Copper-Catalyzed Dearomative Alkynylations



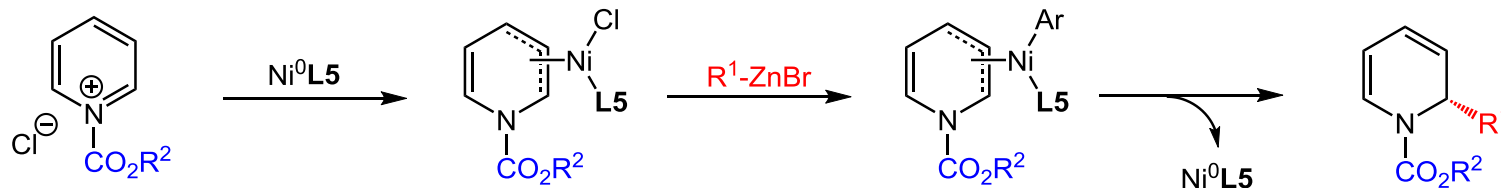
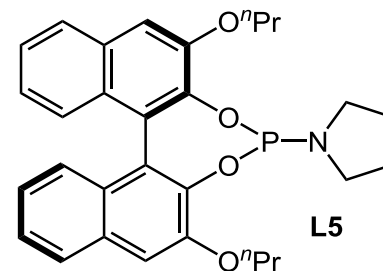
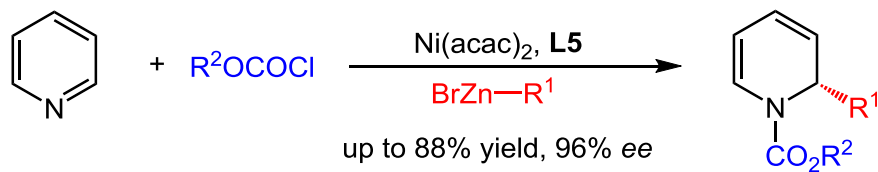
Aponick, A. *et al. Angew. Chem. Int. Ed.* **2015**, 54, 15202

Nickel-Catalyzed Dearomative Arylation



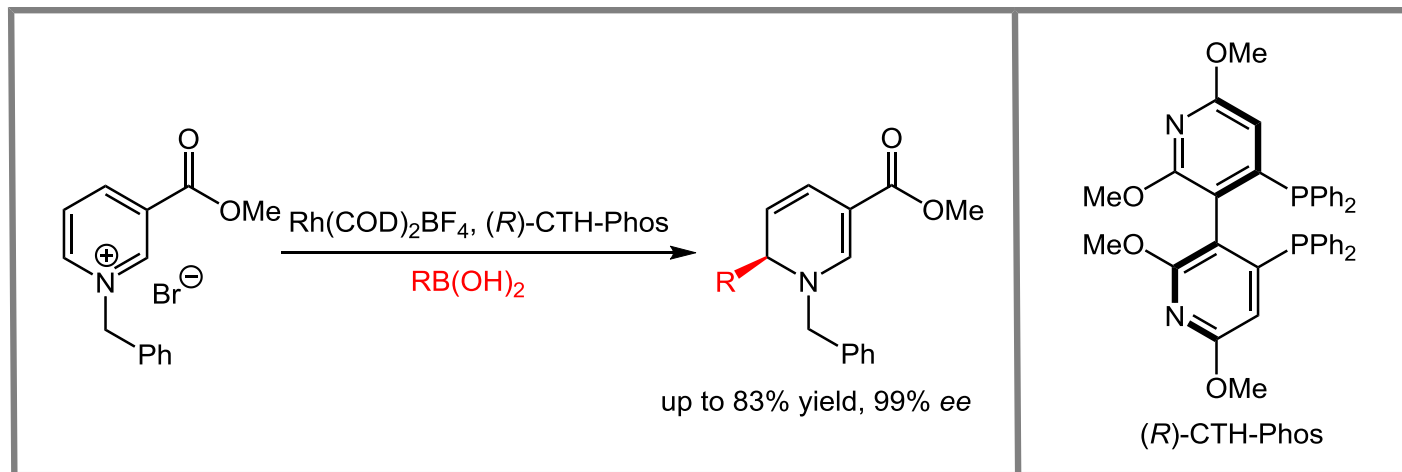
Doyle, A. G. *et al. Angew. Chem. Int. Ed.* **2013**, 52, 9153

Nickel-Catalyzed Dearomative Alkylation



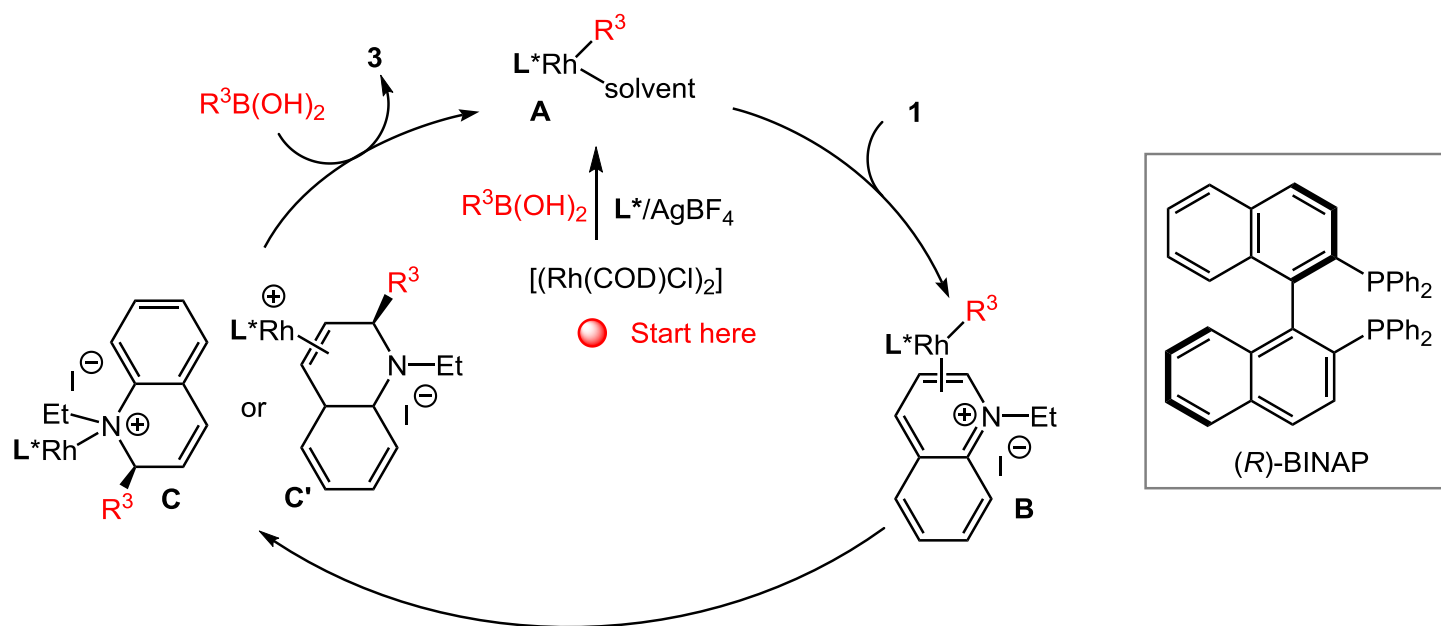
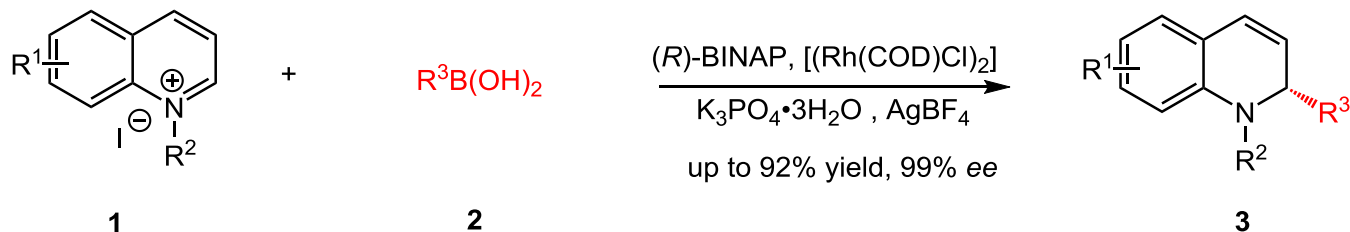
Doyle, A. G. *et al. Chem. Sci.* **2016**, 7, 4105

Rhodium-Catalyzed Dearomative Arylation



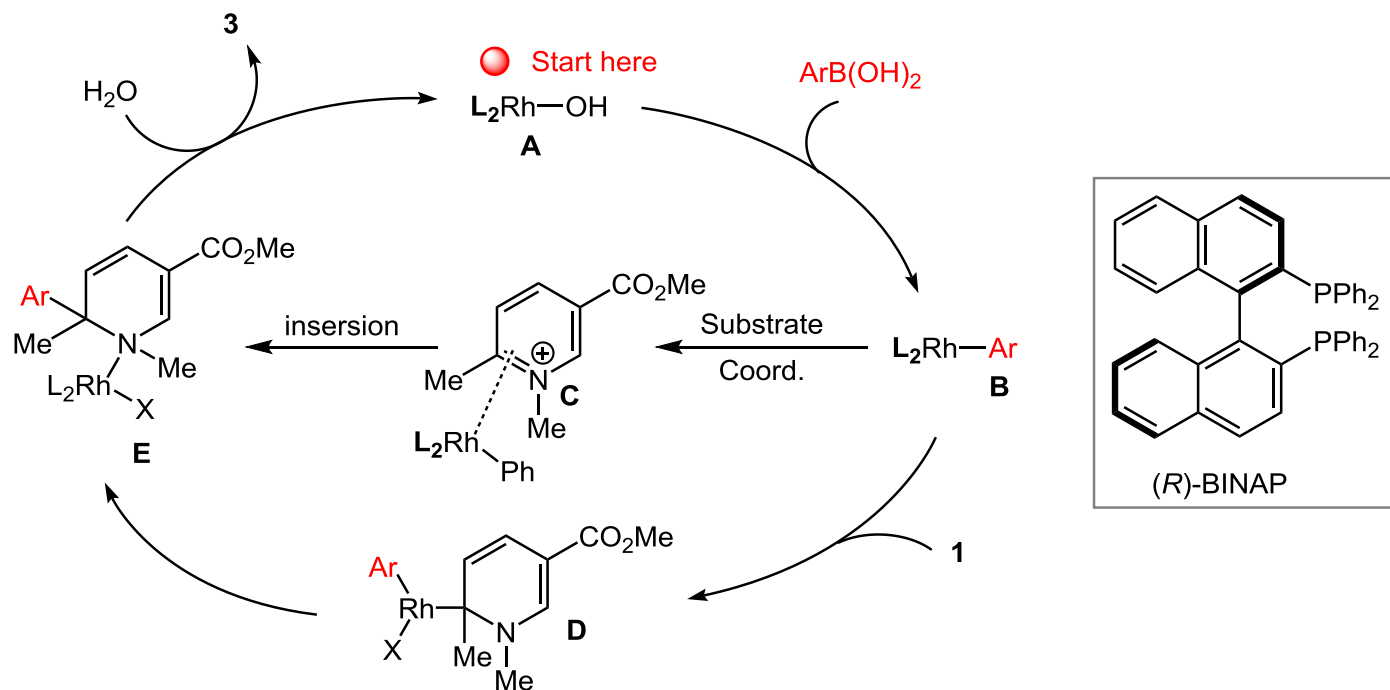
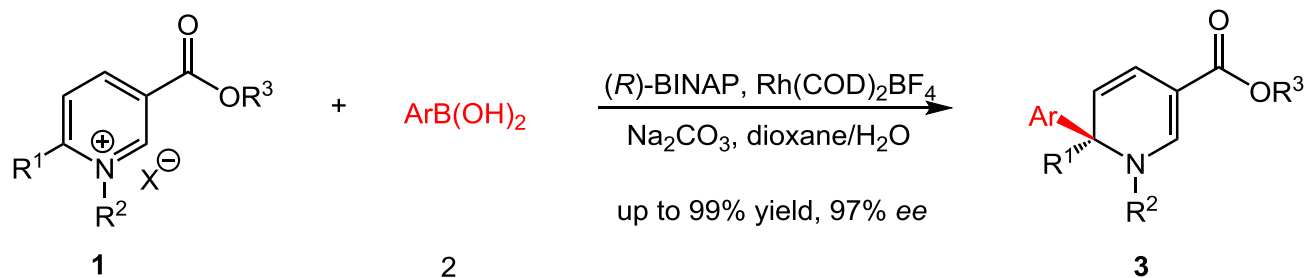
Belyk, K. *et al. J. Am. Chem. Soc.* **2011**, 133, 2878

Rhodium-Catalyzed Dearomative Arylation



Shi, M. *et al. Angew. Chem. Int. Ed.* **2016**, 55, 3776

Rhodium-Catalyzed Dearomative Arylation

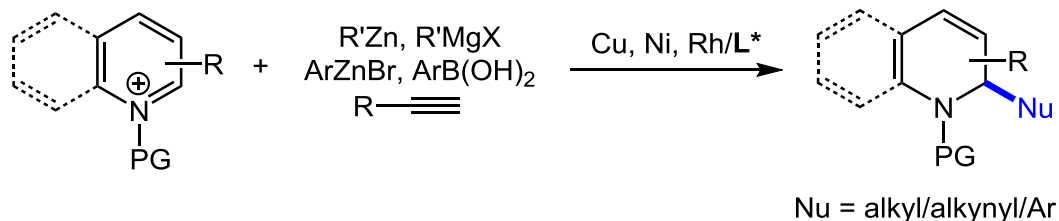


Karimov, R. R. *et al.* *ACS Catal.* **2020**, 10, 51



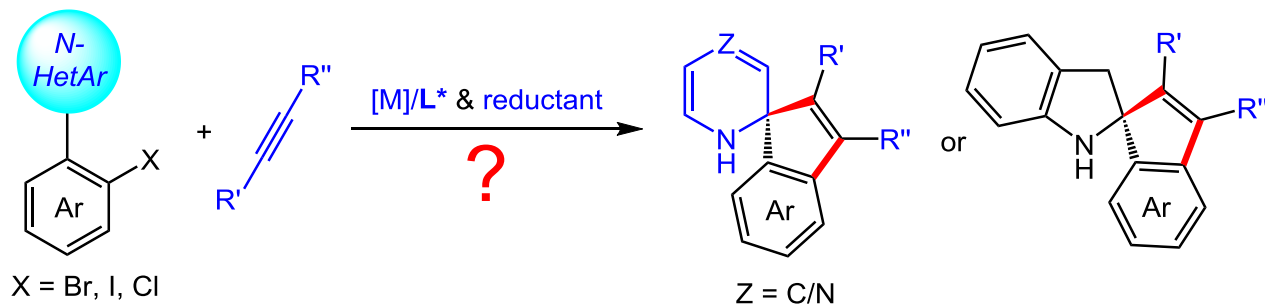
TM-Catalyzed Transformations of *N*-Heteroarenes

Asymmetric dearomative nucleophilic addition of pyridinium/quinolinium salts

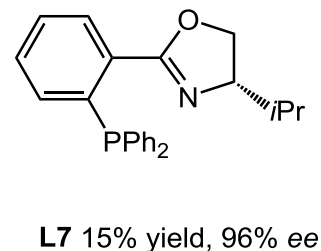
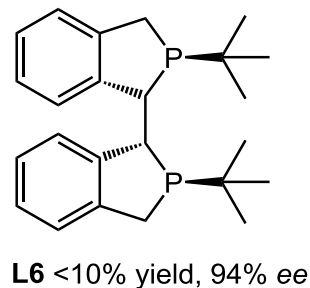
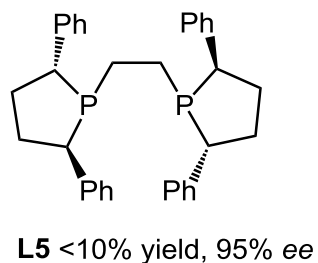
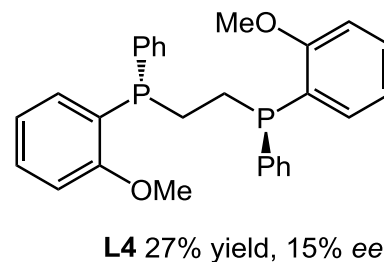
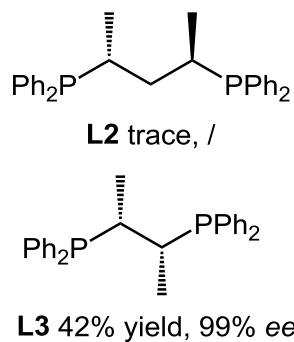
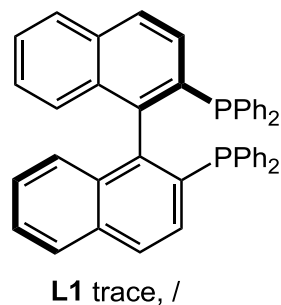
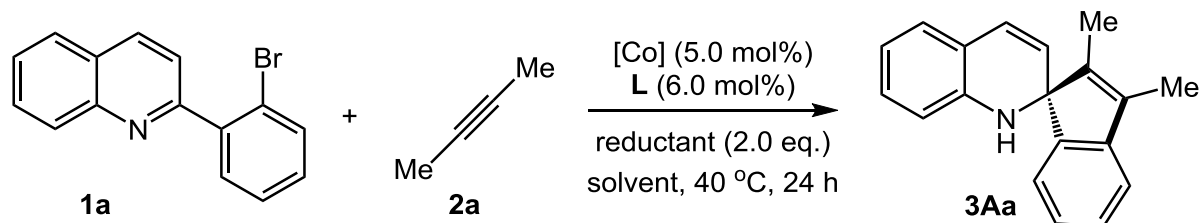


- ♣ Non-preactivated *N*-heteroarenes have been rarely used as substrates
- ♣ The product needed to remove the *N*-protecting groups
- ♣ Organometallic reagents are usually prepared from electrophilic organohalide

Asymmetric [3+2] umpolung annulation of *N*-heteroarenes with alkynes



Optimization of Reaction Conditions



Optimization of Reaction Conditions

Entry	[Co]	L	Reductant	Solvent	Yield (%) ^b	Ee (%) ^c
1	CoCl ₂	dppe	Zn	THF	10	-
2	CoCl ₂	dppe	Zn	Dioxane	42	-
3	CoCl ₂	dppe	Zn	DME	13	-
4	CoCl ₂	dppe	Zn	MeCN	65	-
5	CoCl ₂	L1	Zn	MeCN	trace	-
6	CoCl ₂	L2	Zn	MeCN	trace	-
7	CoCl ₂	L3	Zn	MeCN	42	99
8	CoCl ₂	L4	Zn	MeCN	27	15
9	CoCl ₂	L5	Zn	MeCN	<10	95
10	CoCl ₂	L6	Zn	MeCN	<10	94
11	CoCl ₂	L7	Zn	MeCN	15	96

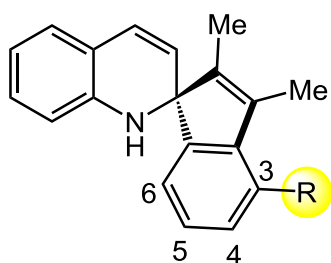
Optimization of Reaction Conditions

Entry	[Co]	L	Reductant	Solvent	Yield (%) ^b	Ee (%) ^c
12 ^d	CoCl ₂	L3	Zn	MeCN	61	99
13 ^e	CoCl ₂	L3	Zn	MeCN	trace	-
14 ^d	CoCl ₂	L3	Mn	MeCN	21	99
15 ^{d,f}	CoCl ₂	L3	In	MeCN	77	99
16 ^{d,g}	CoCl ₂	L3	In	MeCN	79	99
17 ^{d,g}	CoBr ₂	L3	In	MeCN	81	99
18 ^{d,g}	CoI ₂	L3	In	MeCN	84	99

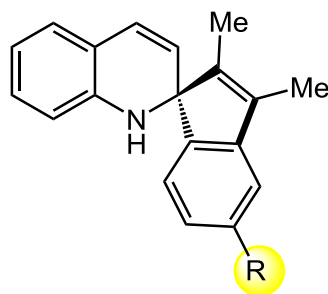
Reaction conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), **[Co]** (5 mol%), **L** (6 mol%), reductant (2.0 equiv), and solvent (2.0 mL) at 40 °C for 24 h. ^bIsolated yield. ^cDetermined by chiral HPLC. ^dIsopropyl alcohol (5.0 equiv). ^eHFIP (5.0 equiv). ^fFor 48 h. ^gAt 60 °C for 36 h.

Substrate Scope of the Reaction

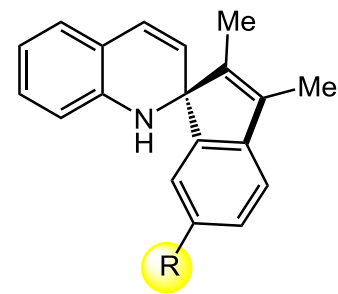
Substituent of Arylbromide



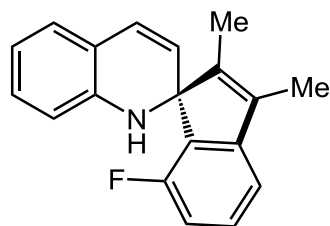
3Aa R = H 84%, 99% ee
3Ab R = Me 68%, 94% ee



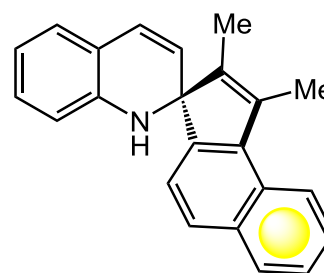
3Ac R = Me 78%, 99% ee
3Ad R = F 72%, 95% ee
3Ae R = Cl 90%, 99% ee
3Af R = OMe 80%, 99% ee



3Ag R = Cl 88%, 98% ee
3Ah R = OMe 64%, 97% ee
3Ai R = F 72%, 99% ee
3Aj R = Me 61%, 95% ee
3Ak R = CF₃ 45%, 99% ee



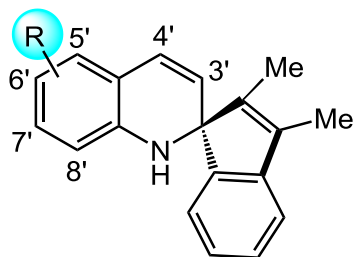
3Al 72%, 99% ee



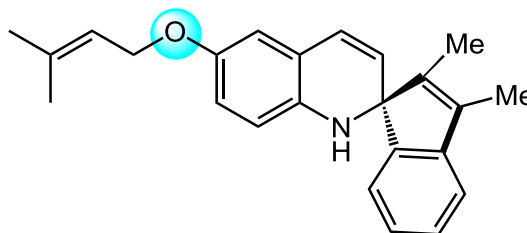
3Am 67%, 99% ee

Substrate Scope of the Reaction

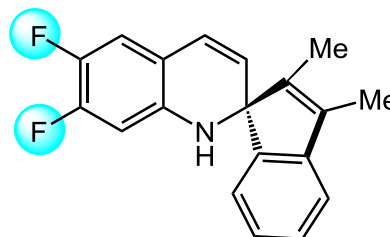
Substituent of Quinoline



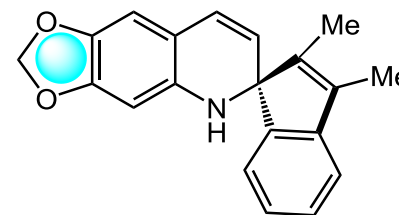
3Ba R = 3'-Me 63%, 69% ee
3Bb R = 4'-Cl 91%, 99% ee
3Bc R = 4'-Me 77%, 99% ee
3Bd R = 5'-F 93%, 99% ee
3Be R = 6'-Me 85%, 95% ee
3Bf R = 6'-OMe 91%, 97% ee
3Bg R = 6'-Cl 80%, 99% ee
3Bh R = 7'-F 81%, 99% ee
3Bi R = 7'-Cl 82%, 99% ee
3Bj R = 7'-NHAc 22%, >99% ee
3Bk R = 8'-F 50%, >99% ee



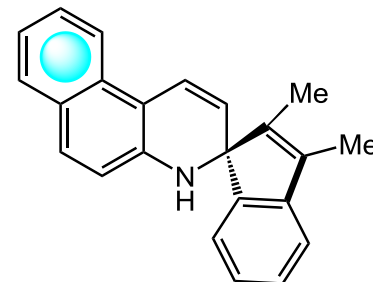
3BI 83%, 99% ee



3Bm 95%, >99% ee



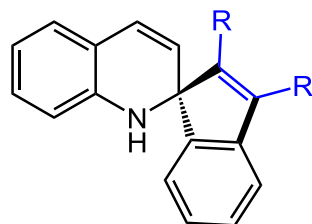
3Bn 82%, 99% ee



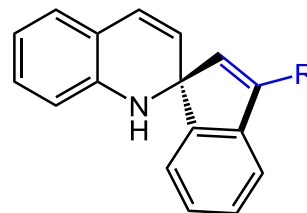
3Bo 46%, 99% ee

Substrate Scope of the Reaction

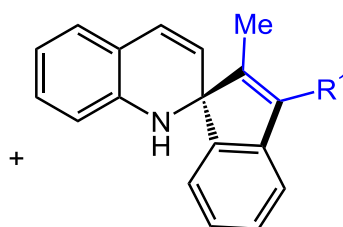
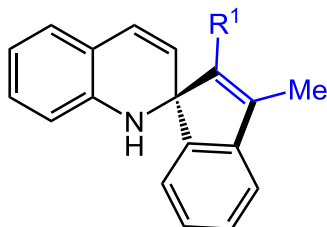
Substituent of Alkyne



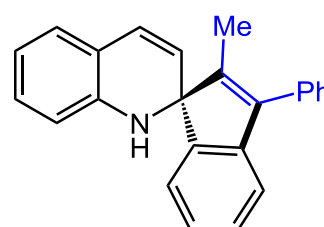
3Ca R = Et 65%, 99% ee
3Cb R = *n*Pr 47%, 96% ee
3Cc R = *n*Bu 44%, 98% ee
3Cd R = C₅H₁₁ 51%, 99% ee^b



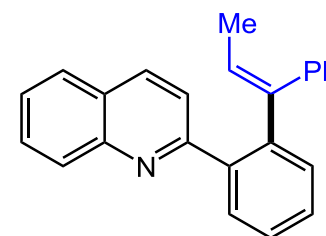
3Ce R = *n*Pr 59%, 96% ee^c
3Cf R = *n*Bu 56%, >99% ee^c
3Cg R = C₅H₁₁ 29%, >99% ee^c



3Ch+3Ch' R¹ = *i*Pr 37%, 8:1 r.r. 91% ee (major)^b
3Ci+3Ci' R¹ = Pr 52%, 3:2 r.r. 99% ee, 95% ee
3Cj+3Cj' R¹ = CH₂OBn 87%, 1:1 r.r. 99% ee, 96% ee



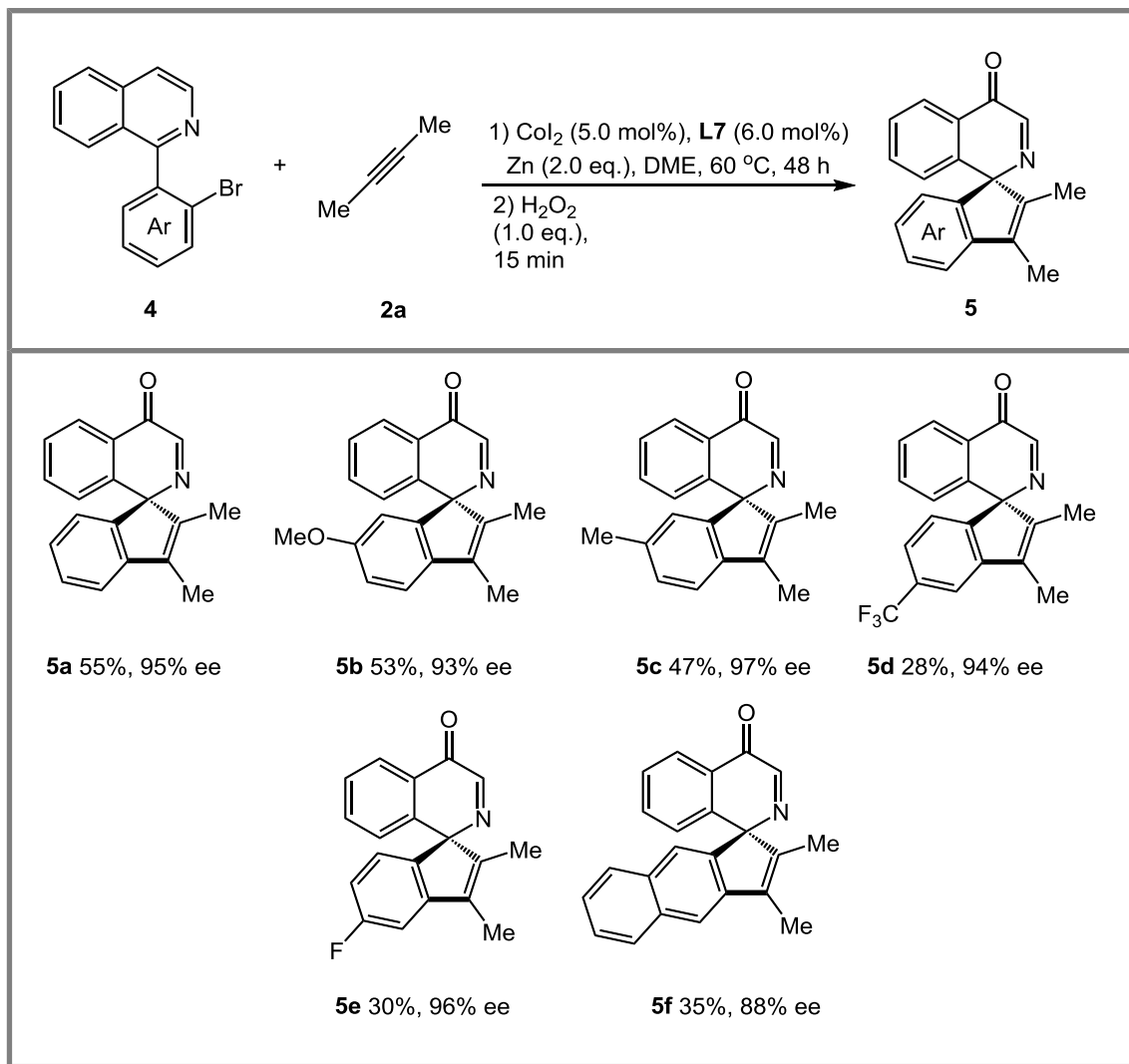
3Ck 30%, 99% ee^b



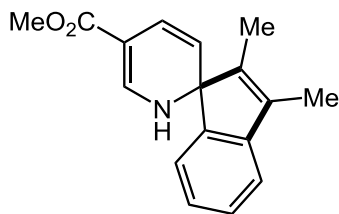
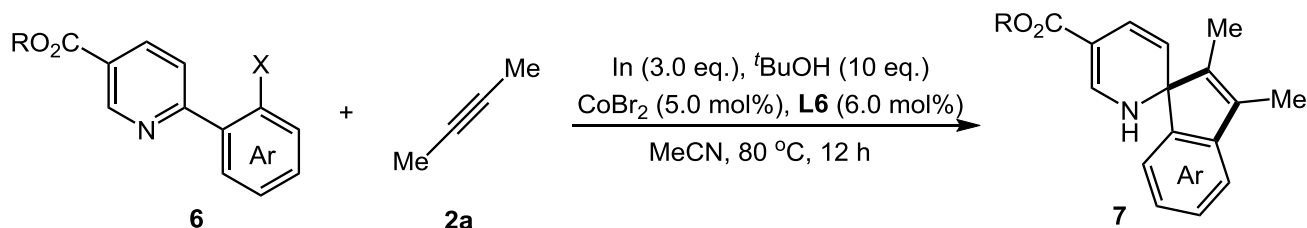
olefin-I 54%^b

^bAt 80 °C. ^cL7 instead of L3 and without *i*PrOH.

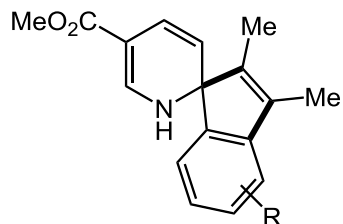
Reaction of 2-Arylisoquinoline and 2-Butyne



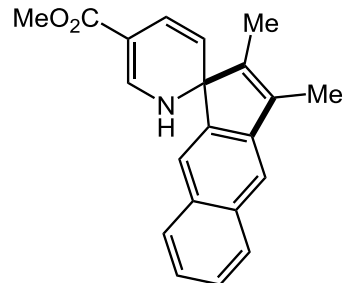
Reaction of 2-Arylpyridines and 2-Butyne



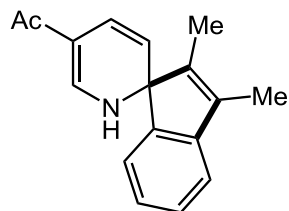
7a 65%, 95% ee (X = Br)
56%, 96% ee (X = I)
58%, 96% ee (X = Cl)



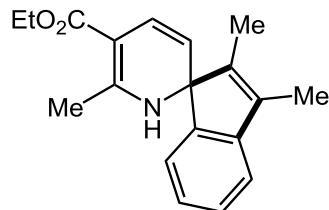
7b R = 4-F 56%, 95% ee (X = Br)
7c R = 4-Me 66%, 96% ee (X = Br)
7d R = 5-F 67%, 96% ee (X = Br)
7e R = 5-Me 68%, 94% ee (X = Br)



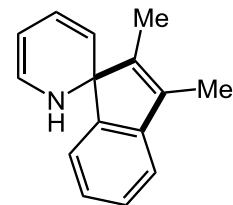
7f 42%, 83% ee (X = Br)



7g 43%, 94% ee (X = Br)

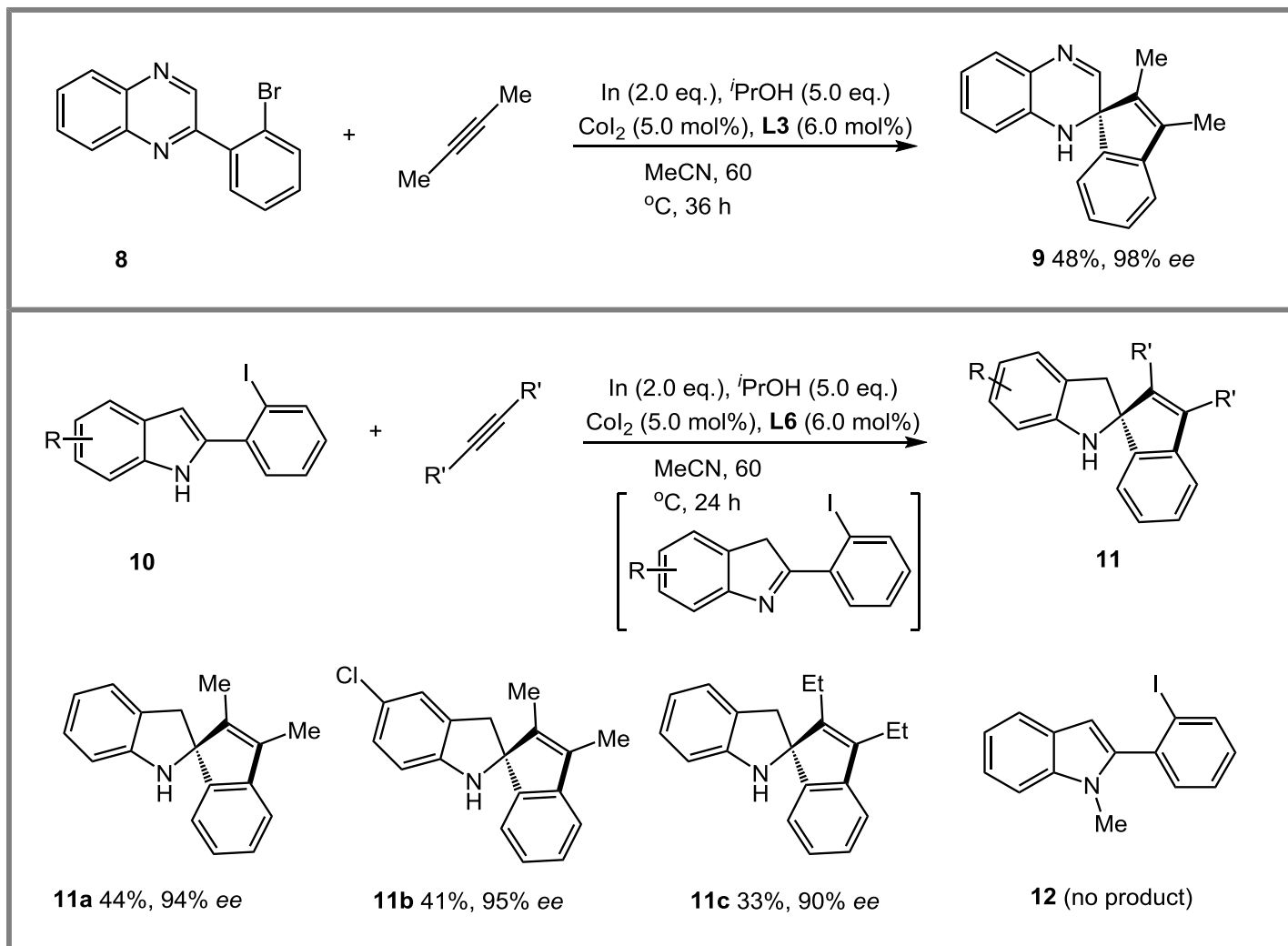


7h 41%, 98% ee (X = Br)

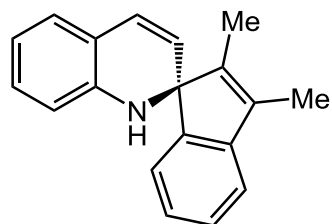


7i ND^b (X = Br)

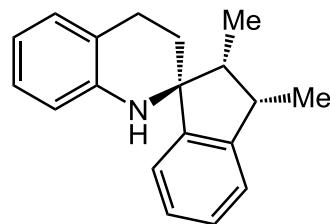
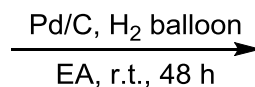
Annulation Reactions of Quinoxaline and Indoles



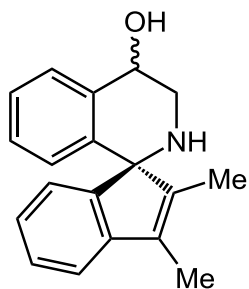
Synthetic Transformations of the Products



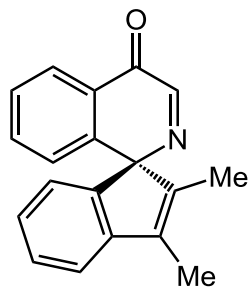
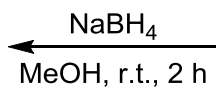
3Aa 99% ee



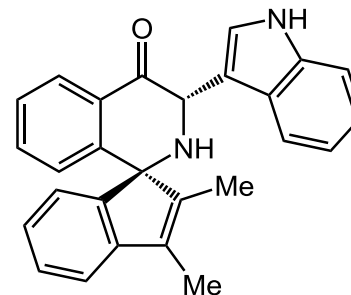
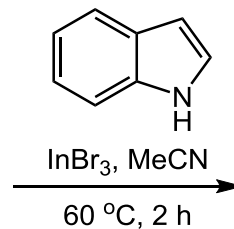
13 80%, 98% ee



15 63%, dr = 2.2:1
94% ee, 97% ee

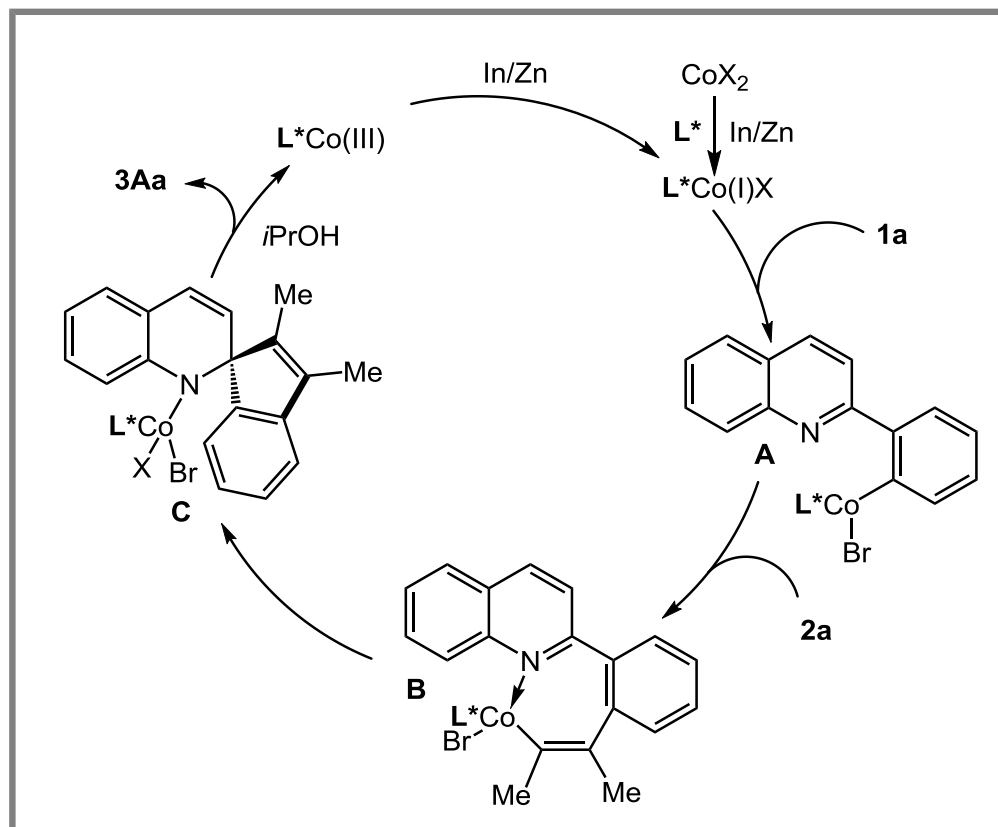


5a 95% ee

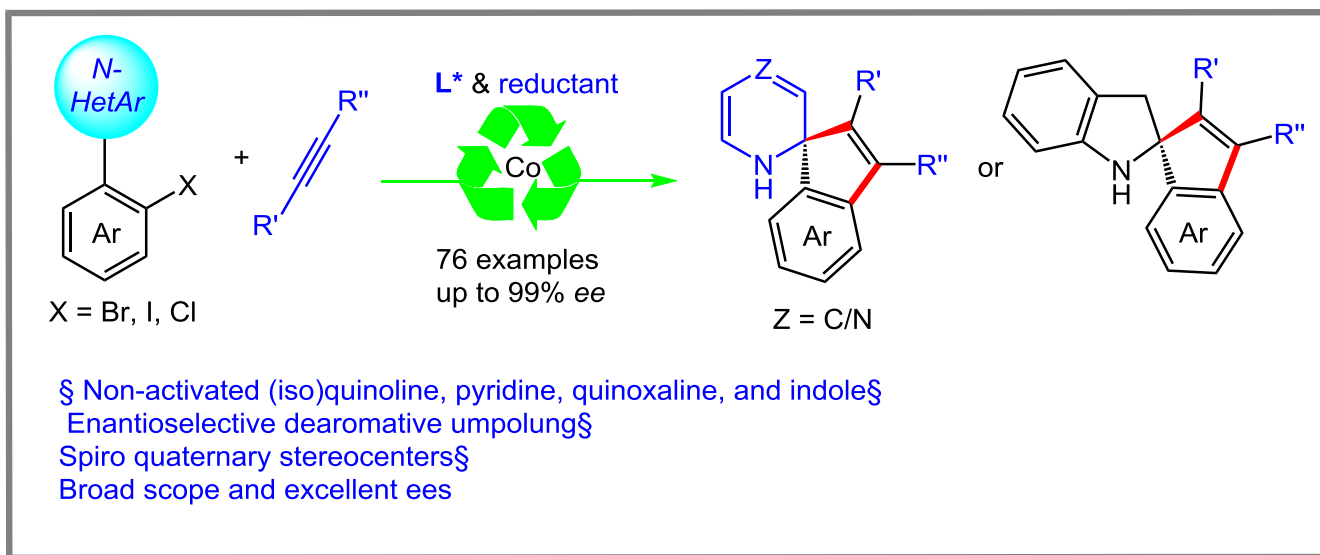


14 52%, 95% ee

Proposed Mechanism



Summary



Writing Strategies

□ The First Paragraph

含N脂肪环的生物、药物活性



传统N杂芳环去芳化策略



该工作极性反转策略

The First Paragraph

Nitrogen-bearing alicycles, such as hydropyridines and hydro(iso)-quinolines, are frequently occurring structural fragments in natural products, pharmaceuticals, and biologically active molecules. As a consequence, extensive attention has been devoted to the asymmetric synthesis of these molecules. Transition-metal-catalyzed enantioselective dearomatization of electron-deficient *N*-heteroarenes represents a reliable approach for this purpose. A range of catalytic asymmetric reactions have been disclosed through nucleophilic addition to active pyridinium or quinolinium salts. In this regard, important contributions include (1) the copper-catalyzed dearomative alkylation and alkynylations with organozinc, Grignard reagent, or terminal alkynes, (2) the nickel-catalyzed dearomative arylations with arylzinc reagents, (3) the rhodium-catalyzed arylations with organoborons.

The First Paragraph

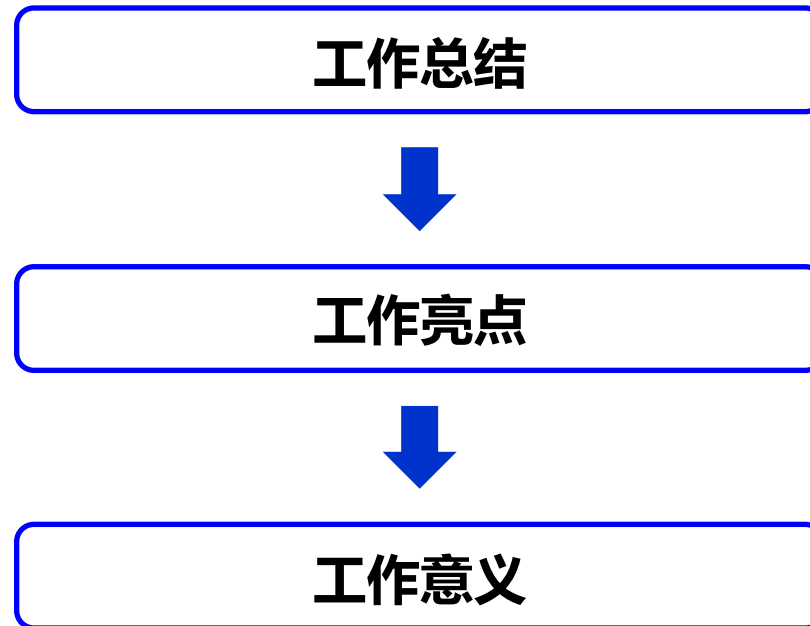
Despite these advances, non-preactivated *N*-heteroarenes have been rarely used as substrates and additional steps are therefore needed to remove the *N*-protecting groups. Moreover, most of the reactions employ nucleophilic organometallic reagents, which are usually prepared from electrophilic organohalides. Undoubtedly, it would be very attractive to develop the direct enantioselective umpolung addition of electrophilic organohalides to non-preactivated *N*-heteroarenes.

The First Paragraph

Recently, enantioselective dearomative Heck reactions and Heck/anionic-capture domino sequences have been established through dearomatizing migratory insertion of aromatic C–C π bonds. We envision that similar migratory insertion of the formal C–N bonds of *N*-heteroarenes might enable a dearomative [3+2] umpolung annulation of 2-*o*-haloaryl-*N*-heteroarenes with alkynes. However, this unprecedented [3+2] annulation is indeed very challenging since pyridine moiety remains inert as directing group for C_{Ar}–H activation in the documented reactions between 2-arylpyridines with alkynes, including vinylation, [4+2] annulation, and [2+2+2] cycloaromatization. Although cobalt catalyst showed the efficiency in above reactions, we are able to develop an enantioselective dearomative [3+2] umpolung annulation of *N*-heteroarenes with alkynes relying on chiral ligand and reducing reagent.

Writing Strategies

□ The Last Paragraph



The Last Paragraph

In conclusion, we have developed an enantioselective dearomative [3+2] umpolung annulation of electron-deficient 2-*o*-haloaryl-*N*-heteroarenes or electron-rich 2-*o*-iodophenyl indoles with alkyl alkynes. In the presence of cobalt catalyst merging with reducing reagent and chiral ligands, this annulation reaction proceeds smoothly under mild conditions to afford various dihydroquinolines, dihydroisoquinolines, dihydropyridines, dihydroquinoxaline, and C2-spiroindolines bearing spiro quaternary stereocenters (76 examples) in moderate to good yields and excellent enantioselectivities (up to 99%).

Representative Examples

- ❑ As a consequence, **extensive attention** has been devoted to the asymmetric synthesis of these molecules. (**对...产生了巨大关注**)
- ❑ **As a complementarity**, our dearomative umpolung reaction under easily available Co-catalysis leads to a wide scope of N-heteroarenes (electron-deficient quinolines, isoquinolines, pyridines, quinoxaline, and electron-rich indoles) and alkynes. (**作为互补**)

Acknowledgement

Thanks for your attention