

The C-H Activation/1,3-Diyne Strategy for Synthesis of Diverse Bisheterocycles

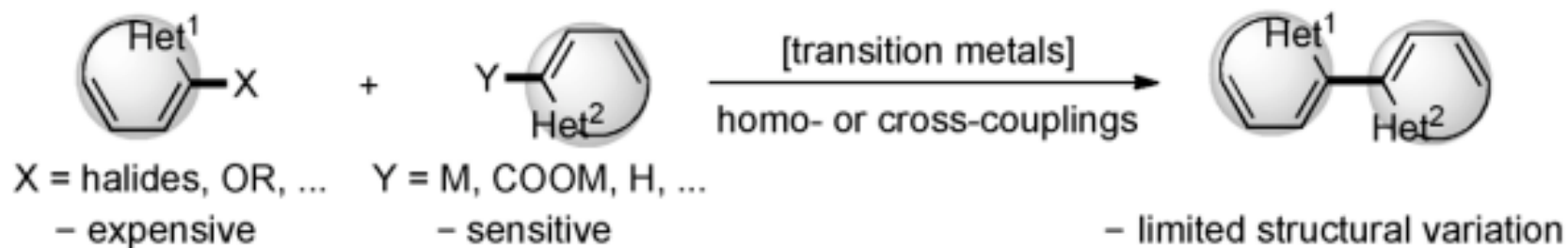
Reporter: Pingping Duan

Supervisor: Prof. Zhao

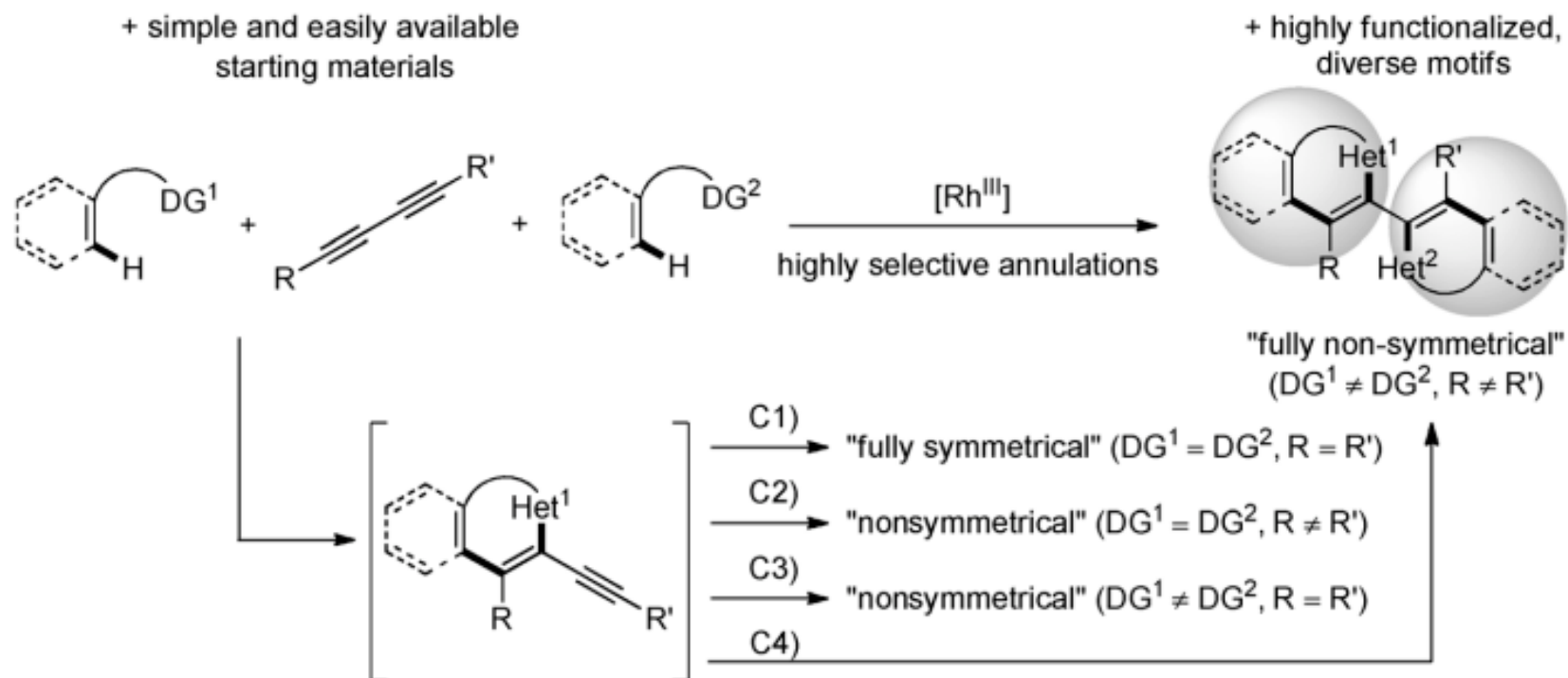
Dr. Hong

2014-08-02

Conventional Strategy

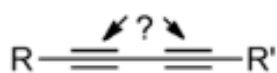


C-H Activation/1,3-Diyne Strategy



challenges in selectivity:

1) chemoselectivity



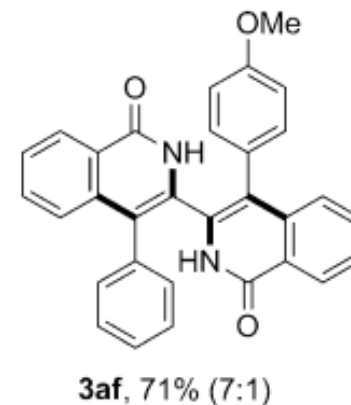
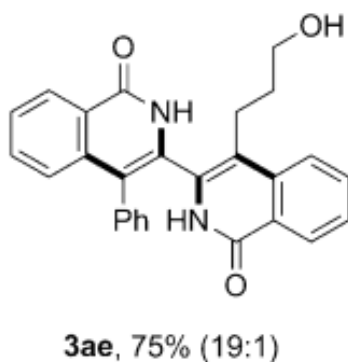
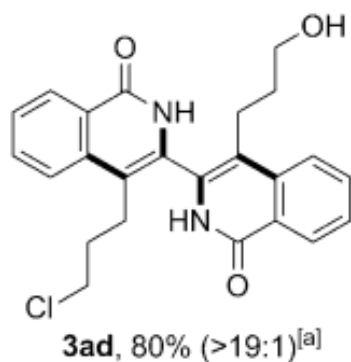
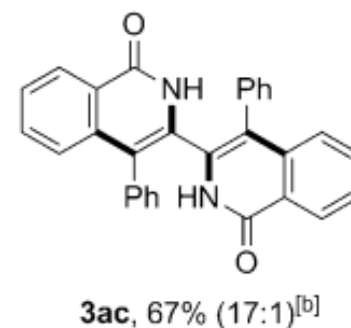
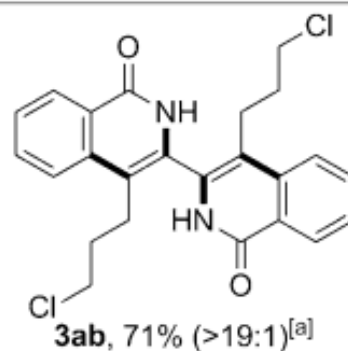
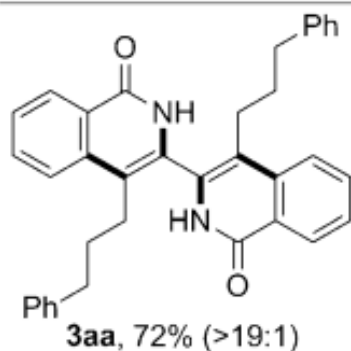
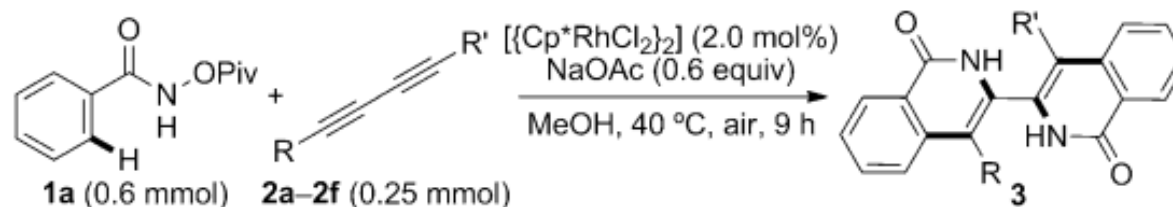
2) regioselectivity



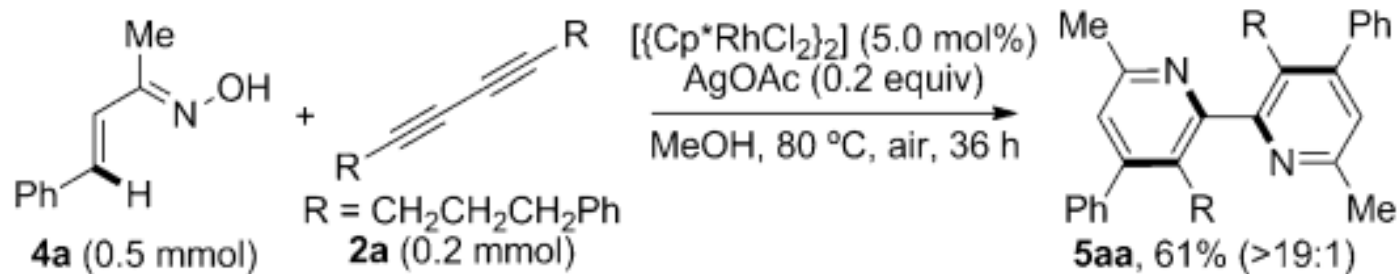
3) mono- vs. diannulation selectivity



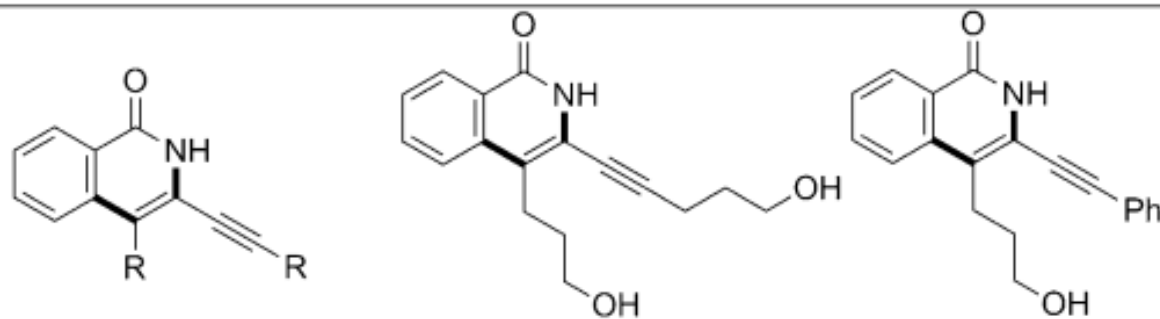
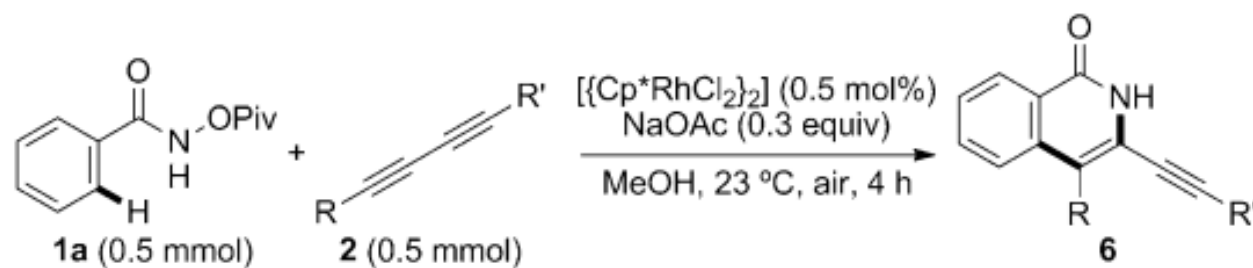
Formation of Bisisoquinolones



Synthesis of 2,2'-Bipyridines



Formation of Alkynylated Heterocycles



R = CH₂CH₂CH₂Ph, **6a**, 97% (>19:1)

4 mmol scale: 93%, 1.51 g

R = CH₂CH₂CH₂Cl, **6c**, 94% (>19:1)

R = CH₂CH₂CH₃, **6d**, 96% (>19:1)

R = TMS, **6e**, 88% (>19:1)

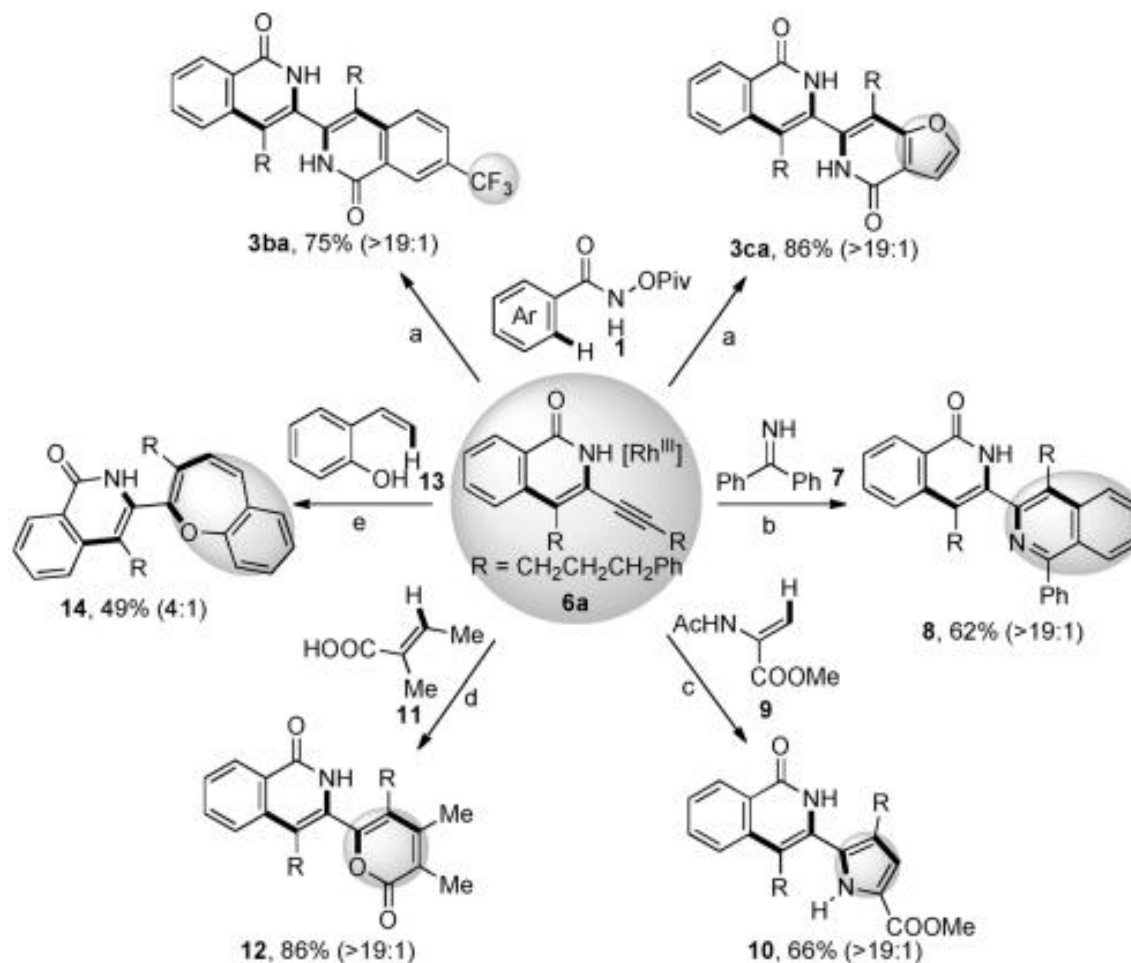
R = CH₂OPh, **6f**, 85% (>19:1)^[a]

R = Ph, **6g**, 89% (13:1)

6b, 92% (>19:1)

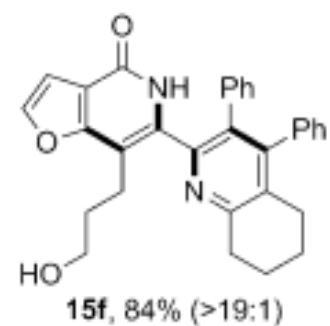
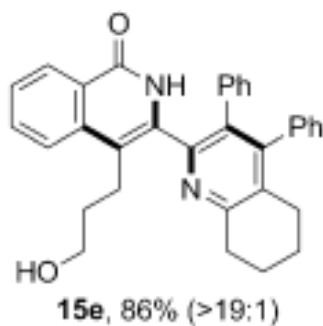
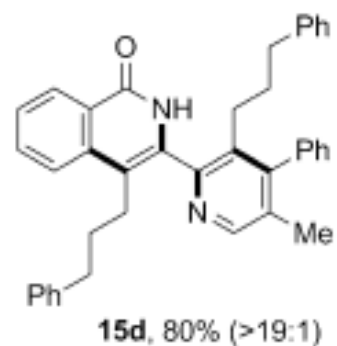
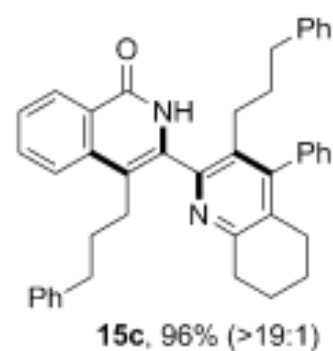
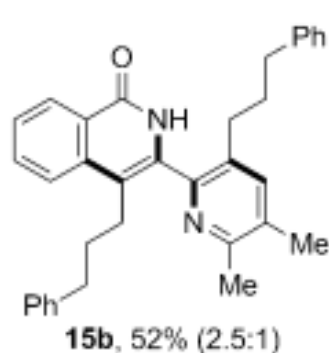
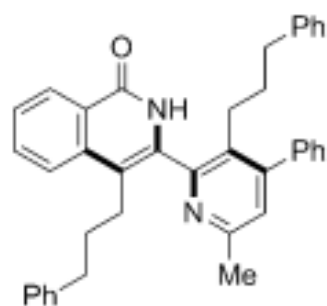
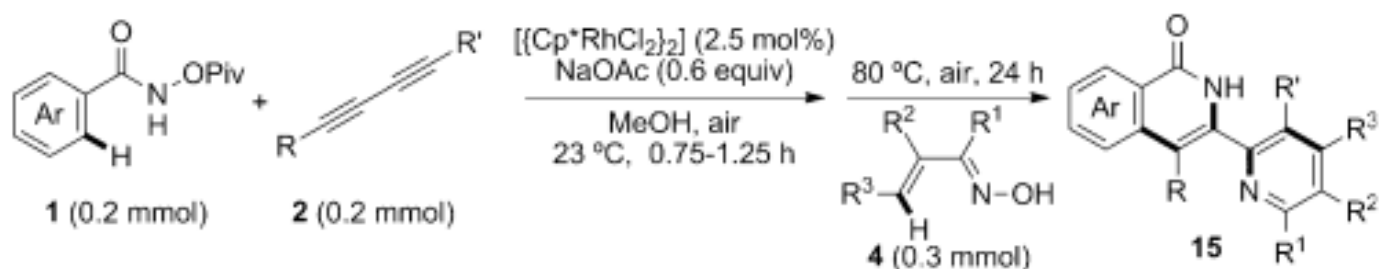
6h, 82% (10:1)^[b]

Synthesis of Nonsymmetrical Bisheterocycles through a Second Annulation

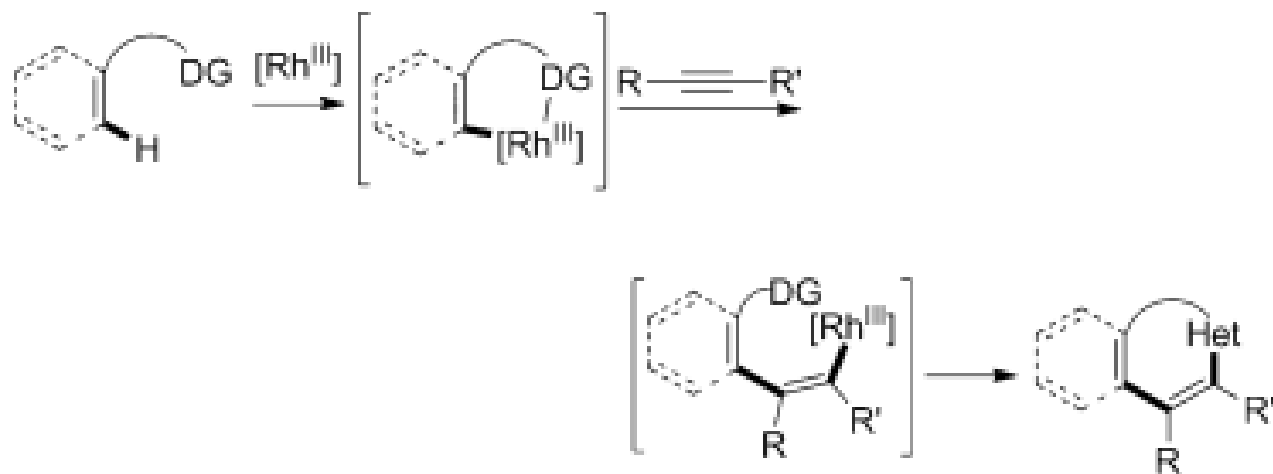


a) $[\{\text{Cp}^*\text{RhCl}_2\}_2]$, NaOAc, MeOH; b) $[\{\text{Cp}^*\text{RhCl}_2\}_2]$, $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$, DMF; c) $[\text{Cp}^*\text{Rh}(\text{MeCN})_3](\text{SbF}_6)_2$, $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$, cyclohexanone, O_2 ; d) $[\{\text{Cp}^*\text{RhCl}_2\}_2]$, Ag_2CO_3 ; e) $[\{\text{Cp}^*\text{RhCl}_2\}_2]$, $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$, air.

One-pot Formation of Bisheterocycles



Regioselectivity of the Migratory Insertion



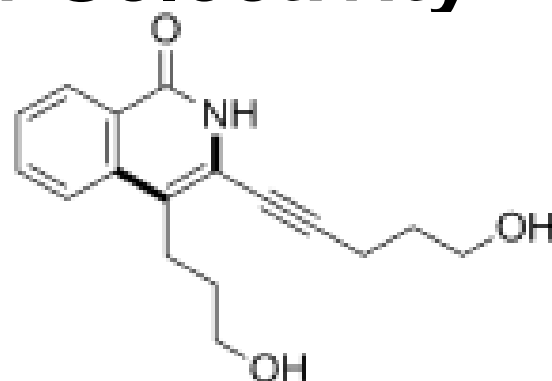
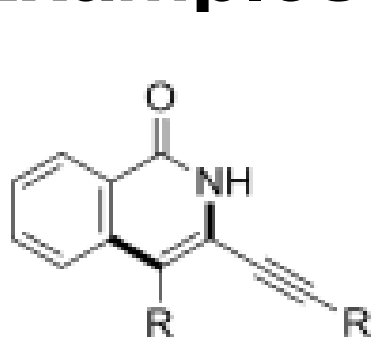
The priority of R' over R in regioselectivity:

Previous observations: Aryl > Alkyl; Alkenyl > Alkyl

New observations: Alkynyl > Phenyl > Alkyl

New observations: Isoquinolonyl > Phenyl > Alkyl

Examples for Selectivity



R = CH₂CH₂CH₂Ph, **6a**, 97% (>19:1) **6b**, 92% (>19:1)

4 mmol scale: 93%, 1.51 g

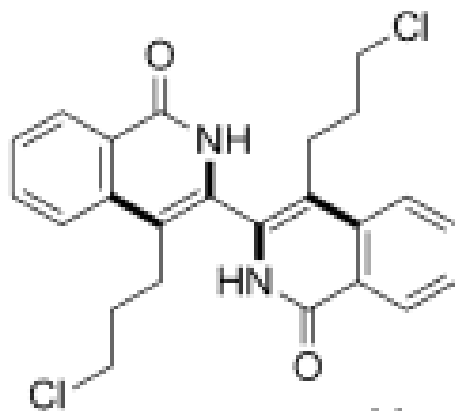
R = CH₂CH₂CH₂Cl, **6c**, 94% (>19:1)

R = CH₂CH₂CH₃, **6d**, 96% (>19:1)

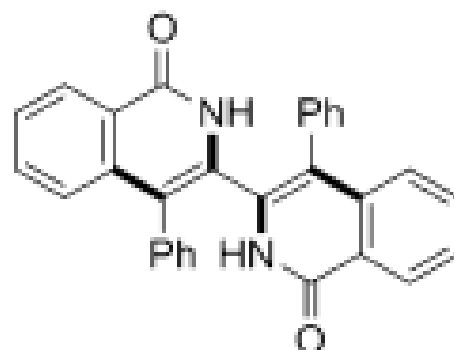
R = TMS, **6e**, 88% (>19:1)

R = CH₂OPh, **6f**, 85% (>19:1)^[a]

R = Ph, **6g**, 89% (13:1)



3ab, 71% (>19:1)^[a]

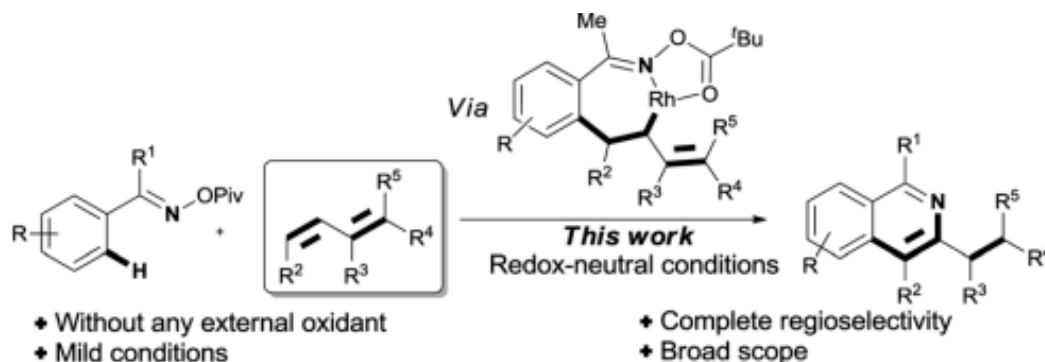


3ac, 67% (17:1)^[b]

Conclusion

- **formation of bisheterocycles in four patterns:**
 - fully symmetrical ones (Scheme 1, C1),
 - nonsymmetrical ones with the same core structures but different substituents (C2),
 - nonsymmetrical ones with two different core structures but with the same substituents arising from the symmetrical diynes (C3),
 - fully nonsymmetrical ones with different cores and substituents (C4).
- **Good functional groups compatibility**
 - halides, alcohols, and heteroarenes

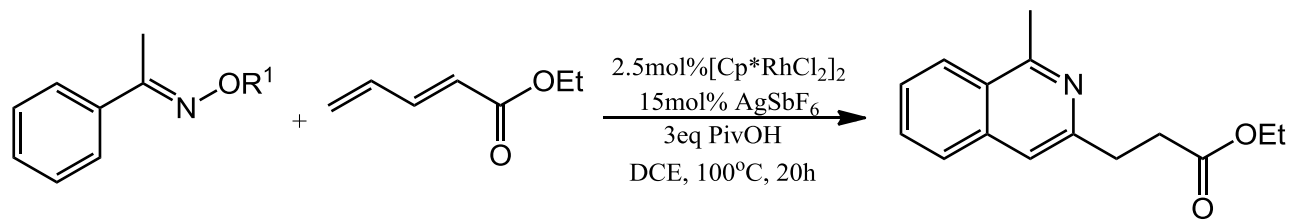
Rh(III)-catalyzed Isoquinoline Synthesis from 1,3-Dienes



Challenges:

- (1) the oxidative Heck reaction of aromatic oxime esters with alkenes is unknown;
- (2) the use of simple 1,3-dienes as the coupling partner in C–H activation has been rarely realized;
- (3) The Rh(III)-catalyzed C–H functionalization/aromatization via a double-bond migration cascade has never been reported.

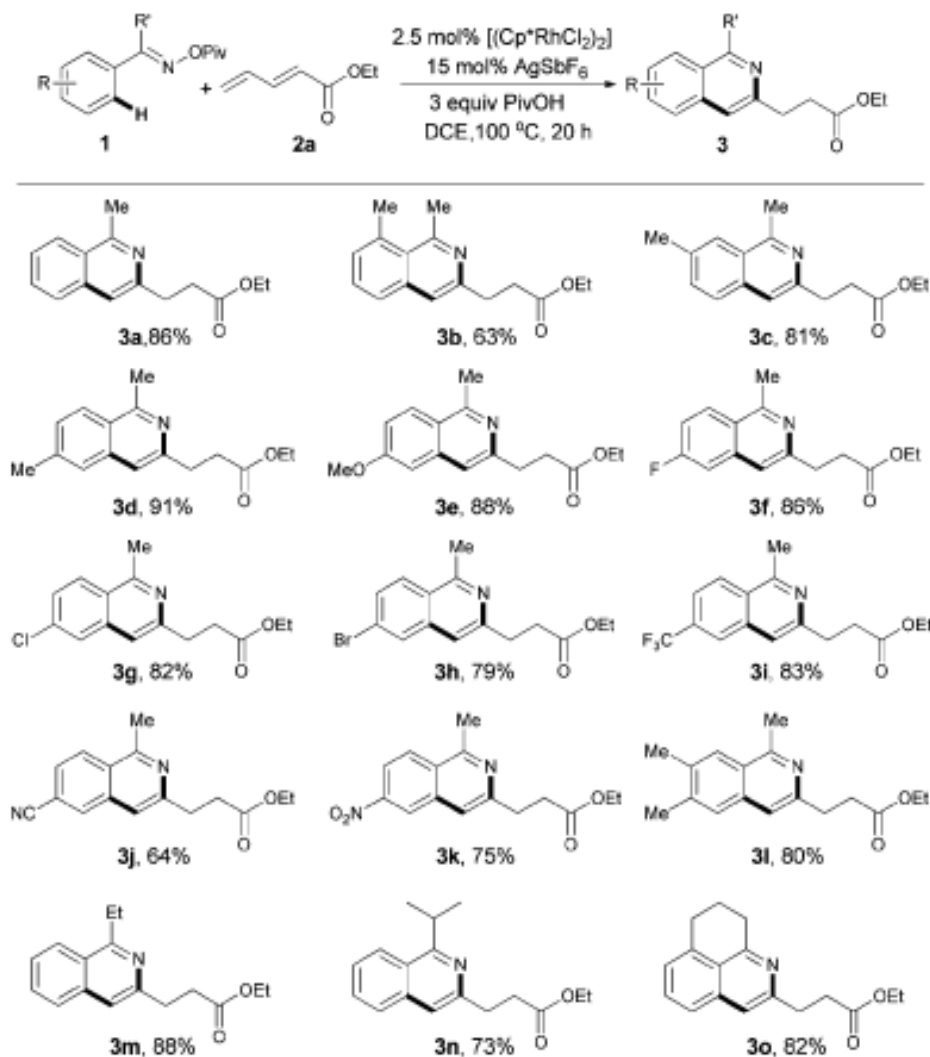
Optimization of Reaction Condition



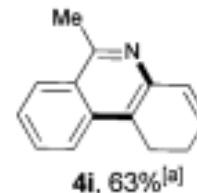
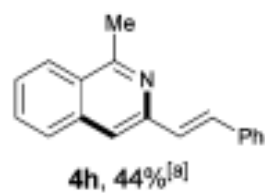
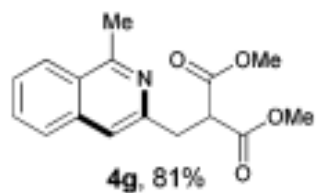
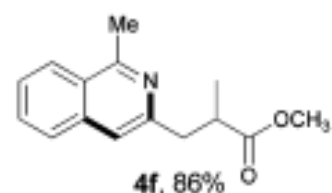
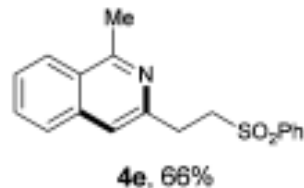
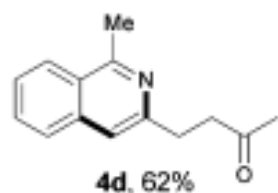
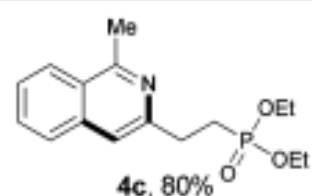
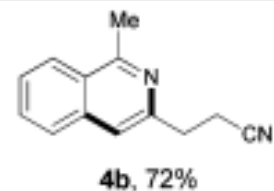
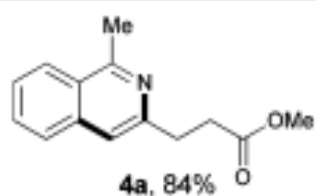
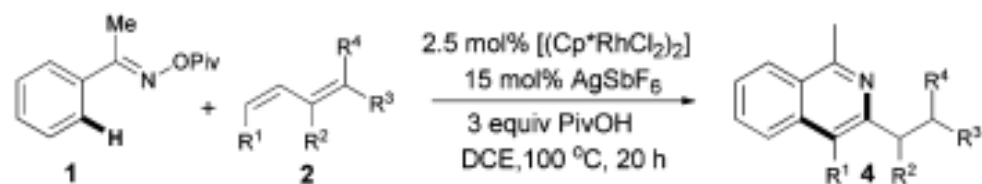
Entry	R ¹	Additive	Solvent	Yield ^b [%]
1	H	—	DCE	n.r
2	Ac	—	DCE	12
3	Boc	—	DCE	n.r
4	Piv	—	DCE	54
5	Piv	PivOH	DCE	86
6	Piv	AcOH	DCE	37
7 ^c	Piv	K ₂ CO ₃	DCE	21
8	Piv	PivOH	Dioxane	66
9	Piv	PivOH	PhCl	73
10	Piv	PivOH	EtOH	Trace
11	Piv	PivOH	CH ₃ CN	Trace
12 ^d	Piv	PivOH	DCE	76
13 ^e	Piv	PivOH	DCE	69
14 ^f	Piv	PivOH	DCE	65
15 ^g	Piv	PivOH	DCE	68

^aRhCp*(CH₃CN)₃(SbF₆)₂ was used as the catalyst. ^ePivOH was used. ^f80°C. ^g12 h.

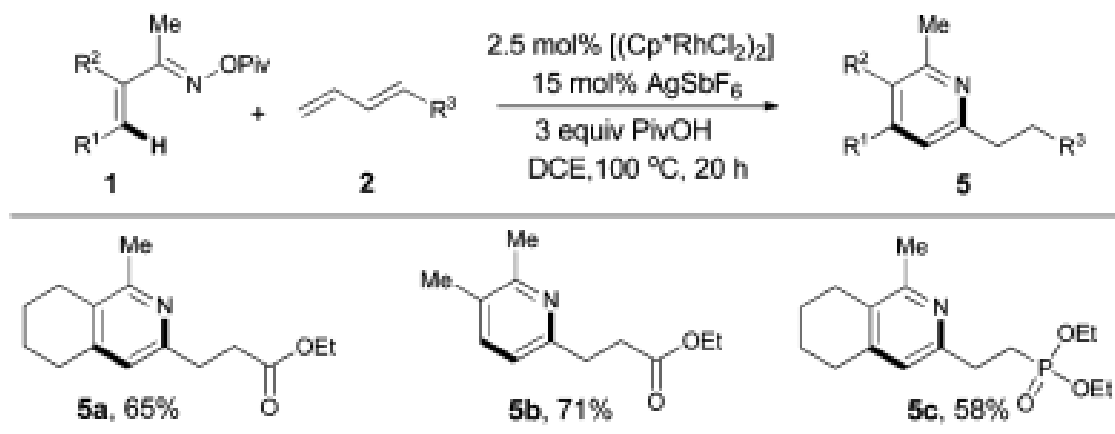
Scope of Aromatic *o*-Pivaloyl Ketoximes



Scope of 1,3-Dienes

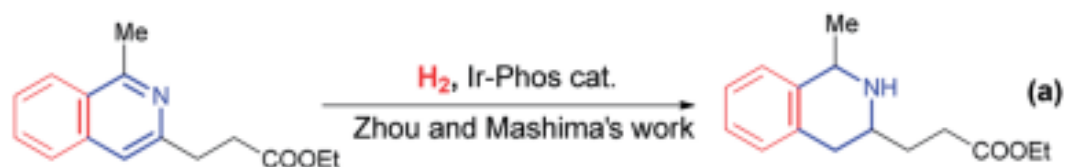


Preparation of Pyridines

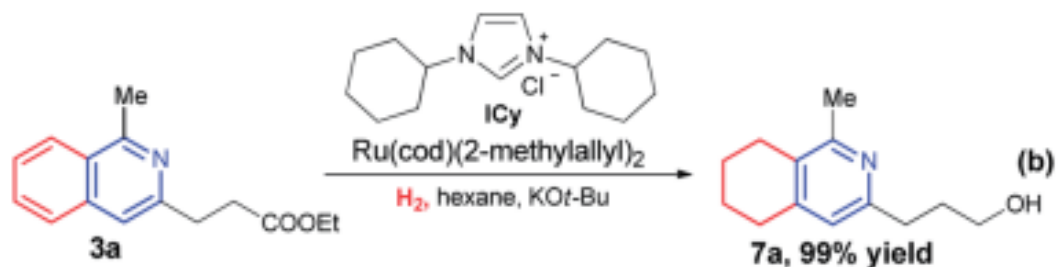


Hydrogenation of Isoquinoline Products

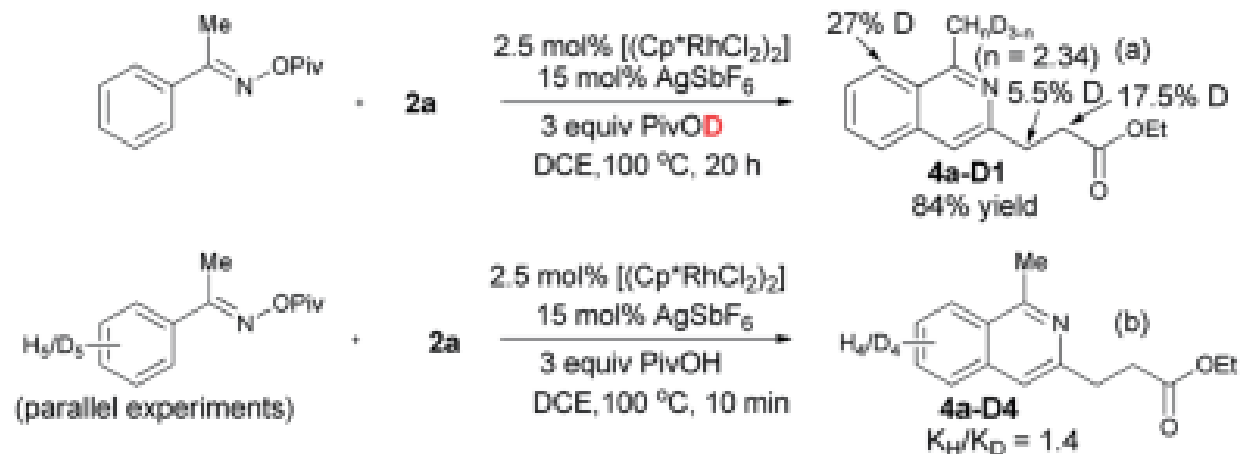
The reported hydrogenation of isoquinoline:



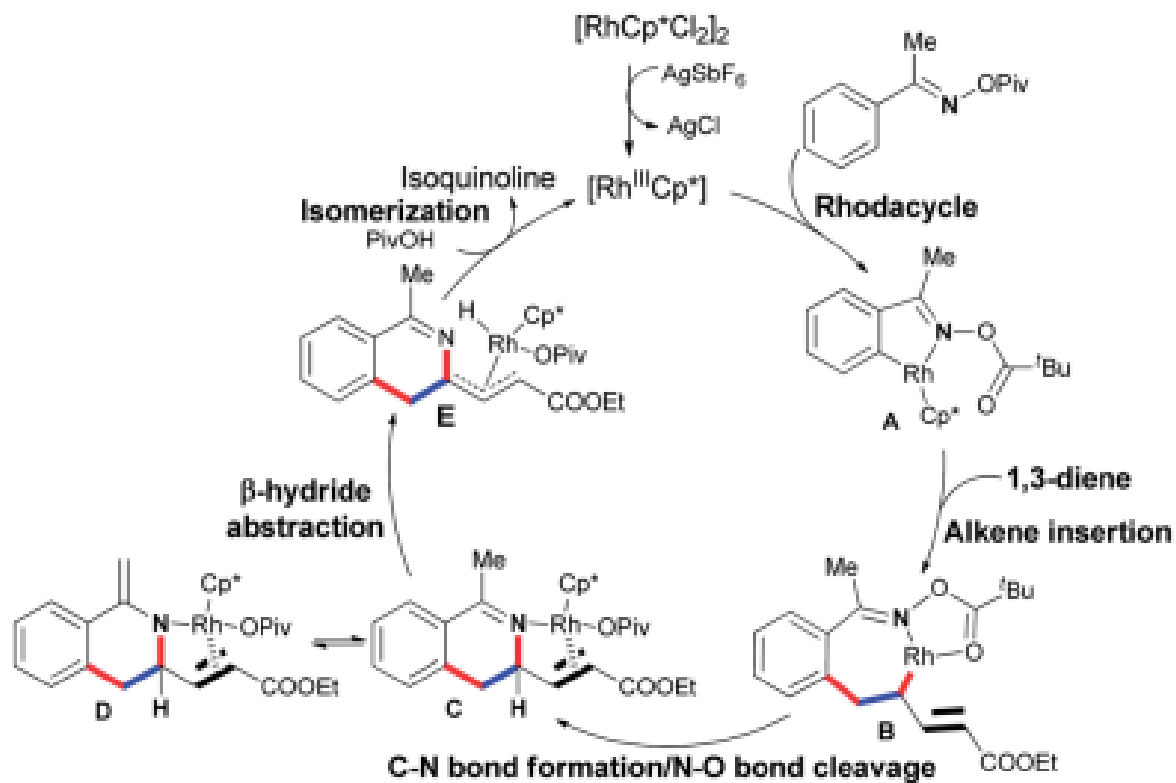
Our present work for application of isoquinoline:



Deuteration Experiments



Proposed Mechanism



Conclusion

- Rhodium(III)-catalyzed redox-neutral C–H activation/
cyclization/isomerization strategy
- Aromatic oxime esters and diverse 1,3-dienes
- Advantages:
 - no need for an external oxidant;
 - simple and convenient reaction conditions;
 - complete regioselectivity;
 - broad scope of substrates.