Asymmetric Catalysis for Fine Chemical Synthesis

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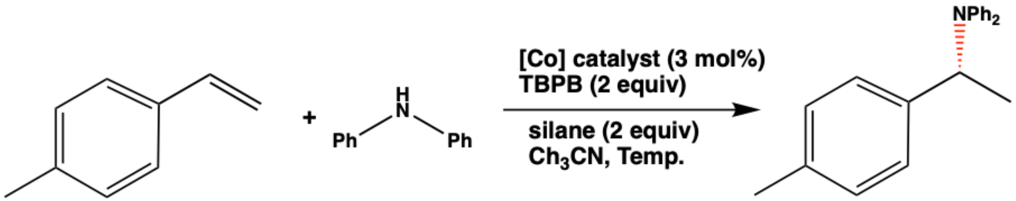
Angewandte
Chemie

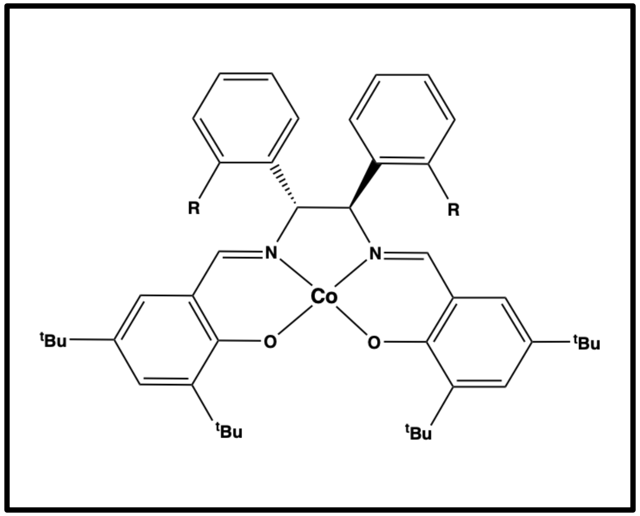
Cobalt-Catalyzed Enantioselective Hydroamination of Arylalkenes with Secondary Amines

H. Miao, M. Guan, T. Xiong, G. Zhang, Q. Zhang

Introduction: Reaction and Reactivity

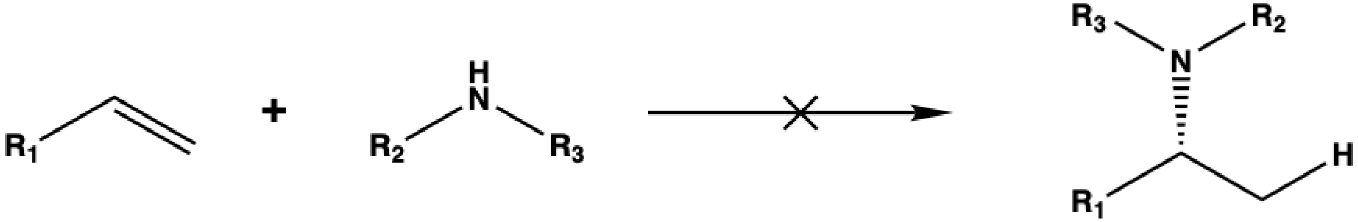
Hydroamination of Arylalkenes





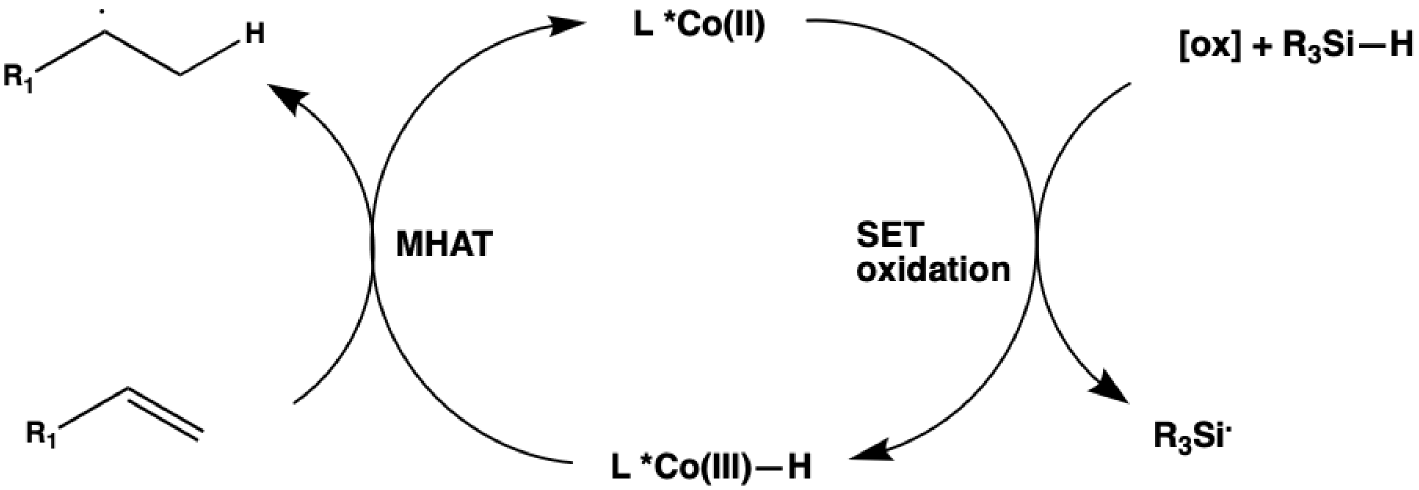
- This reaction is a **Markovnikov hydroamination of Arylalkenes**
- **Nucleophile**: Free secondary aryl/alkyl amines
- **Electrophile:** Arylalkenes
- **Catalyst**: Chiral salen-cobalt(II) complex
- **Bond formation**: Free amine attack on the diastereomeric alkylcobalt(IV) complex

Principle of activation



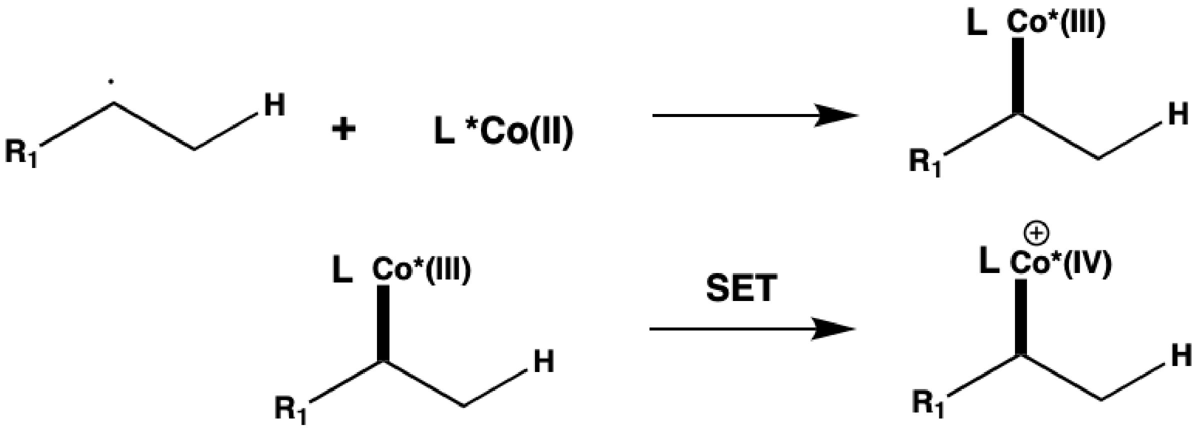
- Reaction challenge : **inert alkene** and **coordinating secondary amine** → require activation

Principle of activation



- Reaction challenge : **inert alkene** and **coordinating secondary amine** → require activation
- Radical activation : **Metal Hydride-hydrogen Atom Transfer** (MHAT) to alkene

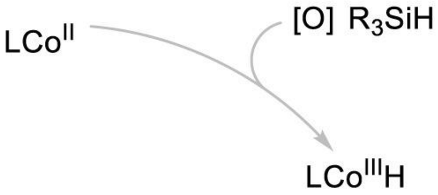
Principle of activation



- Reaction challenge : **inert alkene** and **coordinating secondary amine** ⟶ require activation
- Radical activation : **Metal Hydride-hydrogen Atom Transfer** (MHAT) to alkene
- SET oxidation of **Co(III)-alkyl to Co(IV)-alkyl** activates the intermediate for nucleophilic substitution.
- Enantioselectivity**: ligand-controlled radical capture**, followed by **SN2-like** that leads to an inversion of configuration.

Catalytic Cycle

- **Cat. (re)activation** by reaction of Co^{II} precursor with the oxidant and silane *in situ.*



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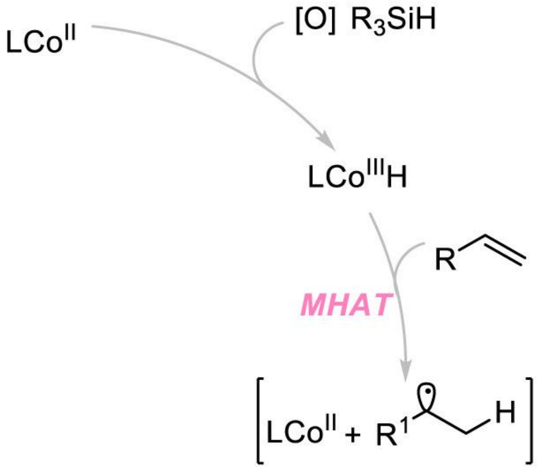

Catalytic Cycle

- **Cat. (re)activation** by reaction of Co^{II} precursor with the oxidant and silane *in situ.*
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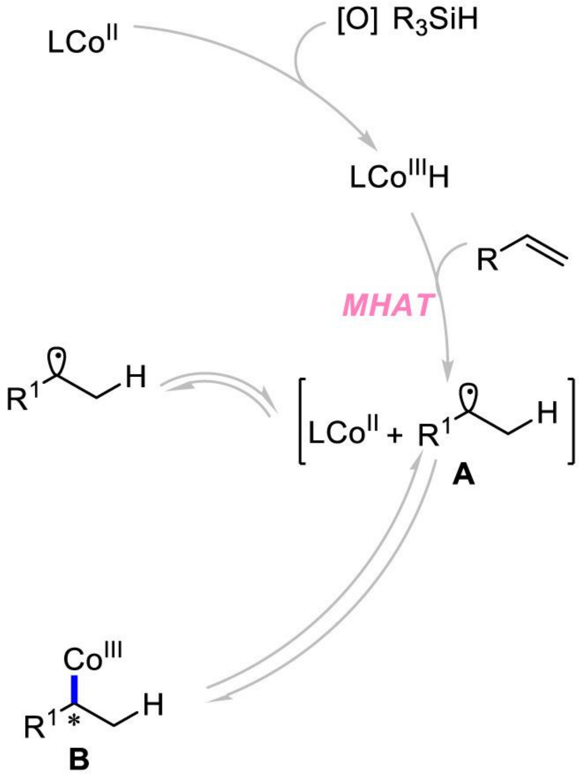
- **Radical capture** to form alkylcobalt(III)



Catalytic Cycle

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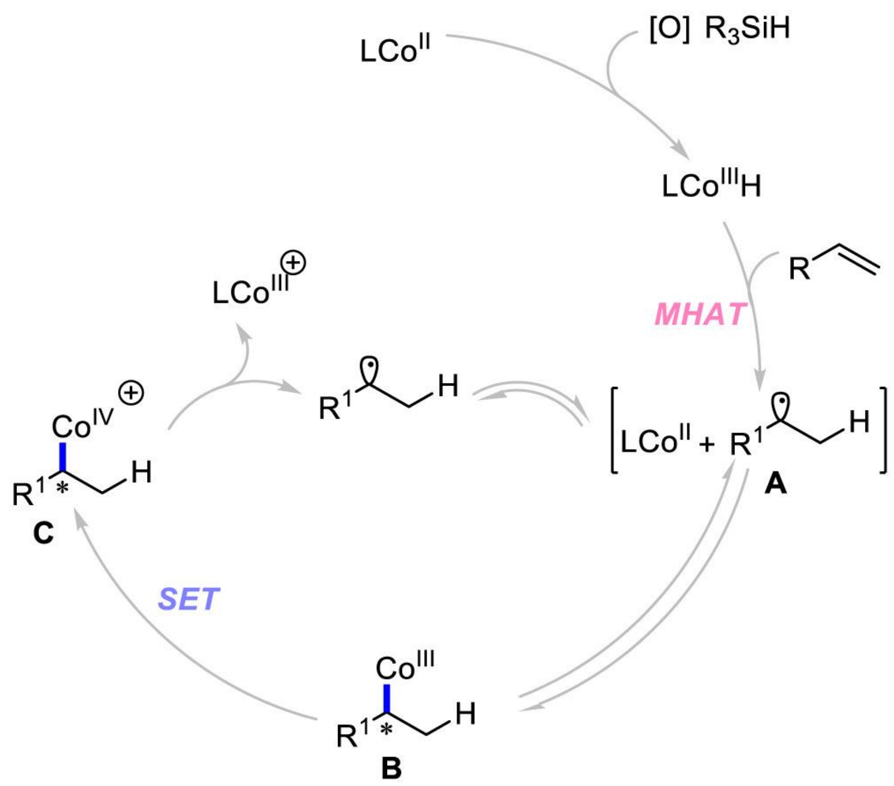
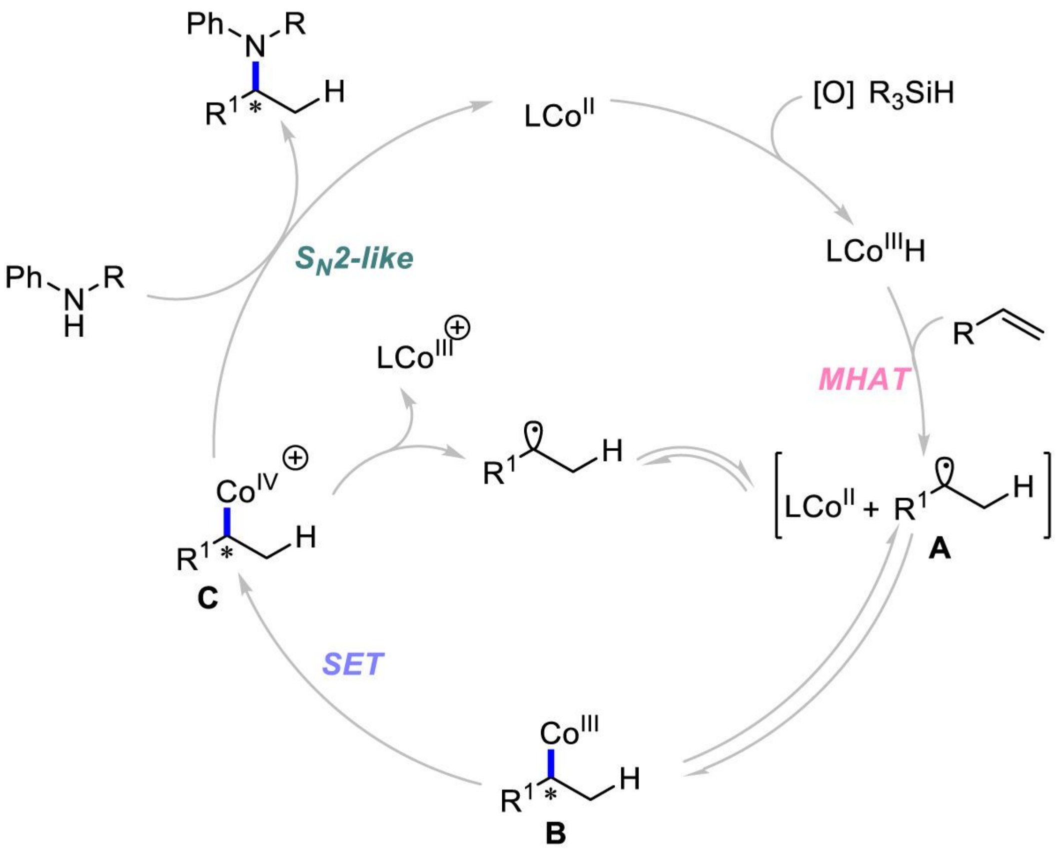
- **MHAT** to alkene
- **Radical capture** to form alkylcobalt(III)
- SET oxidation to generate **LUMO-activated** complex alkylcobalt(IV)

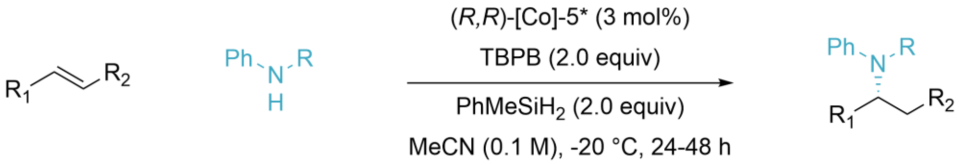


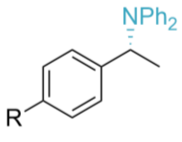
Catalytic Cycle

- **Cat. (re)activation** by reaction of Co^{II} precursor with the oxidant and silane *in situ.*
- **MHAT** to alkene
- **Radical capture** to form alkylcobalt(III)
- SET oxidation to generate **LUMO-activated** complex alkylcobalt(IV)
- **Bond Formation & Catalyst turnover** *via* *S_N2-like* amination of the diastereomeric alkylcobalt(IV)



Scope and limitations

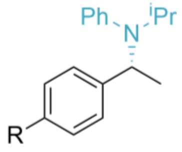




R = Me, Et, iPr, tBu, (OPh)

60-78% (98%)

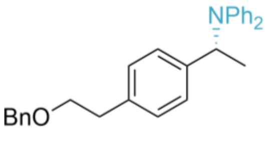
91-95% ee (83% ee)



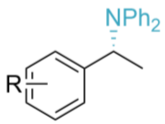
R = H, Cl, Br, F, Ph

42-62%

85-95% ee



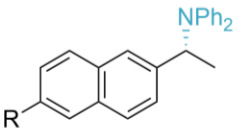
84%, 91% ee



m-Me, 66%, 91% ee

m-OMe, 56%, 92% ee

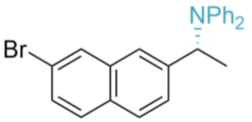
o-Me, 22%, 75% ee



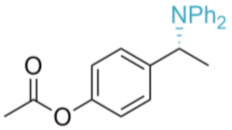
R = H, OTs, F, Br, (OMe)

64 - 80% (78%)

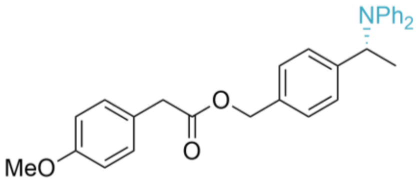
90 - 95% ee (73% ee)



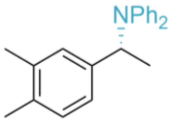
40%, 92% ee



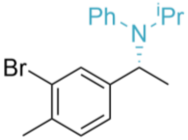
44%, 81% ee



54%, 91% ee



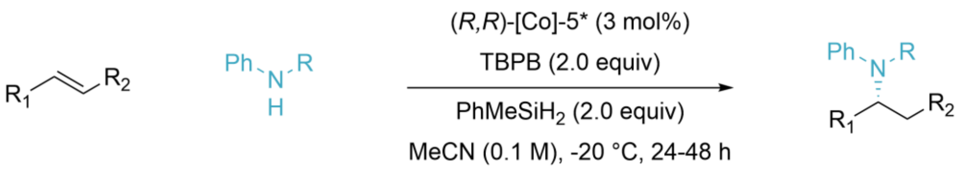
98%, 92% ee

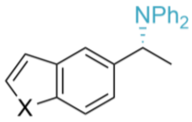


62%, 95% ee

- Wide range of substitution are tolerated on phenyl/naphthyl
- *O*-substitution has low yield, moderate *ee* (likely steric)
- Electron poorer styrene dimerize: overcome with e$^-$ rich ^{i}*Pr*-aniline

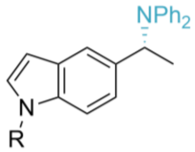
Scope and limitations





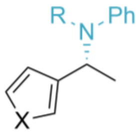
X = O, 56%, 87% ee

X = S, 60%, 88% ee



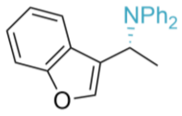
Ts, 68%, 94% ee

Ac, 60%, 91% ee

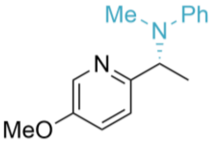


R = Me, X = O
72%, 70% ee

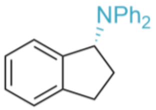
R = iPr, X = S
58%, 80% ee



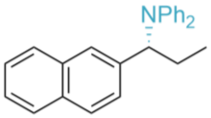
65%, 83% ee



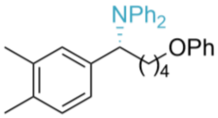
46%, 67% ee



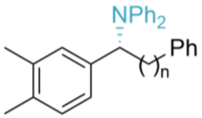
58%, 74% ee



64%, 91% ee

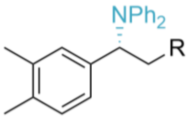


44%, 91% ee



n = 4, 60%, 91% ee

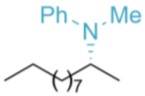
n = 3, 50%, 81% ee



Me, 90%, 80% ee

Et, 48%, 81% ee

nPr, 48%, 91% ee

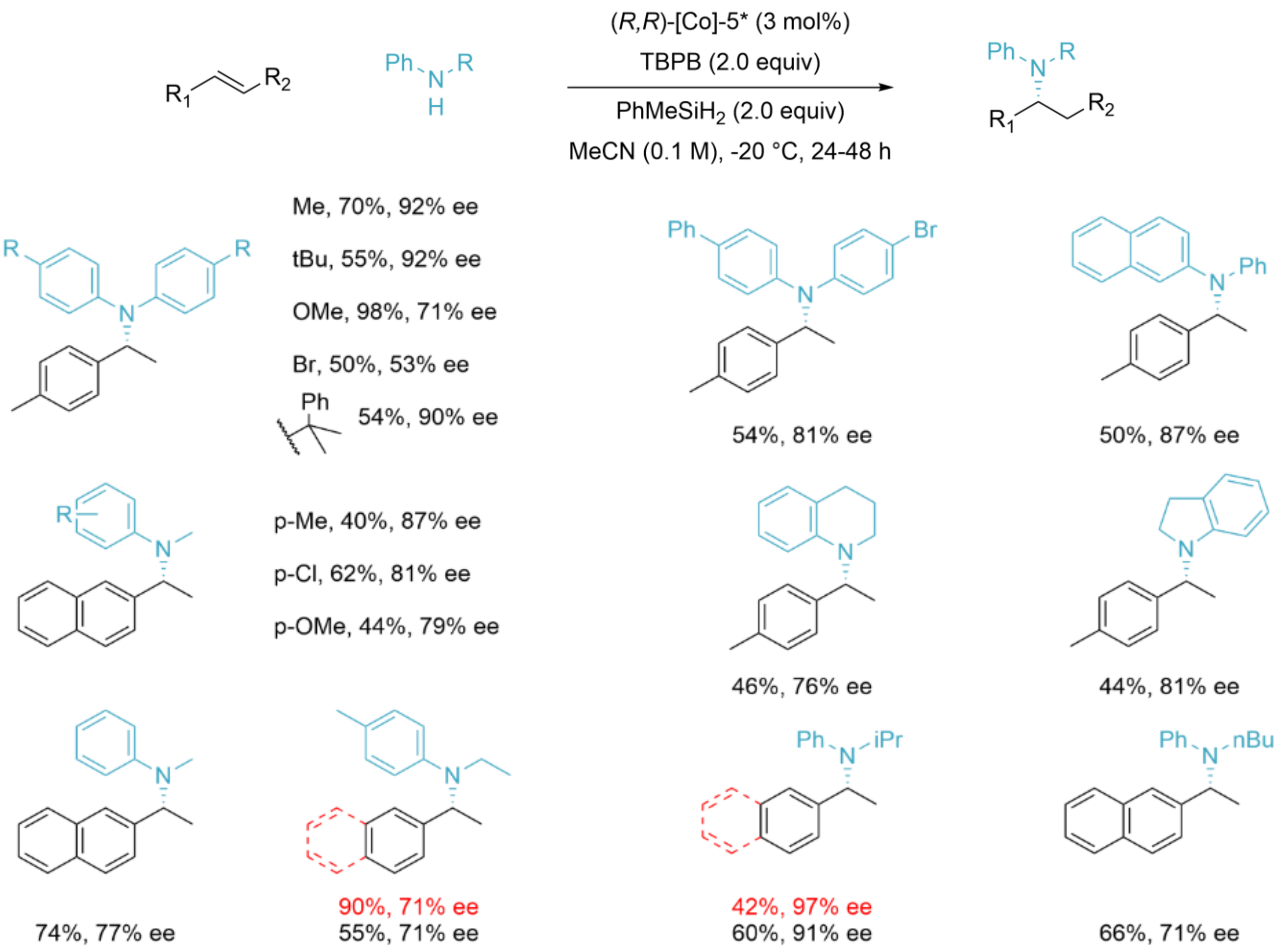


60%, 16% ee

- Heteroaromatics and *β*-substituted arylalkene well supported
- Unactivated alkene works, but low *ee*

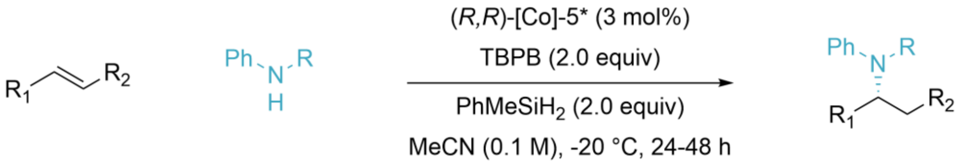
=> low differentiability between the alkyl chains

Scope and limitations

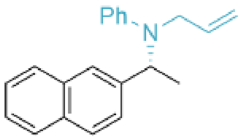


- Broad scope of N-substituted aryl and aliphatic aniline
- More bulky, better stereocontrol
- Electronics of the alkene have low impact on *ee* (naphtyl vs phenyl)

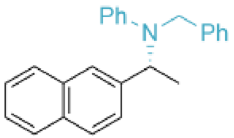
Scope and limitations



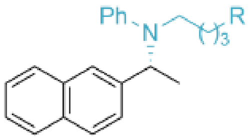
(*R*,*R*)-[Co]-5* (3 mol%)
TBPB (2.0 equiv)
$PhMeSiH_2$ (2.0 equiv)
MeCN (0.1 M), -20 °C, 24-48 h



72%, 77% ee

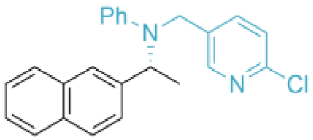


84%, 83% ee



Ph, 72%, 91% ee

CN, 40%, 91% ee



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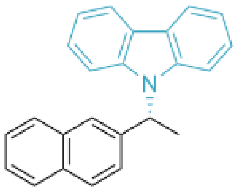
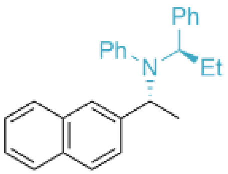
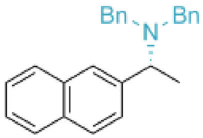


54%, 91% ee



(*R*, *R*)-L*, 58%, 99% de

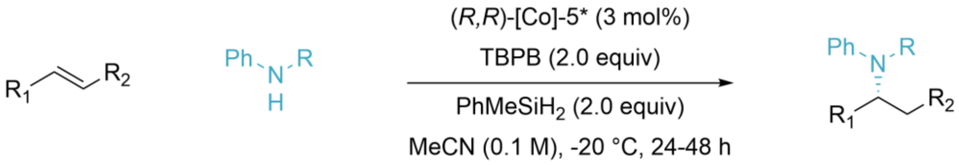
(*S*, *S*)-L*, 50%, -99% de

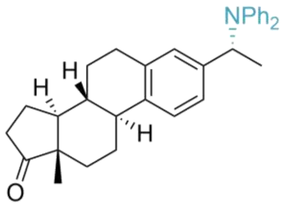


22%, 92% ee

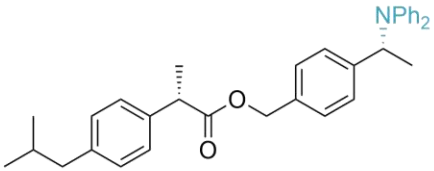
- Ph, CN, pyridyl well tolerated despite potential coordination to Co
- Stereocontrol not influenced by chiral amine
- Dibenzylamine required cat. $Sc(OTf)_3$
- Dialkylamine not tolerated: too Lewis basic

Scope and limitations

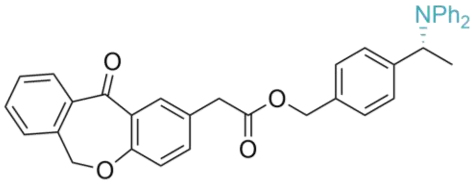




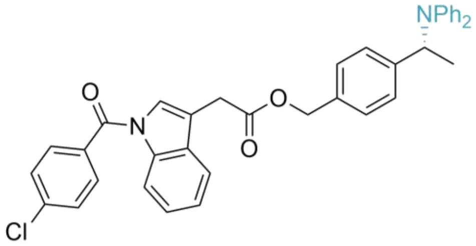
Estrone, 88%, 96% de



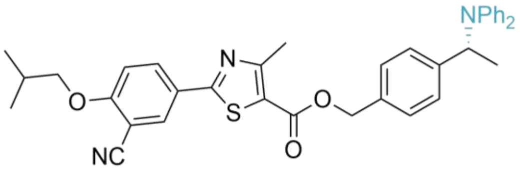
(+)-ibuporofene, 42%, 92% de



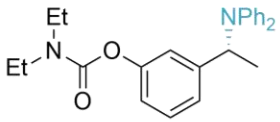
Isoxepac, 61%, 93% ee



Indomethacin, 76%, 85% ee



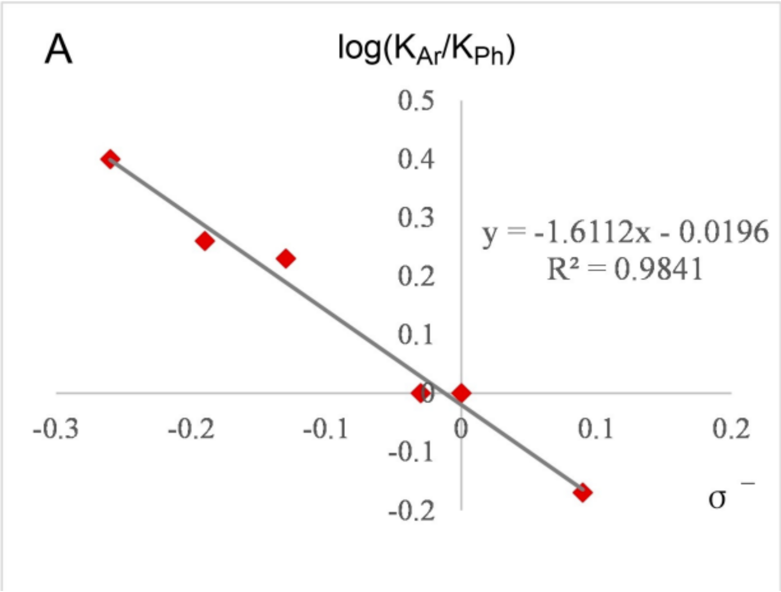
64%, 91% ee

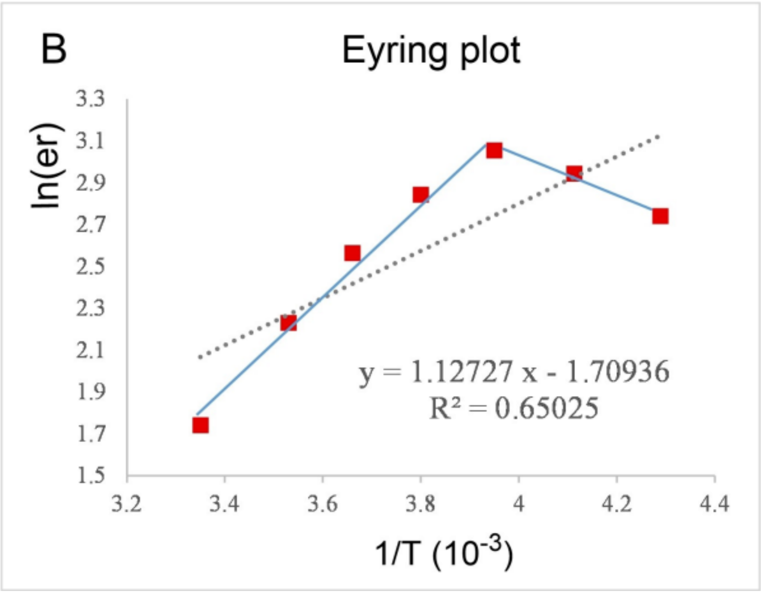


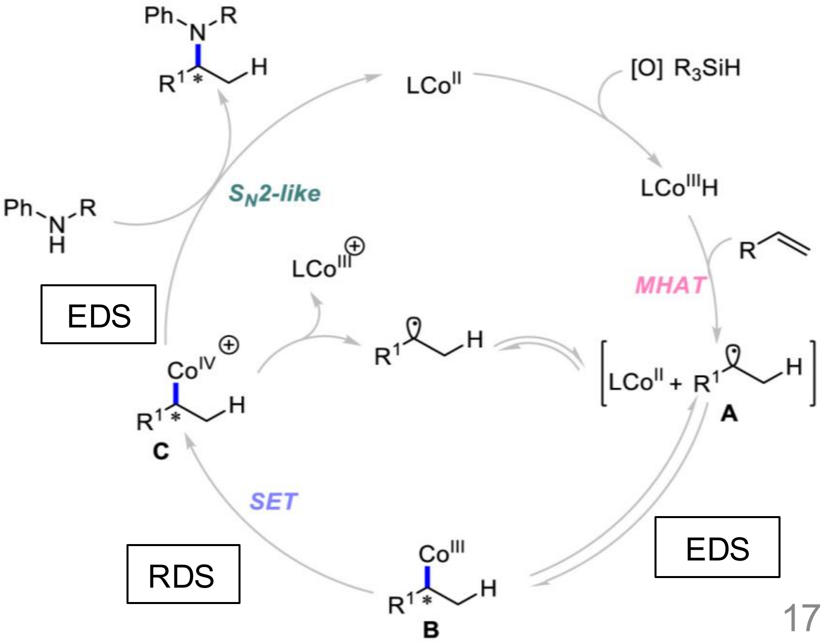
Rivastigmin analogue
46%, 85% ee

- Works also well with complex alkene and bioactive molecule

Mechanistic experiments







- **Hammett analysis:** $\rho < 0$ support cationic $[Co^{IV}]^+$
- **Kinetic experiments**: RDS is formation of $[Co^{IV}]^+$
- **Eyring:** suggest 2 enantiodetermining steps (EDS)

Critical analysis: Novelty

Strong points

- Opened enantioselective hydroamination of alkene to large variety of secondary arylamines
- Usage of Co
- MHAT for enantioselective hydroamination with amines

Weaker points

- Hydroamination of alkenes is a well-established subject
- Cobalt hydrofunctionalization of alkene *via* MHAT and cationic alkylcobalt (IV) species are known

Critical analysis: Practicability

Strong points

- Mild conditions
- Use of Cobalt, a cheap and available metal
- Good functional group tolerance
- Allows late-stage modification of bioactive compounds
- Good enantioselectivity

Weaker points

- Radical mechanism : potential side reaction => moderate yield
- Relatively long reaction time
- Methodology limited to arylalkenes and certain secondary amines

Critical analysis: Sustainability

Strong points

- Use of Earth-abundant Metal as Catalyst w/ Relative Low Loading (3 mol%)
- Easy accesible Ligand synthesis
- Catalyst MeCN is OK (classified as <yellow> solvent)

Weaker points

- Requires Cooling (-20 ºC)
- Stoichiometric amounts of Oxidant and Reductant
- Poor Atom Economy

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Thanks for your attention

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Questions

Question 1

The first reaction of the alkene with the metal-hydride is not following the classical insertion mechanism: What is the mechanism and is this process reversible or not?

Question 2

What is the experimental evidence for the presence of radical intermediates?

Question 3

What could be the rate limiting step and what is the evidence for it?