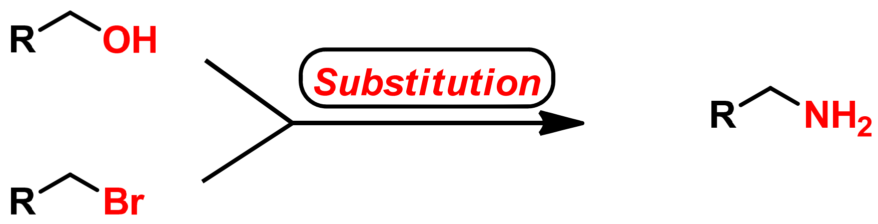
Asymmetric Hydroamination Reactions of Carbon-Carbon Multiple Bonds

Christèle Roux

21 - 01 - 2013

Introduction

- Classical methods for synthesis of molecules contain amine functionalities :



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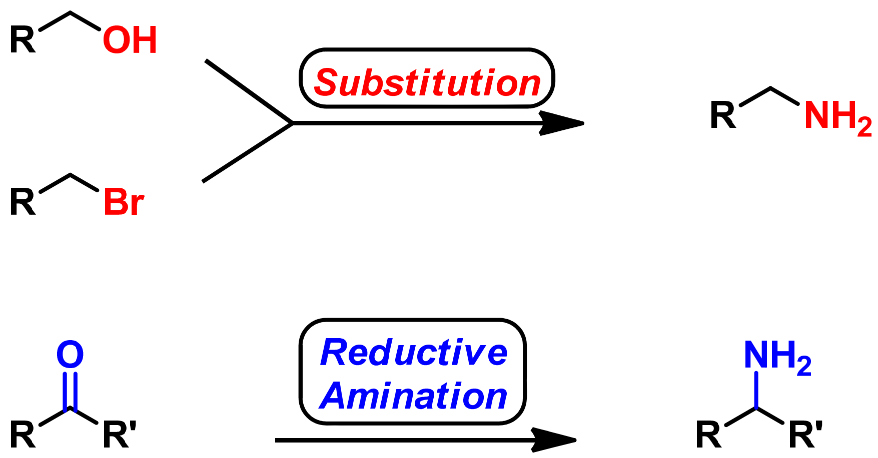
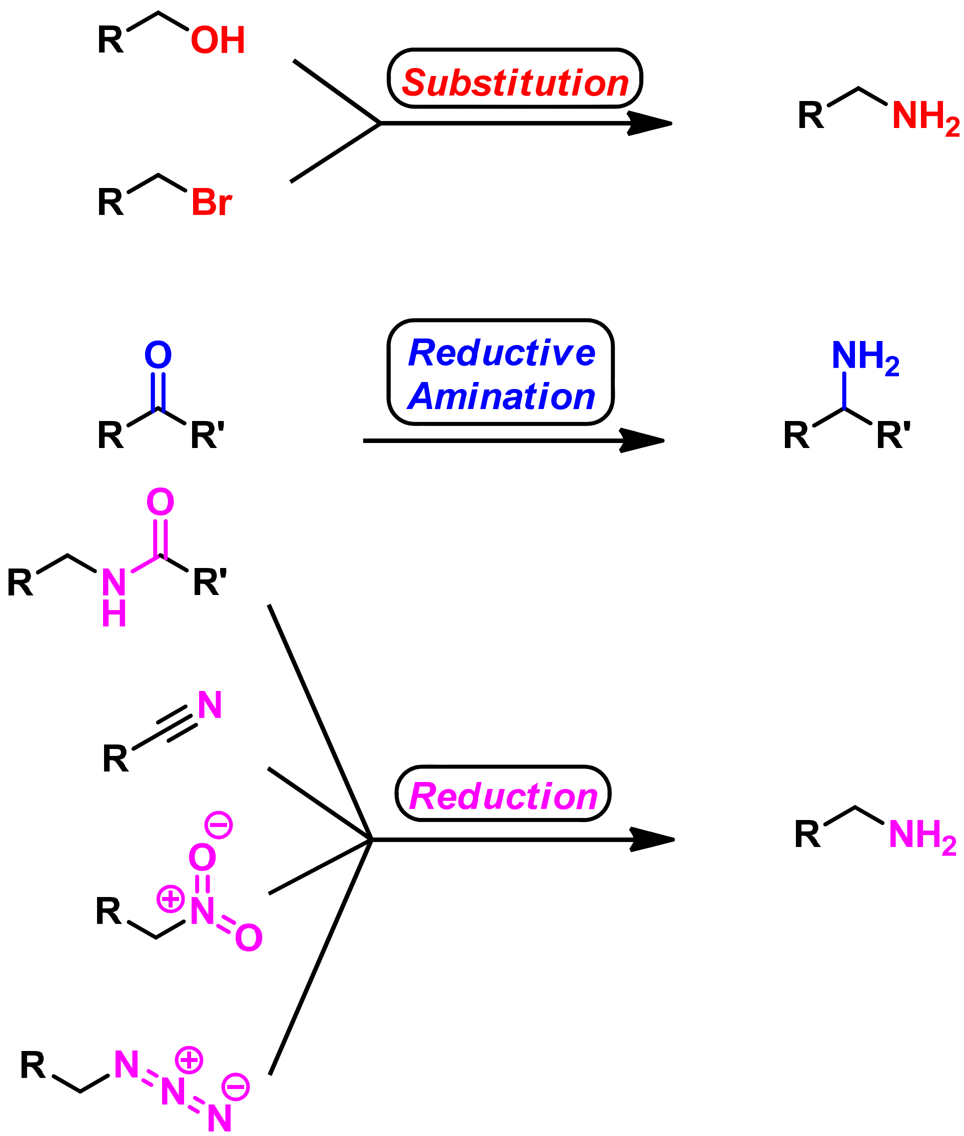


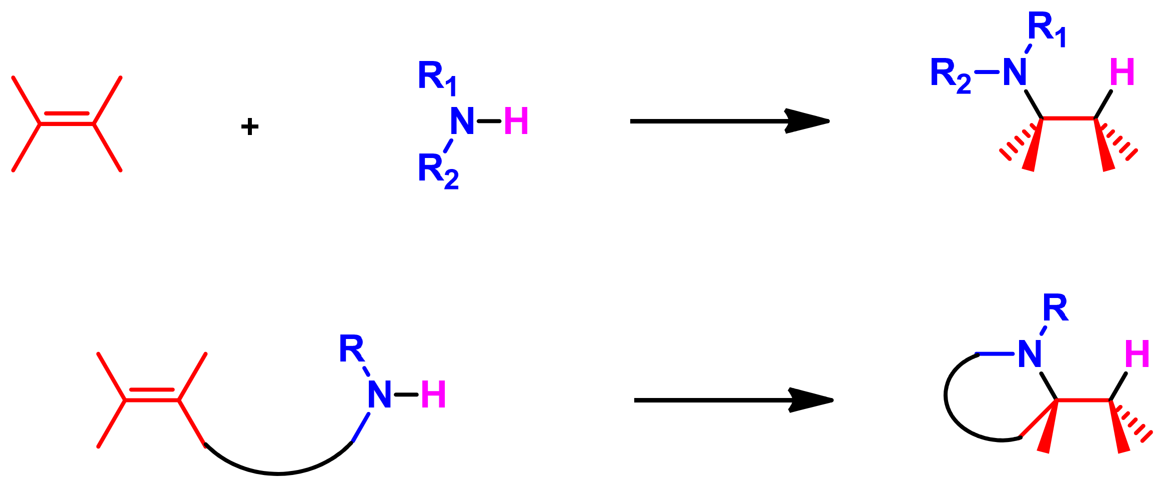
Introduction

➢ Classical methods for synthesis of molecules contain amine functionalities :



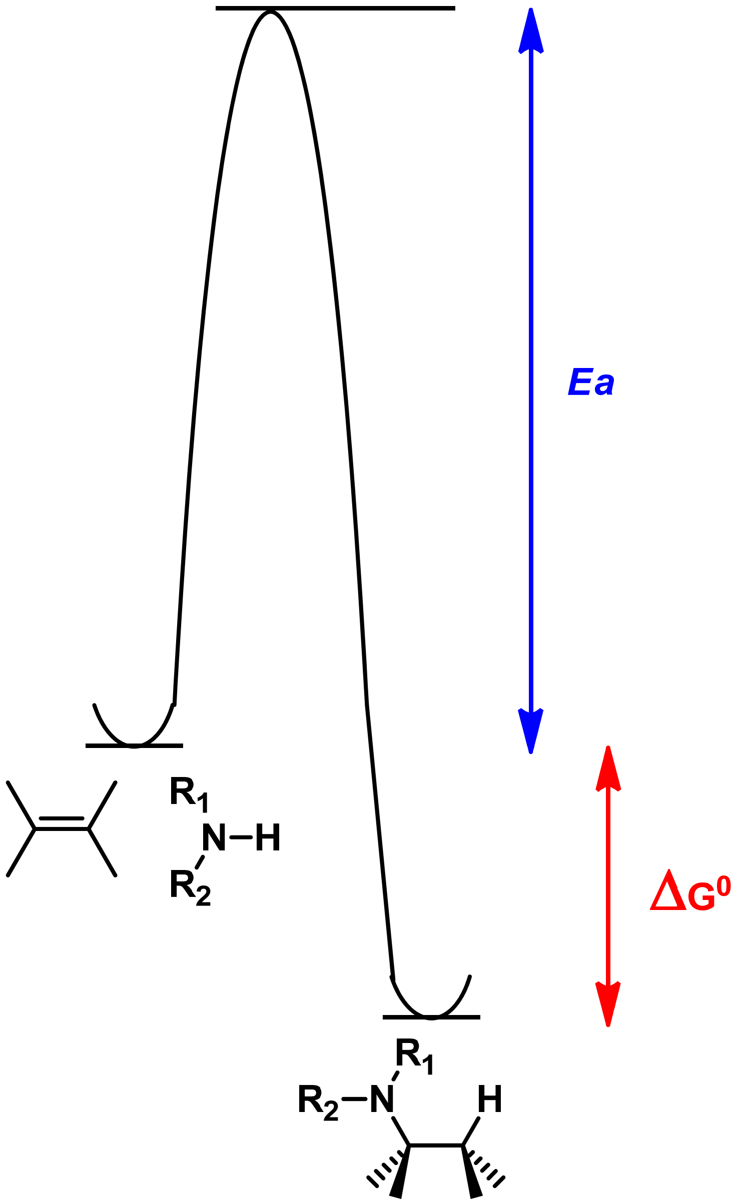
Hydroamination reaction

➢ Hydroamination : a 100% atom-economical, waste free process of fundamental simplicity.



➢ Efficient method for the synthesis of a wide variety of industrially relevant basic and fine chemicals from readily available and inexpensive starting materials.

Mechanistic aspect



➢ The direct addition of amines to alkenes is :

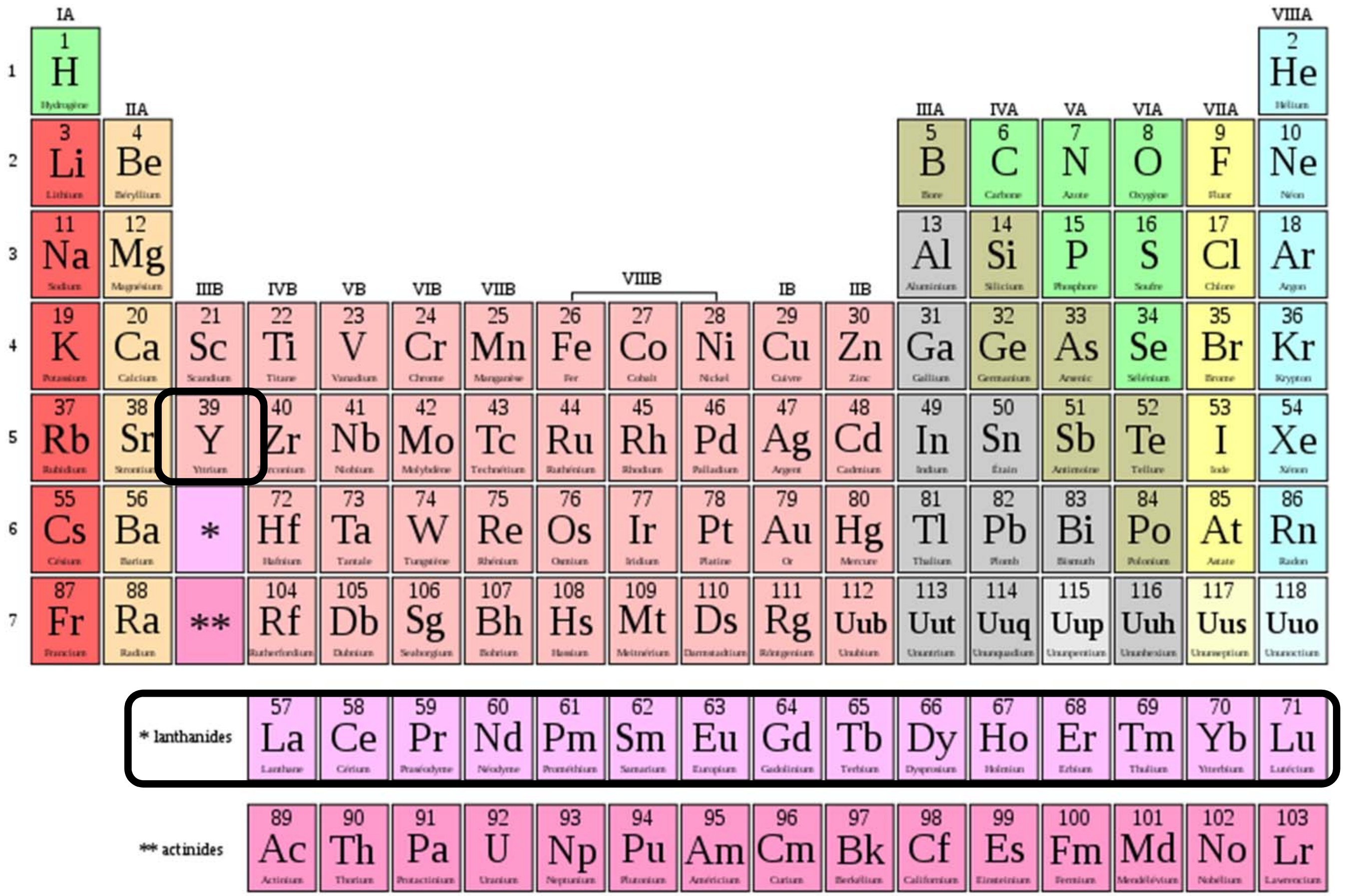
- thermodynamically feasible

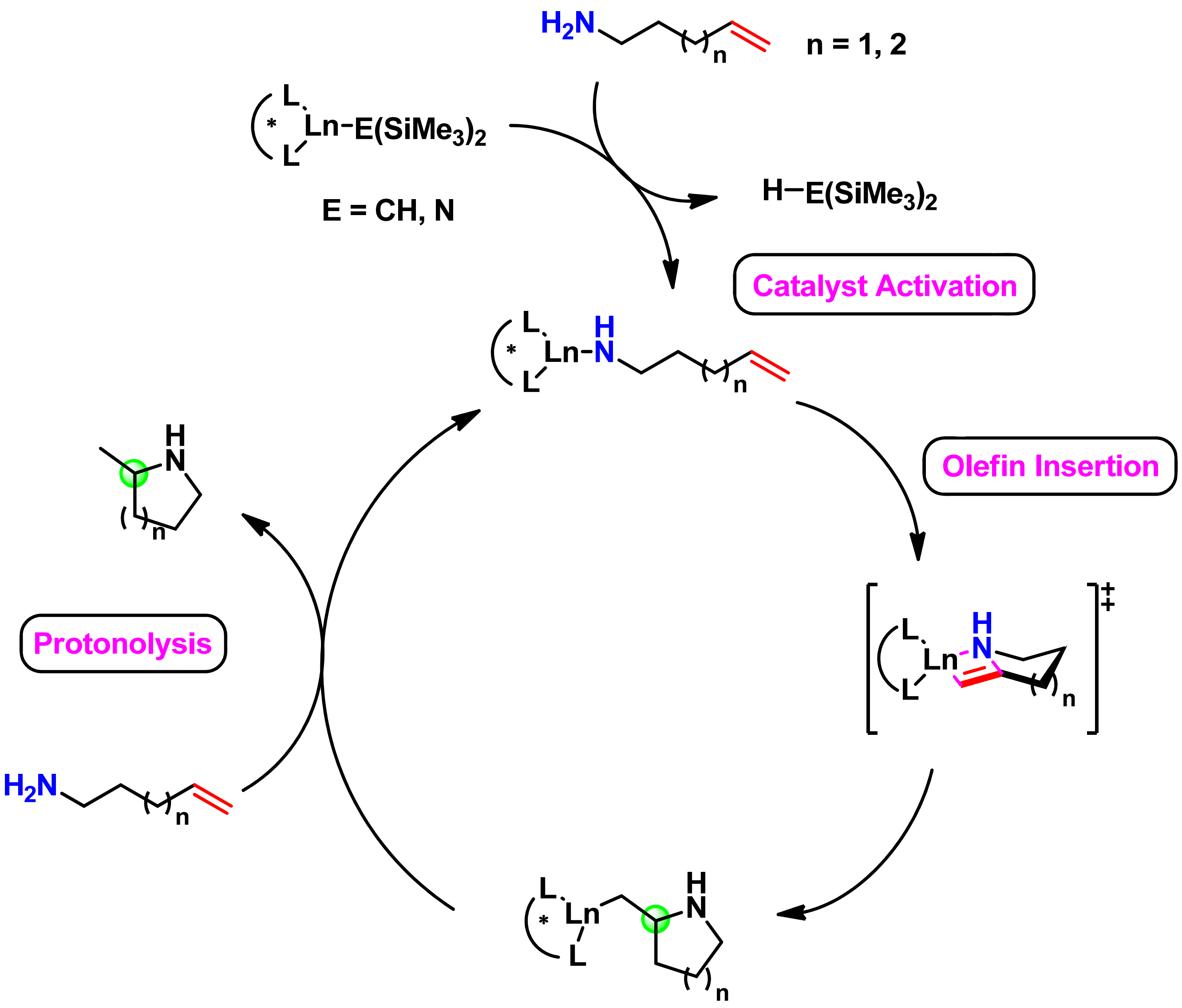
- hampered by a high E_a

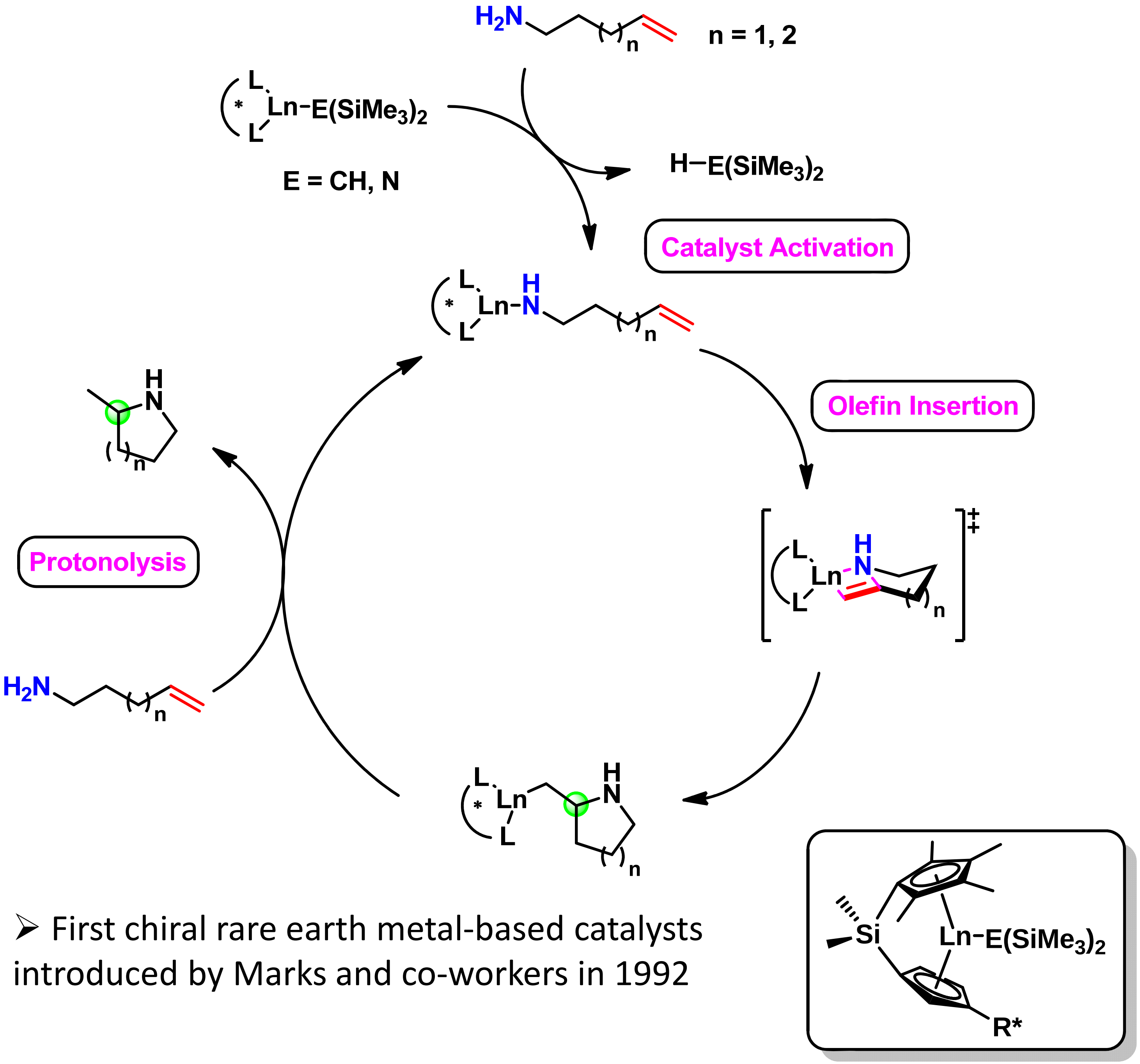
- E_a not overcome by increasing the T°C

➢ **Various catalyst systems based on transition metal could be employed in hydroamination reaction of simple unactivated alkenes**

Rare Earth Metal-Based Catalysts

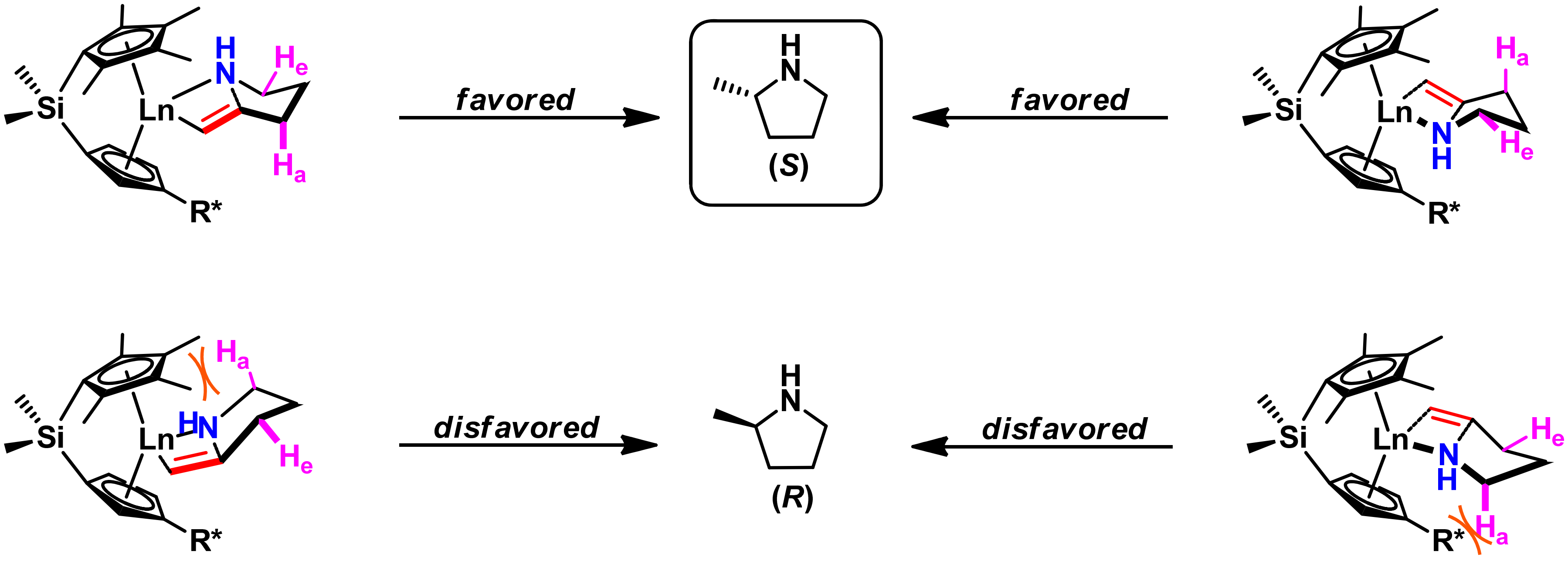



H2N
n = 1, 2
Ln-E(SiMe3)2
E = CH, N
H−E(SiMe3)2
Catalyst Activation
Olefin Insertion
Protonolysis
‡



➢ First chiral rare earth metal-based catalysts introduced by Marks and co-workers in 1992

➢ Stereomodel for aminopentene substrates => formation of (*S*)-pyrrolidine enantiomer



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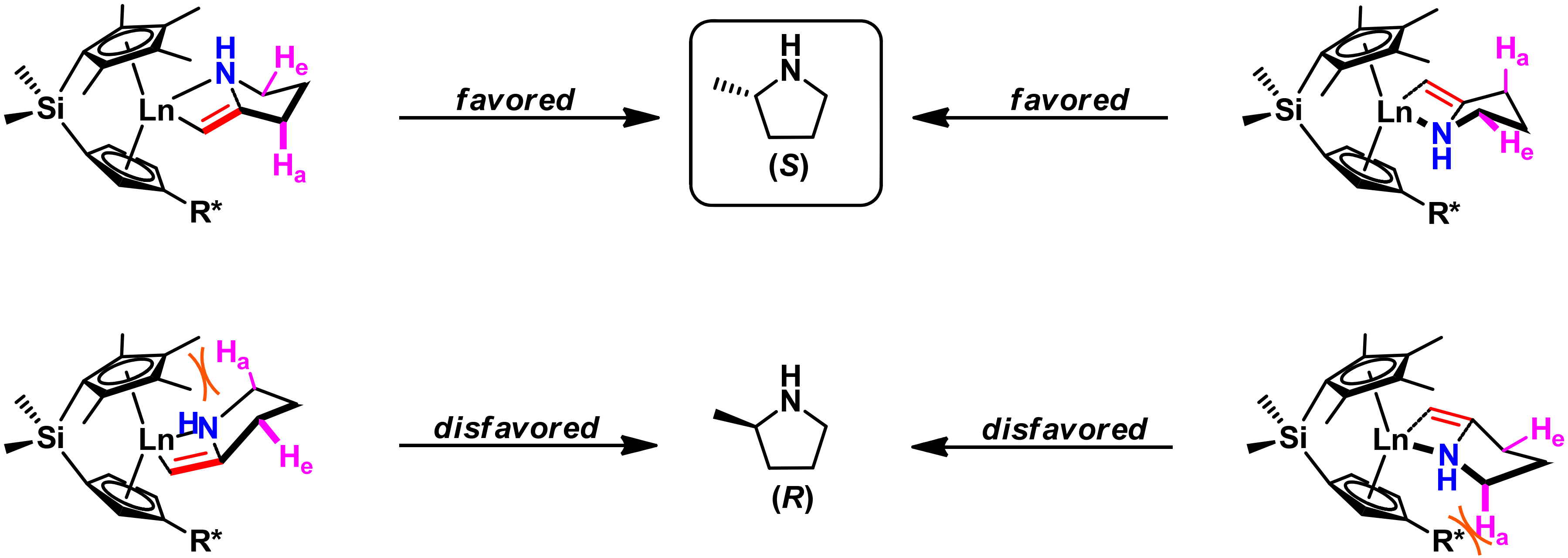
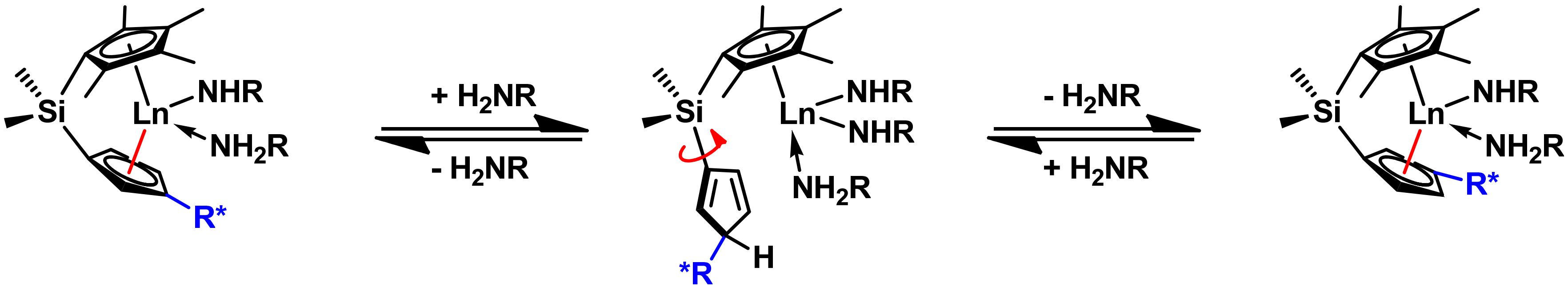
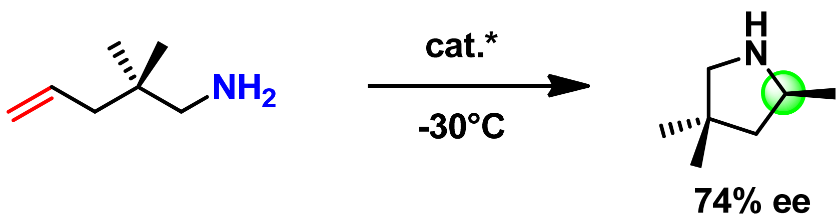
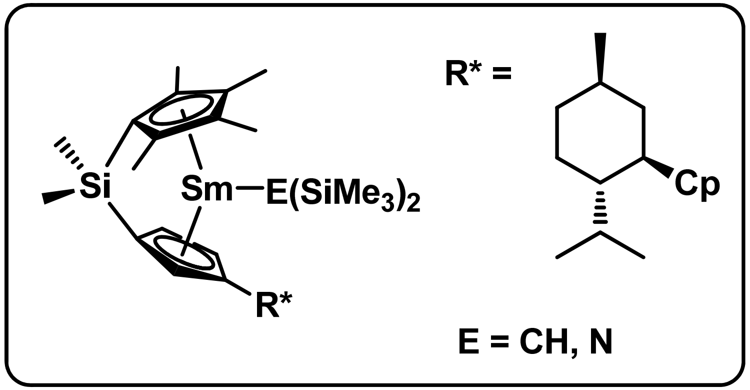


➢ Epimerization under the conditions of catalytic hydroamination







➢ Internal 1,1- or 1,2-disubstituted olefins less reactive for hydroamination

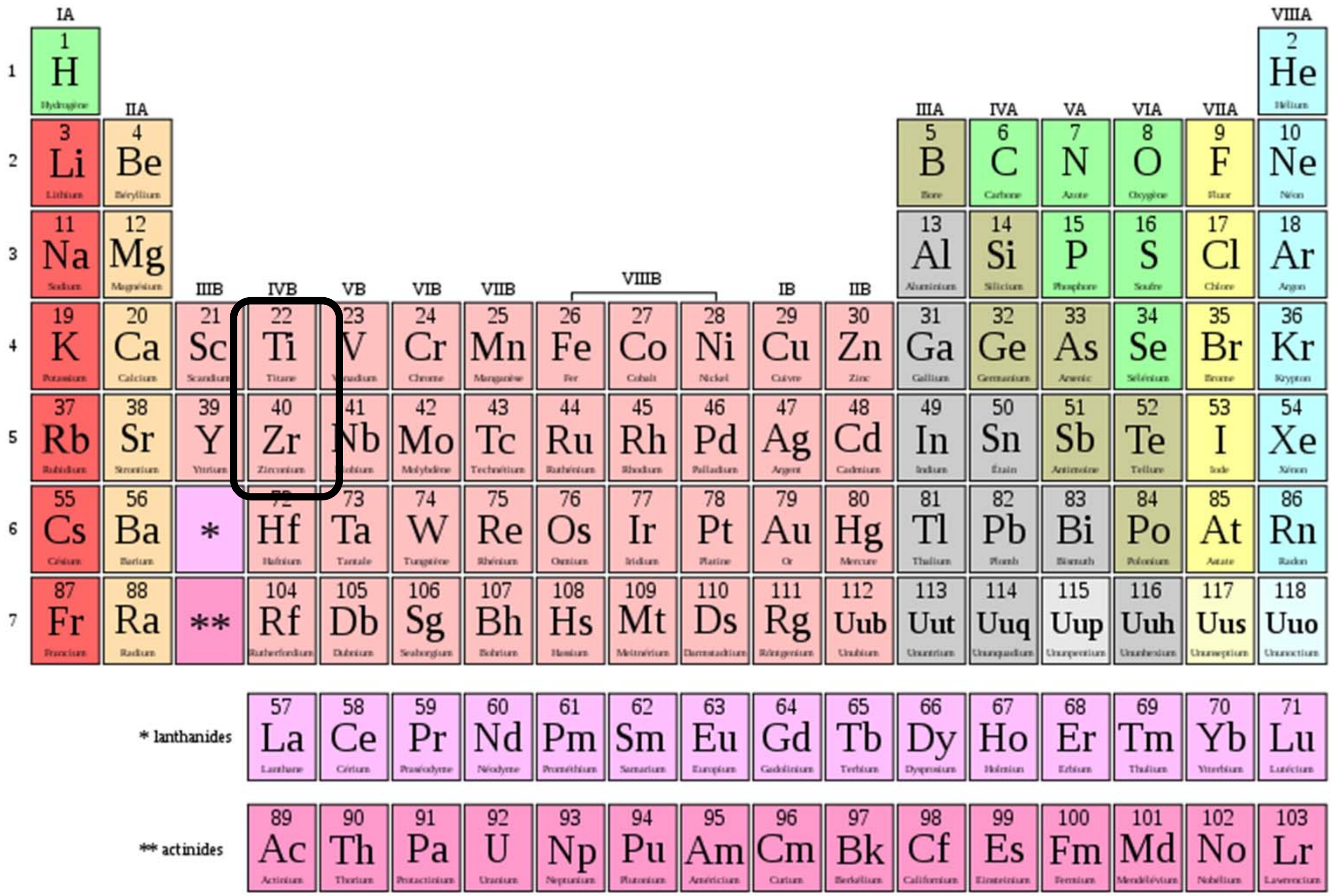
=> require harsher reaction conditions

➢ Drawbacks of rare earth metal :

-sensitive to oxygen and moisture

- limited their use in many applications

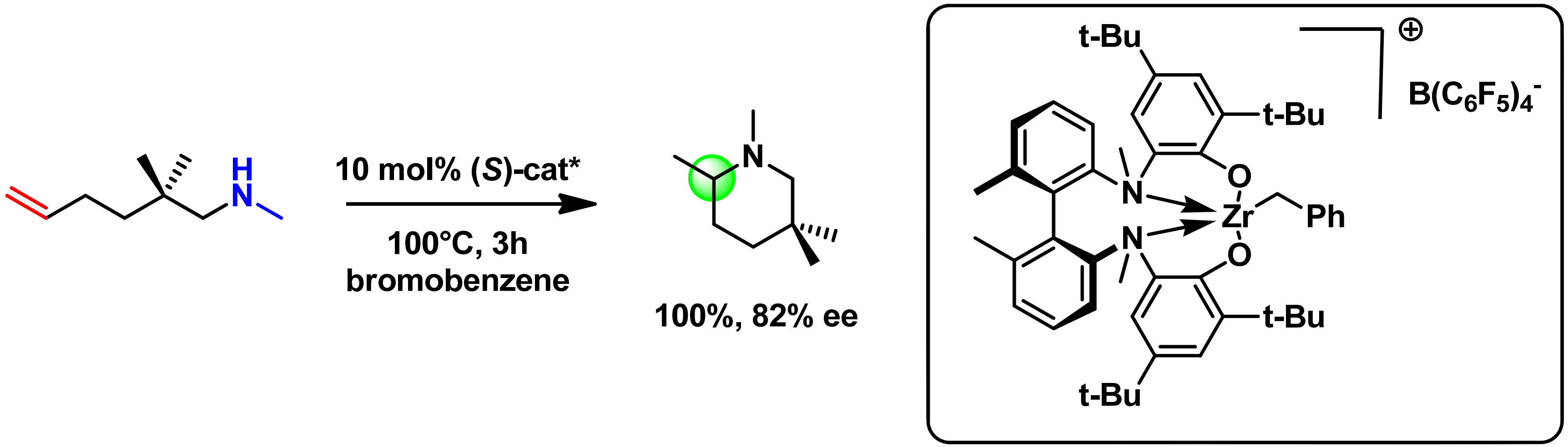
Group 4 Metal-Based Catalysts



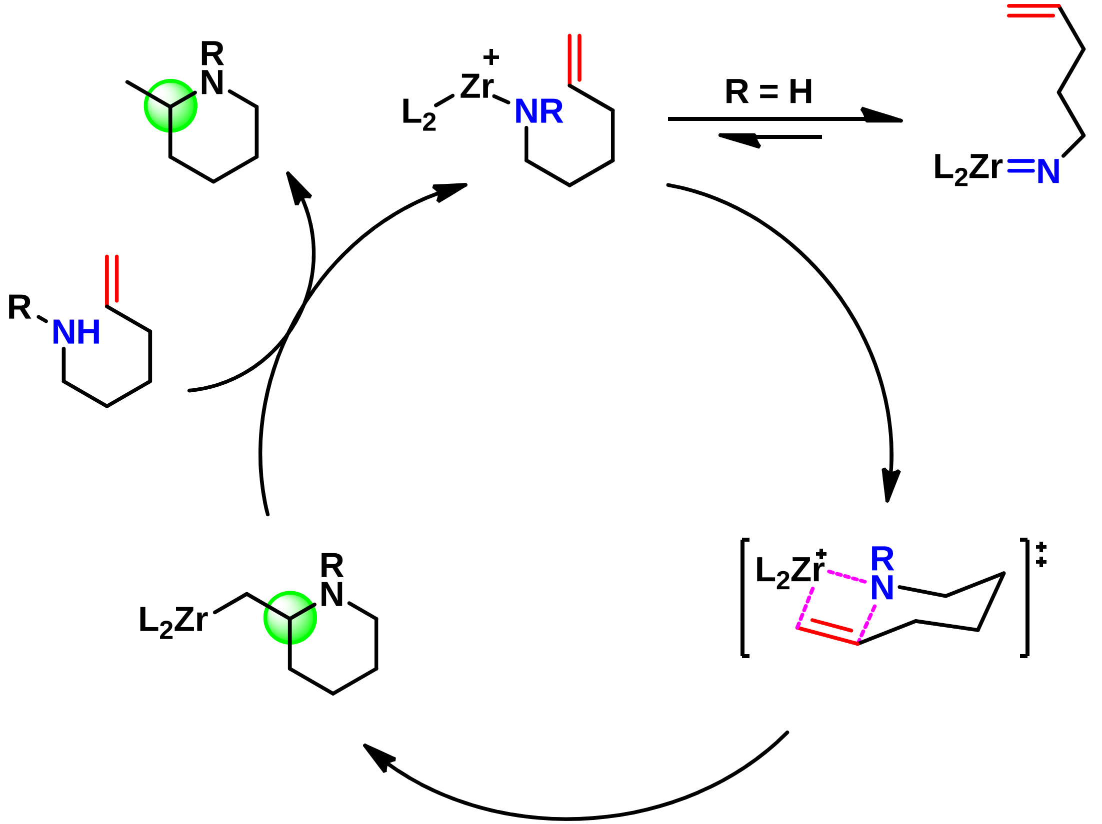
- Organometallic group 4 metal compounds => important in polyolefin synthesis

- Less sensitive and easier to prepare than rare earth metal complexes

- Many potential precatalysts or catalyst precursors => commercially available



- First chiral group 4 metal catalyst system => cationic aminophenolate complex

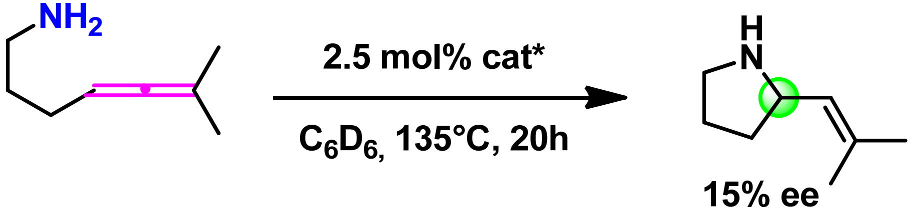


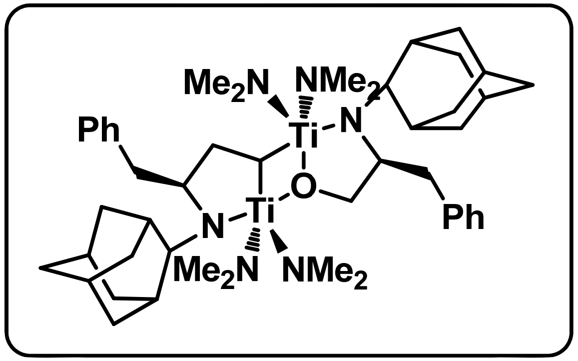
- similar to that proposed for rare earth metal

- no reaction with primary aminoalkenes : cationic Zr amido species are readily deprotonated to yield catalytically inactive Zr imido species.

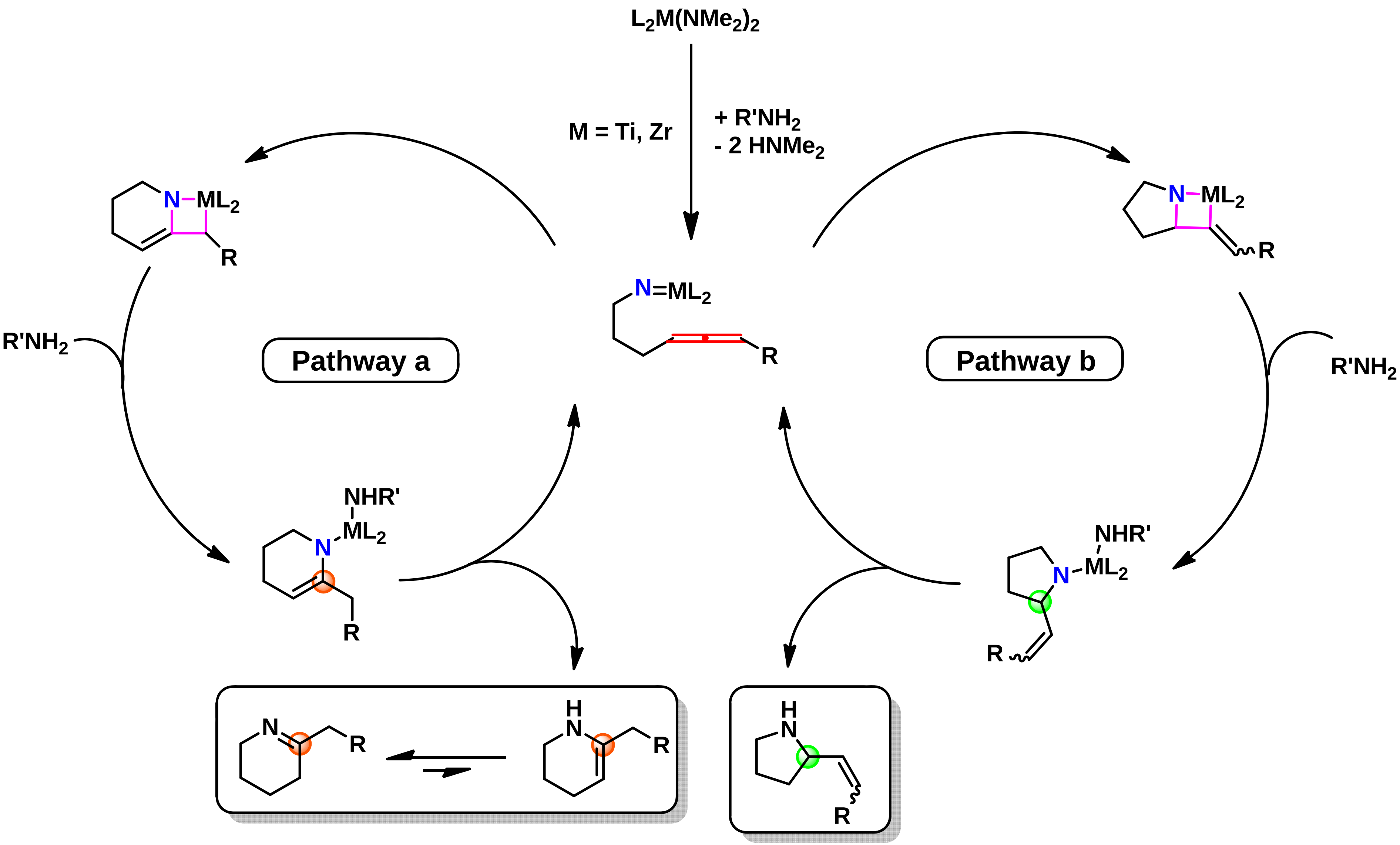
- Neutral zirconium and titanium complexes operates by completely different mechanism

- Chiral aminoalcohol-titanium complexes used by Johnson





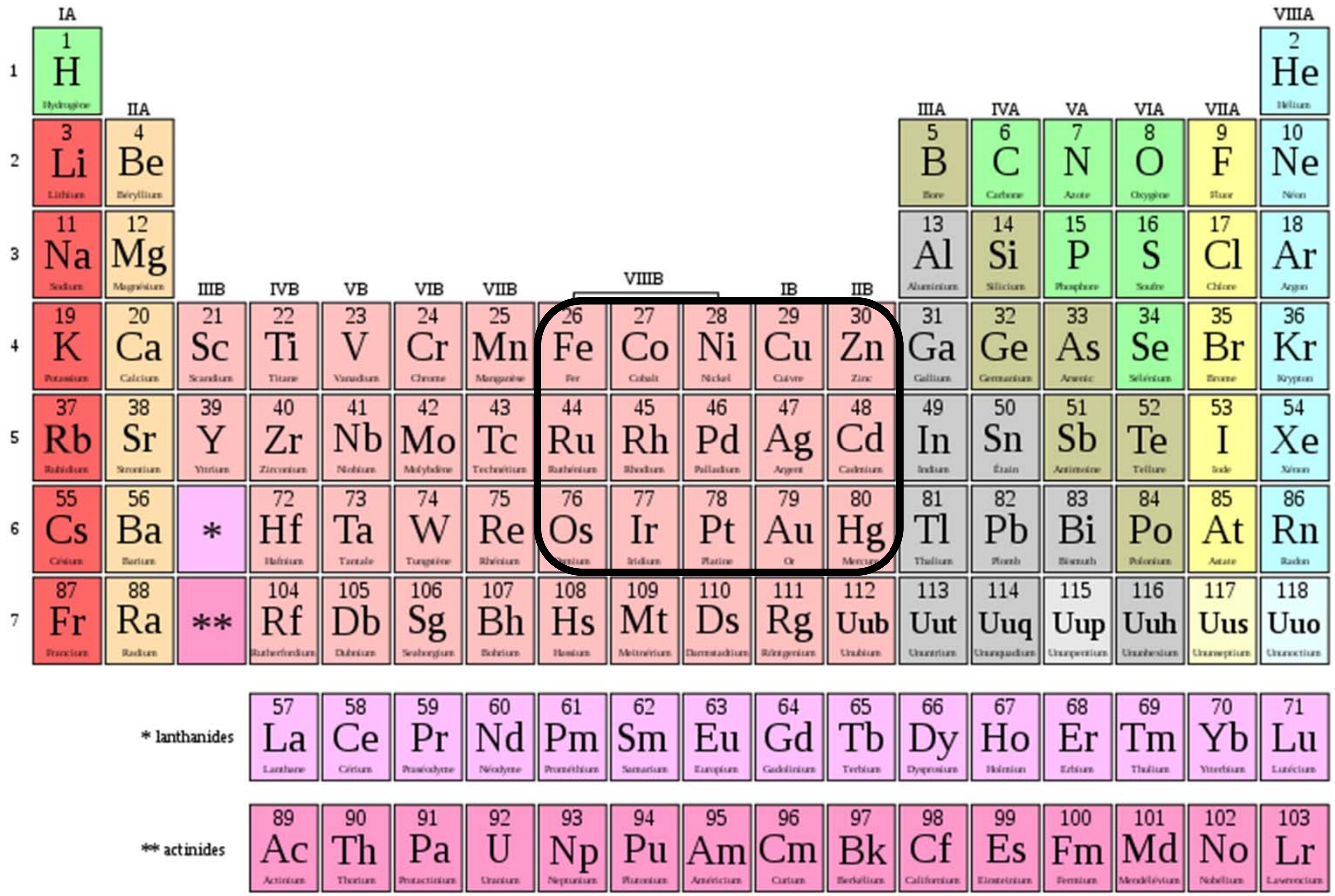
- Reaction restricted to alkynes and allenes => metal imido intermediates unreactive with unactivated alkenes



➢ pathway a : predominates for monosubstitued aminoallenes

➢Pathway b : for 1,3-di or trisubstituted aminoallenes

Late Transition Metal-Based Catalysts

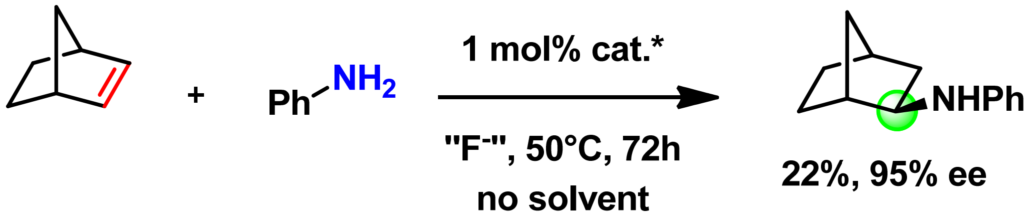


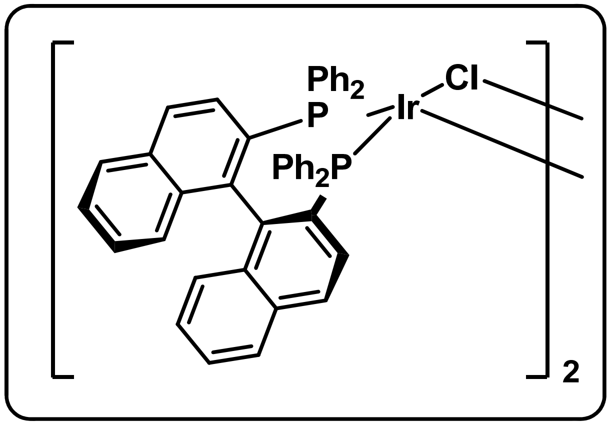
- ➢Late transition metal => more functional group tolerant / air and moisture insensitive

- ➢ Late transition metal hydroamination catalysts restricted to :

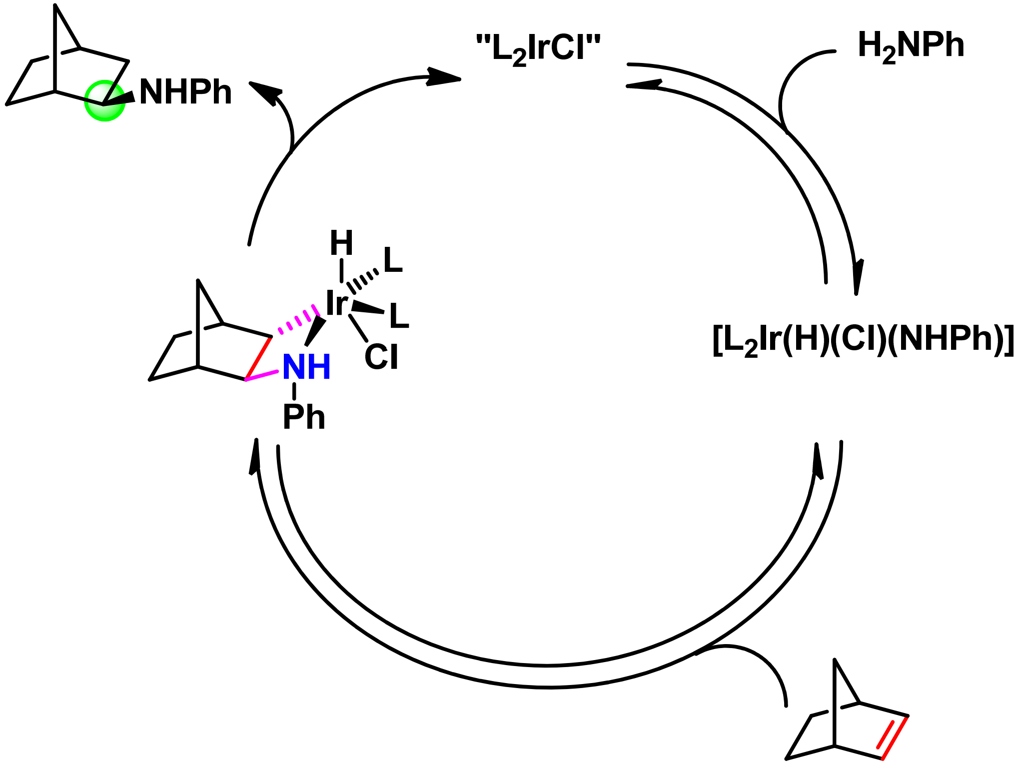
  - activated C-C multiple bonds
  - norbornene / styrene
  - conjugated dienes, alkynes and α,β-insaturated carbonyl compounds

- ➢ Use of various iridium complexes with chiral chelating diphosphines by Togni in 1997





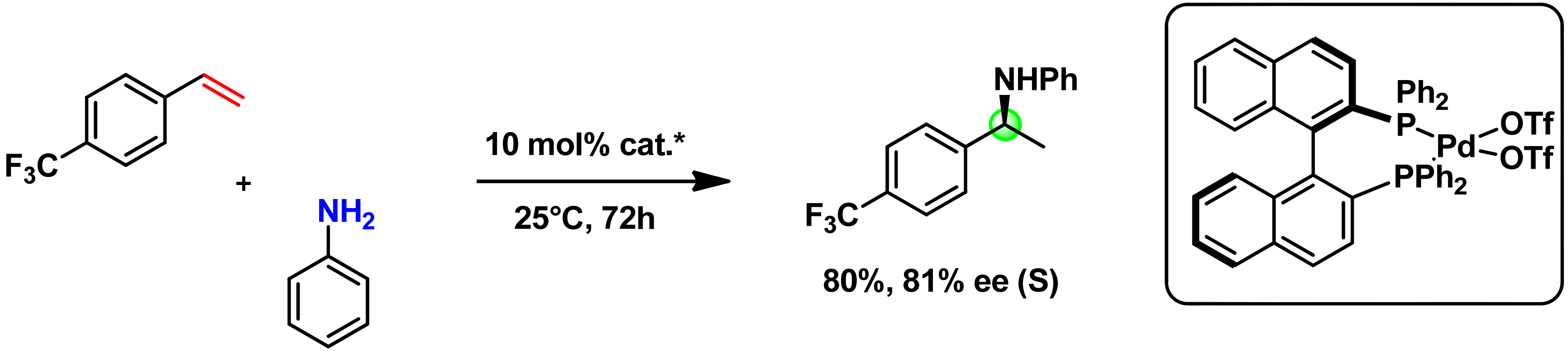
- ➢ Schwesinger's « nacked » fluoride $\{N[P(NMe_2)_3]\}F^-$ to improve the activity and selectivity



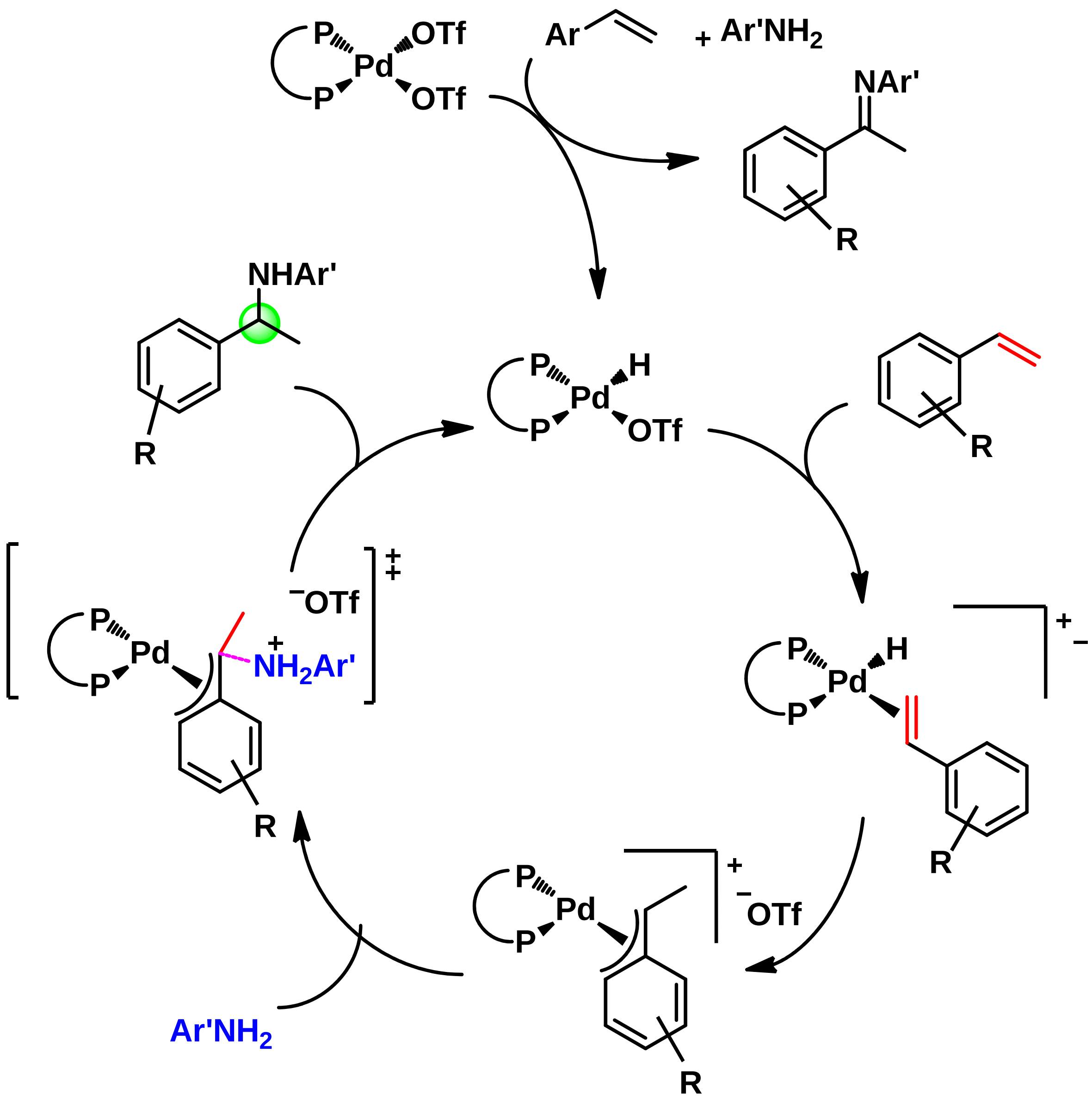
- ➢ Addition takes place across the sterically better accessible *exo* face

- ➢ The scope is not limited to hydroamination of norbornene with aniline

➢ Hydroamination of styrenes / 1,3-dienes using palladium catalyst reported by Hartwig.

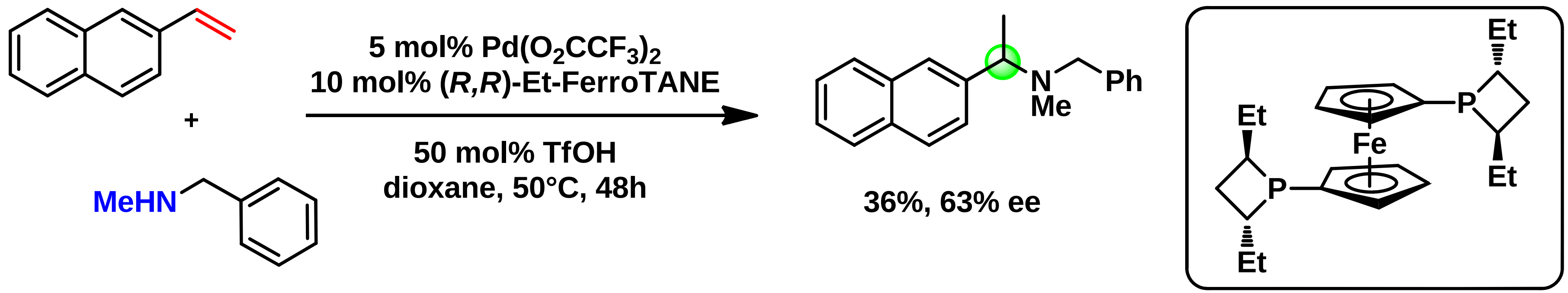


➢ high temperature are not necessarly (demonstrated by Hii).



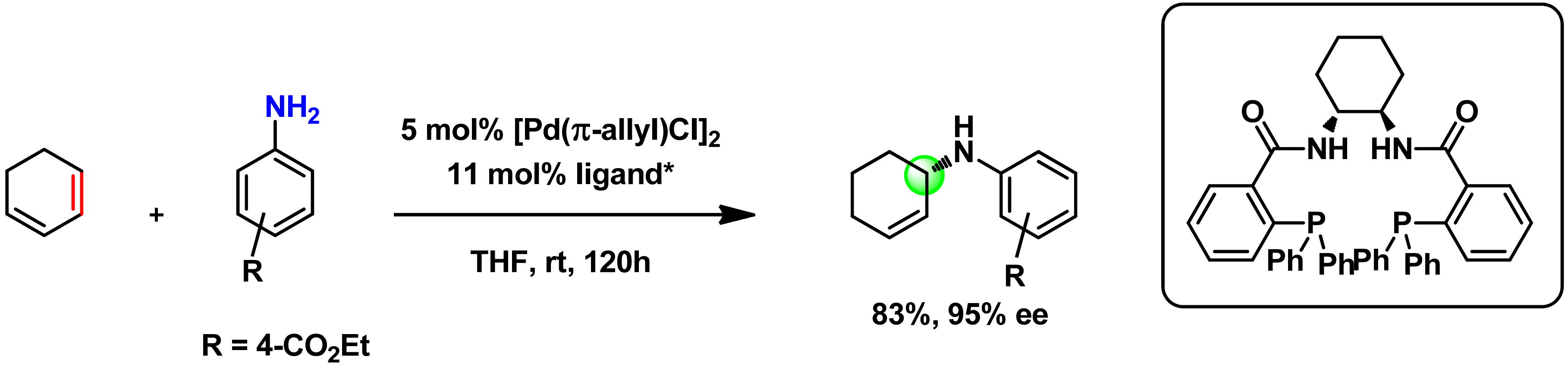
➢ the major diastereomer in solution generated the minor enantiomer of the hydroamination product of the catalytic reaction

➢ limitations with secondary alkylamines



➢ Competition between nucleophilic attack of the amine at the benzylic carbon leading to the hydroamination product and reversible elimination of styrene from η^3-benzyl intermediate.

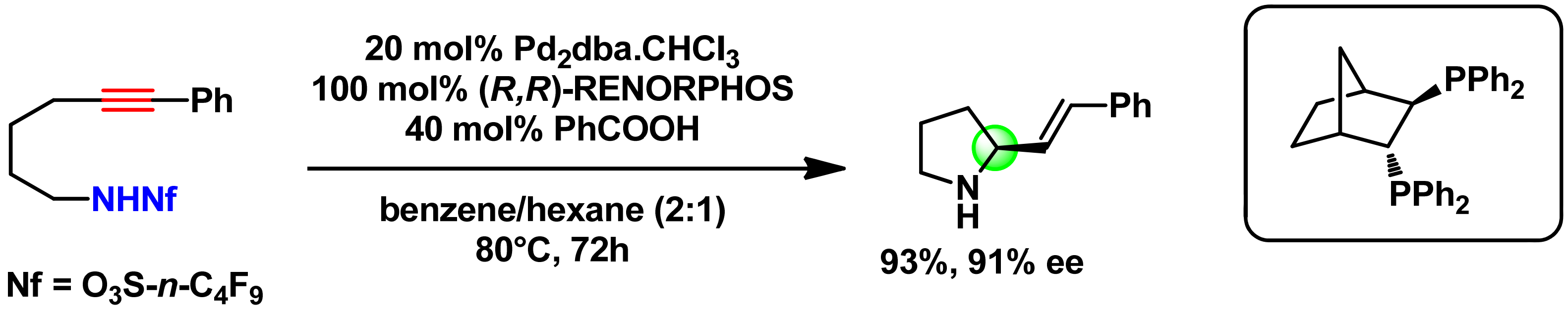
➢ Asymmetric hydroamination of cyclohexadiene with anilines.



➢ For other cyclic or acyclic 1,3-dienes : only the 1,4-addition of aniline to cycloheptadiene in 66% ee but only 22% yield was reported.

➢ Palladium-catalyzed asymmetric intramolecular hydroamination of aminoalkynes.

➢ The asymmetric hydroamination of *N*-protected aminoalkynes reported by Yamamoto.

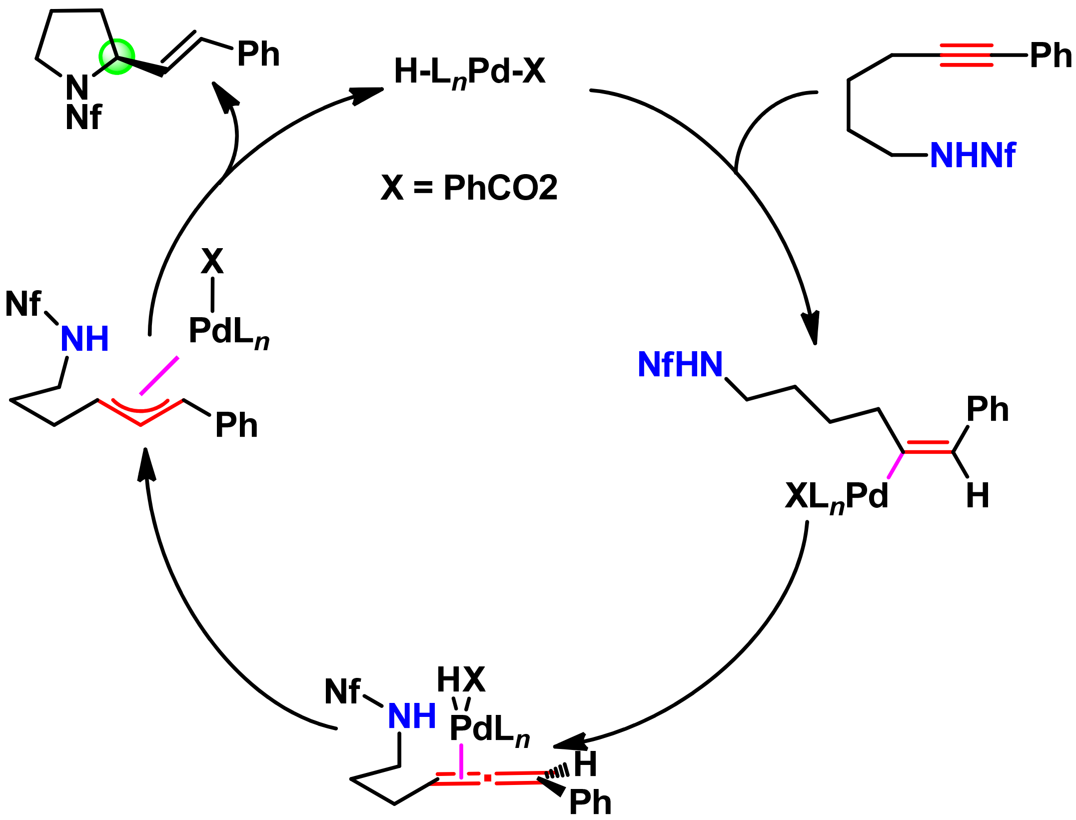


- High catalyst loading were required

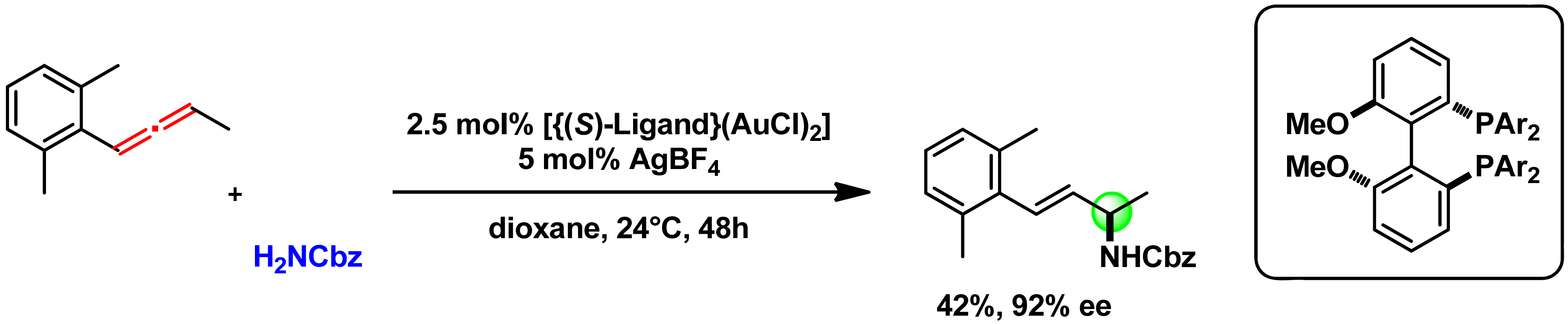
- Lower catalyst loading resulted in reduced yield and enantioselectivities

- Electron-rich alkynes were transformed faster but lower enantioselectivities.

- Plausible postulated mechanism



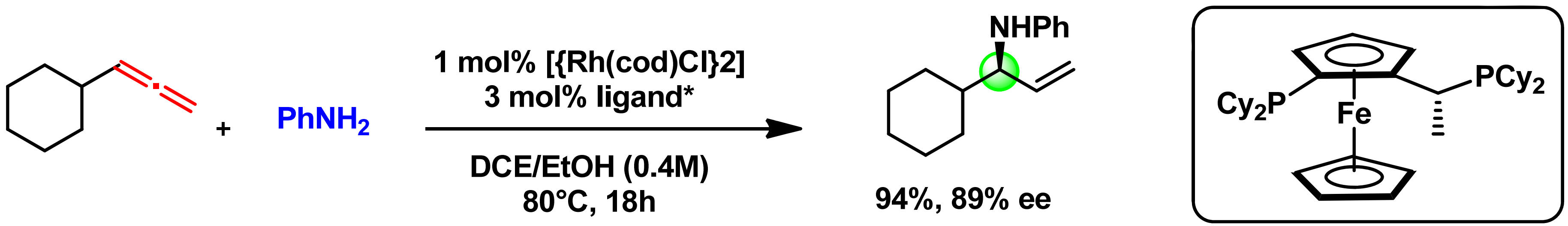
- Gold-catalyzed intermolecular enantioselective hydroamination of allenes



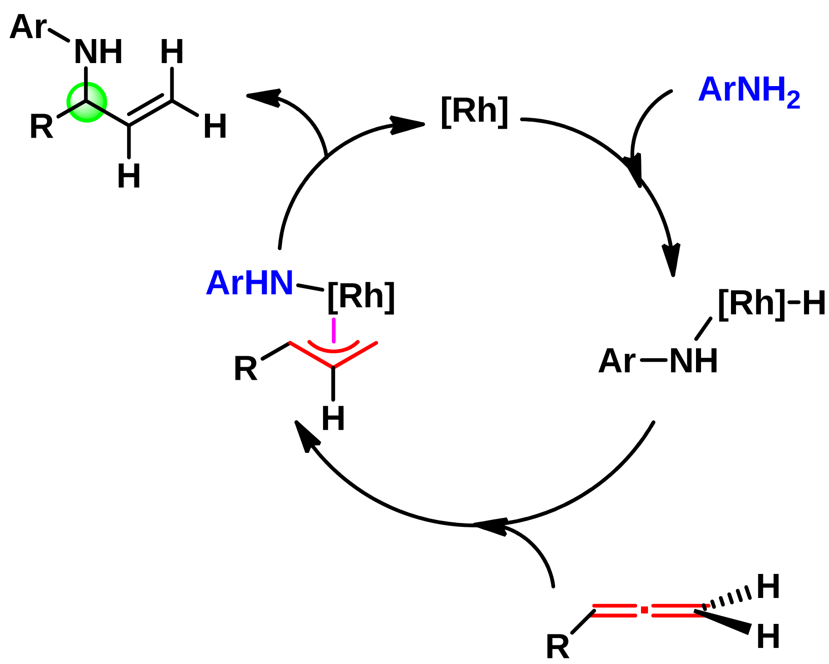
- Access to enantiomerically enriched α-chiral allylic amines => important chiral building blocks in the synthesis of complex nitrogen containig molecules

- Only internal allenes tolerated

➢ Rhodium-catalyzed intermolecular hydroamination of terminal allenes

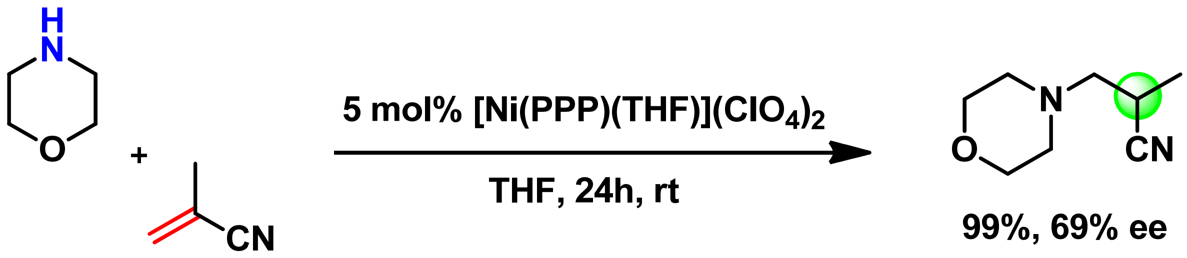


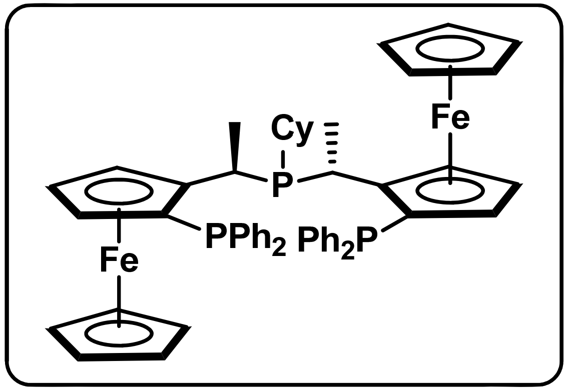
➢ A broad range of valuable branched allylic amines can be isolated in excellent yields and enantioselectivities.



- Addition of anilines to crotonitrile described by Togni
  => moderate yield and low enantioselectivities

- Morpholine more reactive than aniline derivatives

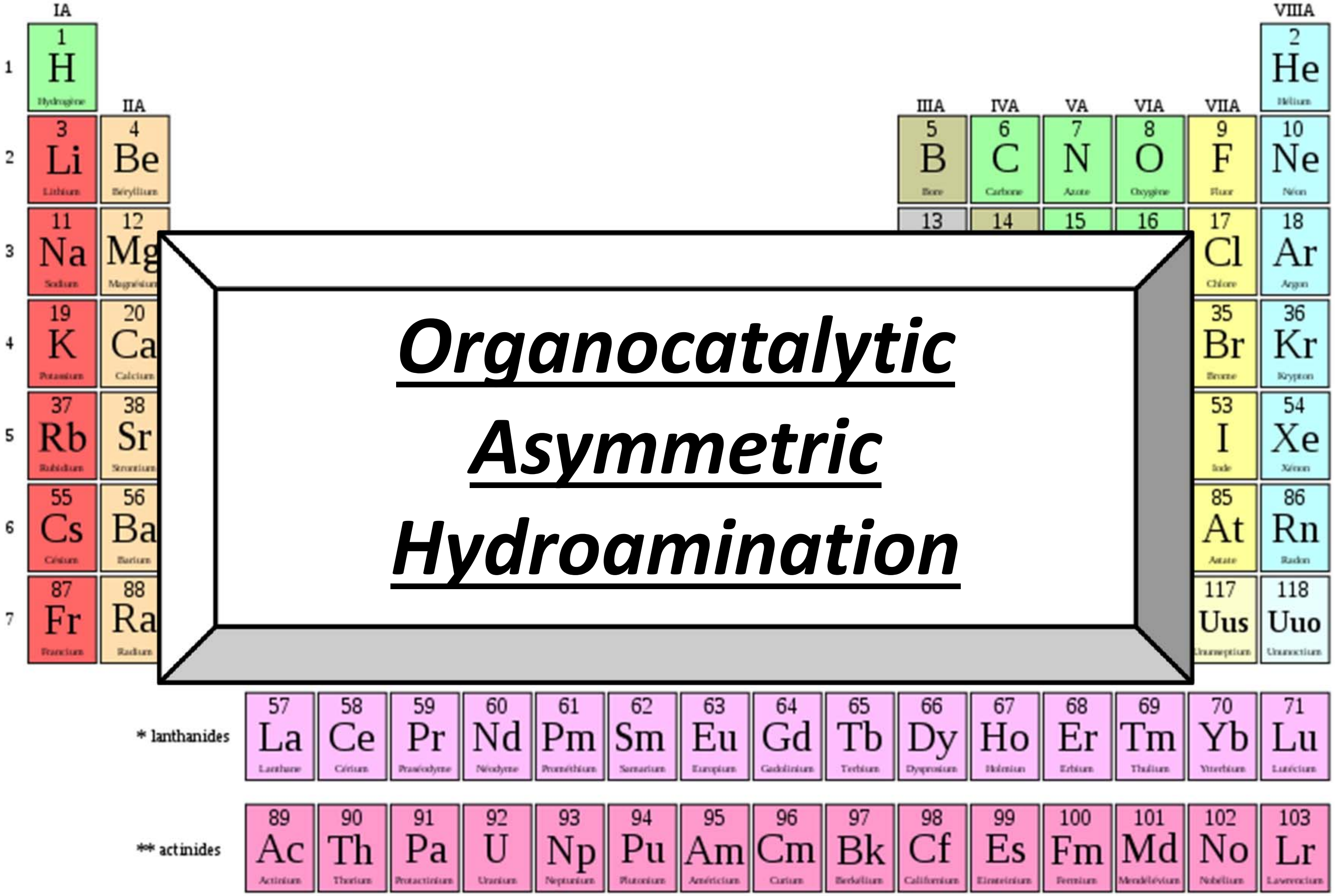




Many **problems** have not been solved :

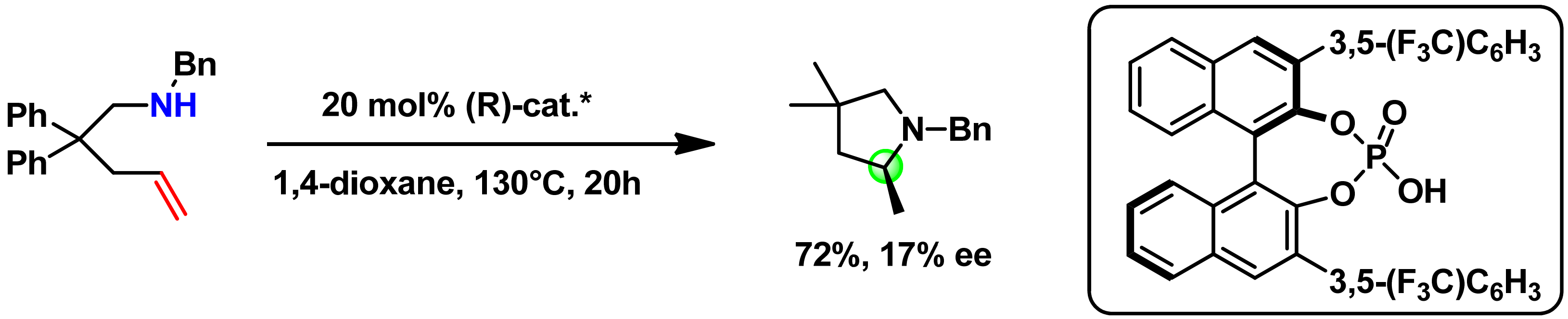
- no general catalyst => combining high catalytic activity and high level of enantioselectivity for a wide range of substrates, high functional group tolerance and user-friendliness

Challenges => intermolecular asymmetric hydroamination reaction of terminal and internal non-activated C-C double bonds.



Organocatalytic Asymmetric Hydroamination

➢ First example of catalytic asymmetric metal free hydroamination using chiral phosphoric acid diester



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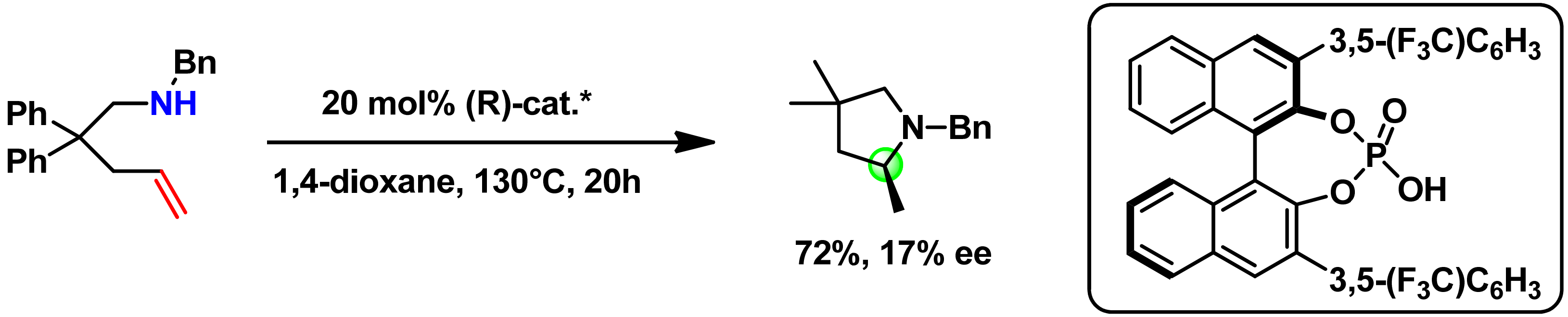
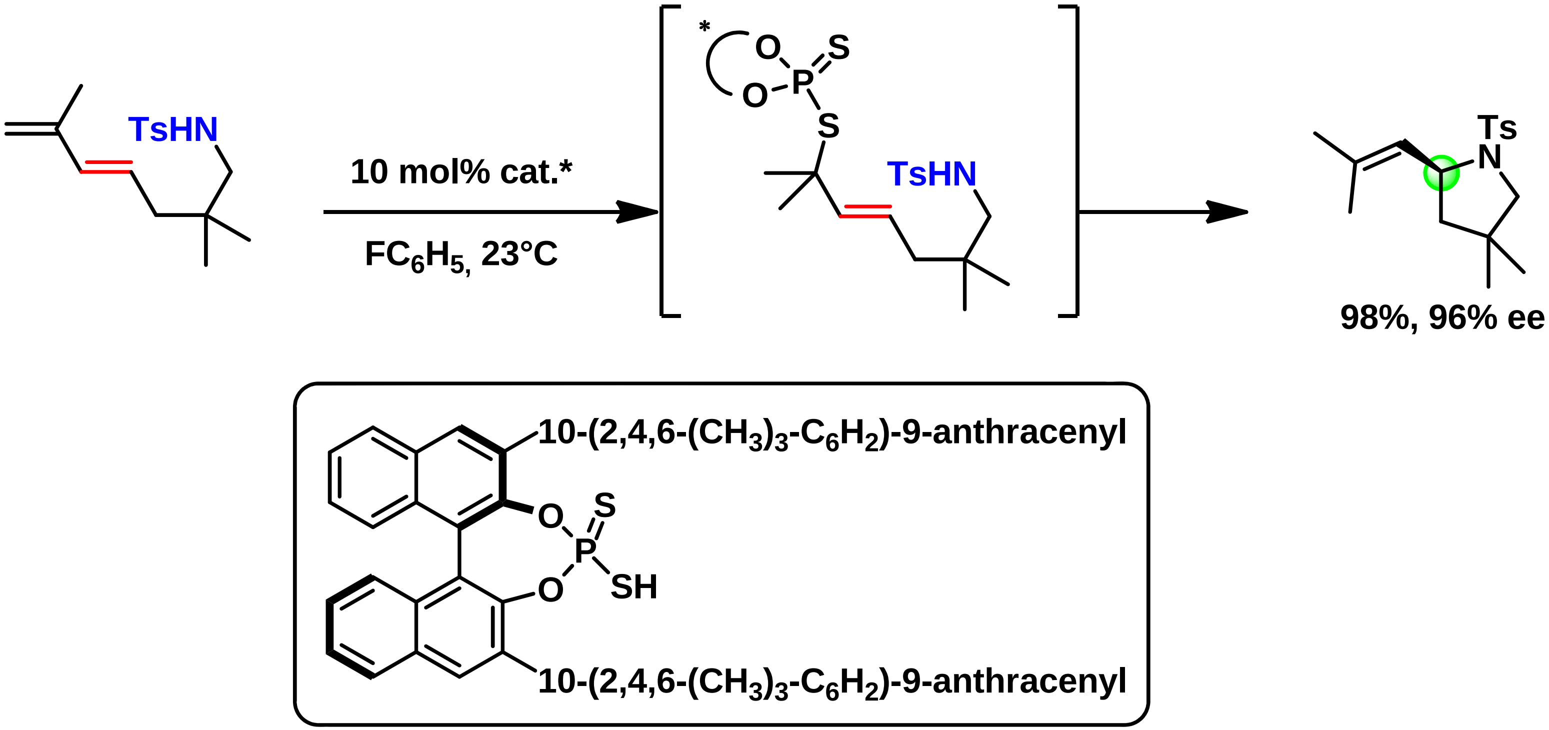
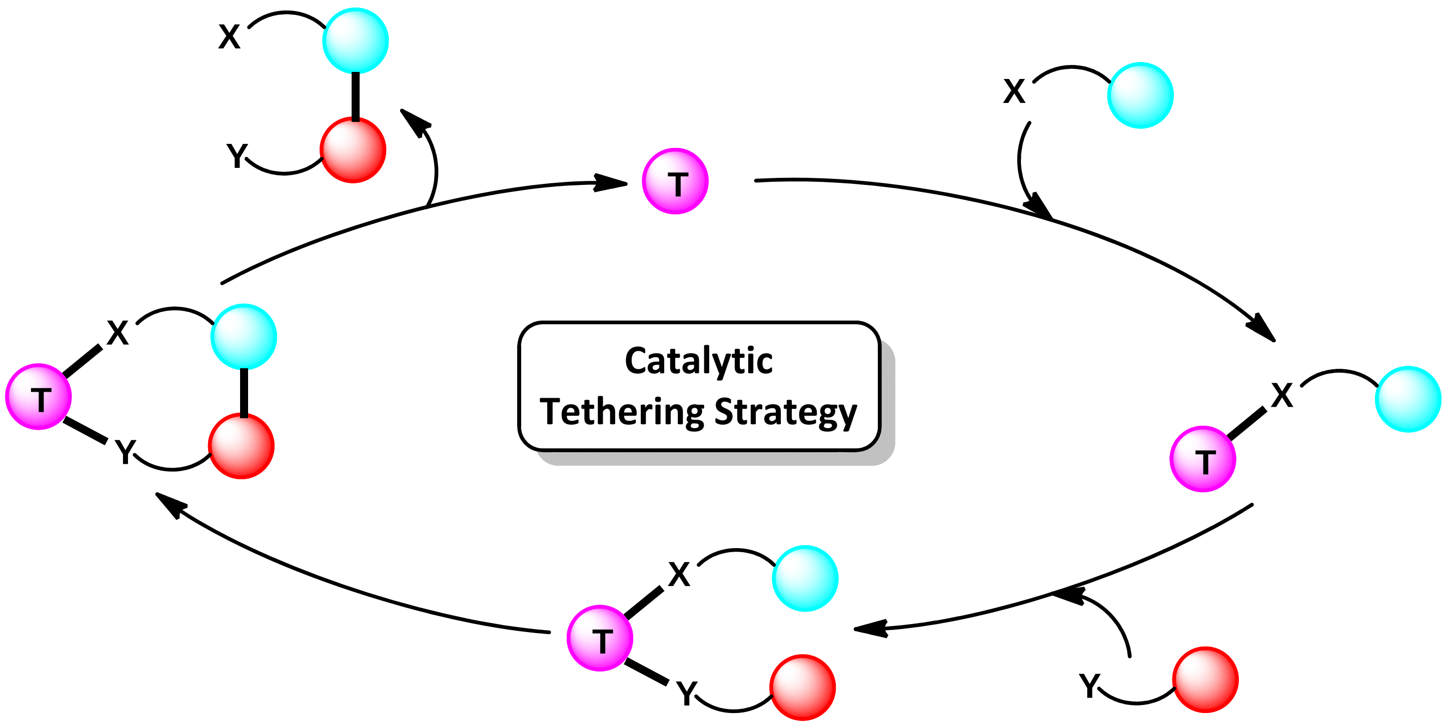


➢ Chiral dithiophosphoric acids can catalyse hydroamination of dienes and allenes



➢Prototypical catalytic tethering strategy : activation only through temporary intramolecularity



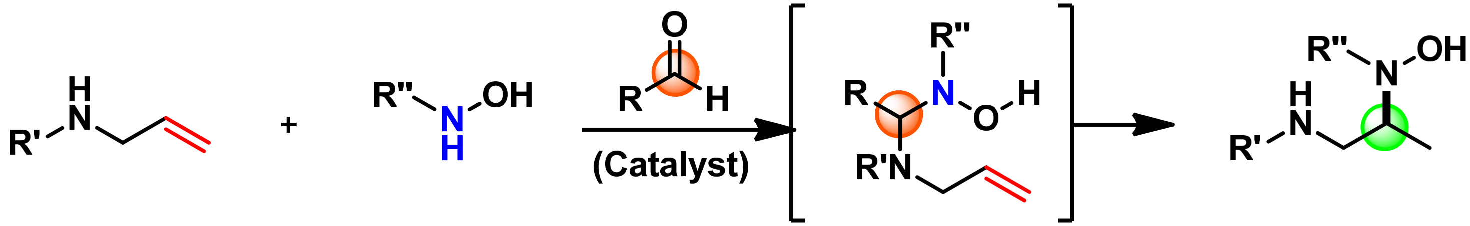
Advantages :

✓Good atom and step economy

✓ Chiral catalysts can enforce stereochemical control

✓ Can target a variety of difficult intermolecular reactions

➢ Aldehyde-based organocatalysts : temporary tether between hydroxylamines and allylic amines => Cope-type hydroamination



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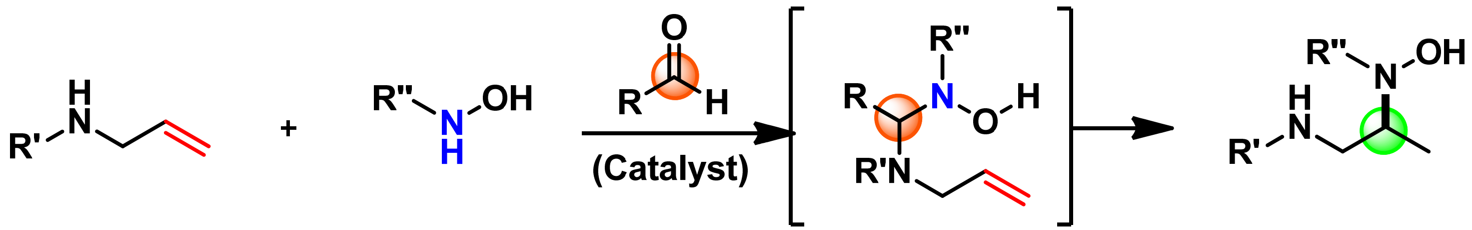
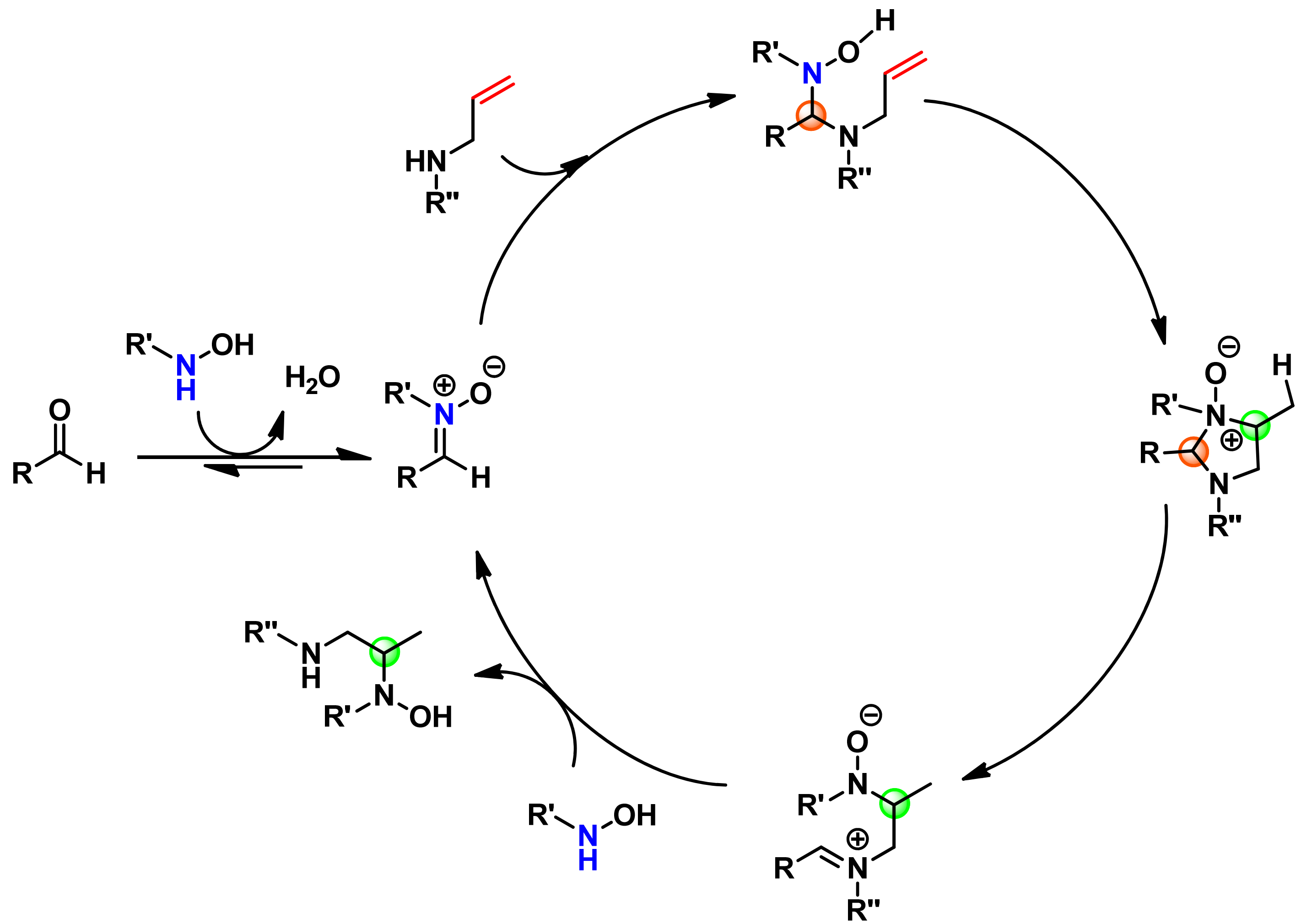
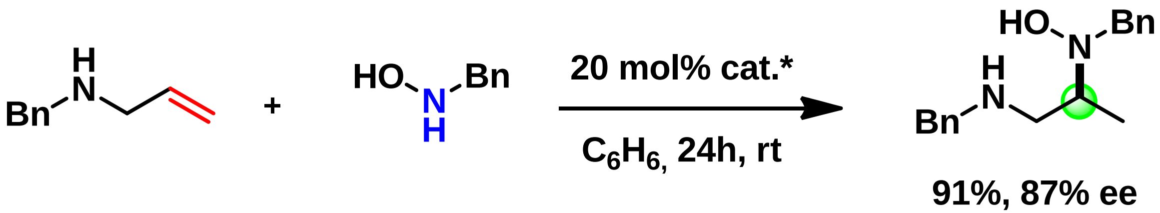
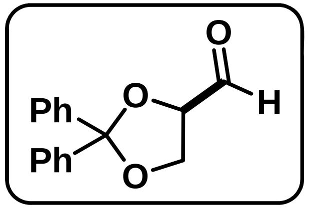




➢This enantioselectivity is the highest for intermolecular hydroaminations of unactivated alkenes by any method, including metal catalyzed reactions





➢ Cope-type hydroamination under mild and metal-free conditions

➢ Chiral α-oxygenated aldehydes capable of efficiently inducing asymmetry only though temporary intramolecularity

CONCLUSION

✓ Significant progress in development of chiral catalysts for asymmetric hydroamination reactions over the last decade

✓ Late transition metal-based catalysts show promising leads

✓Early transition metal-based catalyst remain the most active and versatile catalyst systems.

✓ Significant challenges :

- Asymmetric intermolecular hydroaminations of simple nonactivated alkenes
- Development of a chiral catalyst

References

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For Asymmetric Hydroamination see :

- *Adv. Synth. Catal.* **2005**, *347*, 367-391 ;
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