

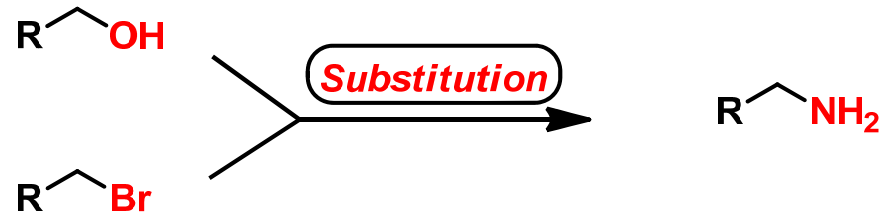
Asymmetric Hydroamination Reactions of Carbon-Carbon Multiple Bonds

Christèle Roux

21 - 01 - 2013

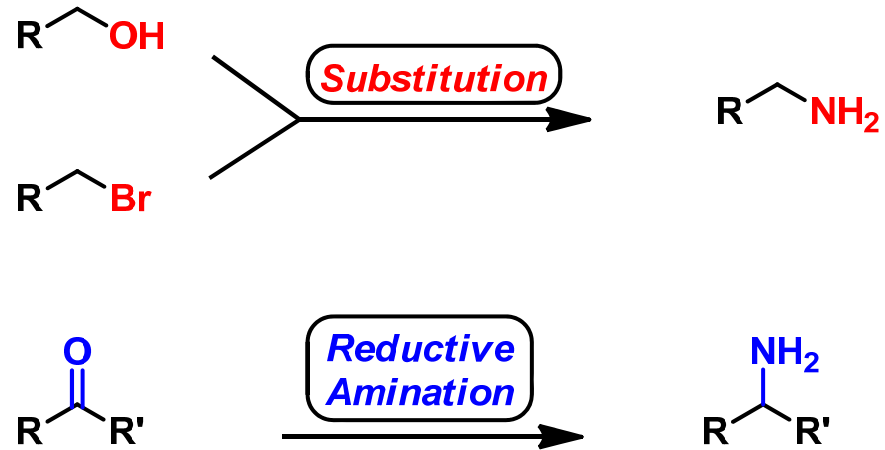
Introduction

- Classical methods for synthesis of molecules contain amine functionalities :



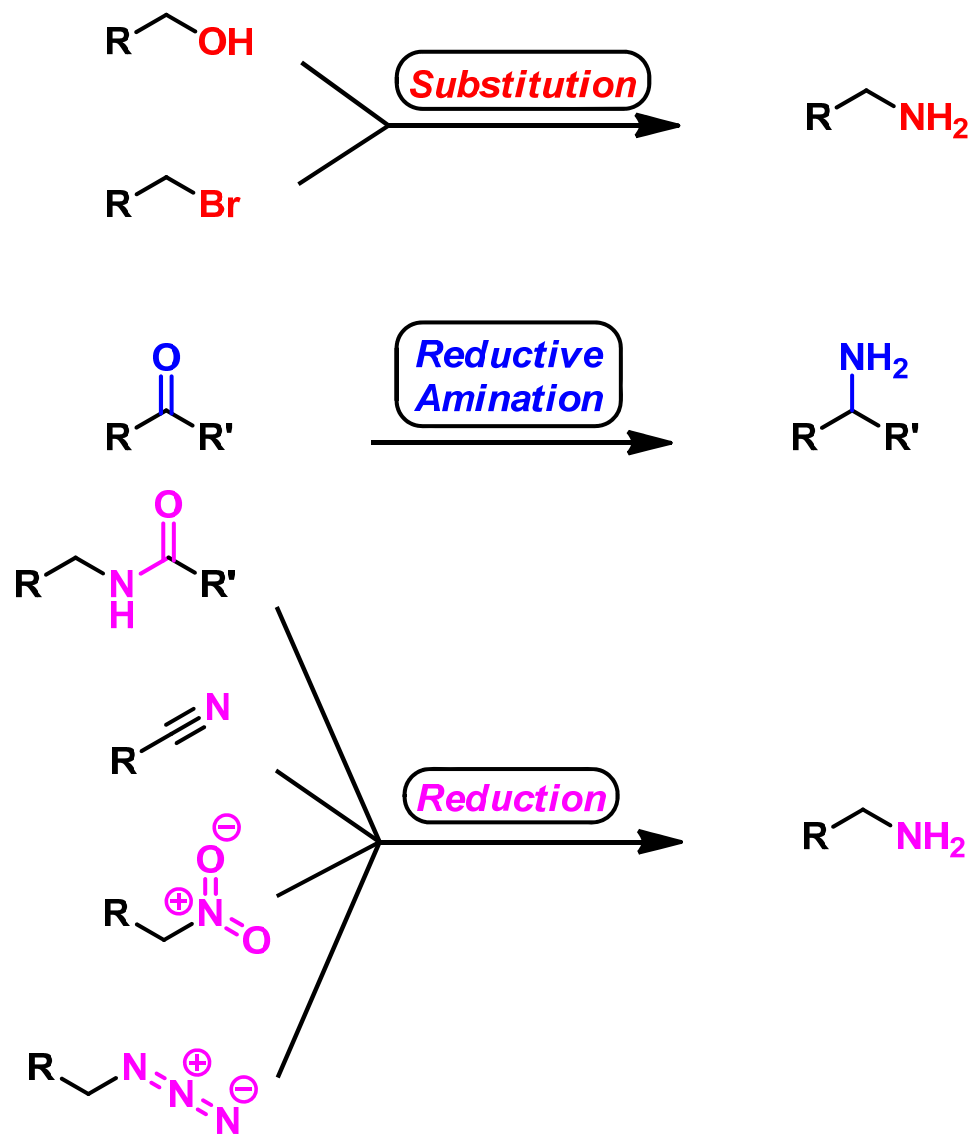
Introduction

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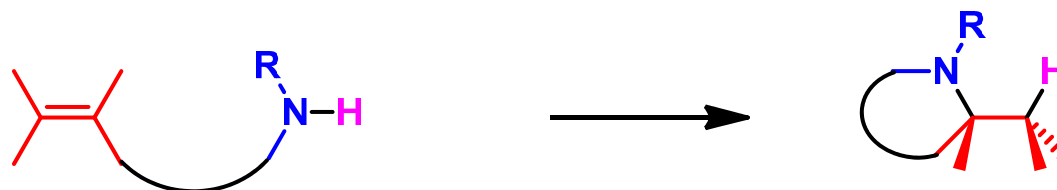
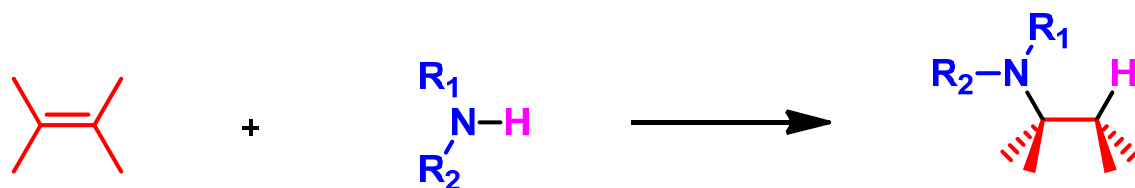
Introduction

➤ Classical methods for synthesis of molecules contain amine functionalities :



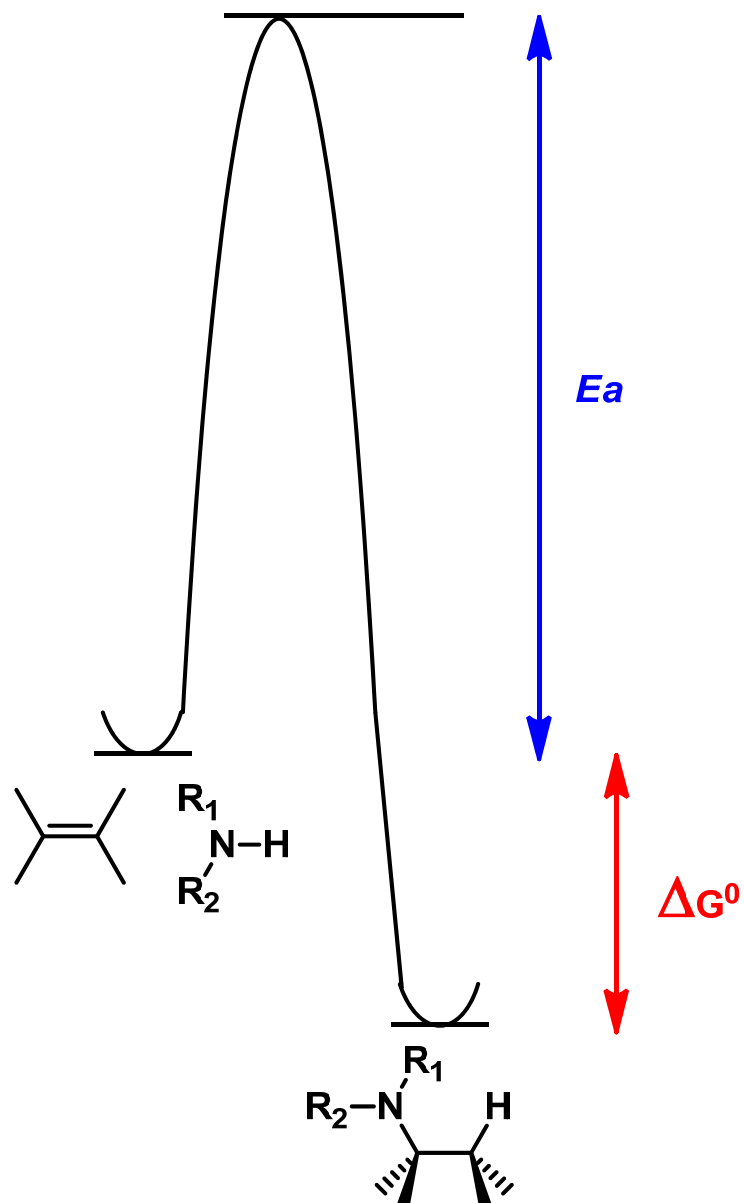
Hydroamination reaction

➤ 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

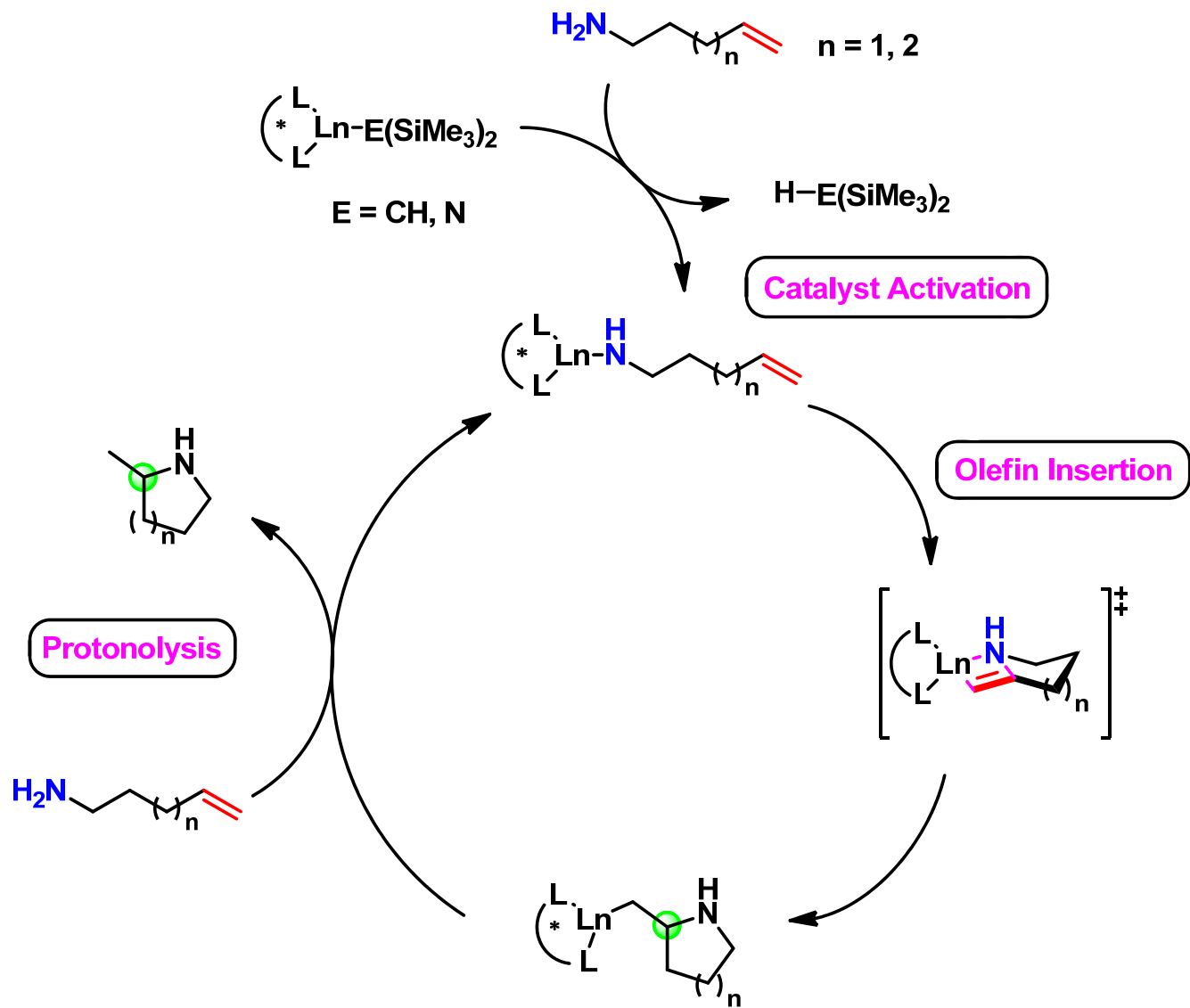
- hampered by a high E_a

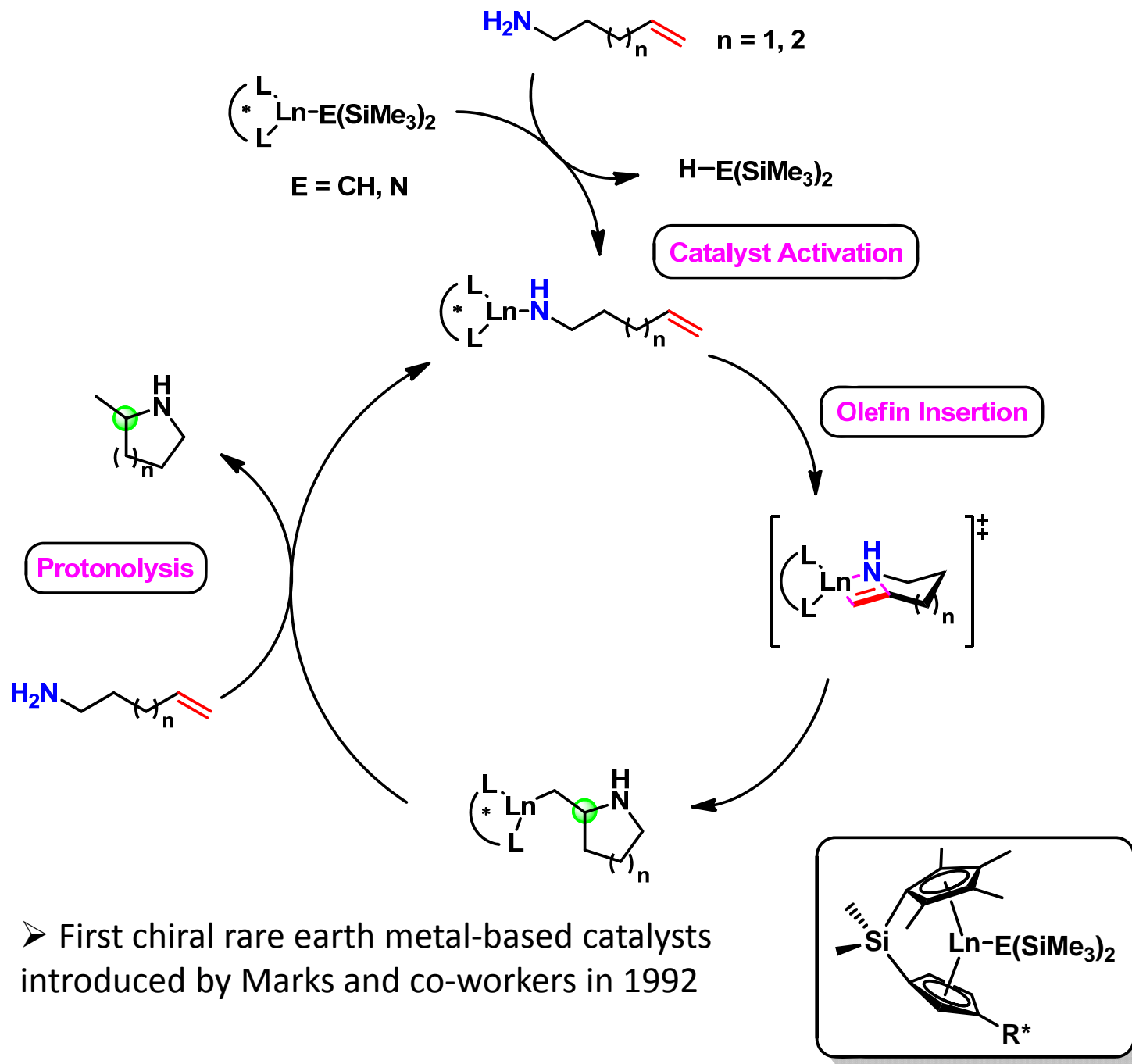
- E_a not overcome by increasing the $T^\circ C$

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

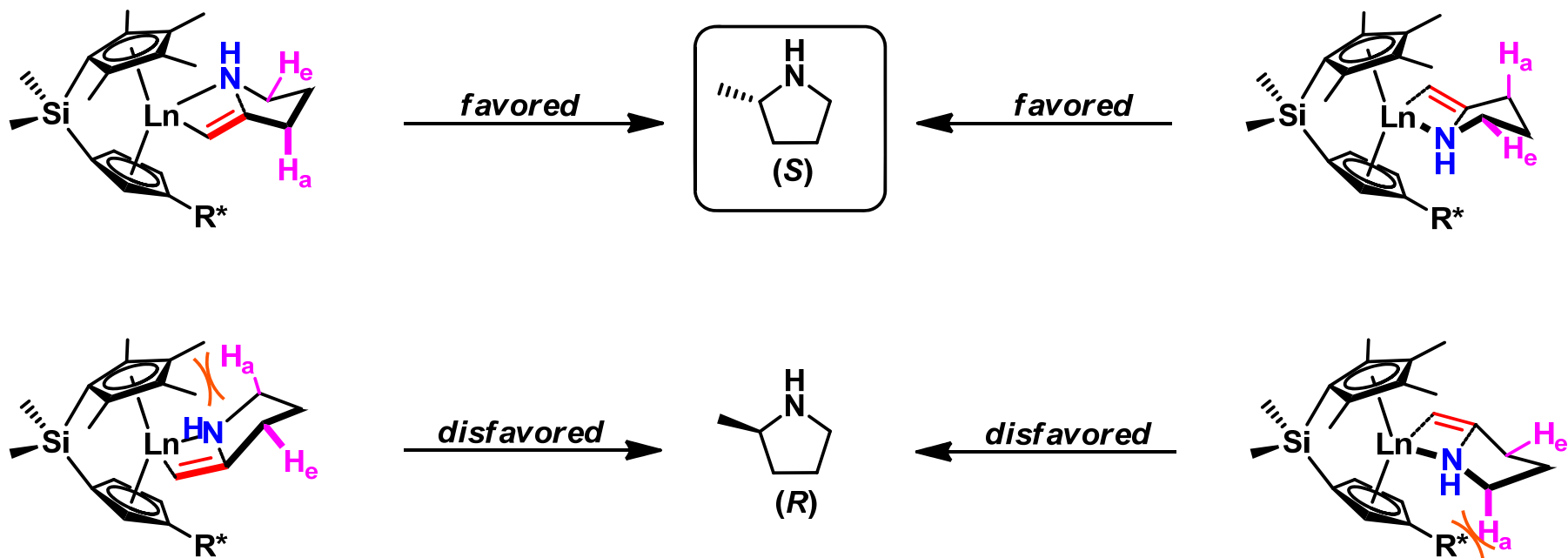
Rare Earth Metal-Based Catalysts

	IA																				VIIIA											
1	1																				2											
	H																				He											
	Hydrogen																				Helium											
2	3	4																			5	6	7	8	9	10						
	Li	Be																			B	C	N	O	F	Ne						
	Lithium	Beryllium																			Boron	Carbon	Nitrogen	Oxygen	Fluorine	Neon						
3	11	12																			13	14	15	16	17	18						
	Na	Mg																			Al	Si	P	S	Cl	Ar						
	Sodium	Magnesium																			Aluminum	Silicon	Phosphorus	Sulfur	Chlorine	Argon						
4	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36														
	K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr														
	Potassium	Calcium	Scandium	Titanium	Vanadium	Chromium	Manganese	Iron	Cobalt	Nickel	Copper	Zinc	Gallium	Germanium	Arsenic	Selenium	Bromine	Krypton														
5	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54														
	Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe														
	Rubidium	Strontium	Yttrium	Zirconium	Niobium	Molybdenum	Technetium	Ruthenium	Rhodium	Palladium	Silver	Cadmium	Indium	Tin	Antimony	Tellurium	Iodine	Xenon														
6	55	56	*	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86														
	Cs	Ba	*	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn														
	Cesium	Barium	*	Hafnium	Tantalum	Tungsten	Rhenium	Osmium	Iridium	Platinum	Gold	Mercury	Thallium	Lead	Bismuth	Polonium	Astatine	Radon														
7	87	88	**	104	105	106	107	108	109	110	111	112	113	114	115	116	117	118														
	Fr	Ra	**	Rf	Db	Sg	Bh	Hs	Mt	Ds	Rg	Uub	Uut	Uuq	Uup	Uuh	Uus	Uuo														
	Francium	Radium	**	Rutherfordium	Dubnium	Seaborgium	Bhassium	Hassium	Moscovium	Darmstadtium	Röntgenium	Ubnium	Ubnium	Ubnium	Ubnium	Ubnium	Ubnium	Ubnium														
																		* lanthanides														
																		57	58	59	60	61	62	63	64	65	66	67	68	69	70	71
																		La	Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu
																		Lanthanum	Cerium	Praseodymium	Niodymium	Promethium	Samarium	Europium	Gadolinium	Terbium	Dysprosium	Holmium	Erbium	Thulium	Ytterbium	Lutetium
																		** actinides														
																		89	90	91	92	93	94	95	96	97	98	99	100	101	102	103
																		Ac	Th	Pa	U	Np	Pu	Am	Cm	Bk	Cf	Es	Fm	Md	No	Lr
																		Actinium	Thorium	Protactinium	Uranium	Neptunium	Plutonium	Americium	Curium	Berkelium	Californium	Einsteinium	Fermium	Mendelevium	Nobelium	Lawrencium

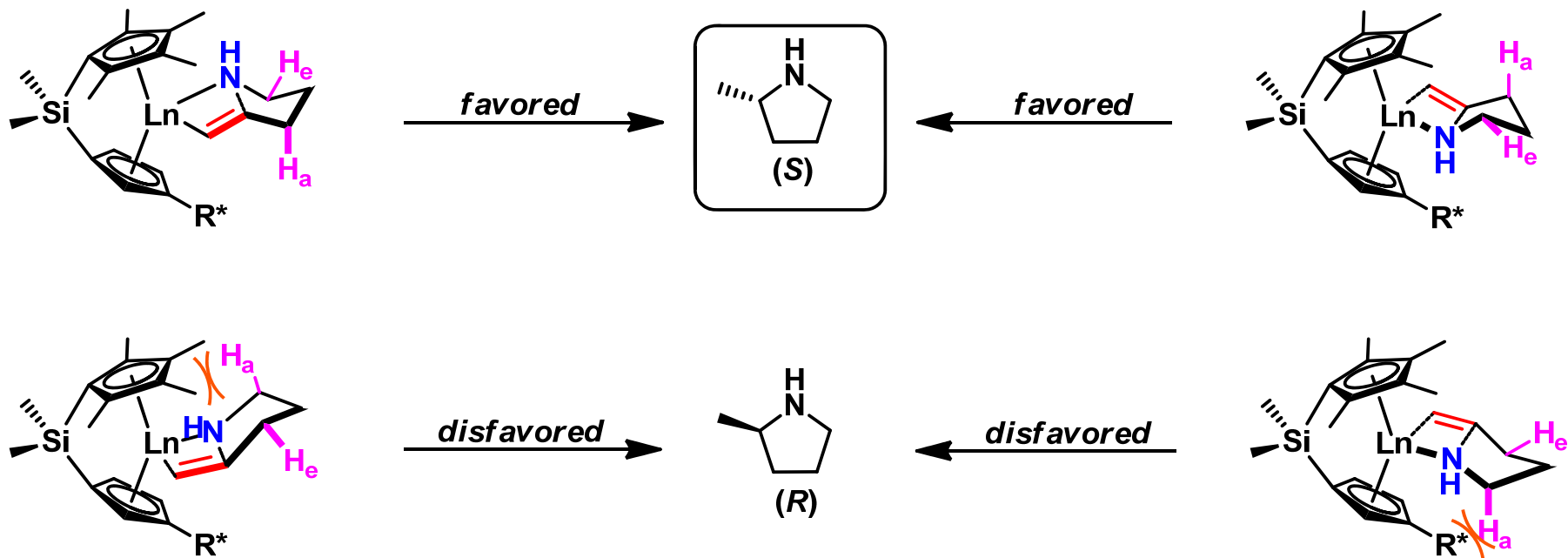




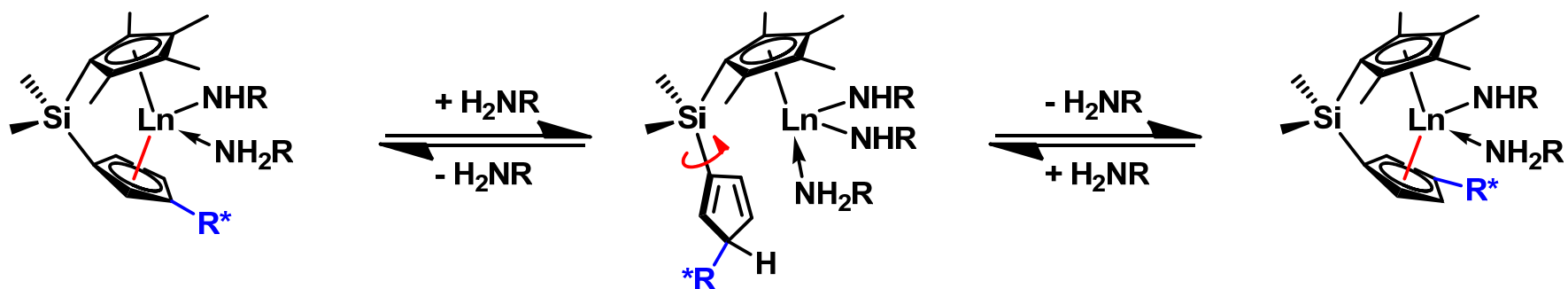
➤ Stereomodel for aminopentene substrates => formation of (S)-pyrrolidine enantiomer

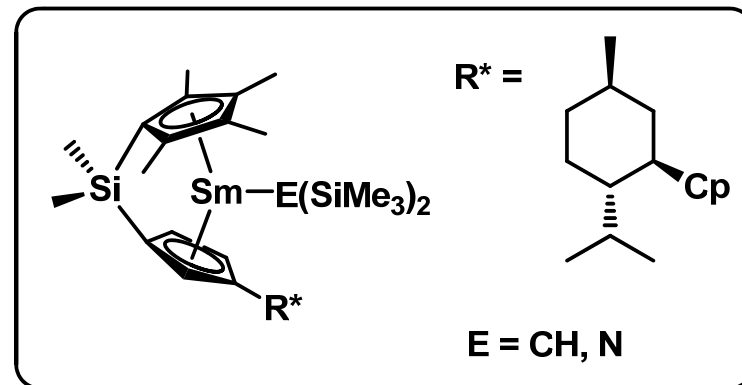
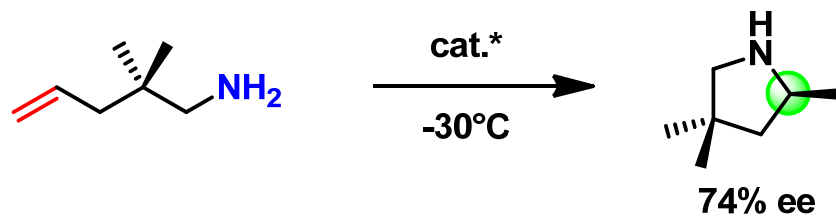


➤ Stereomodel for aminopentene substrates => formation of (S)-pyrrolidine enantiomer



➤ 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 :

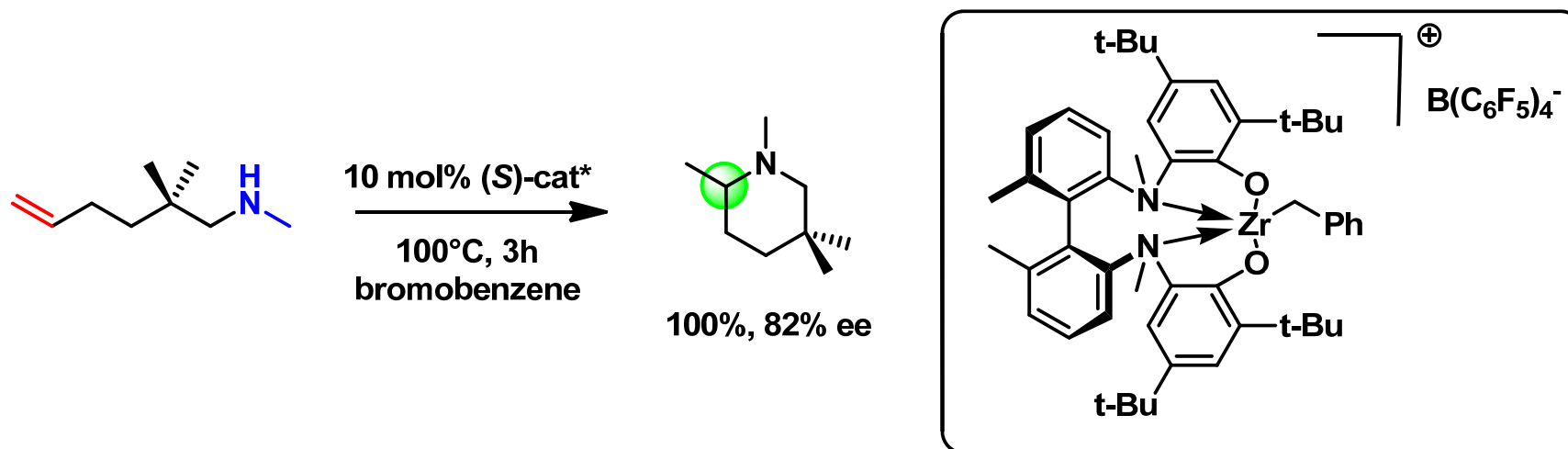
-sensitive to oxygen and moisture

- limited their use in many applications

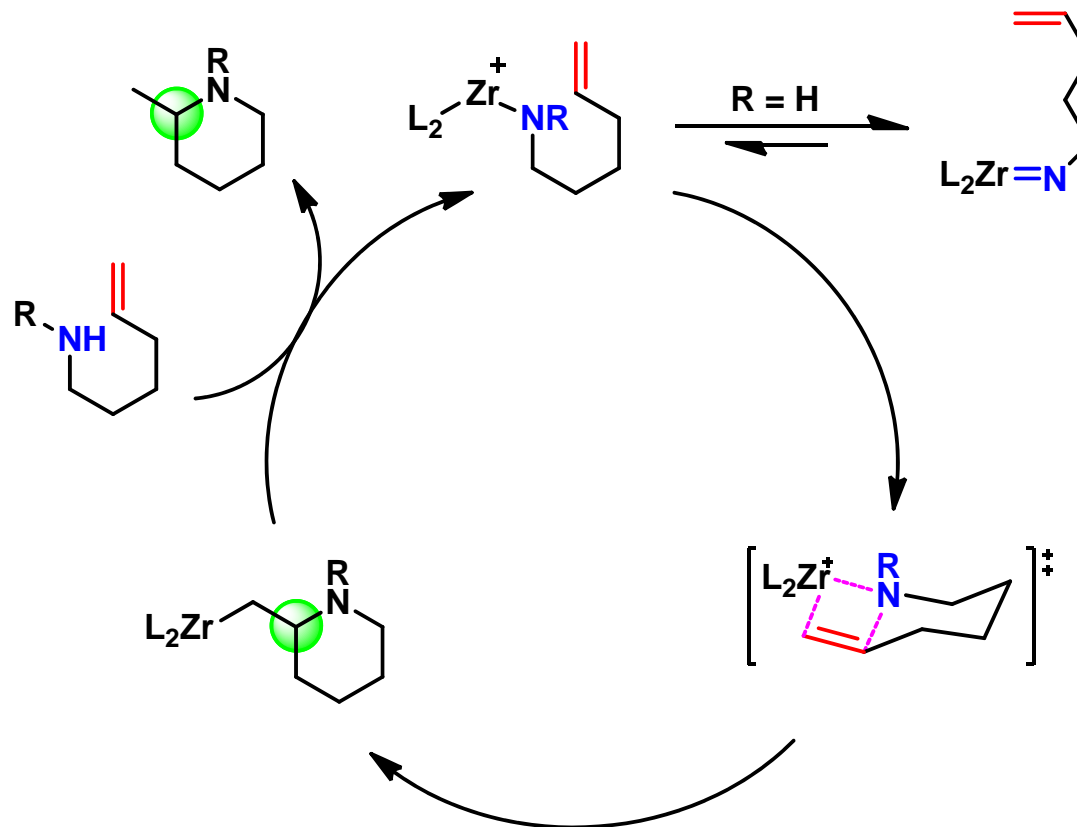
Group 4 Metal-Based Catalysts

	IA																			VIIIA	
1	1 H <small>Hydrogen</small>																				2 He <small>Helium</small>
2	3 Li <small>Lithium</small>	4 Be <small>Beryllium</small>													5 B <small>Boron</small>	6 C <small>Carbon</small>	7 N <small>Nitrogen</small>	8 O <small>Oxygen</small>	9 F <small>Fluorine</small>	10 Ne <small>Neon</small>	
3	11 Na <small>Sodium</small>	12 Mg <small>Magnesium</small>													13 Al <small>Aluminum</small>	14 Si <small>Silicon</small>	15 P <small>Phosphorus</small>	16 S <small>Sulfur</small>	17 Cl <small>Chlorine</small>	18 Ar <small>Argon</small>	
4	19 K <small>Potassium</small>	20 Ca <small>Calcium</small>	21 Sc <small>Scandium</small>	22 Ti <small>Titanium</small>	23 V <small>Vanadium</small>	24 Cr <small>Chromium</small>	25 Mn <small>Manganese</small>	26 Fe <small>Iron</small>	27 Co <small>Cobalt</small>	28 Ni <small>Nickel</small>	29 Cu <small>Copper</small>	30 Zn <small>Zinc</small>	31 Ga <small>Gallium</small>	32 Ge <small>Germanium</small>	33 As <small>Arsenic</small>	34 Se <small>Selenium</small>	35 Br <small>Bromine</small>	36 Kr <small>Krypton</small>			
5	37 Rb <small>Rubidium</small>	38 Sr <small>Strontium</small>	39 Y <small>Yttrium</small>	40 Zr <small>Zirconium</small>	41 Nb <small>Niobium</small>	42 Mo <small>Molybdenum</small>	43 Tc <small>Technetium</small>	44 Ru <small>Ruthenium</small>	45 Rh <small>Rhodium</small>	46 Pd <small>Palladium</small>	47 Ag <small>Silver</small>	48 Cd <small>Cadmium</small>	49 In <small>Indium</small>	50 Sn <small>Tin</small>	51 Sb <small>Antimony</small>	52 Te <small>Tellurium</small>	53 I <small>Iodine</small>	54 Xe <small>Xenon</small>			
6	55 Cs <small>Cesium</small>	56 Ba <small>Barium</small>	* <small>Lanthanides</small>	72 Hf <small>Hafnium</small>	73 Ta <small>Tantalum</small>	74 W <small>Tungsten</small>	75 Re <small>Rhenium</small>	76 Os <small>Osmium</small>	77 Ir <small>Iridium</small>	78 Pt <small>Platinum</small>	79 Au <small>Gold</small>	80 Hg <small>Mercury</small>	81 Tl <small>Thallium</small>	82 Pb <small>Lead</small>	83 Bi <small>Bismuth</small>	84 Po <small>Polonium</small>	85 At <small>Astatine</small>	86 Rn <small>Radon</small>			
7	87 Fr <small>Francium</small>	88 Ra <small>Radium</small>	** <small>Actinides</small>	104 Rf <small>Rutherfordium</small>	105 Db <small>Dubnium</small>	106 Sg <small>Seaborgium</small>	107 Bh <small>Bhassium</small>	108 Hs <small>Hassium</small>	109 Mt <small>Moscovium</small>	110 Ds <small>Darmstadtium</small>	111 Rg <small>Röntgenium</small>	112 Uub <small>Ununbium</small>	113 Uut <small>Ununtrium</small>	114 Uuq <small>Ununquadium</small>	115 Uup <small>Ununpentium</small>	116 Uuh <small>Ununhexium</small>	117 Uus <small>Ununseptium</small>	118 Uuo <small>Ununoctium</small>			
			* lanthanides	57 La <small>Lanthanum</small>	58 Ce <small>Cerium</small>	59 Pr <small>Praseodymium</small>	60 Nd <small>Niodymium</small>	61 Pm <small>Promethium</small>	62 Sm <small>Samarium</small>	63 Eu <small>Europium</small>	64 Gd <small>Gadolinium</small>	65 Tb <small>Terbium</small>	66 Dy <small>Dysprosium</small>	67 Ho <small>Holmium</small>	68 Er <small>Erbium</small>	69 Tm <small>Thulium</small>	70 Yb <small>Ytterbium</small>	71 Lu <small>Lutetium</small>			
			** actinides	89 Ac <small>Actinium</small>	90 Th <small>Thorium</small>	91 Pa <small>Protactinium</small>	92 U <small>Uranium</small>	93 Np <small>Neptunium</small>	94 Pu <small>Plutonium</small>	95 Am <small>Americium</small>	96 Cm <small>Curium</small>	97 Bk <small>Berkelium</small>	98 Cf <small>Californium</small>	99 Es <small>Einsteinium</small>	100 Fm <small>Fermium</small>	101 Md <small>Mendelevium</small>	102 No <small>Nobelium</small>	103 Lr <small>Lawrencium</small>			

- 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



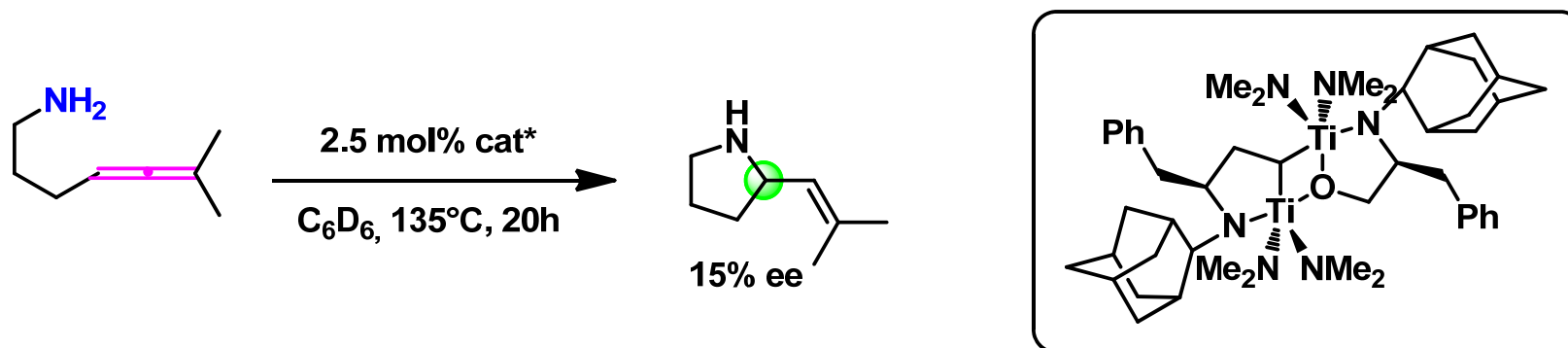
- First chiral group 4 metal catalyst system => cationic aminophenolate complex



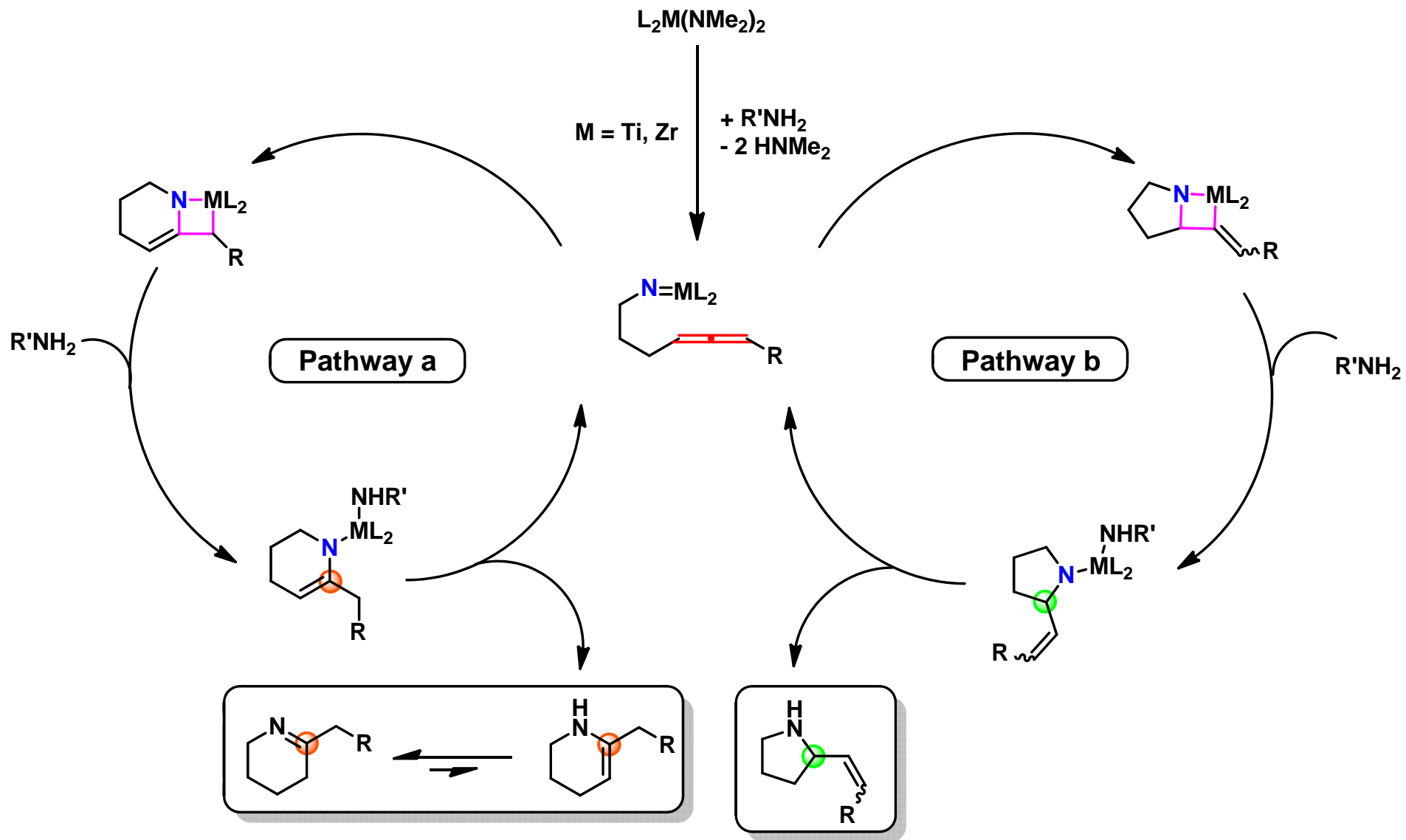
- similar to that proposed for rare earth metal
- no reaction with primary aminoalkenes : cationic Zr amido species are readily deprotonated to yield catalytically inactive Zr imido species.

➤ 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 trisubstitued aminoallenes

Late Transition Metal-Based Catalysts

	IA																		VIIIA	
1	1 H Hydrogen																			2 He Helium
2	3 Li Lithium	4 Be Beryllium													5 B Boron	6 C Carbon	7 N Nitrogen	8 O Oxygen	9 F Fluorine	10 Ne Neon
3	11 Na Sodium	12 Mg Magnesium													13 Al Aluminum	14 Si Silicon	15 P Phosphorus	16 S Sulfur	17 Cl Chlorine	18 Ar Argon
4	19 K Potassium	20 Ca Calcium	III B	IV B	V B	VIB	VII B	VIII B			IB	IIB								
			21 Sc Scandium	22 Ti Titanium	23 V Vanadium	24 Cr Chromium	25 Mn Manganese	26 Fe Iron	27 Co Cobalt	28 Ni Nickel	29 Cu Copper	30 Zn Zinc	31 Ga Gallium	32 Ge Germanium	33 As Arsenic	34 Se Selenium	35 Br Bromine	36 Kr Krypton		
5	37 Rb Rubidium	38 Sr Strontium	39 Y Yttrium	40 Zr Zirconium	41 Nb Niobium	42 Mo Molybdenum	43 Tc Technetium	44 Ru Ruthenium	45 Rh Rhodium	46 Pd Palladium	47 Ag Silver	48 Cd Cadmium	49 In Indium	50 Sn Tin	51 Sb Antimony	52 Te Tellurium	53 I Iodine	54 Xe Xenon		
6	55 Cs Cesium	56 Ba Barium	* Lanthanides	72 Hf Hafnium	73 Ta Tantalum	74 W Tungsten	75 Re Rhenium	76 Os Osmium	77 Ir Iridium	78 Pt Platinum	79 Au Gold	80 Hg Mercury	81 Tl Thallium	82 Pb Lead	83 Bi Bismuth	84 Po Polonium	85 At Astatine	86 Rn Radon		
7	87 Fr Francium	88 Ra Radium	** Actinides	104 Rf Rutherfordium	105 Db Dubnium	106 Sg Seaborgium	107 Bh Bohrium	108 Hs Hassium	109 Mt Meitnerium	110 Ds Darmstadtium	111 Rg Roentgenium	112 Uub Ununbium	113 Uut Ununtrium	114 Uuq Ununquadium	115 Uup Ununpentium	116 Uuh Ununhexium	117 Uus Ununseptium	118 Uuo Ununoctium		
			* lanthanides	57 La Lanthanum	58 Ce Cerium	59 Pr Praseodymium	60 Nd Neodymium	61 Pm Promethium	62 Sm Samarium	63 Eu Europium	64 Gd Gadolinium	65 Tb Terbium	66 Dy Dysprosium	67 Ho Holmium	68 Er Erbium	69 Tm Thulium	70 Yb Ytterbium	71 Lu Lutetium		
			** actinides	89 Ac Actinium	90 Th Thorium	91 Pa Protactinium	92 U Uranium	93 Np Neptunium	94 Pu Plutonium	95 Am Americium	96 Cm Curium	97 Bk Berkelium	98 Cf Californium	99 Es Einsteinium	100 Fm Fermium	101 Md Mendelevium	102 No Nobelium	103 Lr Lawrencium		

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

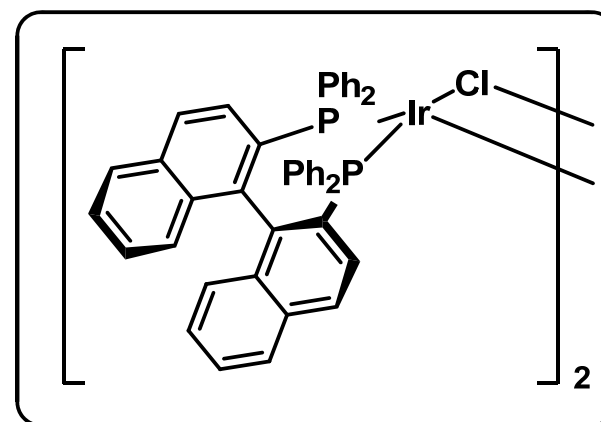
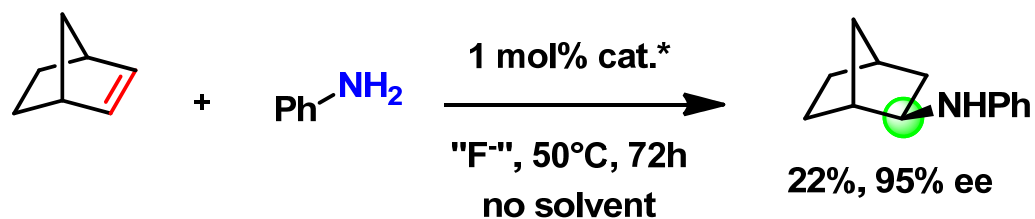
➤ Late transition metal hydroamination catalysts restricted to :

- activated C-C multiple bonds

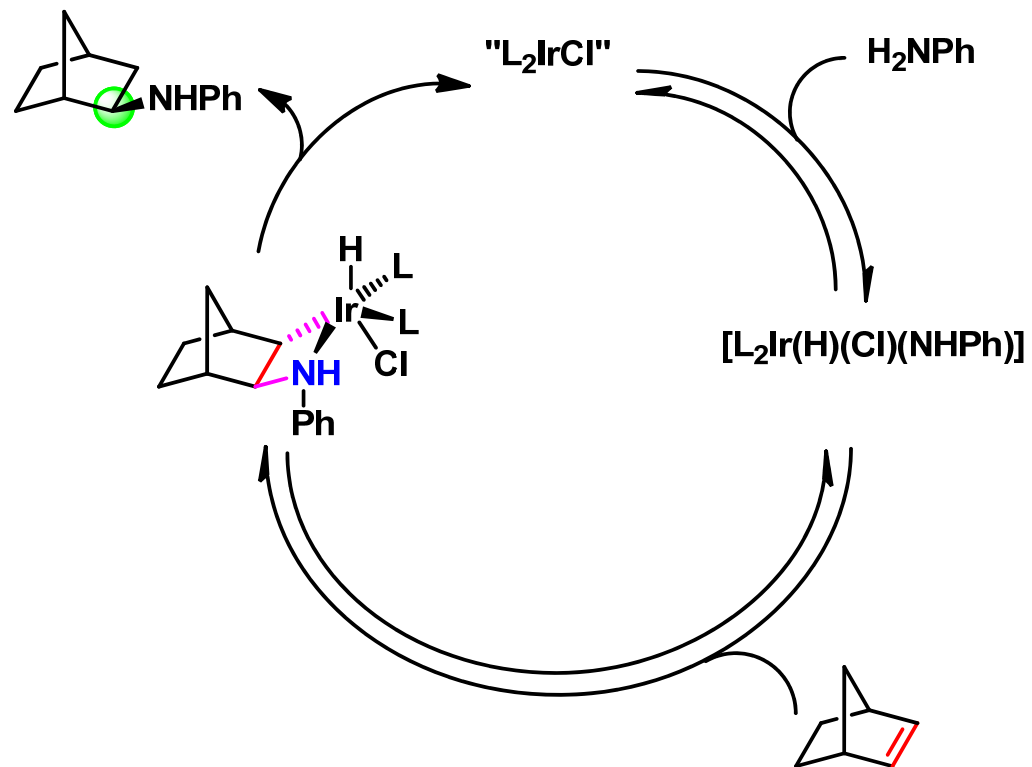
- norbornene / styrene

- conjugated dienes, alkynes and α,β -insaturated carbonyl compounds

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

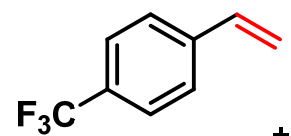


➤ Schwesinger's « naked » fluoride {N[P(NMe₂)₃]}F⁻ to improve the activity and selectivity

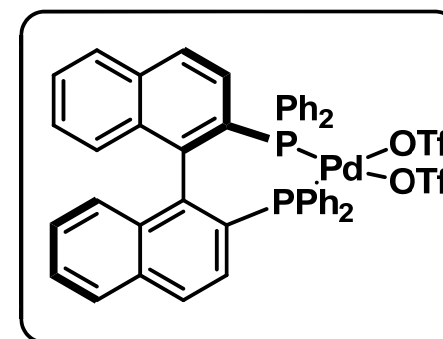
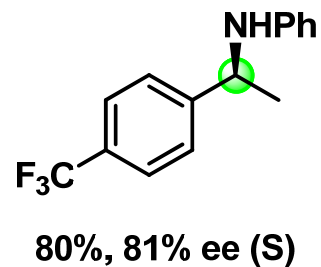
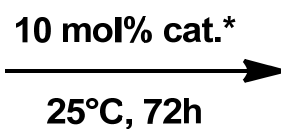
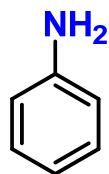


- Addition takes place across the sterically better accessible *exo* face
- The scope is not limited to hydroamination of norbornene with aniline

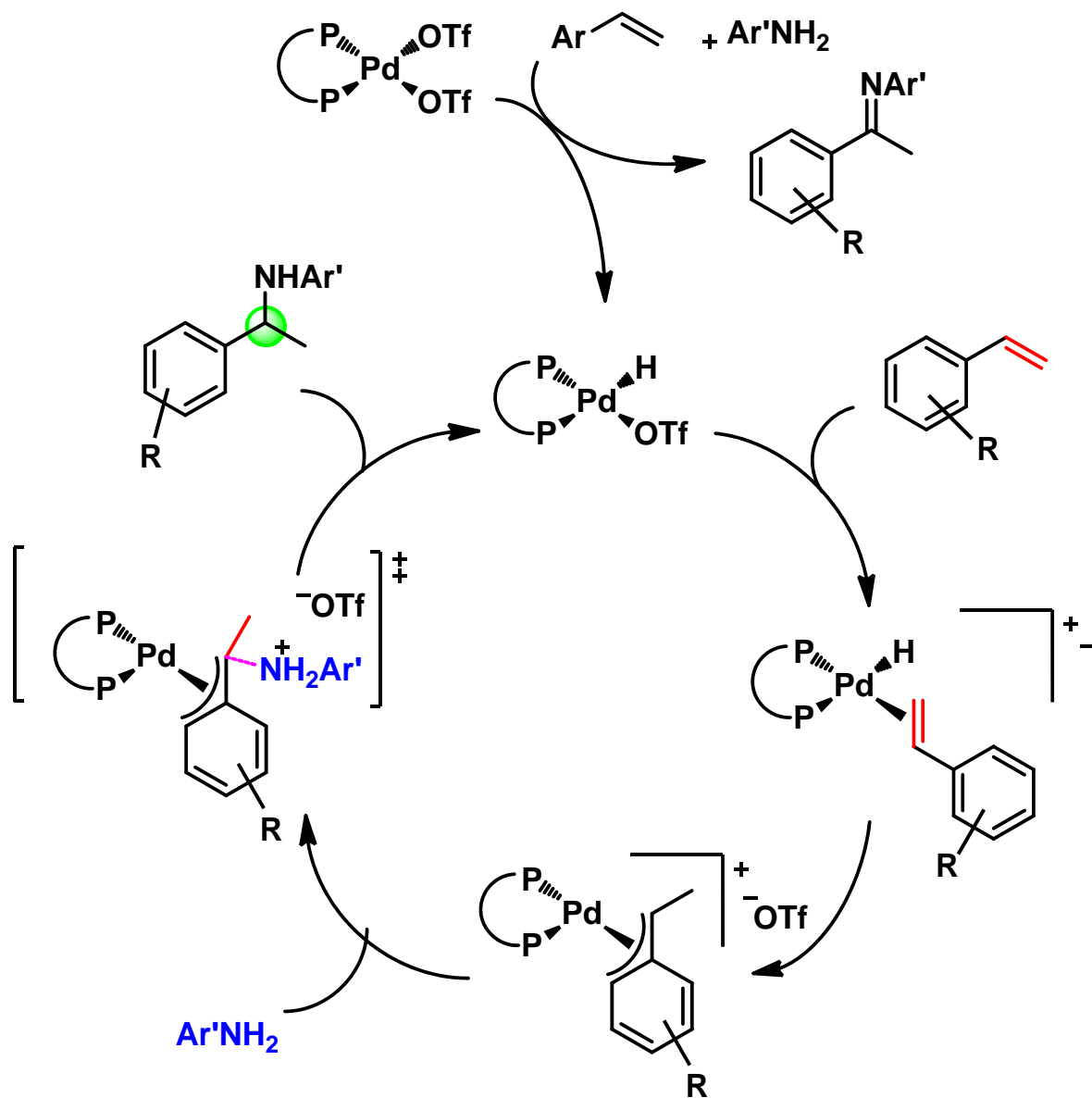
➤ Hydroamination of styrenes / 1,3-dienes using palladium catalyst reported by Hartwig.



+

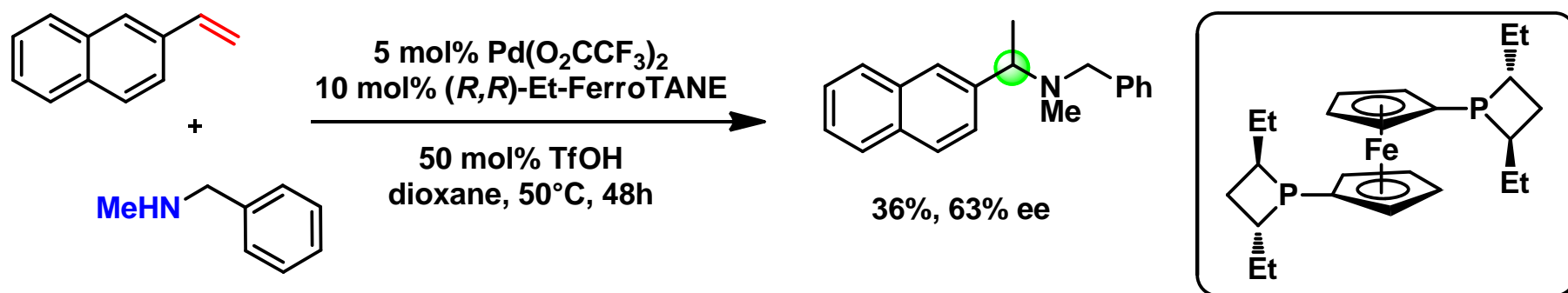


➤ high temperature are not necessarily (demonstrated by Hii).



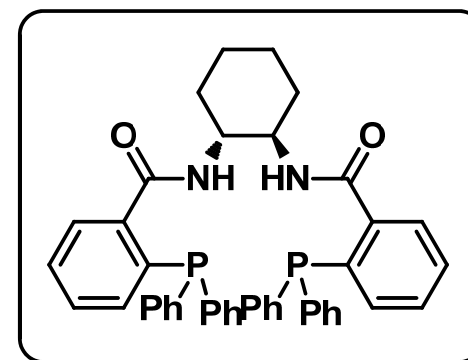
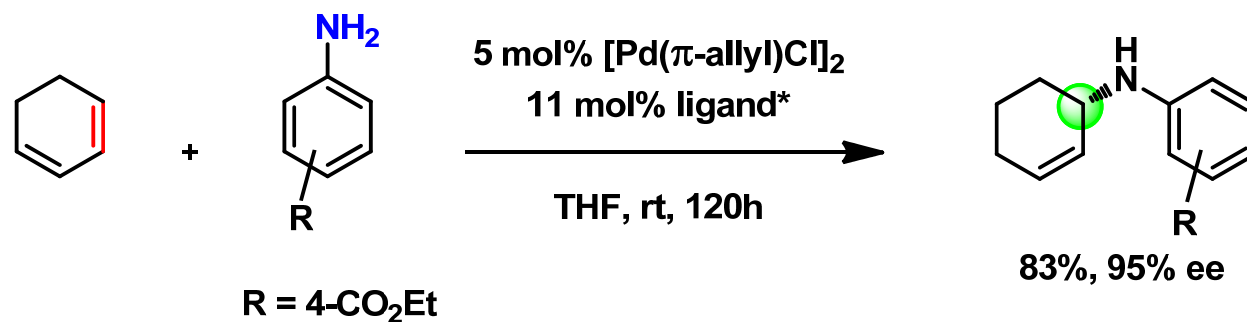
➤ the major diastereomer in solution generated the minor enantiomer of the hydroamination product of the catalytic reaction

➤ limitations with secondary alkylamines



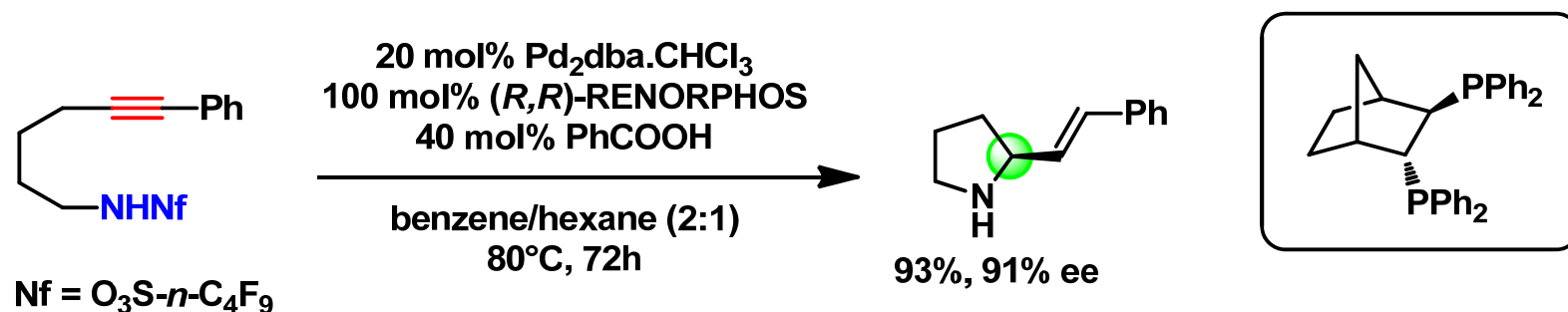
➤ Competition between nucleophilic attack of the amine at the benzylic carbon leading to the hydroamination product and reversible elimination of styrene from η^3 -benzyl intermediate.

➤ Asymmetric hydroamination of cyclohexadiene with anilines.



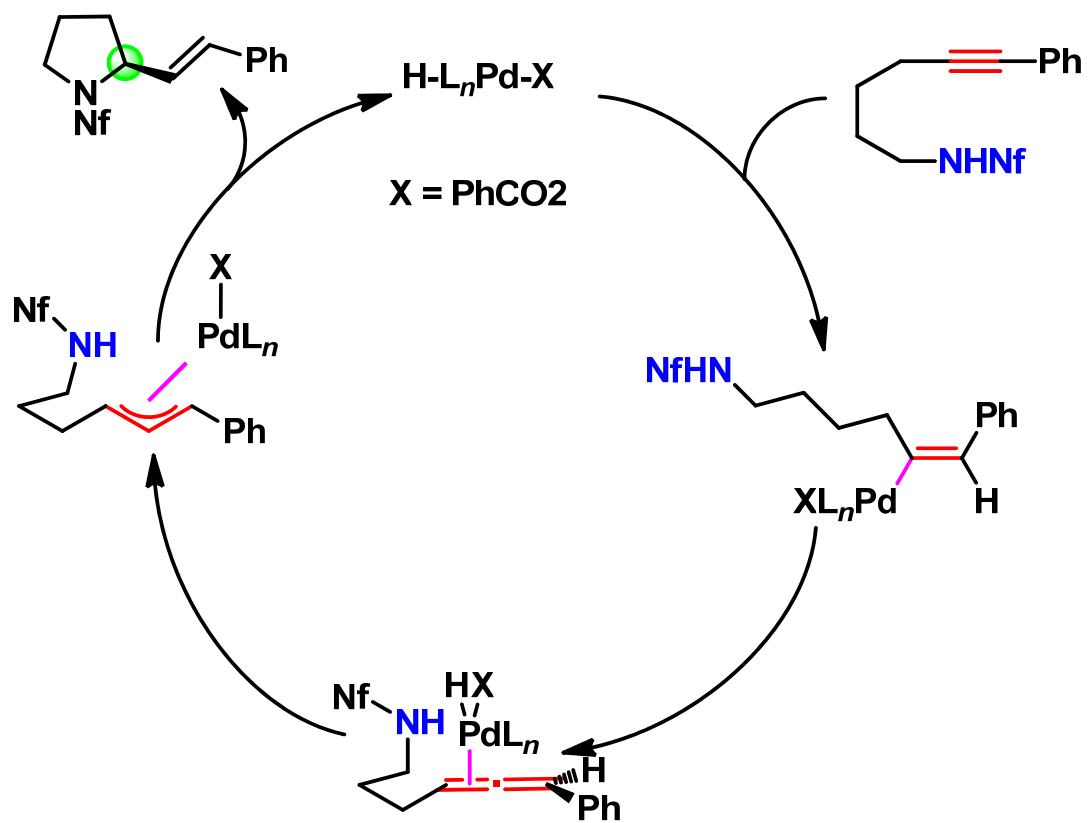
➤ For other cyclic or acyclic 1,3-dienes : only the 1,4-addition of aniline to cycloheptadiene in 66% ee but only 22% yield was reported.

- Palladium-catalyzed asymmetric intramolecular hydroamination of aminoalkynes.
- The asymmetric hydroamination of *N*-protected aminoalkynes reported by Yamamoto.

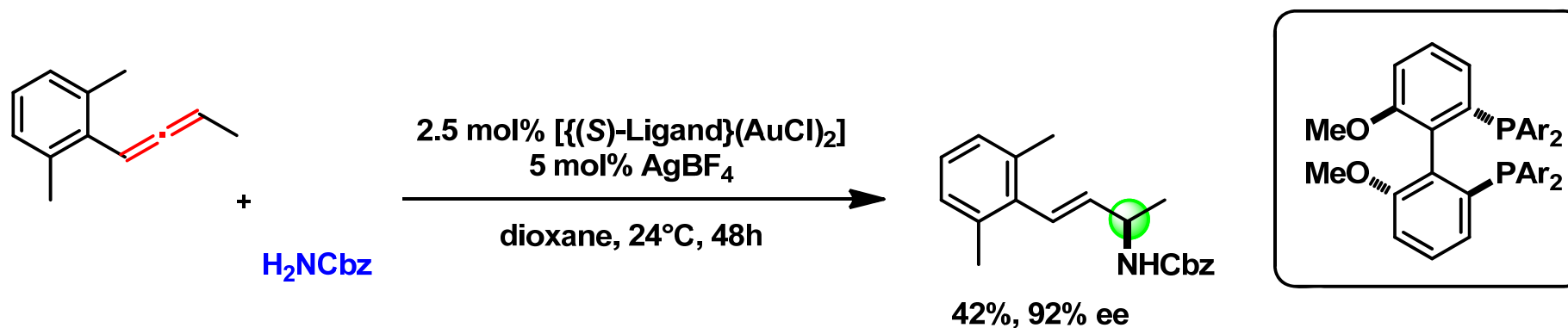


- High catalyst loading were required
- Lower catalyst loading resulted in reduced yield and enantioselectivities
- Electron-rich alkynes were transformed faster but lower enantioselectivities.

➤ Plausible postulated mechanism

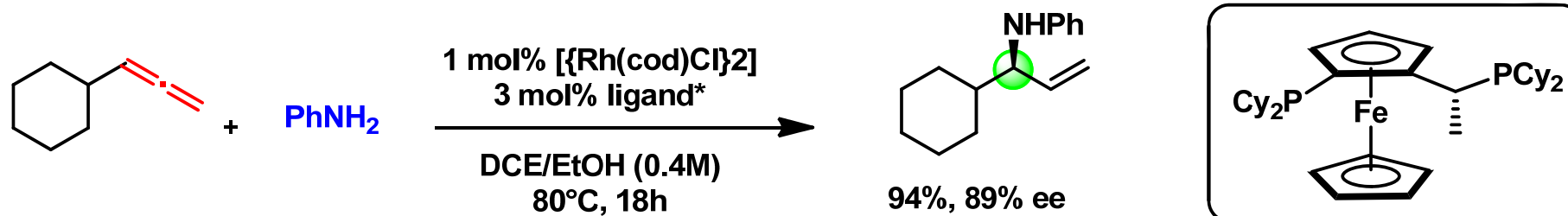


- Gold-catalyzed intermolecular enantioselective hydroamination of allenes

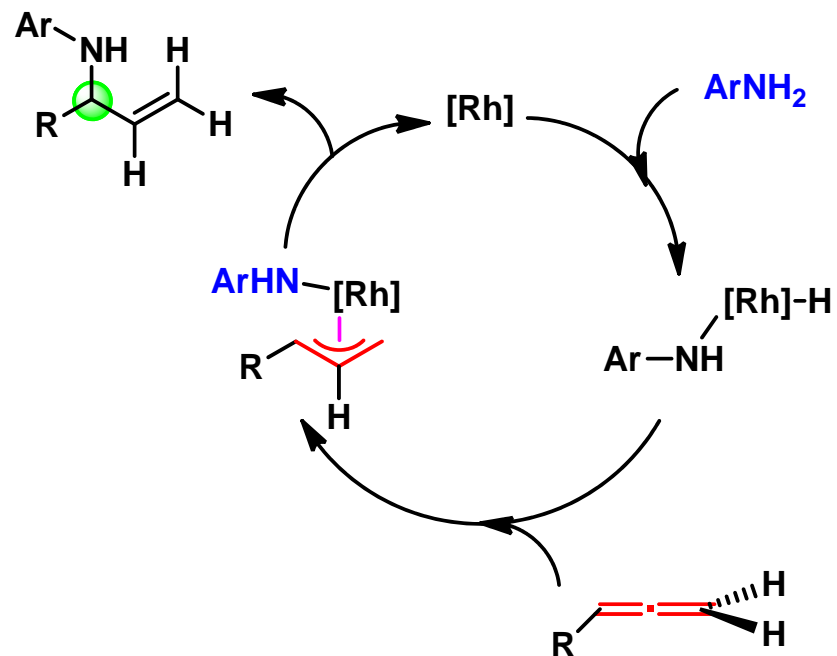


- Access to enantiomerically enriched α -chiral allylic amines => important chiral building blocks in the synthesis of complex nitrogen containing molecules
- Only internal allenes tolerated

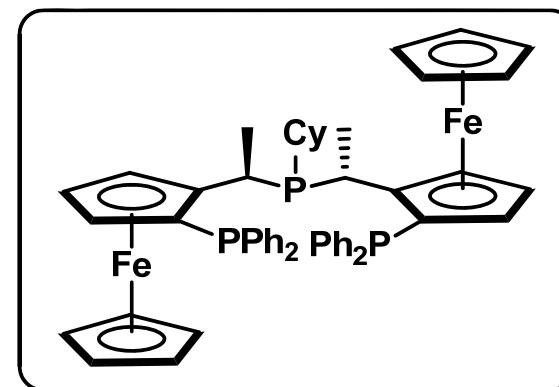
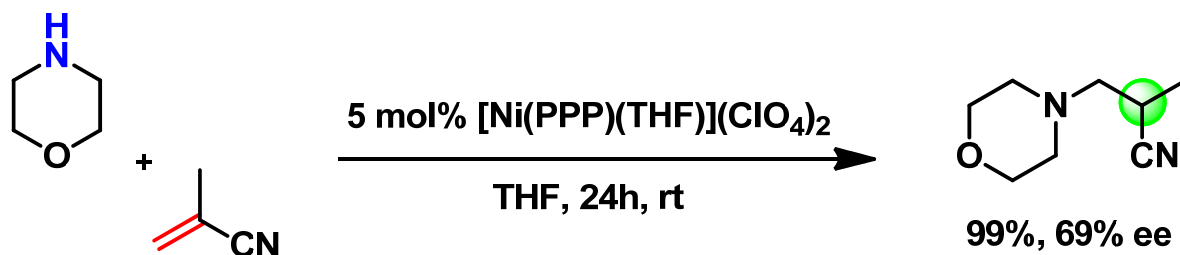
➤ Rhodium-catalyzed intermolecular hydroamination of terminal allenes



➤ 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 :

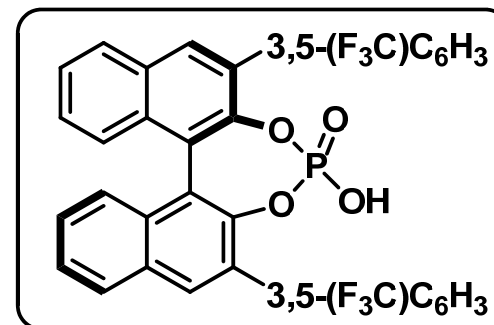
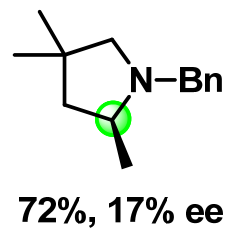
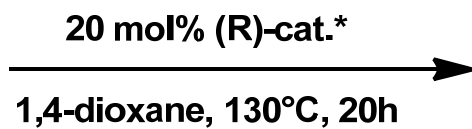
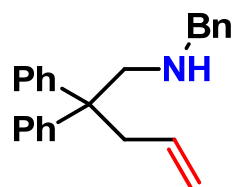
- no general catalyst => combining high catalytic activity and high level of enantioselectivity for a wide range of substrates, high functional group tolerance and user-friendliness

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

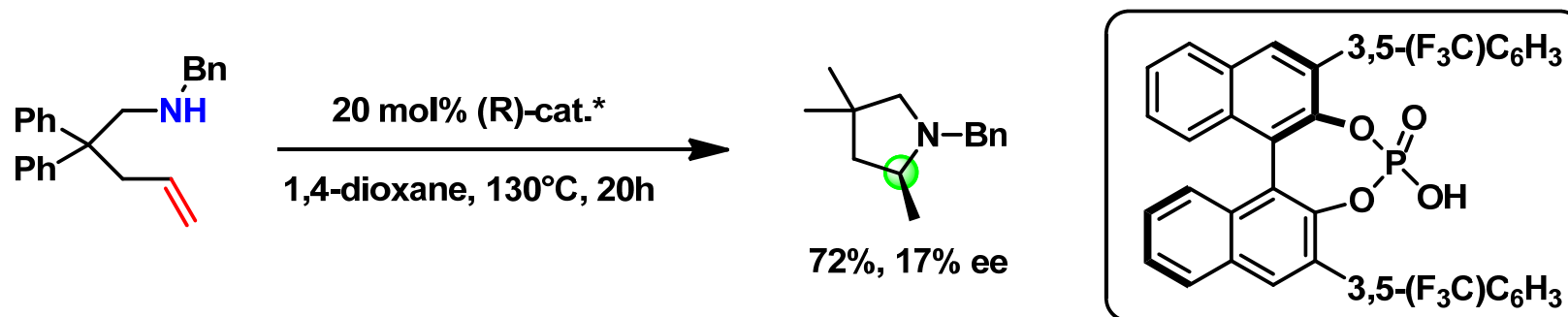
	IA															VIIIA	
1	1 H Hydrogene															2 He Helium	
2	3 Li Lithium	IIA	4 Be Beryllium					III A	IVA	VA	VIA	VIIA			10 Ne Neon		
3	11 Na Natrium		12 Mg Magnesium					13 B Bor	14 C Carbon	15 N Azote	16 O Oxygen	17 F Fluor		18 Ar Argon			
4	19 K Kalium		20 Ca Calcium									19 Cl Chlor		35 Br Brom	36 Kr Krypton		
5	37 Rb Rubidium		38 Sr Strontium									53 I Jod		54 Xe Xenon			
6	55 Cs Cesium		56 Ba Barium									85 At Astat		86 Rn Radon			
7	87 Fr Francium		88 Ra Radium									117 Uus Unseptium		118 Uuo Unoctium			
		* lanthanides	57 La Lanthan	58 Ce Cetium	59 Pr Praseodym	60 Nd Neodym	61 Pm Promethium	62 Sm Samarium	63 Eu Europium	64 Gd Gadolinium	65 Tb Terbium	66 Dy Dysprosium	67 Ho Holmium	68 Er Erbium	69 Tm Thulium	70 Yb Ytterbium	71 Lu Lutetium
		** actinides	89 Ac Actinium	90 Th Thorium	91 Pa Protactinium	92 U Uranium	93 Np Neptunium	94 Pu Plutonium	95 Am Americium	96 Cm Curium	97 Bk Berkelium	98 Cf Californium	99 Es Einsteinium	100 Fm Fermium	101 Md Mendelevium	102 No Nobelium	103 Lr Lawrencium

Organocatalytic
Asymmetric
Hydroamination

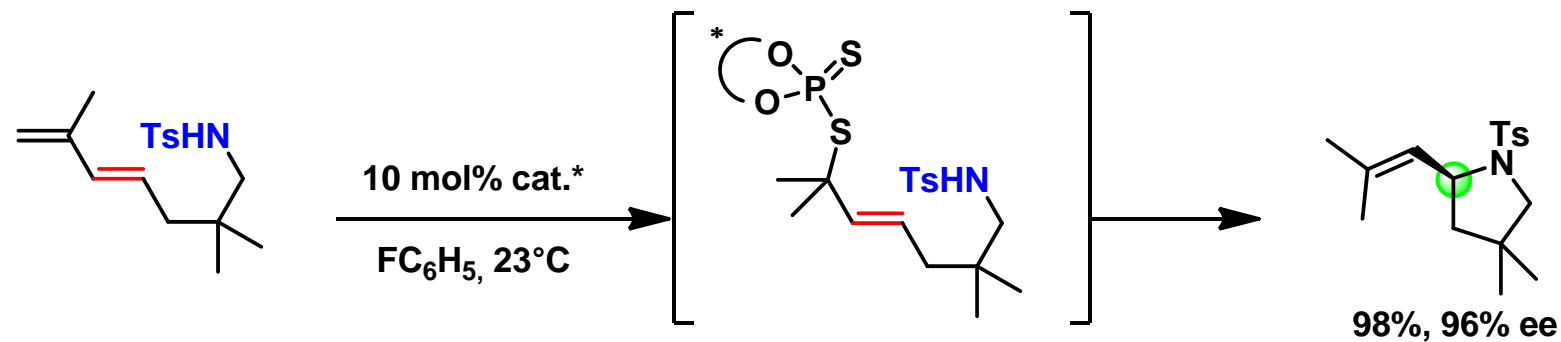
➤ First example of catalytic asymmetric metal free hydroamination using chiral phosphoric acid diester



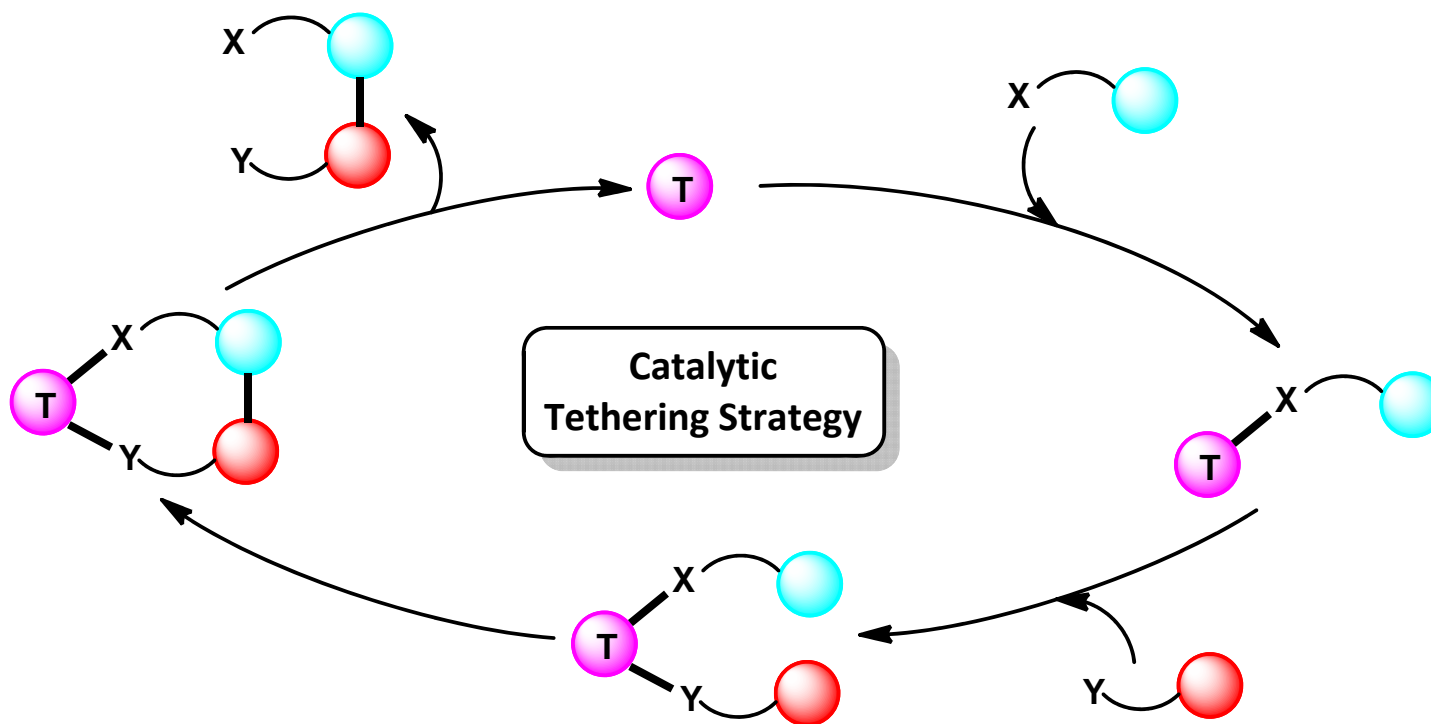
- First example of catalytic asymmetric metal free hydroamination using chiral phosphoric acid diester



- Chiral dithiophosphoric acids can catalyse hydroamination of dienes and allenes



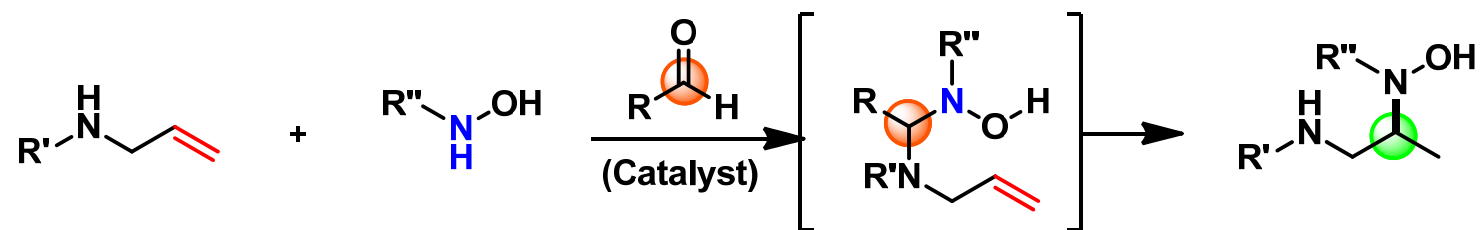
➤ Prototypical catalytic tethering strategy : activation only through temporary intramolecularity



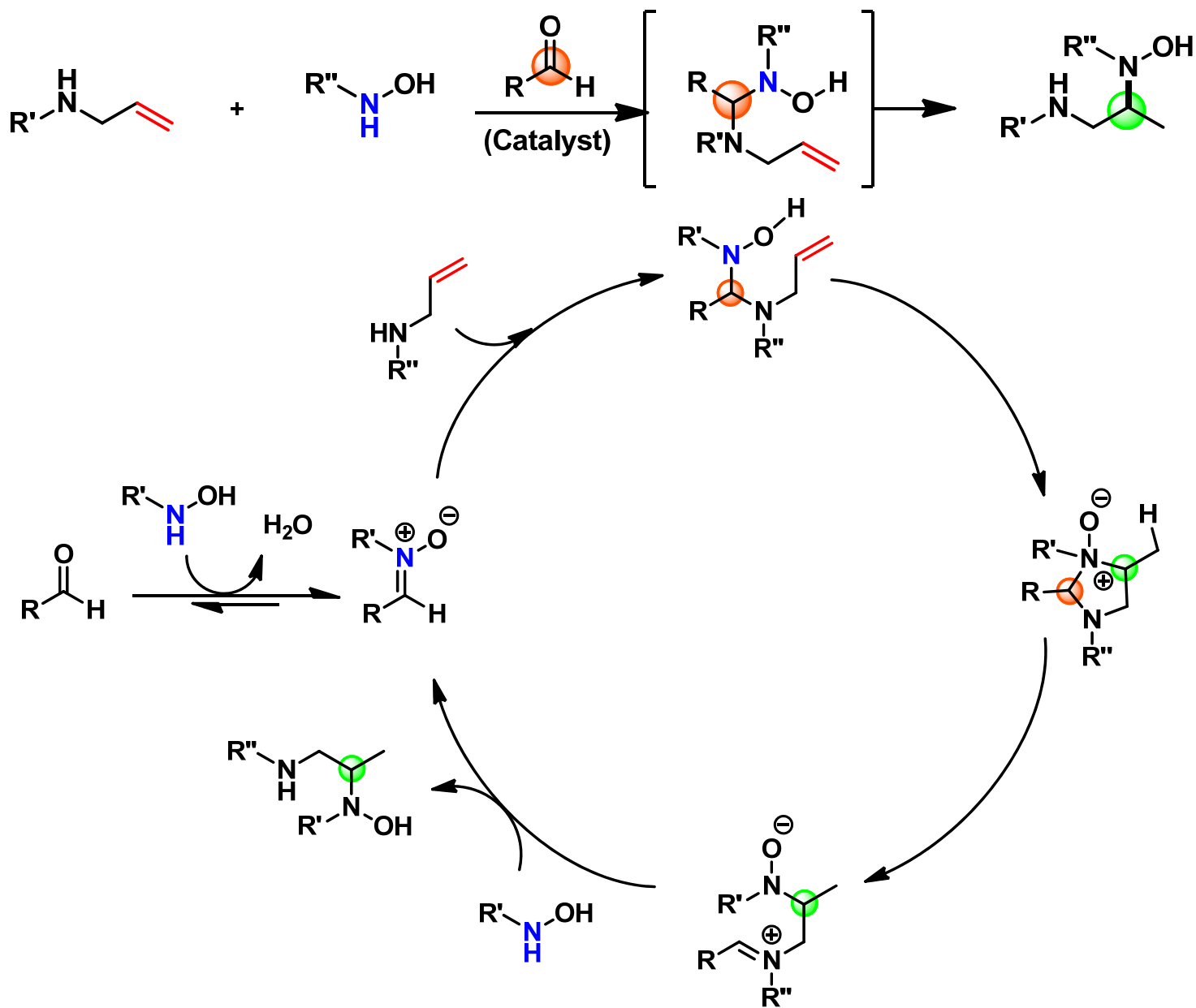
Advantages :

- ✓ Good atom and step economy
- ✓ Chiral catalysts can enforce stereochemical control
- ✓ Can target a variety of difficult intermolecular reactions

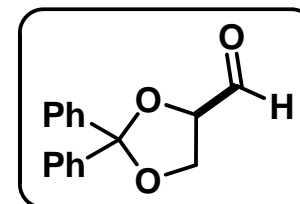
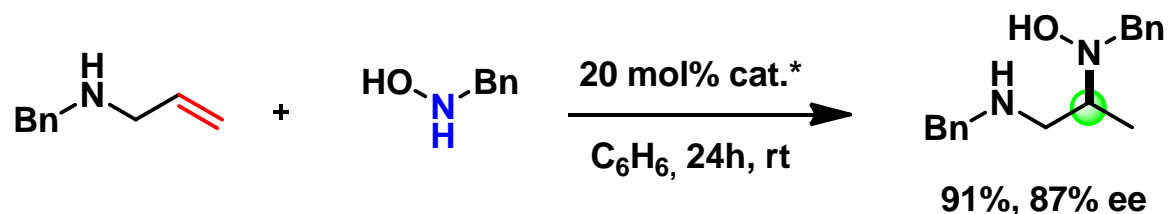
➤ Aldehyde-based organocatalysts : temporary tether between hydroxylamines and allylic amines => Cope-type hydroamination



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



➤ 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 through 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

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