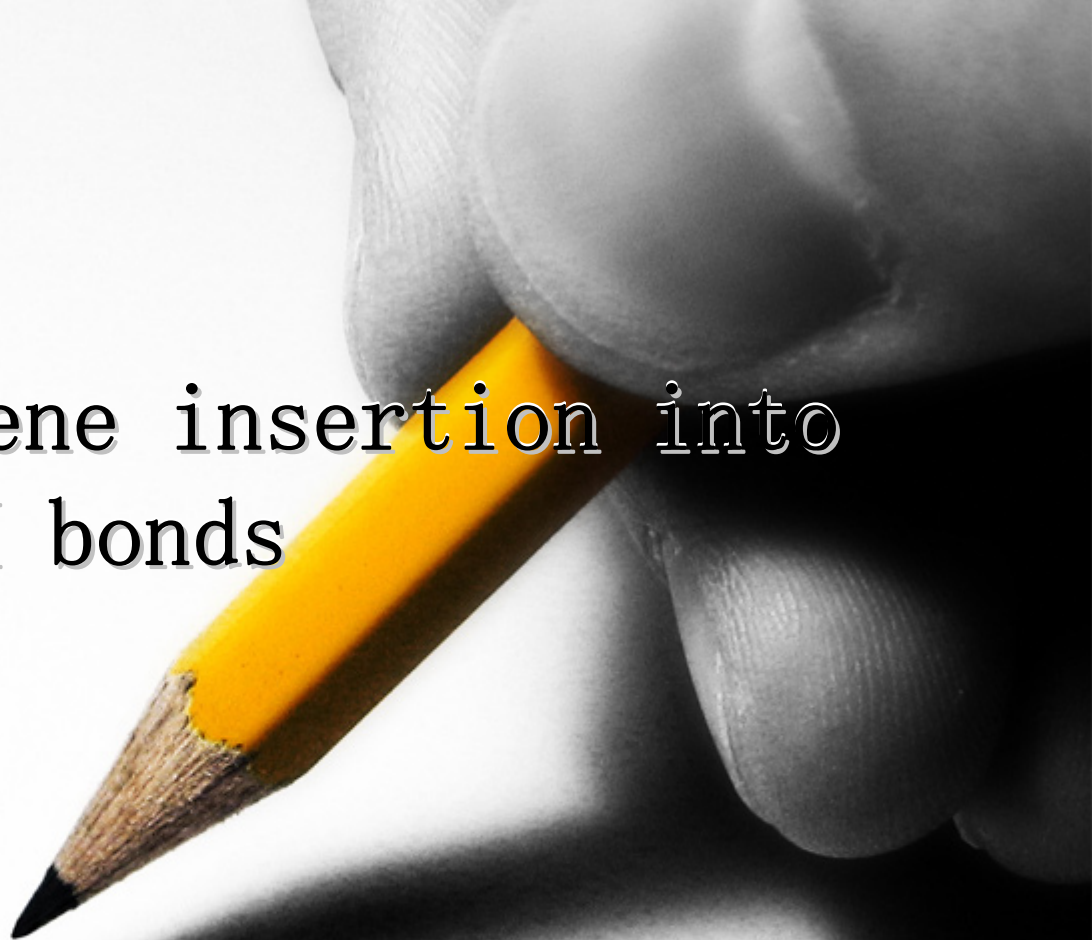




Catalytic carbene insertion into C-H bonds



Reporter: 谢奇强

**December 30,
2015**

Introduction

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Catalysts and reactions

Summary and outlook



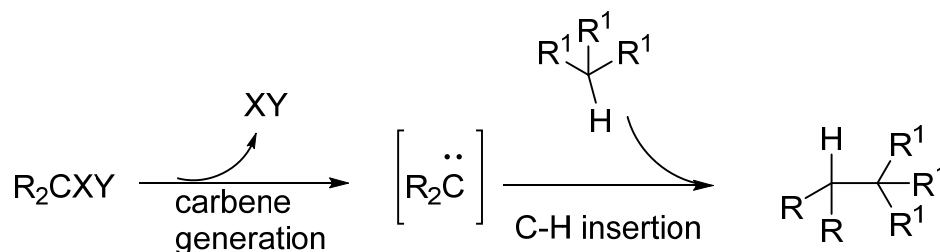
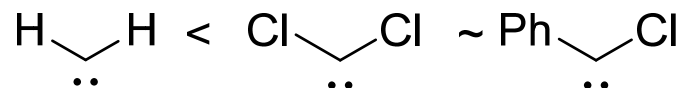


Figure1. Generalized carbene generation and carbon-hydrogen insertion

Selectivity:



No

moderate



Thermally or photochemically generated carbenes show no potential for synthetic uses.

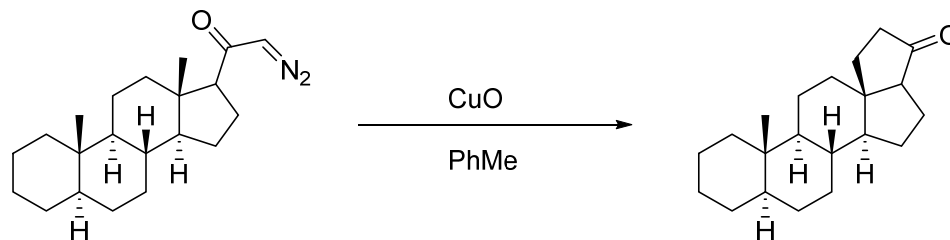


Figure 2. The first transition metal participate carbene insertion into C-H bond reaction

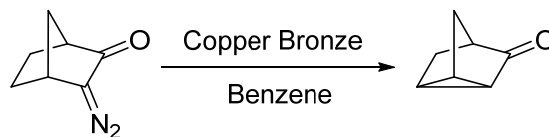
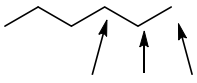
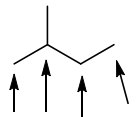
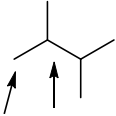


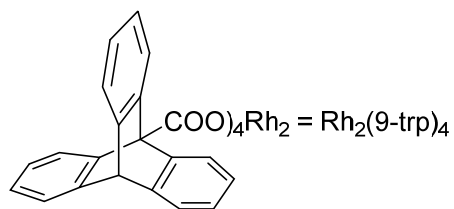
Figure 3. Copper catalysed C-H insertion in rigid system



Introduction

The breakthrough that brought carbon-hydrogen insertion reactions into the realm of viable synthetic applicability was the report of the Teyssie group of intermolecular carbon-hydrogen insertion reactions of ethyl diazoacetate with alkanes, catalyzed by dirhodium(II) tetraacetate and rhodium carboxylate derivatives (Scheme 1)

				
$\text{Rh}_2(\text{OAc})_4$	33 63 4	5 8 90 1	5 95	— typically low yields
$\text{Rh}_2(\text{tfa})_4$	31 64 5	5 25 66 4	12 88	— higher yields
$\text{Rh}_2(9\text{-trp})_4$	9 61 30	18 18 27 37	33 67	— highest yields

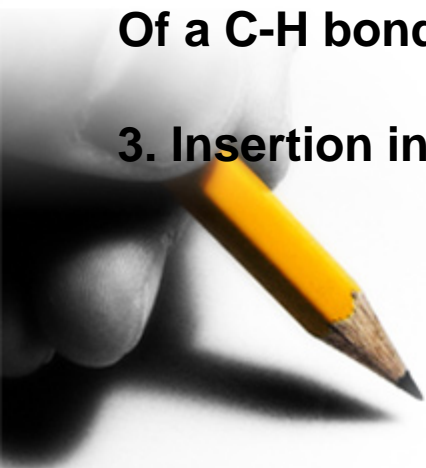


Scheme 1. For reactions with ethyl diazoacetate, arrows define site of C-H insertion

since the early 1990s, the majority of reports have concerned enantioselective C–H insertion reactions, Early work in this area was conducted by Taber and Wenkert, who demonstrated that C–H insertion reactions may occur with high levels of regio- and diastereoselectivities.

Some basic data:

1. The activation enthalpy of the $\text{Rh}_2(\text{OAc})_4$ -catalyzed nitrogen extrusion reaction of ethyl diazoacetate is the rate-limiting step of the catalytic cycle for secondary C-H insertion
2. Reactivity: tertiary > secondary >> primary, and the enhanced reactivity Of a C-H bond adjacent to a heteroatom.
3. Insertion into a C-H bond occurred with retention of configuration



Reaction Mechanism

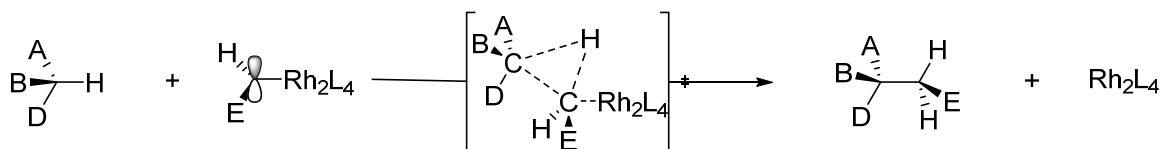


Figure 4. Transition state models of C-H bond activation with dirhodiumcarbene Complex proposed by Doyle



Reaction Mechanism

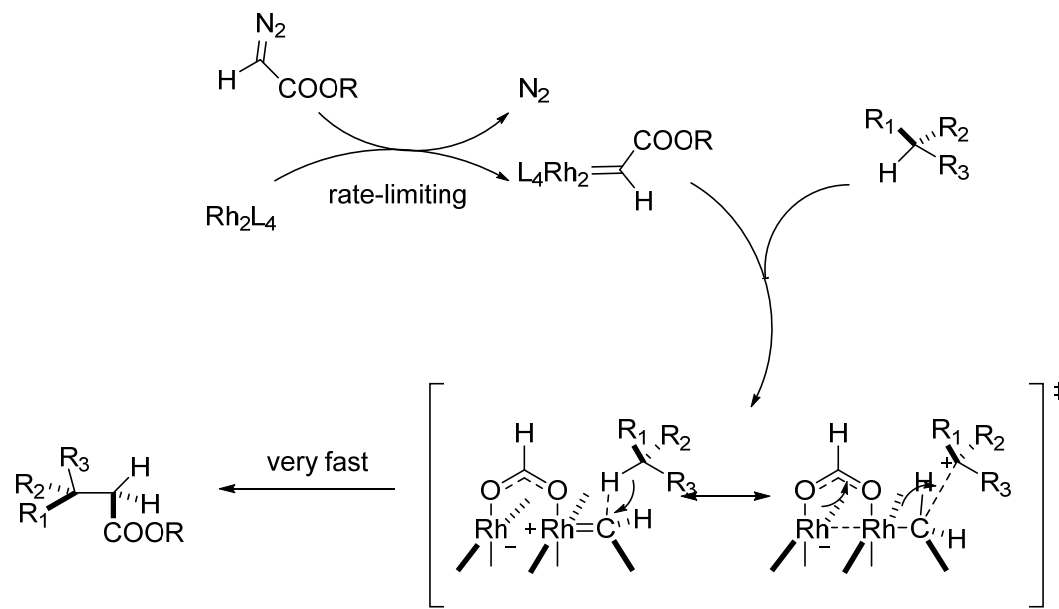
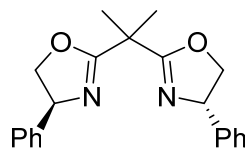
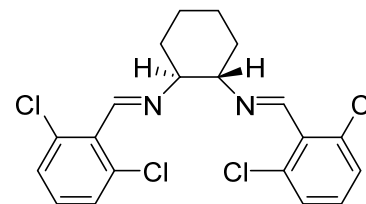


Figure 5. Mechanism fo C-H bond insertion into metal carbene

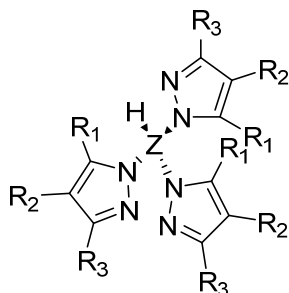
Copper catalyst and related reactions



Bis(oxazoline)

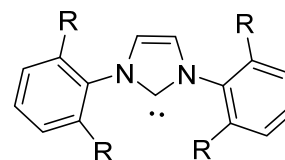


Schiff base



Tp^x (Z=B)

Tpm^x (Z=CH)



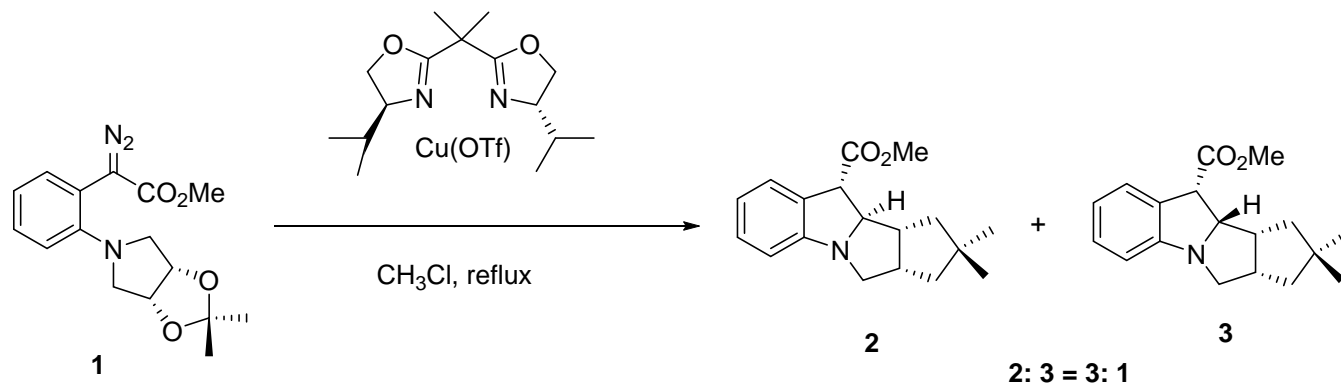
NHC

Scheme 2. Ligands used in copper(I) catalyst

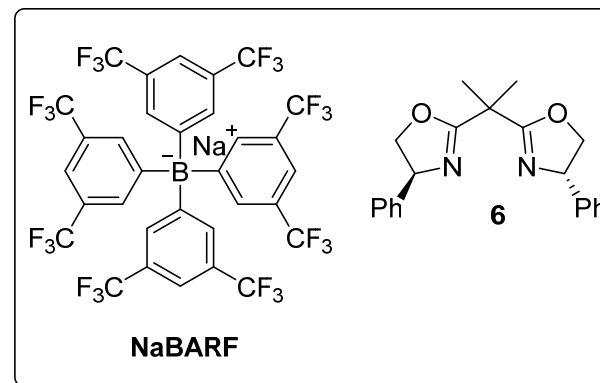
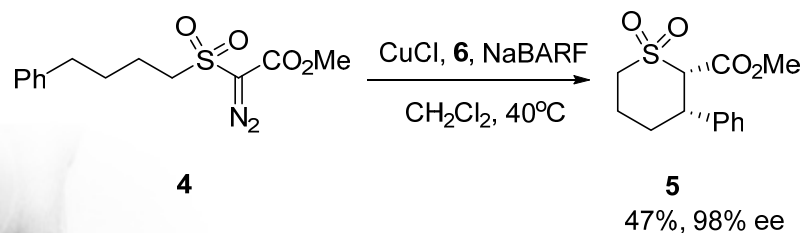


Catalysts and reactions

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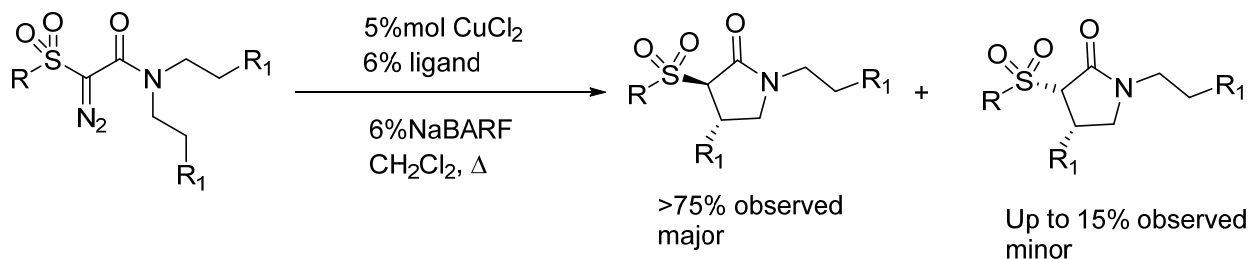


Lim, H.-J; Sulikowski, G. A. *J. Org. Chem.* 1995, 60, 2326



Maguire, A. R. et al. *J. Am. Chem. Soc.* 2010, 132, 1184–1185.

Catalysts and reactions



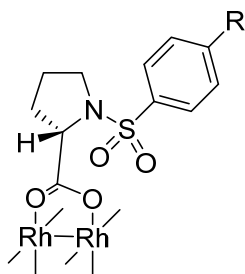
Maguire, A. R. *Org. Biomol. Chem.* 2014, 12, 7612–7628.

High yields (70–90%) and moderate to high enantioselectivities (up to 82% ee) were observed

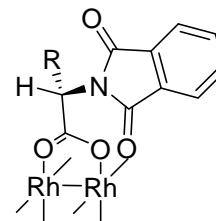


Rhodium catalysts and related reactions

Chiral rhodium carboxylate catalysts

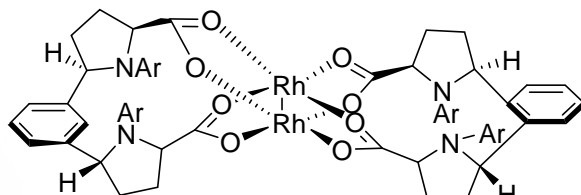


R=H, Rh₂(S-BSP)₄
R=C₁₂H₂₅, Rh₂(S-DOSP)₄



R=Me, Rh₂(S-PTA)₄
R=C(Et)₃, Rh₂(S-PTTEA)₄

Proline complexes

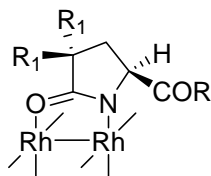


Ar = 2, 4, 6-tri-*i*PrC₆H₂ Rh₂(S-biTISP)₂
Ar = *p*-(C₁₂H₂₅)C₆H₄ Rh₂(S-biDOSP)₂

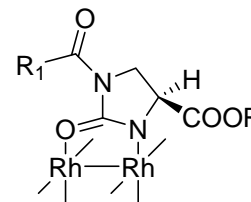
Phthalimide derivatives

bridged proline complexes

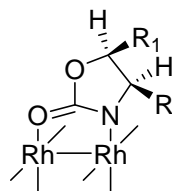
Chiral rhodium carboxamidate catalysts



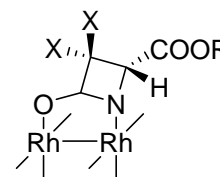
chiral pyrolidinate



chiral imidazolidinate



chiral oxazolidinate

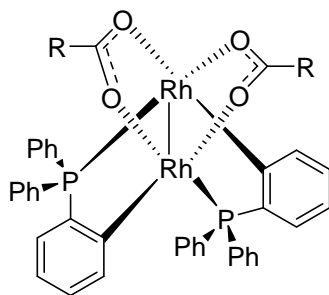


chiral azetidinate

These catalysts have since been much exploited and remain today the primary catalysts for enantioselective C-H insertion reactions of electron-withdrawing group substituted carbenoids derived from diazoacetamides and diazoesters.

Chiral ortho-metalated rhodium complexes

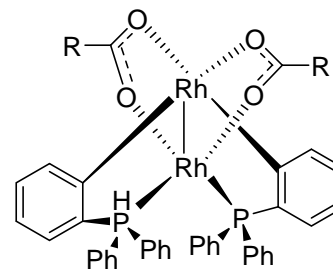
$\text{Rh}_2(\text{RCOO})_2(\text{PC})_4$ Complexes



head-to-tail



high reactivity



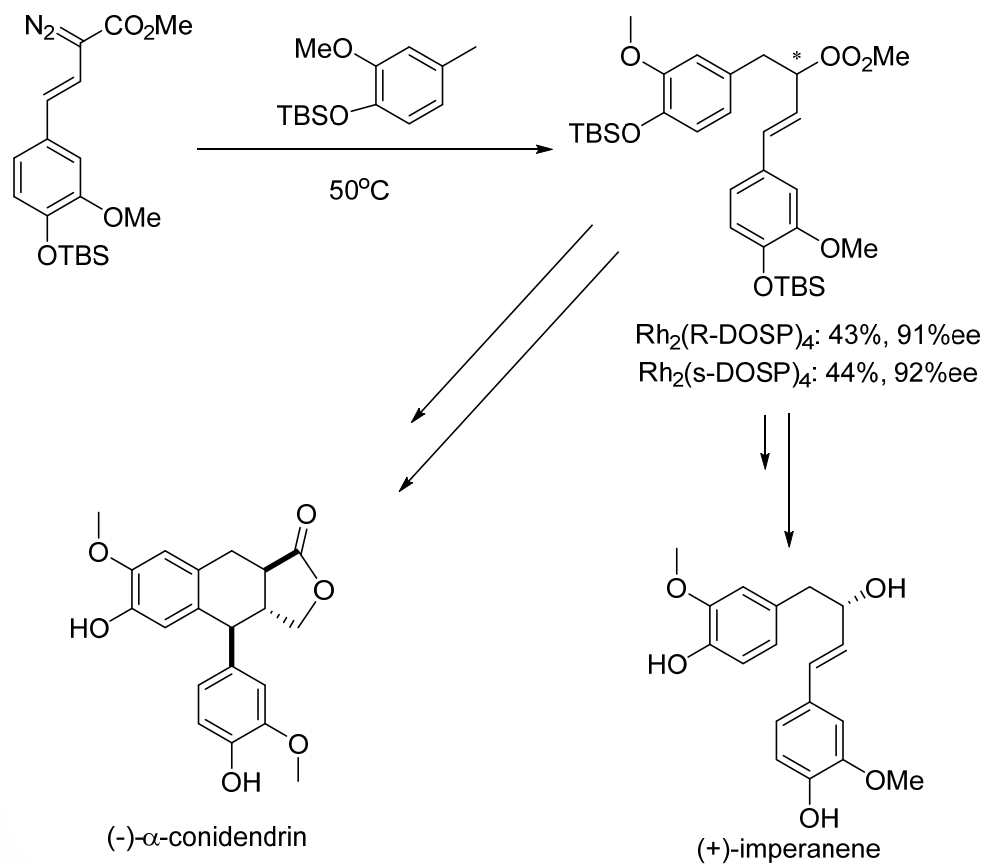
head-to-head



poor reactivity

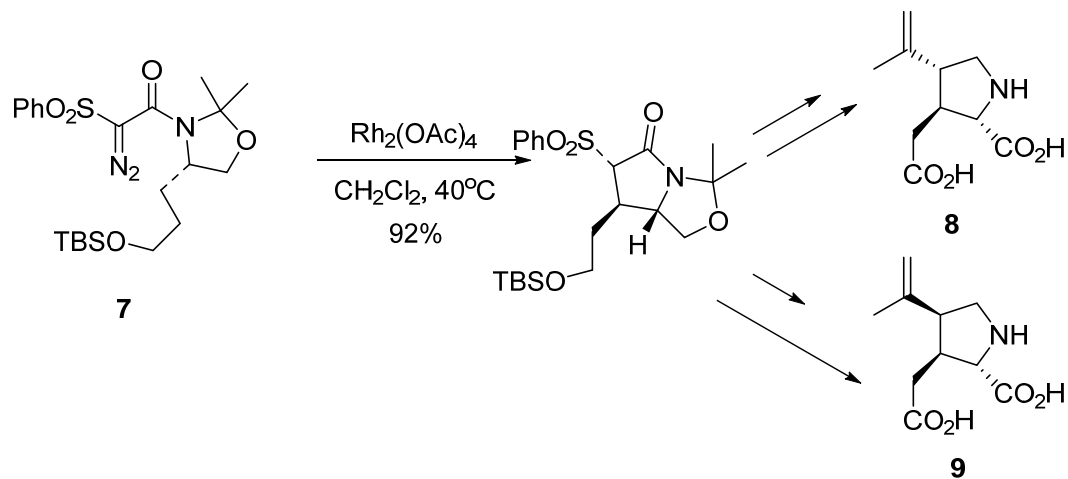


Catalysts and reactions



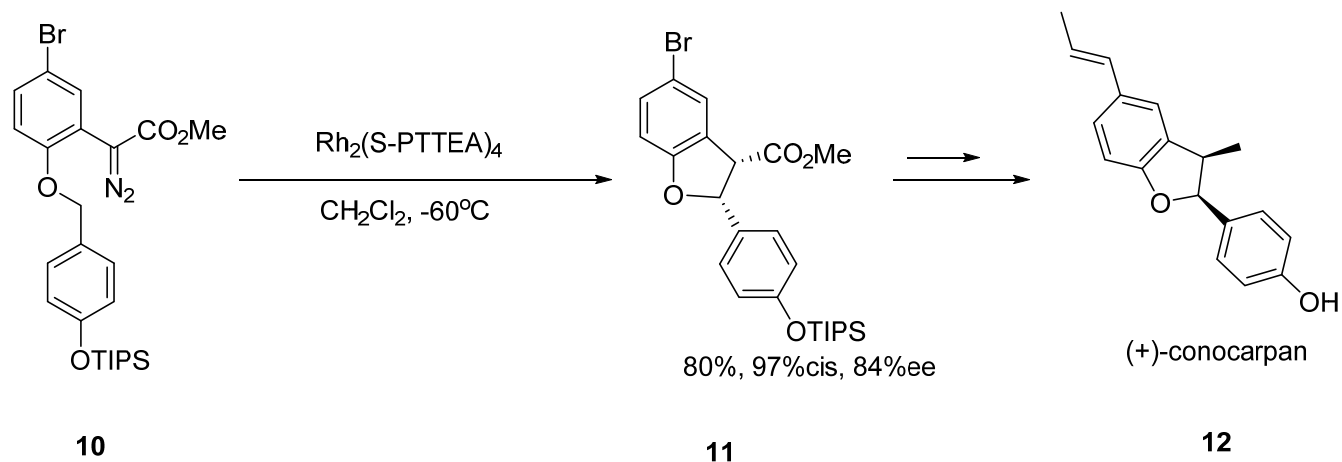
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Catalysts and reactions



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Summary and outlook

1. A rough knowledge about carbene insertion into C-H bonds have been introduced
2. Dirhodium carboxylate and carboxamidate catalysts are most effective in these transformations.
3. While rhodium complexes remain the dominant catalysts for application in enantioselective C-H insertion reactions, developing alternative cheaper metal catalysts is a possible way for future studies.
4. Development of a catalyst system with general applicability across the spectrum of intramolecular and intermolecular C-H insertion reactions remains challenging.



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