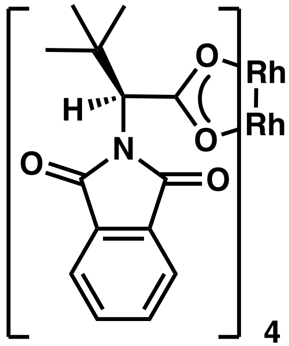
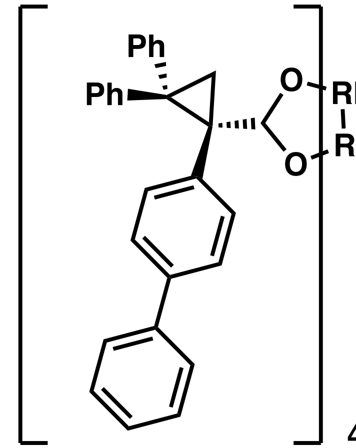
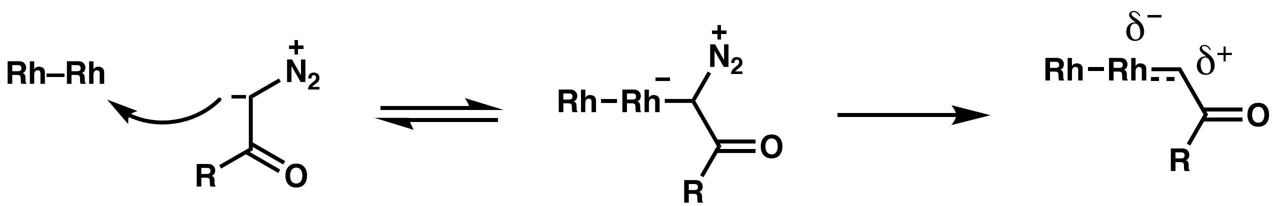
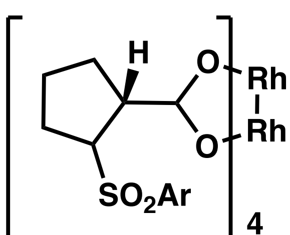


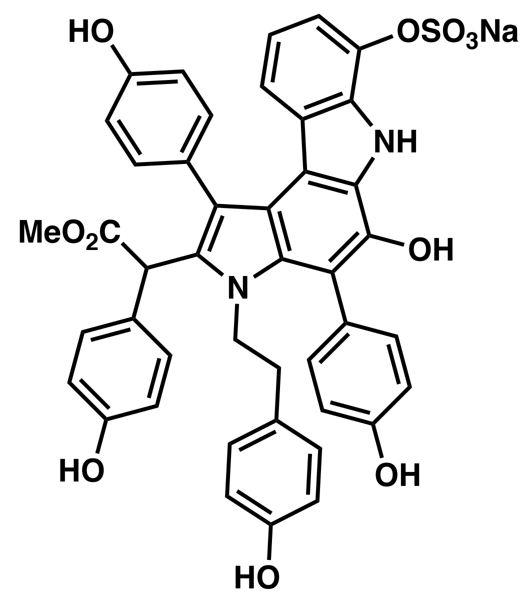
Rhodium Carbenes and C–H functionalization







Elizabeth Goldstein
Stoltz/Reisman Lit Meeting
December 15th, 2017



Seminar Outline

I. Introduction to Carbenes

II. Mechanism of C–H insertion

III. Intramolecular C–H insertion

IV. Intermolecular C–H insertion

V. C–H insertion in Synthesis

VI. Further Resources

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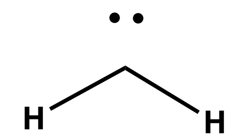
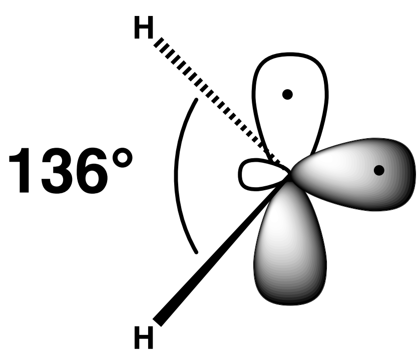
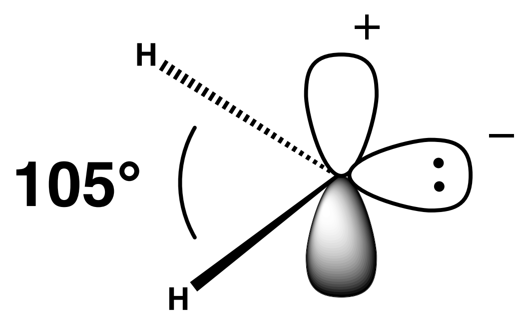
What is a Carbene?

a neutral, divalent carbon atom with 2 unpaired electrons.

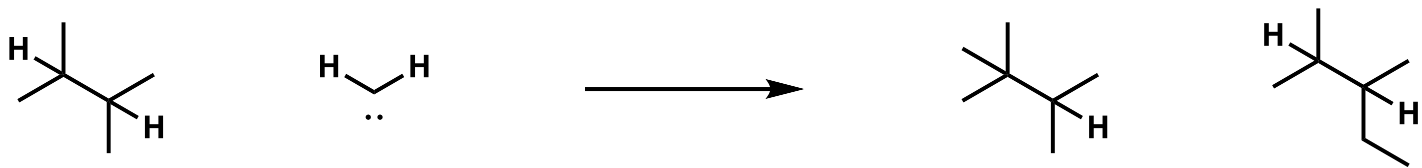
Can exist in 2 electronic states: triplet or singlet.



Triplet:	**Singlet:**
	
ground state of most carbenes	**substituents on the carbene carbon can lead to a singlet ground state**
can be thought of as diradicals	**can be thought of as a zwitterion**
partially filled p and sp^2 orbitals	**empty p orbital (+) and filled sp^2 hybrid orbital (–)**

Reactivity of Free Carbenes

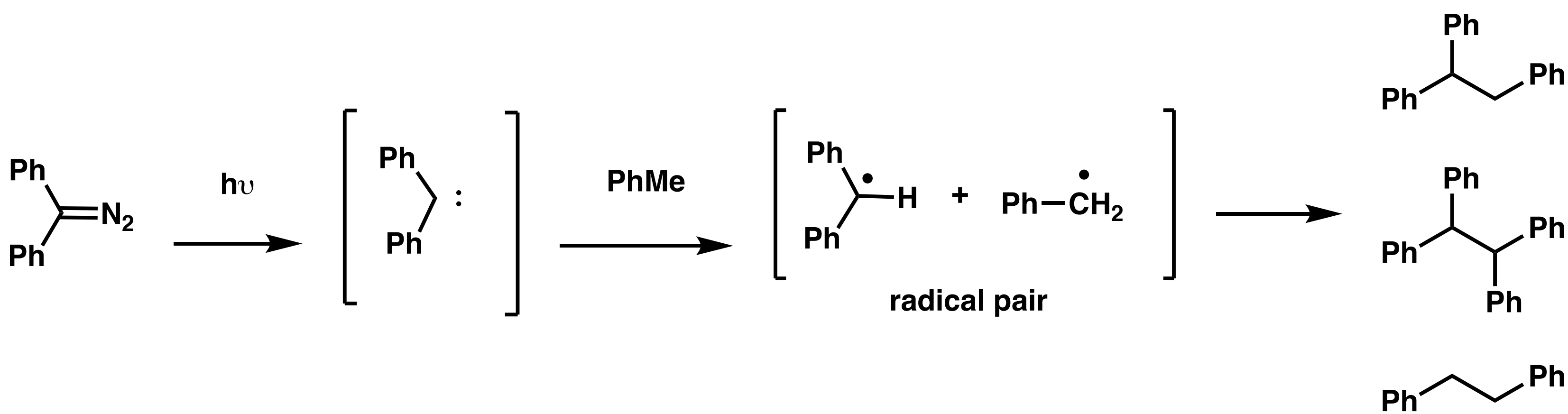
Free Carbenes undergo insertion reactions yielding a statistical mixture of products.



1 : 6

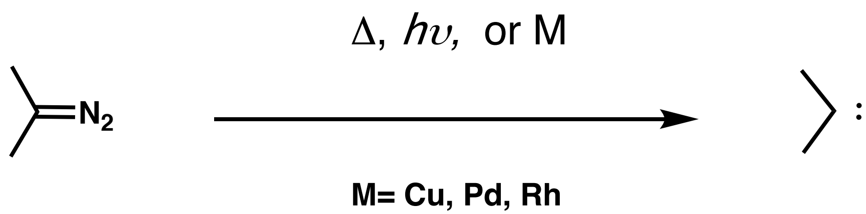
"methylene must be classified as the most indiscriminate reagent known in organic chemistry"

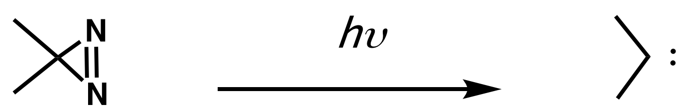
von E. Doering, *JACS* **1956**, *78*, 3224.



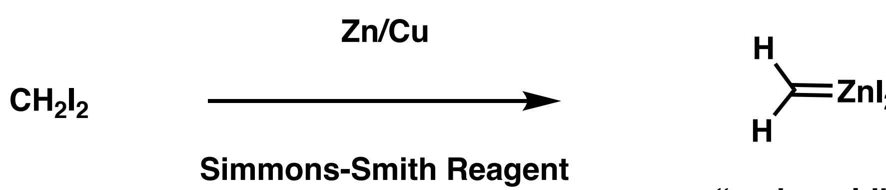
Closs, *JACS* **1969**, *91*, 4549 & 4554.

Generation of Carbenes



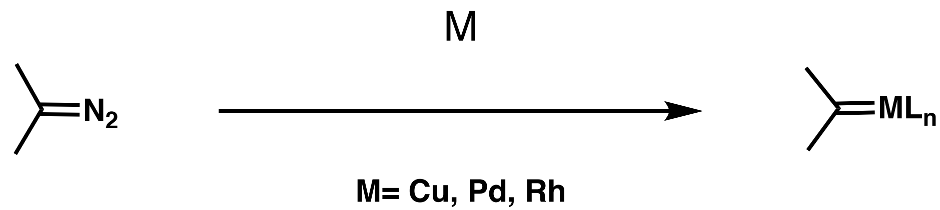


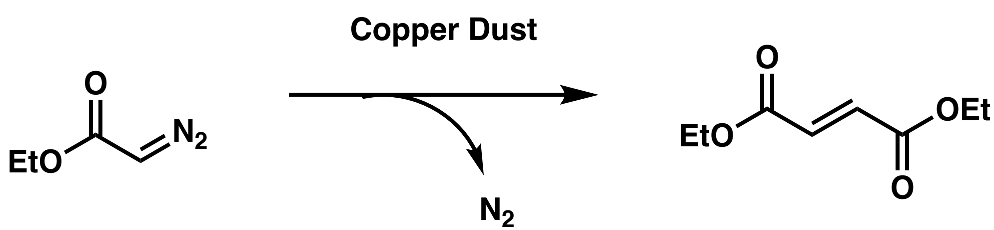
diazirine



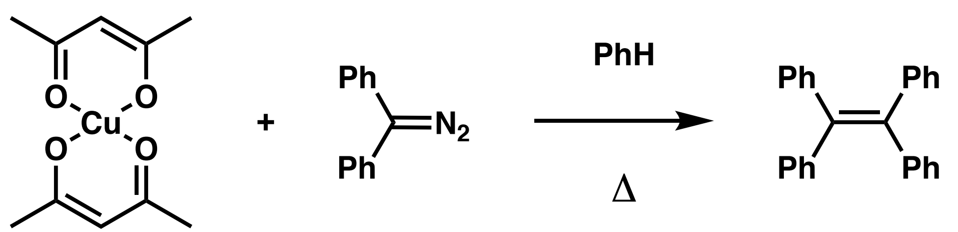
“carbenoid”
“metal carbene”

Generation of Metal Carbenes/Carbenoids



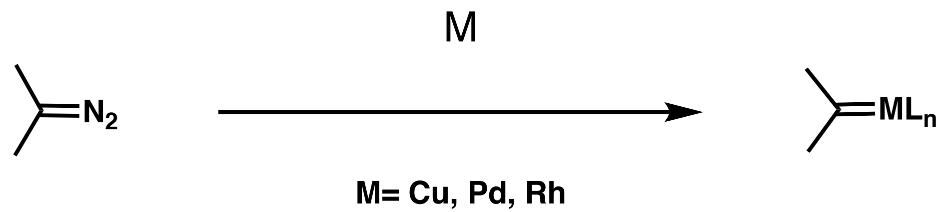


Silberrad, *J.Chem. Soc., Trans.* **1906**, *89*, 179.

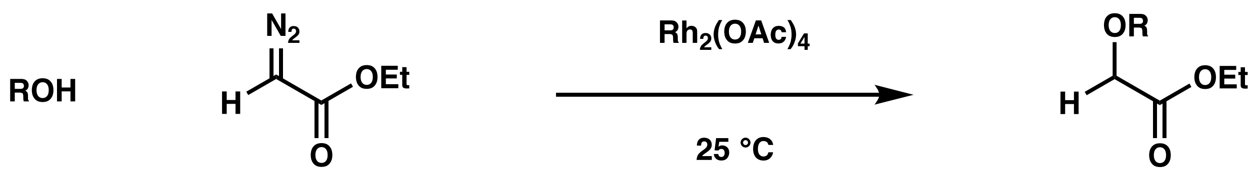


Noyori, *TL* **1966**, 59

Generation of Metal Carbenes



First Example of $Rh_2(OAc)_4$ catalyzed Diazo decomposition:



Teyssie, *Tetrahedron Lett.* **1973**, 2233.

“The discovery by Teyssie and co-workers that Rhodium (II) acetate, a binuclear rhodium compound with one available coordination site per metal center, is an exceptionally effective catalyst for a wide variety of catalytic transformations involving diazo compounds holds singular importance in the history of this developing methodology.”
—Doyle, *Acc. Chem. Res*. **1986**, *19,* 348–356.

Why Rhodium Carbenes

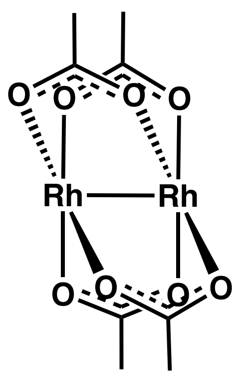
Metal Carbenes are less reactive than free carbenes

Lower reactivity allows for the possibility of controlling selectivity

Rhodium carbenes have become popular due to their selectivy and ease of catalyst modification

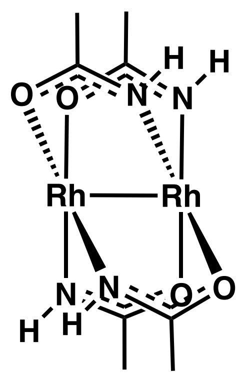
Compounds are usually air-stable and are relatively easy to handle.

The following catalyst classes were some of the first utilized:



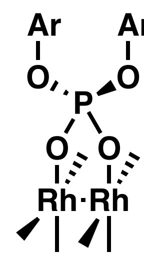
$Rh_2(OAc)_4$

Teyssie
TL **1973**, 2233



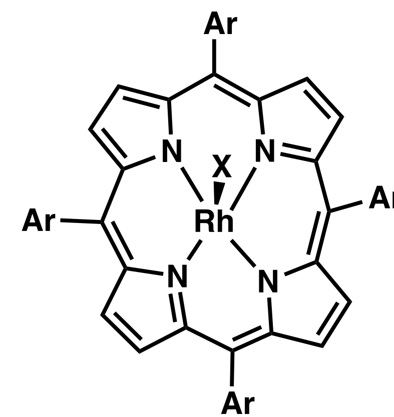
carboxamidates

Bernal, Bear
Inorg. Chem. **1986**, *25*, 260



phosphates

Doyle
TL **1992**, *33*, 5983 & 5987



porphoryns

Callot
TL **1980**, *21*, 3489

$Rh_2(CO)_{16}$

Doyle
TL **1981**, *22*, 1783

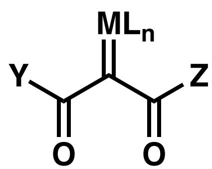
$Rh_2(TFA)_4$

Doyle
Inorg. Chem. **1984**, *23*, 3684

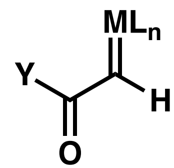
Classes of Carbenes

Selectivity in C-H insertion reactions can be tuned by electronics in the Carbene or Catalyst.

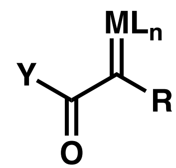
Acceptor/Acceptor



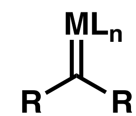
Acceptor



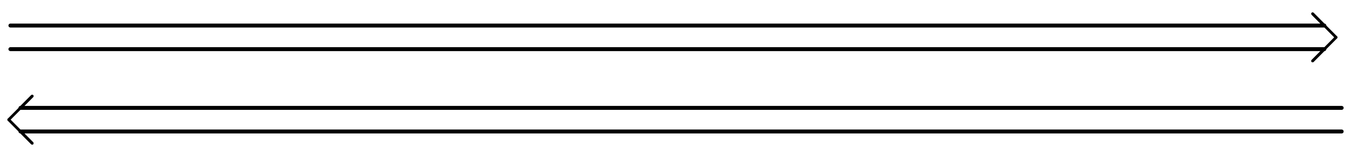
Donor/Acceptor



Donor/Donor



increasing stability and selectivity



increasing reactivity and electrophilicity

More reactive carbenes can be difficult to use selectively.

More stable carbenes can be difficult to form

Most commonly used classes are acceptor and donor/acceptor

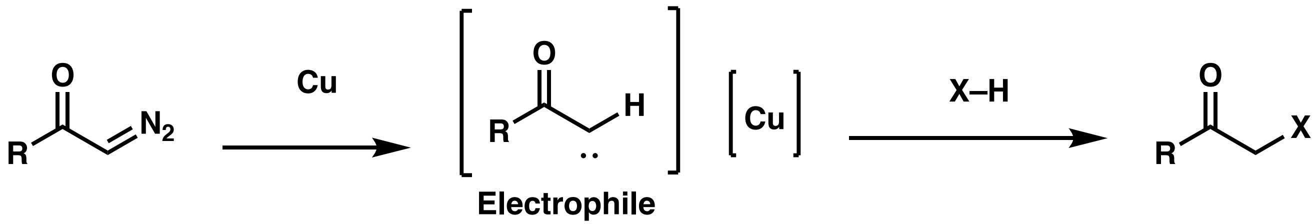
acceptor carbenes are commonly used in intramolecular C-H insertions

donor/acceptor carbenes have been utilized in many asymmetric C-H insertions

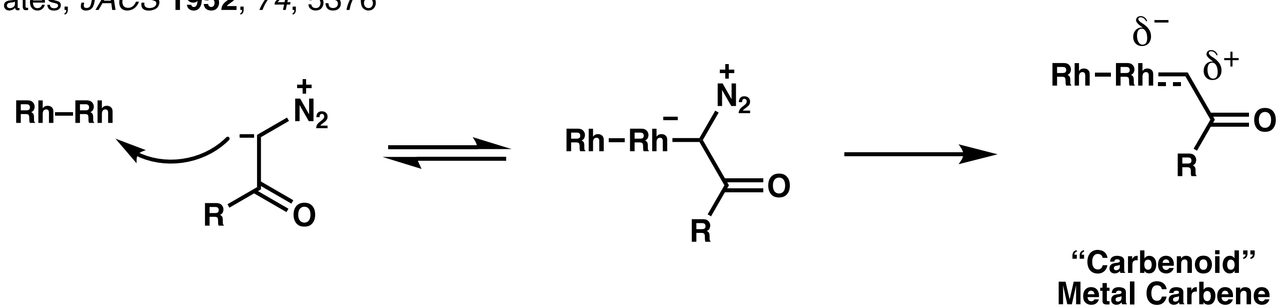
Seminar Outline

Metal Carbenes

Yates proposed that metal carbenes were transient electrophiles that could react with nucleophiles:

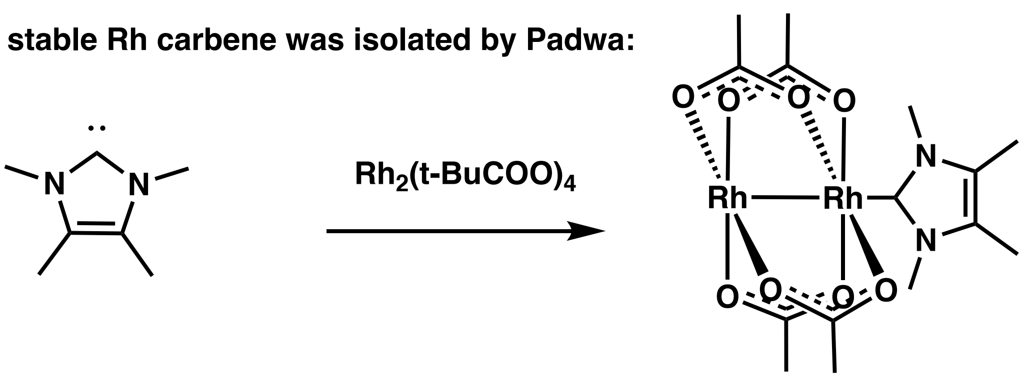


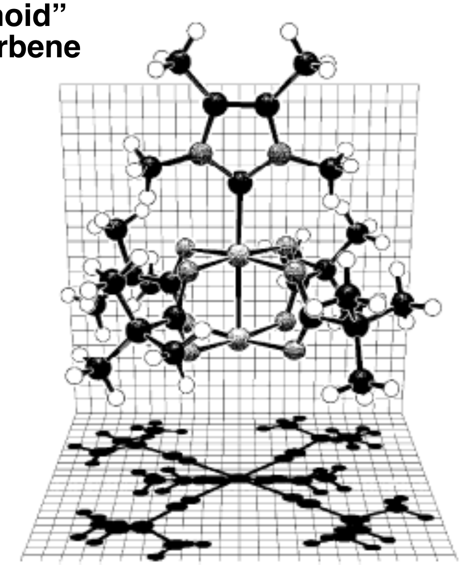
Yates, *JACS* **1952**, *74*, 5376



Pirrung, *JACS* **1996**, *118*, 8162.

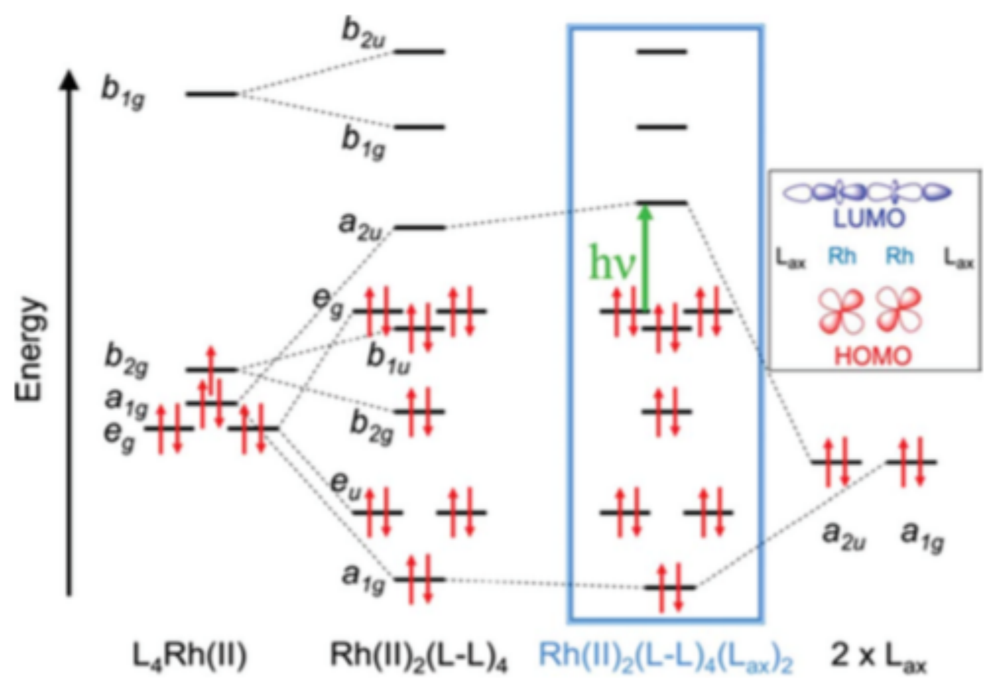
A stable Rh carbene was isolated by Padwa:





Arduengo, Padwa, Snyder, *JACS* **2001**, *123*, 11318

Electronics of Carbenes



Molecular Orbital Diagram of Fischer Carbene

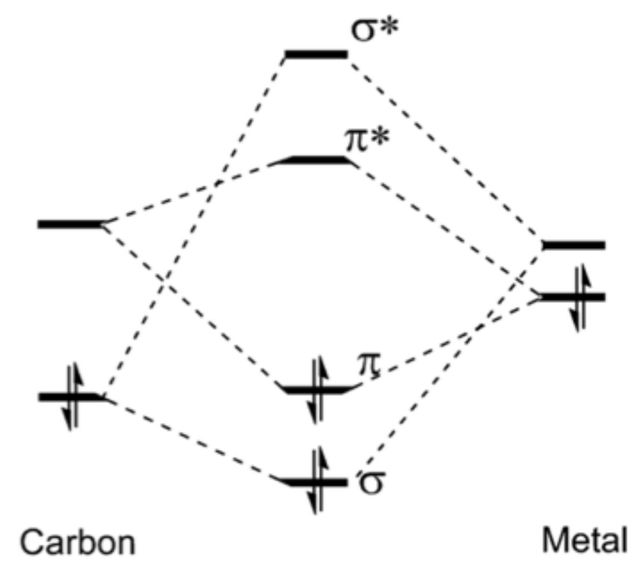
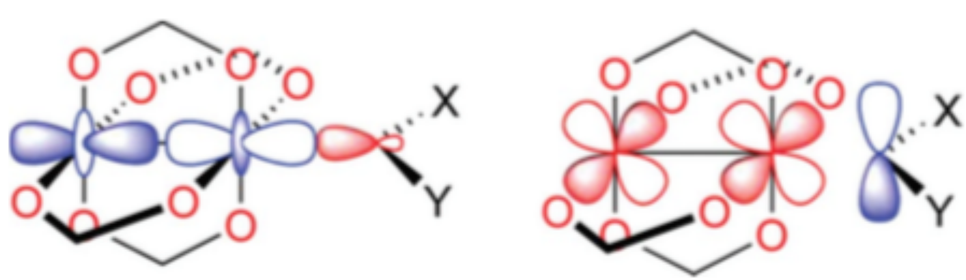


Diagram of orbital overlap between Rhodium complex and Carbene



Donor/Acceptor carbenes are similar to Fischer carbenes.

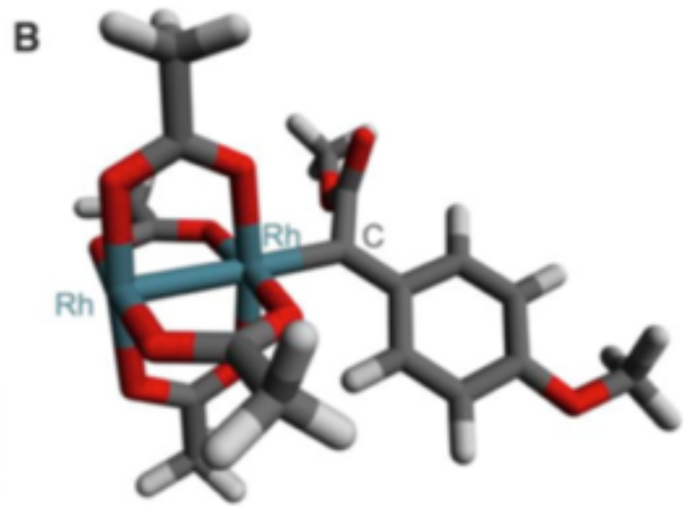
Donor/Acceptor carbenes display more σ electronic character on the carbene carbon, and more π electronic character on the metal center, resulting in more electrophilic character on the carbene carbon.

Traditional Fischer carbenes are more stable due to the presence of a heteroatom that also lowers the electrophilicity

Berry, *Dalton Trans.*, **2012**, *41*, 700

Metal Carbenes

A more "relevant" metal carbene has been isolated and studied.



This donor/acceptor type carbene has been investigated for physical and chemical properties.

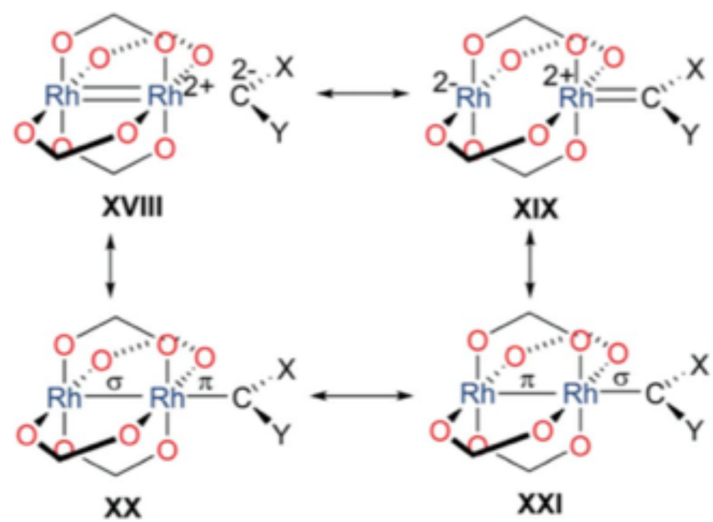
The isolated carbene can be utilized in stoichiometric C–H functionalization reactions in comparable yields

first confirmation that a genuine rhodium carbene is formed under these reaction conditions (as proposed by Pirrung)

Exhibits similar Raman vibrations to those previously observed for Fischer-type carbenes

NMR spectroscopy reveals that the cabenoid carbon is highly deshielded.

The Rh-Rh=C bonding framework has been shown to follow the 3-center orbital paradigm (i.e.The double bond character is distributed between the three centers (the two Rhodiums and the carbene carbon)



Berry, *Dalton Trans.*, **2012**, *41*, 700. Berry, Davies *Sciencexpress* **2013**

C–H functionalization

C–H functionalization has become a very popular field of study recently

Direct C–H functionalization can introduce complexity quickly

C–H bonds are very prevalant in organic molecules

Selectivity can therefore be a problem

Directing groups can be utilized to improve selectivity

Alternatively, sterics and electronics can be used to influence selectivity

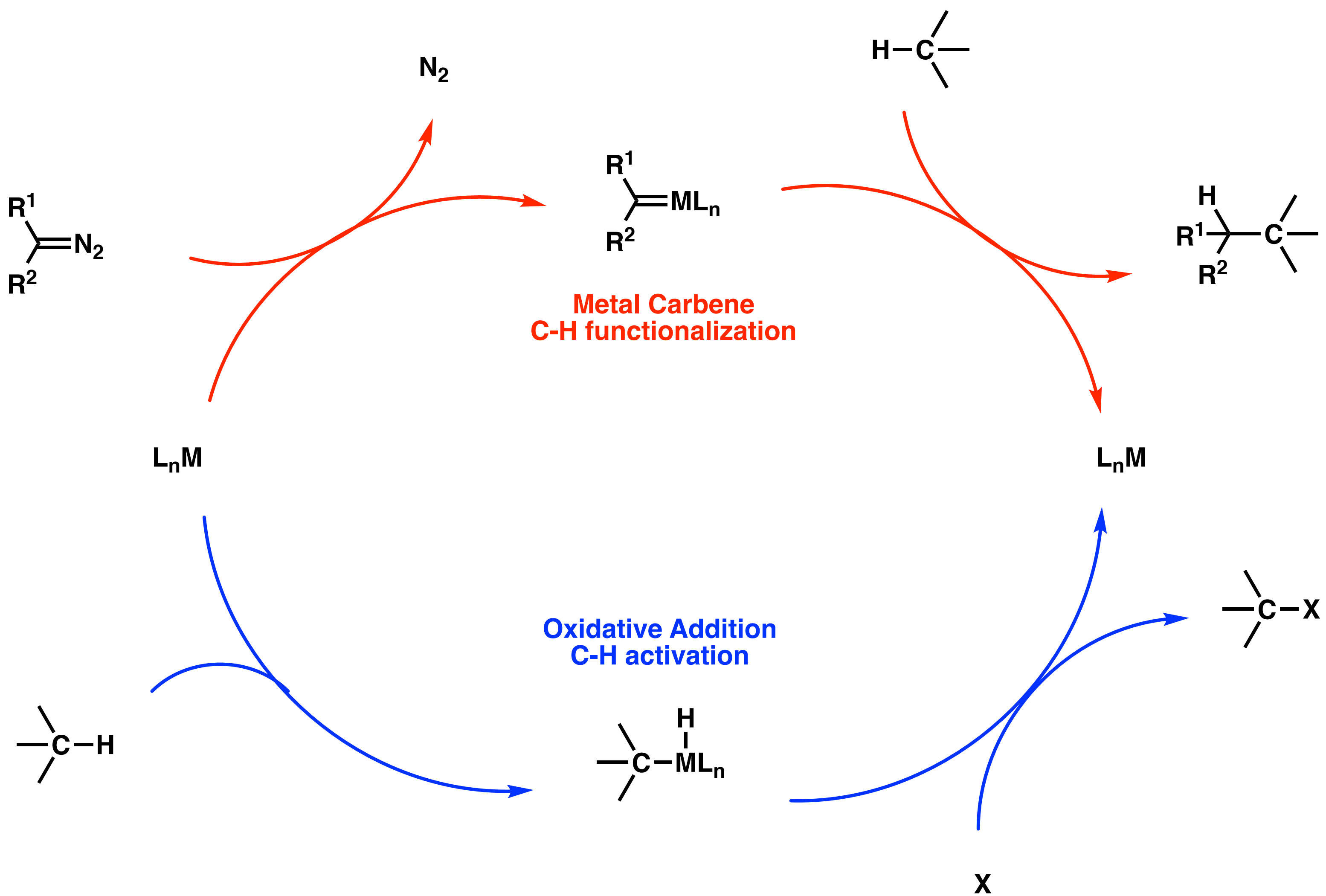
There are many different types of C–H functionalization

C–H oxidations are common functionalization reactions

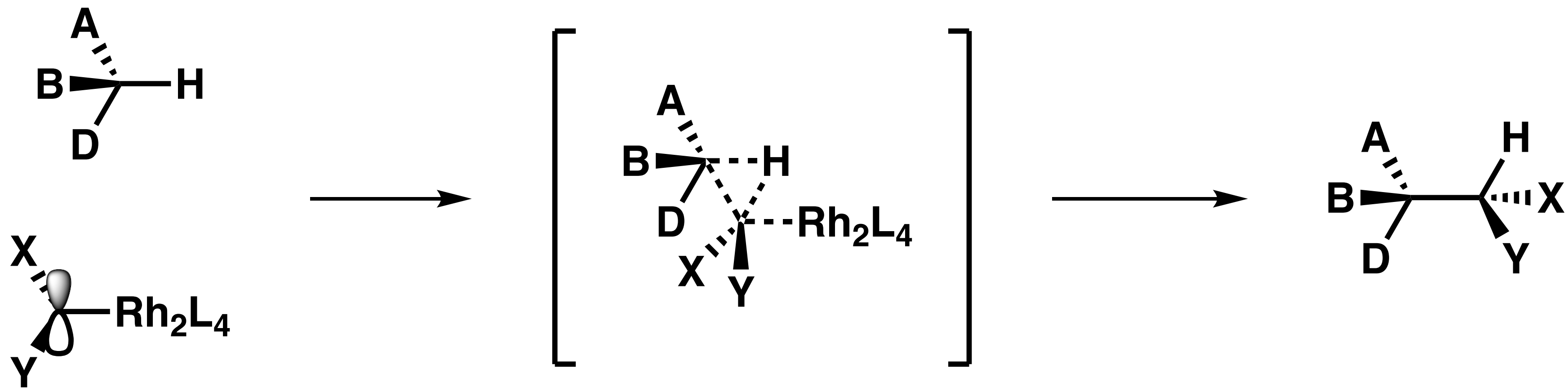
metal carbene C–H functionalization proceeds through a different mechanism

CCHF

Mechanism of C–H functionalization

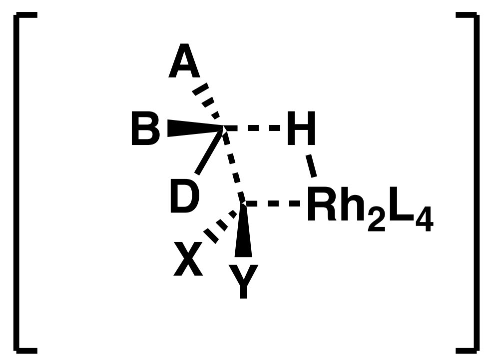


Mechanism of C–H functionalization



or

Carbenoids empty p orbital interacts with the σ–bond of the C–H bond



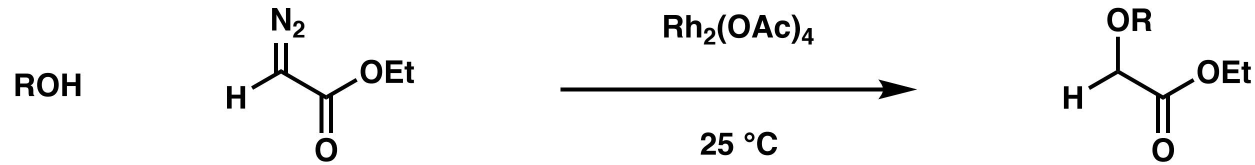
bond formation may proceed as Rhodium dissociates (top)

Or there may be a transfer of H to Rhodium followed by reductive elimination (bottom)

Doyle, *JACS* **1993**, *115*, 958–964. Taber, *JACS* **1996**, *118*, 547.

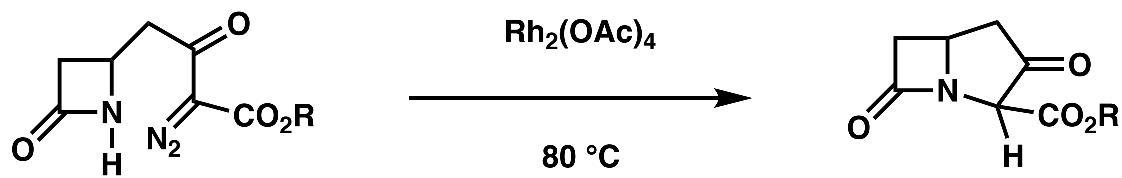
Reactivity of Rhodium Carbenes

Insertion into O–H bond:



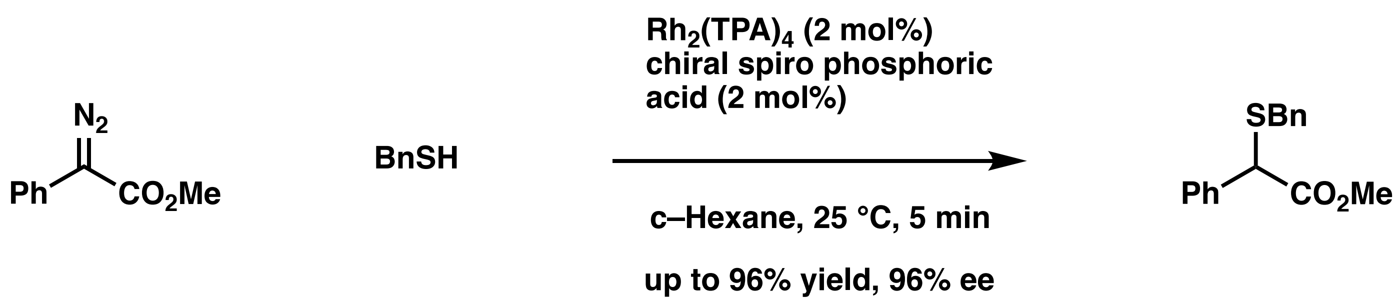
Teyssie, *Tetrahedron Lett.* **1973,** 2233.

Insertion into N–H bond:



Ratcliffe, *Tetrahedron Lett.* **1980**, *21*, 31

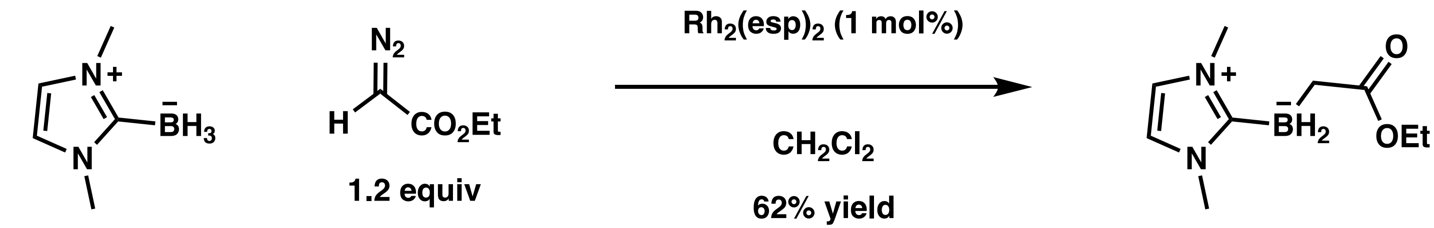
Insertion into S–H bond:



Zhu, Yu, Zhou *Chem Sci.* **2014**, *5*, 1442–1448.

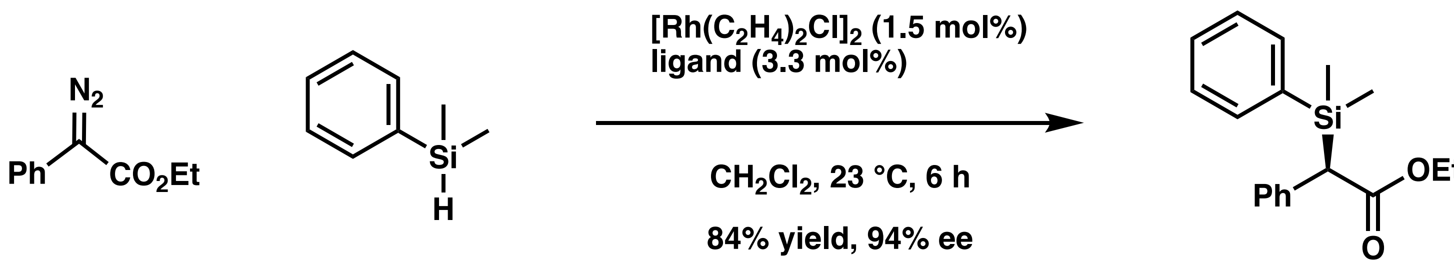
Reactivity of Rhodium Carbenes

Insertion into B–H bond:



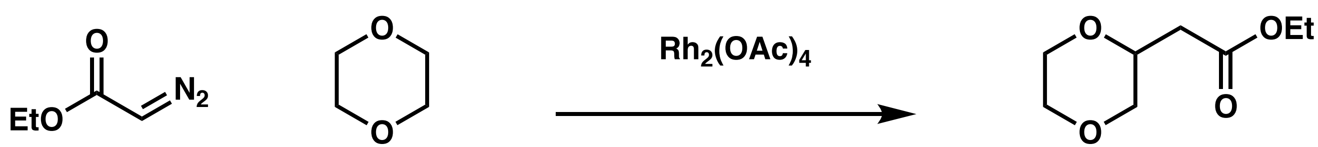
Curran, *JACS* **2013**, *135*, 12076–12081.

Insertion into Si–H bond:



Xu, *JACS* **2016**, *138*, 1498–1501.

Insertion into C–H bond:



Alonso, *Tetrahedron* **1989**, *45*, 69.

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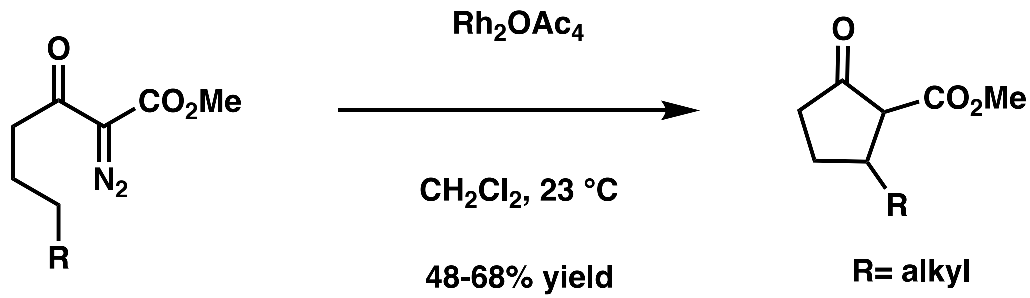
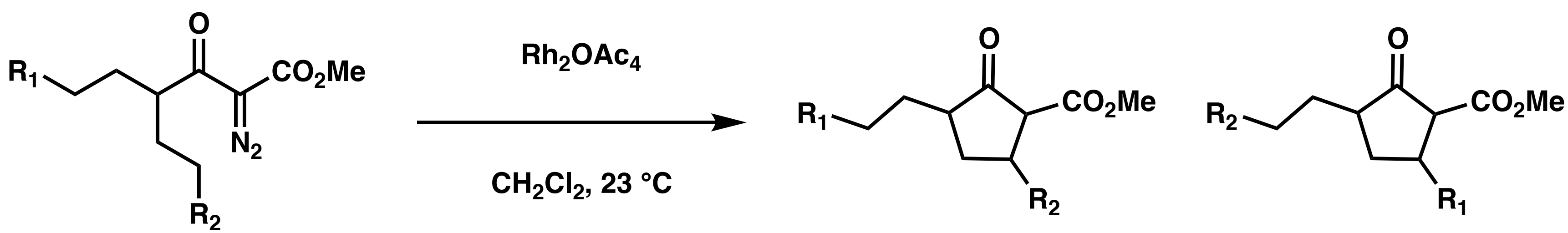
Intramolecular C–H insertion



Competion Experiments to determine inherent selectivity:



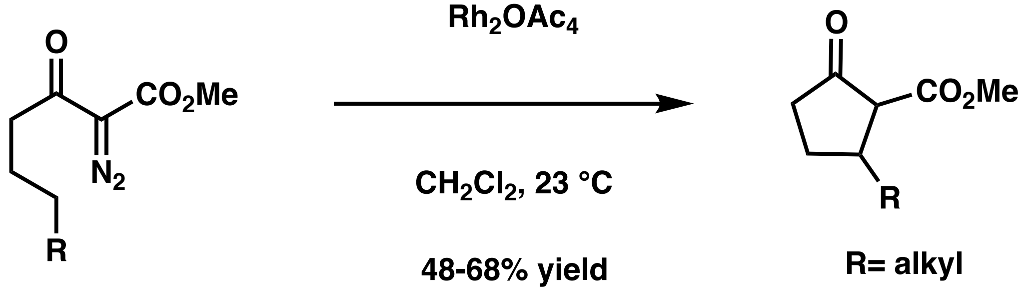
methine > methylene > methyl, potentially due to electron donating ability of alkyl groups.

allylic and benzylic methylenes also disfavored due to their electron withdrawing characteristics

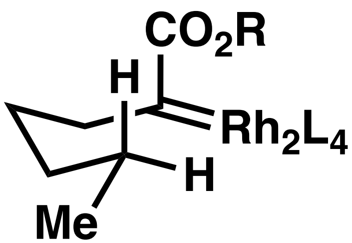
insertion into aromatic rings occur readily

Rappoport*, J. Org. Chem.* **1982**, *47*, 4809–4812. Taber, *JACS* **1986**, *108*, 7686–7693.

Intramolecular C–H insertion

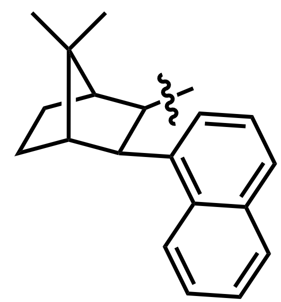


High selectivity for 5-membered ring formation can be explained by a highly ordered transition state:



chiral ester:

R=



diastereoselective reaction:
>8.1 dr
55–62% yield

Alkyl Chain Substituents can lead to >95% diastereoselectivity

The Hydrogen in the ring is the one that is transfered

The alkyl group is equatorial

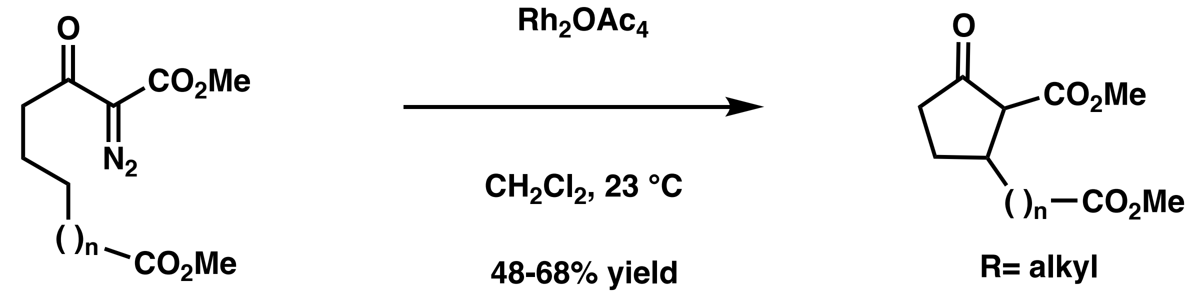
diastereoselectivity can be achieved by destabilizing one of the chair-like transition states.

This can be done by using a chiral ester (see above) or substitution on the alkyl chain.

Rappoport, *J. Org. Chem.* **1982**, *47*, 4809–4812. Taber, *JACS* **1983**, *105*, 5935–5937.

Intramolecular C–H insertion

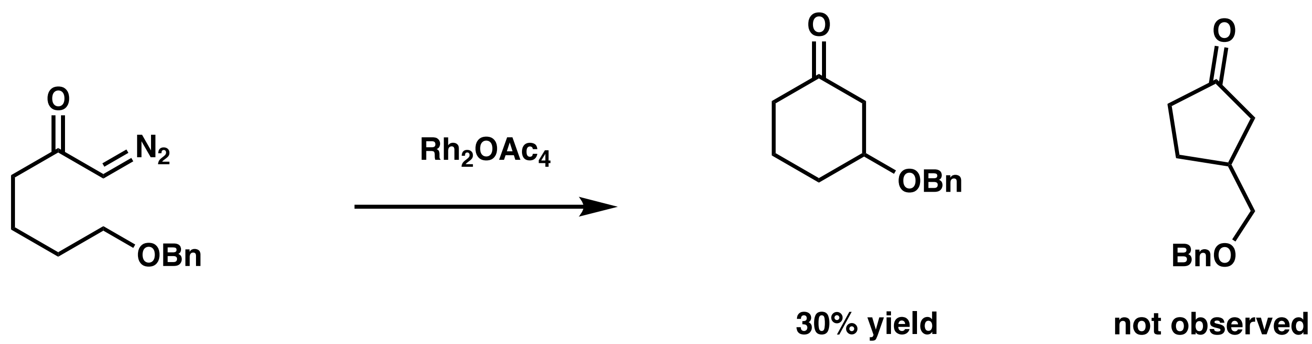
electron-withdrawing groups inhibit adjacent C–H bonds.



n=0 no reaction
n=1 no reaction
n=2 64% yield

Stork, *Tetrahedron Lett.* **1988**, *29*, 2283.

Alkoxy groups activate C–H bonds.



Spero, *Tetrahedron* **1991**, *47*, 1765.

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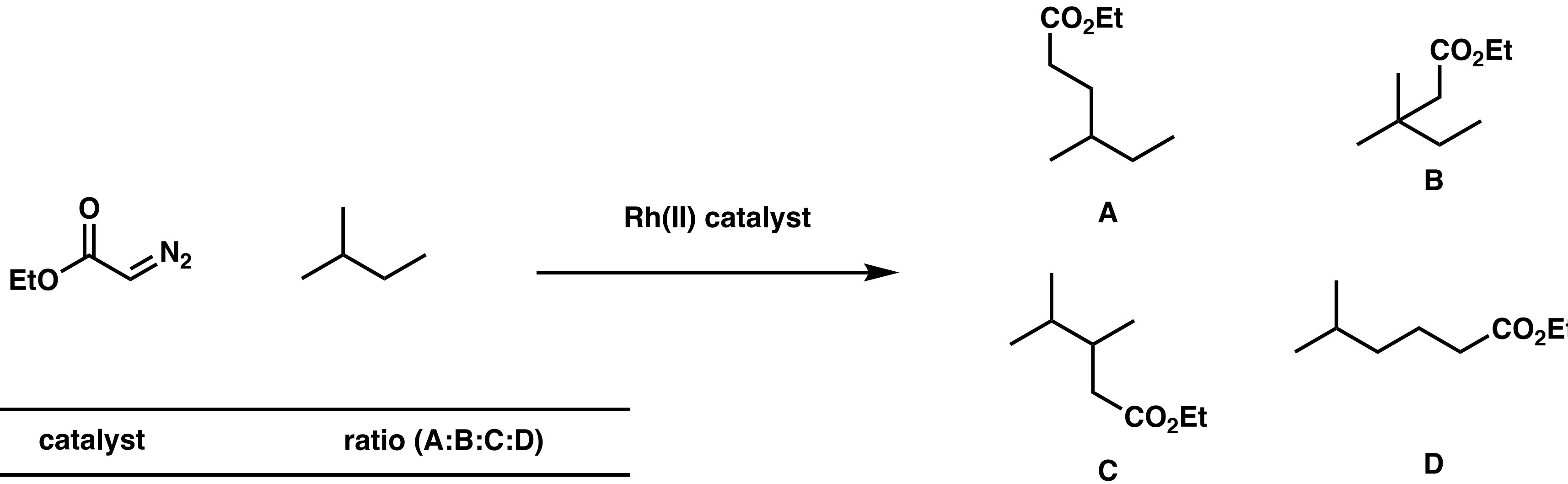
Intermolecular C–H insertion

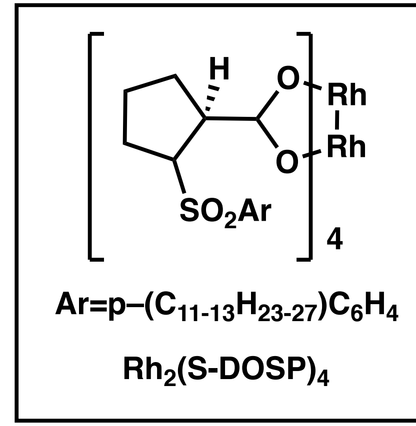


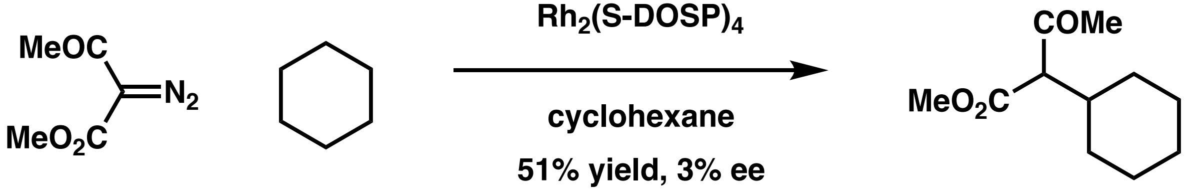
catalyst	ratio (A:B:C:D)
$Rh_2(OAc)_4$	1:8:90:1
$Rh_2(9\text{-trp})_4$	18:18:27:37
$Rh_2(TFA)_4$	5:25:66:4

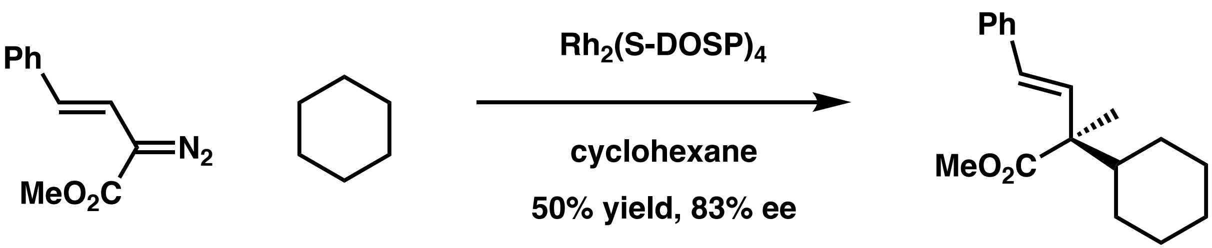
Teyssie, *Bull. Soc. Chim. Belg.* **1984**, *93*, 945

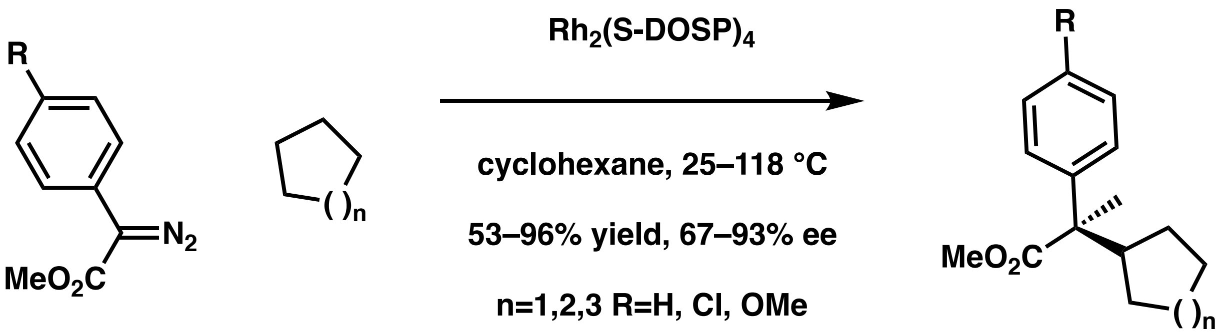
"Intermolecular CH insertions of carbenes and metal carbenoids have the reputation of being unselective, resulting usually in mixtures of products and are, therefore, considered of no synthetic significance. In addition to their lack of selectivity, the intermolecular carbenoid insertions suffer from competing secondary reactions, such as formation of formal carbene dimers."
Müller, *Tetrahedron* **2000**, *56*, 1725–1731

Intermolecular C–H insertion







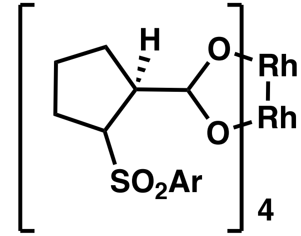


Davies, *JACS* **1997**, *119*, 9075–9076.

It was later shown that the enantioselectivity could be improved to 88–96% by performing the reaction at 10*C, with no appreciable loss in yield.

Davies, *JACS* **2000**, *122*, 3063–3070.

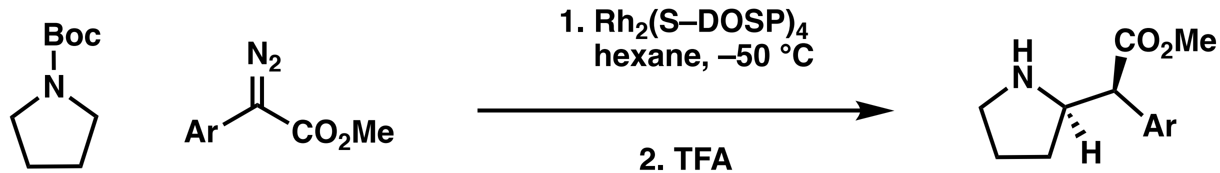
Intermolecular C–H insertion



Ar=p–($C_{11\text{-}13}H_{23\text{-}27}$)$C_6H_4$

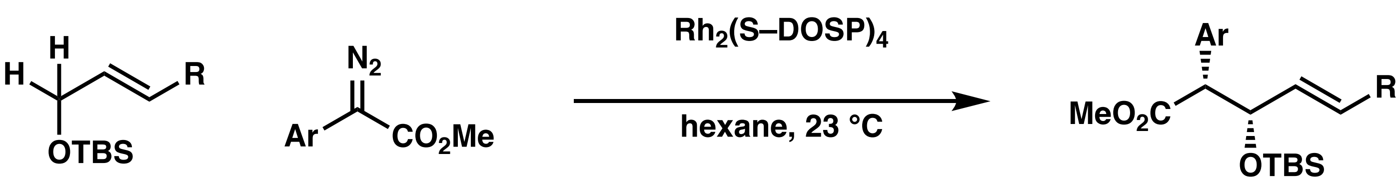
Rh_2(S-DOSP)$_4$

Early site selectivity was achieved by using heteroatom directing groups:



up to 72% yield
up to 94% ee
up to 94% de

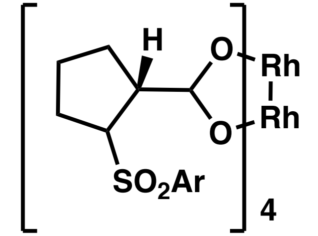
Davies, *JACS* **1999**, *121*, 6509–6510



up to 72% yield
up to 92% ee
up to 98% de

Davies, *Org. Lett.* **1999**, *1*, 383–386.

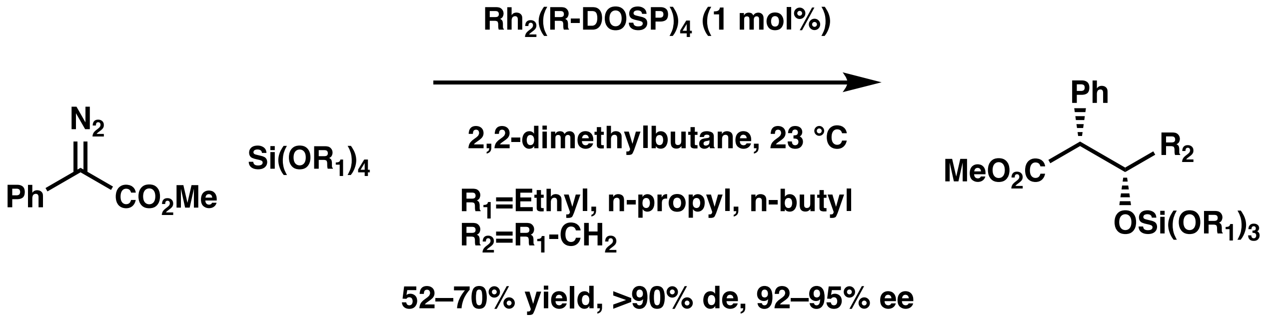
Intermolecular C–H insertion

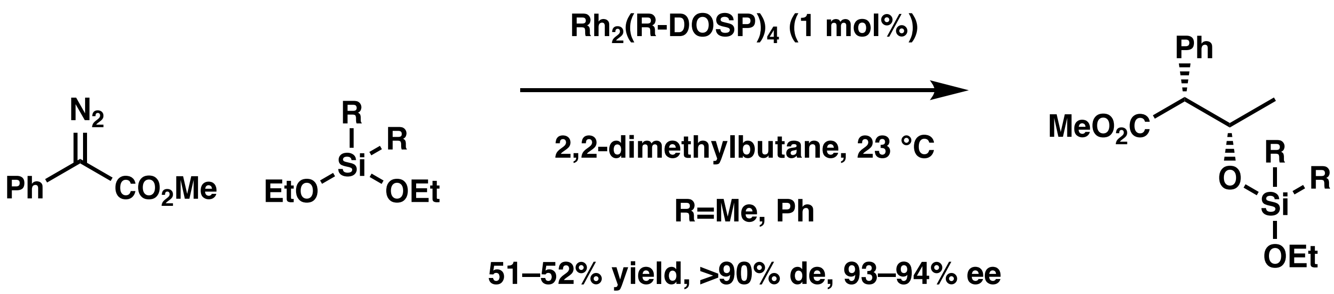


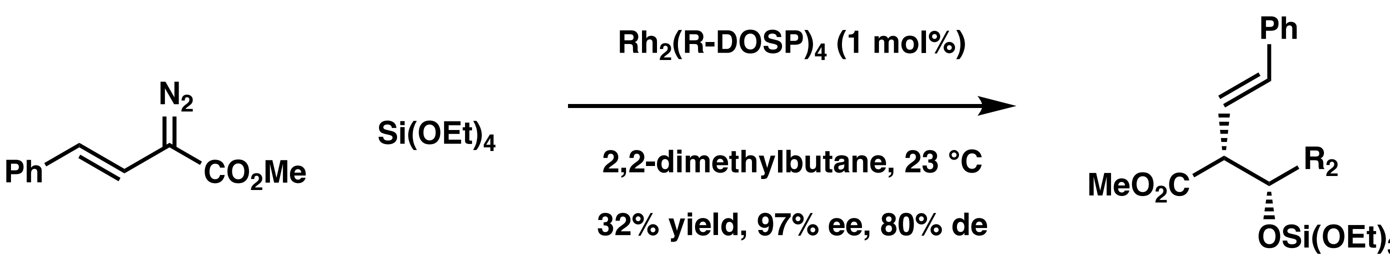
$Ar=p–(C_{11\text{-}13}H_{23\text{-}27})C_6H_4$

Rh_2(R-DOSP)$_4$

C–H insertion can act as a formal aldol reaction leading to syn–aldol products

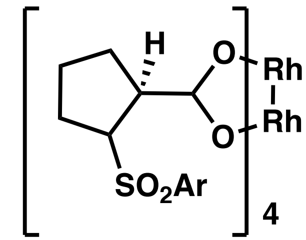






Davies, *Org. Lett.* **2000**, *2*, 4153–4156.

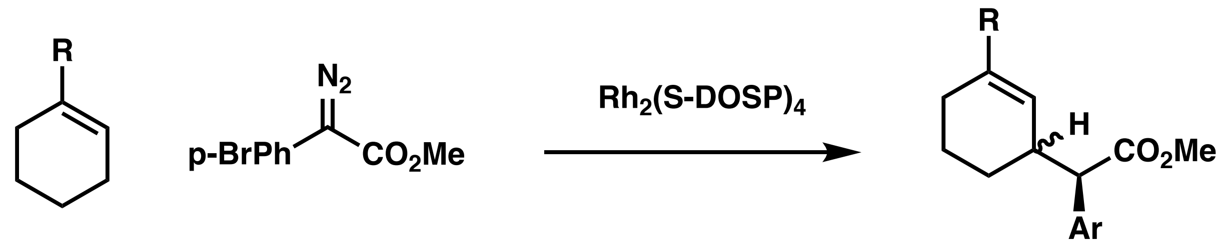
Intermolecular C–H insertion



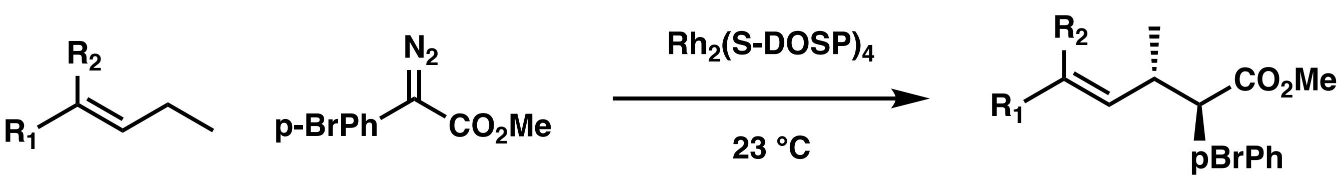
Ar=p–($C_{11\text{-}13}H_{23\text{-}27}$)$C_6H_4$

Rh_2(S-DOSP)$_4$

C–H insertion can also act as a formal claisen reaction



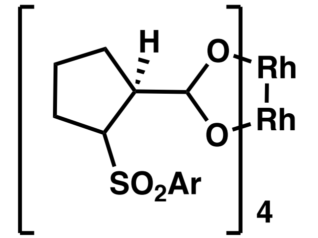
R	yield	de	ee
TMS	48	40	88
TBDPS	64	88	95



R_1	R_2	yield	dr	ee (major)	ee (minor)
Me	Me	67	75:25	86	66
Et	H	56	56:44	92	80
Ph	Ph	33	85:15	96	30

Davies, *Org. Lett.* **2001**, *3*, 3587–3590

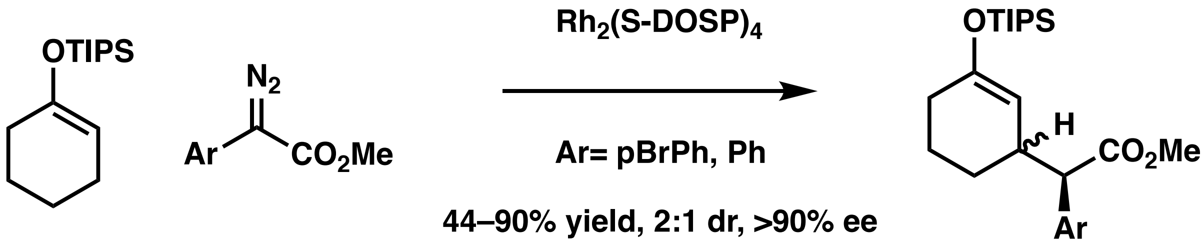
Intermolecular C–H insertion

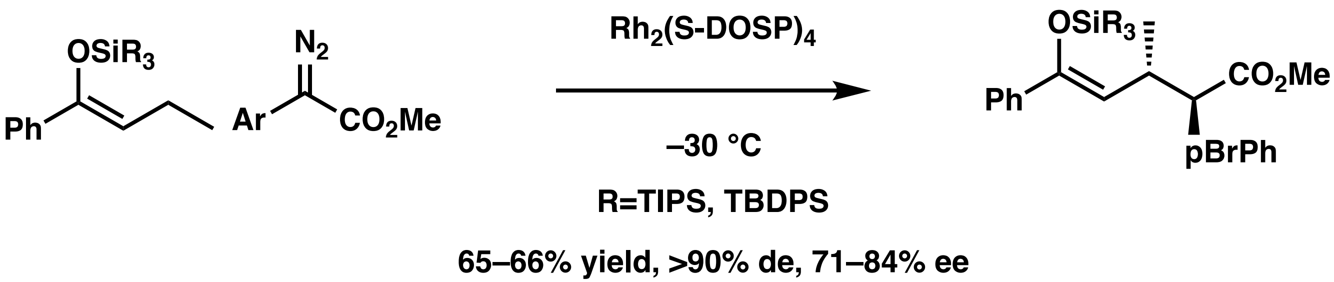


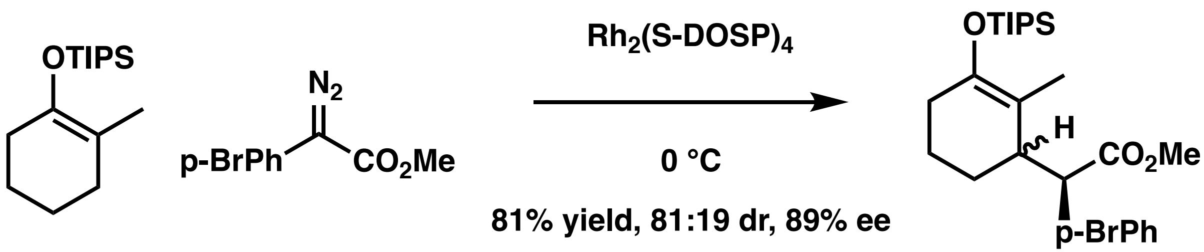
Ar=p–($C_{11\text{-}13}H_{23\text{-}27}$)$C_6H_4$

Rh_2(S-DOSP)$_4$

C–H insertion can also act as a formal michael reaction

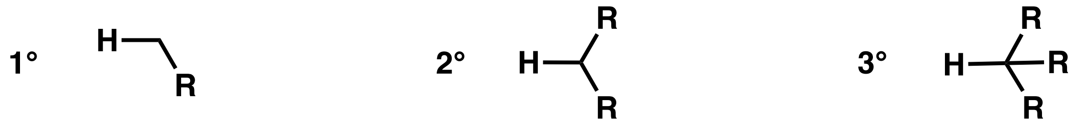


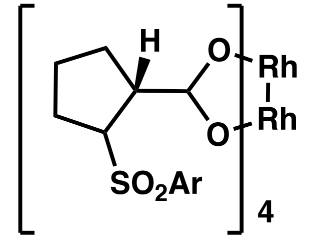




Davies, *JACS* **2001**, *123*, 2070–2071

Intermolecular C–H insertion





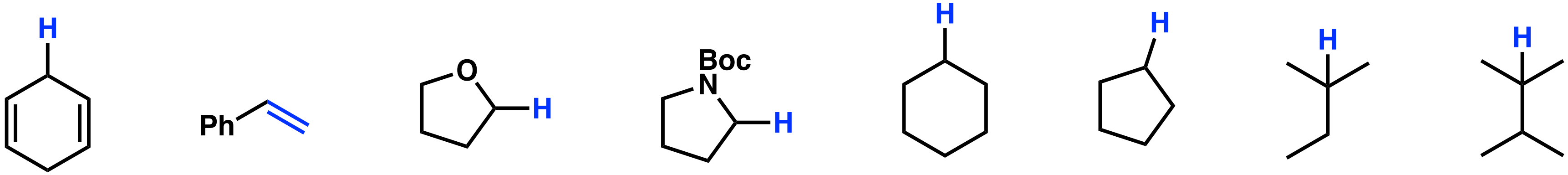
$Ar = p–(C_{11-13}H_{23-27})C_6H_4$

$Rh_2(R\text{-}DOSP)_4$

Increasing Reactivity due to electronics

Increasing reactivity due to sterics

Relatives rates with $Rh_2(R\text{-}DOSP)_4$

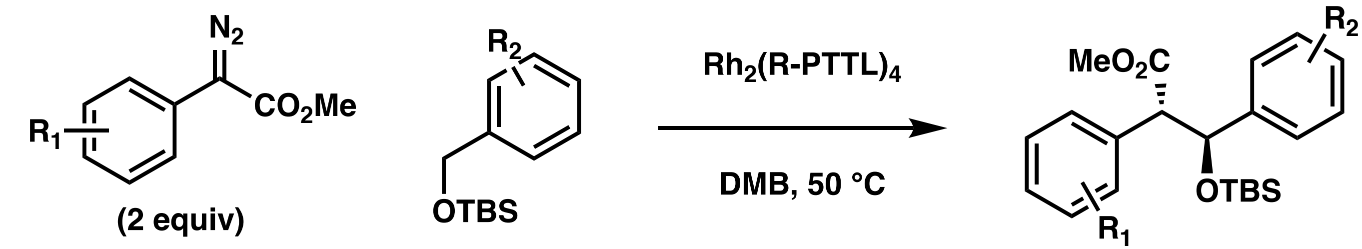


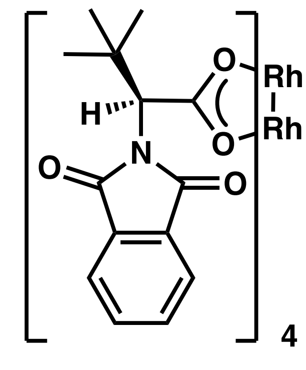
26,000	24,000	2700	1700	1.0	0.66	0.078	0.011

increasing rate of reactivity

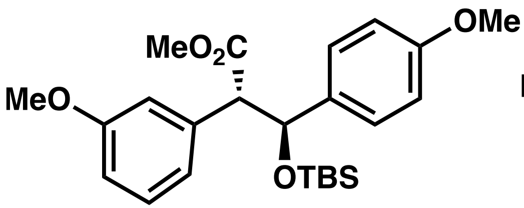
Davies, *Chem. Soc. Rev.*, **2011**, *40*, 1857–1869

Intermolecular Insertion

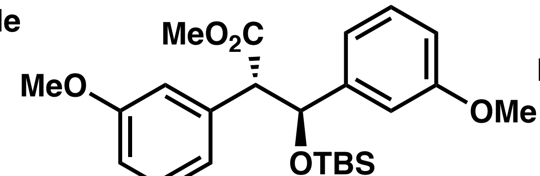




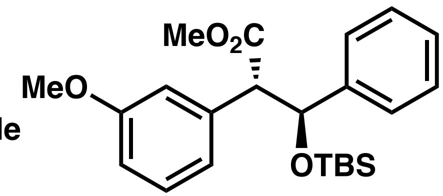
$Rh_2(R\text{-}PTTL)_4$



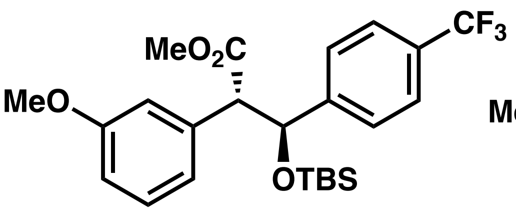
76% yield, >97:3 d.r., 93% ee



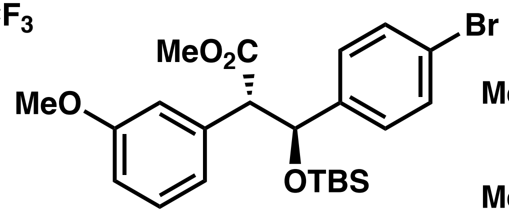
58% yield, >97:3 d.r., 95% ee



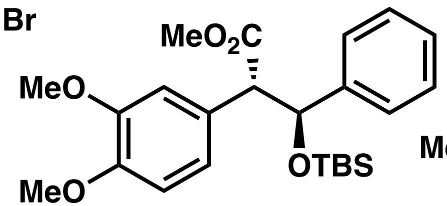
86% yield, >97:3 d.r., 96% ee



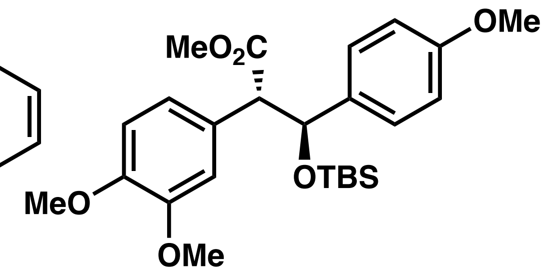
86% yield, >97:3 d.r., 98% ee



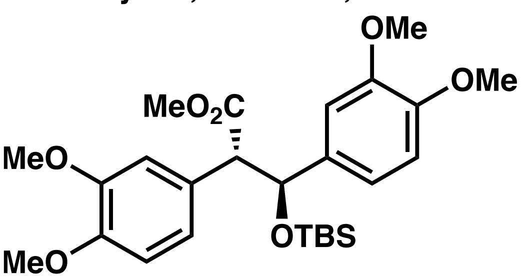
92% yield, >97:3 d.r., 97% ee



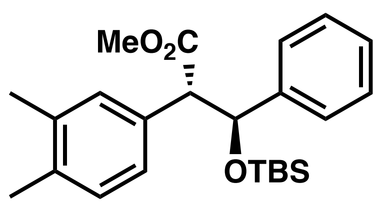
86% yield, >97:3 d.r., 97% ee



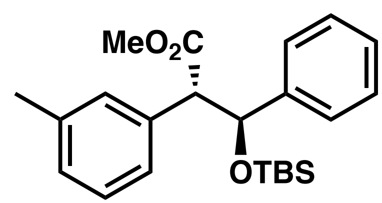
74% yield, >97:3 d.r., 97% ee



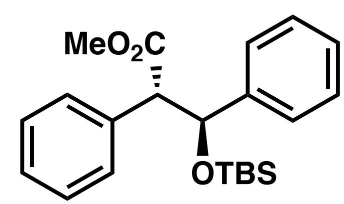
77% yield, >97:3 d.r., 97% ee



92% yield, 94:6 d.r., 99% ee



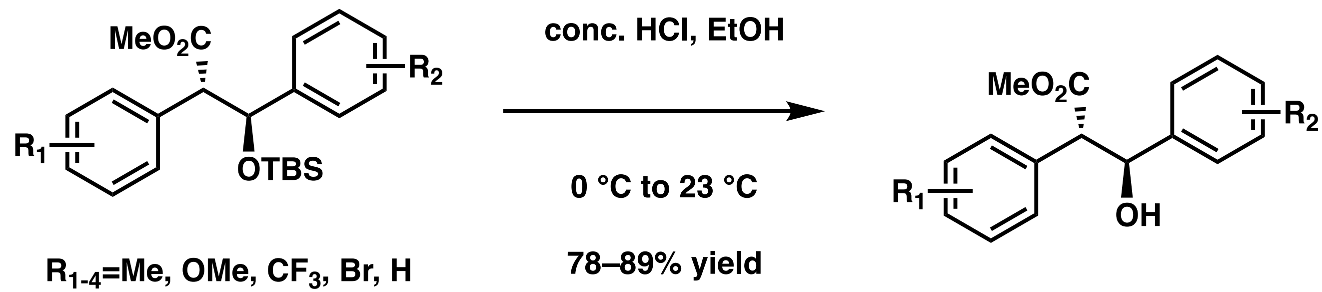
77% yield, >97:3 d.r., 98% ee

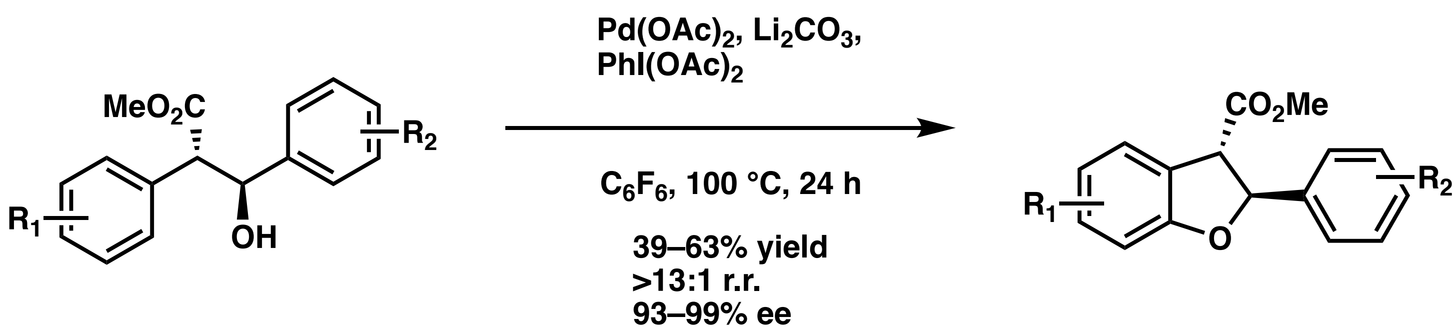


76% yield, >97:3 d.r., 96% ee

Davies, Yu *JACS* **2013**, *135*, 6774–6777.

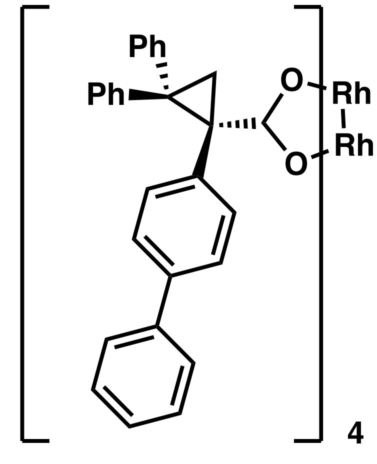
Intermolecular Insertion





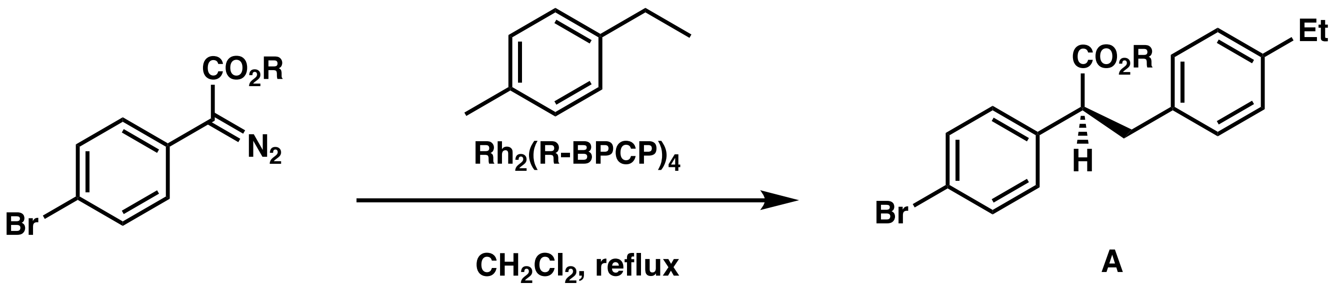
Davies, Yu, *JACS* **2013**, *135*, 6774–6777.

Intermolecular C–H insertion

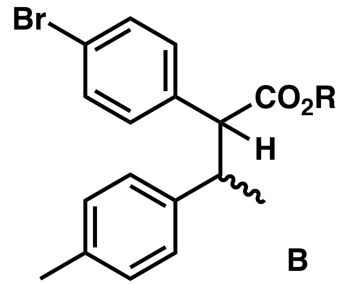


Rh_2(R-BPCP)$_4$

The ester motif can be very important for selectivity and reactivity:

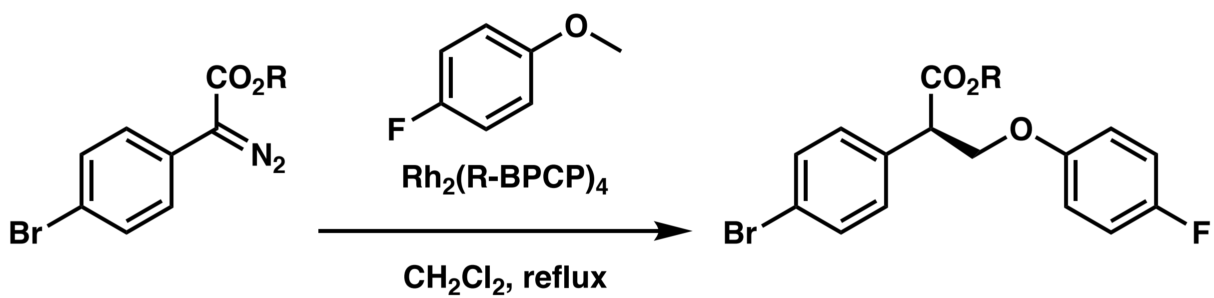


A



B

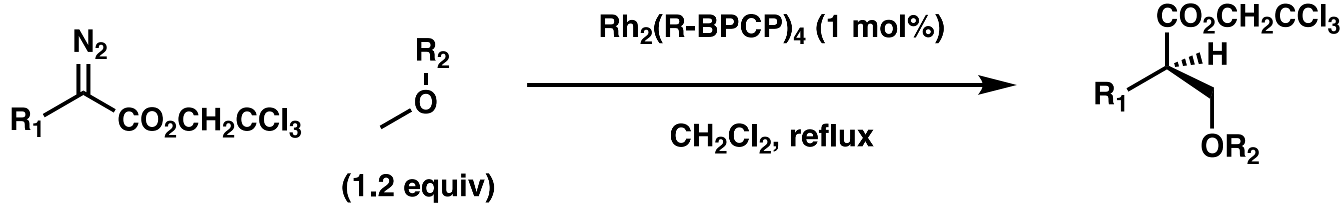
R	A:B	yield	ee
Me	5:1	74	92
CH_2CCl3	13:1	75	99

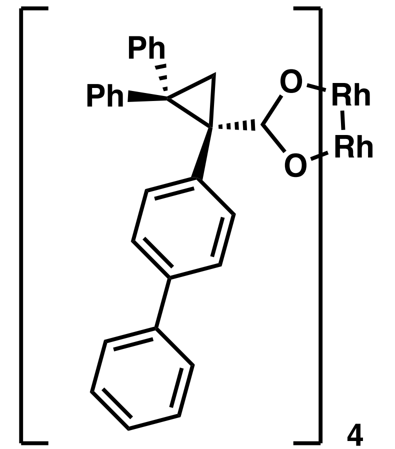


R	yield	ee
Me	15	n.d.
CH_2CCl3	65	97

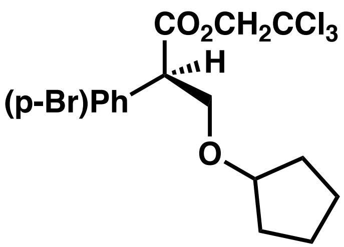
Davies, *JACS* **2014**, *136*, 17718–17721.

Intermolecular C–H insertion

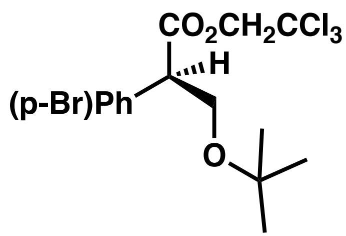




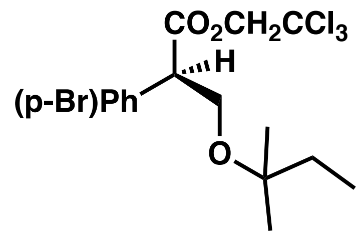
$Rh_2(R\text{-}BPCP)_4$



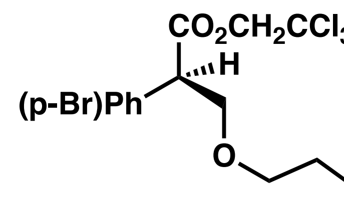
83% yield
91% ee



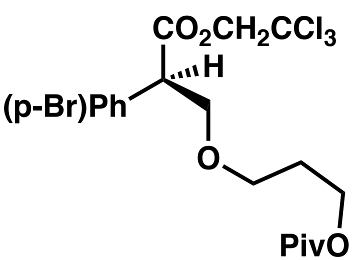
80% yield
94% ee



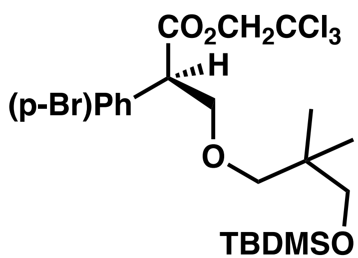
70% yield
93% ee



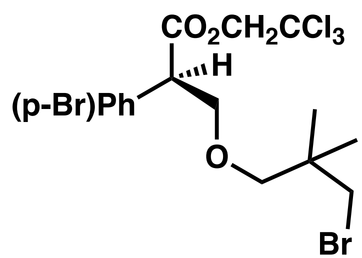
62% yield
89% ee



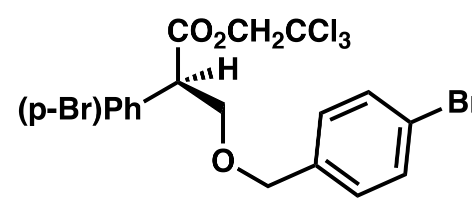
83% yield
92% ee



58% yield
93% ee



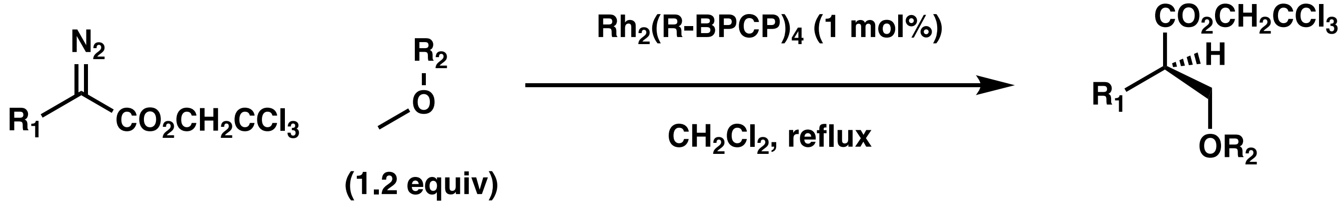
77% yield
97% ee

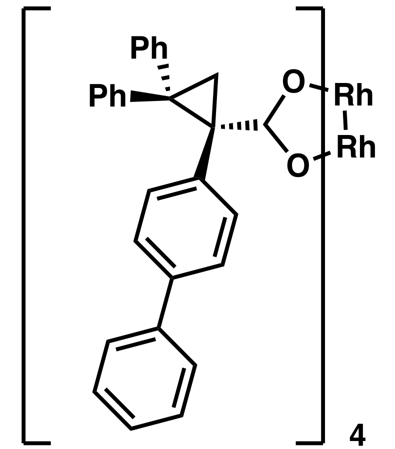


62% yield
89% ee

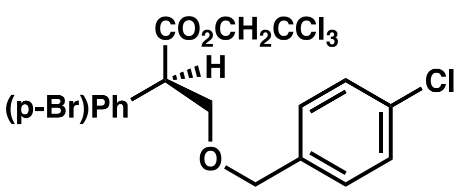
Davies, *JACS* **2014**, *136*, 17718–17721.

Intermolecular C–H insertion

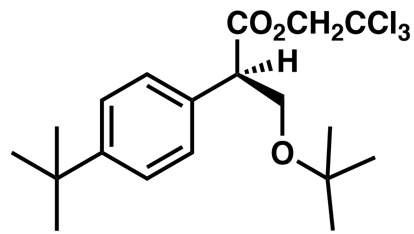




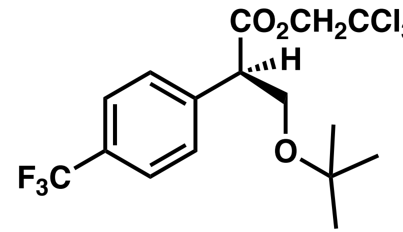
$Rh_2(R\text{-}BPCP)_4$



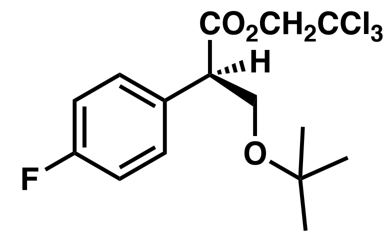
74% yield
88% ee



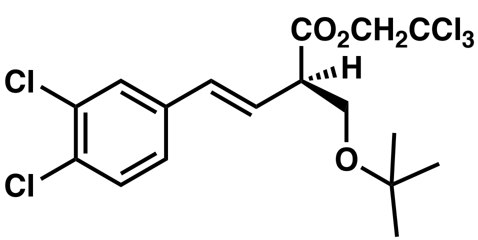
61% yield
99% ee



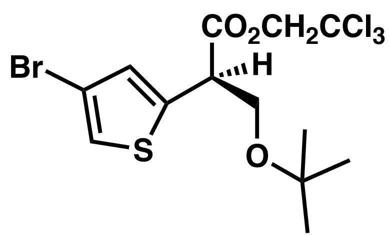
80% yield
98% ee



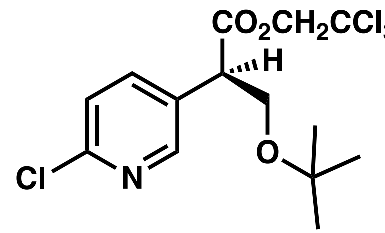
74% yield
82% ee



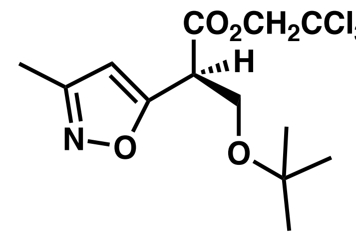
41% yield
94% ee



57% yield
96% ee



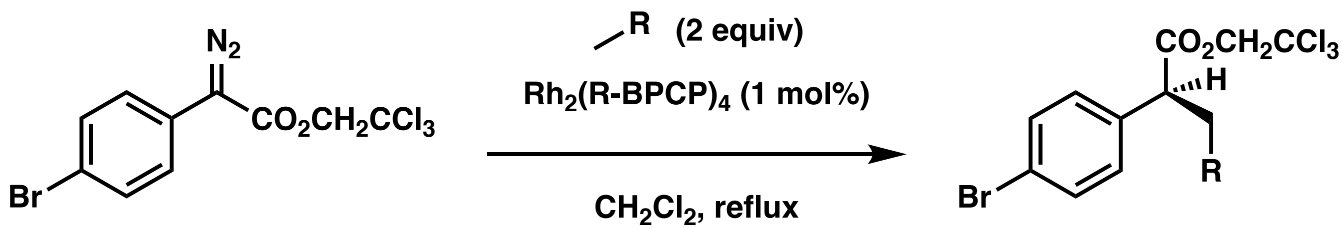
46% yield
82% ee

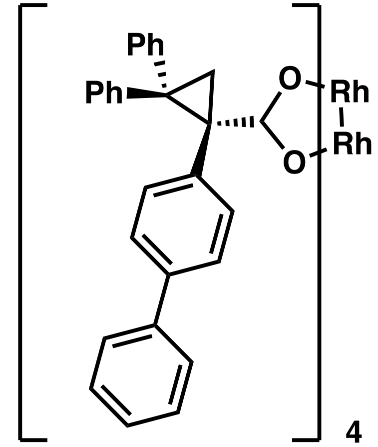


34% yield
75% ee

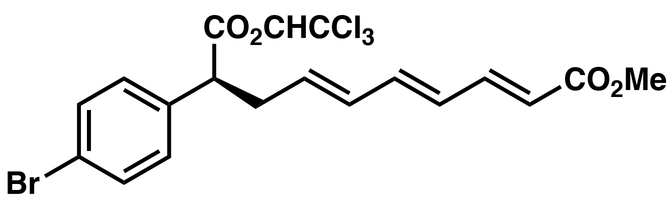
Davies, *JACS* **2014**, *136*, 17718–17721.

Intermolecular C–H insertion

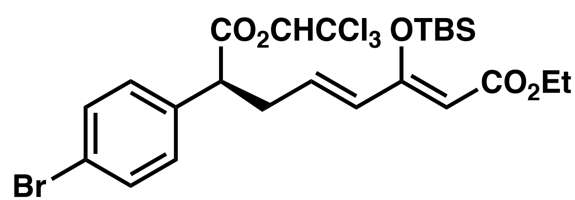




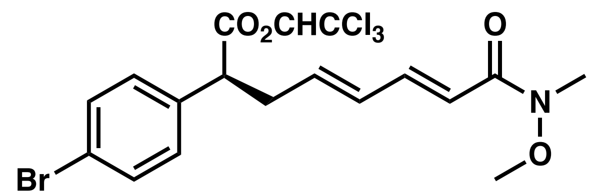
$Rh_2(R\text{-}BPCP)_4$



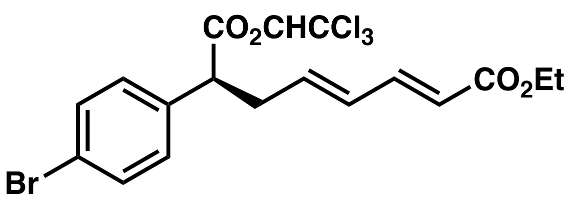
80% yield
92% ee



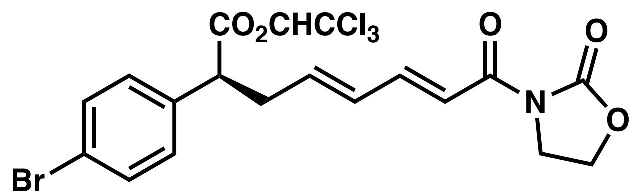
84% yield
58% ee



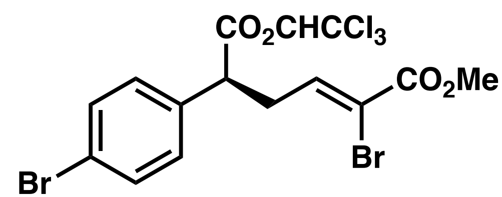
35% yield
97% ee



80% yield
95% ee



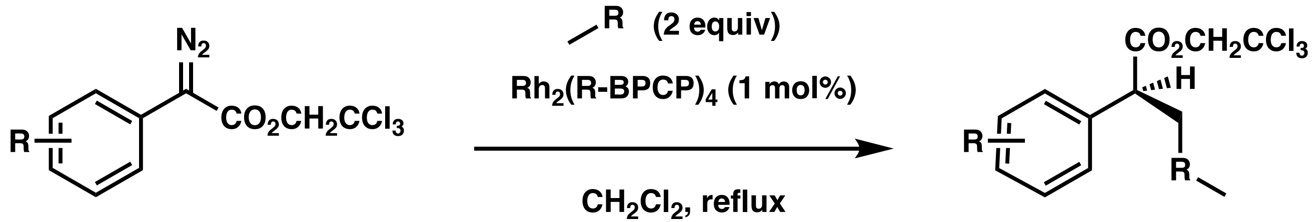
81% yield
97% ee

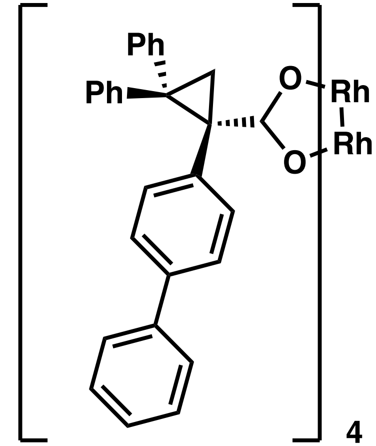


28% yield
99% ee

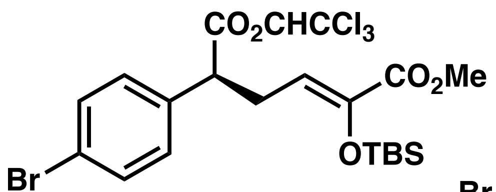
Davies, *JACS* **2016**, *138*, 5761–5764.

Intermolecular C–H insertion

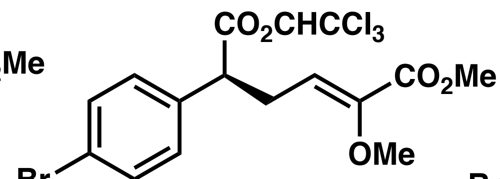




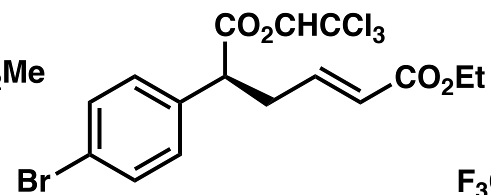
$Rh_2(R\text{-}BPCP)_4$



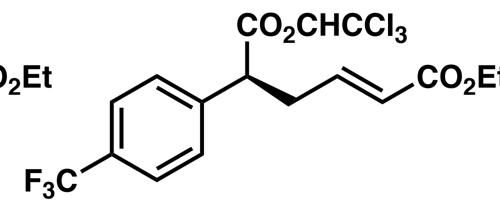
50% yield
93% ee



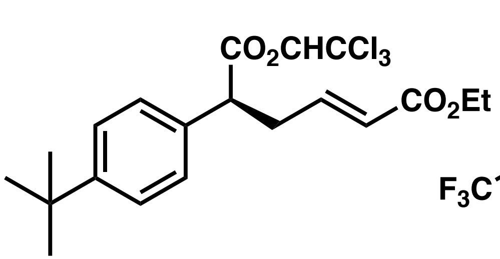
88% yield
98% ee



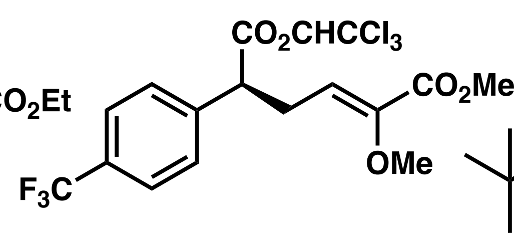
74% yield
95% ee



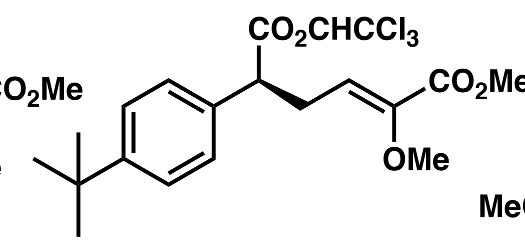
67% yield
98% ee



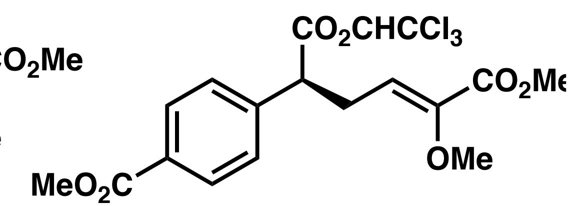
70% yield
99% ee



82% yield
99% ee



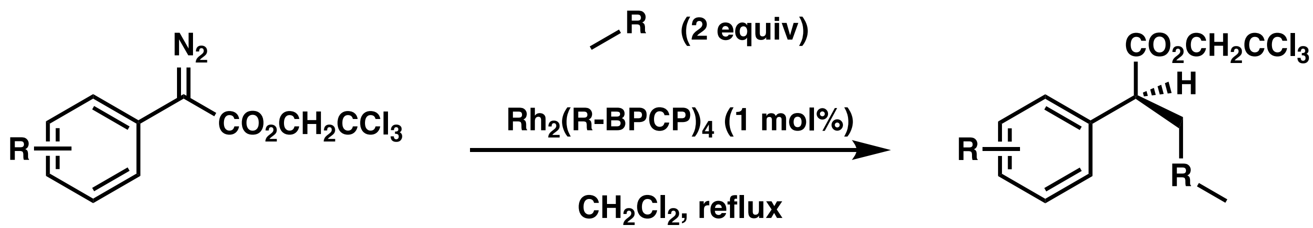
78% yield
>99% ee

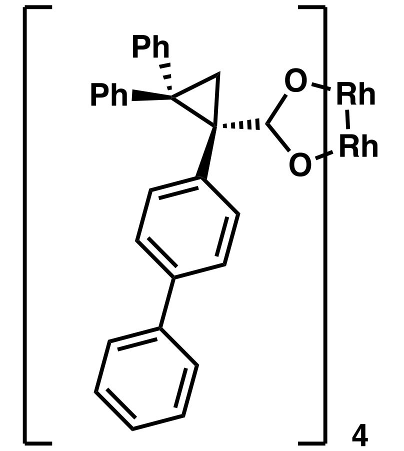


60% yield
89% ee

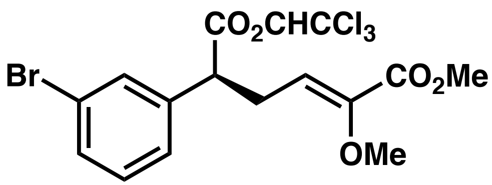
Davies, *JACS* **2016**, *138*, 5761–5764.

Intermolecular C–H insertion

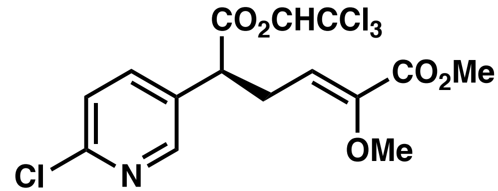




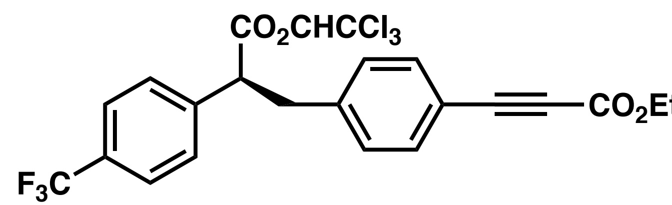
$Rh_2(R\text{-}BPCP)_4$



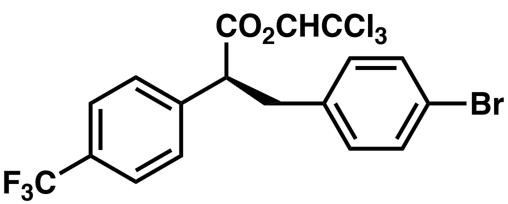
87% yield
88% ee



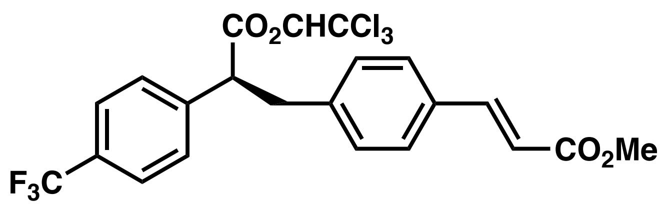
48% yield
92% ee



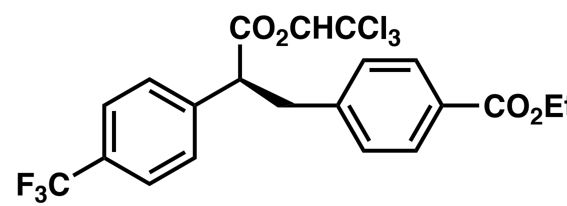
81% yield
96% ee



89% yield
98% ee



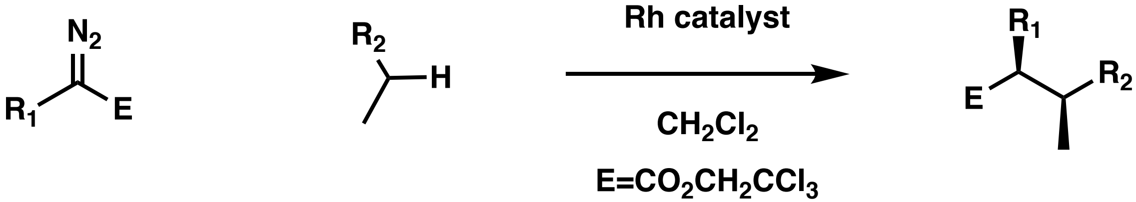
86% yield
97% ee

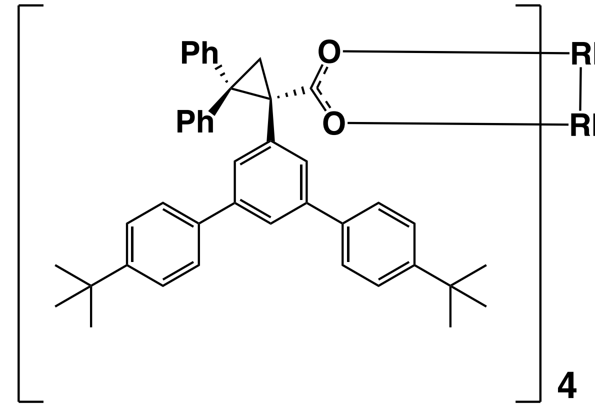


77% yield
97% ee

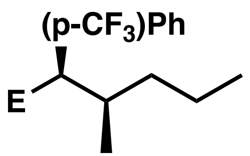
Davies, *JACS* **2016**, *138*, 5761–5764.

Intermolecular C–H insertion

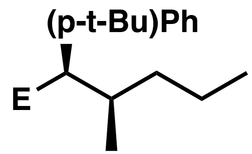




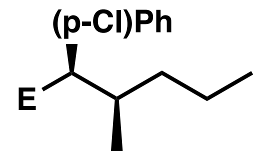
Rh_2[*R*-3,5-di(p-tBuC_6H_4)TPCP]$_4$



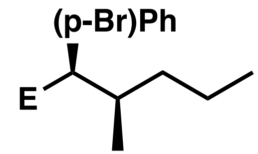
15:1 r.r.
14:1 d.r.
97% ee
91% yield



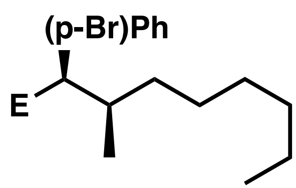
22:1 r.r.
24:1 d.r.
>99% ee
91% yield



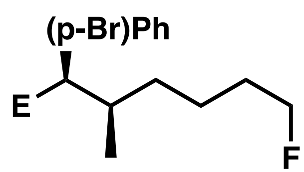
28:1 r.r.
55:1 d.r.
91% ee
87% yield



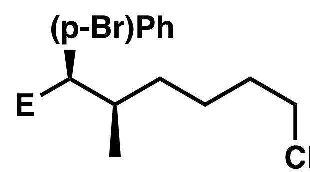
25:1 r.r.
20:1 d.r.
99% ee
99% yield



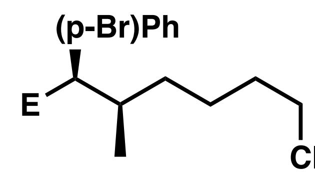
27:1 r.r.
9:1 d.r.
91% ee
82% yield



18:1 r.r.
9:1 d.r.
97% ee
86% yield



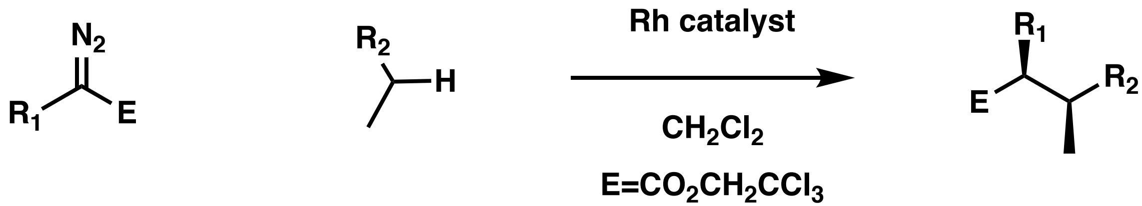
18:1 r.r.
9:1 d.r.
93% ee
84% yield

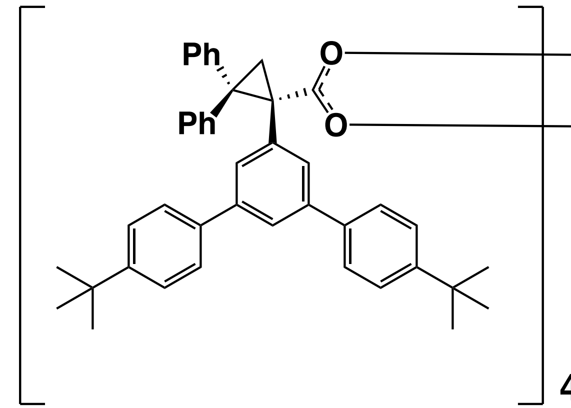


18:1 r.r.
9:1 d.r.
92% ee
89% yield

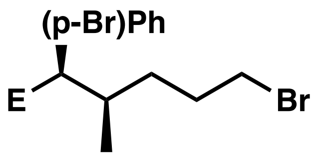
Davies, Musaev *Nature* **2016**, *533*, 230–234.

Intermolecular C–H insertion

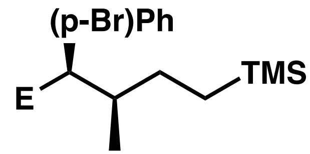




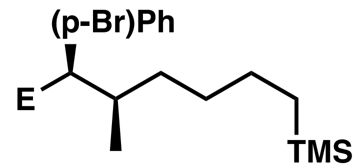
Rh_2[*R*-3,5-di(p-tBuC_6H_4)TPCP]$_4$



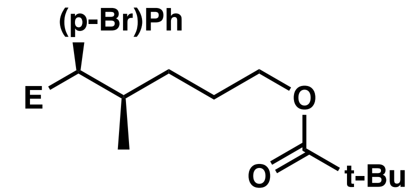
9:1 r.r.
9:1 d.r.
95% ee
65% yield



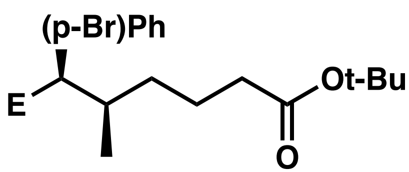
34:1 r.r.
4:1 d.r.
>99% ee
40% yield



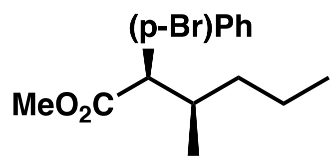
20:1 r.r.
9:1 d.r.
90% ee
85% yield



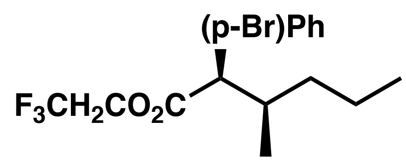
21:1 r.r.
7:1 d.r.
92% ee
83% yield



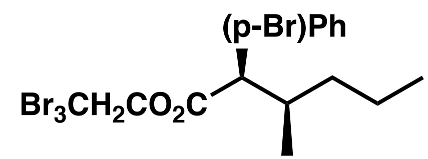
16:1 r.r.
9:1 d.r.
91% ee
84% yield



18:1 r.r.
8:1 d.r.
92% ee
89% yield



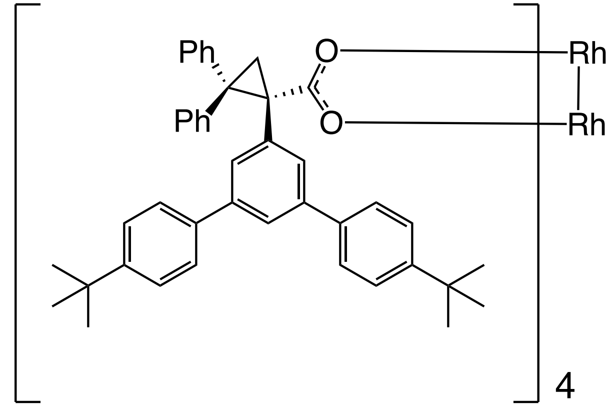
30:1 r.r.
15:1 d.r.
99% ee
91% yield



19:1 r.r.
21:1 d.r.
98% ee
90% yield

Davies, Musaev *Nature* **2016**, *533*, 230–234.

Intermolecular C–H insertion



Rh_2[*R*-3,5-di(p-tBuC_6H_4)TPCP]$_4$

Computational studies were conducted to determine the origin behind the high selectivity observed:

By X–ray crystallography, the catalyst was determined to be D_2 symmetrical, i.e. both faces of the catalyst are the same.

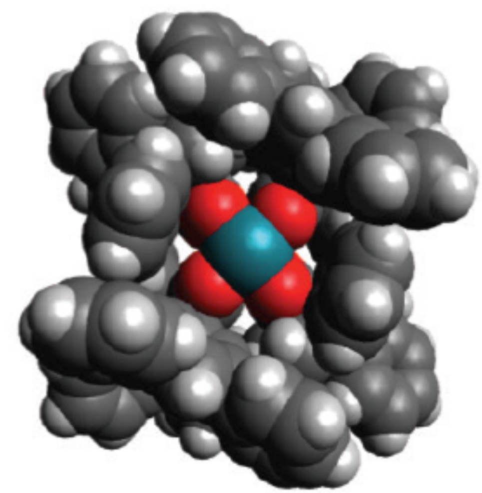
the ligand adopts an $\alpha,\beta,\alpha,\beta$ ligand geometry

computationally, the $\alpha,\alpha,\alpha,\alpha$ ligand geometry was shown to be disfavored by 5 kcal/mol

primary C–H bonds are not electronically activated enough for C–H insertion

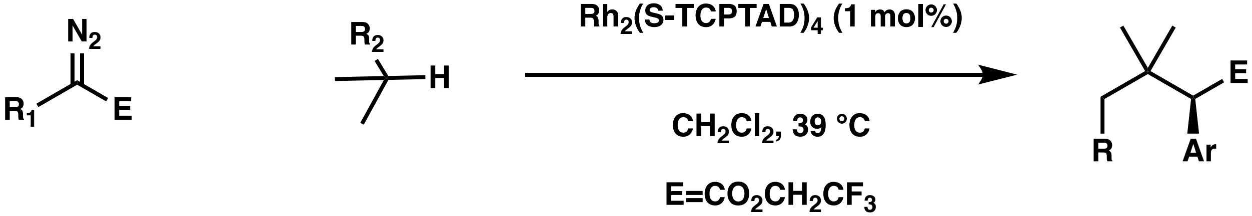
A bulky catalyst allows for selective insertion into the most accesible secondary C–H bond.

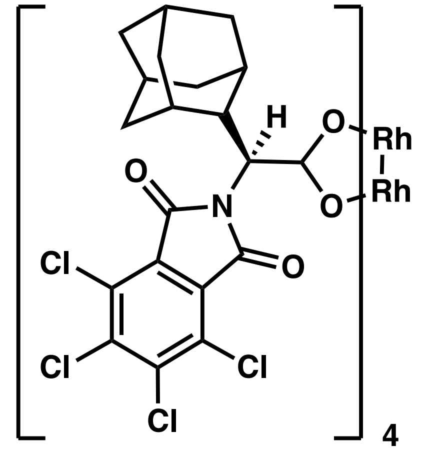
a



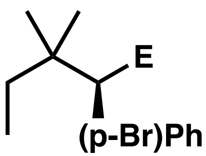
Davies, Musaev *Nature* **2016**, *533*, 230–234.

Intermolecular C–H insertion

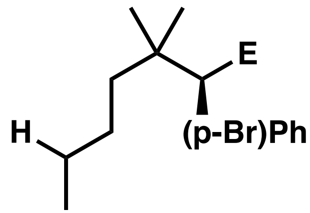




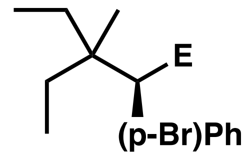
$Rh_2(S\text{-}TCPTAD)_4$



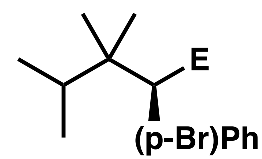
>98:2 r.r.
81% ee
86% yield



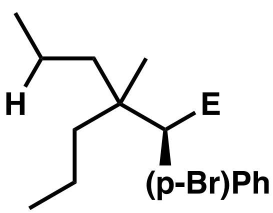
39 °C	–40 °C
87:13 r.r.	96:4 r.r.
77% ee	87% ee
76% yield	65% yield



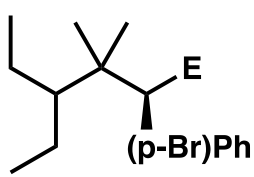
39 °C	–40 °C
92:8 r.r.	98:2 r.r.
82% ee	92% ee
73% yield	64% yield



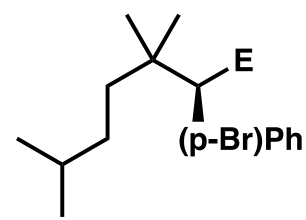
>98:2 r.r.
83% ee
93% yield



11:89 r.r.
81% ee
9% yield



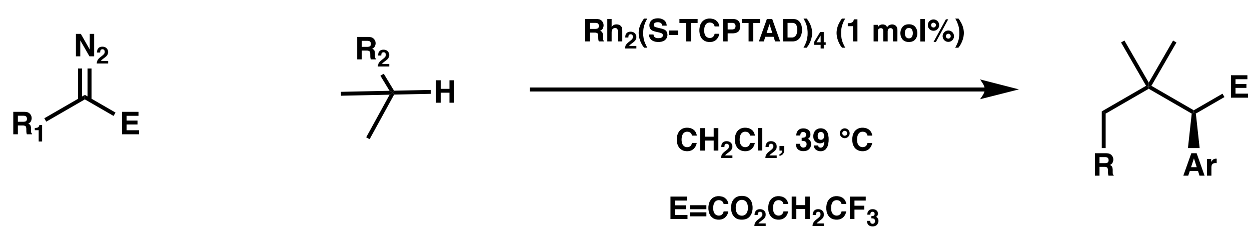
>98:2 r.r.
86% ee
66% yield

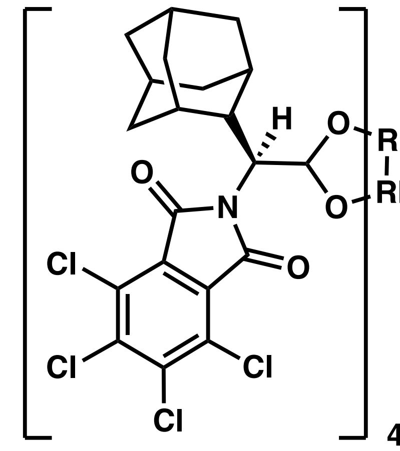


>98:2 r.r.
78% ee
87% yield

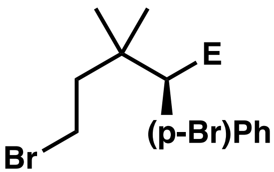
Davies, Musaev *Nature* **2017**, *551*, 609–613

Intermolecular C–H insertion

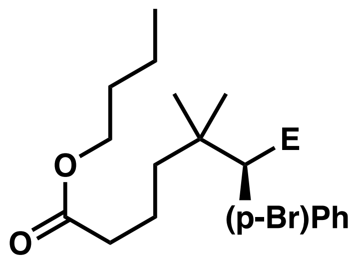




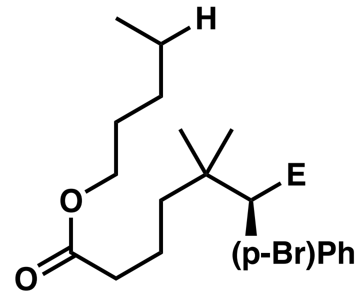
Rh_2(S-TCPTAD)$_4$



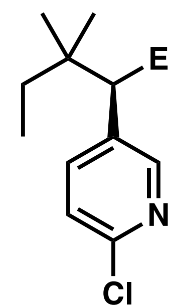
>98:2 r.r.
84% ee
70% yield



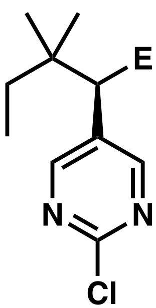
>98:2 r.r.
77% ee
90% yield



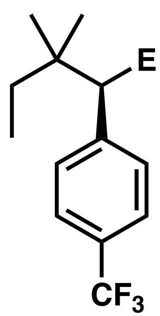
39 °C	–40 °C
88:12 r.r.	**91:9 r.r.**
76% ee	**94% ee**
73% yield	**66% yield**



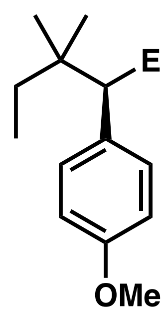
>96:4 r.r.
68% ee
60% yield



98:2 r.r.
75% ee
81% yield



>98:2 r.r.
74% ee
89% yield

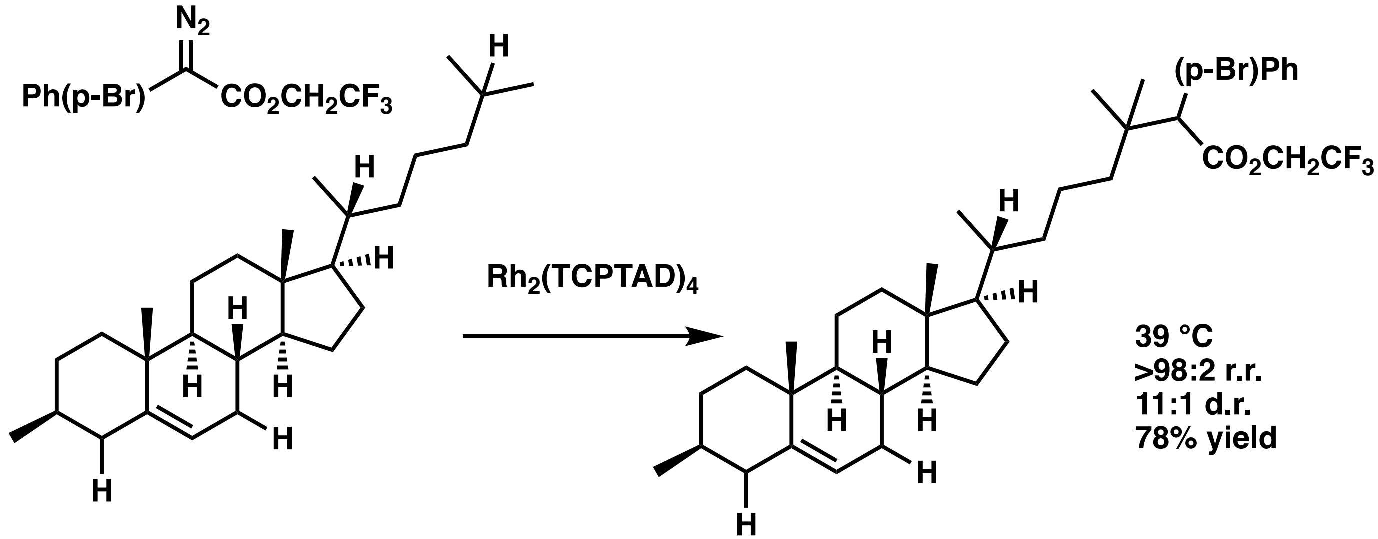


>98:2 r.r.
63% ee
94% yield

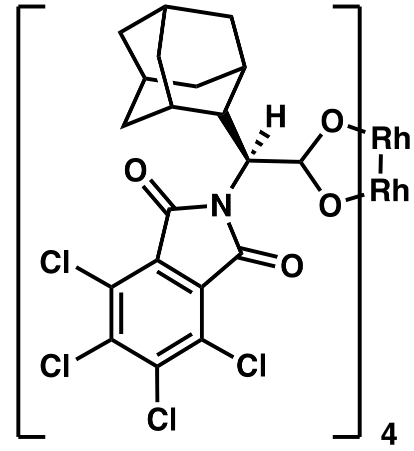
Davies, Musaev *Nature* **2017**, *551*, 609–613.

Intermolecular C–H insertion

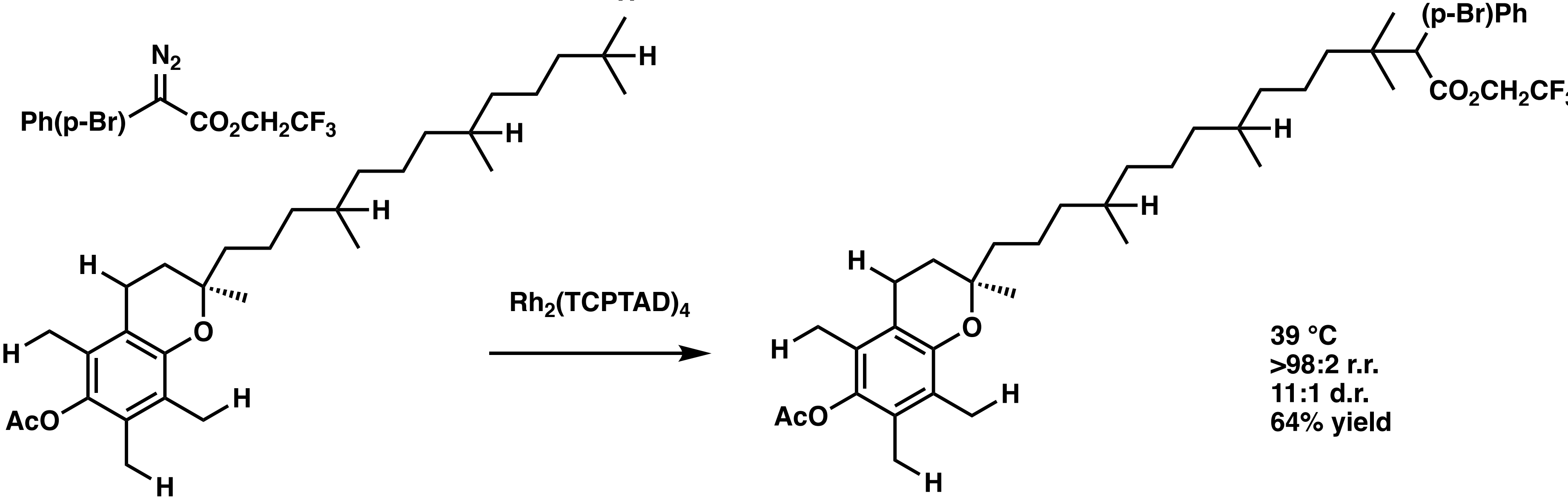
The rhodium carbene inserts selectively into the most accesible tertiary C–H bond:



39 °C
>98:2 r.r.
11:1 d.r.
78% yield



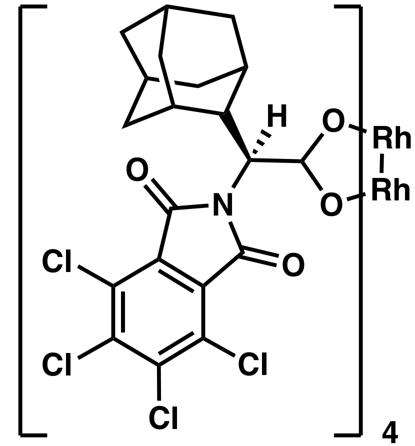
Rh$_2$(S-TCPTAD)$_4$



39 °C
>98:2 r.r.
11:1 d.r.
64% yield

Davies, Musaev *Nature* **2017,** *551*, 609–613.

Intermolecular C–H insertion



Rh_2(S-TCPTAD)$_4$

Computational Studies were undertaken to determine how the site selectivity arises:

less sterically demanding catalyst leads to favored tertiary bond insertion

tertiary bond insertion is most favored electronically

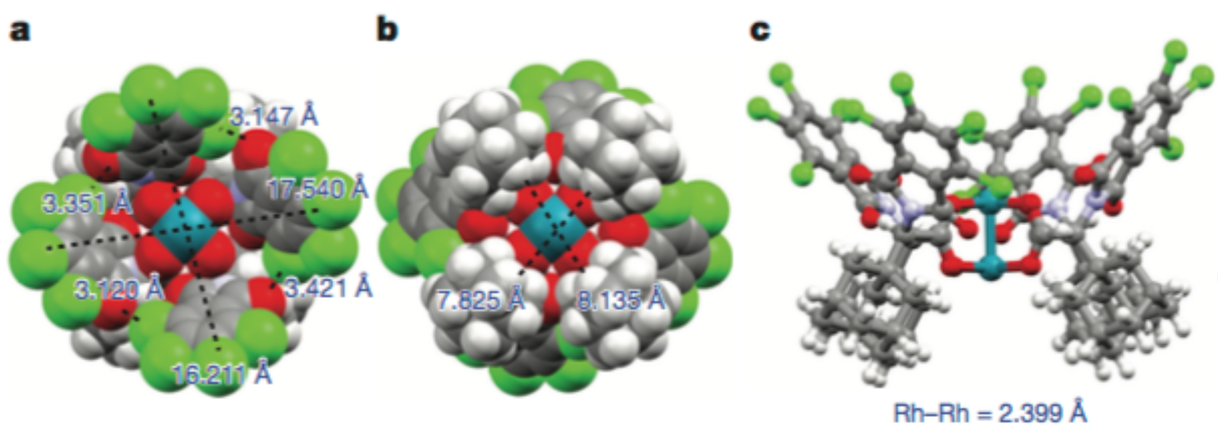
X–ray crystallography and computational studies show the catalyst adopts a slightly distorted C_4 symmetric structure

The steric enviornment is different on either side of the catalyst.

The rhodium face with the phtalimido groups is more accesible than the face with the adamantyl groups.

a π-stacking interaction between the carbene and rhodium leads to a preferential attack at the Re face of the carbene.

The approach of the substrate leads to the selectivity for the most accesible tertiary C–H bond



Davies, Musaev *Nature* **2017**, *551*, 609–613.

Seminar Outline

I. Introduction to Carbenes

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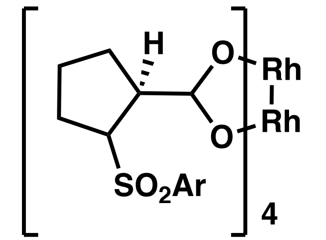
VI. Further Resources

Synthesis of Ritalin

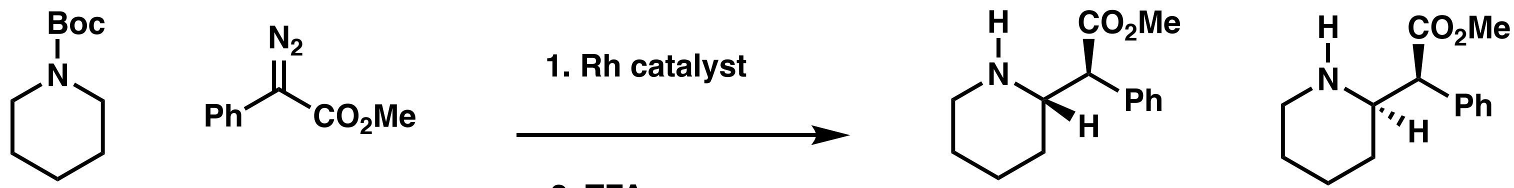


Ar=p–($C_{11\text{-}13}H_{23\text{-}27}$)$C_6H_4$

Rh_2(S-DOSP)$_4$

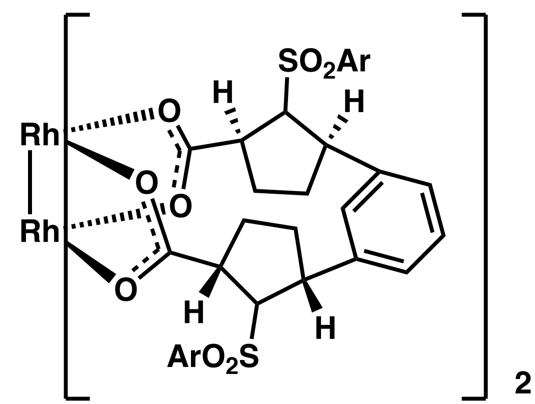
***threo*-methylphenidate (marketed as Ritalin, etc.) is used to treat ADHD and narcolepsy.**

A is the active component as the 2R enantiomer



1 **2** **A** **B**

cat	eq. 1	yield	A:B	ee (A)
DOSP	**4**	**49**	**43:57**	**34 (2S)**
DOSP	**0.25**	**86**	**50:50**	**25 (2S)**
biDOSP	**0.25**	**73**	**71:29**	**86 (2R)**

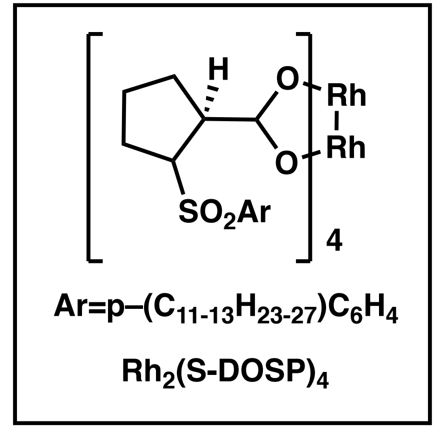


Ar=p–($C_{11\text{-}13}H_{23\text{-}27}$)$C_6H_4$

Rh_2(S-biDOSP)$_4$

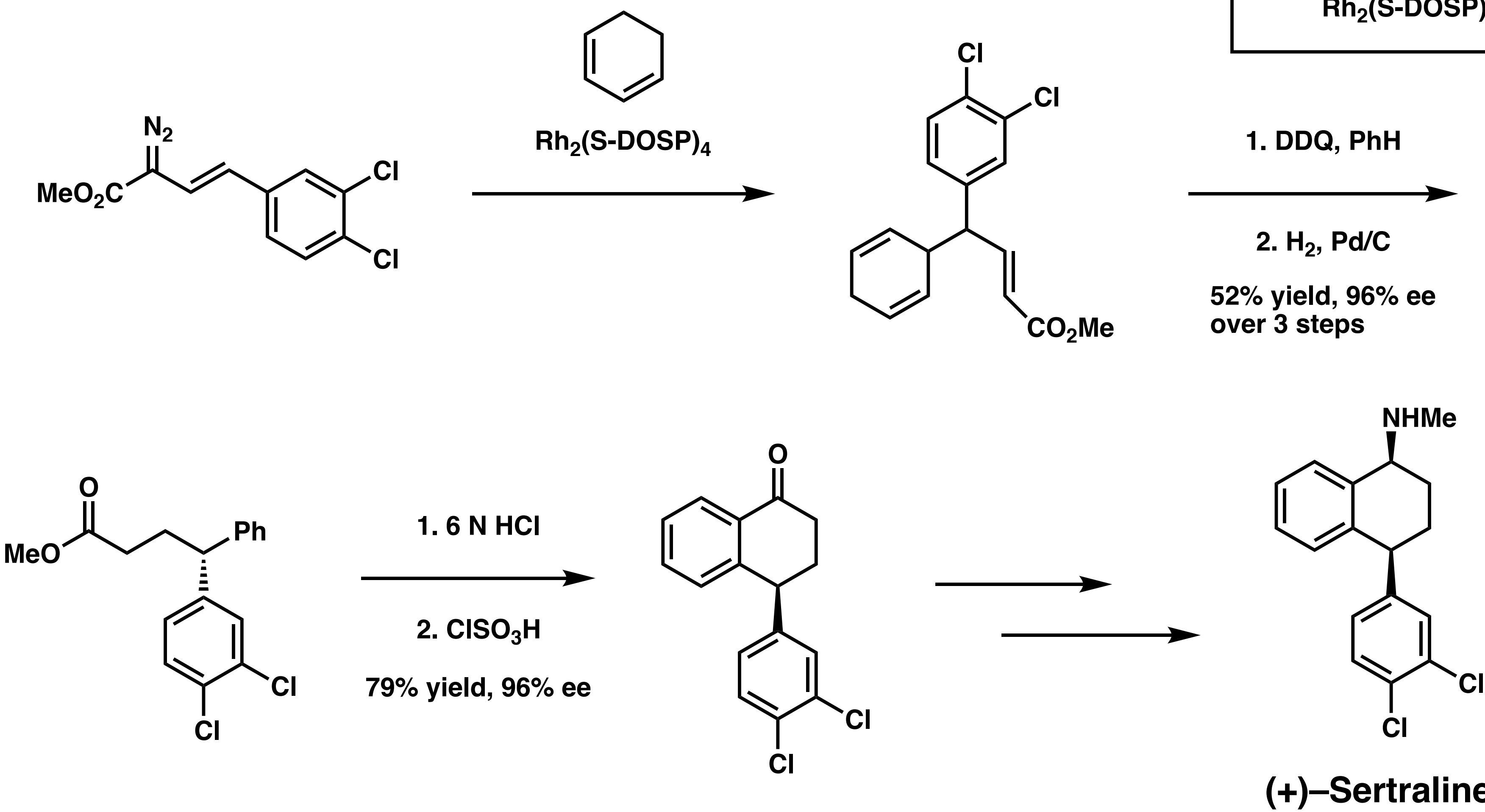
Davies, *JACS* **1999**, *121*, 6509–6510.

Formal Synthesis of (+)–Sertraline



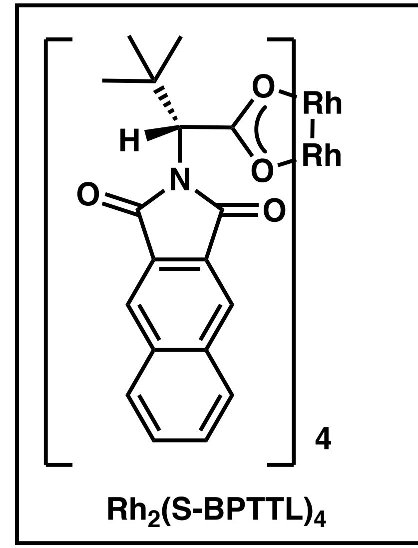
(+)–Sertraline (Zoloft) is an antidepressant of the SSRI class.

Introduced by Pfizer in 1991, and still in use today.



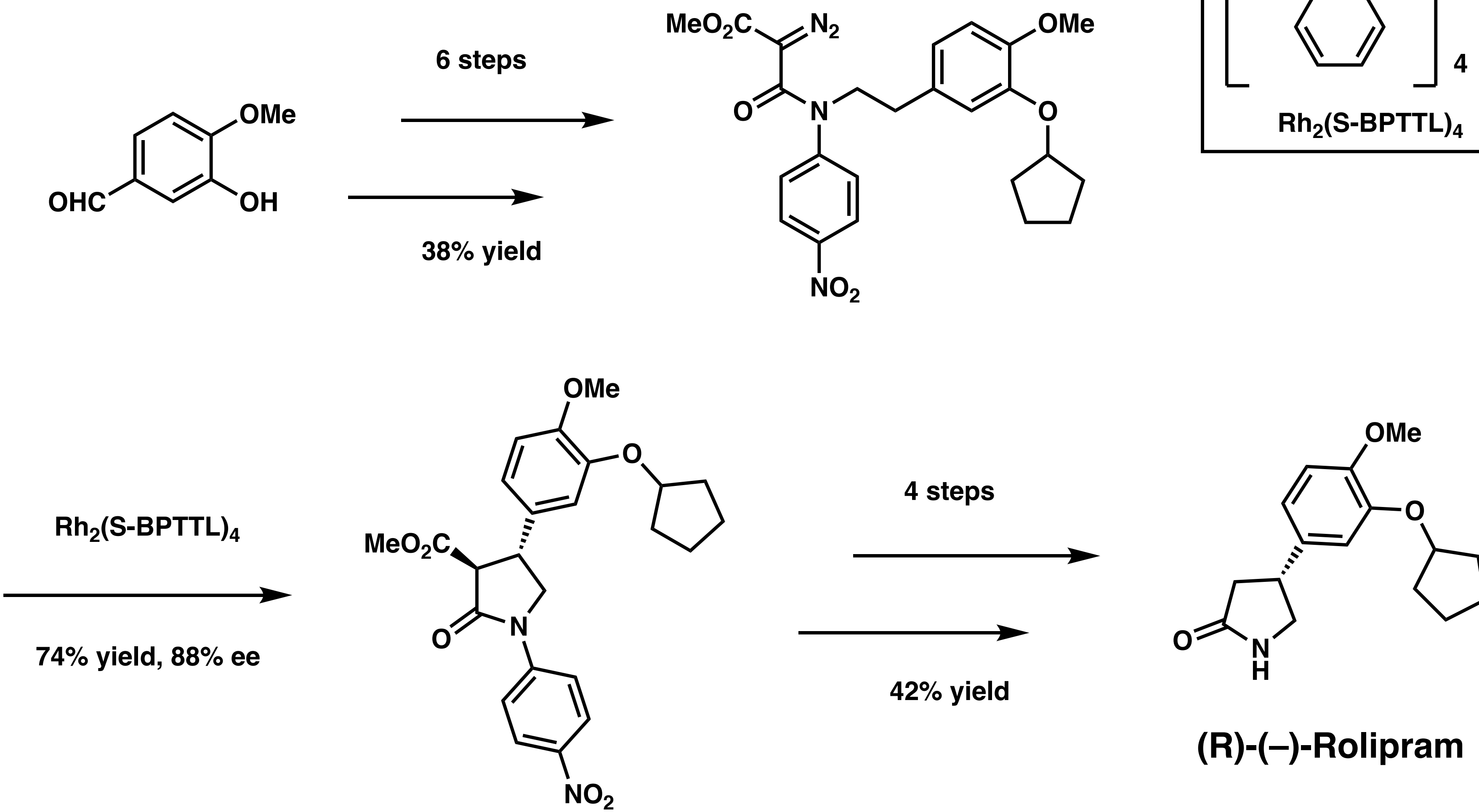
Davies, *Org. Lett.* **1999**, *1*, 233–236.

Synthesis of (R)-(–)-Rolipram



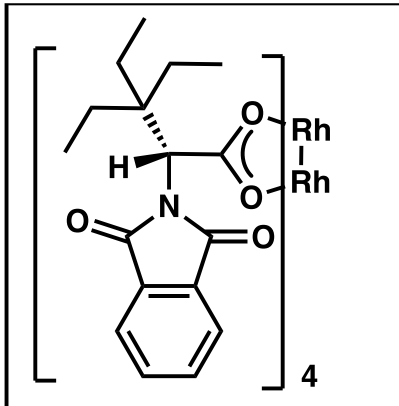
(R)-(–)-Rolipram is a potent and selective phosphodiesterase type IV inhibitor.

Used as a prototype molecule for drug discovery, though not used itself due to side effects and a need for high dosages.



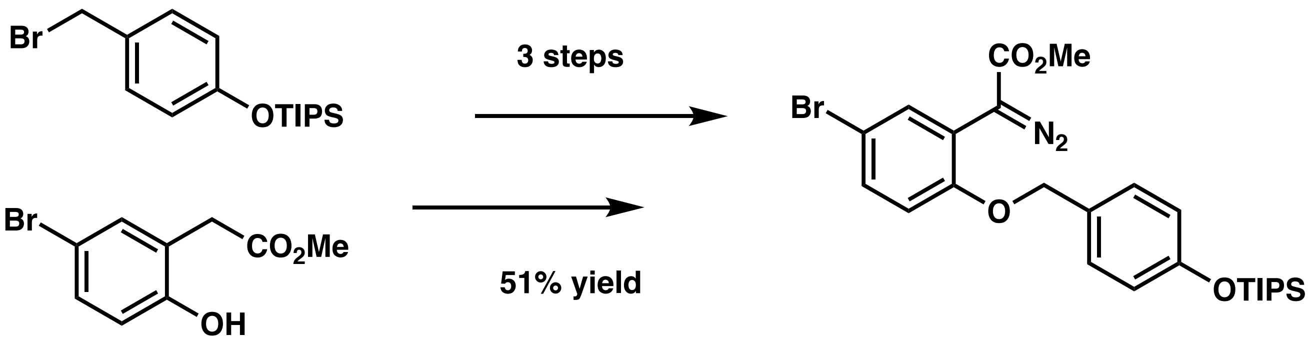
Hanefeld, *Synlett* **1999**, *11*, 1775–1777.

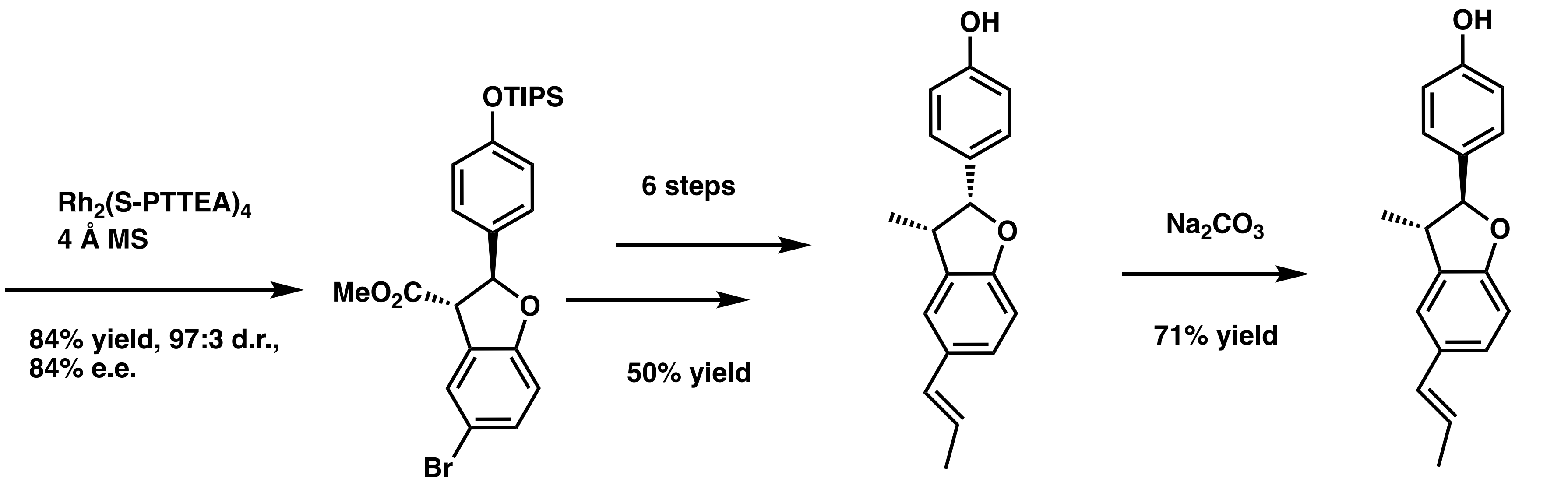
Synthesis of (+)-Conocarpan



$Rh_2(S\text{-}PTTEA)_4$

(+)–Conocarpan is a natural product with various biological activities



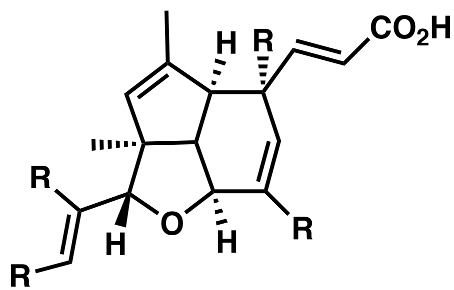


(–)–epi-conocarpan **(+)–conocarpan**

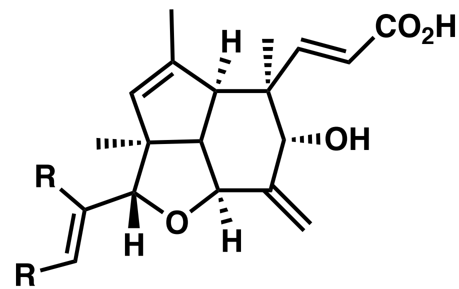
Hashimoto, *J. Org. Chem.* **2009**, *74*, 4418–4421.

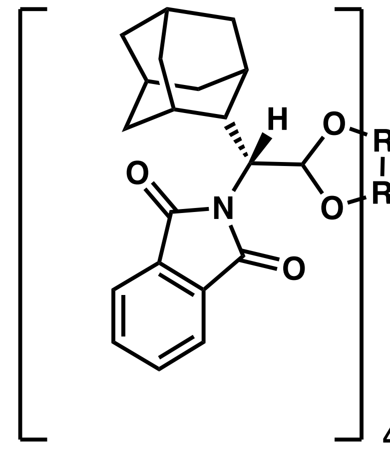
Synthesis of (–)-Indoxamycin Core

Indoxamycins A–E

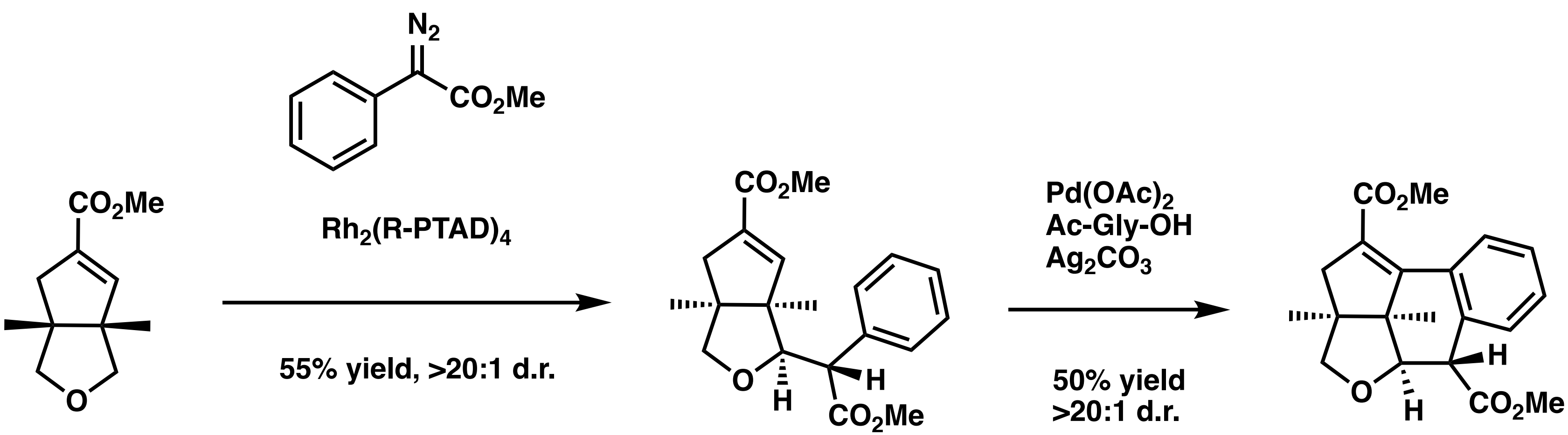


Indoxamycin F





Rh_2(R-PTAD)$_4$

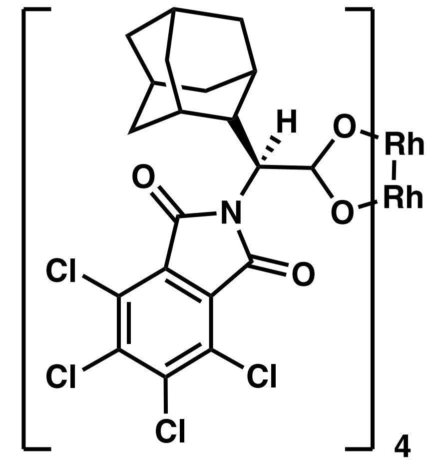


Davies, Sorensen, *ACIE* **2016**, *55*, 8270–8274.

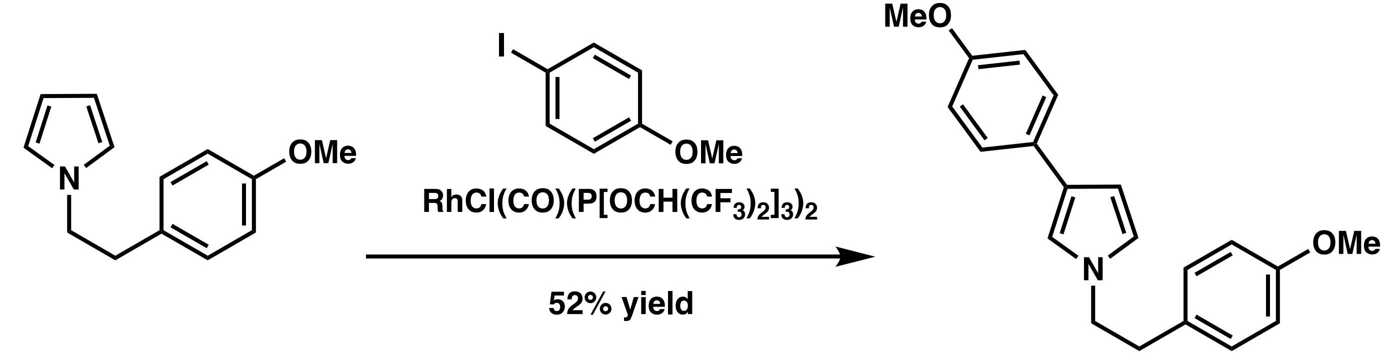
Synthesis of Dictyodendrins A and F

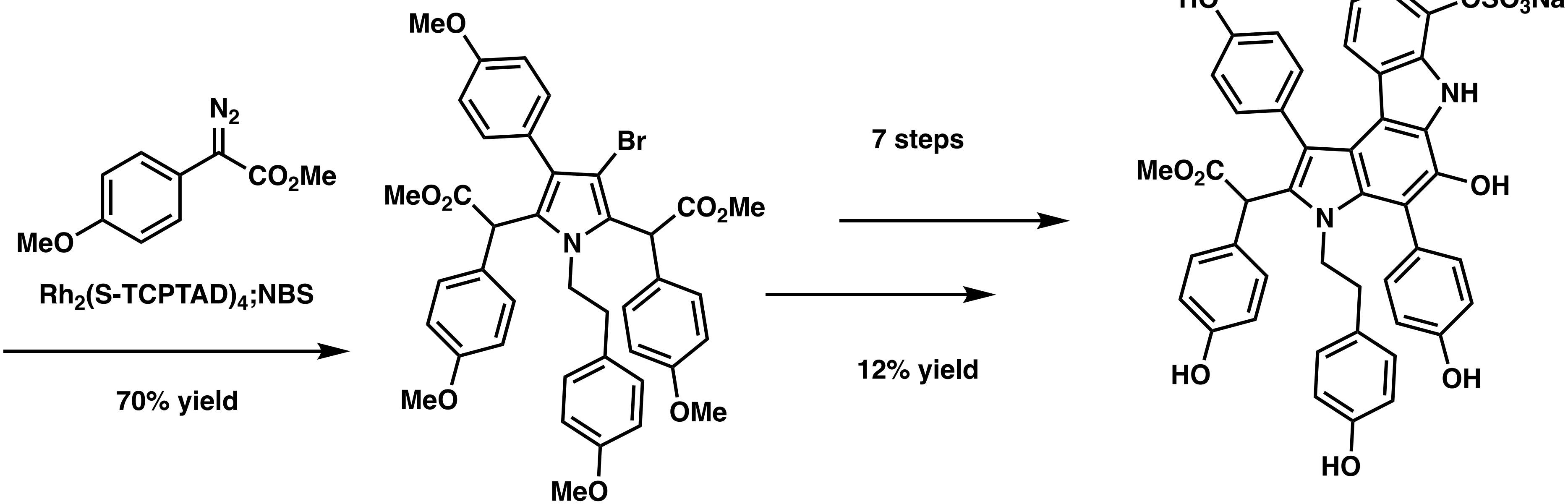
A formal synthesis of Dictyodendrin A and a synthesis of Dictyodendrin F was reported utilizing a sequential C–H functionalization strategy.

Collaboration between Davies and Itami Groups.



Rh_2(S-TCPTAD)$_4$

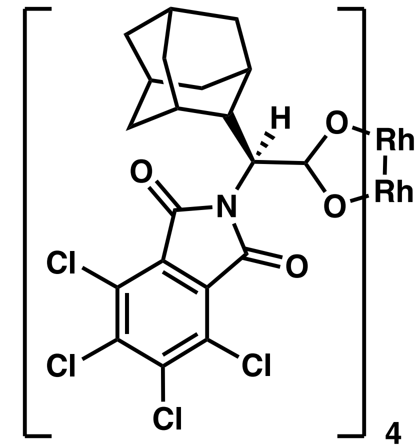




Dictyodendrin A

Davies, Itami, *JACS* **2015**, *137*, 644–647.

Synthesis of Dictyodendrins A and F



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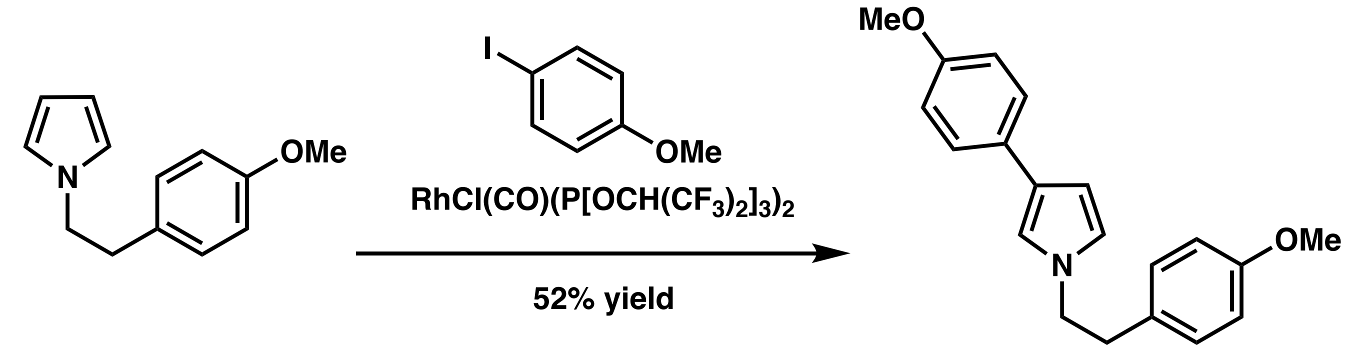

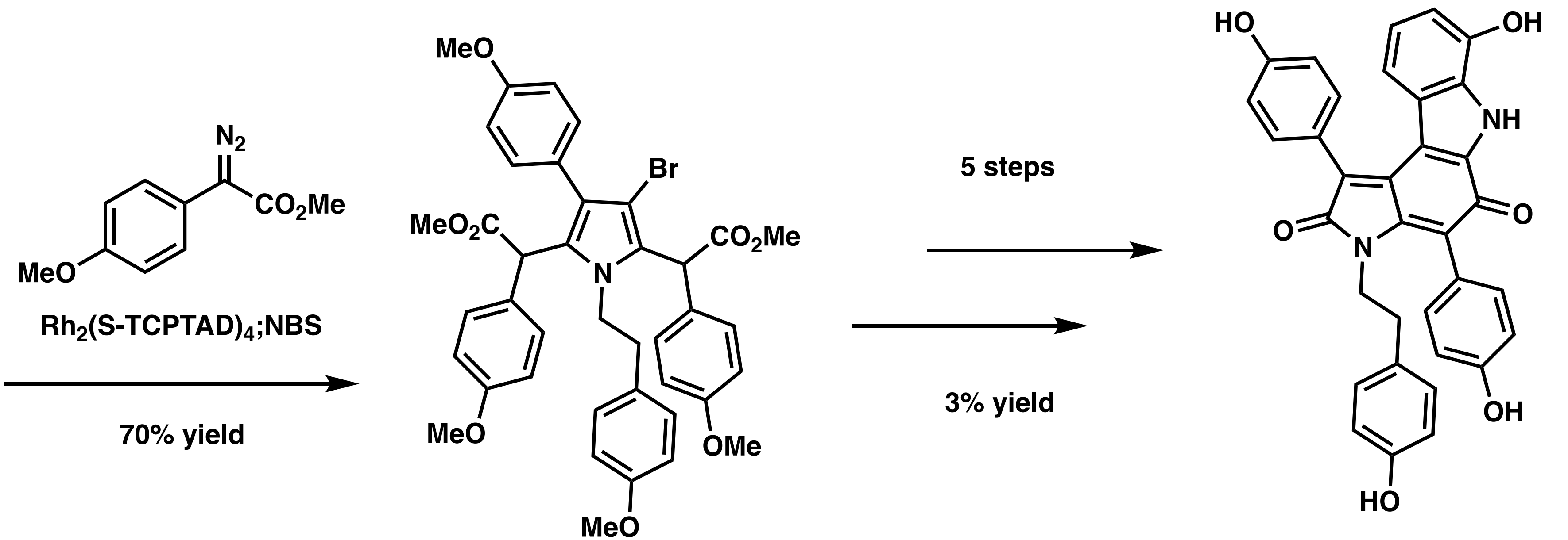

Dictyodendrin F

Davies, Itami, *JACS* **2015**, *137*, 644–647.

Conclusions

Carbene chemistry has come a long way in recent years

C–H functionalization reactions are simplifying disconnections

Discovery of Rhodium carbenes resulted in the development of selective C–H functionalization reactions

The electronics of the carbene carbon center and the Rhodium catalyst serve key roles

Site selectivity was first discovered by exploiting heteroatom effects

More recently, tuning of the catalyst has resulted in selective insertions into unactivated C–H bonds

C–H insertion reactions have been utilized in various synthetic efforts

A more thorough understanding of the mechanism and electronics of the system will help drive the field further

While a lot of progress has been made, many questions remain unanswered

Selectivity is still a problem in many cases for this chemistry, especially in more complex systems

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Additional Resources

Other lit meetings:

Uttam Tambar, Stoltz/Reisman group, 2004 (on the Stoltz Group Website)

https://www.princeton.edu/chemistry/macmillan/group-meetings/JEC-chact.pdf

Brian Ngo Laforteza, 2010, Princeton, Macmillan Group Lit seminars (online)

Books:

Doyle, 2013, Contemporary Carbene Chemistry (specifically Chapter 12 on Rhodium Carbenes by Davies)

Doyle, 1998 Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides

Reviews:

Machado, *Beilstein J. Org. Chem.* **2016,** *12,* 882–902.

You *RSC Adv.*, **2014**, *4*, 6173.

Maguire, McKervey *Beilstein J. Org. Chem.* **2016,** *12,* 882–902.

Davies *Chem. Soc. Rev.*, **2011**, *40*, 1857–1869.

Doyle *Chem. Rev.* **2010**, *110*, 704–724.

Davies *Chem. Rev.* **2003**, *103*, 2861-2903.

Doyle *Chem Rev.* **1986**, *86*, 919.