Carbene-Mediated C-H Activation and Insertion

Presentation outline

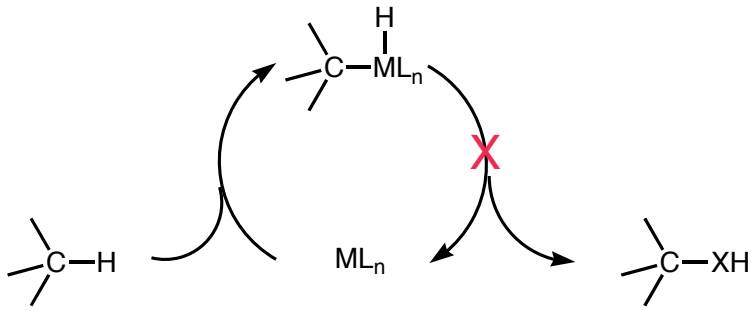
- Introduction
  - Classification of carbene precursors: diazocarbonyls
  - Synthesis of diazocarbonyls
  - Decomposition of diazocarbonyl to metal-carbenoids
- Intermolecular C-H activation
  - Acceptor-Substituted Carbenoids
  - Acceptor/Acceptor-Substituted Carbenoids
  - Donor/Acceptor-Substitued Carbenoids
- Catalysts and models for asymmetric induction
- Conclusions

Interesting Reviews:

- Davies, H. M. L.; Øystein, L. *Synthesis* **2004**, 16, 2595.
- Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, 103, 2861.
- Bourissou, D.; Guerret, O.; Gabbai, F. P.; Bertrand, G. *Chem. Rev.* **2000**, 100, 39.

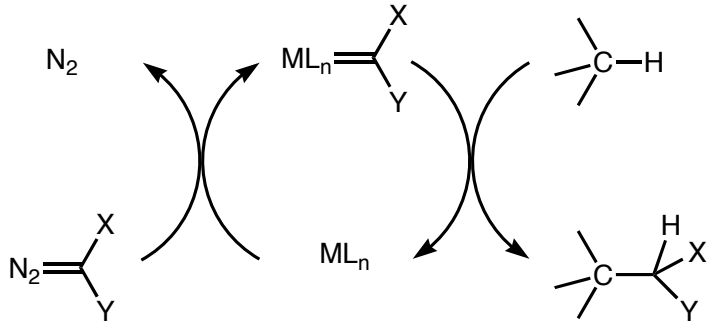
Introduction to Carbene-Mediated C-H Activation

■ Activation through insertion of highly reactive metal complex



Regeneration of the metal complex can be difficult

■ Activation using a metal-carbenoid complex



No direct interaction between the metal and alkane C-H bond

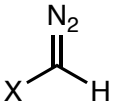
Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, 103, 2861.

Classification of the Carbene Precursor

Most commonly used diazo compounds

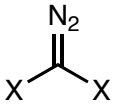
■ The carbenes used for C-H activation can be divided into three groups

Acceptor-Substututed



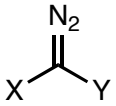
X= EWG: COR, CO_2R, NO_2, $PO(OR)_2$, SO_2R

Acceptor/Acceptor-Substituted



X= EWG: COR, CO_2R, SO_2R, CN

Donor/Acceptor-Substituted



X= EWG: COR, CO_2R

Y= EDG: aryl, vinyl, alkynyl, heteroaryl

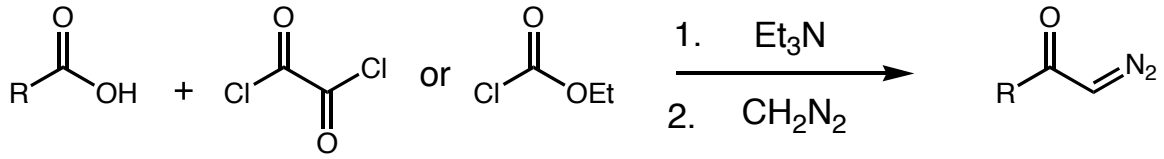
Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, 103, 2861.

Synthesis of Diazocarbonyls

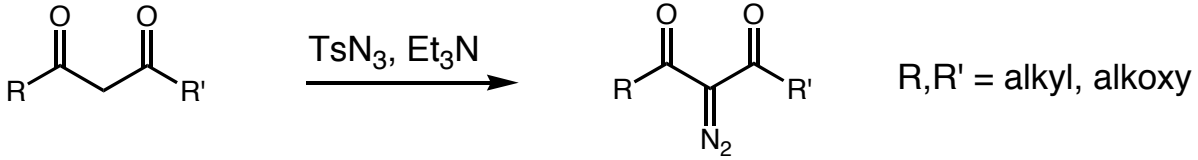
A Brief Look

Curtius 1883

Acyl transfer

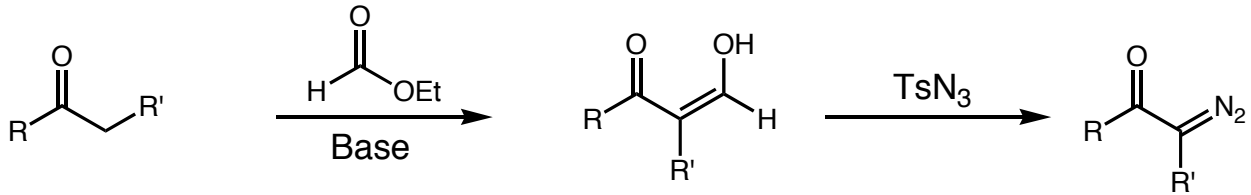


Diazo transfer



R,R' = alkyl, alkoxy

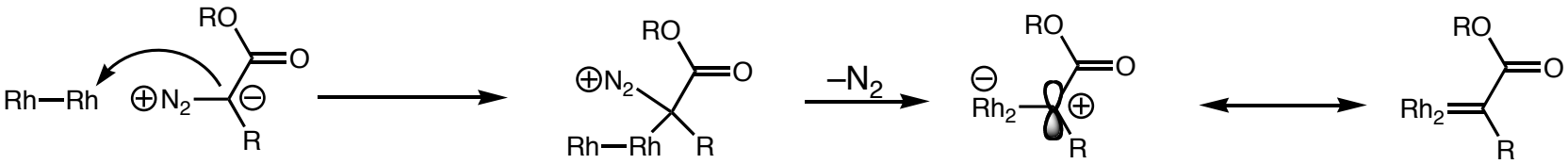
Deformylating diazo transfer

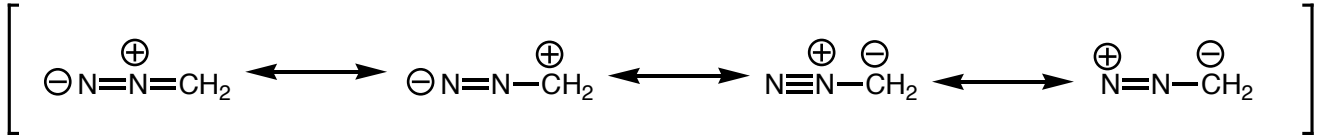


R = alkyl, alkoxy
R'= alkyl, aryl

Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, 94, 1091.

Decomposition of Diazocarbonyls to Metal-Carbenoids

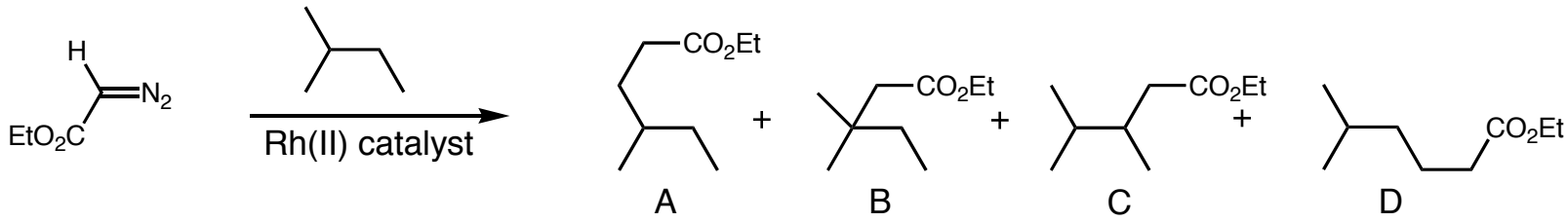




Acceptor-Substituted Carbenoids

Intermolecular C-H activation

■ C-H Activation of Alkanes



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

[a]Dirhodium(II) tetrakis(9-triptycenecarboxylate).

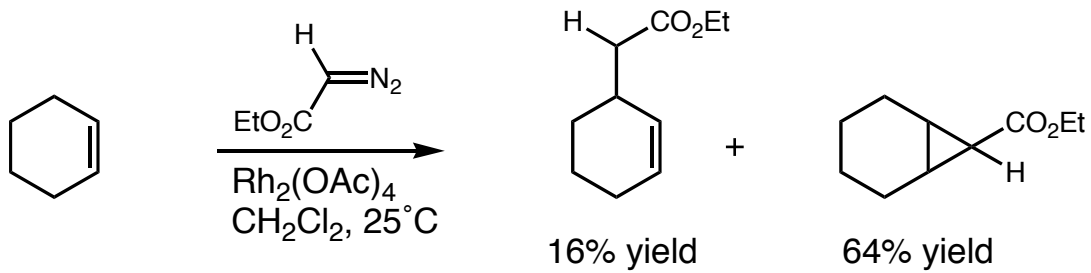
Carbene dimerization is also a major side reaction.
Other Rh(II) catalysts did not improve selectivity.

Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, 103, 2861.

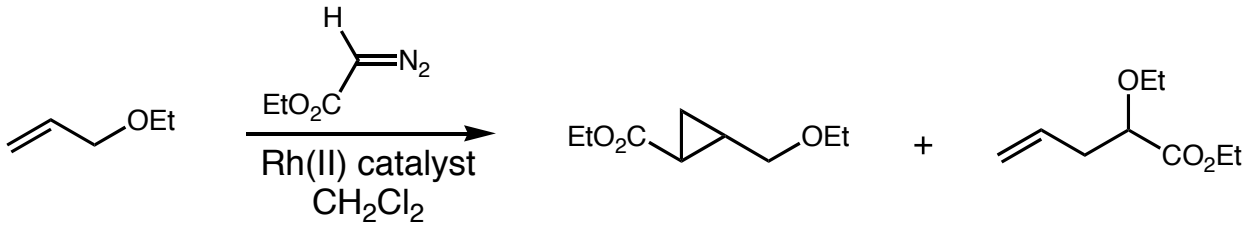
Acceptor-Substituted Carbenoids

Intermolecular C-H activation

■ C-H Activation of Functionalized Organic Substrates



Cyclopropanation out competes C-H insertion.



Only products obtained are from cyclopropanation and ylide rearrangement.

Doyle, M. P.; Hu, W. *J. Org. Chem.* **2000**, *65*, 8839.

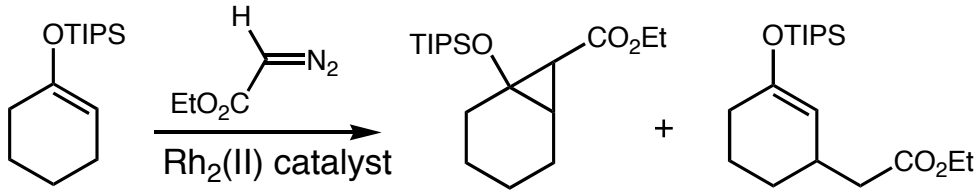
Muller, P.; Tohill, S. *Tetrahedron* **2000**, *56*, 1725.

Davies, H. M. L.; Hansen, T. *J. Am. Chem. Soc.* **1997**, *119*, 9075.

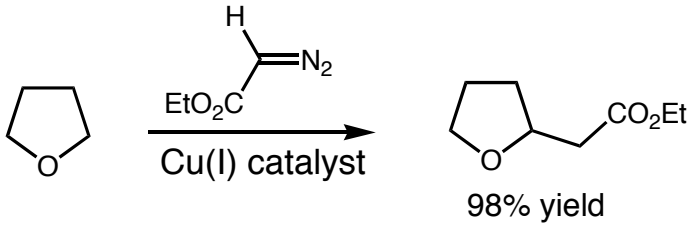
Acceptor-Substituted Carbenoids

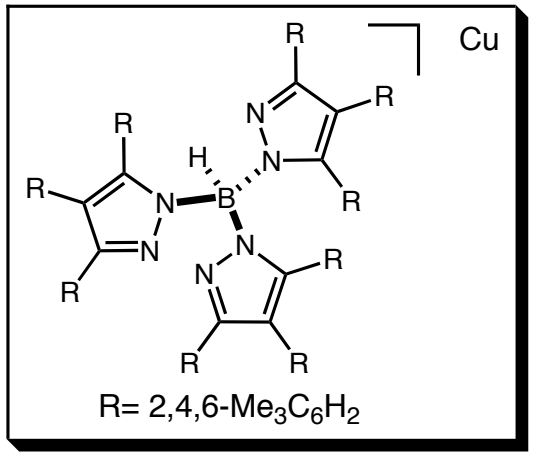
Intermolecular C-H activation

■ C-H Activation of Functionalized Organic Substrates



catalyst	yield, A+B	ratio, A:B
$Rh_2(OOct)_4$	66	96:4
$Rh_2(S\text{-DOSP})_4$	54	76:24





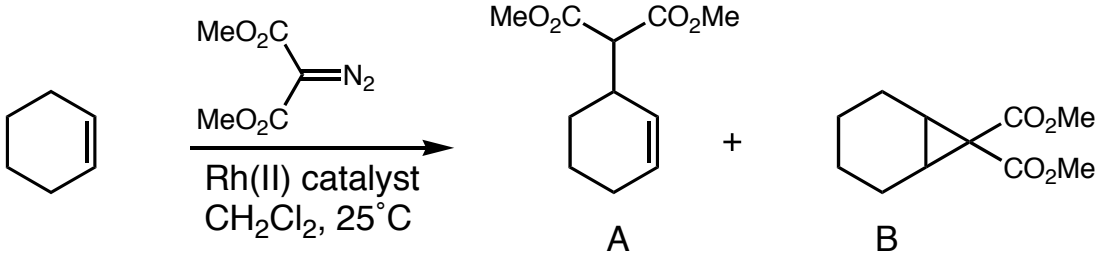
Diaz-Requejo, M. M.; Belderrain, T. R.; Nicasio, M. C.; Trofimenko, S.; Perez, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 896.

Davies, H. M. L.; Ren, P. *J. Am. Chem. Soc.* **2001**, *123*, 2070.

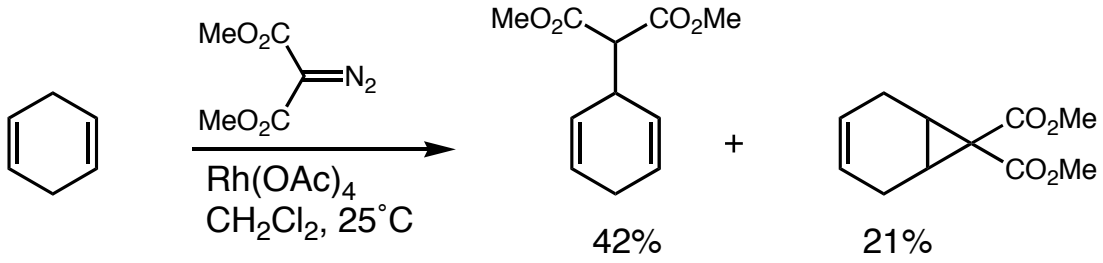
Acceptor/Acceptor-Substituted Carbenoids

Intermolecular C-H activation

■ C-H Activation of Functionalized Organic Substrates



catalyst	yield, A+B	ratio, A:B	ee B, %
$Rh_2(OAc)_4$	96	38:62	
Rh_2(*S*-PTPA)$_4$	86	24:76	24
Rh_2(*R*-BPN)$_4$	30	49:51	7

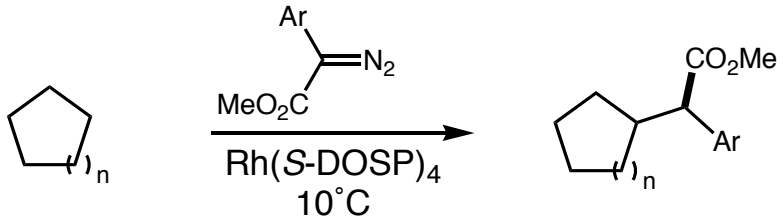


Müller, P.; Tohill, S. *Tetrahedron* **2000**, *56*, 1725.

Donor/Acceptor-Substituted Carbenoids

Intermolecular C-H activation

■ C-H Activation of cycloalkanes



n	Ar	yeild, %	ee, %[a]
1	C_6H_5	72	96(*R*)
1	*p*-ClC_6H_4	70	95(*R*)
2	C_6H_5	80	95(*R*)
2	*p*-BrC_6H_4	64	95(*R*)
2	*p*-ClC_6H_4	76	94(*R*)
2	*p*-$MeOC_6H_4$	23	88(*R*)
2	*p*-$C_3C_6H_4$	78	94(*R*)
2	*o*-ClC_6H_4	81	90(*R*)

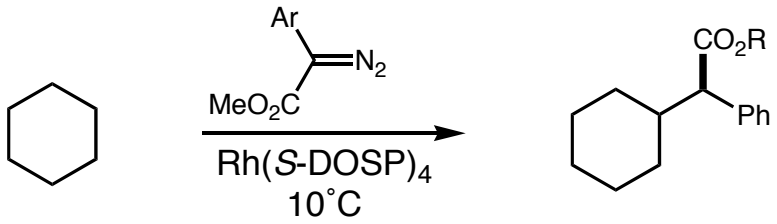
[a]Configurational assignment in parentheses.

Davies, H. M. L.; Hansen, T. *J. Am. Chem. Soc.* **1997**, *119*, 9075.

Donor/Acceptor-Substituted Carbenoids

Intermolecular C-H activation

■ C-H Activation of cycloalkanes



R	yeild, %	ee, %
CH_3	80	92
$CH(CH_3)_2$	39	86
$C(CH_3)_3$	45	20

We can see the delicate balance between steric and electronic effects in these systems

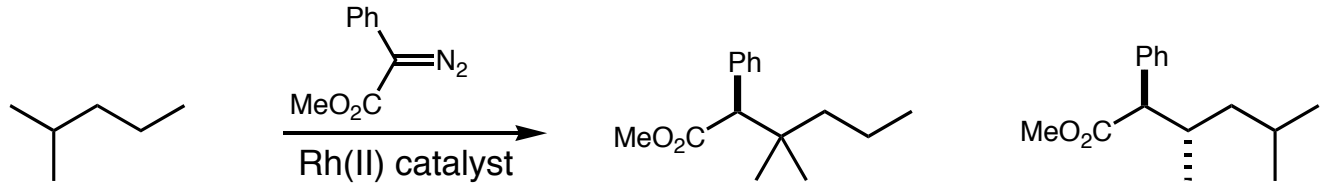
Davies, H. M. L.; Hansen, T.; Churchill, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 3063.

Donor/Acceptor-Substituted Carbenoids

Intermolecular C-H activation

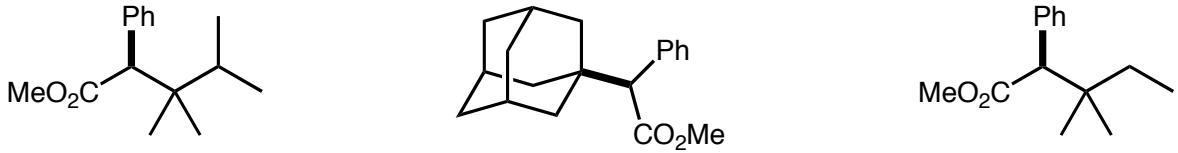
■ C-H Activation of alkanes

Relative reactivity of alkyl C-H bonds 3° ≈ 2° >> 1°



44% yield
26% ee

31% yield
86% ee



27% yield
66% ee

67% yield
90% ee

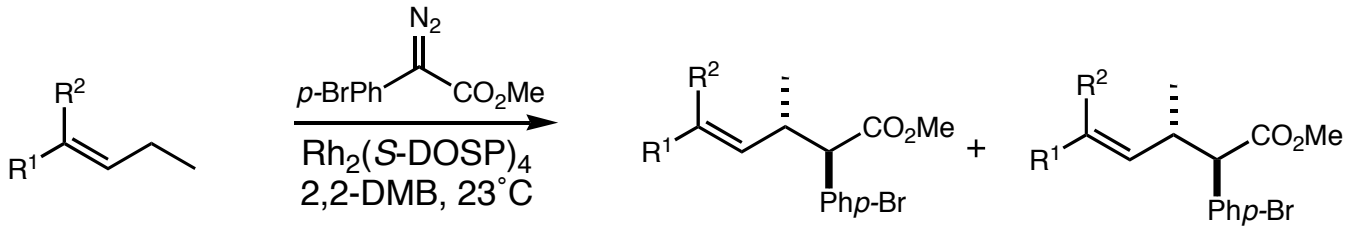
60% yield
68% ee

Davies, H. M. L.; Hansen, T.; Churchill, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 3063.

Donor/Acceptor-Substituted Carbenoids

Intermolecular C-H activation

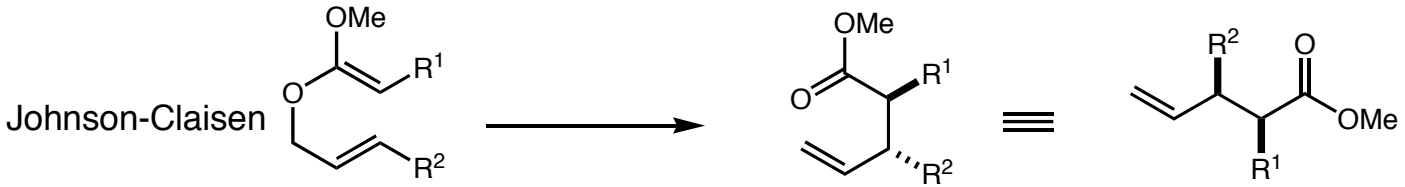
■ Allylic C-H Activation



R^1	R^2	yeild, %	de, %	ee A, %	ee B, %
C_2H_5	H	56	12	92	80
CH_3	CH_3	67	50	86	66
C_6H_5	C_6H_5	33	70	96	30

No cyclopropanation products were observed

γ,δ-Unsaturated esters with two stereocenters are analagous to typical products from Claisen rearrangements

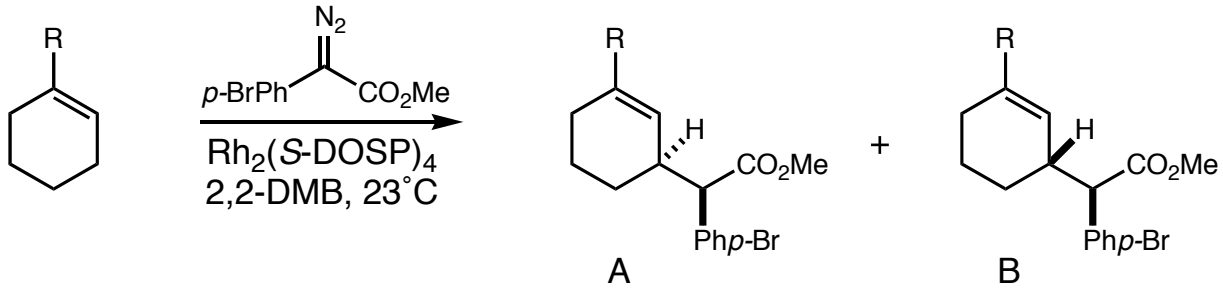


Davies, H. M. L.; Ren, P.; Jin, Q. *Org.Lett.* **2001**, *3*, 3587

Donor/Acceptor-Substituted Carbenoids

Intermolecular C-H activation

■ Allylic C-H Activation



Reactions are highly regioselective.

R^1	yeild, %	ratio, A:B	ee A, %	ee B, %
CH_3	53	17:83	94	98
C_2H_5[a]	46	25:75	90	94
$CH(CH_3)_2$	65	36:64	90	93
$C(CH_3)_3$	46	62:38	91	81
C_6H_5	65	23:77	90	95
Cl	58	65:35	96	91
TMS	48	70:30	88	–
TBDPS	64	94:6	95	–

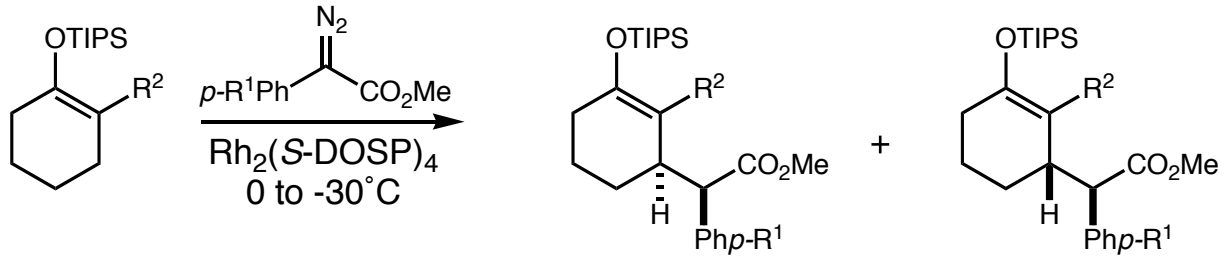
[a] Also isolated 2% yield from insertion into pendant ethyl group.

Davies, H. M. L.; Ren, P.; Jin, Q. *Org.Lett.* **2001**, *3*, 3587

Donor/Acceptor-Substituted Carbenoids

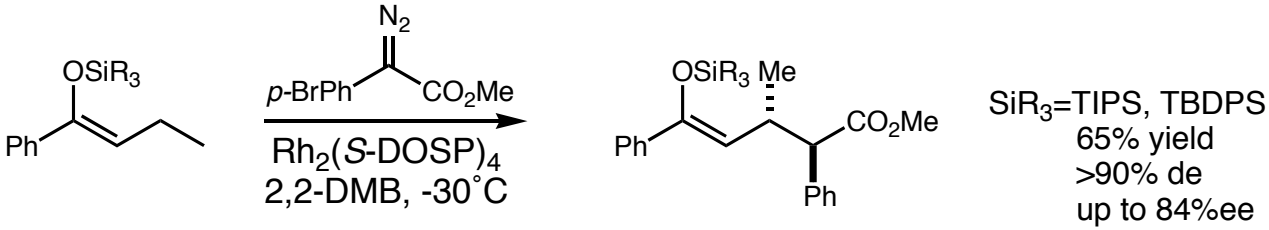
Intermolecular C-H activation

■ Allylic C-H Activation of Cyclic and Acyclic Silyl Enol Ethers



R_1 = H, Br
R_2 = H, CH_3

Yields from86–90% and up to 96%ee



SiR_3=TIPS, TBDPS
65% yield
>90% de
up to 84%ee

Products are comparable to those obtained from asymmetric Michael additions

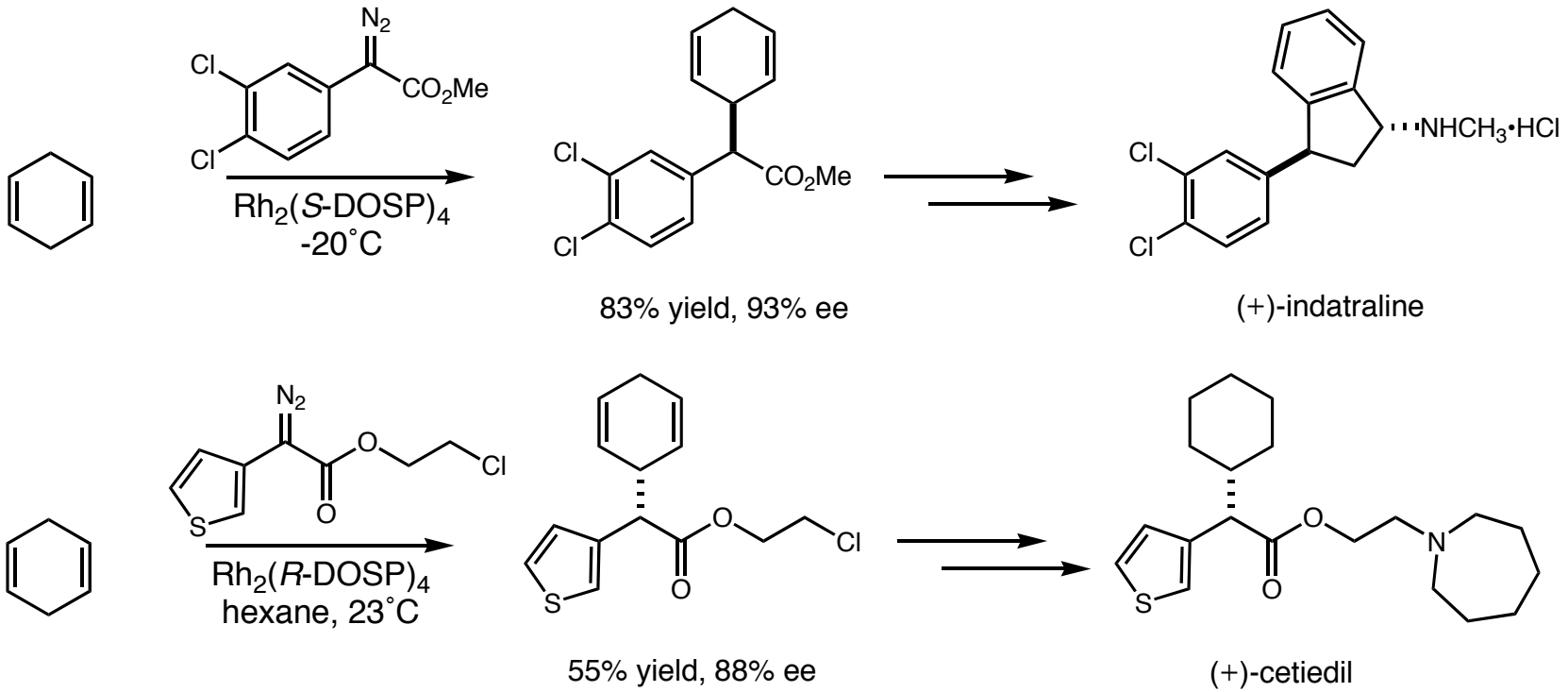
But can these reactions be applied to the synthesis of useful targets?

Davies, H. M. L.; Ren, P. *J. Am. Chem. Soc.* **2001**, *123*, 2070.

Donor/Acceptor-Substituted Carbenoids

Intermolecular C-H activation

■ Application Toward Pharmaceutically Relevant Targets



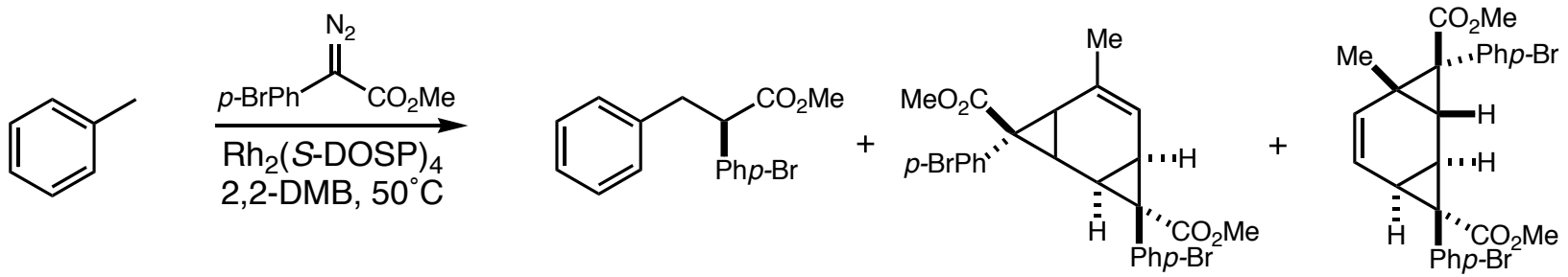
Davies, H. M. L.; Gregg, T. M. *Tetrahedron Lett.* **2002**, *43*, 4951.

Davies, H. M. L.; Walji, A. M. Townsend, R. J. *Tetrahedron Lett.* **2002**, *43*, 4981.

Donor/Acceptor-Substituted Carbenoids

Intermolecular C-H activation

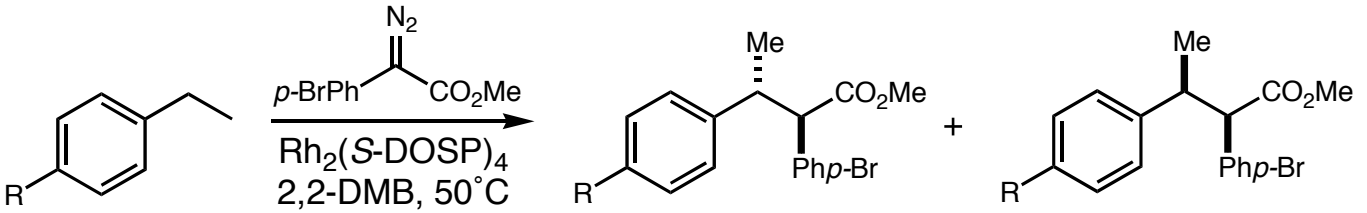
■ Benzylic C-H Activation



A B C

50% combined yield
A:(B+C) = 28:72

Complex mixtures of products can be avoid using substituted rings or by C-H activation of secondary benzylic sites.



R=H, alkyl, alkoxy, halogen, Acetoxy, Acetate

50-86% yield
up to 5.25:1 d.r.
up to 89% ee

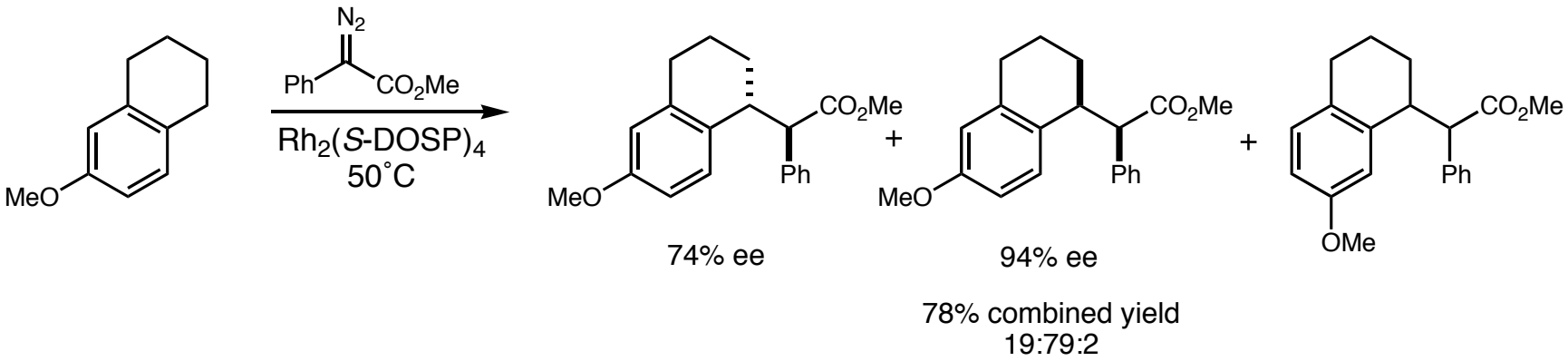
No cyclopropanation products

Davies, H. M. L.; Jin, Q.; Ren, P.; Kovalevsky, A. Y. *J. Org. Chem.* **2002**, *67*, 4165.

Donor/Acceptor-Substituted Carbenoids

Intermolecular C-H activation

■ Benzylic C-H Activation



78% combined yield
19:79:2

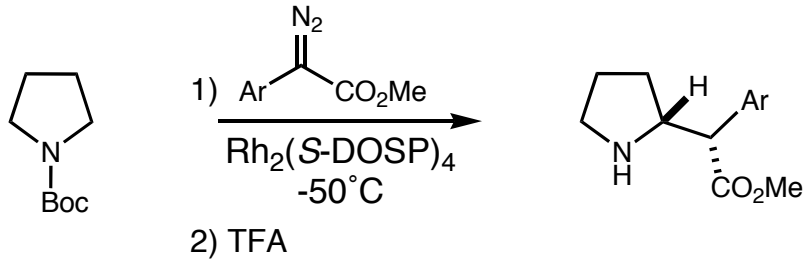
An electron donating group helps stabilize the positive charge that builds-up in the transition state at the site of carbene insertion

Davies, H. M. L.; Jin, Q.; Ren, P.; Kovalevsky, A. Y. *J. Org. Chem.* **2002**, *67*, 4165.

Donor/Acceptor-Substituted Carbenoids

Intermolecular C-H activation

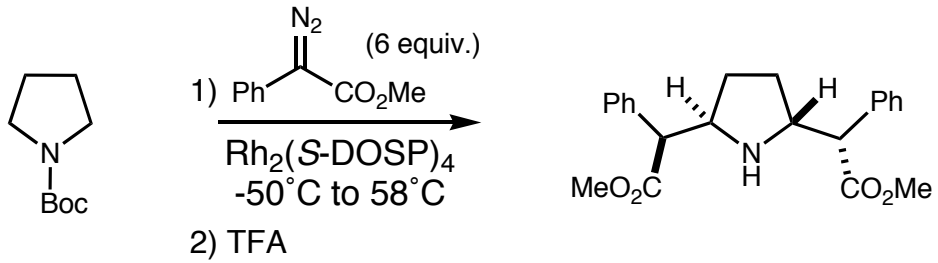
■ C-H Activation α to Nitrogen



Route to β-amino acids.
Products comparable to Mannich reaction products.

Ar	yeild, %	de, %	ee, %
C_6H_5	72	92	94
p-ClC_6H_4	70	94	94
p-MeC_6H_4	67	93	93
2-naphthyl	49	93	93
3-thiophenyl[a]	64	91	67

[a] Reaction conducted at 23˚C



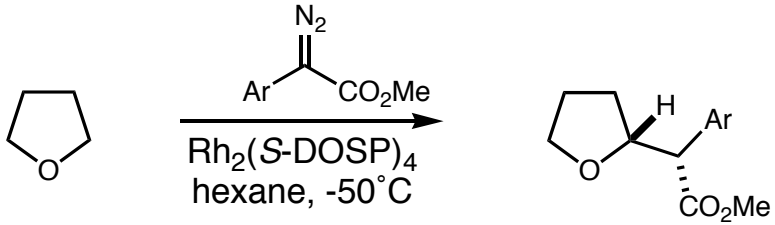
Davies, H. M. L.; Walji, A. M. Townsend, R. J. *Tetrahedron Lett.* **2002**, *43*, 4981.

Davies, H. M. L.; Hansen, T.; Hopper, D. W.; Panaro, S. A. *J. Am. Chem. Soc.* **1999**, *121*, 6509.

Donor/Acceptor-Substituted Carbenoids

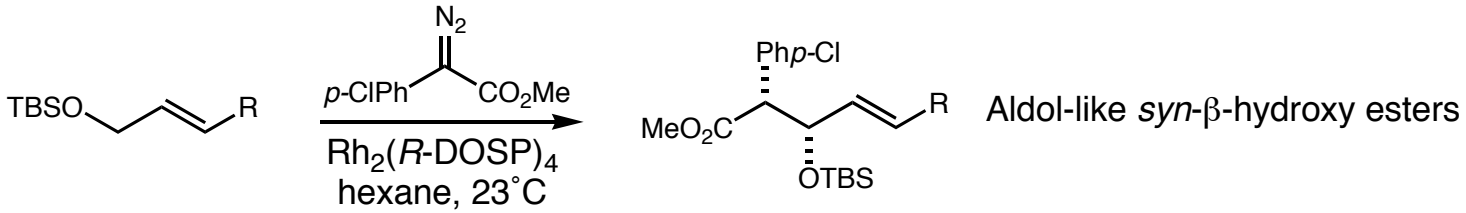
Intermolecular C-H activation

■ C-H Activation α to Oxygen



Ar	yeild, %	de, %	ee, %
p-ClC_6H_4	74	41	98
p-MeC_6H_4	60	60	97
p-$MeOC_6H_4$	56	55	96

■ C-H Activation α to Oxygen



Aldol-like *syn*-β-hydroxy esters

R= H, alkyl, vinyl, aryl

35–70% yield
up to 98% de, 90%ee

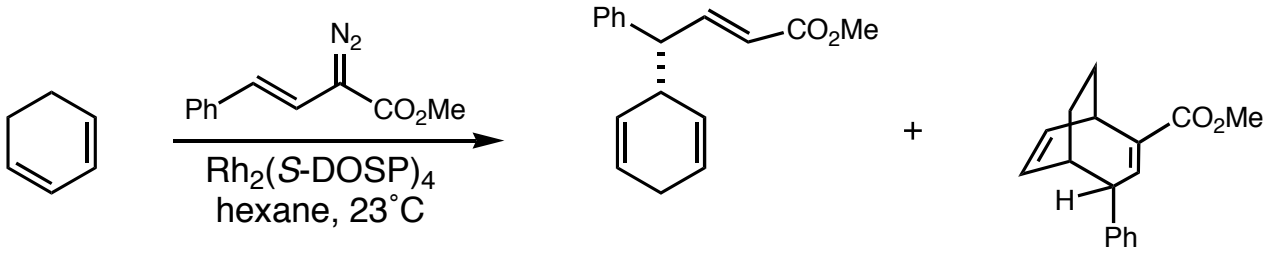
Davies, H. M. L.; Hansen, T.; Churchill, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 3063.

Davies, H. M. L.; Hansen, T. *J. Am. Chem. Soc.* **1997**, *119*, 9075.

Donor/Acceptor-Substituted Carbenoids

Intermolecular C-H activation

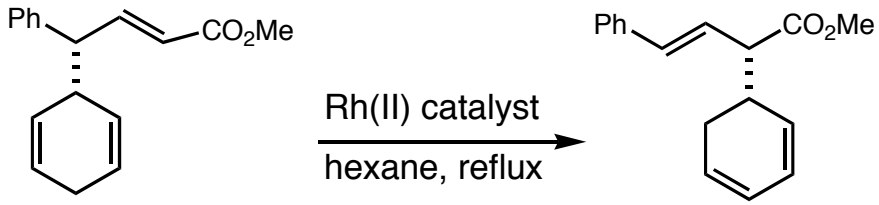
■ Carbenoids Derived from Vinyldiazoacetates



63% yield, 98% ee

12% yield

This reaction gave an unexpected major product in addition to a product arising from a well known cyclopropanation/Cope pathway. Athough it appears to come from C-H insertion followed by a Cope rearrangement, this is not the case.



The 1,3 diene undergoes a retro-Cope to the thermodynamic product.

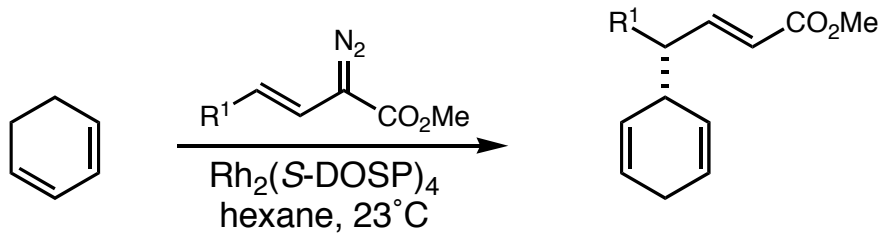
Proposed mechanisms include a one-step C-H activation/Cope or the vinylcarbenoid may react as a 2π-system analgous to an ene reaction.

Davies, H. M. L.; Stafford, D. G.; Hansen, T. *Org. Lett.* **1999**, *1*, 233.

Donor/Acceptor-Substituted Carbenoids

Intermolecular C-H activation

■ The C-H Insertion/Cope Tolerates Various Substituents on the Vinyldiazoacetate



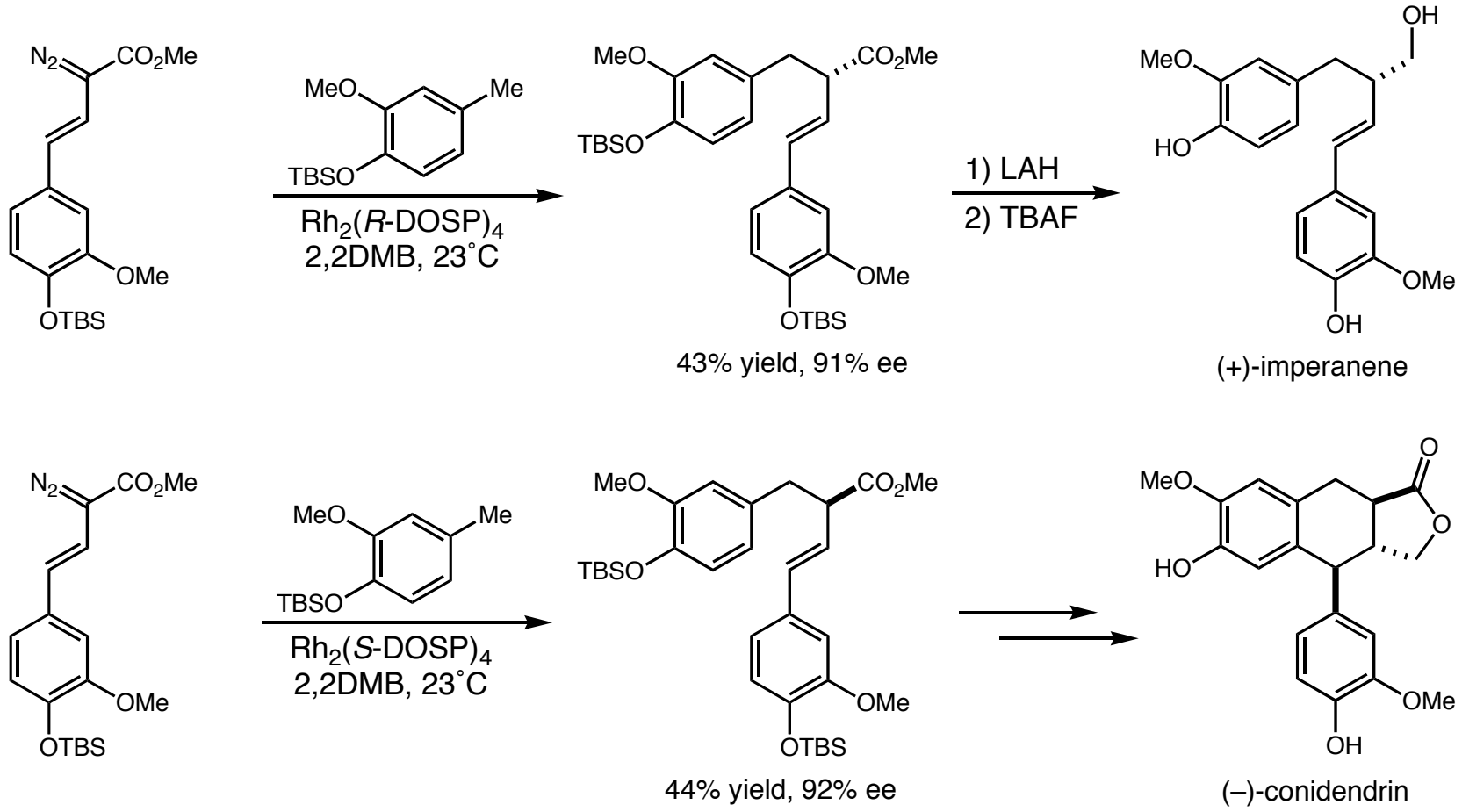
R	yeild, %	ee, %
C_6H_5	63	96
p -$MeOC_6H_4$	58	99
3,4-$Cl_2C_6H_3$	59	99
2-naphthyl	50	99
o -$MeOC_6H_4$	17	86
1-naphthyl	22	84
(*E*)-$CH{=}CHC_6H_5$	60	99
–$(CH_2)_4$–	73	97

Davies, H. M. L.; Stafford, D. G.; Hansen, T. *Org. Lett.* **1999**, *1*, 233.

Donor/Acceptor-Substituted Carbenoids

Intermolecular C-H activation

■ C-H Insertion/Cope Utilized in the Synthesis of (+)-Imperaene and (–)-Conidendrin

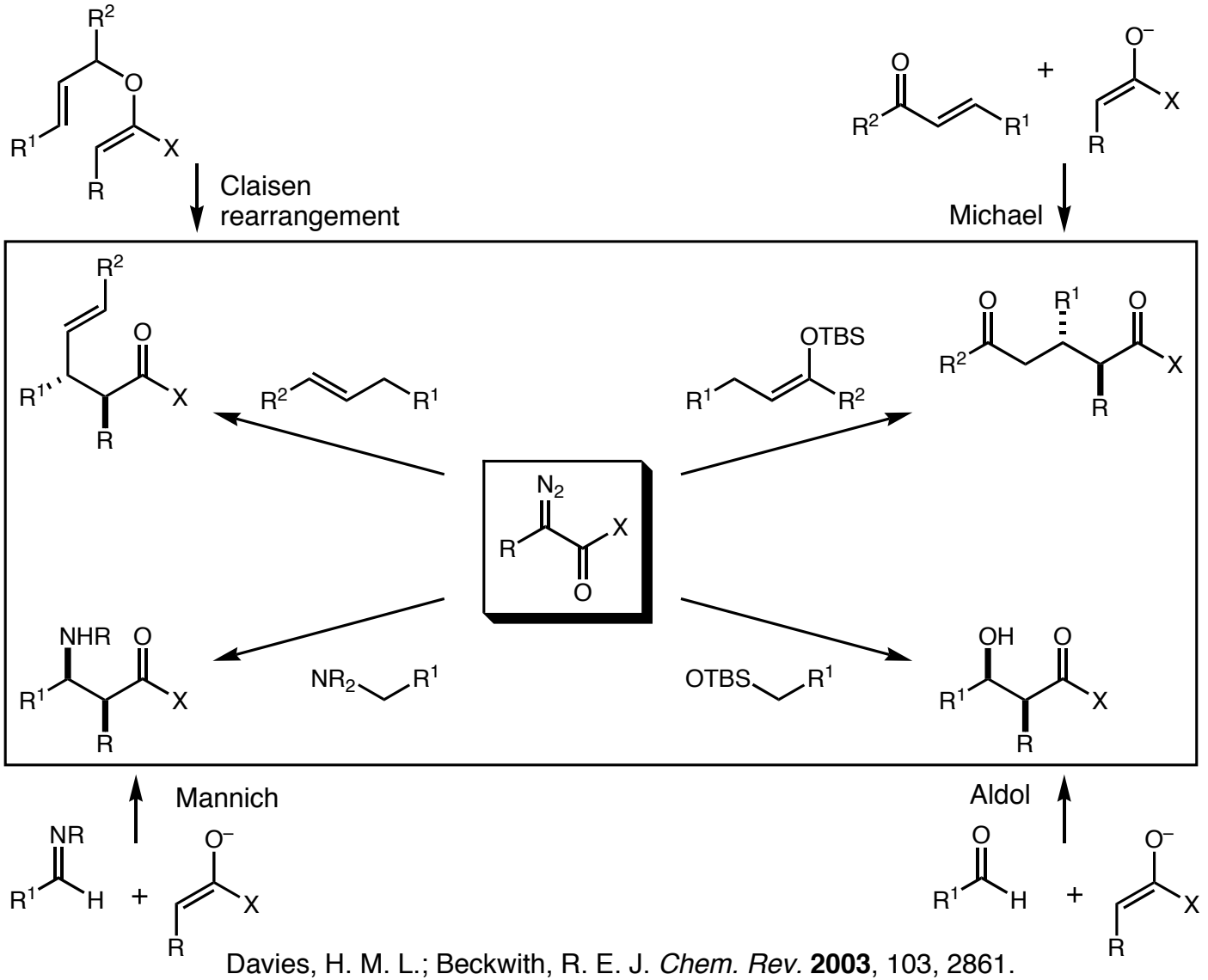


Davies, H. M. L.; Jin, Q. *Tetrahedron: Asymmetry* **2003**, *14*, 941.

Donor/Acceptor-Substituted Carbenoids

Intermolecular C-H activation

■ Synthons Accesible Through Asymmetric C-H Activation

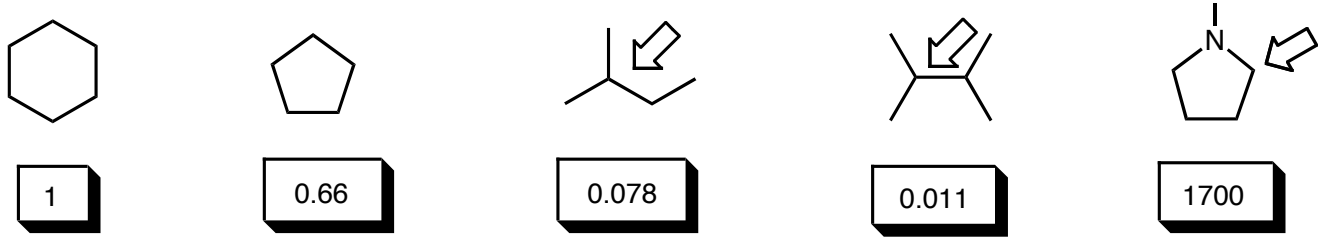


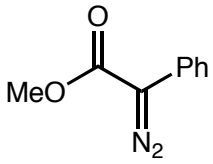
Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, 103, 2861.

Donor/Acceptor-Substituted Carbenoids

Intermolecular C-H activation

■ Relative Reactivity



Reactions with  and Rh_2(*S*-DOSP)$_4$.

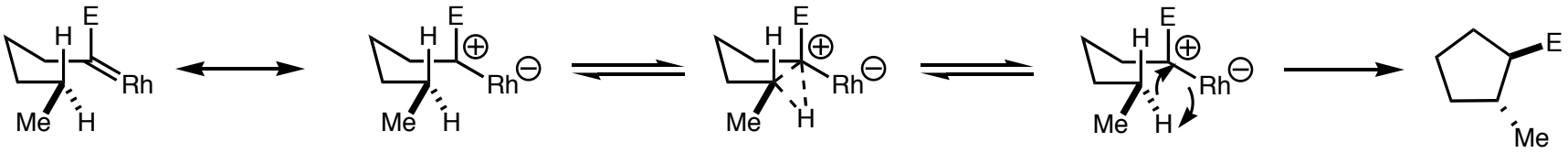
Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, 103, 2861.

Catalytic Asymmetric C-H Activation

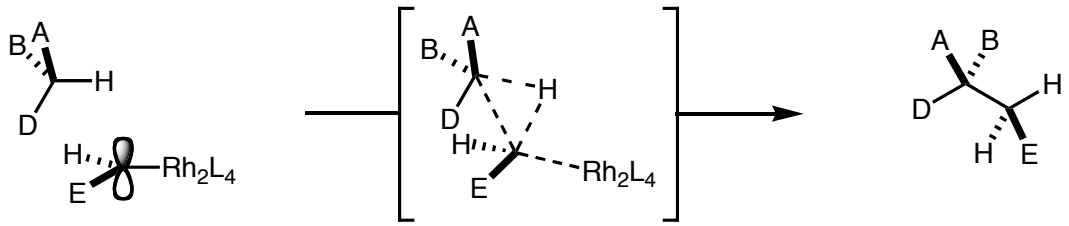
Mechanistic Considerations

■ The Mechanism is not Well Understood and a Source of Dispute

Taber: four-centered



Doyle: three-centered concerted



Taber, D. F.; You, K. K.; Rheingold, A. L. *J. Am. Chem. Soc.* **1996**, *118*, 547.

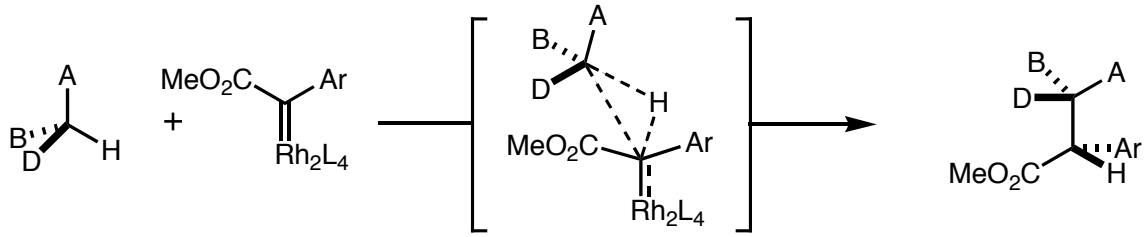
Doyle, M.P.; Westrum, L.J.; Wolthuis, W.N.E.; See, M.M.; Boone, W.P.; Bagheri, V.; Pearson, M.M. *J. Am. Chem. Soc.* **1993**, *115*, 958.

Catalytic Asymmetric C-H Activation

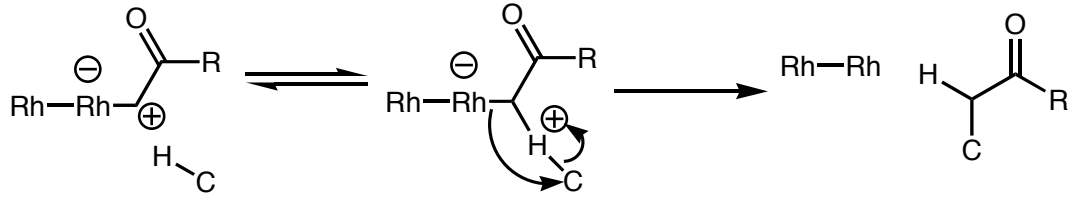
Mechanistic Considerations

■ The Mechanism is not Well Understood and a Source of Dispute

Davies: three-centered concerted yet nonsynchronous process



Pirrung: stepwise approach



σ complex

Davies, H.M.L.; Hansen, T.; Churchill, M.R. *J. Am. Chem. Soc.* **2000**, *122*, 3063.

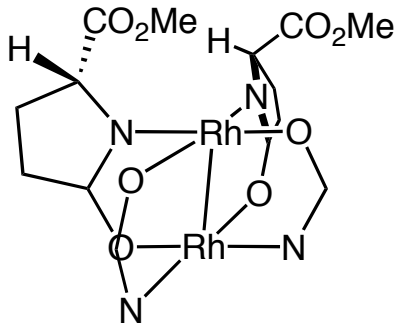
Pirrung, M.C.; Morehead Jr, A.T.; *J. Am. Chem. Soc.* **1994**, *116*, 8991.

Catalytic Asymmetric C-H Activation

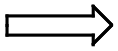
Mechanistic Considerations

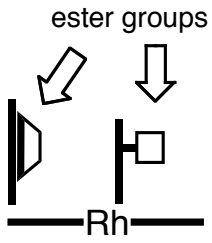
■ Stereochemical Rationale for the Catalysts that Give the Highest ee's.

These simplified models of the catalyst systems help rationalize stereoselectivity.

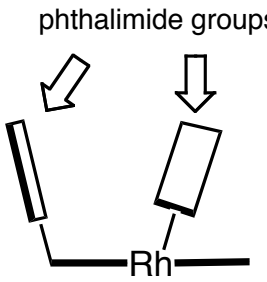


$Rh_2(5R\text{-MEPY})_4$

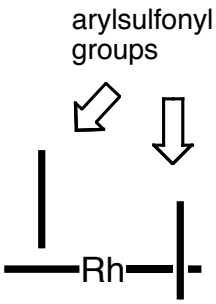




Doyle's catalysts



Hashimoto's catalysts



Davies/McKervey's
prolinate catalysts

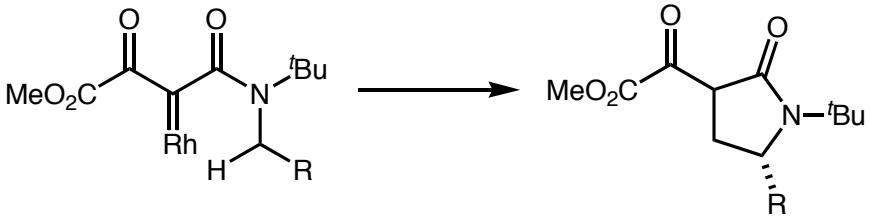
Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, 103, 2861.

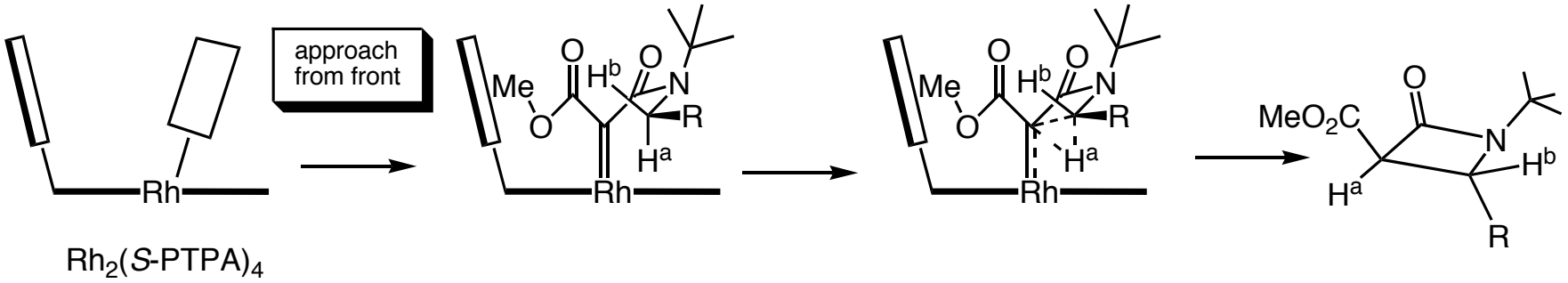
Catalytic Asymmetric C-H Activation

Mechanistic Considerations

■ Stereochemical Rationale

β-Lactam formation with Hashimoto's catalyst.





Rh_2(*S*-PTPA)$_4$

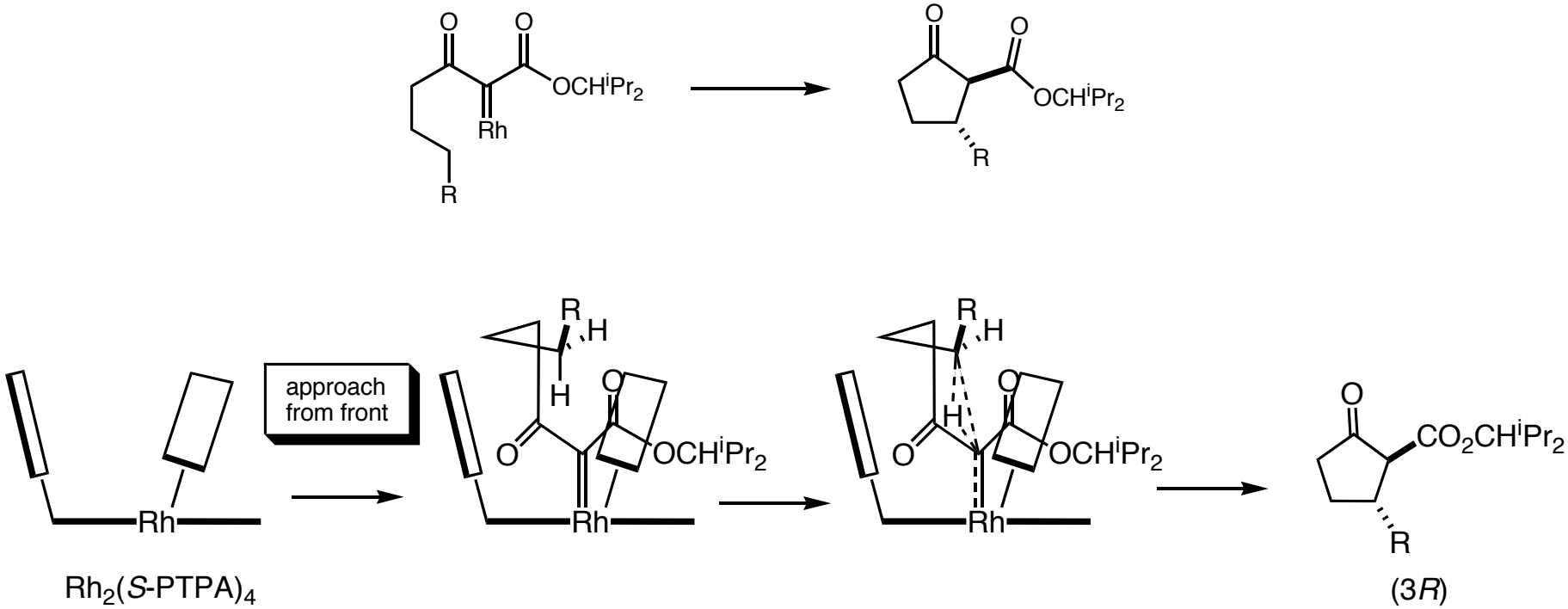
Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, 103, 2861.

Catalytic Asymmetric C-H Activation

Mechanistic Considerations

■ Stereochemical Rationale

Cyclopentanone formation with Hashimoto's catalyst.



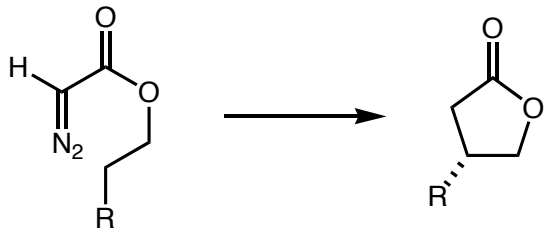
Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, 103, 2861.

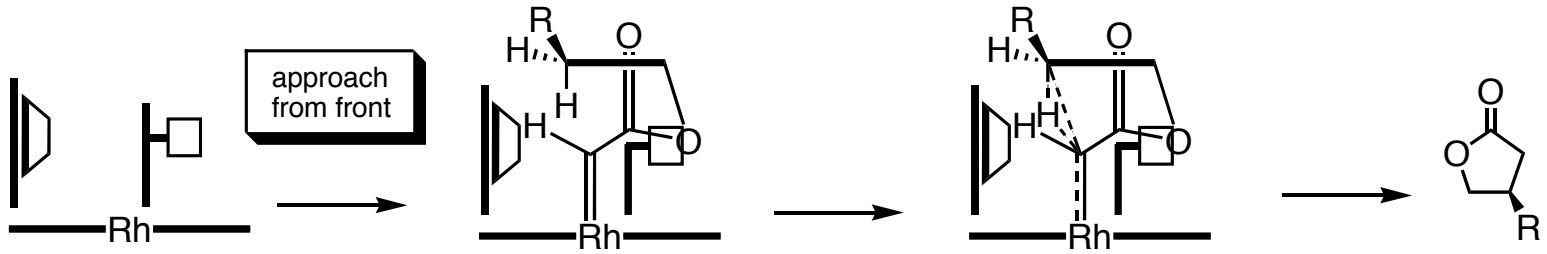
Catalytic Asymmetric C-H Activation

Mechanistic Considerations

■ Stereochemical Rationale

Asymmetric induction with Doyle's catalyst.





$Rh_2(5R\text{-MEPY})_4$

(4*R*)

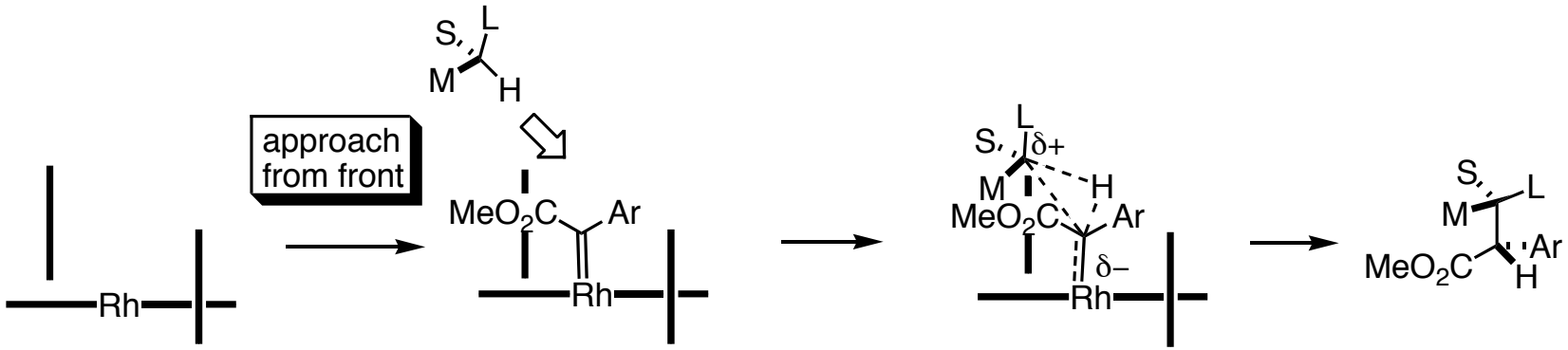
Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, 103, 2861.

Catalytic Asymmetric C-H Activation

Mechanistic Considerations

■ Stereochemical Rationale

Asymmetric induction with dirhodium tetraprolinates.



Rh_2(*S*-DOSP)$_4$

Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, 103, 2861.