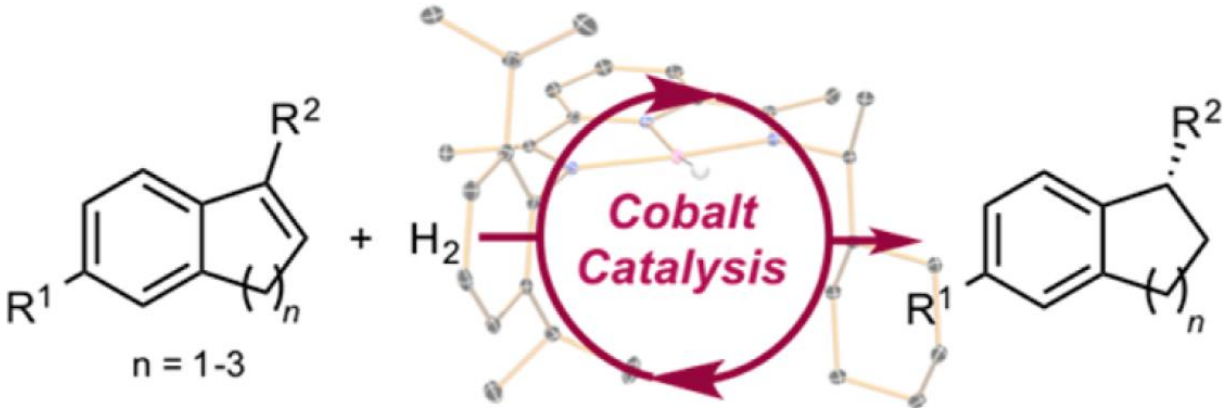
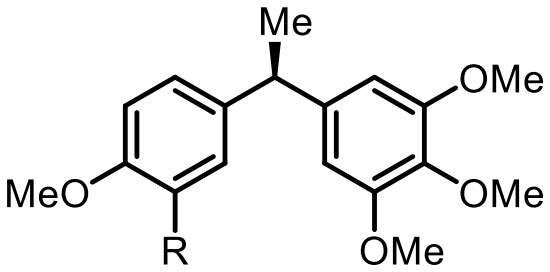
Cobalt-Catalyzed Enantioselective Hydrogenation of Minimally Functionalized Alkenes

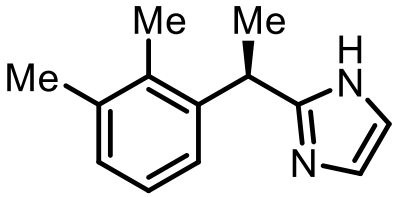
M. R. Friedfeld, M. Shevlin, G. W. Margulieux, L.-C. Campeau & P. J. Chirik, *JACS*, ASAP DOI : 10.1021/JACS5b10148



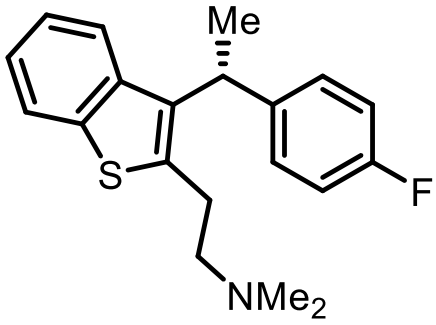
Bioactive molecules



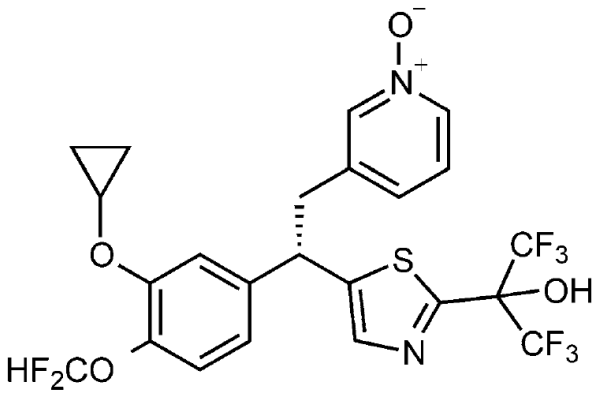
R = OH, anti lung cancer reagent
R = H, anti viral agent

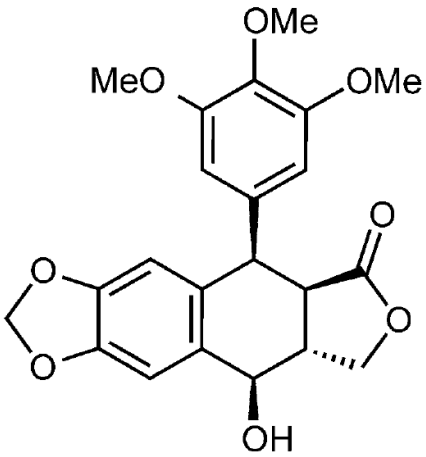


pesticide

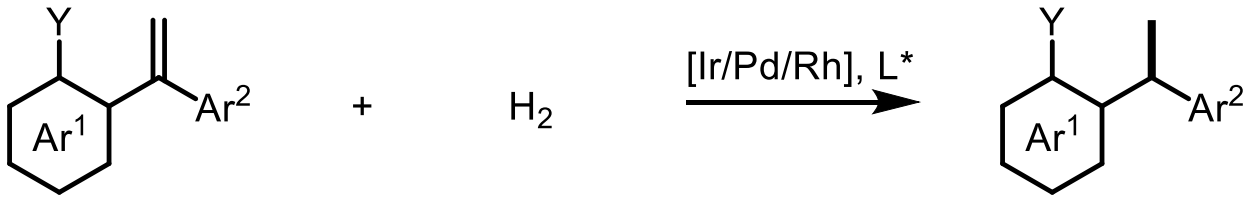


anti-insomnia agent



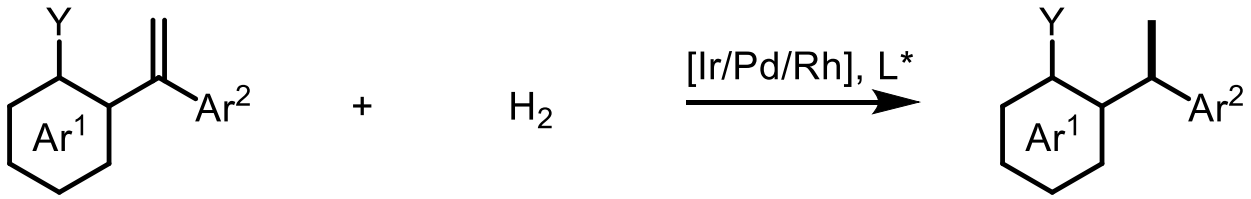


Enantioselective hydrogenation using metal complexes

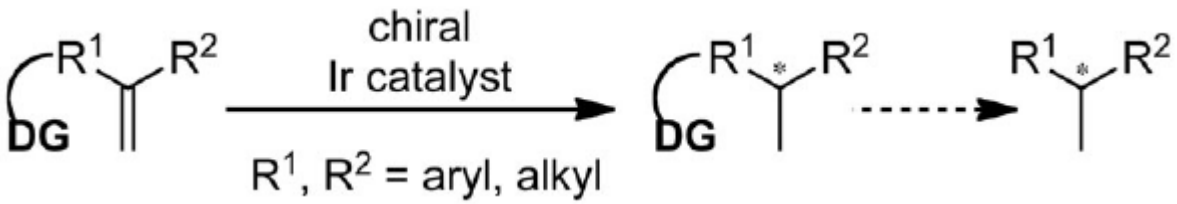


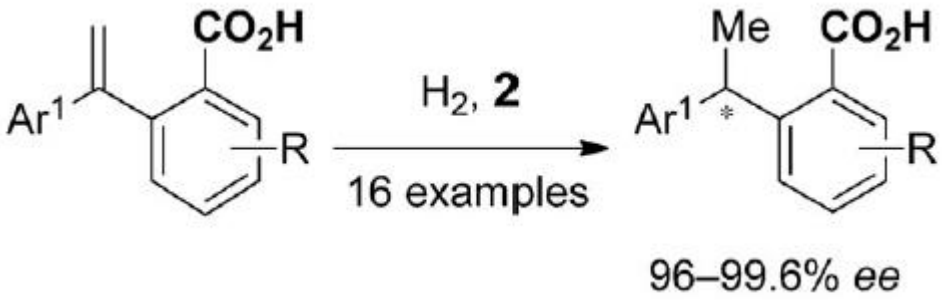
Y = H or DG (Directing group)

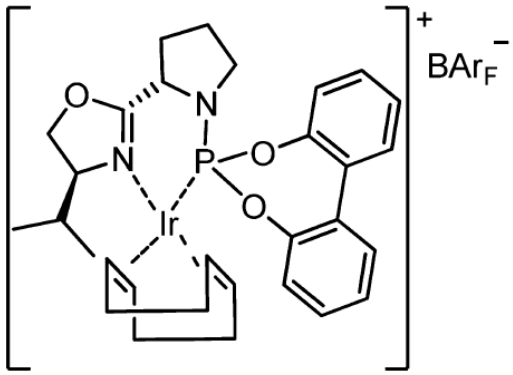
Enantioselective hydrogenation using metal complexes



Y = H or DG (Directing group)



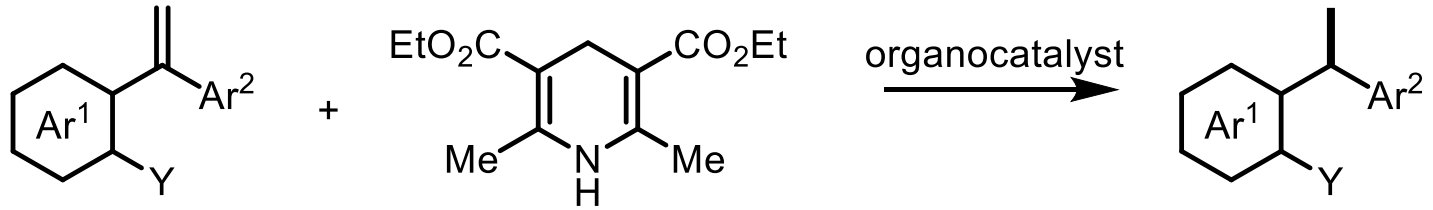




[IrCOD**PhosPrOx**]BAr_F

Angew. Chem. Int. Ed., **2013**, 8795

Enantioselective hydrogenation using organocatalyst

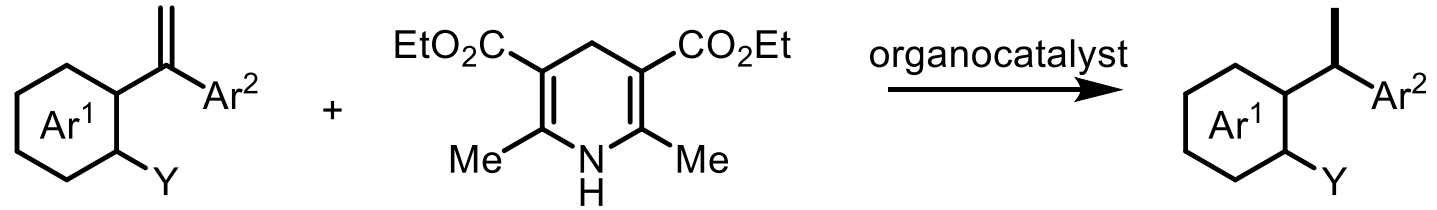


Y = H or DG

Hanzche Ester

JACS, **2015**, 383

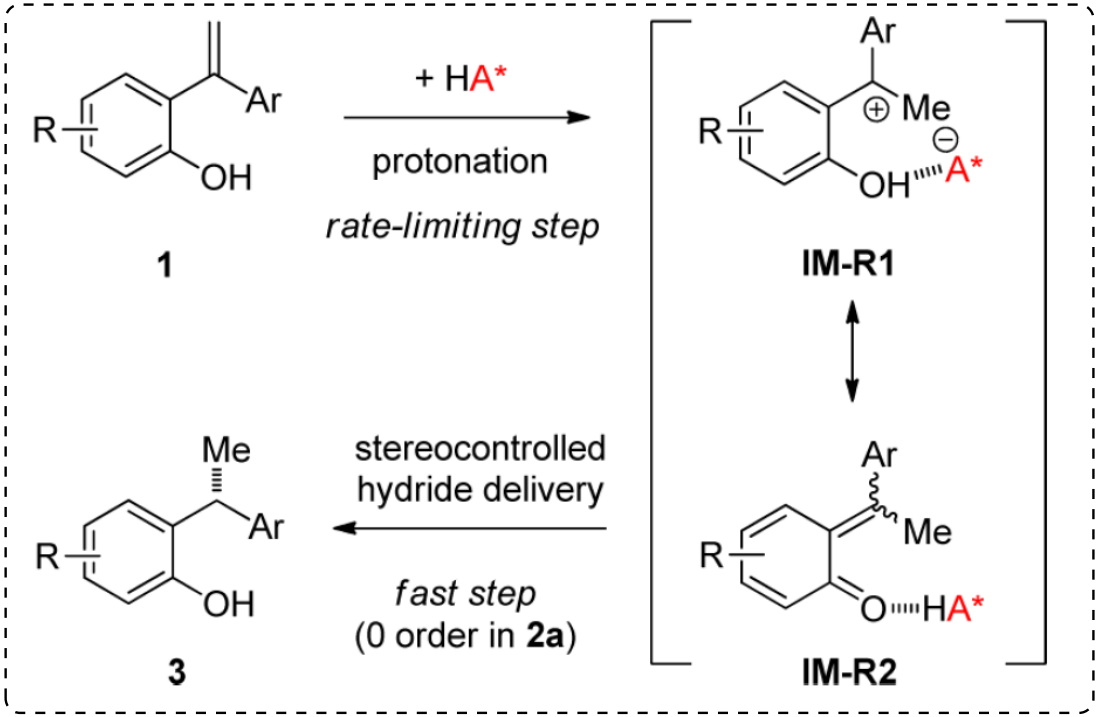
Enantioselective hydrogenation using organocatalyst

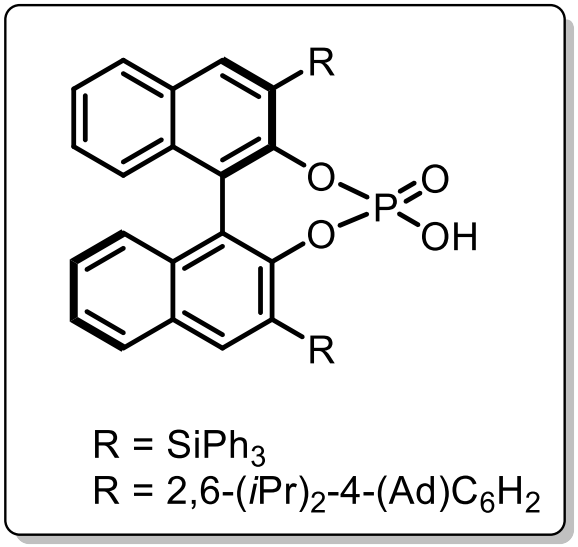


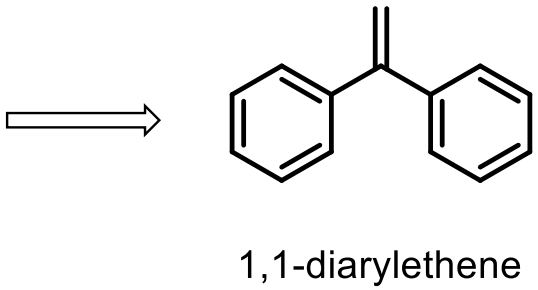
Y = H or DG

Hanzche Ester

JACS, **2015**, 383



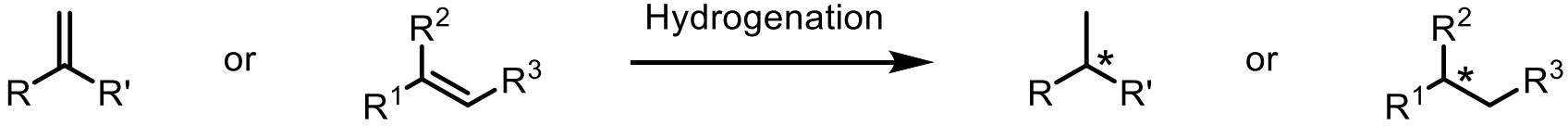




1,1-diarylethene

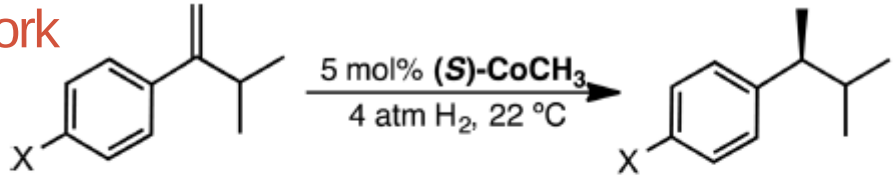
- Use of precious metal catalysts or organocatalysts
- Specific catalyst-substrate combinations
- Substrate must contain coordinating directing group

Enantioselective hydrogenation of minimally functionalized alkenes



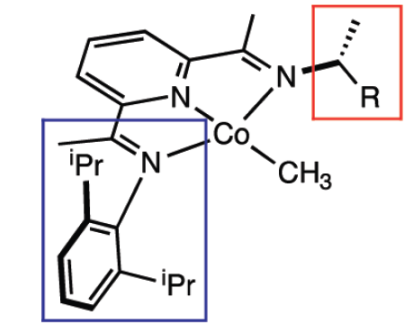
- Lack of coordinating functionality
- Stereodirecting elements

Previous work



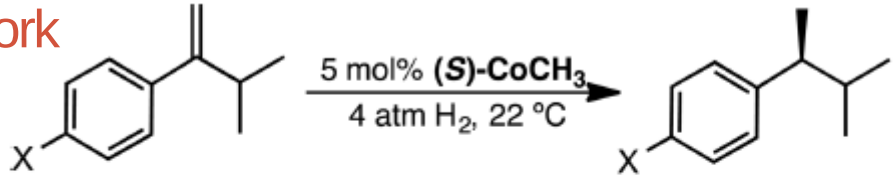
JACS, **2012**, 4561

X = H	87% y	90% *ee* (*S*)
= NMe_2	>98% y	96% *ee* (*S*)
= OMe	>98% y	94% *ee* (*S*)
= CH_3	>98% y	90% *ee* (*S*)
= F	>98% y	78% *ee* (*S*)



1-Me: R = Cy
2-Me: R = ^{t}Bu

Previous work



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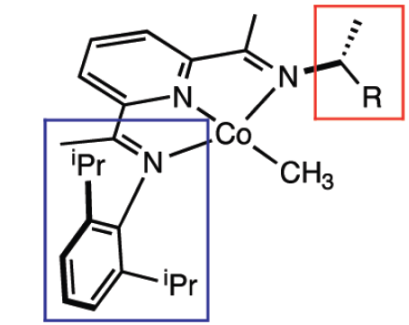
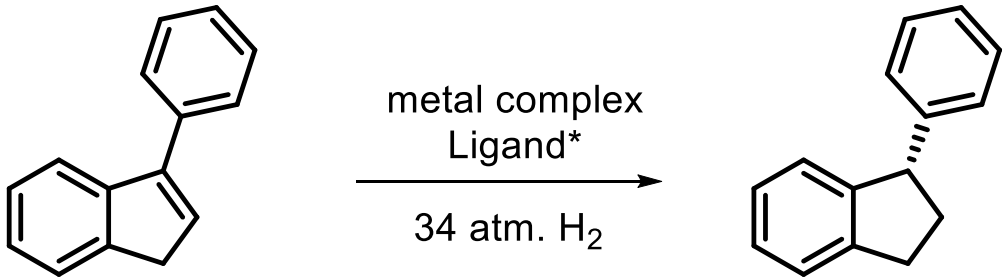


Chiral Element

1-Me: R = Cy
2-Me: R = ^{t}Bu

Protecting Element

This work

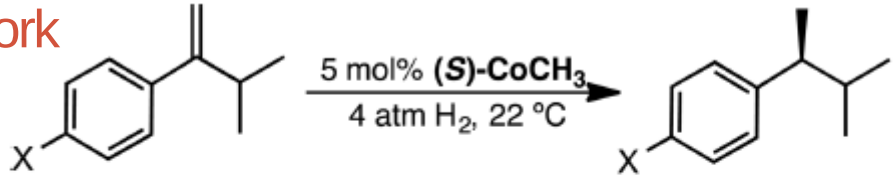


(methylallyl)$_2$-RuCOD **[(NBD)$_2$Rh][BF$_4$]** **[(COD)$_2$Ir][BArF$_4$]** **(S)-CoCH$_3$**

no metal-ligand combinations identified
to produce alkane in >50 % *ee*

94% *ee*

Previous work



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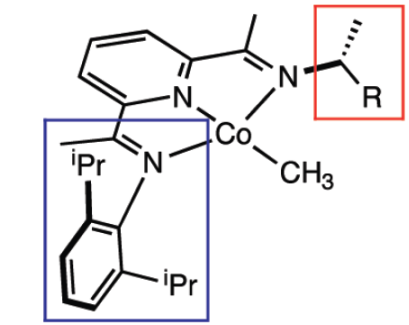
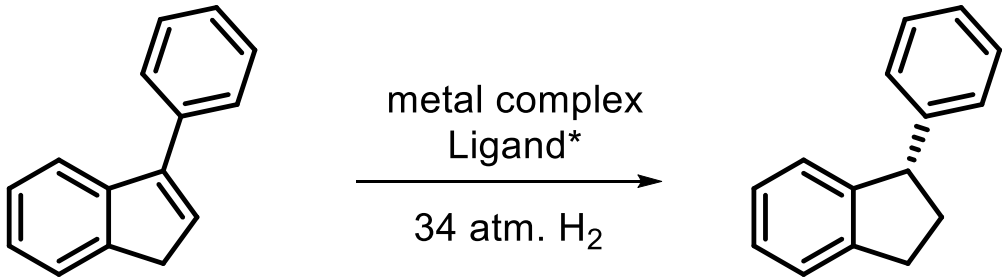
JACS, **2012**, 4561



This work



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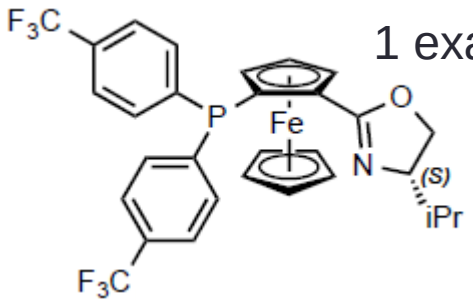
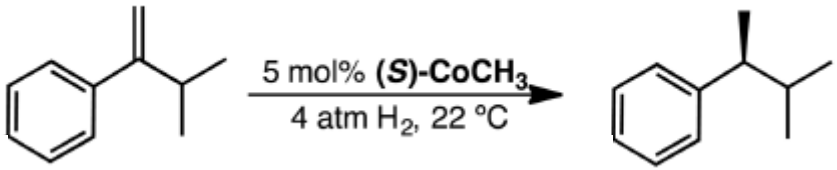
full conv.
63 < % *ee* < 90

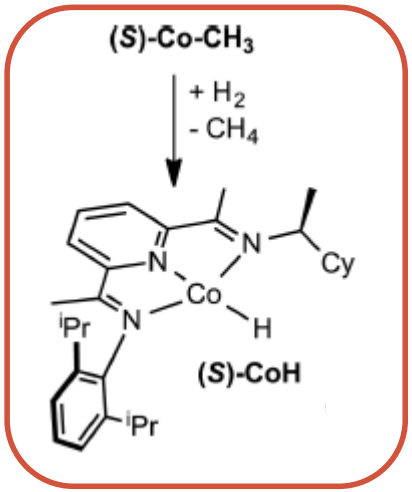
94% *ee*



1 example: 98% *ee*

Monitored reaction by 1H NMR





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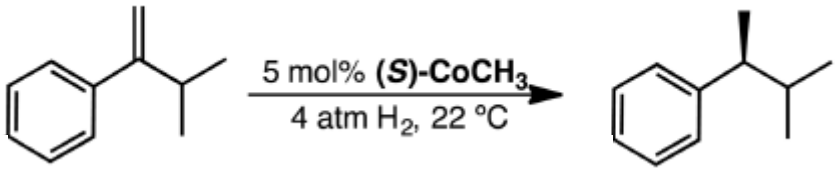

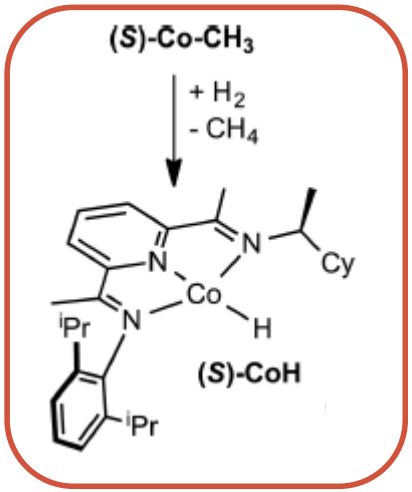

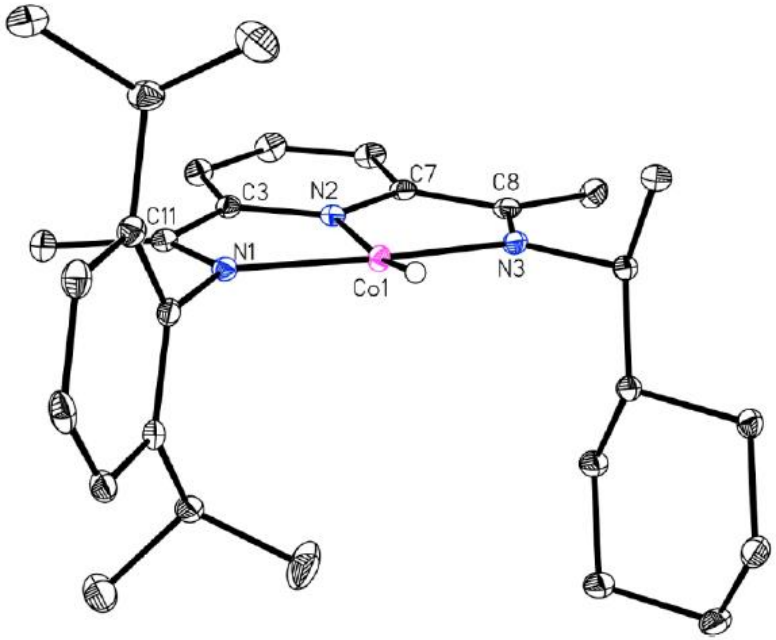

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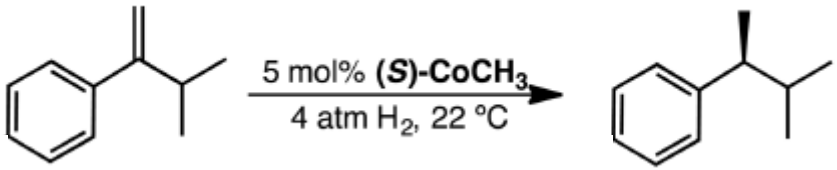
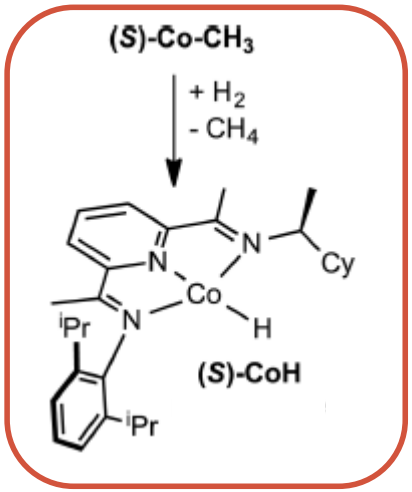
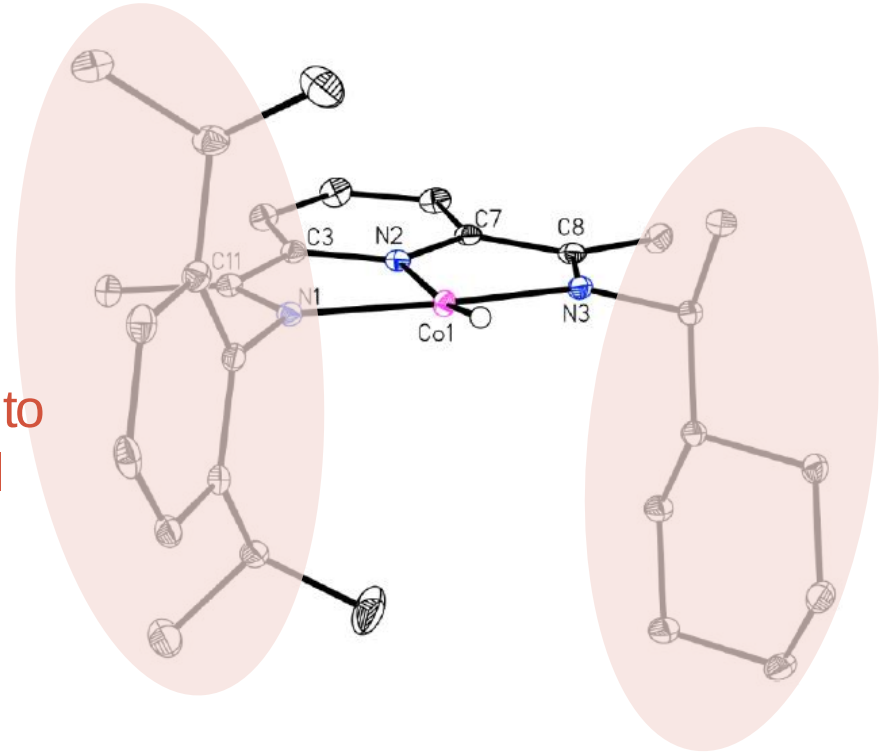


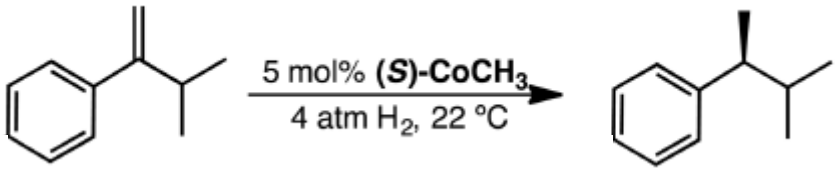


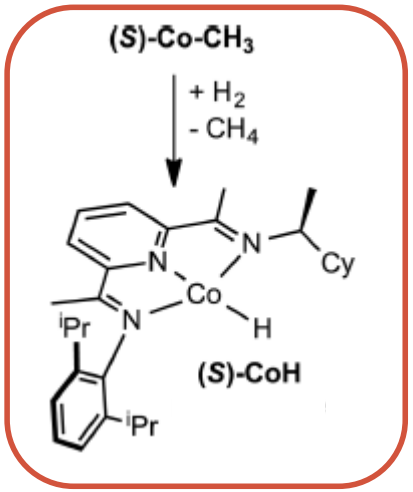


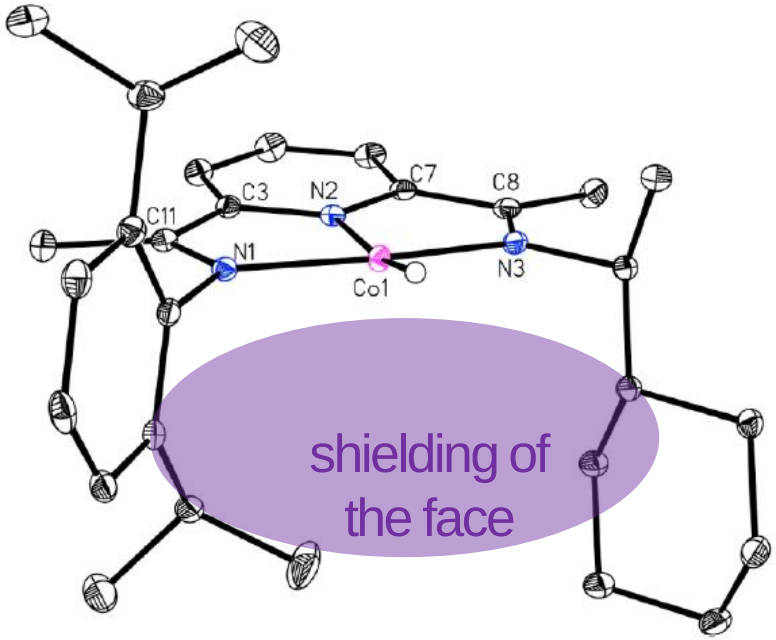
orthogonal to the metal

orthogonal to the metal

Monitored reaction by 1H NMR



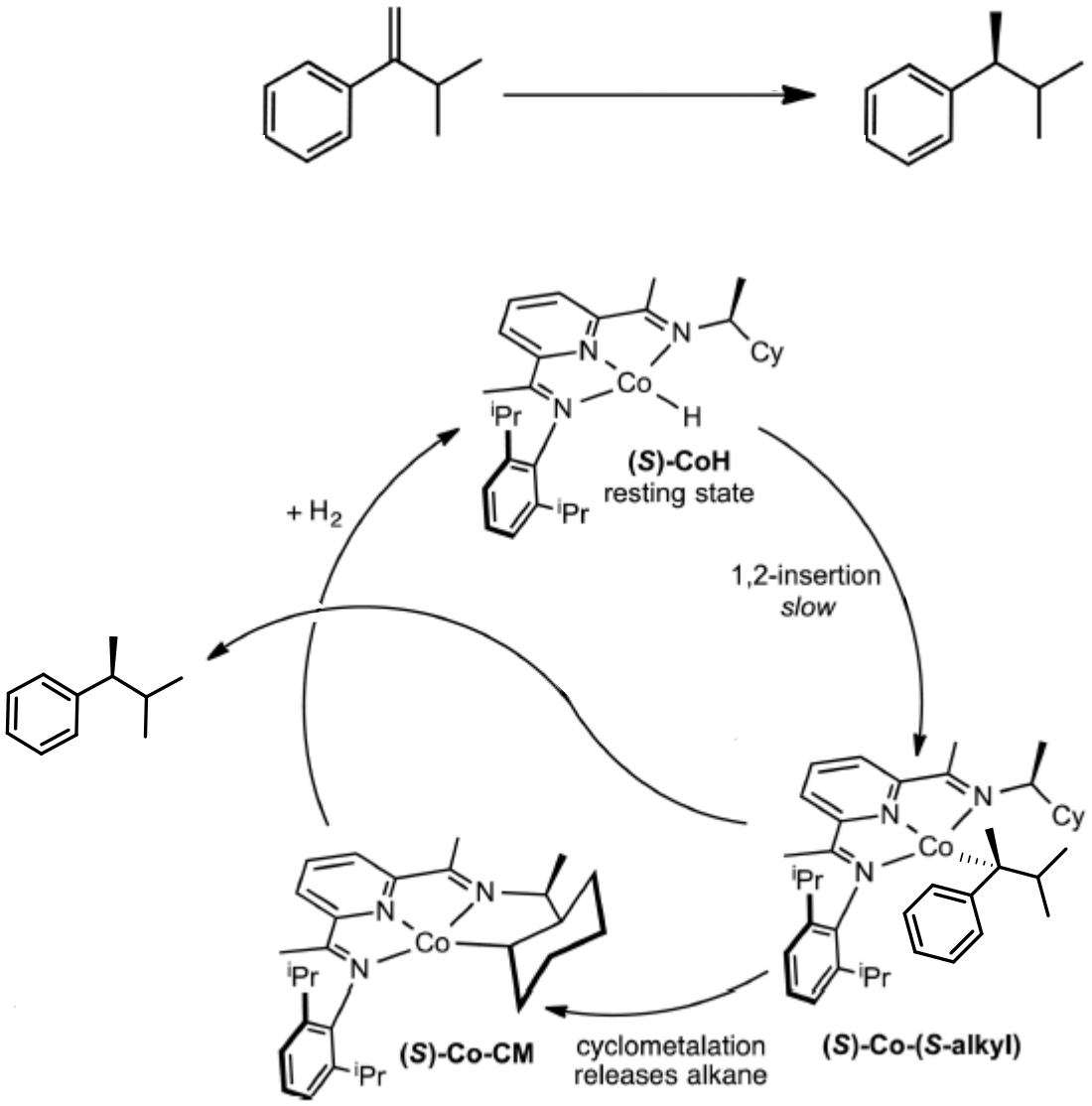


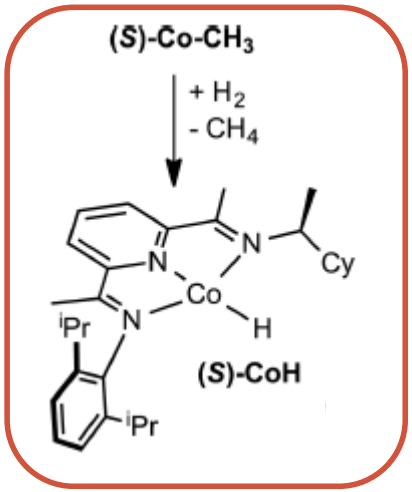


orthogonal to the metal

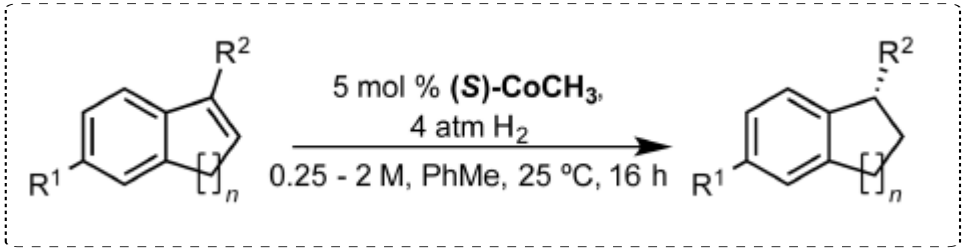
orthogonal to the metal

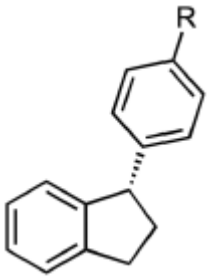
Monitored reaction by 1H NMR



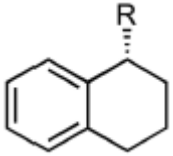


not observed

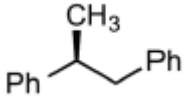


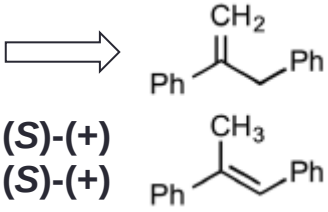


89-98% yield, 94-97% *ee* (*S*)-(-)
R = H, OCH_3, $N(CH_3)_2$, Cl, F

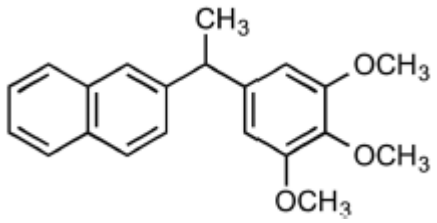


94-96% yield, 98% *ee* (*S*)-(+)
R = Ph, p-OCH_3-Ph

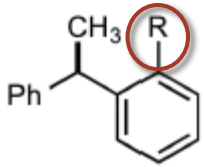




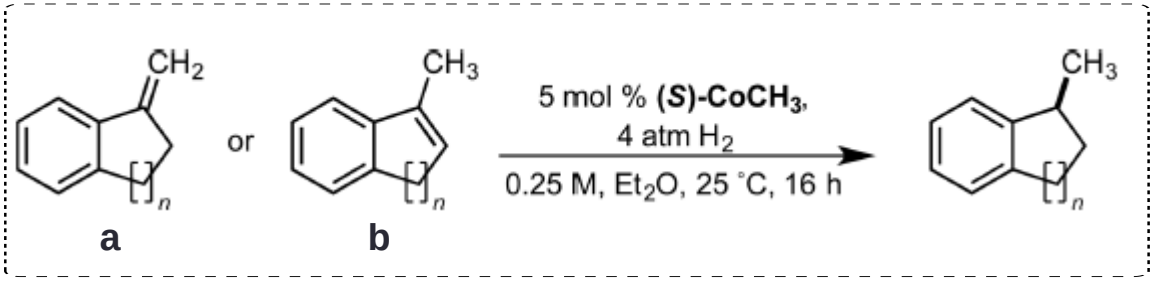
92% yield, 66% *ee* (*S*)-(+)
93% yield, 56% *ee* (*S*)-(+)

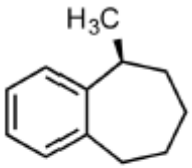


>95% yield, <5% *ee*
No influence with meta substitution

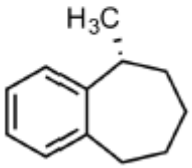


90-95% yield, 36-77% *ee* (+)
R = CH_3, Cl, Et, OCH_3

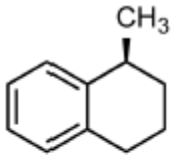




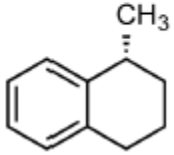
(*S*)-16 97%, 85% (S)-(–)



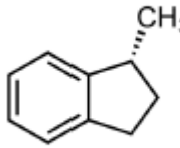
(*R*)-16 95%, 89% (*R*)-(+)



(*S*)-18 87%, 53% (*S*)-(+)

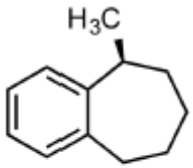


(*R*)-18 88%, 95% (*R*)-(–)
96%, 93% (*R*)-(–)[b]

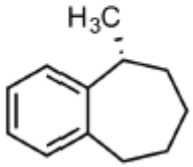


(*R*)-20 84%, 74% (*R*)-(+)

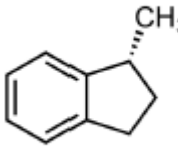
(*R*)-20 88%, 89% (*R*)-(+)[c]



(*S*)-16 97%, 85% (S)-(–)



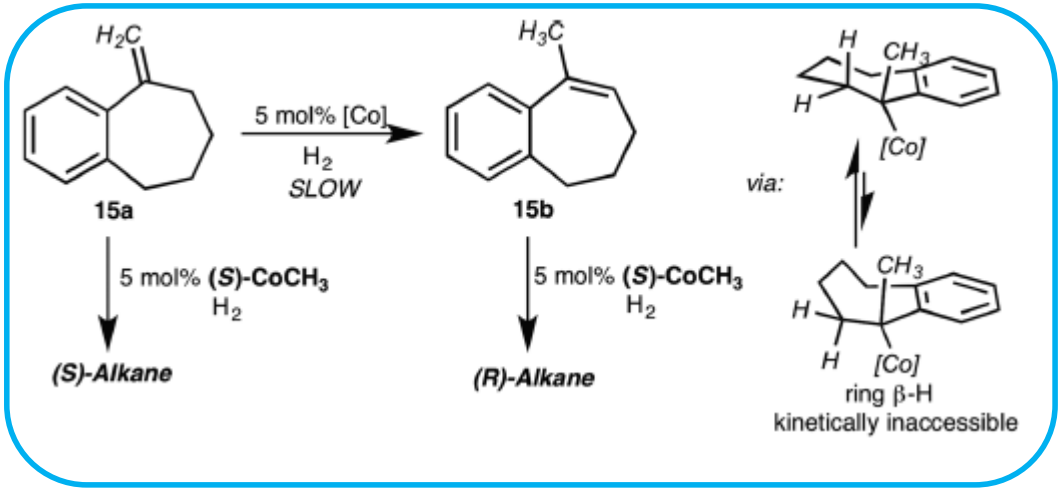
(*R*)-16 95%, 89% (*R*)-(+)

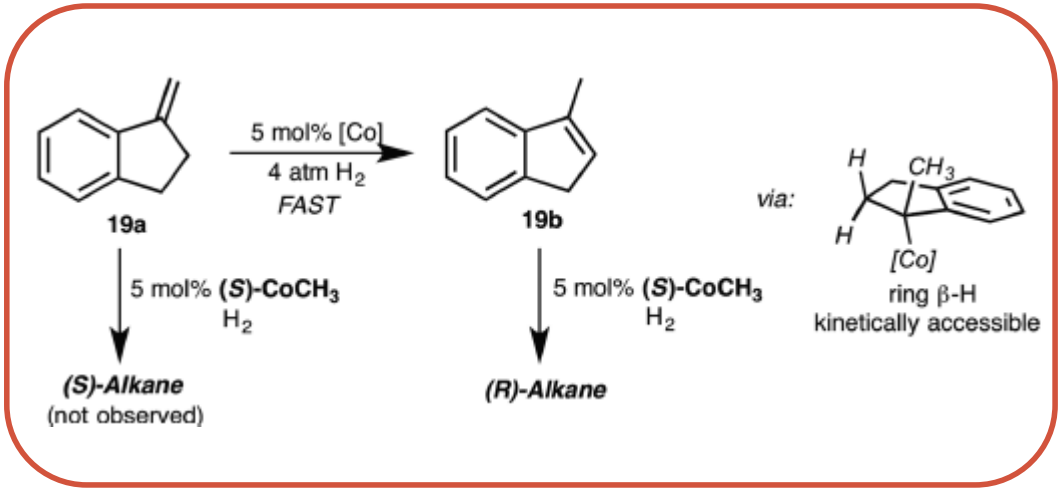


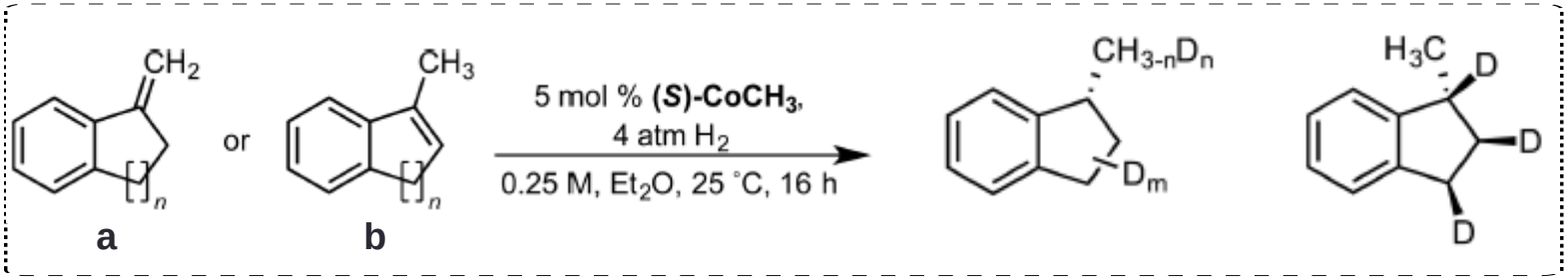
(*R*)-20 84%, 74% (*R*)-(+)

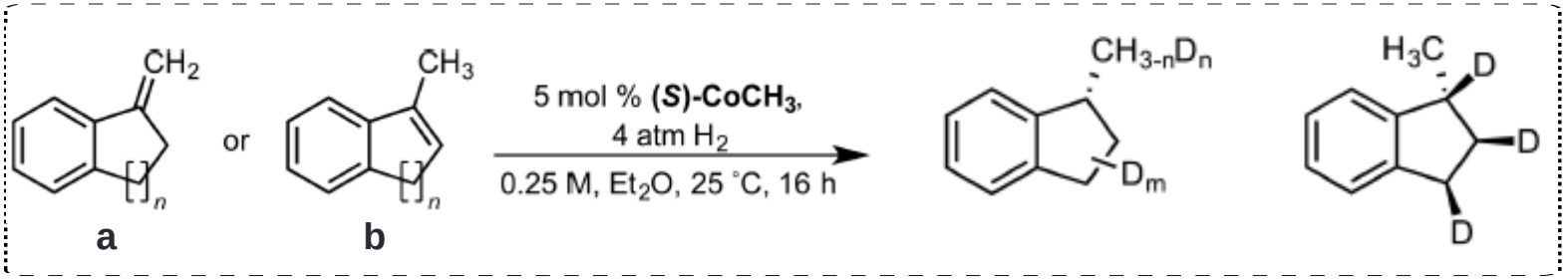
(*R*)-20 88%, 89% (*R*)-(+)[c]

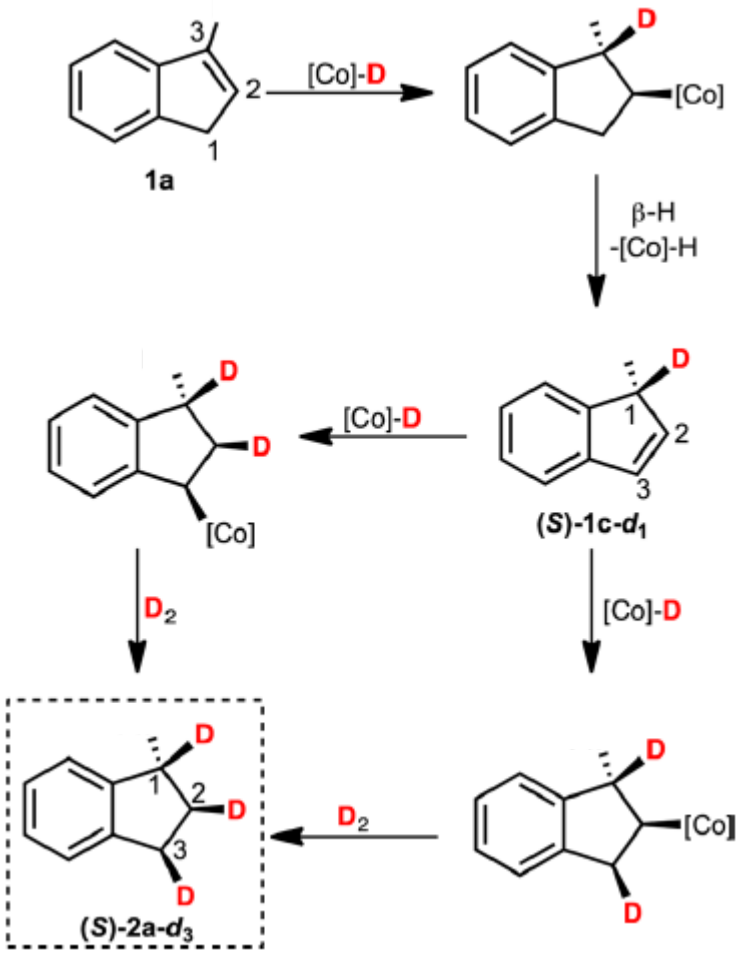
By ^{1}H NMR spectroscopy

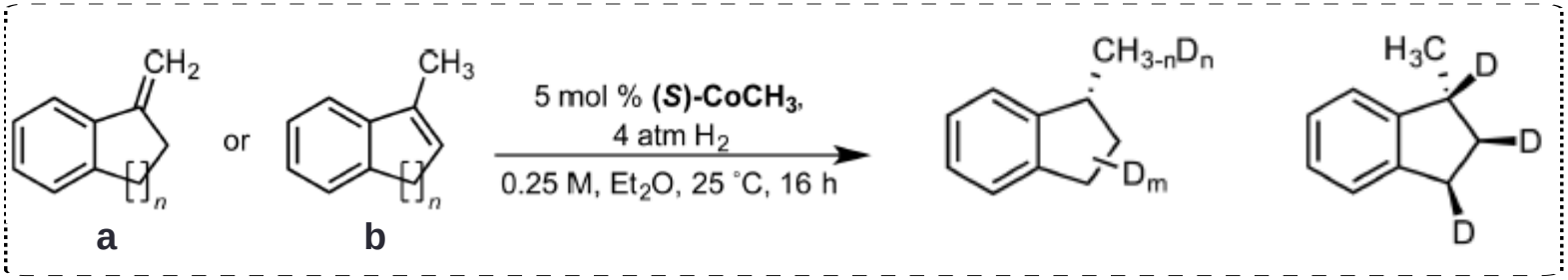


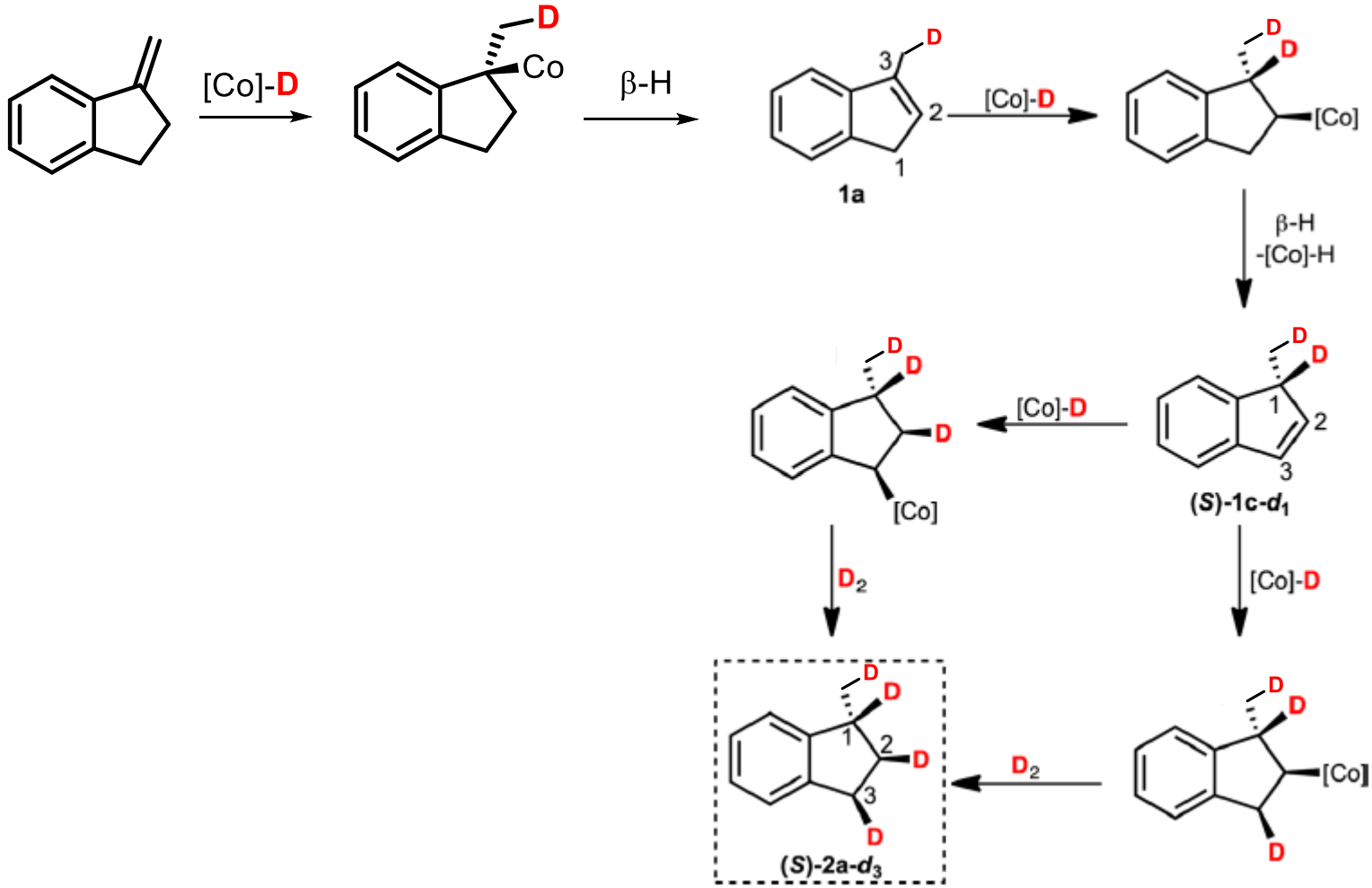


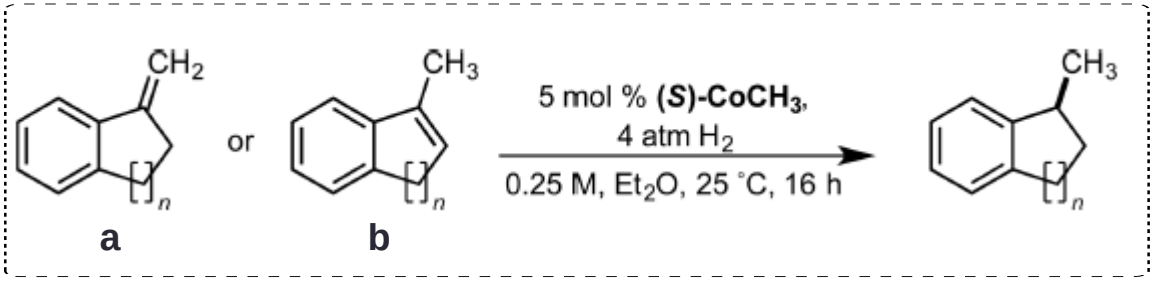

CH2
n
or
CH3
n
a
b
5 mol % (S)-CoCH3,
4 atm H2
0.25 M, Et2O, 25 °C, 16 h
CH3-nDn
Dm
H3C
D
D
D

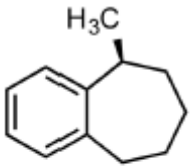

CH2
or
CH3
n
a
b
5 mol % (S)-CoCH3,
4 atm H2
0.25 M, Et2O, 25 °C, 16 h
CH3-nDn
Dm
H3C
D
D
D


3
2
1
1a
[Co]-D
D
[Co]
β-H
-[Co]-H
D
1
2
3
(S)-1c-d1
[Co]-D
D
D
[Co]
D2
[Co]-D
D
1
2
D
3
D
(S)-2a-d3
D2
D
[Co]
D

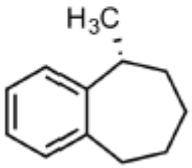

CH2
CH3
or
n
a
b
5 mol % (S)-CoCH3,
4 atm H2
0.25 M, Et2O, 25 °C, 16 h
CH3-nDn
Dm
H3C
D
D
D


[Co]-D
D
Co
β-H
3
2
1
D
1a
[Co]-D
D
D
[Co]
β-H
-[Co]-H
D
D
1
2
3
(S)-1c-d1
[Co]-D
D
D
[Co]
D2
[Co]-D
D
D
1
2
D
3
D
(S)-2a-d3
D2
D
D
[Co]
D

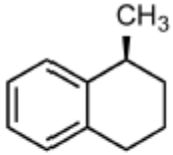




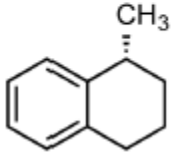
(*S*)-16 97%, 85% (S)-(–)



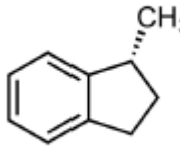
(*R*)-16 95%, 89% (*R*)-(+)



(*S*)-18 87%, 53% (*S*)-(+)

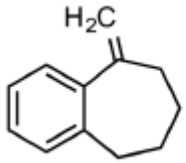


(*R*)-18 88%, 95% (*R*)-(–)
96%, 93% (*R*)-(–)[b]

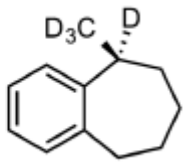


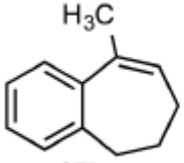
(*R*)-20 84%, 74% (*R*)-(+)

(*R*)-20 88%, 89% (*R*)-(+)[c]

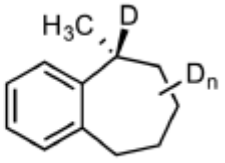


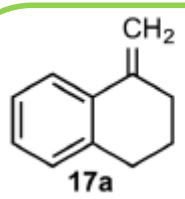
15a



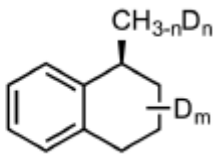


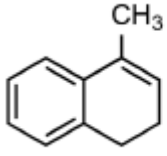
15b



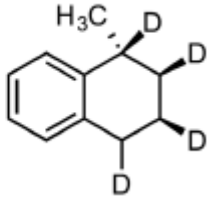


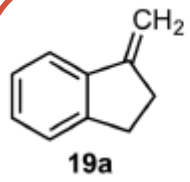
17a



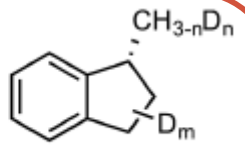


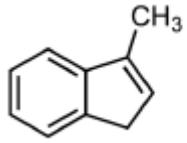
17b



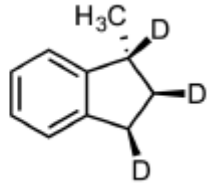


19a

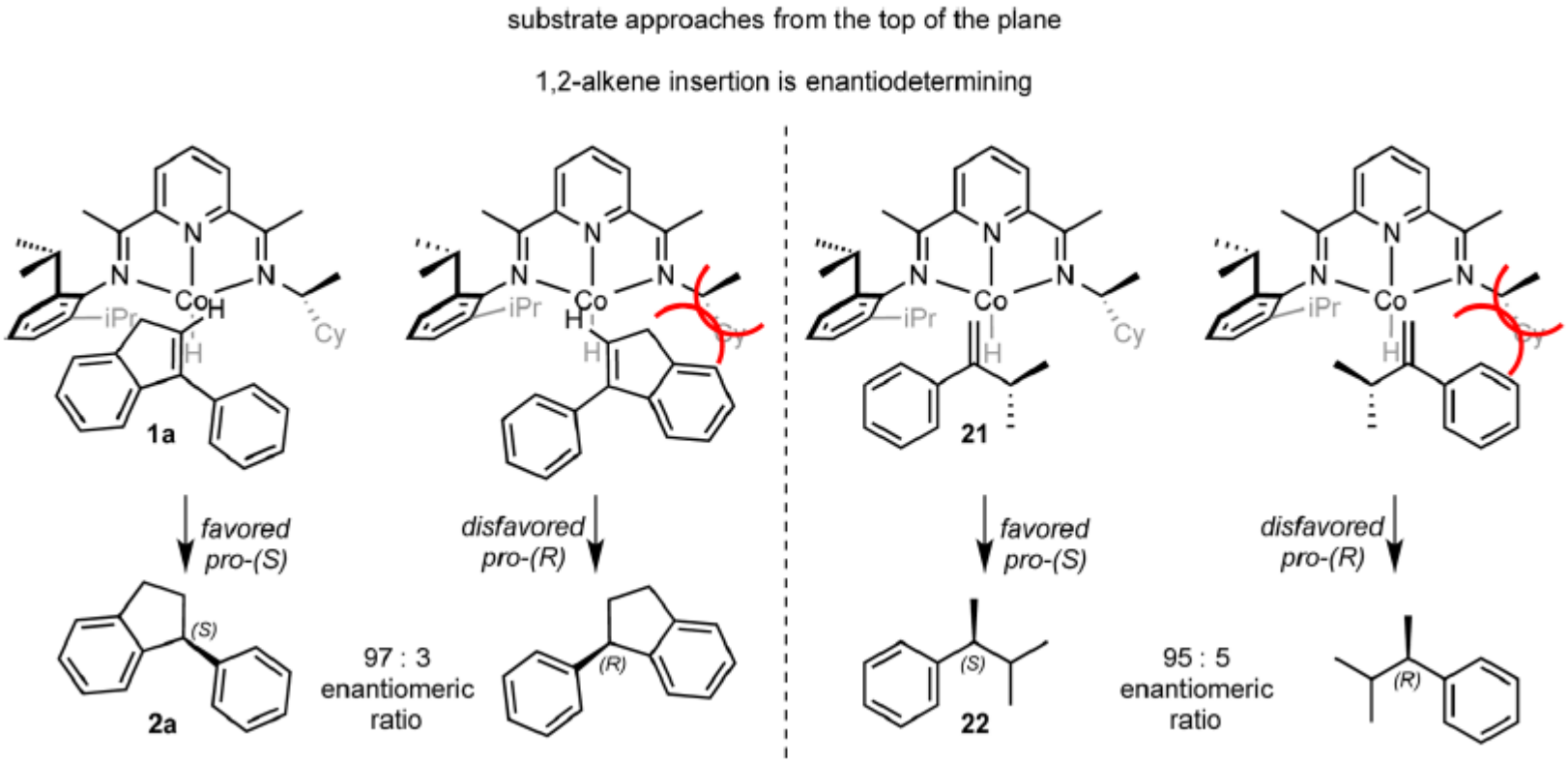




19b



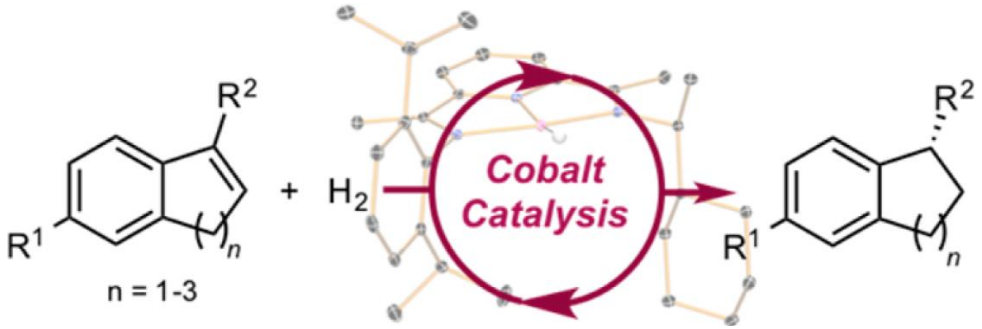
Proposed transition states



Conclusion

Deuterium labeling, stoichiometric experiments and stereochemical outcome provide a comprehensive picture for the enantioselective hydrogenation of non-functionalized alkenes.

- Proof of (S)-CoH as resting state catalyst
- Cyclohexyl side more hindered: control enantioselectivity
- 1,2-insertion turnover-limiting & enantiodetermining step
- Different non-functionalized alkenes



Thank you for your attention