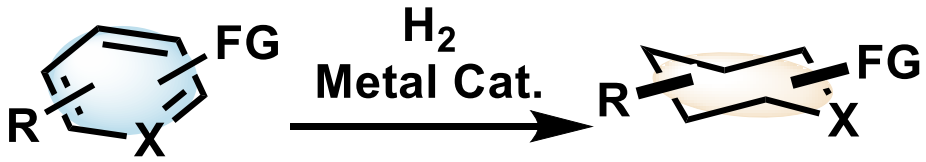
Hydrogenation of Arenes for Organic Synthesis



Literature Seminar #3

2020/10/23

M2 Yuki Hirao

Catalytic Hydrogenation

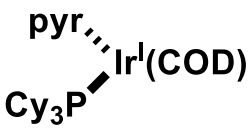
✓**Hydrogenation of unsaturated compounds has been intensively studied and is considered as a versatile method for the synthesis of new compounds.**

Pd/C

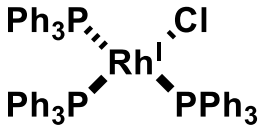
PtO_2

$Pd(OH)_2$

Raney Ni



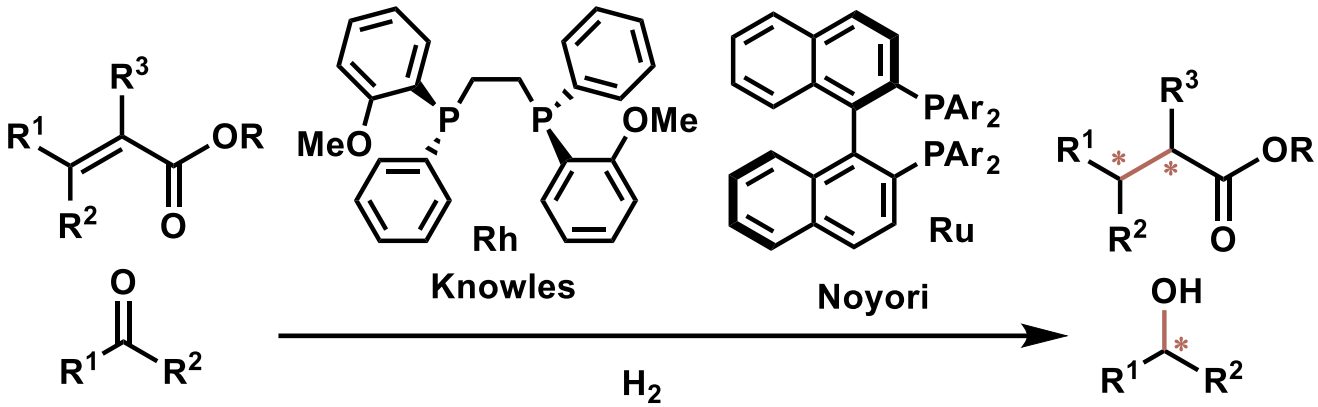
Crabtree's cat

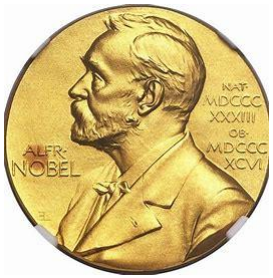


Wilkinson's cat

+ H_2

Catalytic Asymmetric Hydrogenation

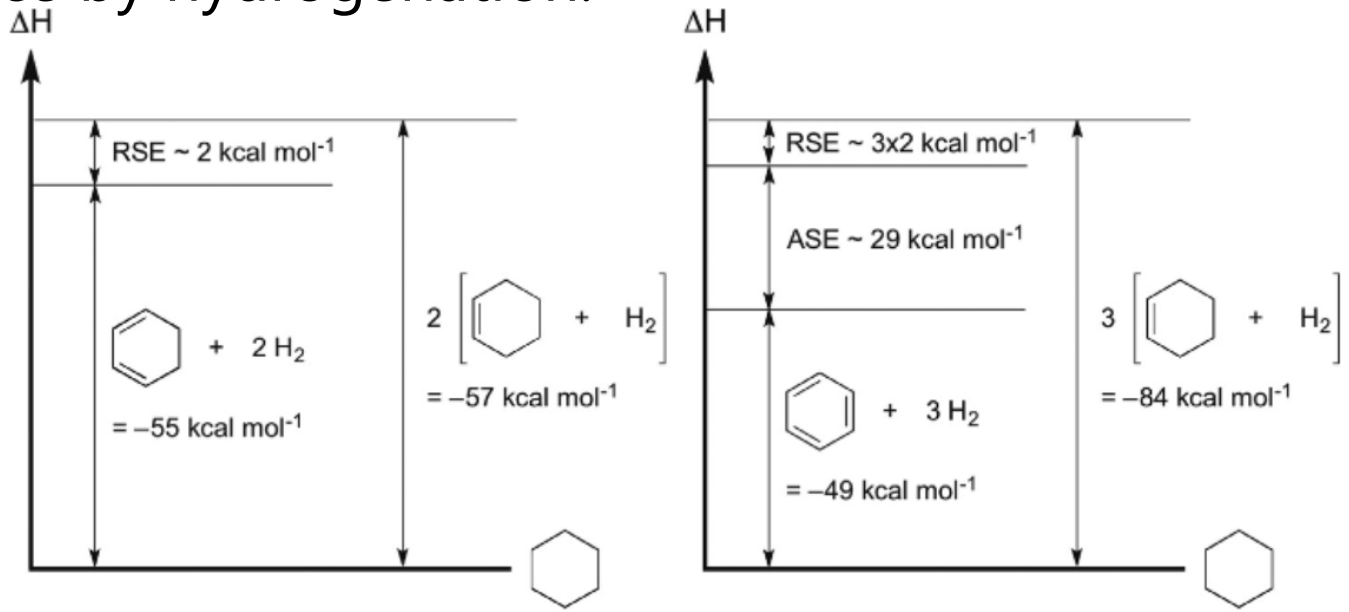




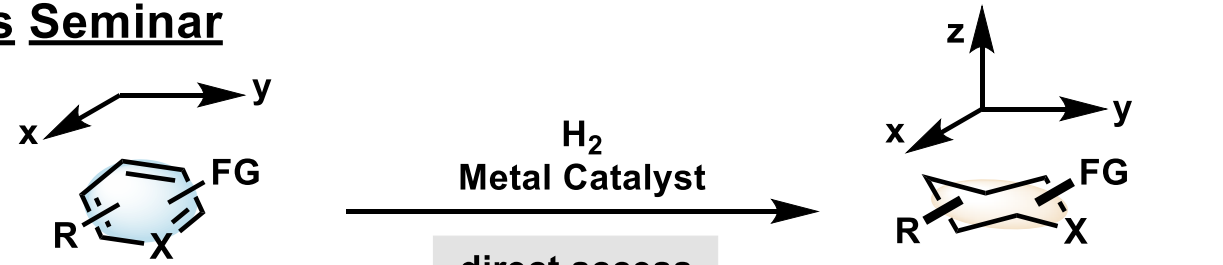
Nobel Prize in 2001

Hydrogenation of Arenes

Aromatic Stabilization Energy (ASE) contributes to the greater resistance by hydrogenation.



This Seminar



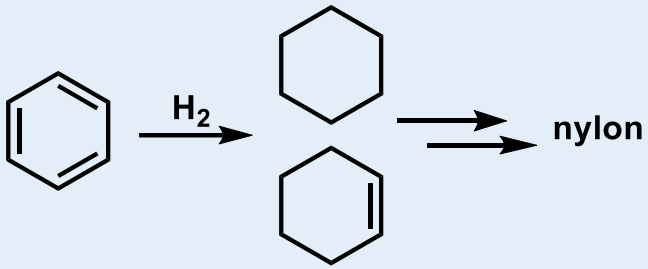
2D structure
readily available

3D structure
versatile building blocks

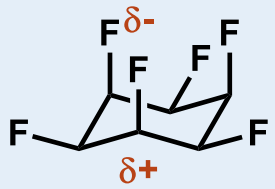
Coord. Chem. Rev. **2016**, *314*, 134.

Application

Industrial Application



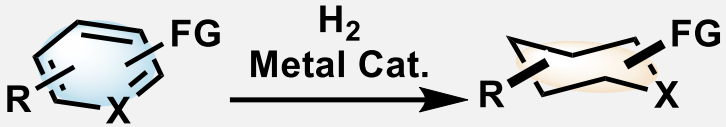
Material Science



facially polarized cyclohexane

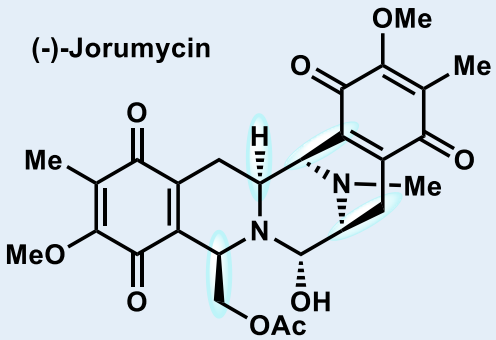
1 step

formerly 12 steps



Natural Product

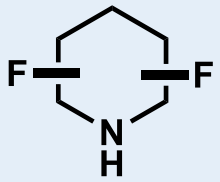
(-)-Jorumycin



16 steps

Medicinal Chemistry

fluorinated piperidines



1 step

Angew. Chem. Int. Ed. **2019,** *58,* 10460.

Challenges

Reactivity

The hydrogenation of arenes is hindered by the added kinetic barrier resulting from the **aromatic stabilization energy**.

Stereoselectivity

The hydrogenation of multisubstituted arenes may form several **diastereomers**. Substituted saturated carbo- & heterocycles are often **chiral**.

Chemoselectivity

Elaborate substrates often exhibit competing **side reactions**.
ex.) more reductively labile units, such as carbonyls, hydrodefunctionalizations

Angew. Chem. Int. Ed. **2019,** *58,* 10460.

Contents

cis-Selectivity

cis **isomer** vs ***trans*** **isomer**

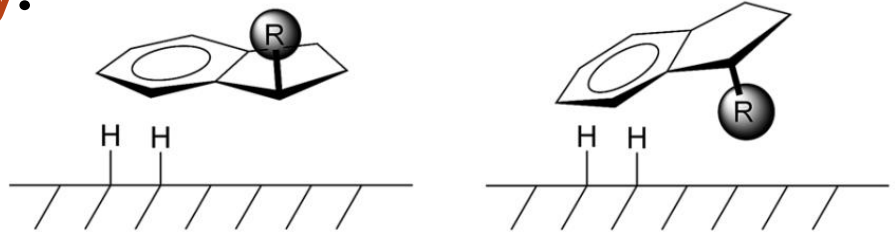
kinetically thermodynamically

The formation of the *trans* isomer requires a **π-facial exchange** (catalyst dissociation-reassociation process).

✓Hydrogenation of dearomatized intermediates should be faster than that of stabilized aromatic substrate.

✓The catalyst would have to bind to the sterically more hindered π-face.

Arene hydrogenation generally proceeds with high cis selectivity.



I II

RSC Adv. **2016**, *6*, 18419.

Enantioselectivity

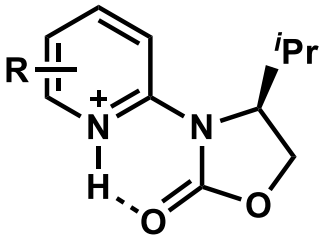
✓some strategies for asymmetric hydrogenation of aromatics

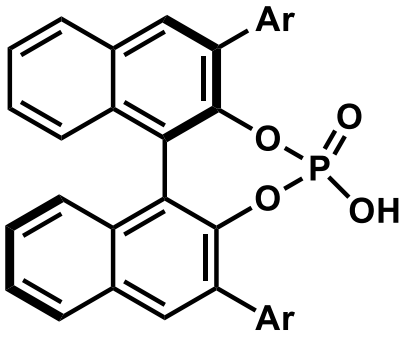
1. Substrate Activation:

low active substrate → (Activator) → high active substrate

✓introduction of activator to interact with the substrate
✓secondary coordination group to assist coordination between substrate and catalyst

ex.)





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2. Catalyst Activation:

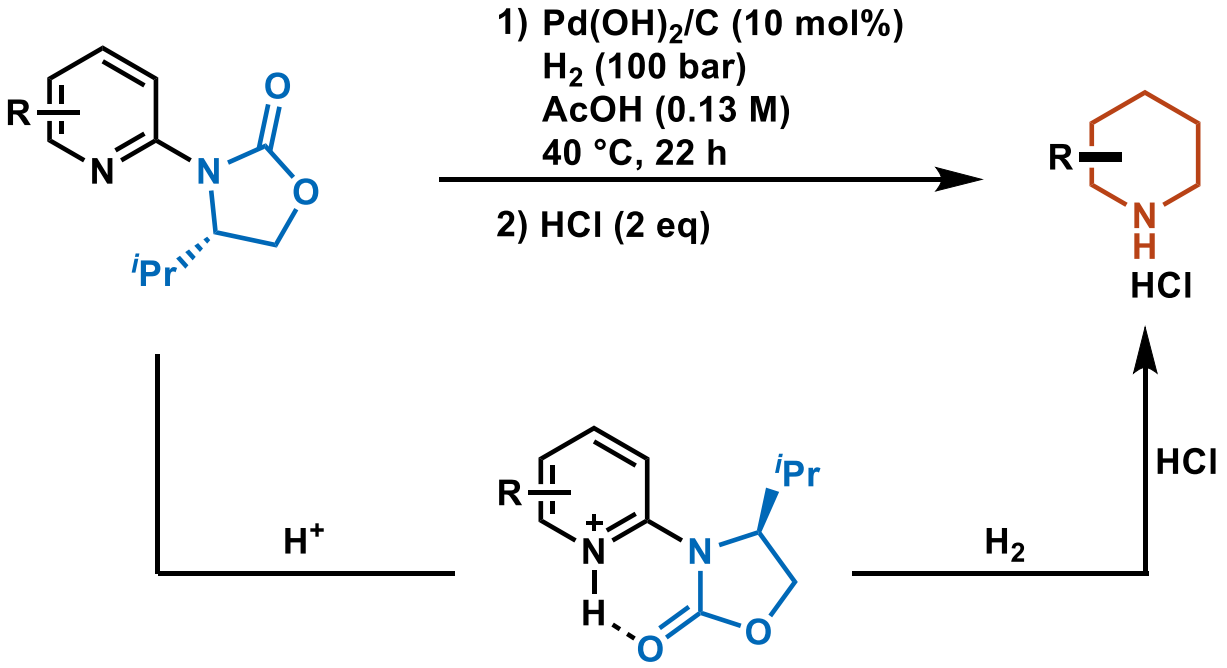
low active catalyst → (Activator) → high active catalyst

✓addition of additives
✓fine-tuning of steric and electronic effects of the chiral ligands

ex.)

P-P, P-N, N-N, NHC additive

Chiral Auxiliary



R = CHO, CF_3, $CONMe_2$, ...

✓up to 3 stereocenters ✓up to 98% ee

✓quantitative recovery of Evans' auxiliary

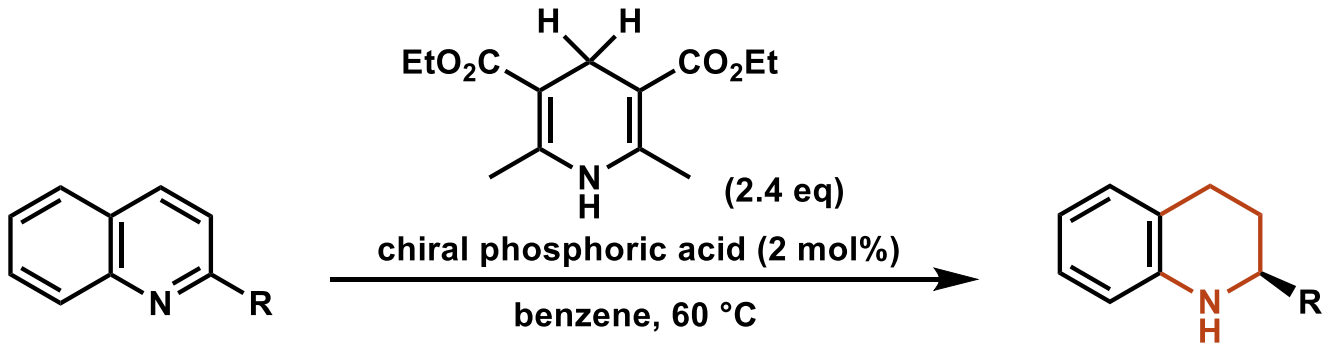
- acidic medium plays important roles
  1. formation of pyridinium ion
  2. protection of Lewis basic moiety
  3. locking the conformation of the chiral auxiliary

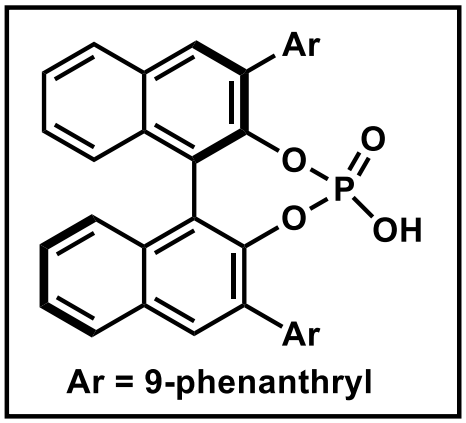
△ The introduction and removal of the stoichiometric chiral auxiliary must be facile

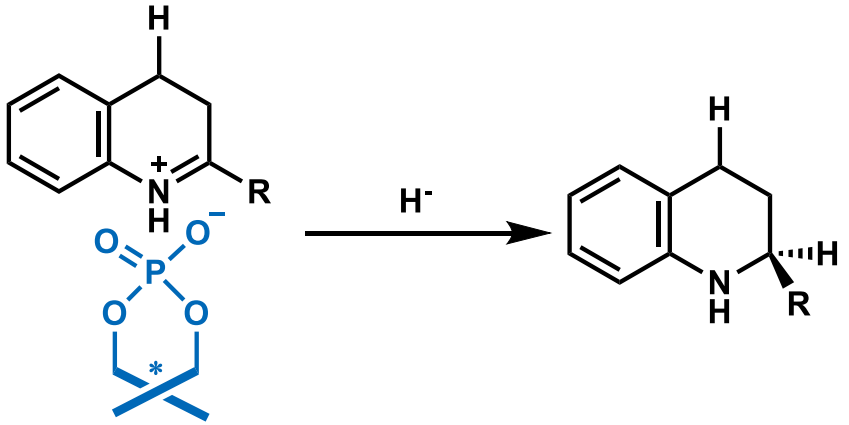
limiting the scope

Angew. Chem. Int. Ed. **2004,** *43, 2850.*

Chiral Brønsted Acid Catalyst



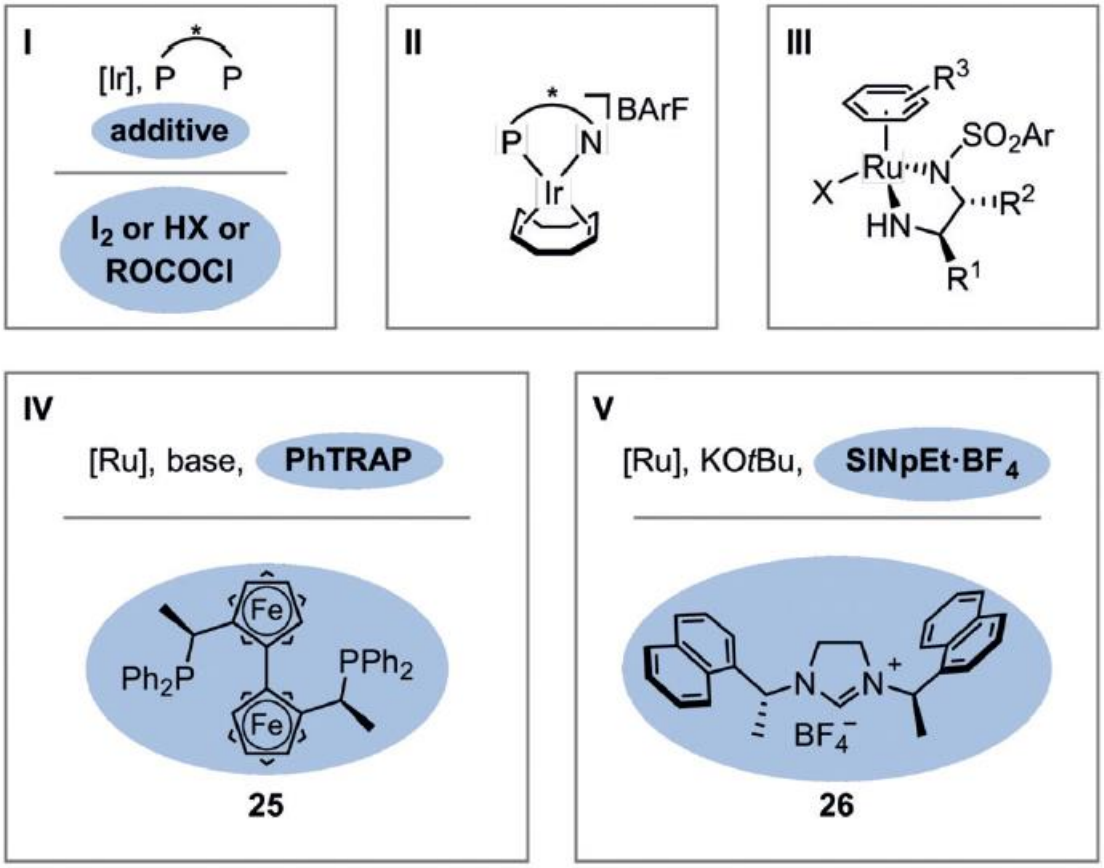




○ good tolerance of functional groups and applicability in a laboratory scale
△ limited to basic N-heteroarene substrates

Angew. Chem. Int. Ed. **2006,** *45, 3683.*

Chiral Ligand



✓**homogeneous metal complexes with chiral ligands is the most general strategy.**

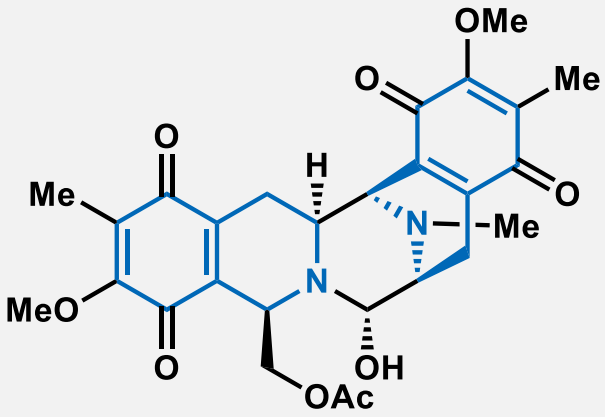
○ **tunable chiral moiety**

△ **limited in terms of functional group tolerance and substrate substitution pattern**

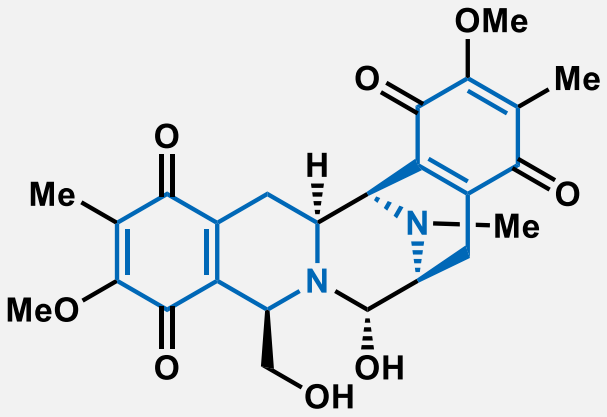
Angew. Chem. Int. Ed. **2019,** *58,* 10460.

Application in Total Synthesis

Bis-Tetrahydroisoquinoline (bis-THIQ) natural products:
Alkaloids that display exceptional anticancer activity



(-)-Jorumycin

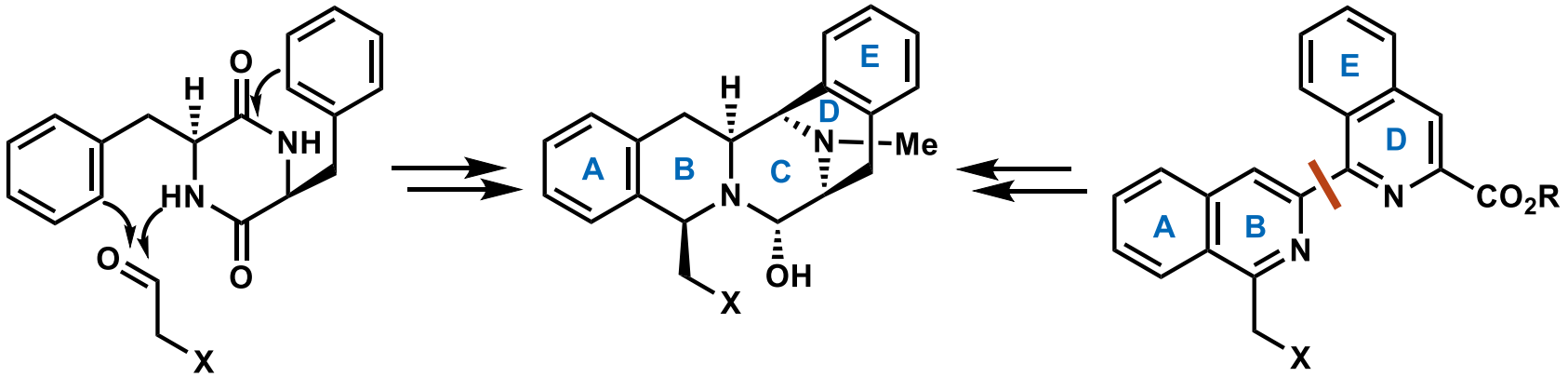


Jorunnamycin A

Conventional, Biomimetic Approach:
Pictet-Spengler

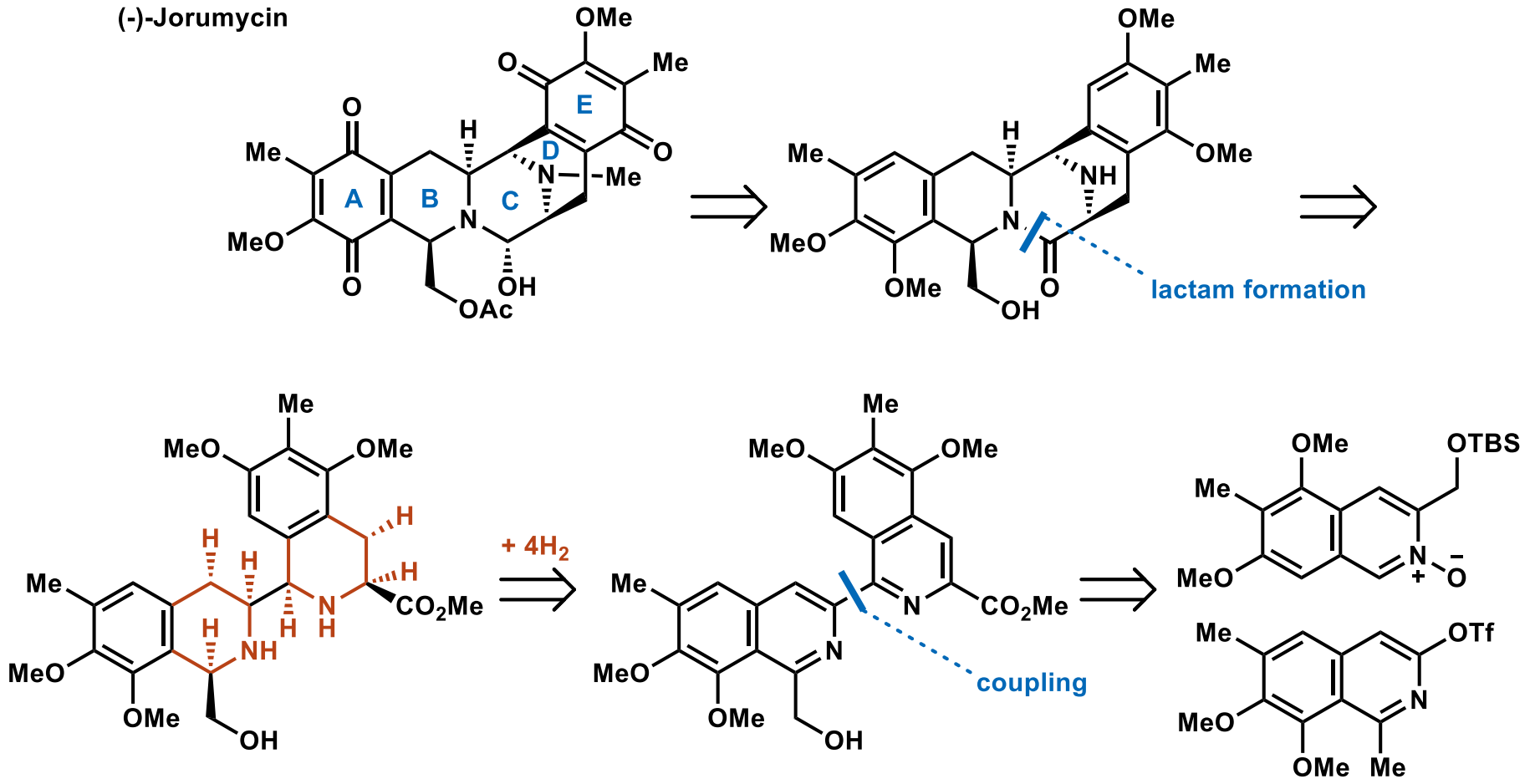
Pentacyclic bis-THIQ Core

Stoltz Group:
Cross Coupling/Ruductive Cyclization



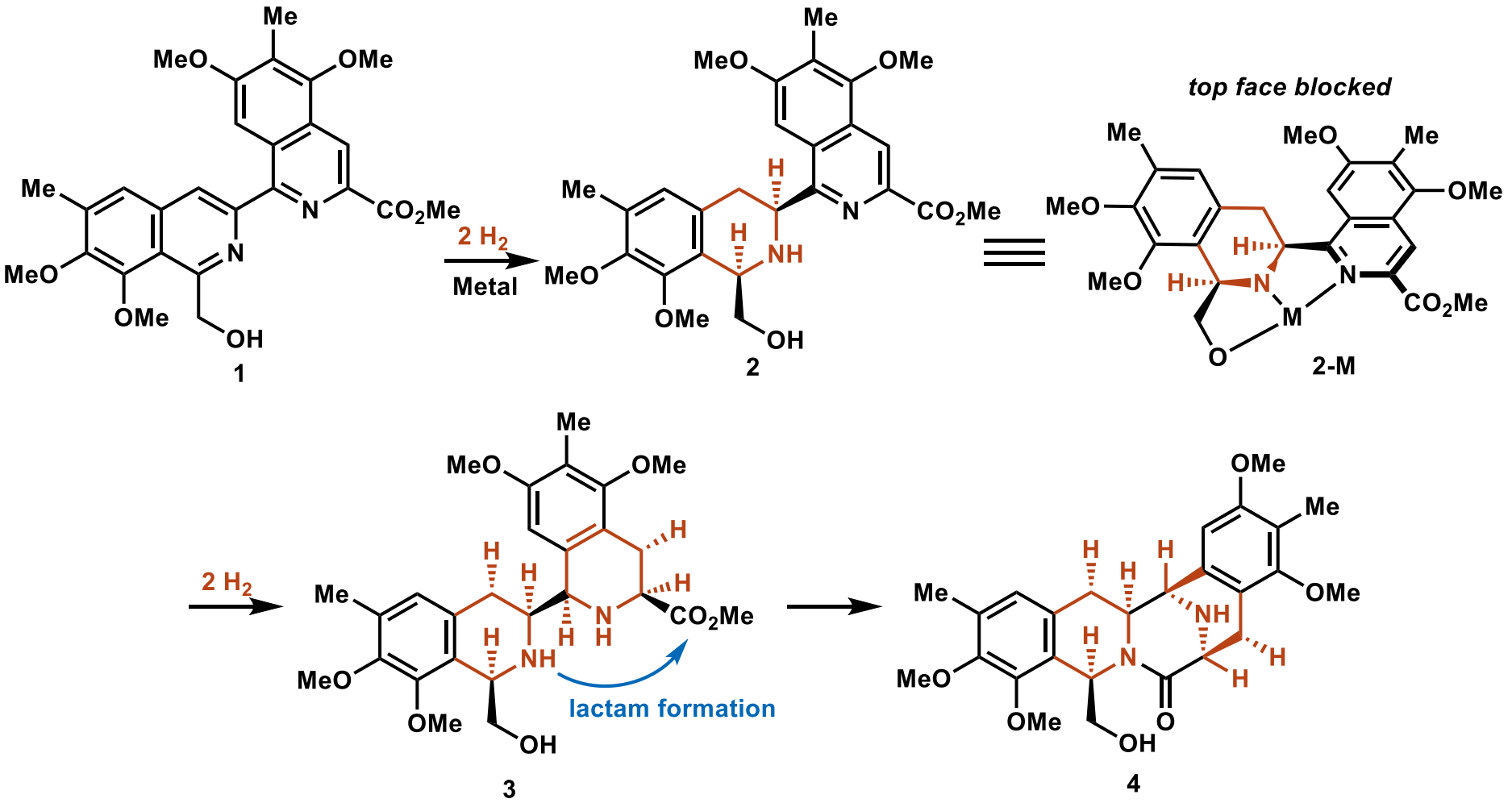
B. M. Stoltz *et al.* Science **2019**, *363*, 270.

Retrosynthesis of (-)-Jorumycin



B. M. Stoltz *et al.* Science **2019**, *363*, 270.

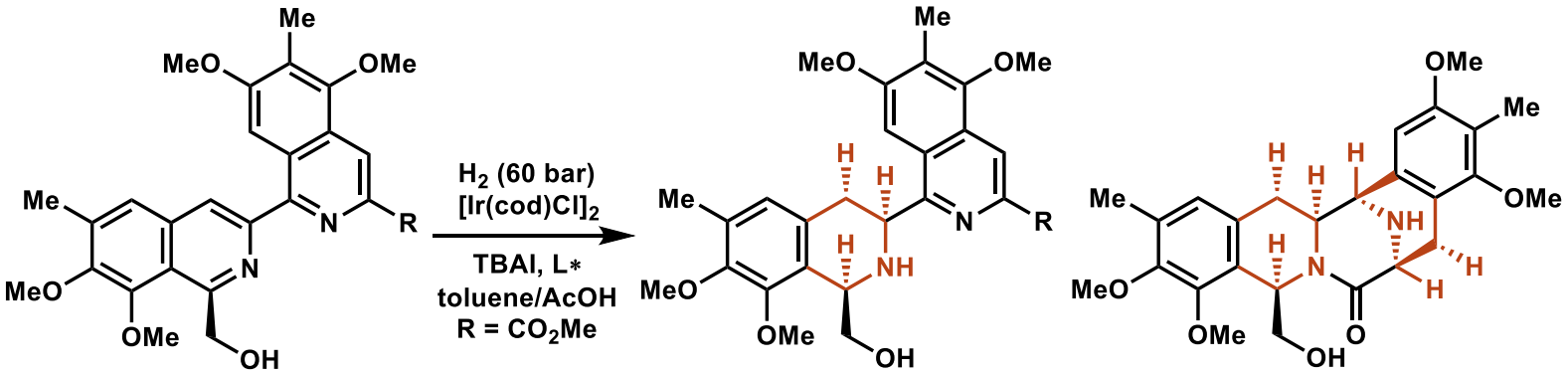
Enantio- & Diastereoselective Hydrogenation



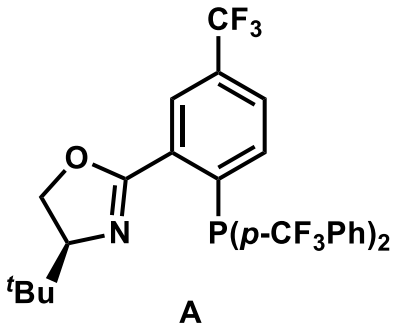
- ✓ **directed *Si*-face reduction leads to enantioenriched generation of intermediate 2**
- ✓ **three-dimensional structure of 2-M leads to substrate-reinforced diastereoselectivity**

B. M. Stoltz *et al.* Science **2019**, *363*, 270.

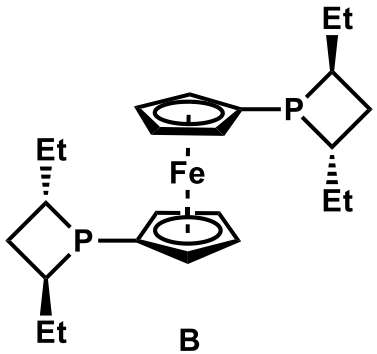
Catalyst Screening



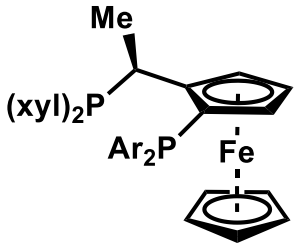
Entry	Catalyst loading	Ligand	temp	2 (ee)	4 (dr) (ee)
1	5 mol%	C	rt	2% (ND)	0%
2	5 mol%	A	60 °C	22% (-82% ee)	0%
3	5 mol%	B	60 °C	26% (-87% ee)	0%
4	5 mol%	C	60 °C	30% (80% ee)	0%
5	5 mol%	D	60 °C	83% (94% ee)	10% (>20:1 dr)(ND)
6	5 mol%	D	80 °C	31% (87% ee)	43% (>20:1 dr)(ND)
7	5 mol%	D	60 °C→80 °C	7% (94% ee)	59% (>20:1 dr)(88% ee)
8	10 mol%	D	60 °C→80 °C	3% (94% ee)	83% (>20:1 dr)(88% ee)



A



B



C: Ar = Ph
D: Ar = 3,5-$(CF_3)_2$Ph

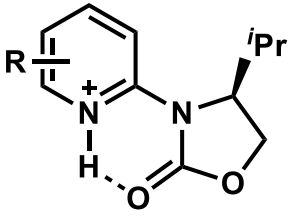
B. M. Stoltz *et al.* Science **2019**, *363*, 270.

Short Summary

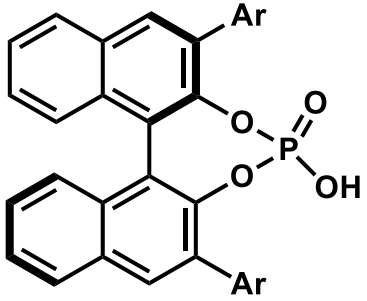
✓**diastereoselectivity** ***cis*-selectivity**

✓**enantioselectivity**

1. chiral auxiliary



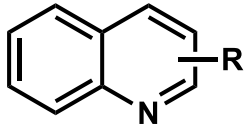
2. chiral bronsted acid



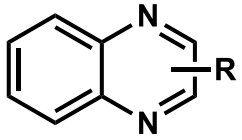
3. chiral ligand

P-P, P-N, N-N, NHC

• number of published enantioselective method



>30



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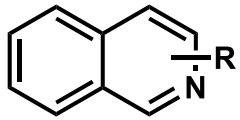

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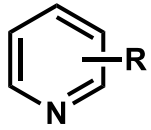

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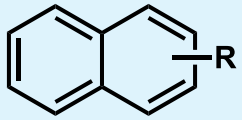

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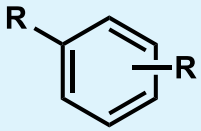


0

Challenges: benzene derivatives

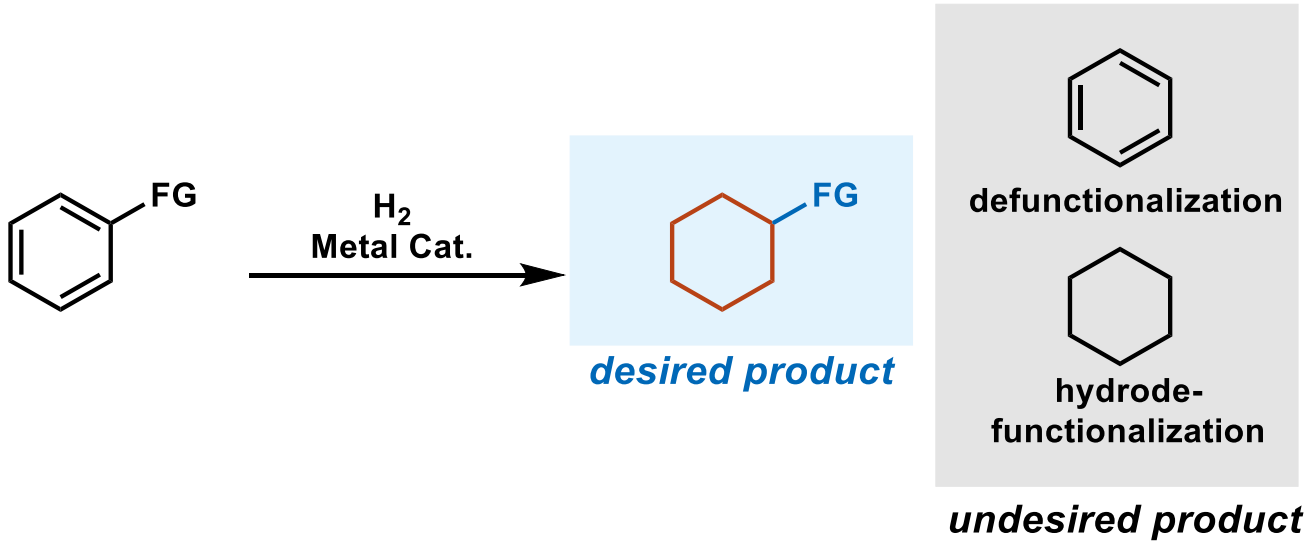
Angew. Chem. Int. Ed. **2019,** *58,* 10460.

Contents

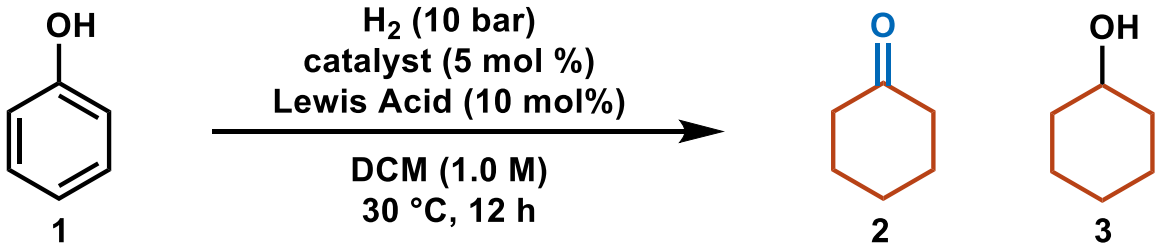
Chemoselectivity | FG tolerance

Challenges

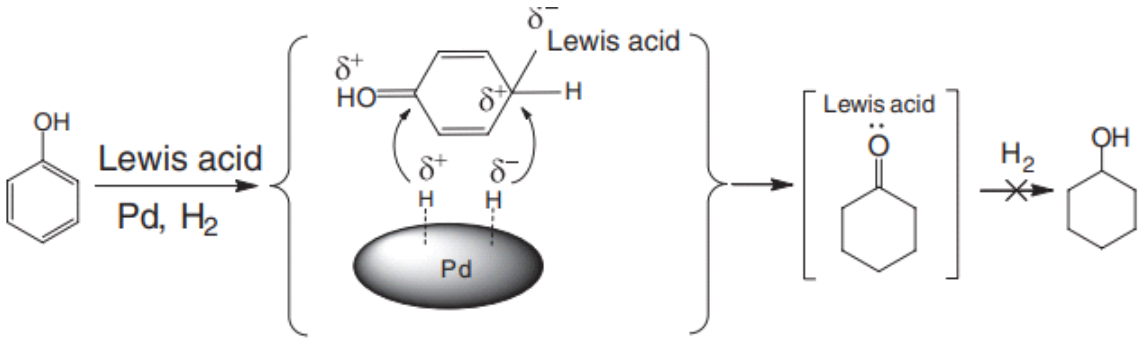
1. Other reducible sites
2. Hydrodefunctionalization
3. Sterically hinderance
4. Negative influence in electronical properties



Phenol Hydrogenation to Cyclohexanone



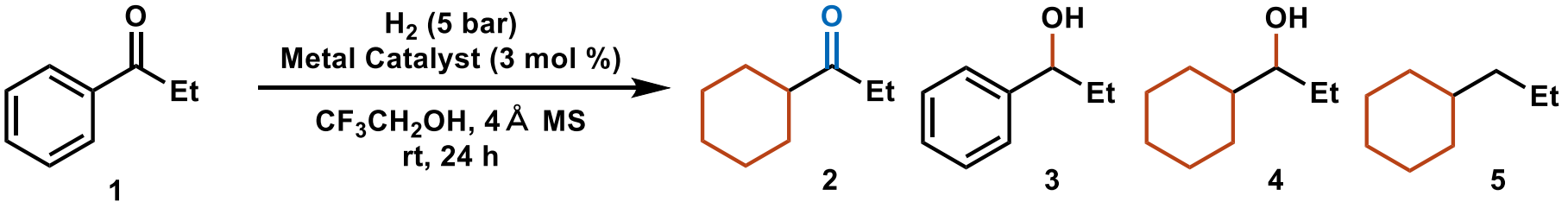
Entry	Catalyst	Lewis Acid	Conversion (%)	Selectivity (2:3)
1	Pd/C	-	13	94:6
2	-	$AlCl_3$	0	-
3	Pd/C	$AlCl_3$	>99	>99:1
4	Pd/C	$InCl_3$	>99	>99:1
5	Pd/C	$ZnCl_2$	>99	>99:1



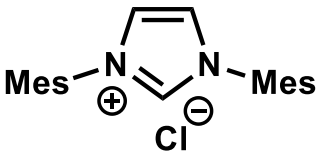
✓**Lewis acid makes the benzene ring of phenol more active and inhibits further hydrogenation to cyclohexanol.**

T. Jiang, B. Han *et al*. Science **2009**, *326*, 1250.

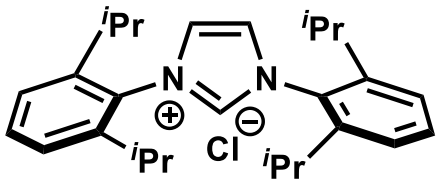
Aromatic Carbonyl Compounds



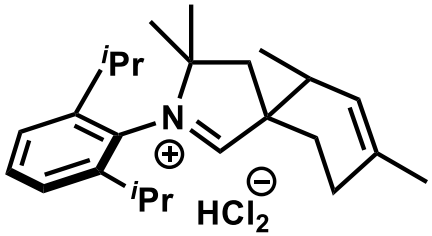
Entry	Metal Catalyst	2 (%)	3 (%)	4 (%)	5 (%)
1	none	nd	nd	nd	nd
2	$Rh(PPh_3)_3Cl$	<1	nd	nd	nd
3	$RhCl_3•H_2O$	<5	nd	11	nd
4	$[Rh(COD)Cl]_2$	29	10	25	10
5	$[Rh(COD)Cl]_2$ / IMes•HCl / NaOBu	9	21	10	12
6	$[Rh(COD)Cl]_2$ / IPr•HCl / NaOBu	12	<1	<5	11
7	$[Rh(COD)Cl]_2$ / CAAC-1/2HCl / LDA	80	nd	<5	<1
8	CAAC-Rh(COD)Cl	98	nd	<1	<1



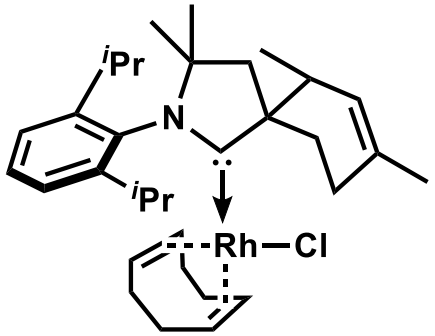
IMes•HCl



IPr•HCl



CAAC-1/2HCl
(cyclic alkyl amino carbene)

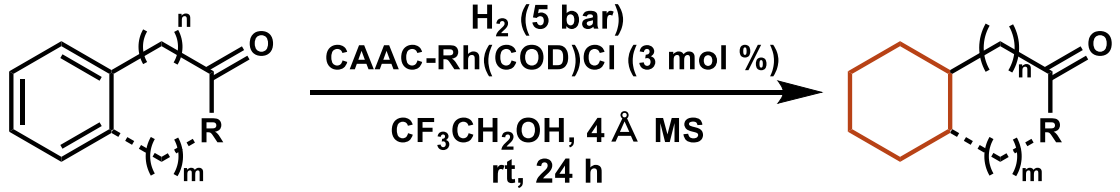


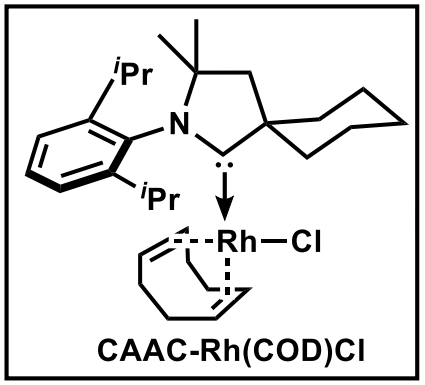
CAAC-Rh(COD)Cl

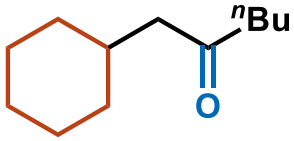
✓ highly electron-rich metal center would favor arene binding through back-donation into the antibonding π orbitals of the arene.

X. Zeng *et al. J. Am. Chem. Soc.* **2015**, *137*, 9250.

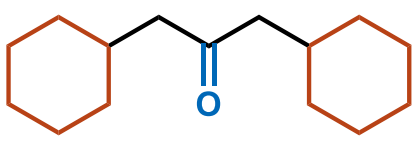
Substrate Scope



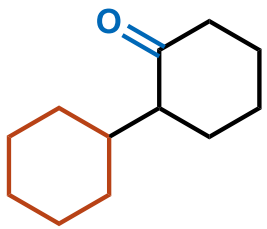




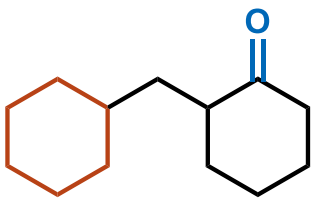
95%
(10 bar)



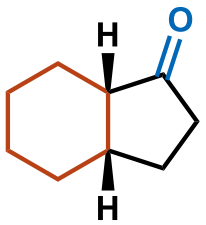
93%
(15 bar)



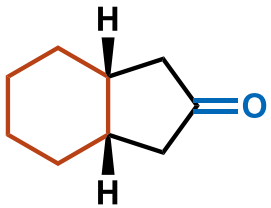
88%
(25 bar)



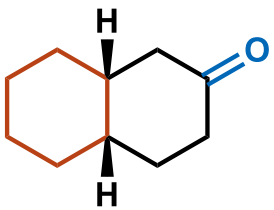
95%
(25 bar)



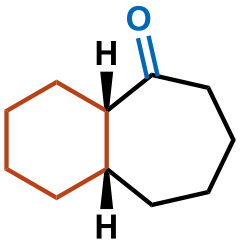
96%
(18 bar)



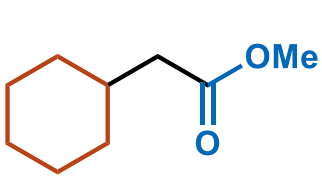
76%
(20 bar)



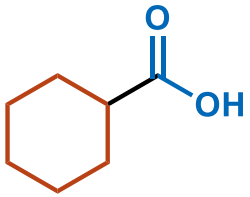
95%
(20 bar)



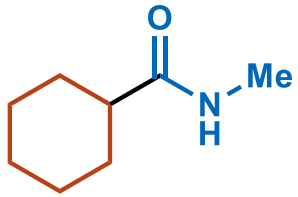
98%
(18 bar)



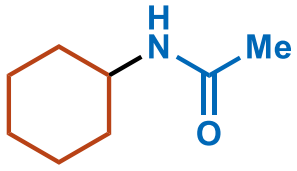
83%
(10 bar)



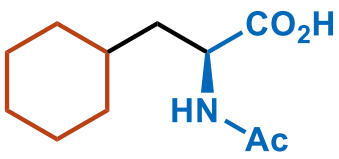
99%
(68 bar)



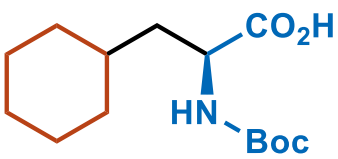
95%
(40 bar)



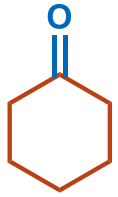
97%
(60 bar)



93%
(60 bar)



97%
(70 bar)

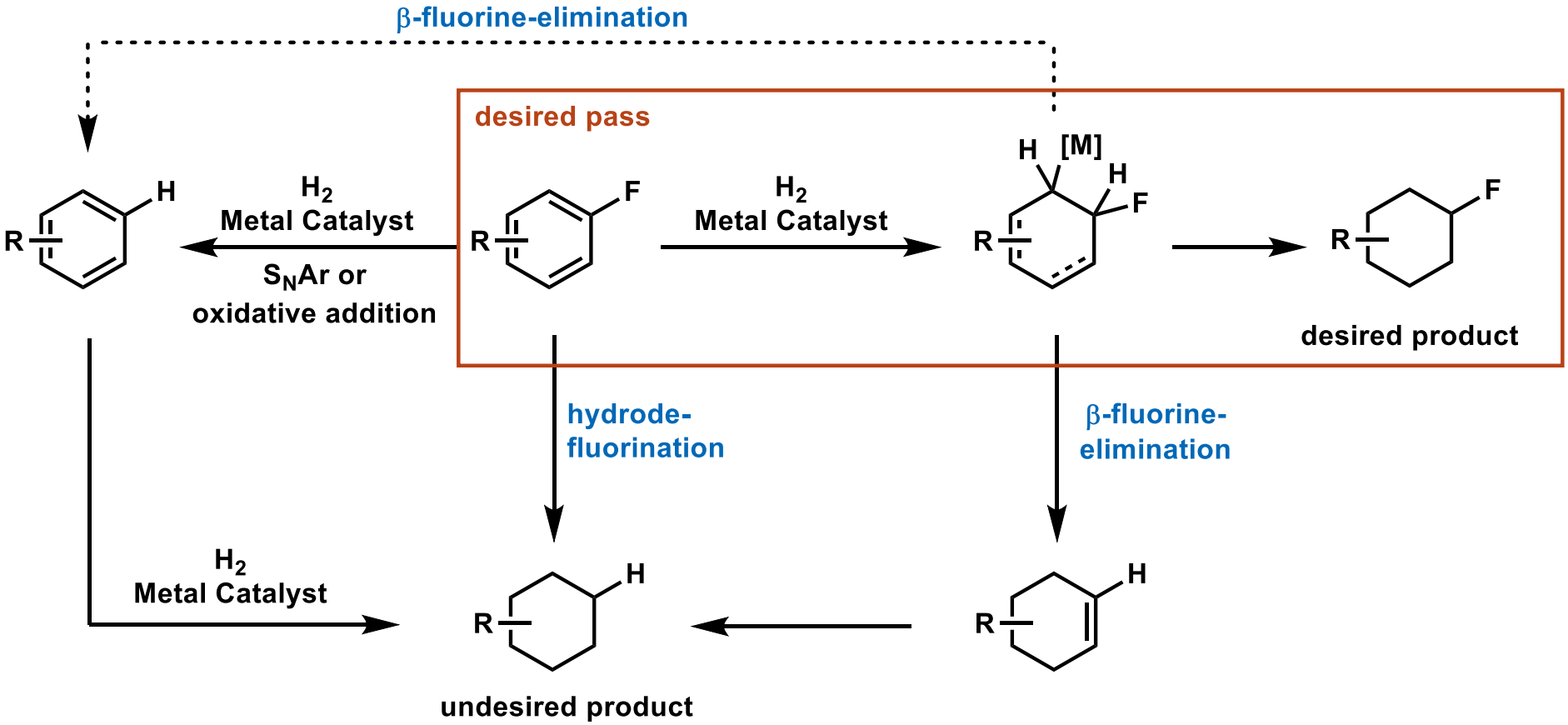


99%
(10 bar)

CF_3CH_2OH/H_2O (19:1)
70 °C

X. Zeng *et al. J. Am. Chem. Soc.* **2015**, *137*, 9250.

Hydrogenation of Fluoroarenes



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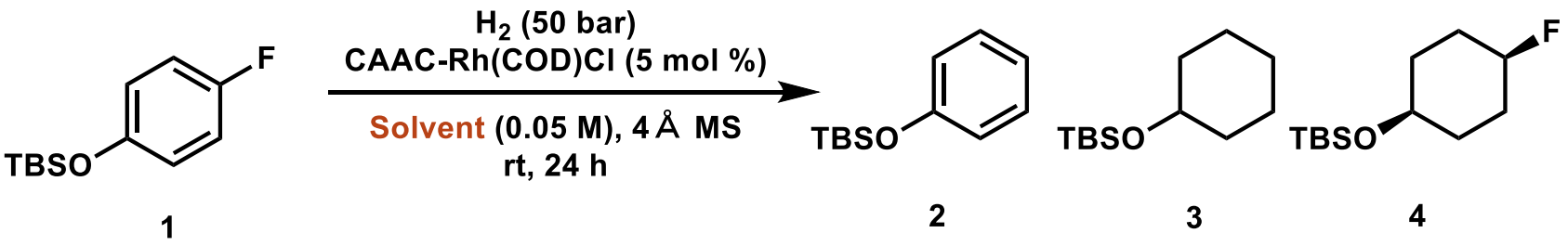
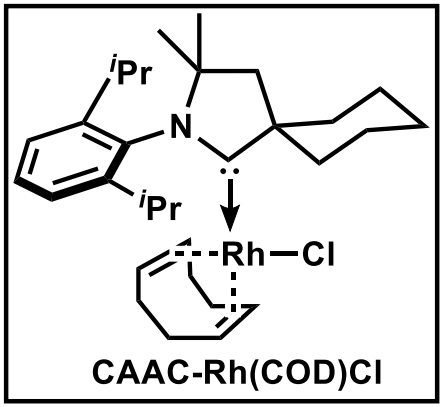
Reaction Optimization



Entry	Solvent	Conversion (%)	2 (%)	3 (%)	4 (%) (dr)
1	MeCN	0	0	0	0
2	MeOH	92	1	75	8 (6:1)
3	CF_3CH_2OH	100	0	52	24 (10:1)
4	DCE	100	0	19	80 (12:1)
5	DCM	100	0	16	77 (13:1)
6	THF	98	0	26	69 (25:1)
7	Et_2O	100	0	9	91 (18:1)
8	Hexane	100	0	4	95 (15:1)

polarity



✓Less polar solvents decrease the rate of defluorination

- defluorination via a polar intermediate?
- higher solubility of hydrogen gas?
- interaction between catalysts and polar solvents?

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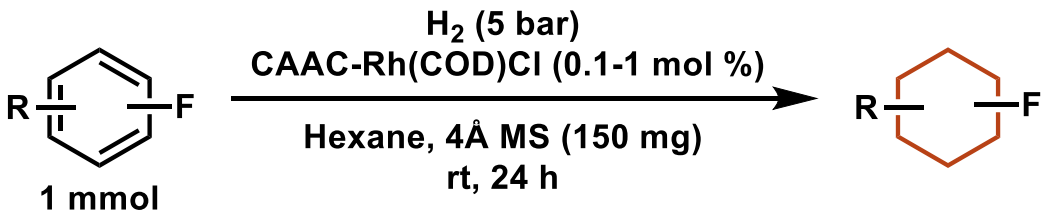
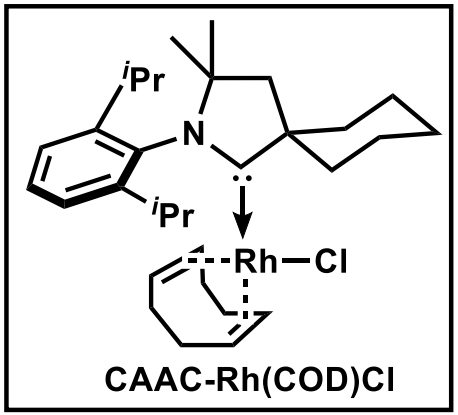
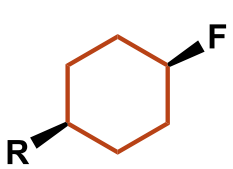
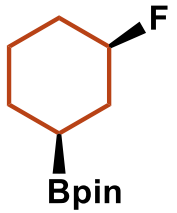
Substrate Scope



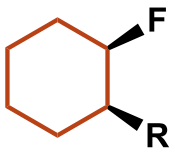




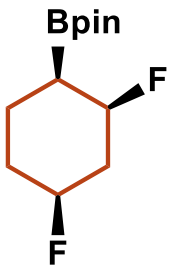
R = H, 90%
OTBS, 93% (13:1 dr)
Bpin, 88% (9:1 dr)
NHBoc, 81% (6:1 dr)
OMe, 80% (7:1 dr)
CO_2Me, 80% (9:1 dr)
CH_2NHBoc, 90% (7:1 dr)



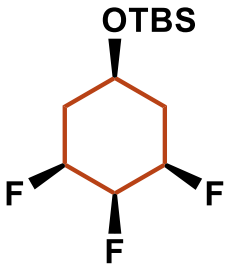
82% (8:1 dr)



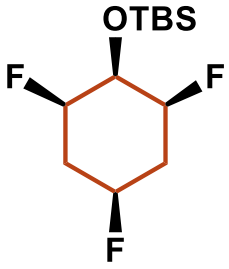
R = OTBS, 96% (16:1 dr)
NHBoc, 63% (>20:1 dr)
Bpin, 61% (>20:1 dr)
F, 96% (17:1 dr)



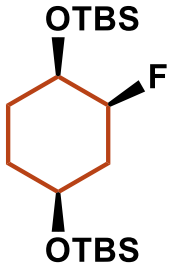
71% (9:1 dr)



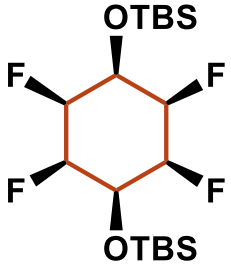
68% (7:1 dr)



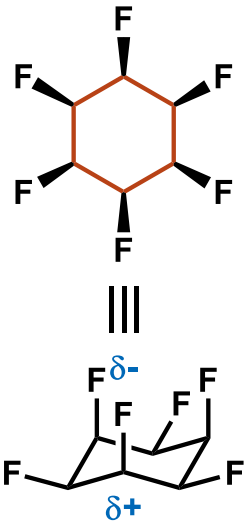
97% (>20:1 dr)



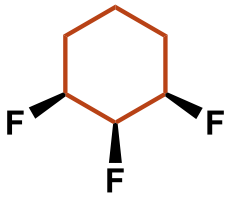
38% (>20:1 dr)



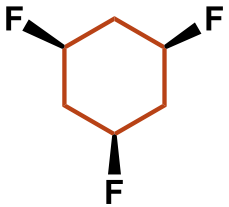
21% (>20:1 dr)



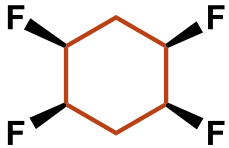
facially polarized cyclohexane
34% (>20:1 dr)
previously 12 steps



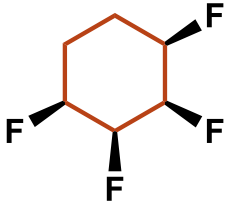
81% (6:1 dr)



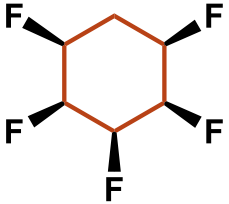
65% (>20:1 dr)



60% (>20:1 dr)



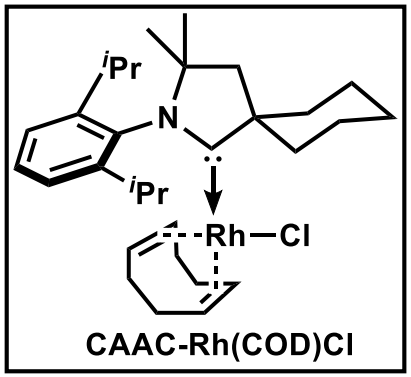
26% (>20:1 dr)



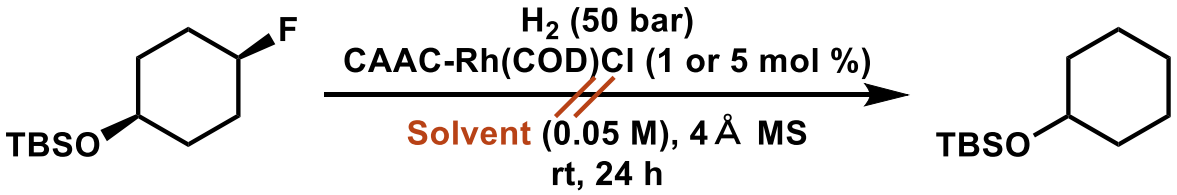
42% (>20:1 dr)

F. Glorius *et al.* Science **2017**, *357*, 908.

Mechanistic Experiments



Product decomposition

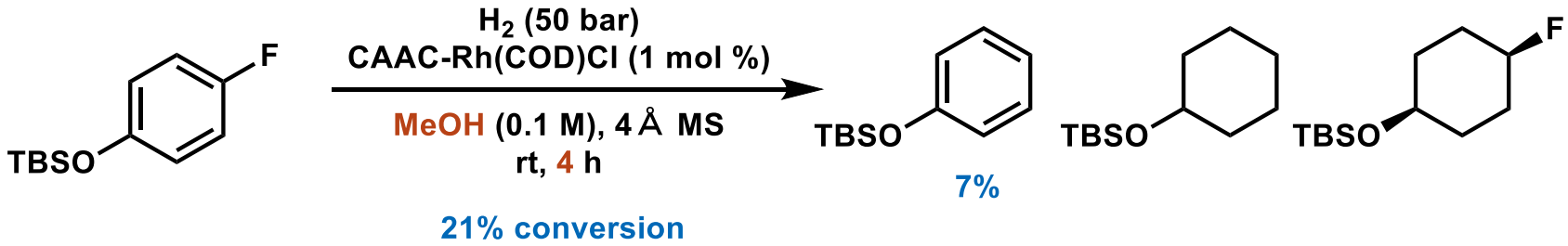


<5%

Hexane, DCM, Methanol

HF-elimination from the reduced product is not the reason for the hydrodefluorinated side products.

Detection of defluorinated arene



7%

21% conversion

Hydrodefluorination in methanol proceeds via oxidative addition or S_NAr, or β-F-elimination from a dearomatized metal complex.

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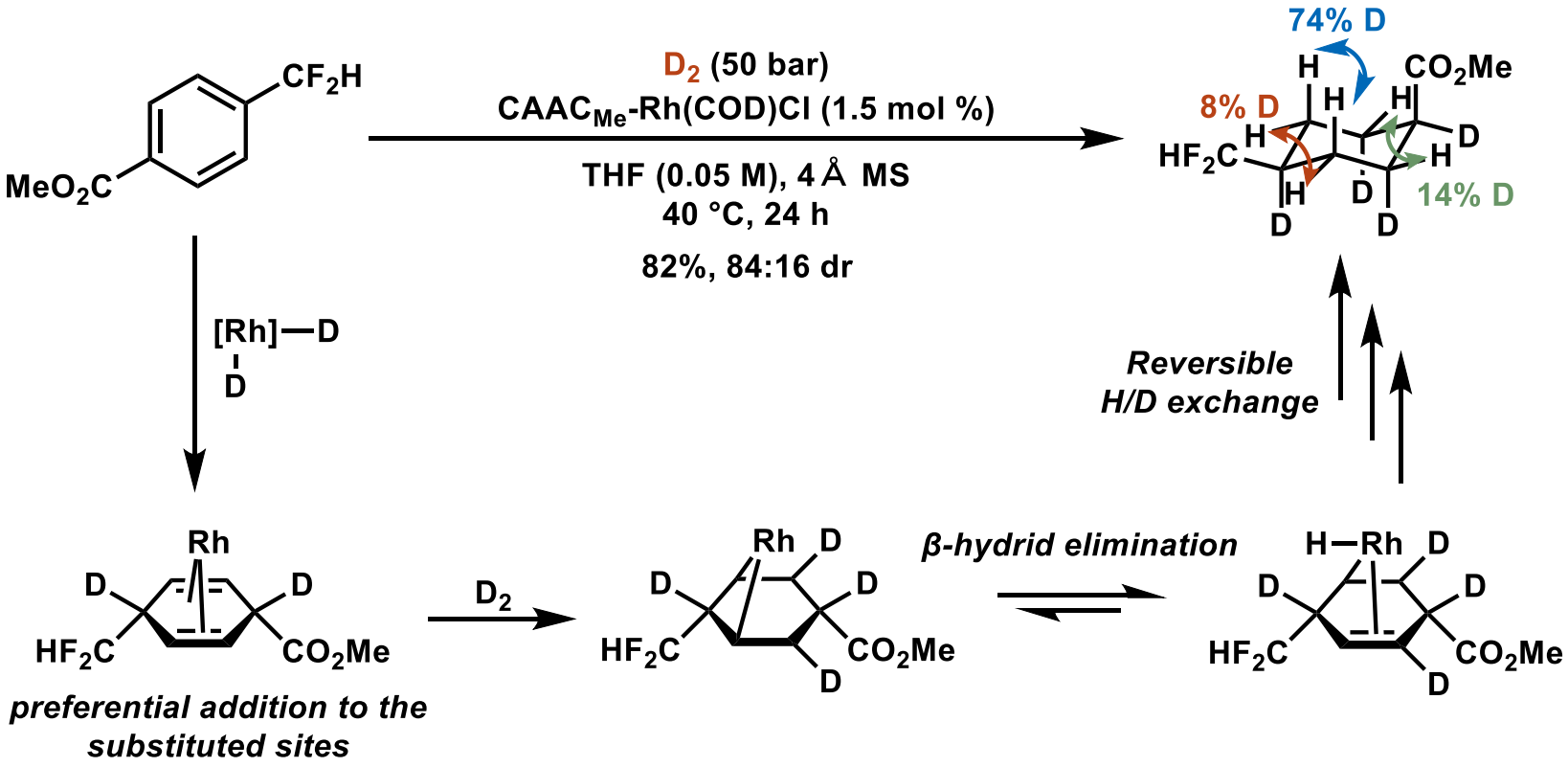
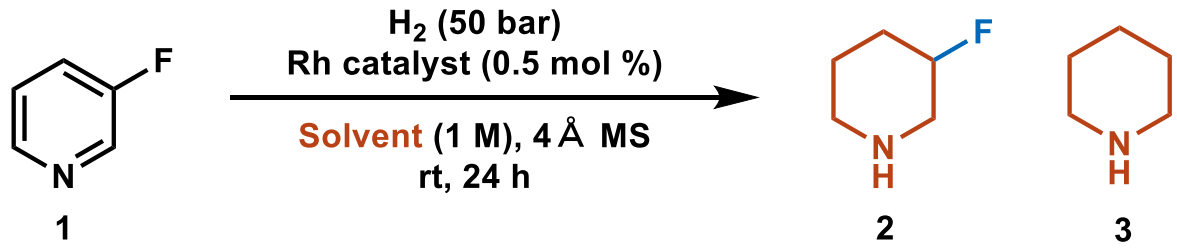
Deuterium-Labeling Experiments

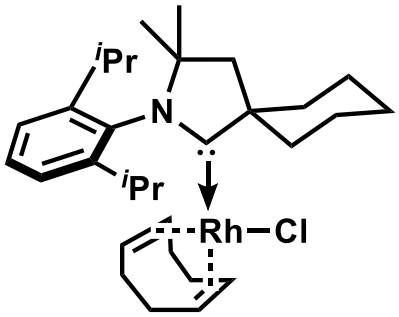


X. Zeng *et al. Angew. Chem. Int. Ed* **2019**, *58*, 16785.

Fluoropyridines



Entry	Solvent	Rh catalyst	Additive	Conversion (%)	2 (%)
1	MeOH	cat.A		>99	<5
2	THF	cat.A		<5	nd
3	Hexane	cat.A		<5	nd

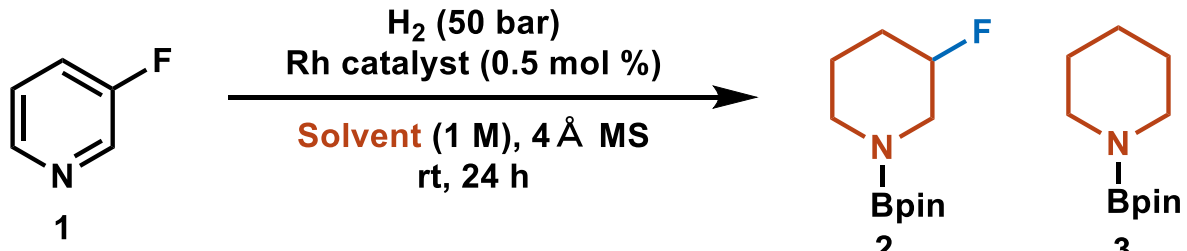


CAAC-Rh(COD)Cl
cat.A

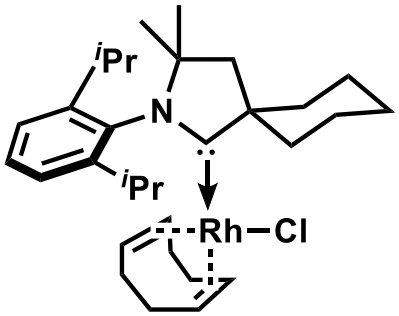
- ✓ catalyst deactivation by the Lewis-basic heterocycles
- ✓ uncontrolled hydrodefluorination side reactions

F. Glorius *et al. Nat. Chem.* **2019**, *11*, 264.

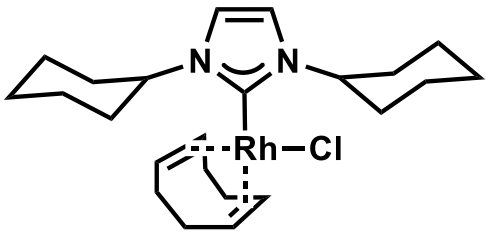
Dearomatization Strategy



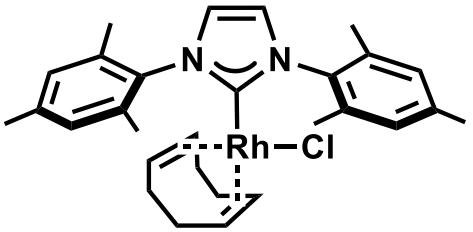
Entry	Solvent	Rh catalyst	Additive	Conversion (%)	2 (%)
1	MeOH	cat.A		>99	<5
2	THF	cat.A		<5	nd
3	Hexane	cat.A		<5	nd
4	THF	cat.A	HBpin	>99	92
5	Hexane	cat.A	HBpin	<5	nd
6	THF	cat.B	HBpin	95	80
7	THF	cat.C	HBpin	20	17



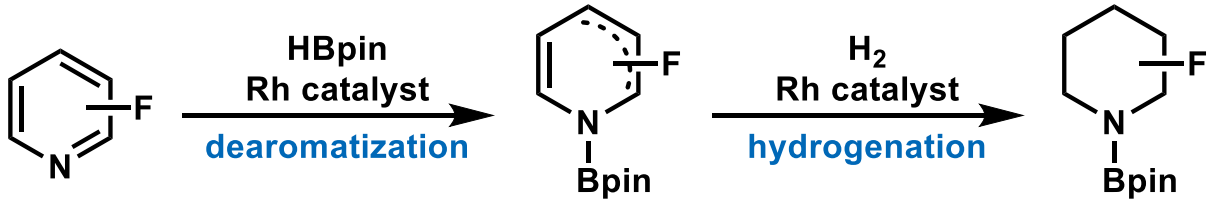
CAAC-Rh(COD)Cl
cat.A



ICy-Rh(COD)Cl
cat.B



IMes-Rh(COD)Cl
cat.C



N protection

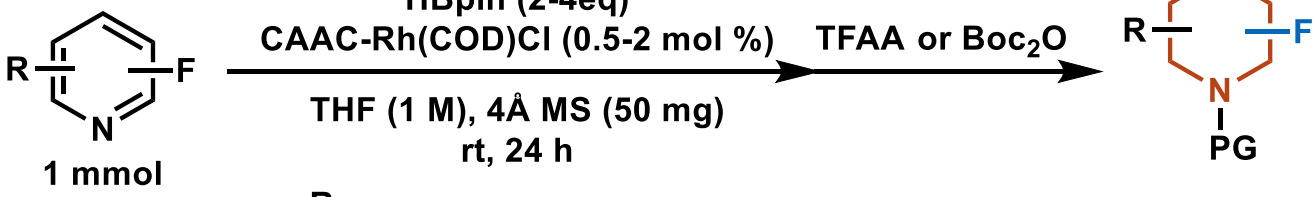
✓dearomatization →easily hydrogenation

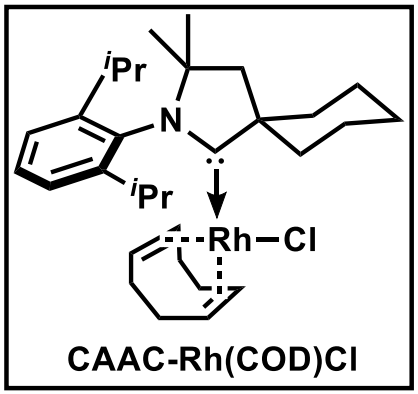
✓N-protection →preventing catalyst poisoning

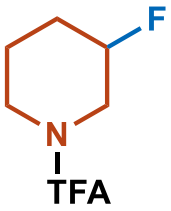
T. Ohmura, M. Suginome *et al. J. Am. Chem*. Soc. **2012**, *134*, 3699.

F. Glorius *et al. Nat. Chem*. **2019**, *11*, 264.

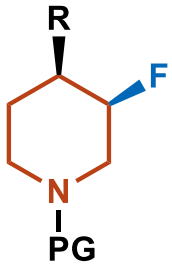
Substrate Scope





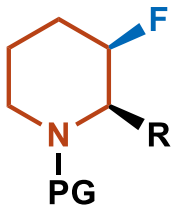


81%

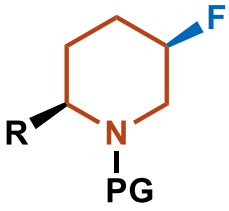


[PG = TFA]
R = Me, 90% (95:5 dr)
Bu, 80% (99:1 dr)
OMe, 70% (99:1 dr)
TMS, 71% (>99:1 dr)

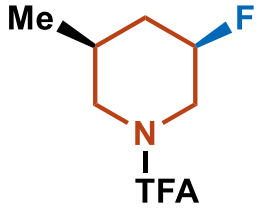
[PG = Boc]
R = CH_2OTBS, 85% (95:5 dr)
NHBoc, 94% (97:3 dr)
Bpin, 73% (96:4 dr)



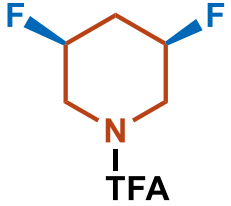
R = [PG = TFA]
Me, 77% (95:5 dr)
[PG = Boc]
CH_2OTBS, 84% (99:1 dr)
CH_2NHBoc, 88% (99:1 dr)



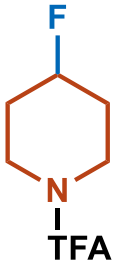
R = [PG = TFA]
Me, 84% (90:10 dr)
CF_3, 79% (93:7 dr)
[PG = Boc]
CH_2OTBS, 94% (97:3 dr)
CH_2NHBoc, 75% (97:3 dr)



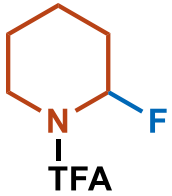
81% (90:10 dr)



79% (99:1 dr)

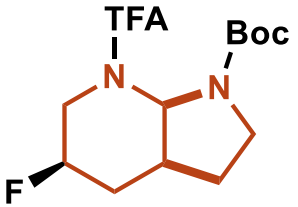


20%

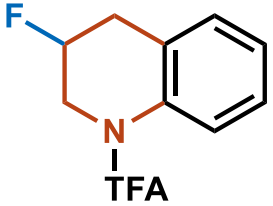


0%

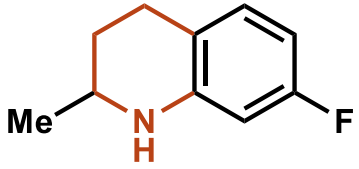
HBpin (4 eq), 40 °C



44% (86:14)



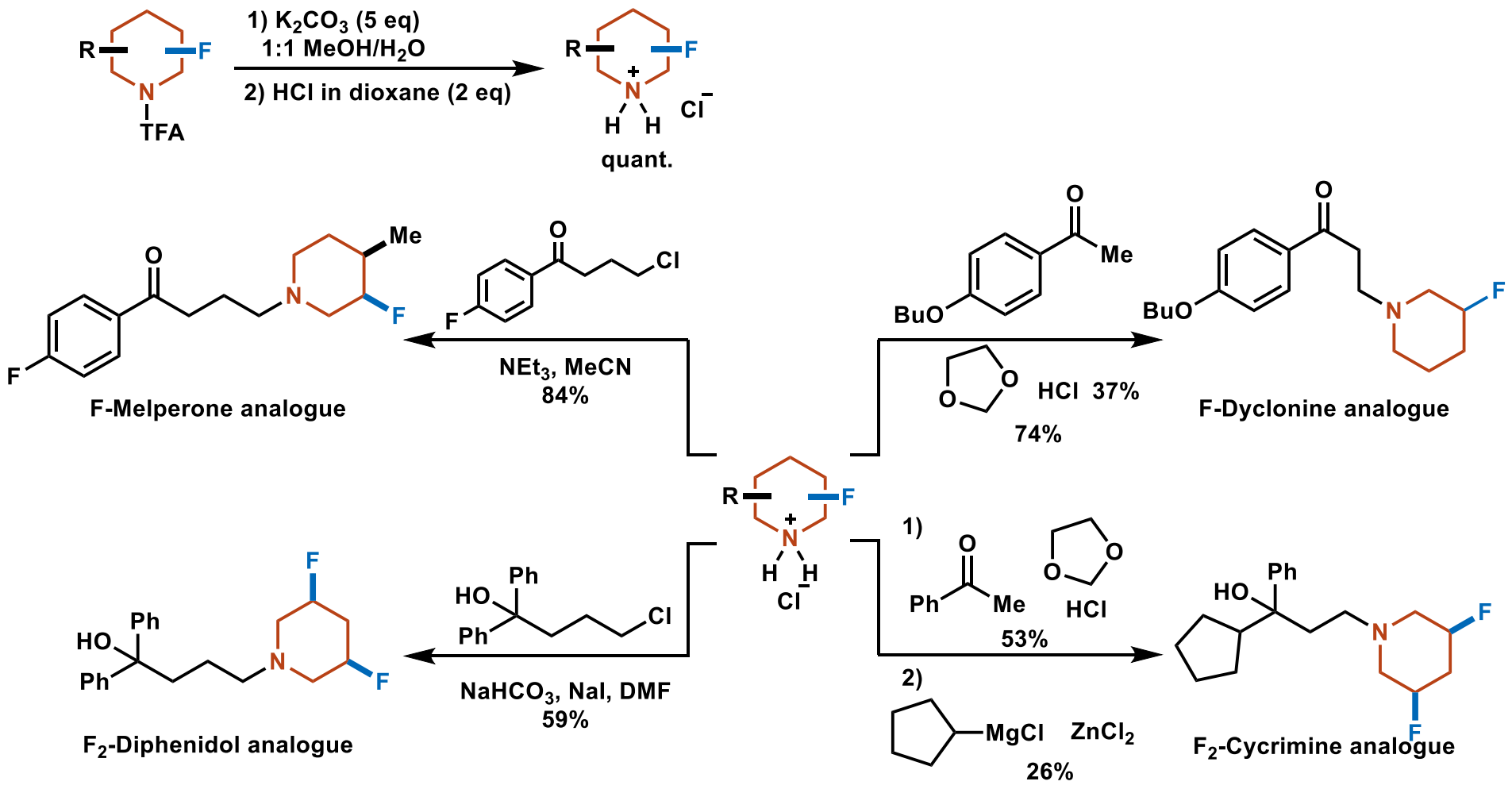
78%



91%

F. Glorius *et al. Nat. Chem.* **2019**, *11*, 264.

Application

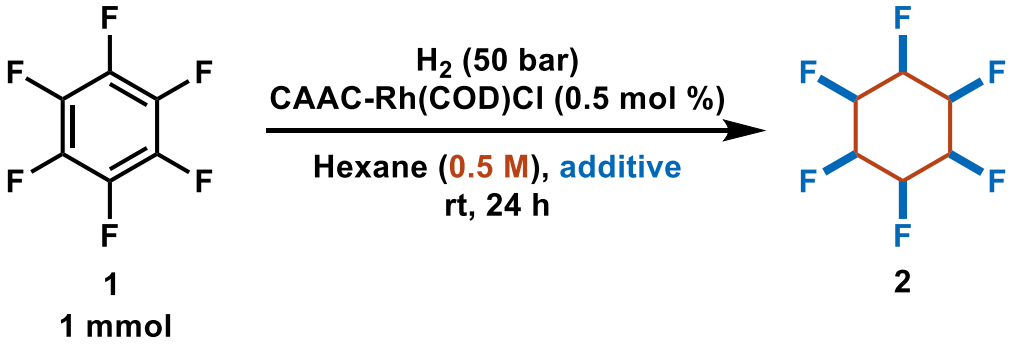


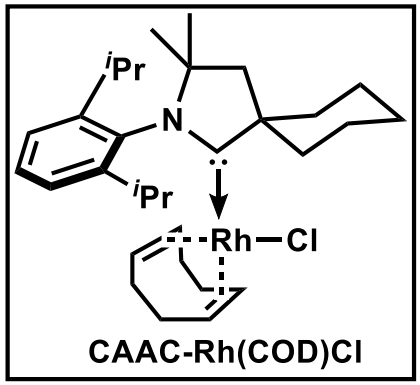
✓**Incorporation of fluorine into aliphatic N-heterocycles may accelerate drug discovery.**

F. Glorius *et al. Nat. Chem.* **2019**, *11*, 264.

Contents

Sillica gel improves the reactivity





Entry	Additive	amount [mg]	4 (%) (dr)
1	4Å MS (0.07 M)	150	34 (>20:1)
2	4Å MS	150	12 (>20:1)
3	4Å MS	450	10 (>20:1)
4	SiO_2	150	44 (>20:1)
5	SiO_2	300	80 (>20:1)
6	SiO_2	450	94 (>20:1)
7	powdered 4Å MS	450	89 (>20:1)

✓In more concentrated conditions, SiO_2 showed good results.

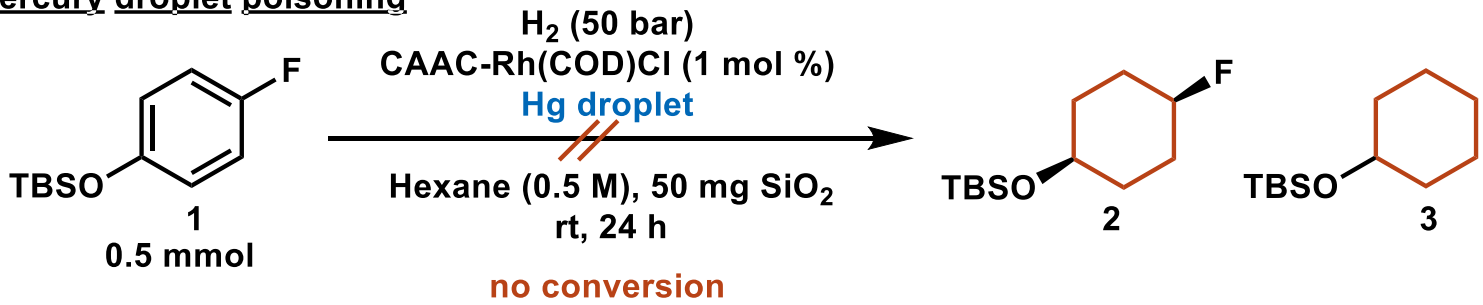
- High surface area of the insoluble additive is crucial for an efficient reaction??

Heterogeneous Catalyst??

F. Glorius *et al. Angew. Chem. Int. Ed* **2018**, *57*, 8297.

Catalyst Poisoning Study

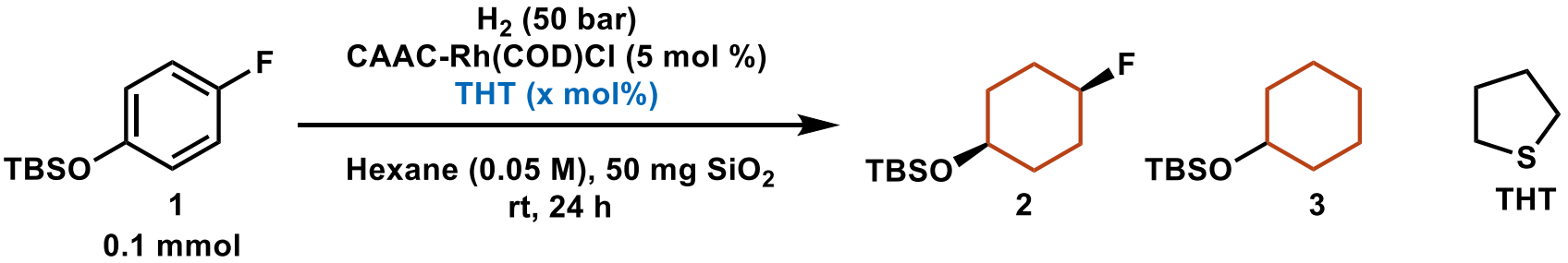
Mercury droplet poisoning



no conversion

✓**poisoning via formation of an amalgame**

Substoichiometric poisoning with tetrahydrothiophene (THT)



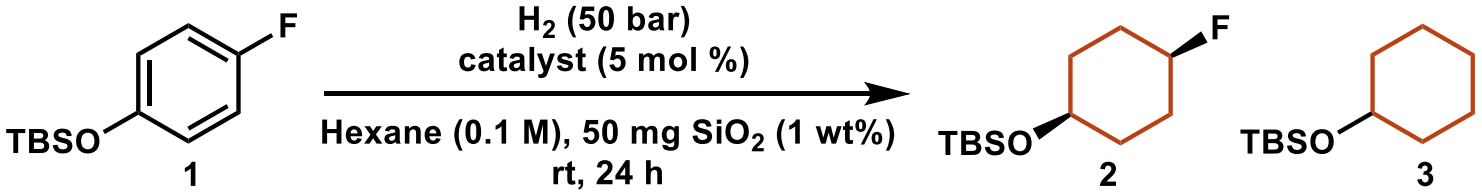
Entry	THT (mo%)	conversion (%)	2 (%) (dr)	3 (%)
1	0	>99	86 (>20:1)	4
2	0.5	>99	87 (>20:1)	5
3	1.5	>99	83 (>20:1)	6
4	2.5	86	71 (>20:1)	6
5	3.5	0	nd	nd
6	5	0	nd	nd

✓**deactivation by a substoichiometric amount of the catalyst poison**

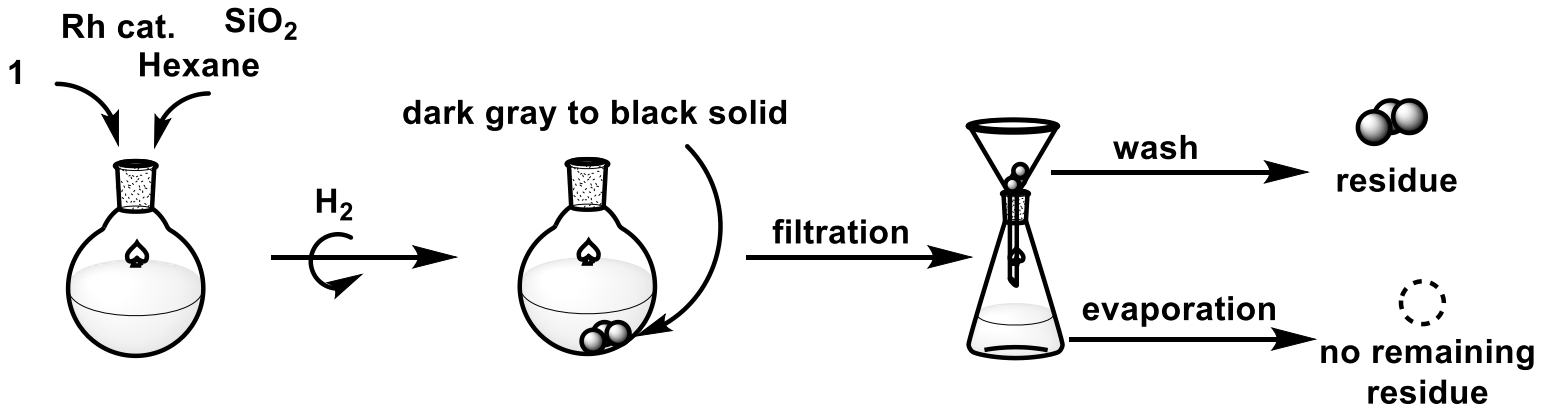
F. Glorius *et al. ACS Catal.* **2020**, *10*, 6309.

Catalyst Filtlation & Rycycling

Maitlis' test - catalyst recovery



Entry	Solvent	Conversion (%)	2 (%) (dr)	3 (%)
1	CAAC-Rh(COD)Cl and SiO_2	>99	90 (94:6)	3
2	residue obtained from entry 1	>99	91 (94:6)	4
3	residue obtained without substrate	>99	89 (94:6)	3

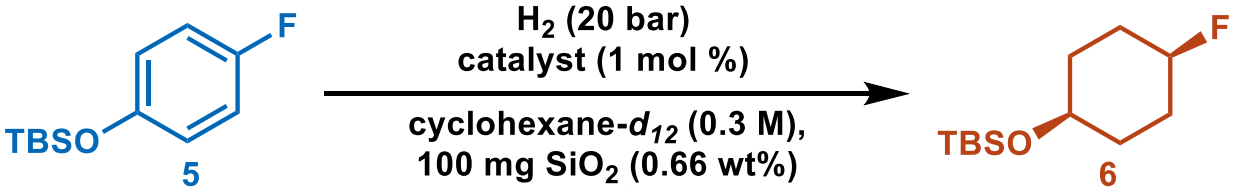


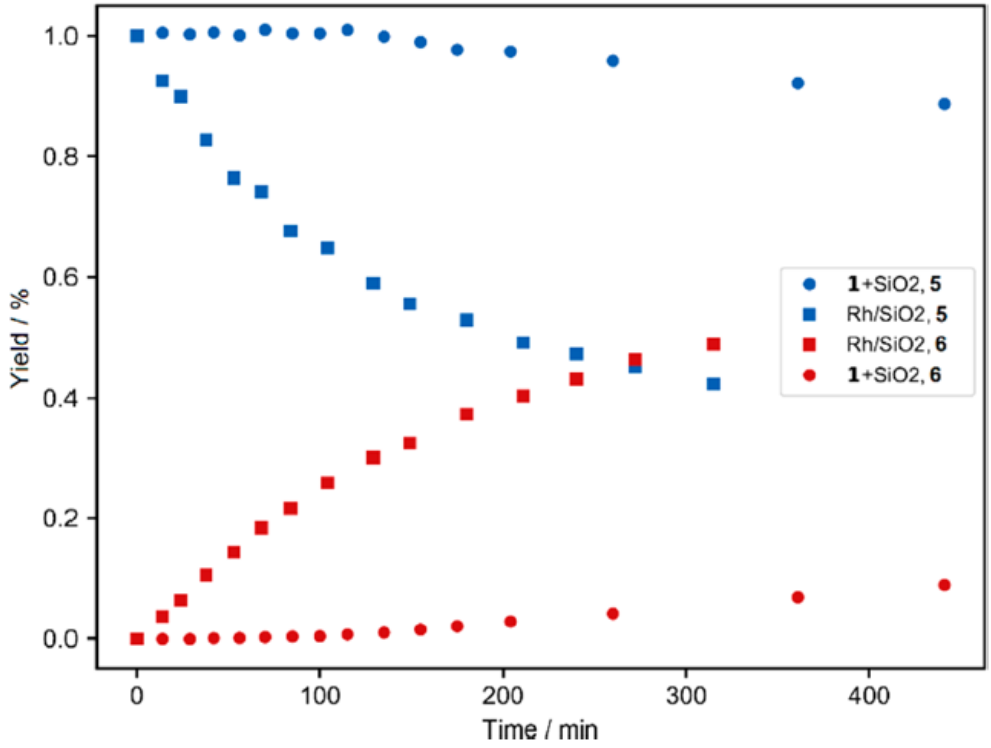
✓**All obtained yields were identical.**

- **active catalyst is contained in the black residue obtained after the reaction**
- **the active catalyst can be recycled without loss of activity**

F. Glorius *et al. ACS Catal.* **2020**, *10*, 6309.

Kinetic Study





1
CAAC-Rh(COD)Cl

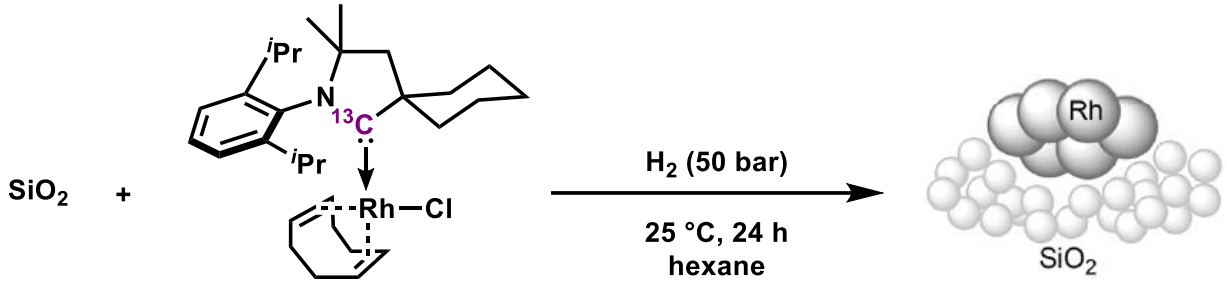
Rh-SiO_2
residue

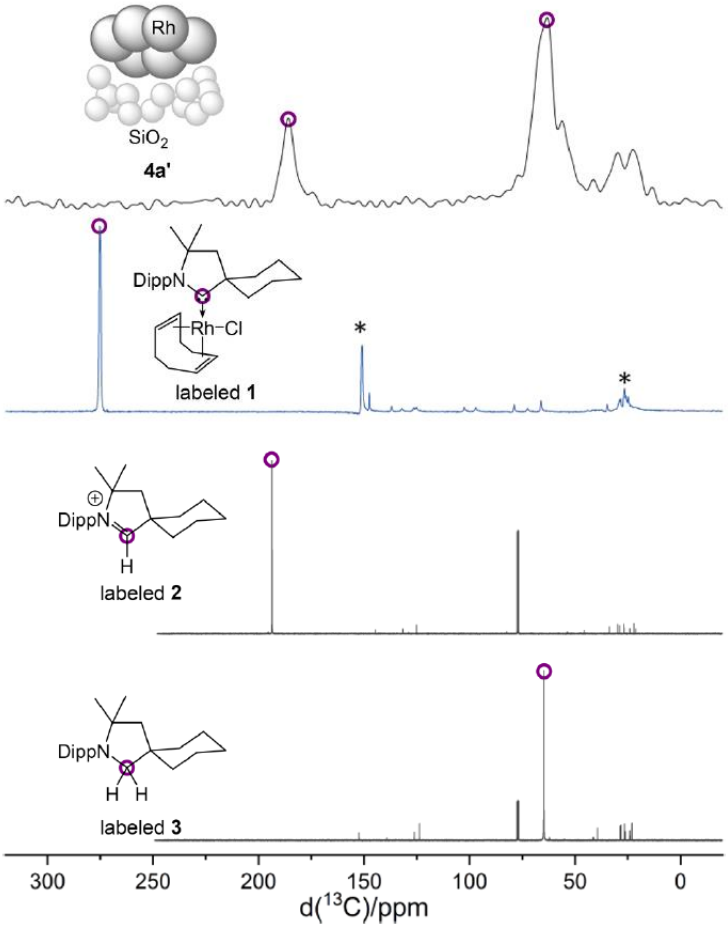
✓**when using 1 (CAAC-Rh(COD)Cl) as precatalyst, induction period was observed.**

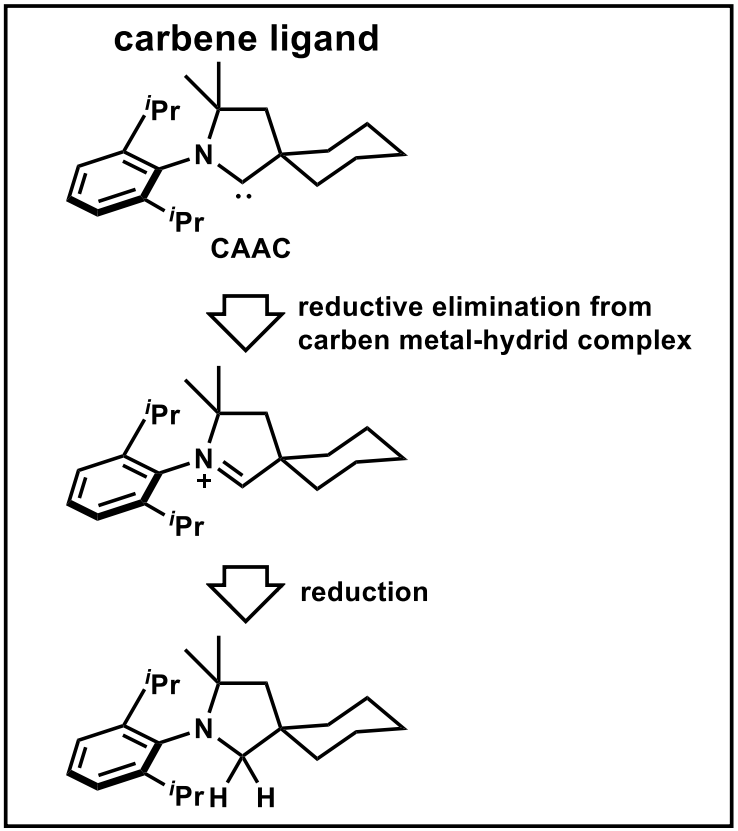
- **insoluble black residue obtained after the reaction is active catalyst.**

F. Glorius *et al. ACS Catal.* **2020**, *10*, 6309.

Observation of Ligand

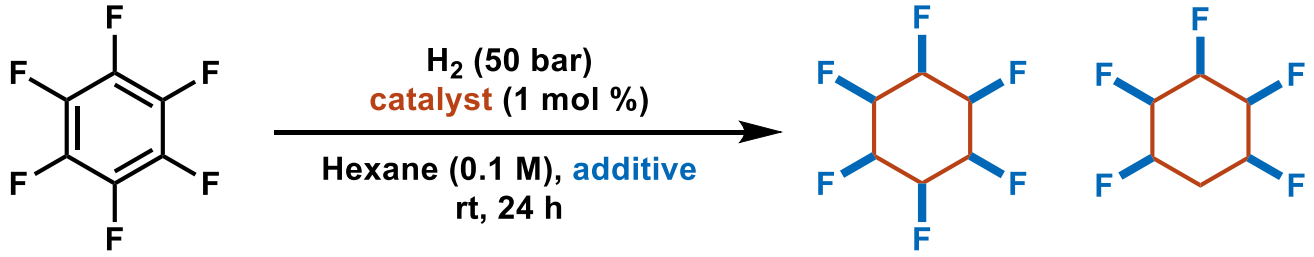




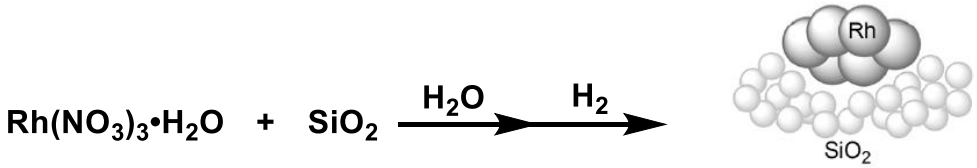


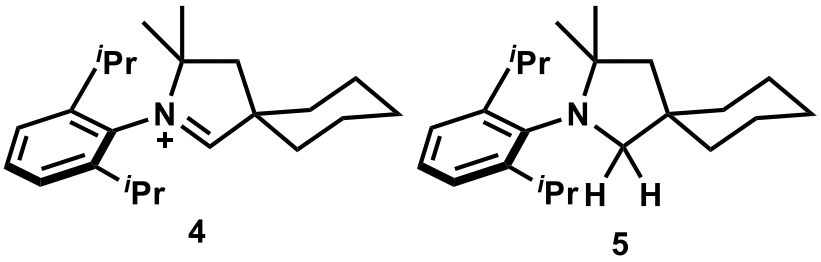
F. Glorius *et al. ACS Catal.* **2020**, *10*, 6309.

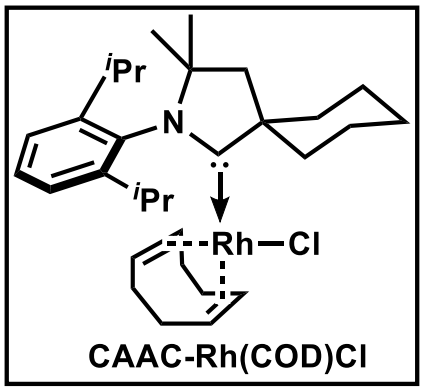
Comparing the Performance



Entry	Catalyst	additive	2 (%)	3 (%)
1	CAAC-Rh(COD)Cl + SiO_2	-	39	22
2	Rh/SiO_2 NPs	4 and 5 (1:1)	29	8
3	Rh/SiO_2 NPs	-	4	57



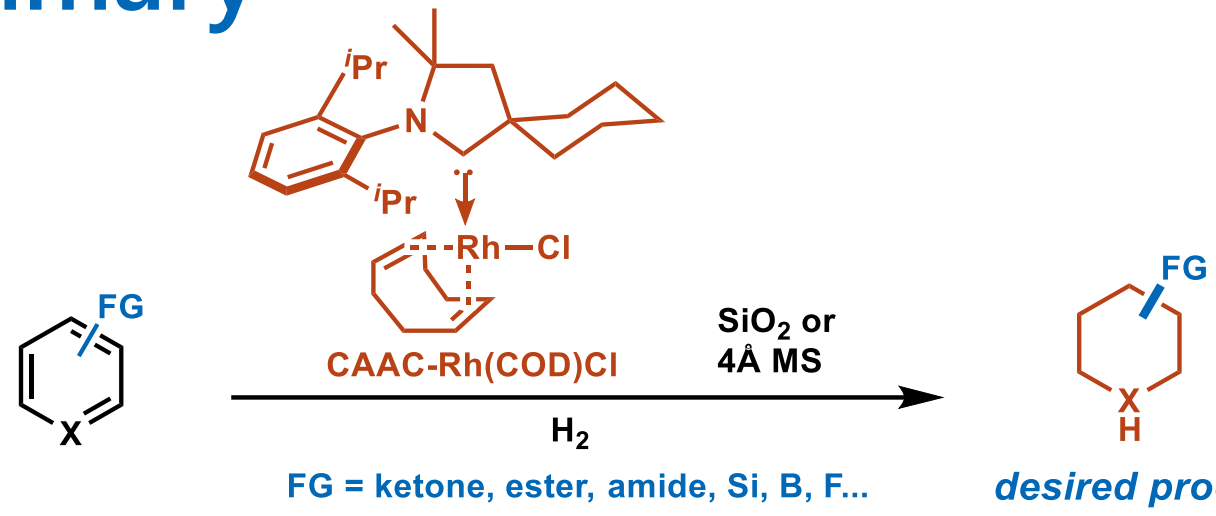


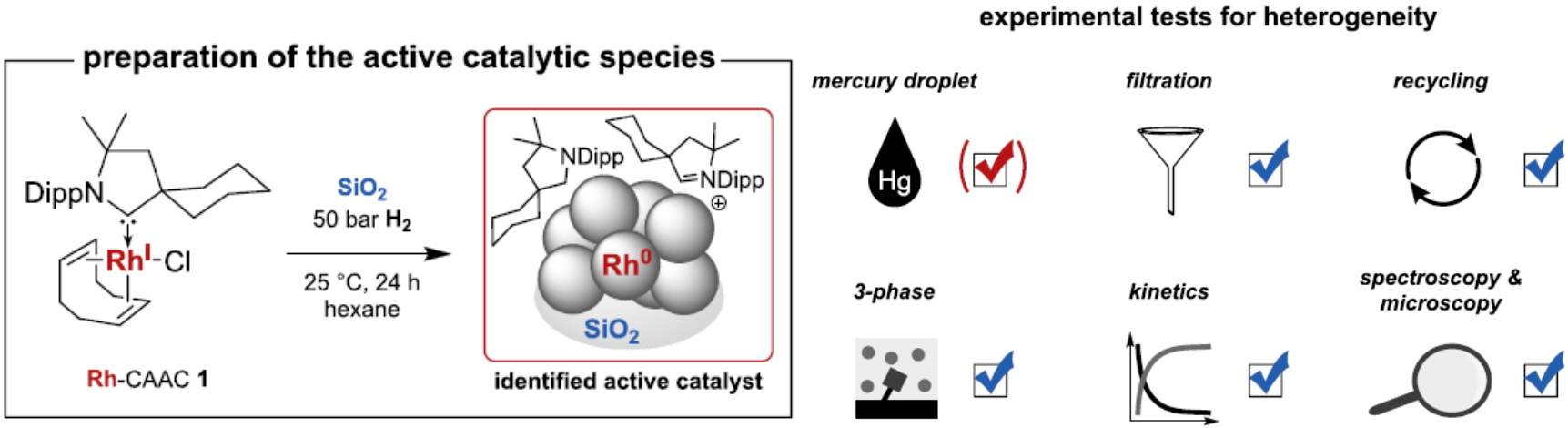


✓ **When applying the optimized modifiers to the Rh NPs the yield of the desired product could be increased .**

F. Glorius *et al. ACS Catal.* **2020**, *10*, 6309.

Summary



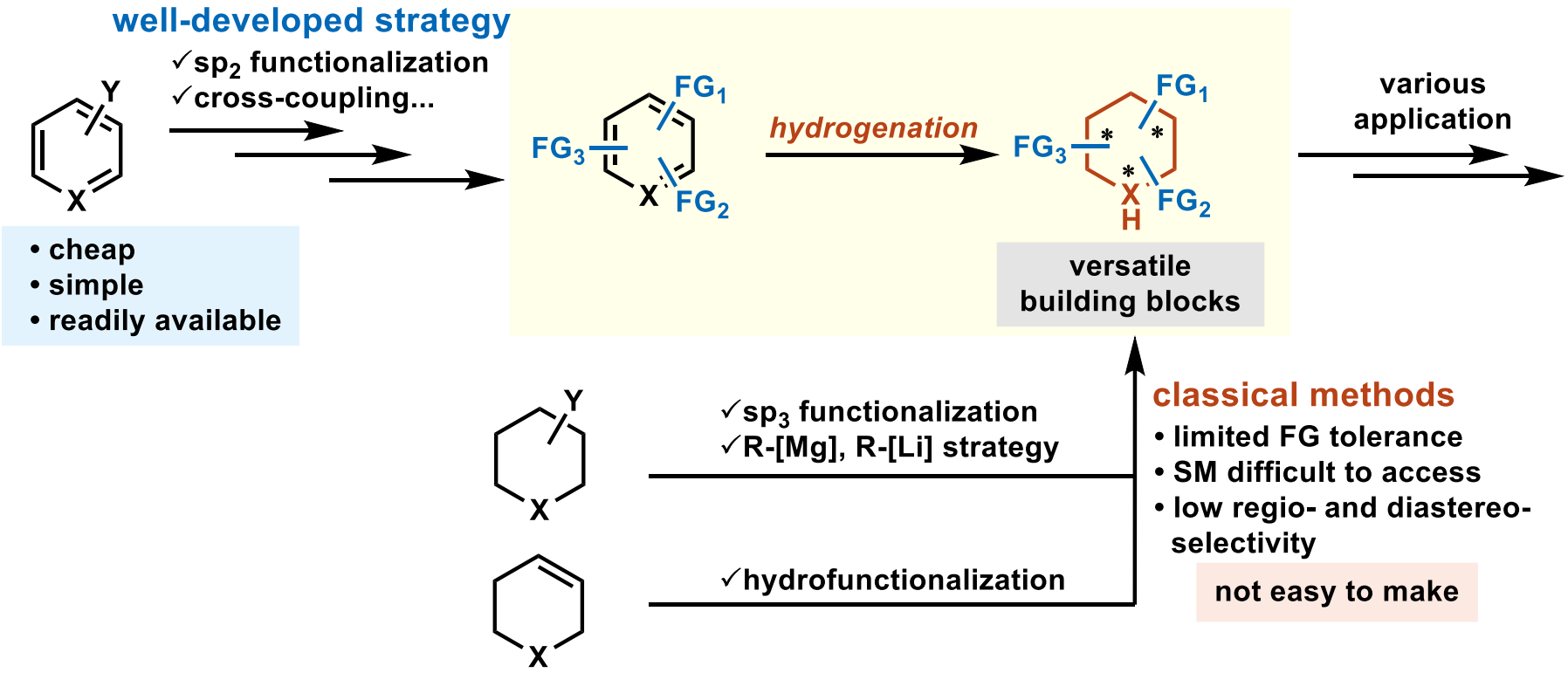


Silica gel-supported Rh(0) NPs as active catalytic species

CAAC-derived pyrrolidium and pyrrolidine act as modifiers that are key in controlling the chemoselectivity.

F. Glorius *et al. ACS Catal.* **2020**, *10*, 6309.

Summary



Functionalization of arene is more facile than that of the saturated products.