

Selectivity in Arene Hydrogenation

Tropical Seminar

November 19, 2024

Julia Greenbaum

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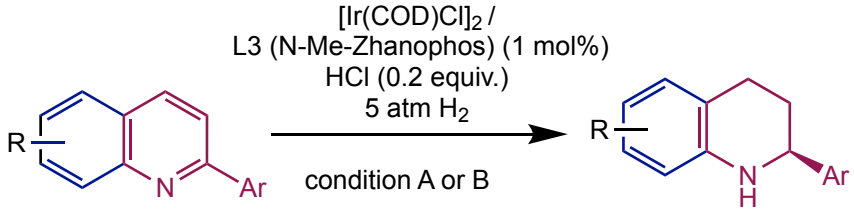
I. Regioselectivity

II. Chemoselectivity

III. Diastereoselectivity

Controlling Regioselectivity in Quinoline Hydrogenation

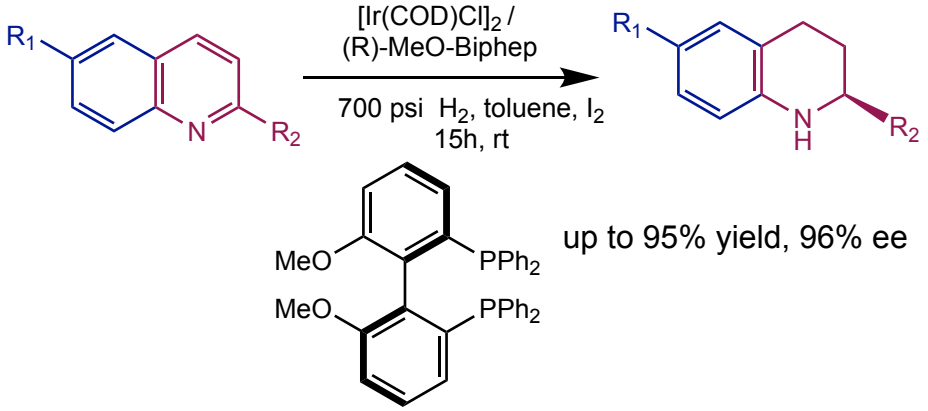
Many examples of quinoline partial reduction of the heterocycle…



A: toluene: 1, 4-dioxane (4:1), rt, 24h — up to 99% yield, 98% ee (R)

B: EtOH, rt, 12h — up to 99% yield, 94% ee (S)

Z. Han, G. Liu, X. Yang, X. Q. Dong and X. Zhang, *ACS Catal.,* 2021, 11, 7281–7291.



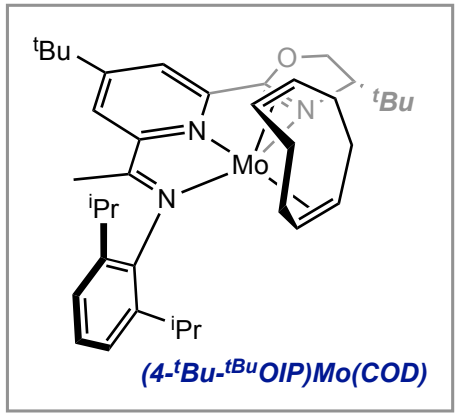
up to 95% yield, 96% ee

W. B. Wang, S. M. Lu, P.Y. Yang, X. W. Han, Y.G. Zhou, *J. Am. Chem. Soc.,* 2003, 125, 10536–10537.

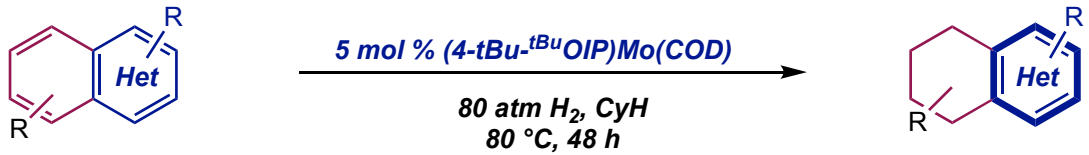
*How can we overcome aromaticity barrier and control selectivity for **carbocycle** or **heterocycle**?*

- *Sterics*
- *Influence of ligand, solvent, conditions*
- *Electrochemically*

Controlling Regioselectivity in Quinoline Hydrogenation

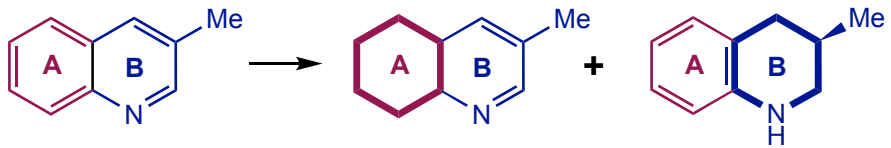


(4-^{t}Bu-^{tBu}OIP)Mo(COD)

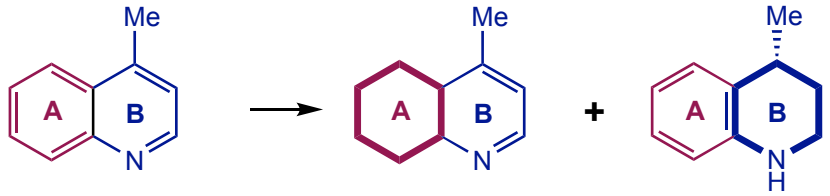




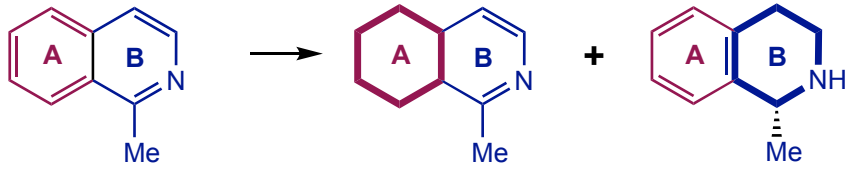
1g, 50% conv. — *2g-A (22%)* — *2g-B (20%)*



1h, full conv. — *2h-A 75% (80%)* — *2h-B 13% (15%) 87% ee*



1i, full conv. — *2i-A 67% (92%)* — *2i-B (8%) 99% ee*



1j, 60% conv. — *2j-A 20% (46%)* — *2j-B (13%) 15% ee*



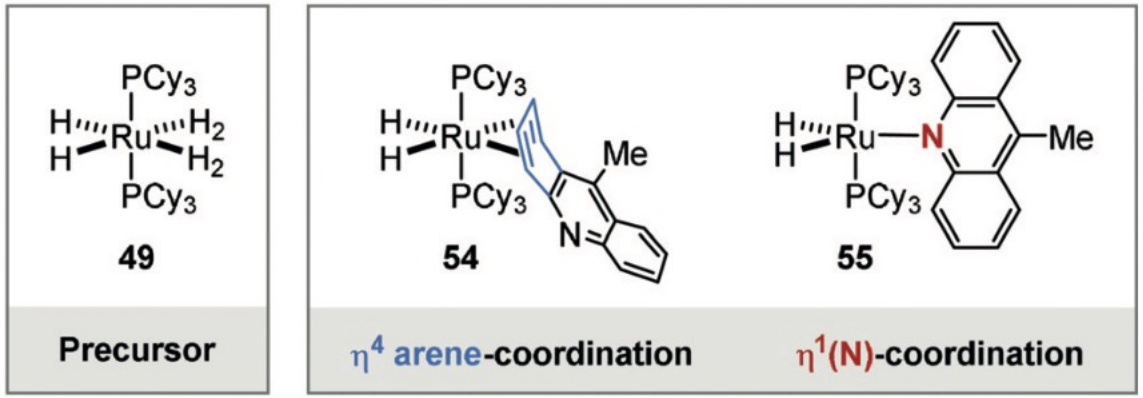
1k, 54% conv. — *2k-A(43%)* — *2k-B (11%) 55% ee*

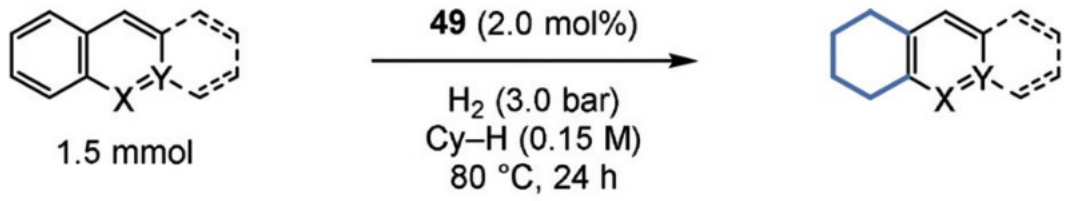
Steric Crowding on the Heterocycle Leads to Exclusive Carbocycle Reduction

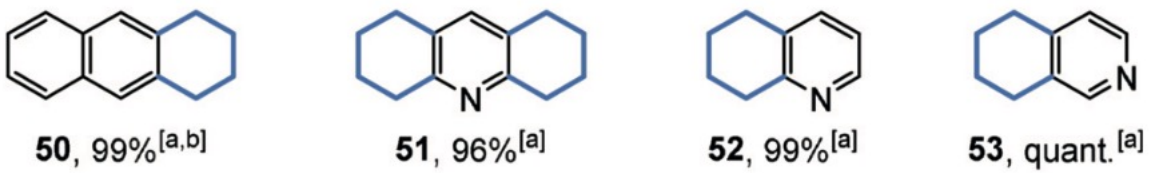
P. Viereck, G. Hierlmeier, Pabst, T. P., Tosatti, P., Puentener, K., Chirik, P. J.; *J. Am Chem. Soc.* **2022**, 144, 11203–11214.

Controlling Regioselectivity in Quinoline Hydrogenation

Ru Examples of Exclusive Carbocycle Hydrogenation







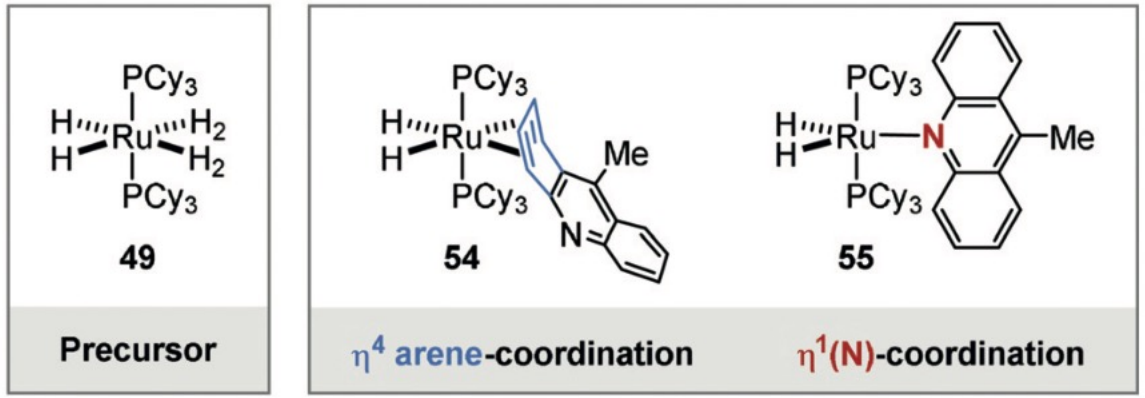
50, 99%[a,b] **51**, 96%[a] **52**, 99%[a] **53**, quant.[a]

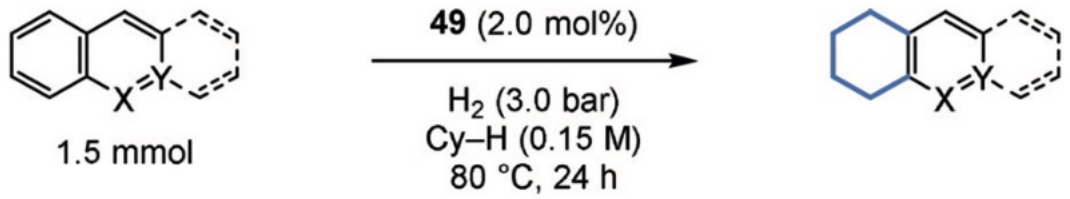
a) gc yields b) 1h rxn time

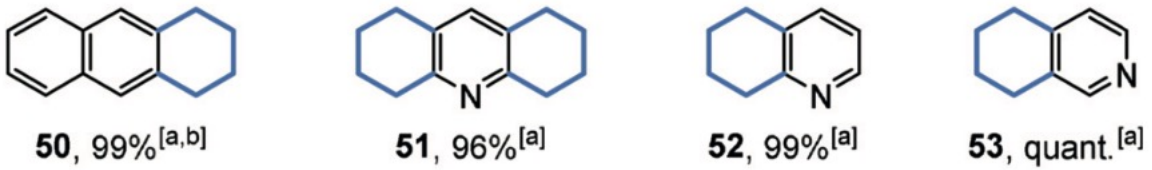
A. F. Borowski, S. Sabo-Etienne, B. Donnadieu, B. Chaudret, *Organometallics.* **2003**, *22*, 1630.

Controlling Regioselectivity in Quinoline Hydrogenation

Ru Examples of Exclusive Carbocycle Hydrogenation







Substrates with no conversion:



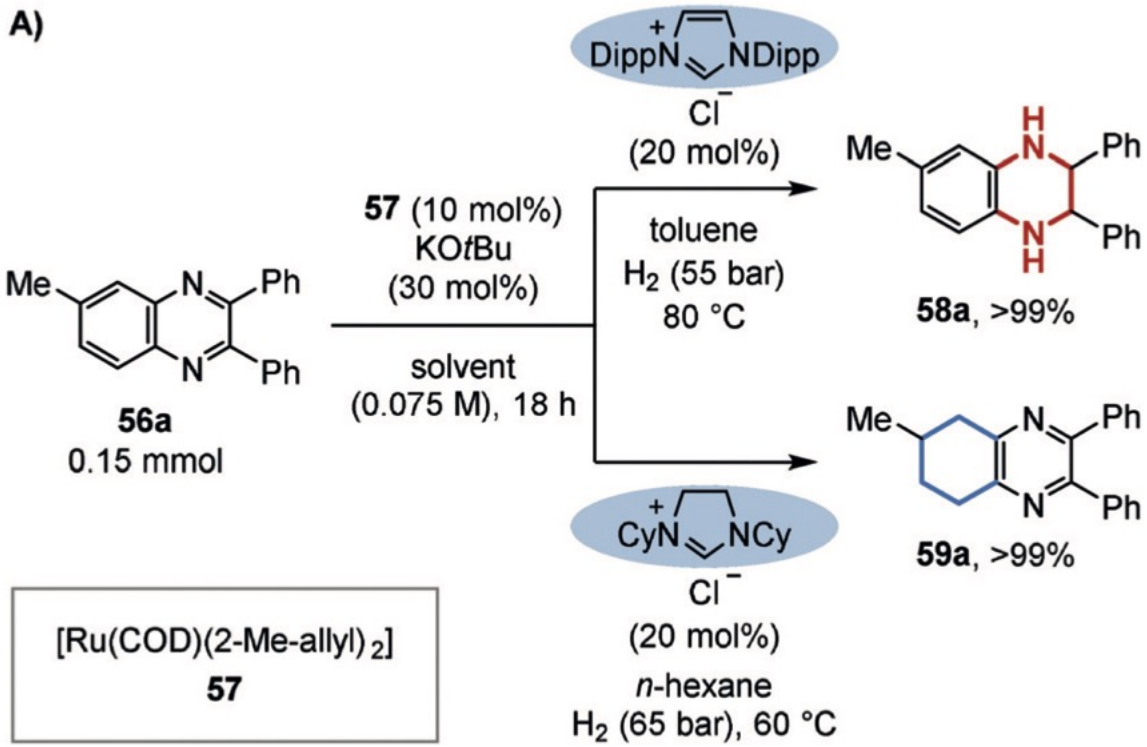
a) gc yields b) 1h rxn time

Preferential Ru-η^4-arene coordination determines regioselectivity – η^1-(N)-displaced by dihydrogen

A. F. Borowski, S. Sabo-Etienne, B. Donnadieu, B. Chaudret, *Organometallics.* **2003**, *22*, 1630.

Controlling Regioselectivity in Quinoline Hydrogenation

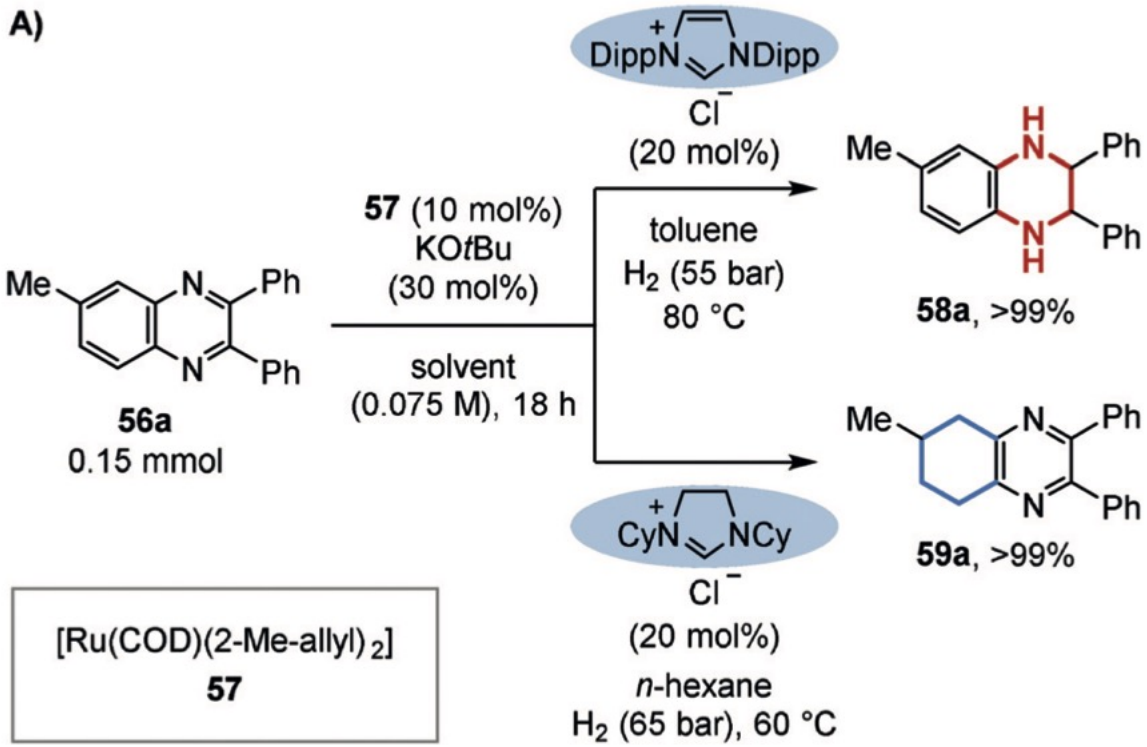
Ru Examples of Exclusive Carbocycle Hydrogenation



S. Urban, N. Ortega, F. Glorius, *Angew. Chem. Int. Ed.* **2011**, *50*, 3803.

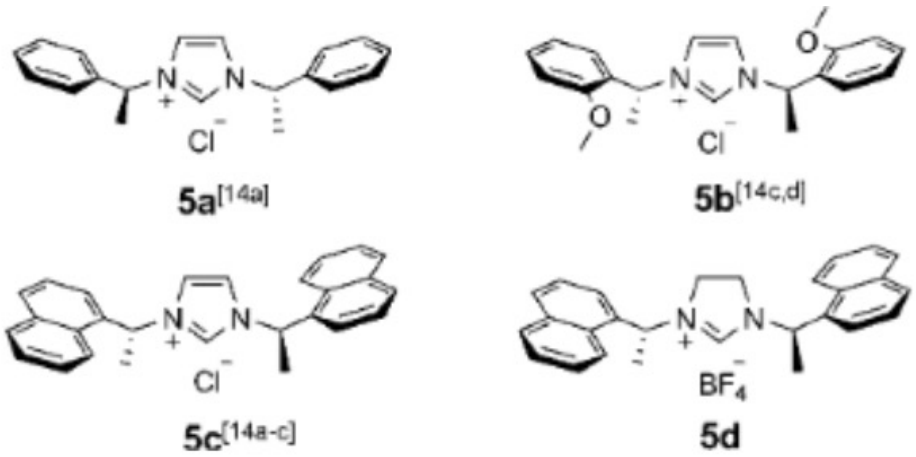
Controlling Regioselectivity in Quinoline Hydrogenation

Ru Examples of Exclusive Carbocycle Hydrogenation



Key to carbocycle-selective hydrogenation:
steric crowding close to metal center

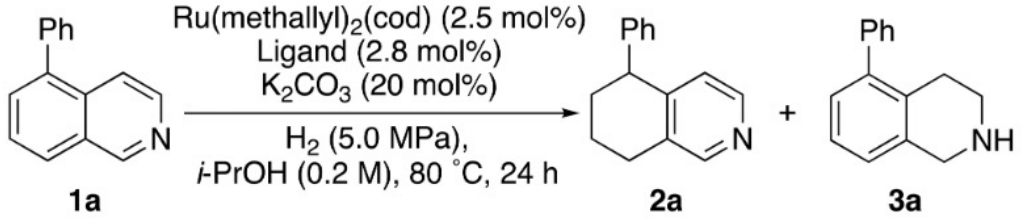
Carbocycle-reduced product selectively:

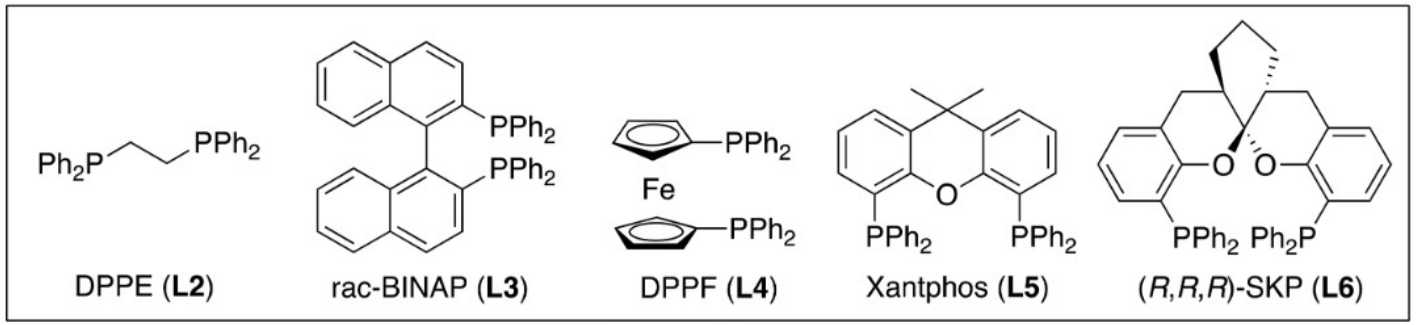


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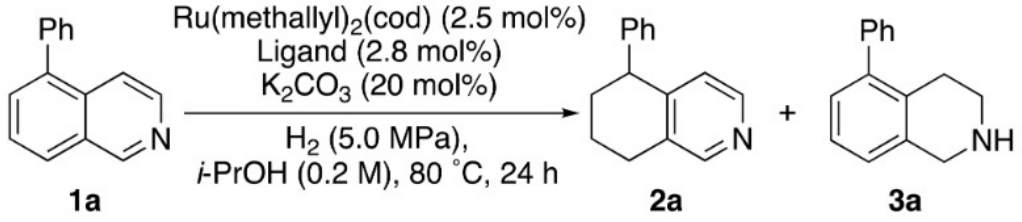


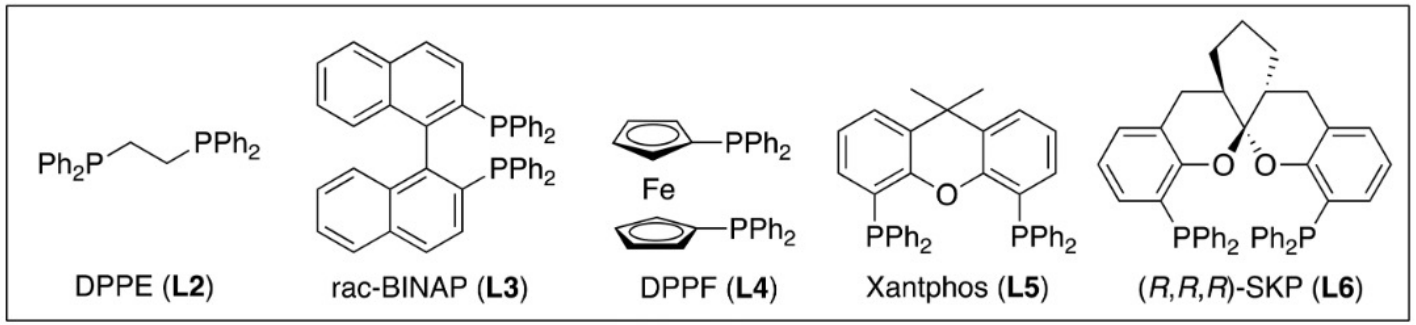


Y. Jin, Y. Makida, T. Uchida, R. Kuwano, J. *Org. Chem.* **2018**, *83*, 3829.

Controlling Regioselectivity in Quinoline Hydrogenation

Ru Examples of Exclusive Carbocycle Hydrogenation





entry	ligand	yield of **2a** (%)[b]	yield of **3a** (%)[b]	**2a**:**3a**[b]	er of **2a**[c]
1	PPh_3[d]	0	21	0:100	
2	**L2**	0	21	0:100	
3	**L3**	2	92	2:98	
4	**L4**	5	77	6:94	
5	**L5**	9	49	16:84	
6	**L6**	54	44	55:45	70:30
7[e]	**L1**	>99[f]	0	100:0	79:21

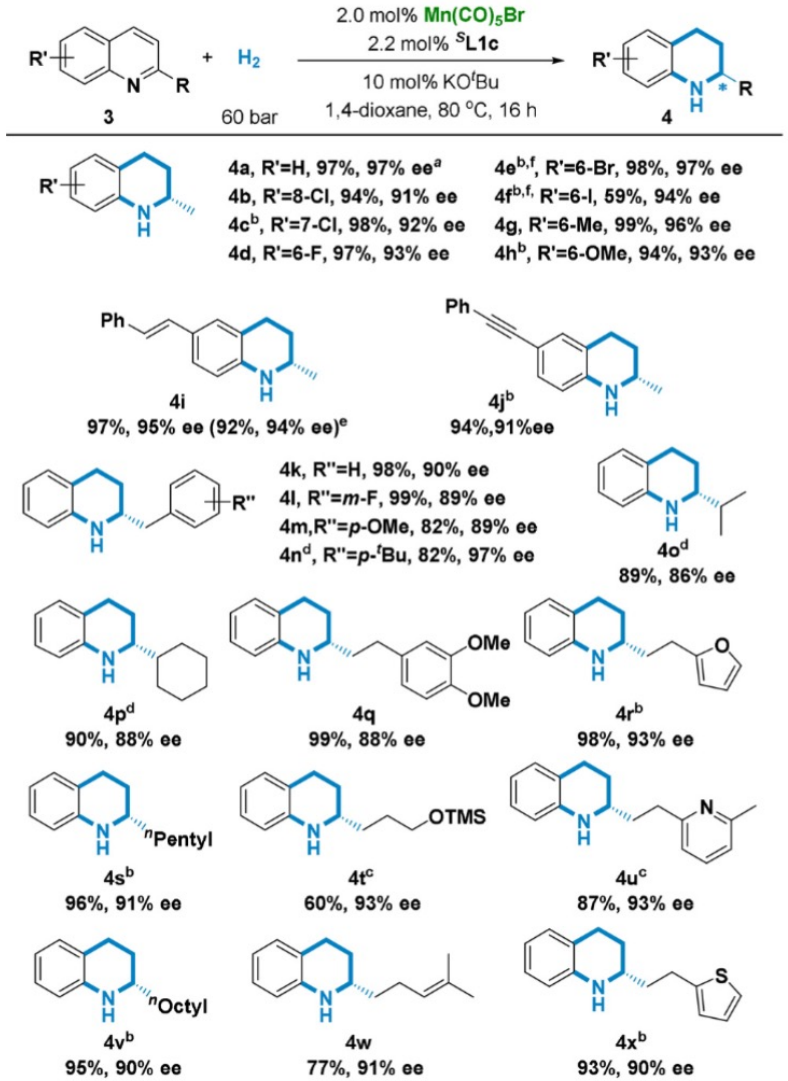
[a]Reactions were conducted on a 0.1 mmol scale under 5.0 MPa of H_2 at 80 °C for 24 h unless otherwise noted. The ratio of **1a** (0.2 M)/Ru/**L1**/K_2CO_3 was 40/1.0/1.1/8.0. [b]Determined by ^1H NMR analysis. [c]Determined by chiral HPLC analysis. [d]5.5 mol % of PPh_3 was used. [e]On a 0.2 mmol scale. [f]**2a** was isolated from the reaction mixture quantitatively.

A large bite angle of bisphosphine = key to achieving carbocycle regioselective hydrogenation

Y. Jin, Y. Makida, T. Uchida, R. Kuwano, J. *Org. Chem.* **2018**, *83*, 3829.

Controlling Chemoselectivity in Quinoline Hydrogenation

First-row Chemoselective Arene Hydrogenation

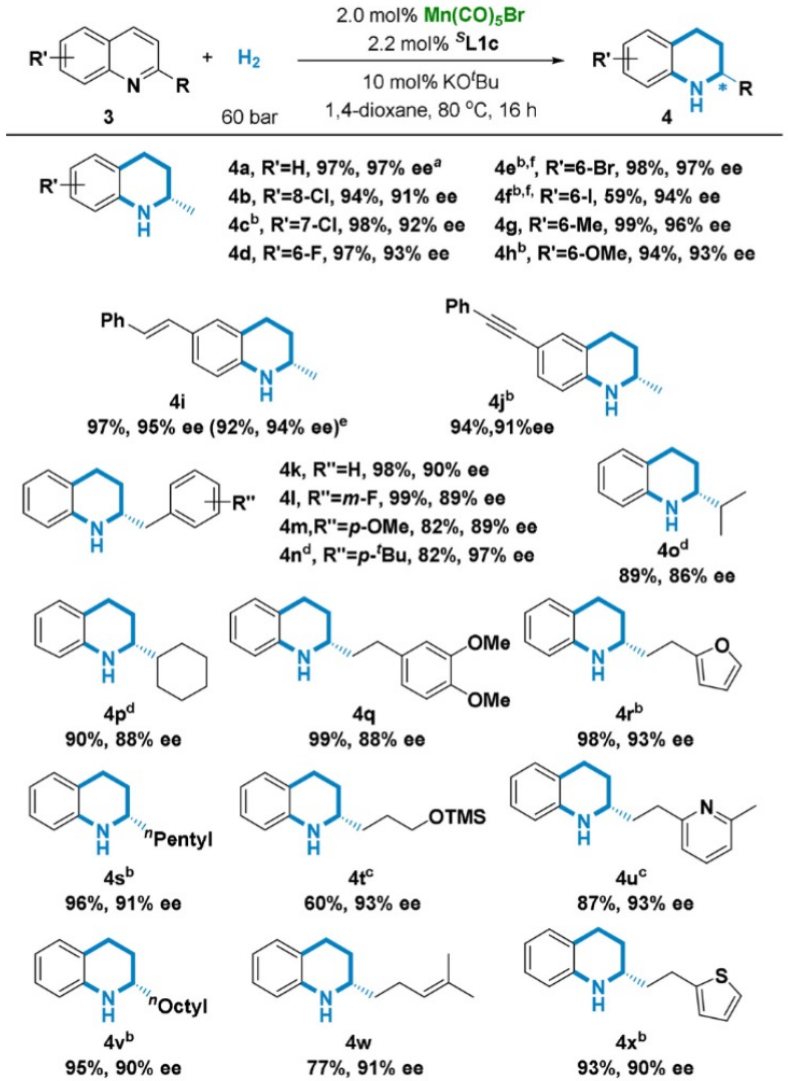


Wide range of functional group tolerances

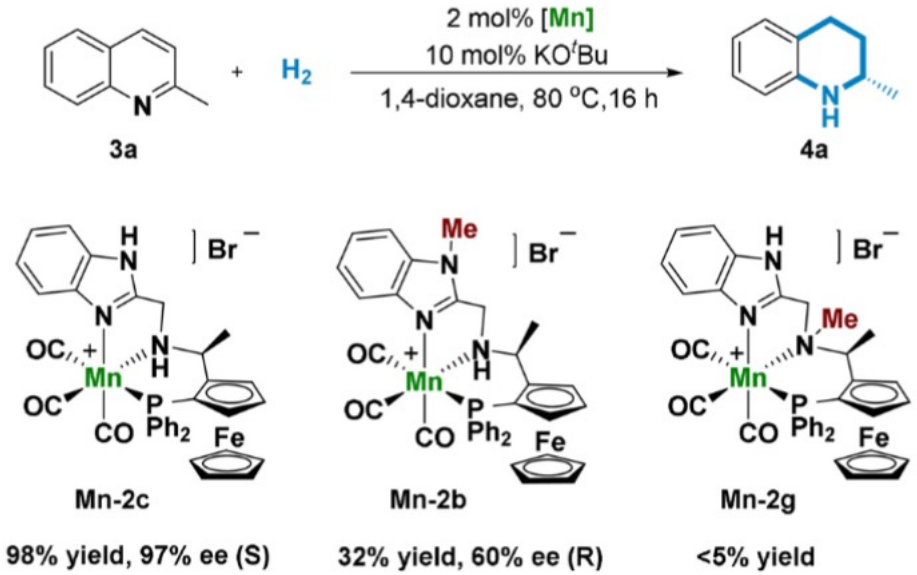
C. Liu, M. Wang, S. Liu, Y. Wang, Y. Peng, Y. Lan and Q. Liu, Angew. Chem., Int. Ed., **2021**, *60*, 5108–5113.

Controlling Chemoselectivity in Quinoline Hydrogenation

First-row Chemoselective Arene Hydrogenation



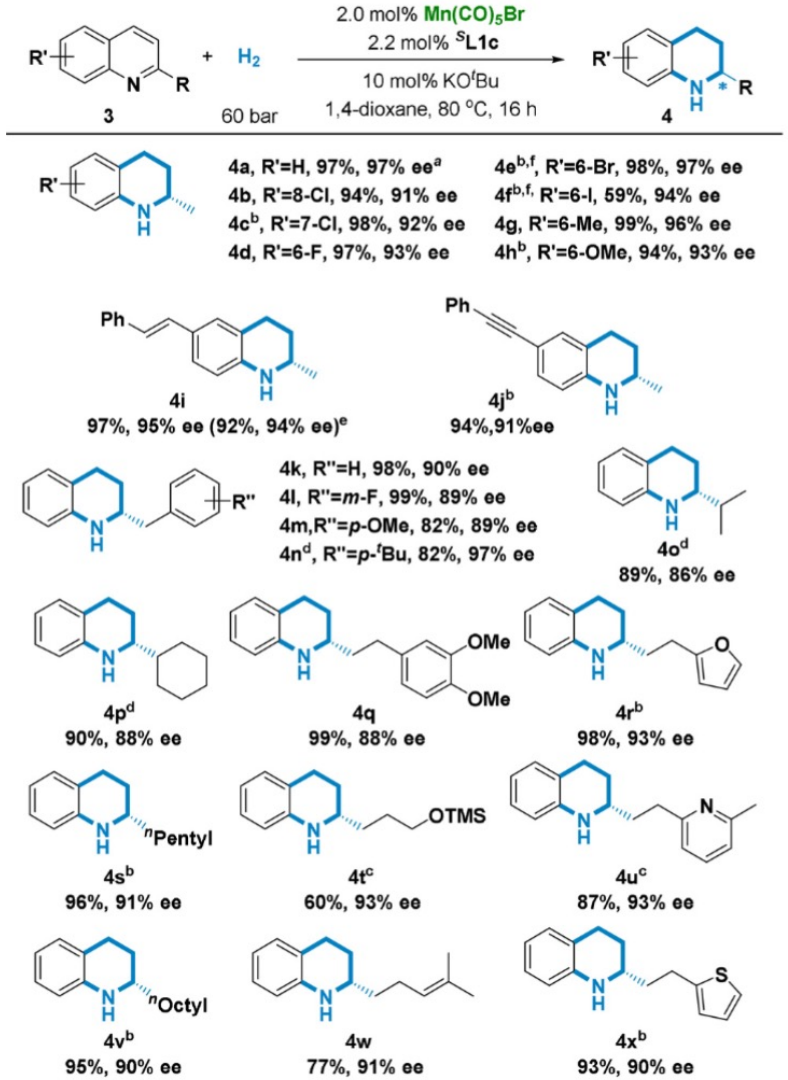
Wide range of functional group tolerances



The central NH group is crucial for reactivity via metal-ligand cooperation

C. Liu, M. Wang, S. Liu, Y. Wang, Y. Peng, Y. Lan and Q. Liu, Angew. Chem., Int. Ed., **2021**, *60*, 5108–5113.

Controlling Chemoselectivity in Quinoline Hydrogenation



Wide range of functional group tolerances

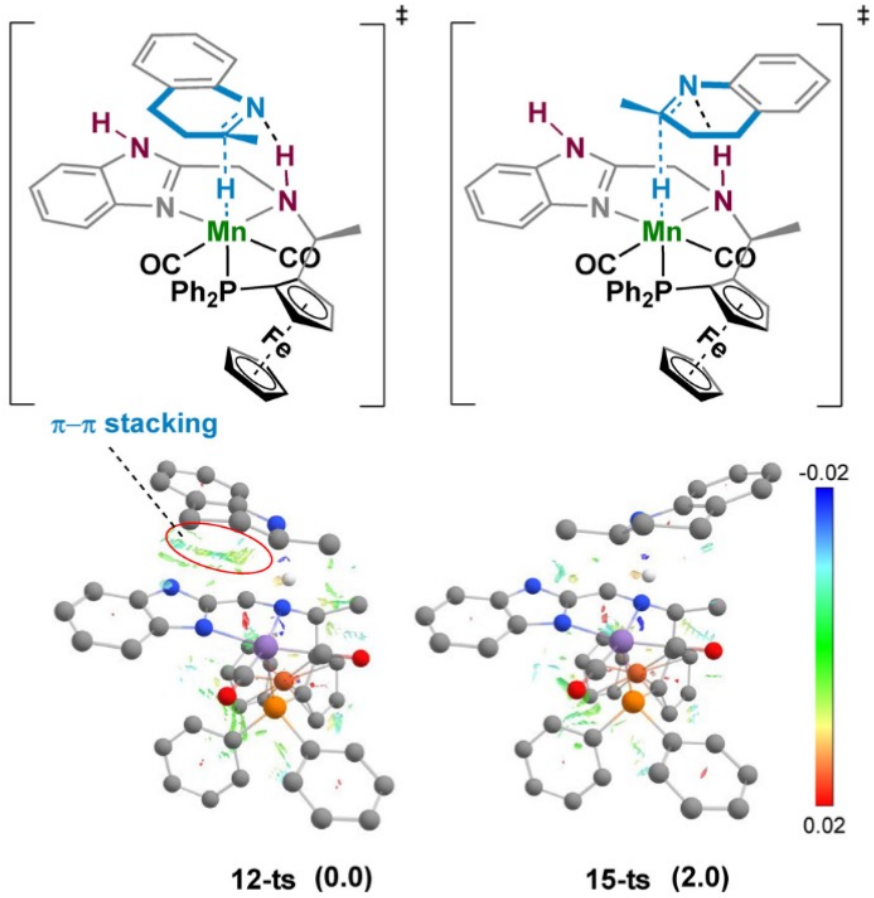


Figure 1. NCI analysis of **12-ts** and **15-ts** (blue: attraction; green: wea interaction; red: repulsion). Relative Gibbs free energies (in kcal mol⁻ are reported in parentheses.

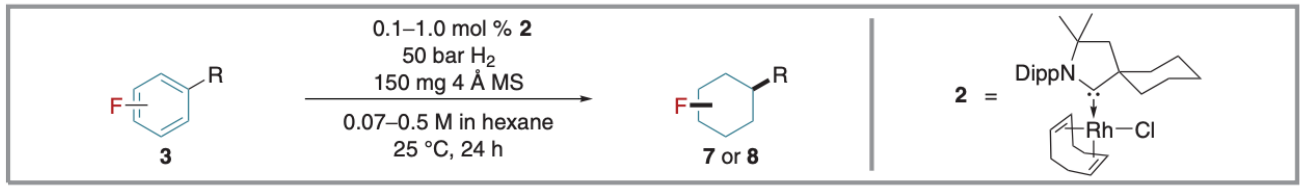
The central NH group is crucial for enantioselectivity via metal-ligand cooperation

C. Liu, M. Wang, S. Liu, Y. Wang, Y. Peng, Y. Lan and Q. Liu, Angew. Chem., Int. Ed., **2021**, *60*, 5108–5113.

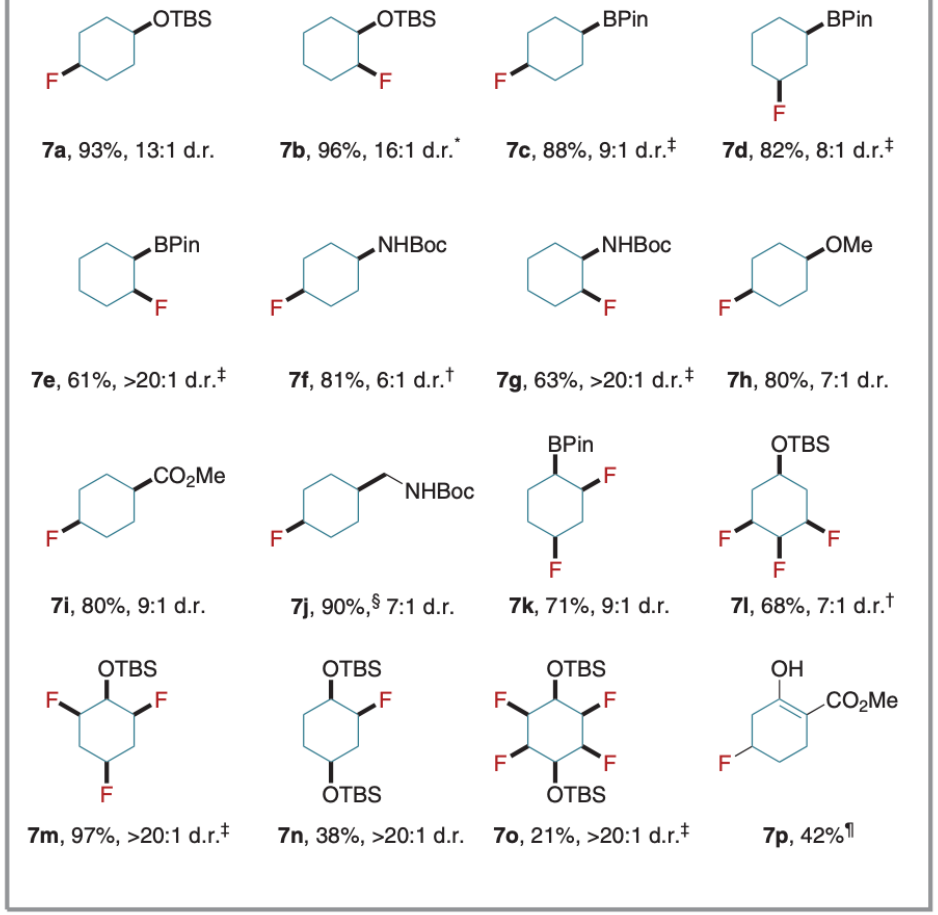
Controlling Diastereoselectivity in Arene Hydrogenation

All-cis-(multi)fluorinated cycloalkanes- A Highly Polar Substrate Class

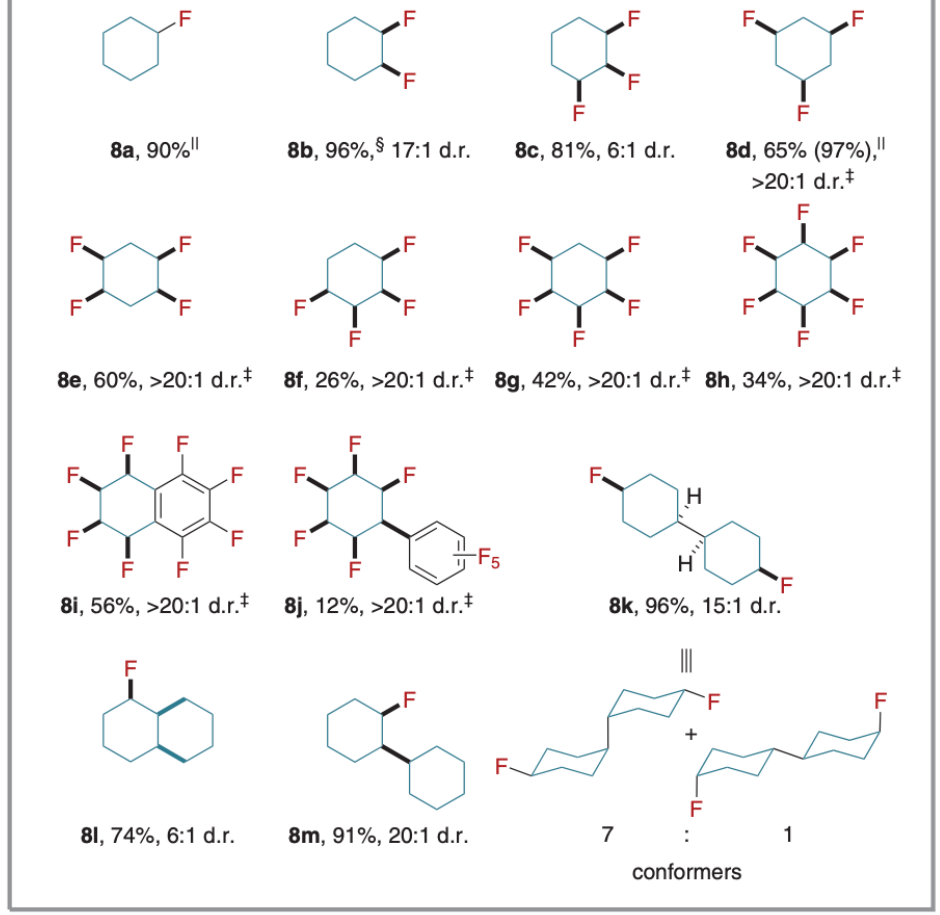
A



Fluorinated building blocks



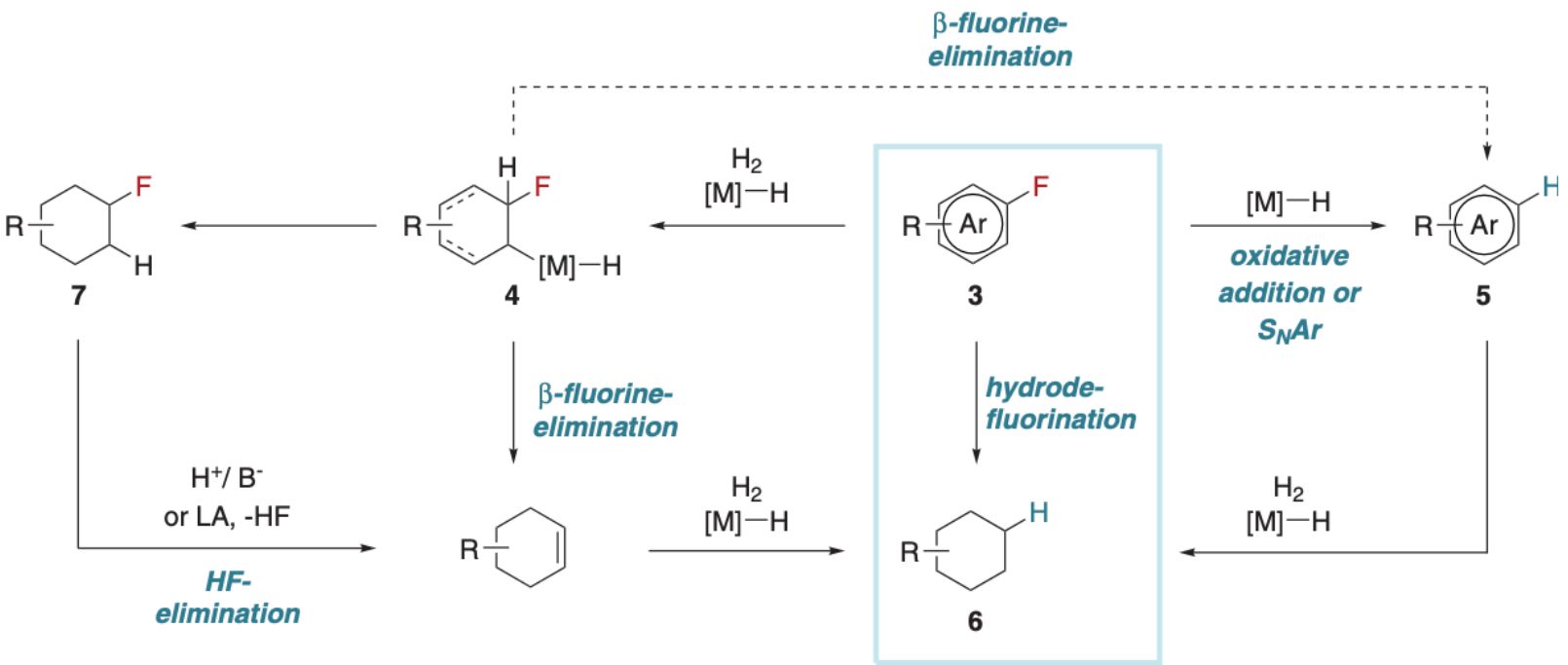
All-*cis*-(multi)fluorinated cyclohexanes



M. P. Wiesenfeldt, Z. Nairoukh, W. Li, F. Glorius, *Science* **2017**, *357*, 908.

Controlling Diastereoselectivity in Arene Hydrogenation

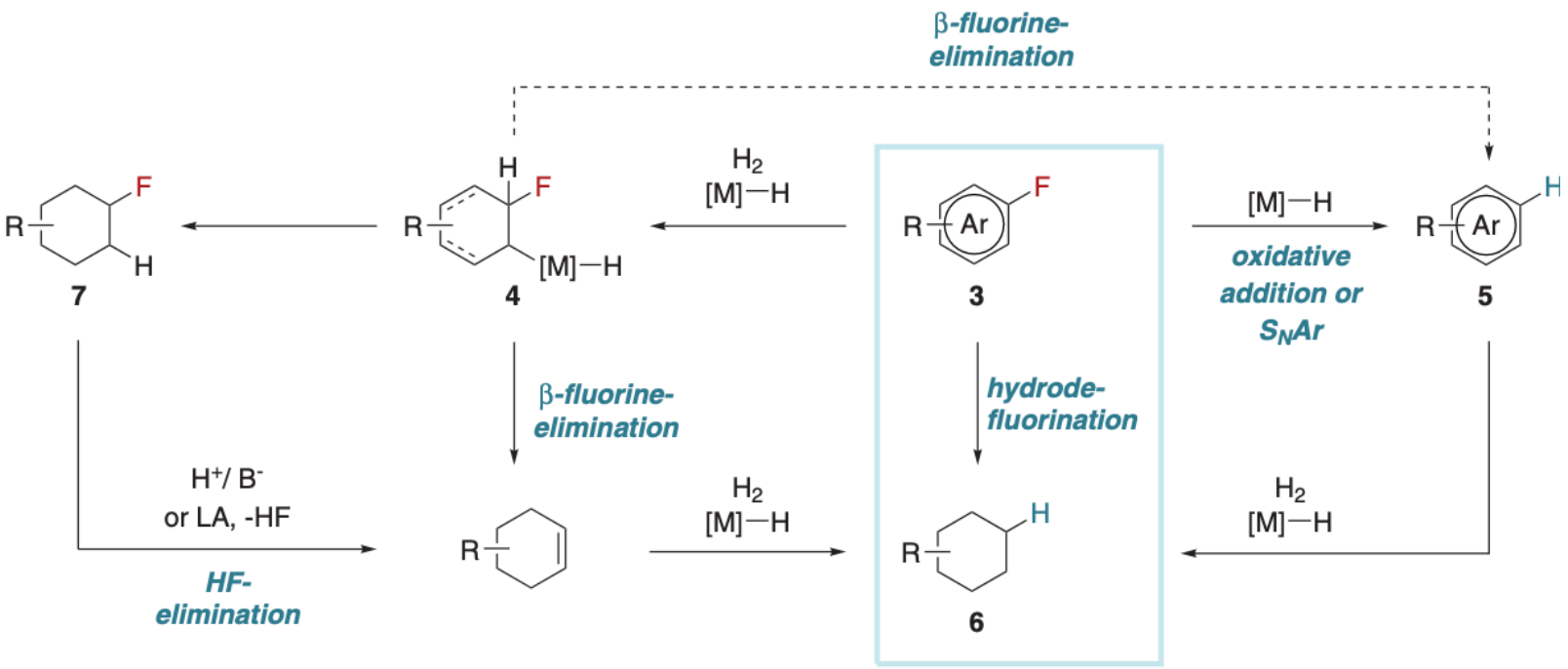
All-cis-(multi)fluorinated cycloalkanes- A Highly Polar Substrate Class



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Controlling Diastereoselectivity in Arene Hydrogenation

All-cis-(multi)fluorinated cycloalkanes- A Highly Polar Substrate Class



How to prevent hydrodefluourination? Solvent Choice

M. P. Wiesenfeldt, Z. Nairoukh, W. Li, F. Glorius, *Science* **2017**, *357*, 908.

Controlling Diastereoselectivity in Arene Hydrogenation

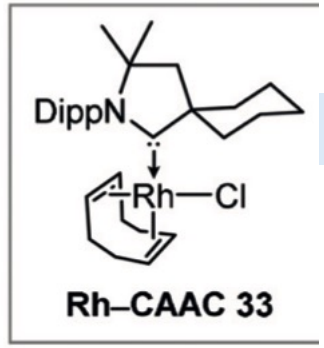
All-cis-(multi)fluorinated cycloalkanes- A Highly Polar Substrate Class

	Entry	Solvent	Conversion [%]	Yield **5a** [%]	Yield **6a** [%]	Yield **7a** [%] (d.r.)	Ratio (**7a**:**5a**+**6a**)
Polarity ↑	1	MeCN	0	0	0	0	-
	2	MeOH	92	1	75	8 (6:1)	1:9
	3	CF_3CH_2OH	100	0	52	24 (10:1)	1:2
	4	DCE	100	0	19	80 (12:1)	4:1
	5	CH_2Cl_2	100	0	16	77 (13:1)	5:1
	6	THF	98	0	26	69 (25:1)	3:1
	7	Et_2O	100	0	9	91 (18:1)	10:1
	8	Dioxane	54	0	12	39 (21:1)	3:1
	9	Cyclohexane	100	0	3	92 (14:1)	30:1
	10	**Hexane**	**100**	**0**	**4**	**95 (15:1)**	**25:1**

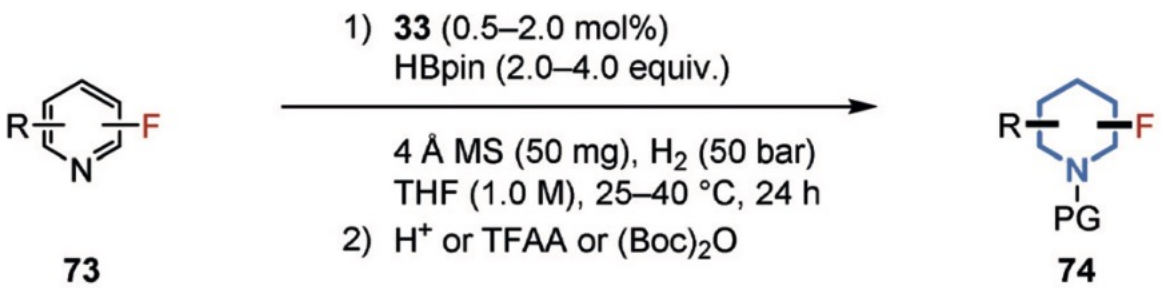
M. P. Wiesenfeldt, Z. Nairoukh, W. Li, F. Glorius, *Science* **2017**, *357*, 908.

Controlling Diastereoselectivity in Arene Hydrogenation

A Privileged System: Rh-CAAC

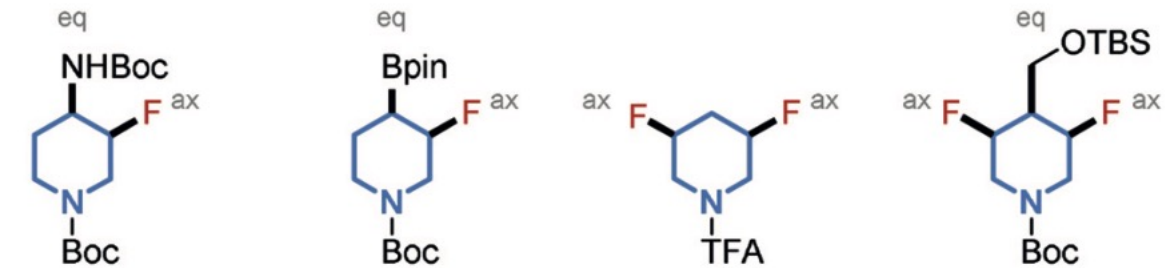


Rh–CAAC 33



73 **74**

Scope – over 40 examples – up to 10 mmol scale



74a, 94%
97:3 d.r.

b, 73%
24:1 d.r.

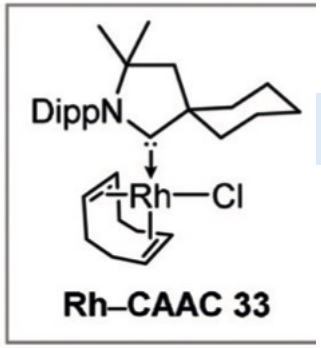
7a, 79%
>99:1 d.r.

74c, 34%
9:1 d.r.

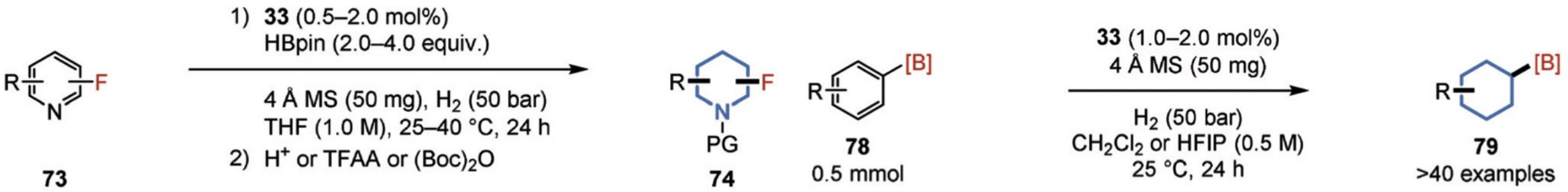
M. P. Wiesenfeldt, Z. Nairoukh, T. Dalton and F. Glorius, *Angew. Chem., Int. Ed.,* **2019**, *58*, 10460.

Controlling Diastereoselectivity in Arene Hydrogenation

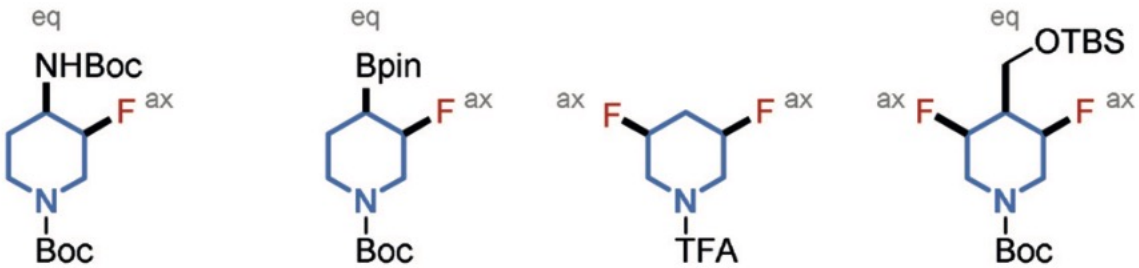
A Privileged System: Rh-CAAC

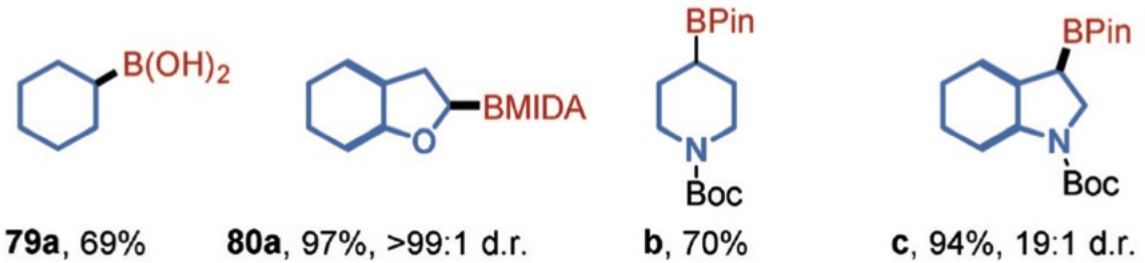


Rh–CAAC 33



Scope – over 40 examples – up to 10 mmol scale

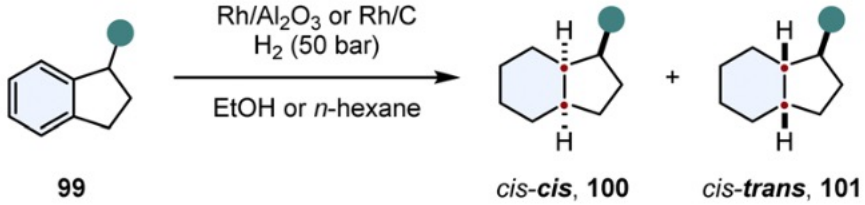




M. P. Wiesenfeldt, Z. Nairoukh, T. Dalton and F. Glorius, *Angew. Chem., Int. Ed.,* **2019**, *58*, 10460.

Controlling Diastereoselectivity in Arene Hydrogenation

Sterics vs. Electronics in Diastereoselective Hydrogenation



99 *cis*-***cis***, **100** *cis*-***trans***, **101**

Sterically-driven

- if ● = -Me, -COOR, -COOH, -CONHR, -OR, -OH
  → *cis*-***cis*** as major diastereomer (*d.r.* up to 92:8)
- if ● = $-NH_2$
  → *cis*-***trans*** as major diastereomer (*d.r.* = 1.5:98.5)

Electronically-driven

If steric repulsive interactions dominate, then hydrogen is transferred to the opposite face of the substituent and the cis–cis product is obtained

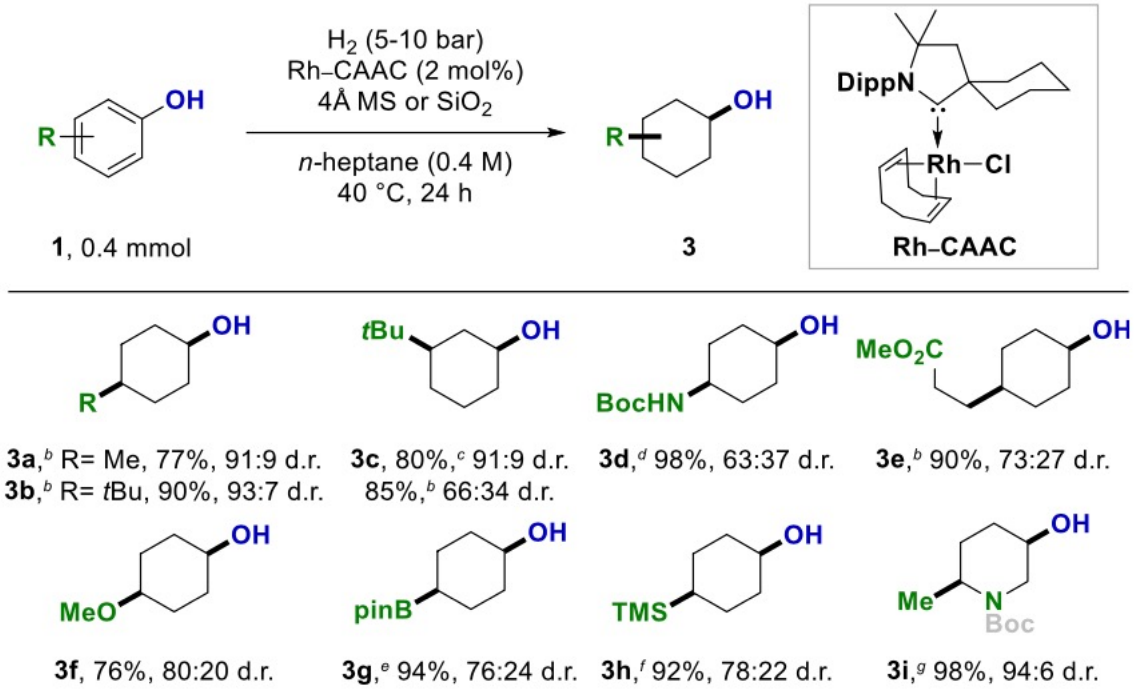
If the substituent is haptophilic, hydrogen is transferred to the same face of the substituent and the cis–trans product is favored

V. S. Ranade, G. Consiglio and R. Prins, *J. Org. Chem.*, **1999**, *64*, 8862.; V. S. Ranade, G. Consiglio and R. Prins, *J. Org. Chem.,* **2000**, *65*, 1132.

Controlling Diastereoselectivity in Arene Hydrogenation

Metal Dictates Selectivity of Cyclohexanol

Rh: cis-selective



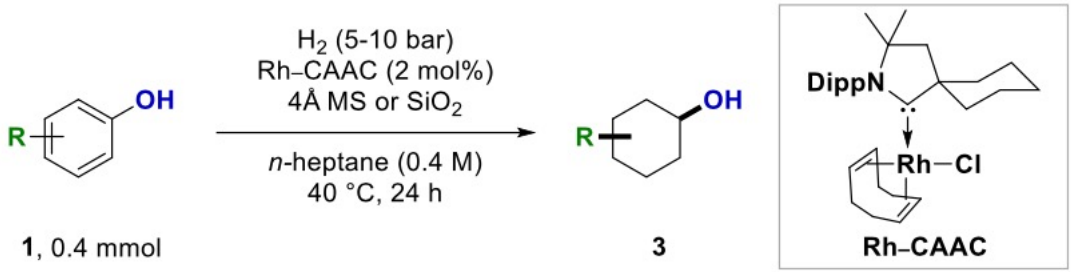
Note: Phenols with simple alkyl chains could be hydrogenated using $[Rh(COD)Cl]_2$ as a precatalyst

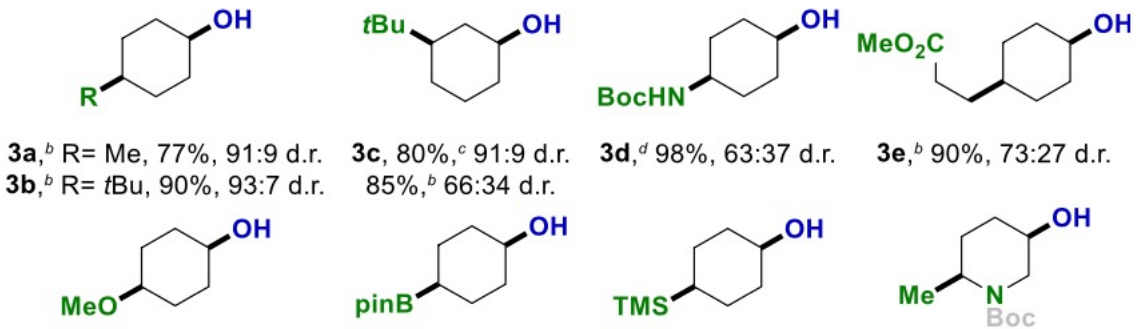
M. Wollenburg, A. Heusler, K. Bergander and F. Glorius, *ACS Catal.*, **2020**, *10*, 11365.

Controlling Diastereoselectivity in Arene Hydrogenation

Metal Dictates Selectivity of Cyclohexanol

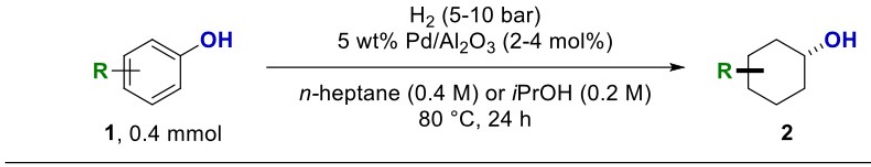
Rh: cis-selective

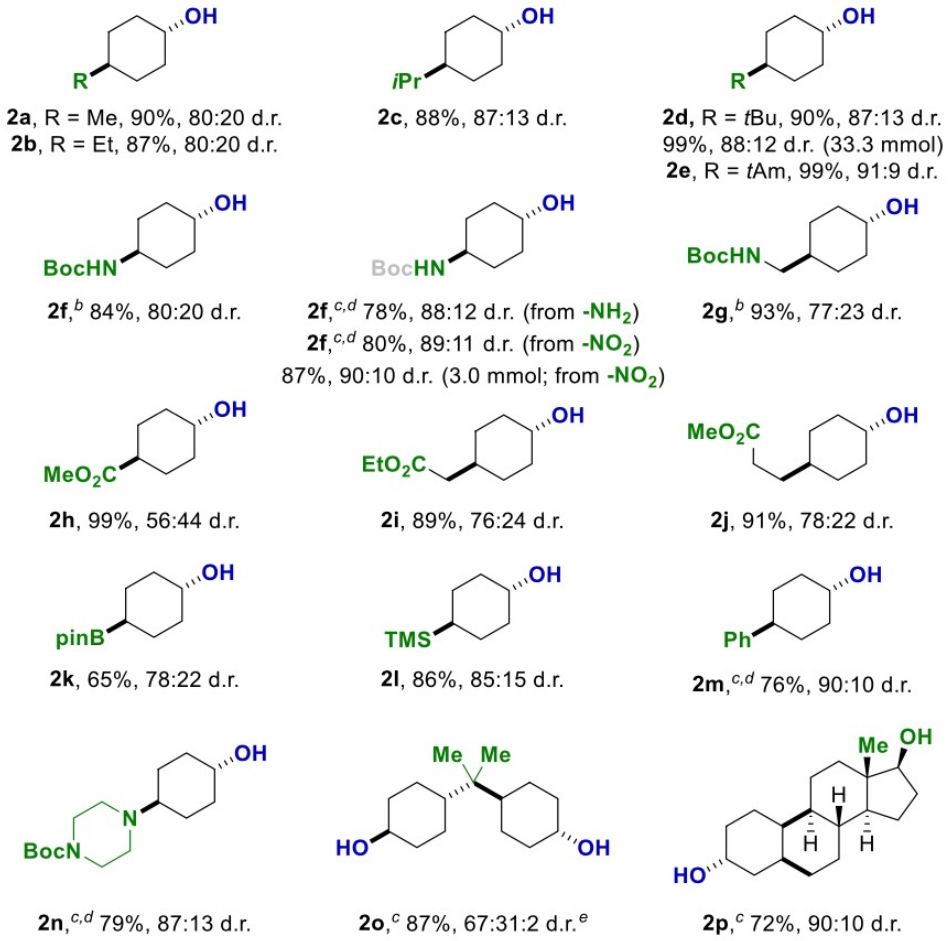




Note: Phenols with simple alkyl chains could be hydrogenated using $[Rh(COD)Cl]_2$ as a precatalyst

Pd: trans-selective

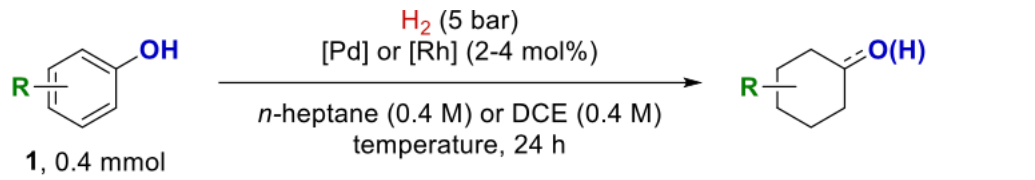




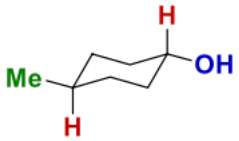
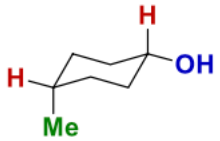
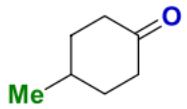
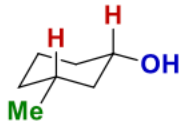
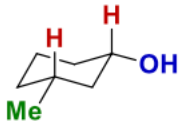
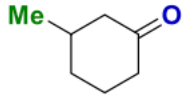
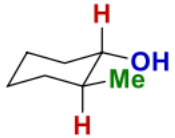
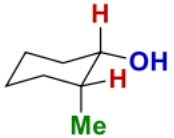
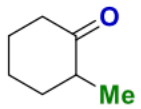
M. Wollenburg, A. Heusler, K. Bergander and F. Glorius, *ACS Catal.*, **2020**, *10*, 11365.

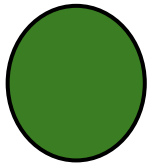
Controlling Diastereoselectivity in Arene Hydrogenation

Metal Dictates Selectivity of Cyclohexanol *: Exceptions to the Rule*

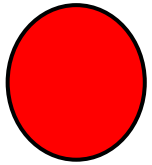


1, 0.4 mmol

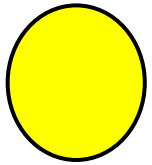
	5 wt% Pd/Al_2O_3 *n*-heptane, 80 °C	$[Rh(COD)Cl]_2$ + 4Å MS *n*-heptane, 40 °C	5 wt% Pd/Al_2O_3 DCE, 60 °C
1,4	 *trans* **2a**, 90% (99%), 80:20 d.r.	 *cis* **3a**, 77% (93%), 91:9 d.r.	 **4a**, 81%
1,3	 *cis* **3ab**,[b] 86% (98%), 83:17 d.r.	 *cis* **3ab**, 74% (92%), 73:27 d.r.	 **4ab**, 77%[c]
1,2	 *trans* **2ac**,[b] 82% (98%), 55:45 d.r.	 *cis* **3ac**, 70% (94%), >95:5 d.r.	 **4ac**, 90%[c]



Follows the trend



Both give the thermodynamically more stable cis-diastereomer



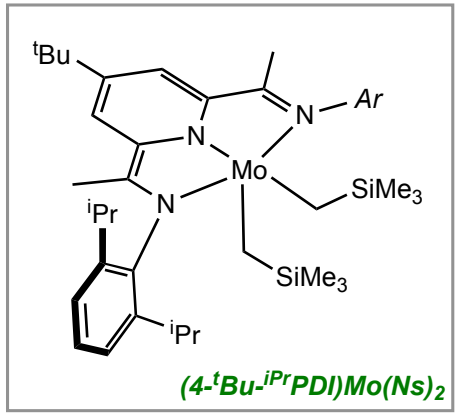
Follows the trend, but only slightly for Pd

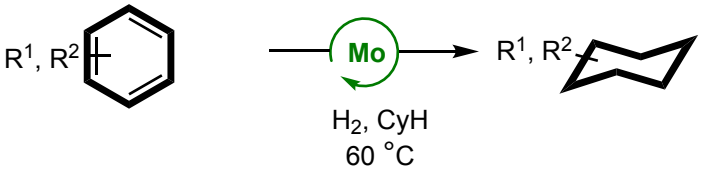
The catalytic system based on rhodium provides cis-products consistently, whereas the catalytic system based on palladium gives access to the thermodynamically more stable diastereomers

M. Wollenburg, A. Heusler, K. Bergander and F. Glorius, *ACS Catal.*, **2020**, *10*, 11365.

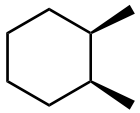
Controlling Diastereoselectivity in Arene Hydrogenation

Disubstitution Pattern Determines Diastereoselectivity



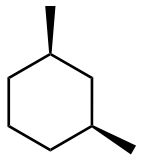


5 mol% [Mo], 4 atm H_2, 48h

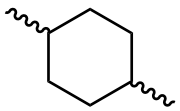


81% NMR Yield
79:21 d.r.

10 mol% [Mo], 32 atm H_2, 24h



40% NMR Yield
75:25 d.r.



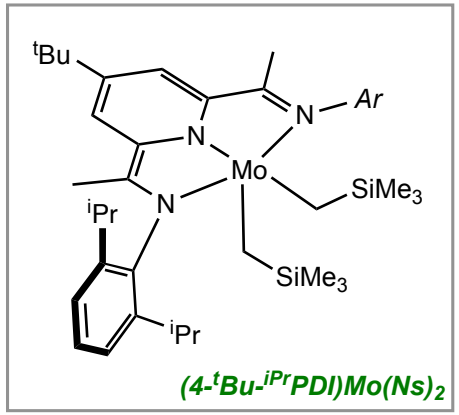
24% NMR Yield
50:50 d.r.

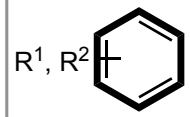
Similarity amongst PDIMo and OIPMo: Diastereoselectivity decreases from 1,2→ 1,3→ 1,4

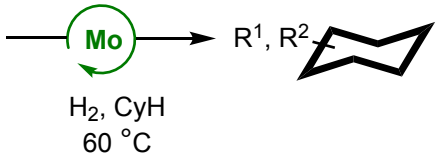
Joannou, M. V.; Bezdek, M. J.; Chirik, P. J. *ACS Catal*. **2018**, *8*, 5276.; Greenbaum, J.; Pecoraro, M.; Tosatti, P.; Püntener, K.; Chirik, P. J. *Manuscript in Preparation.*

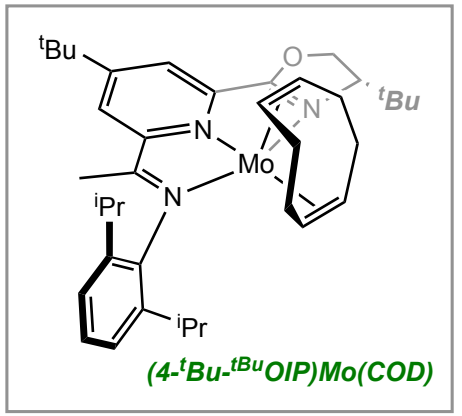
Controlling Diastereoselectivity in Arene Hydrogenation

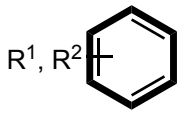
Disubstitution Pattern Determines Diastereoselectivity

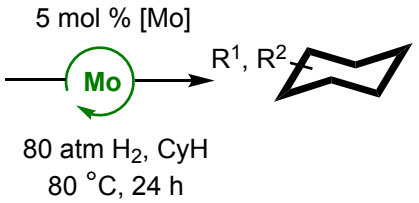




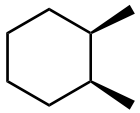






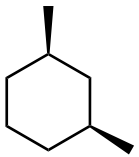


5 mol% [Mo], 4 atm H_2, 48h

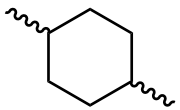


81% NMR Yield
79:21 d.r.

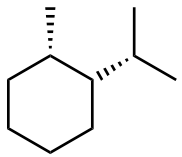
10 mol% [Mo], 32 atm H_2, 24h



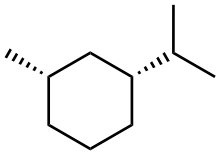
40% NMR Yield
75:25 d.r.



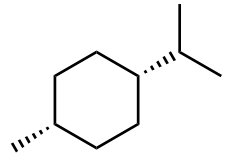
24% NMR Yield
50:50 d.r.



39% Yield
>20:1 d.r.
87% ee



83% Yield
10:1 d.r.



96% Yield
3:1 d.r.

Similarity amongst PDIMo and OIPMo: Diastereoselectivity decreases from 1,2→ 1,3→ 1,4

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