Catalytic Synthesis of Anti-Markovnikov Alcohols from Epoxides and Unactivated Alkenes

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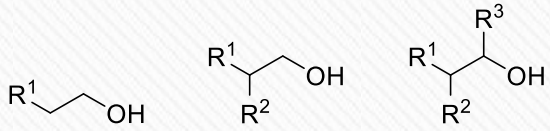
Supervisor: Prof. Shengming Ma
2019-10-18

Introduction

Markovnikov's rule: The rule formulated in 1869 by V. V. Markovnikov predicts the products of an electrophilic addition of asymmetrical reagents (e.g. hydrogen halides, water and alcohols) to asymmetric alkenes. It states that the reaction favors the formation of the regioisomer in which the more electrophilic part of the reagent has been added to the carbon atom of the double with the most hydrogens.

e.g.

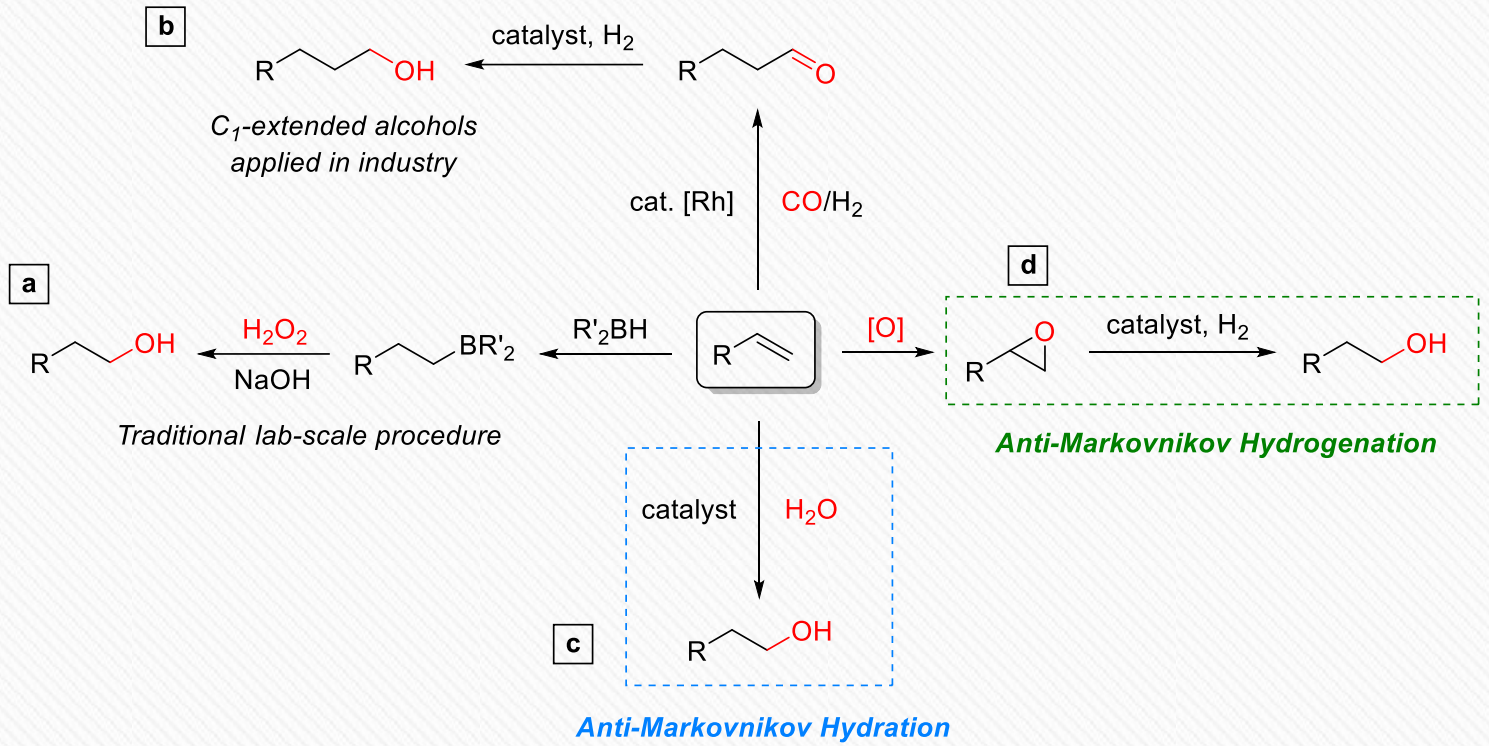
Anti-Markovnikov alcohol*: the hydroxyl group is bound to the less substituted of two adjacent carbons.



anti-Markovnikov alcohols

* Yao, C.; Dahmen, T.; Gansäuer, A.; Norton, J. *Science* **2019**, *364*, 764.

Primary alcohols are widely demand in the chemical industry (bulk/fine chemicals, specialties) and life sciences (pharmaceuticals, flavouring, fragrances and so on).

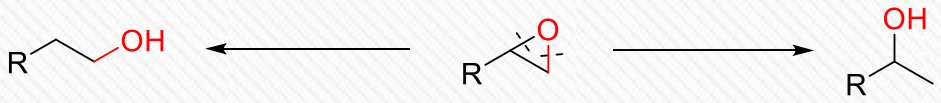


Synthesis of primary alcohols from olefins.
(a) Hydroboration/oxidation process.
(b) Hydroformylation/hydrogenation process.
(c) Anti-Markovnikov hydration.
(d) Epoxidation/anti-Markovnikov hydrogenation process.

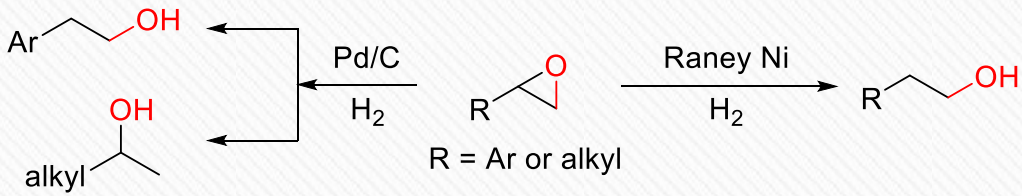
Catalytic Anti-Markovnikov Hydrogenation of Epoxides

02 Catalytic Anti-Markovnikov Hydrogenation of Epoxides

Selective C-O bond cleavage for the formation of alcohol



Heterogeneous catalysis enabled epoxide hydrogenation



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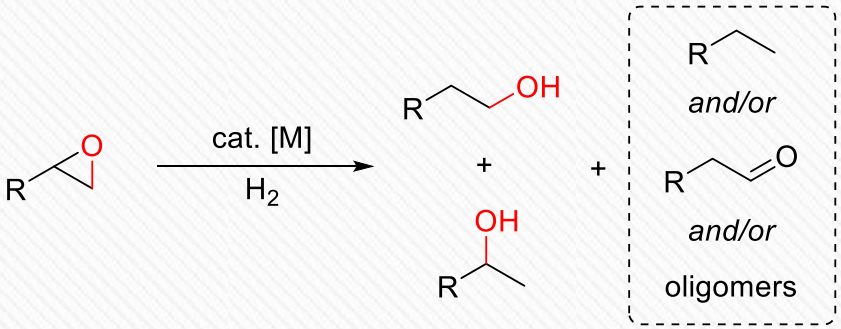
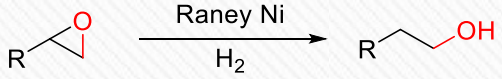
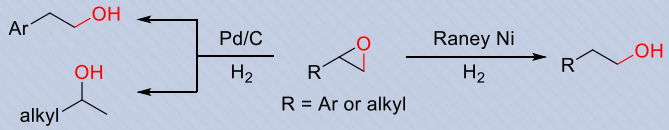


02 Catalytic Anti-Markovnikov Hydrogenation of Epoxides

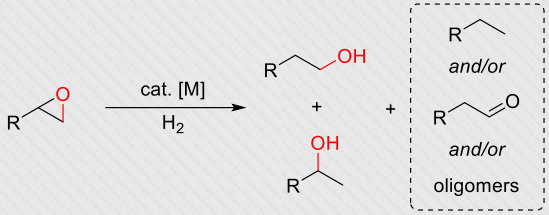


Newman, M. S.; Underwood, G.; Renoll, M. *J. Am Chem. Soc.* **1949**, *71*, 3362.

Heterogeneous catalysis enabled epoxide hydrogenation

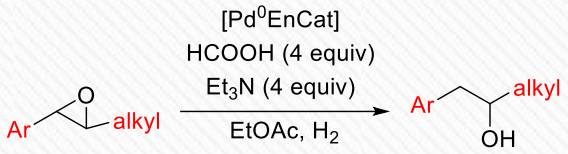


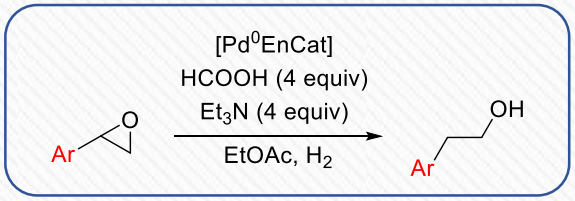
Homogeneous catalysis enabled epoxide hydrogenation



when R = alkyl, branch alcohols are major products
when R = aryl, linear alcohols are major products

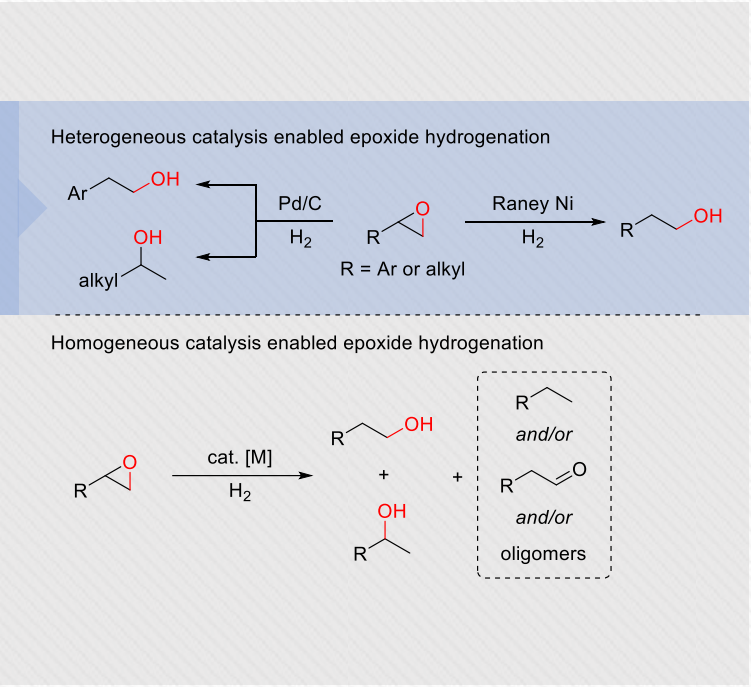
Sjiki, H.; Hattori, K.; Hirota, K. *Chem. Commun.* **1999**, 1041.

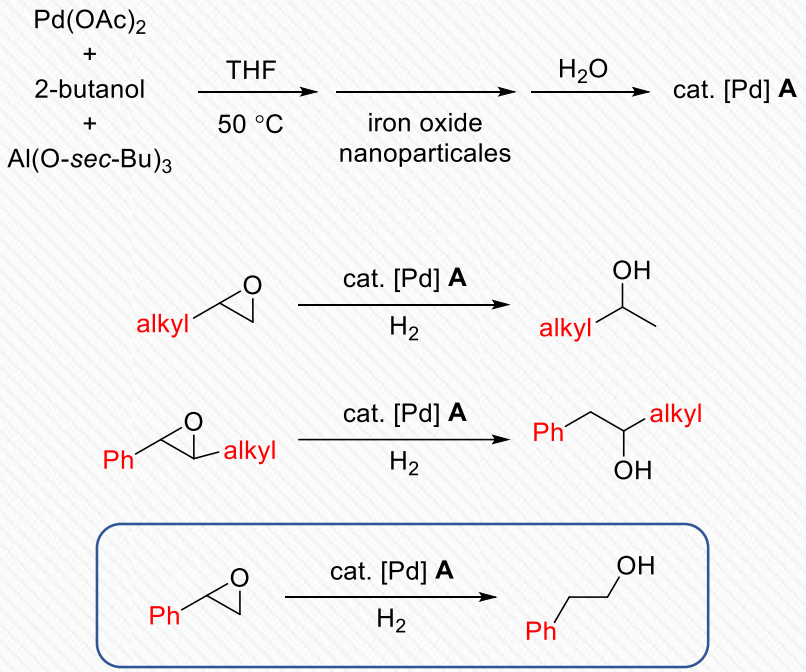




Ley, S. V.; Mitchell, C. M.; Pears, D.; Ramarao, C.; Yu, J.-Q.; Zhou, W. *Org. Lett.* **2003**, *5*, 4665.

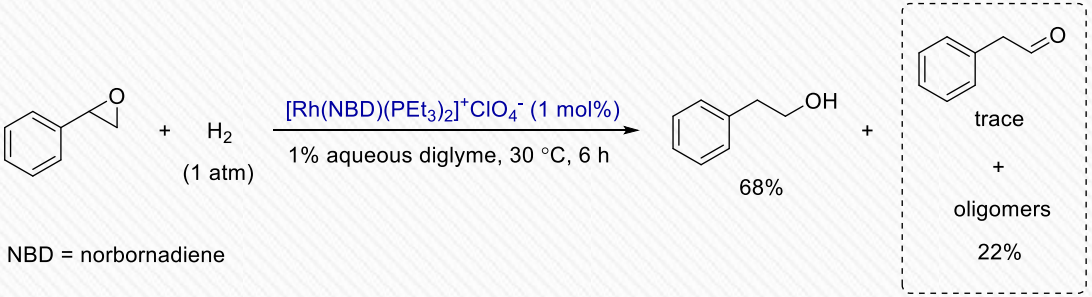
02 Catalytic Anti-Markovnikov Hydrogenation of Epoxides





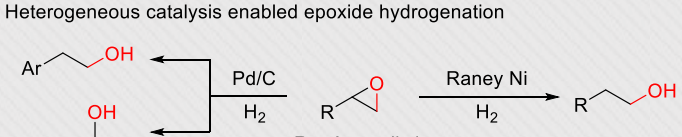
Kwon, M. S.; Park, I. S.; Jang, J. S.; Lee, J. S.; Park, J. *Org. Lett.* **2007**, *9*, 3417.

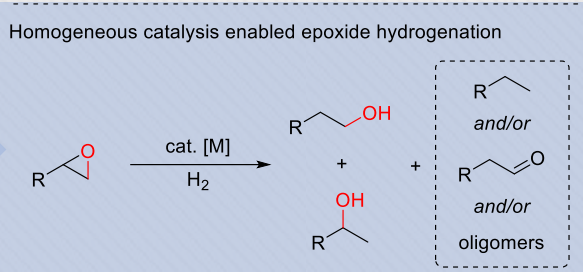
02 Catalytic Anti-Markovnikov Hydrogenation of Epoxides

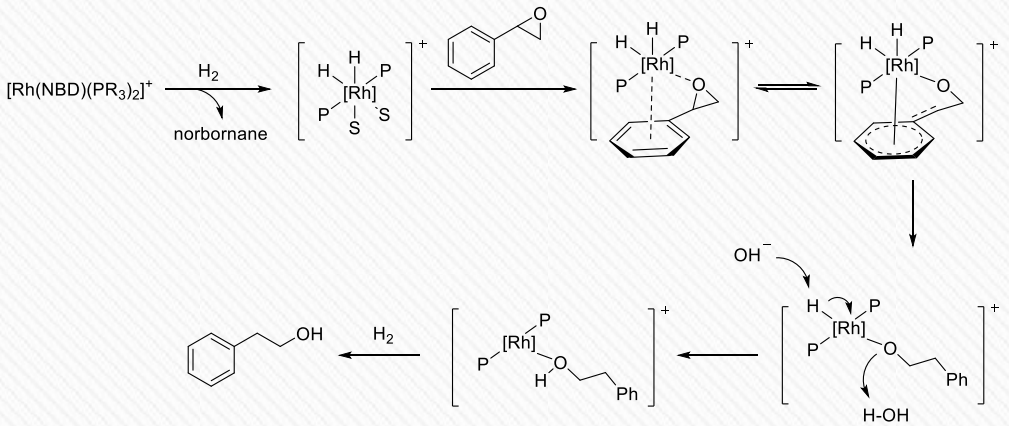


NBD = norbornadiene

conversion: 90%
without either α-phenylethyl alcohol or acetophenone

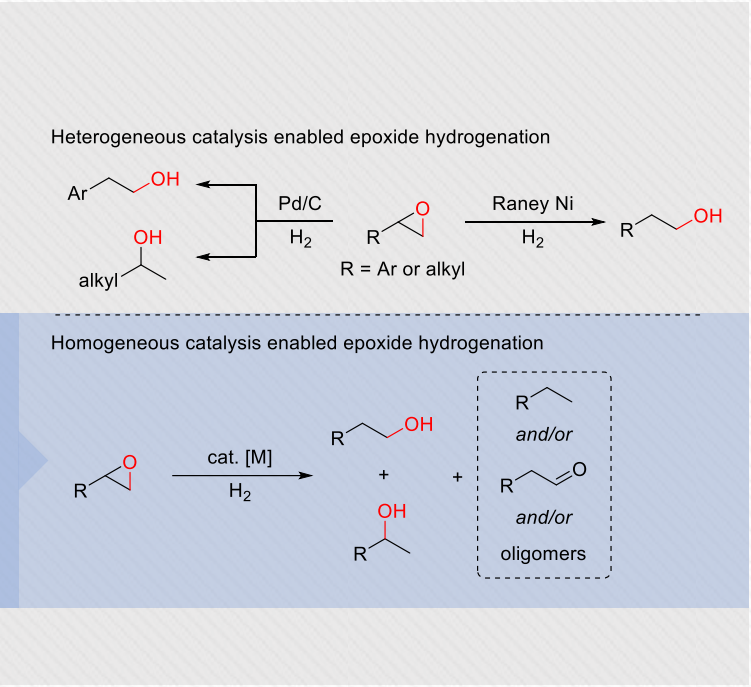


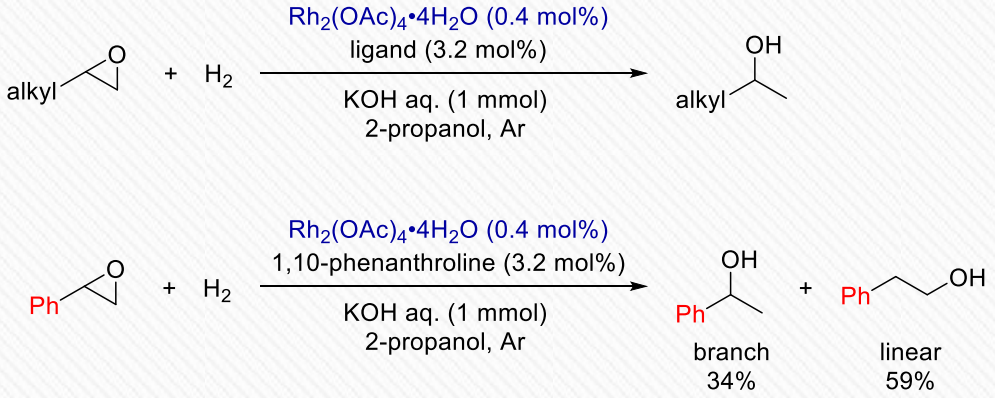




Mochida, I.; Shirahama, S; Fujitsu, H.; Takeshita, K. *Chem. Lett.* **1977**, 421.
Fujitsu, H.; Shirahama, S.; Matsumura, E.; Takeshita, K.; Mochida, I. *J. Org. Chem.* **1981**, *46*, 2287.

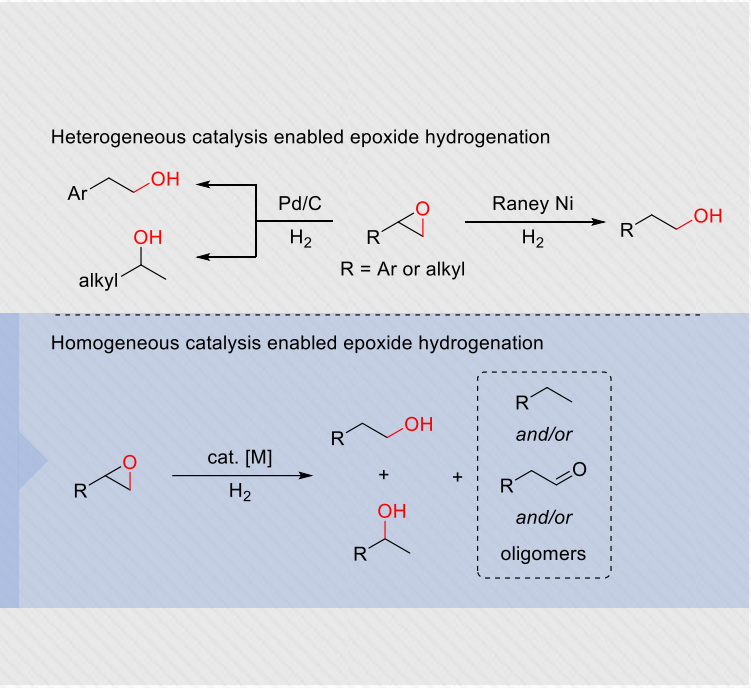
02 Catalytic Anti-Markovnikov Hydrogenation of Epoxides

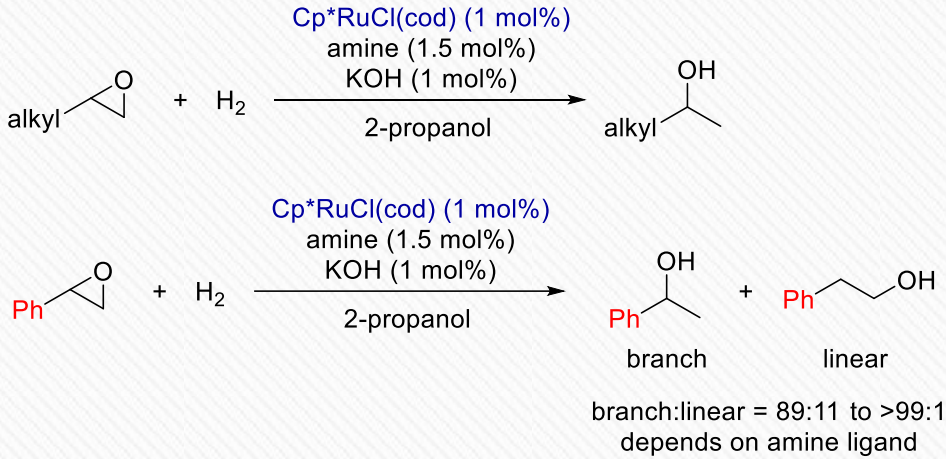


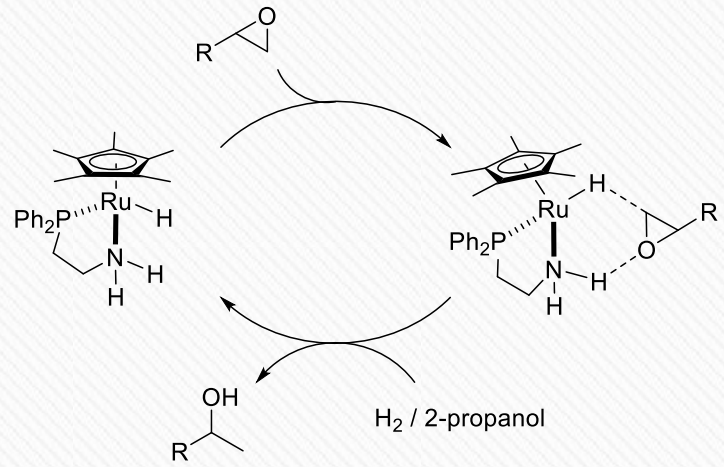


Ricci, M.; Slama, A. *J. Mol. Catal.* **1994**, *89*, L1.

02 Catalytic Anti-Markovnikov Hydrogenation of Epoxides



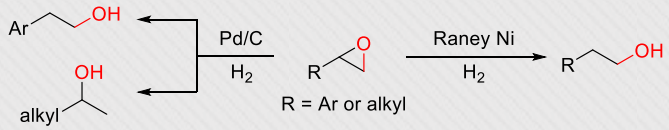




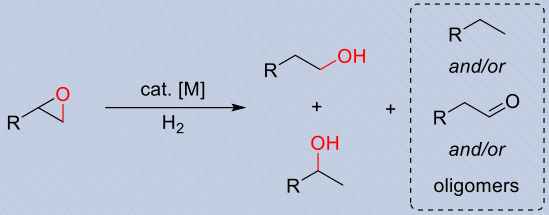
Ito, M.; Hirakawa, M.; Osaku, A.; Ikariya, T. *Organometallics* **2003**, *22*, 4190.

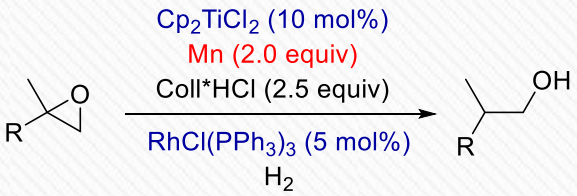
02 Catalytic Anti-Markovnikov Hydrogenation of Epoxides

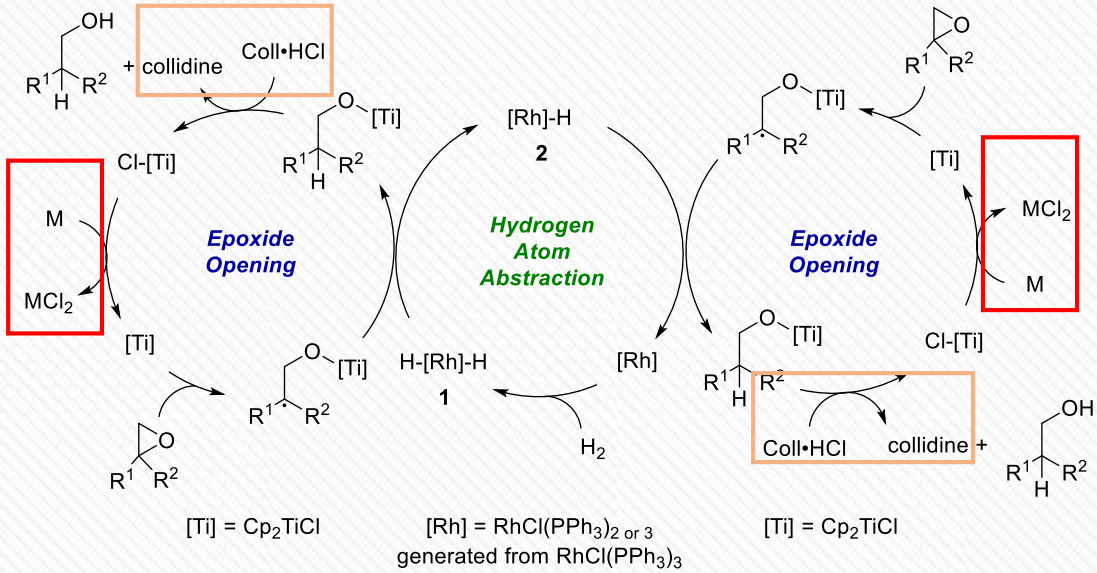
Heterogeneous catalysis enabled epoxide hydrogenation



Homogeneous catalysis enabled epoxide hydrogenation

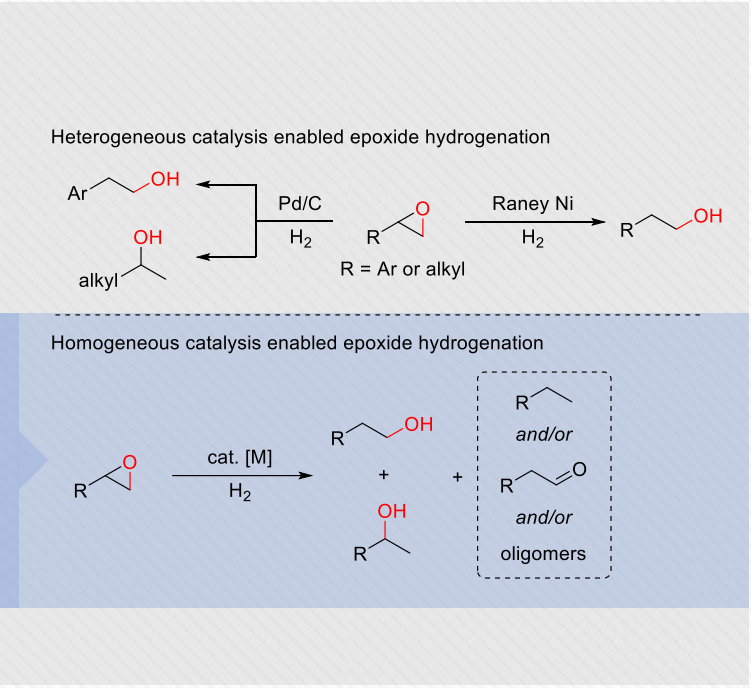


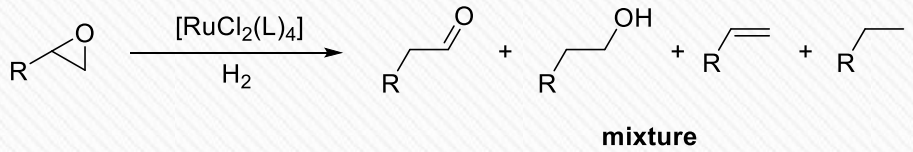




Gansäuer, A.;Fan, C.-A.; Piestert, F. *J. Am. Chem. Soc.* **2008**, *130*, 6916.

02 Catalytic Anti-Markovnikov Hydrogenation of Epoxides





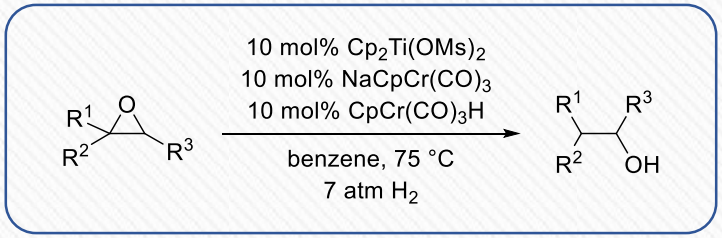
R = aryl, alkyl; L = DMSO or TMSO

Murru, S.; Nicholas, K. M.; Srivastava, R. S. *J. Mol. Cata. A-Chem.* **2012**, *363-364*, 460.

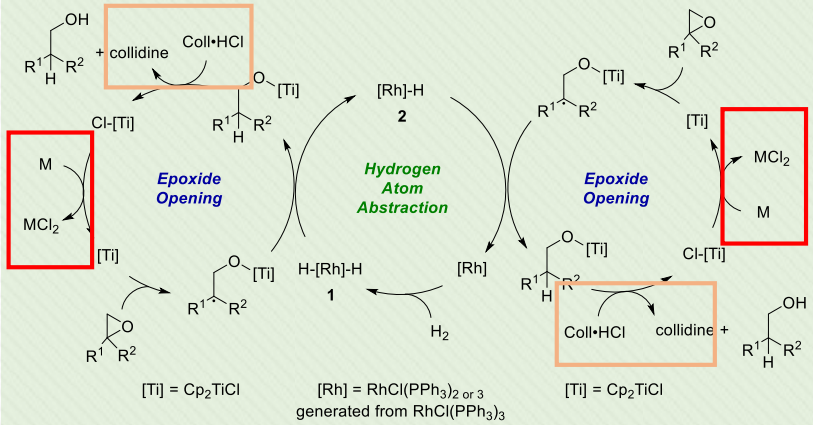
02 Catalytic Anti-Markovnikov Hydrogenation of Epoxides

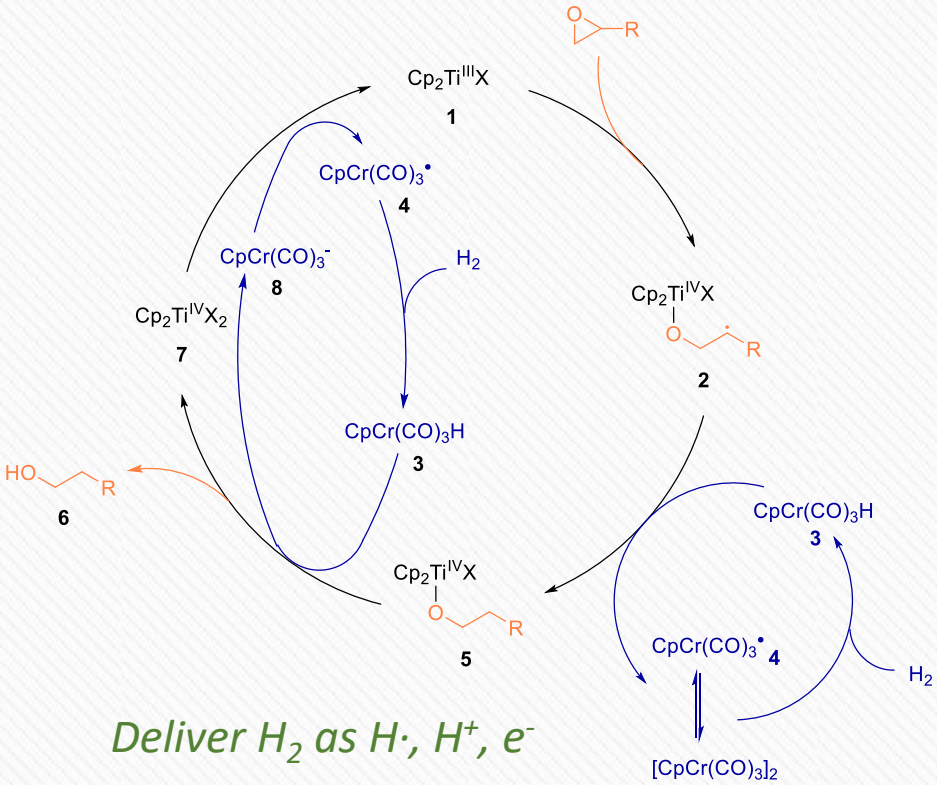
Gansäuer and Norton, 2019:

100% atom economy



Previous work (Gansäuer, 2008):





Deliver H_2 as H·, H^+, e^-

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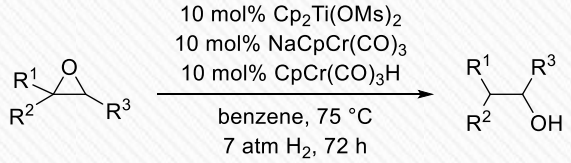
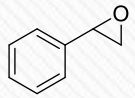
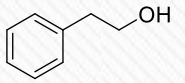
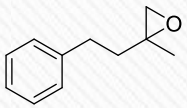
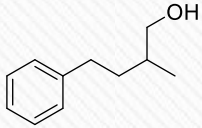
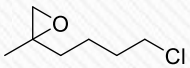
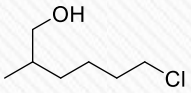
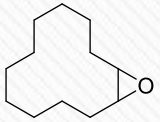
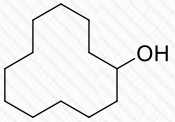
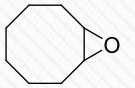
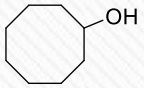
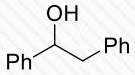
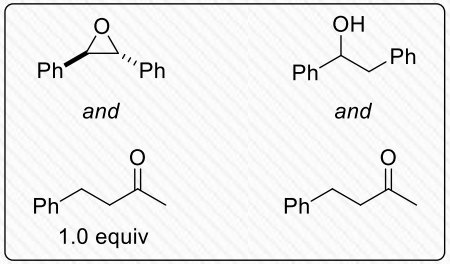
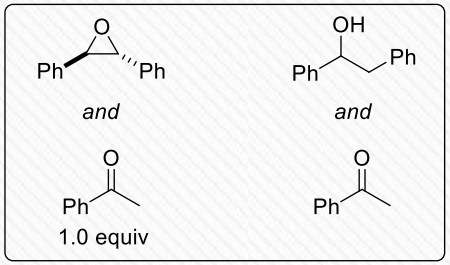
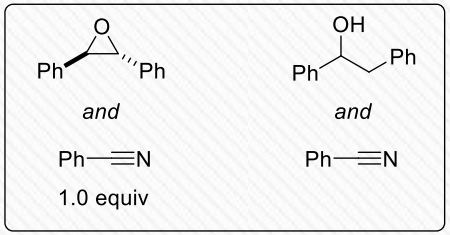
02 Catalytic Anti-Markovnikov Hydrogenation of Epoxides

Selected examples:



entry	epoxide	product	yield (%)
1			51
2			70
3			55
4			65 (26)
5			52 (33)
6			96
7			88 99% recovery
8			94 85% recovery
9			91 81% recovery

Reactions were conducted on a 1 or 0.5 mmol scale. Yield of allylic alcohol is shown in parentheses.

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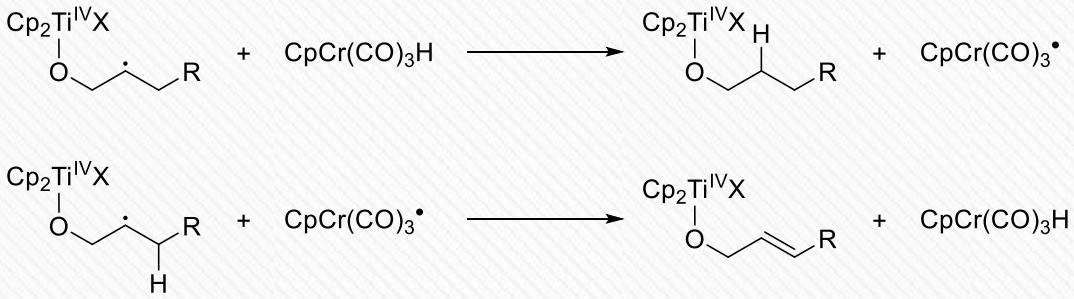

Competition reactions between hydrogen atom transfer (top) and hydrogen atom abstraction (bottom).

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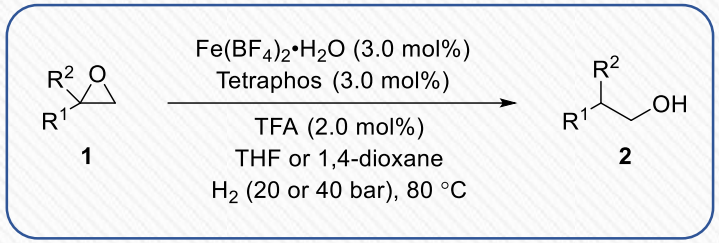
Beller, 2019:

Hydrogenation of benchmark epoxides with various catalyst

Catalyst \ Reaction	Ph (1a) → Ph OH (2a)		n-C_4H_9 (1b) → n-C_4H_9 OH (2b)	
	With TFA	Without TFA	With TFA	Without TFA
$Fe(BF_4)_2$•$6H_2O$/ tetraphos	+	–	+	–
$Ru(acac)_3$/[a] tetraphos	×	–	×	×
$Rh(PPh_3)_3Cl$	×	×	×	×
(*S*)BINAP/ (*S*)diamine-$RuCl_2$[b]	×	×	×	×
PtO_2	–	×	×	×
Pd/C[c]	+	–	×	×



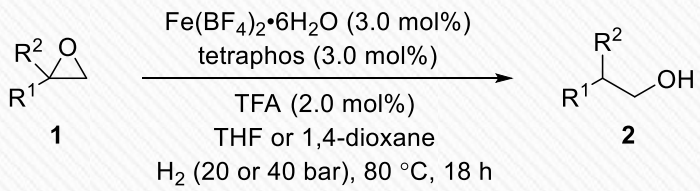
Reaction conditions: from **1a** to **2a**: **1a** (0.5 mmol), catalyst (3.0 mol%), ligand (3.0 mol%), TFA (2.0 mol%), THF (4.0 mL), H_2 (20 bar), 80 °C, 18 h; from **1b** to **2b**: 1,4-dioxane (6.0 mL), H_2 (40 bar); yields were determined by GC using *n*-hexadecane as internal standard. [a] $HNTf_2$ was the additive in cases without TFA. [b] *t*-BuOK was the additive in cases without the TFA. [c] Hexan-2-ol was formed as major product from **1b.**

Yields: +, >80%; –, 20-80%; ×, <20%.

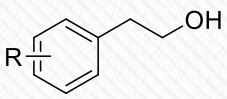
Liu, W.; Li, Wu.; Spannenberg, A.; Junge, K.; Beller, M. *Nat. Catal.* **2019**, *2*, 523.

02 Catalytic Anti-Markovnikov Hydrogenation of Epoxides

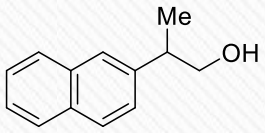
Selected examples:



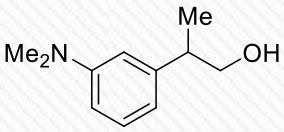
Condition A:



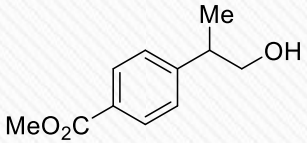
R = H, 94%
R = 4-F, 87%
R = 4-Cl, 81%
R = 4-Br, 61%
R = 4-CF_3, 56%
R = 4-Ph, 96%
R = 2-F, 90%
R = 2-Me, 87%
R = 3-Cl, 82%



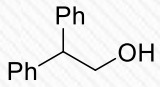
95%



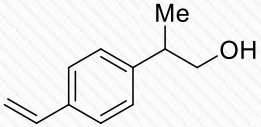
96%



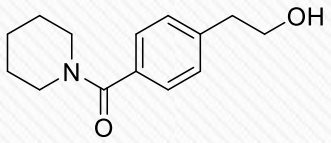
91%



89%[c]

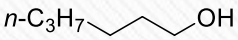


90%

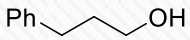


78%

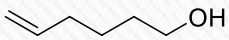
Condition B:



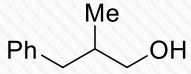
84%[b]



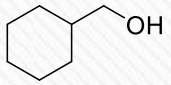
66%[b]



61%[b]



91%[c]



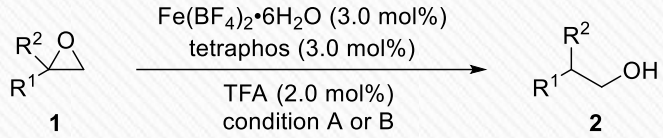
82%[b,c]

[a] **1** (0.5 mmol), $Fe(BF_4)_2$•$6H_2O$ (3.0 mol%), tetraphos (3.0 mol%), TFA (2.0 mol%), 80 °C, 18 h, isolated yields. Condition for A: THF (4.0 mL), H_2 (20 bar). Condition for B: 1,4-dioxane (6.0 mL), H_2 (40 bar).[b] Yields were determined by GC using n-hexadecane as internal standard. [c] 120 °C

Liu, W.; Li, Wu.; Spannenberg, A.; Junge, K.; Beller, M. *Nat. Catal.* **2019**, *2*, 523.

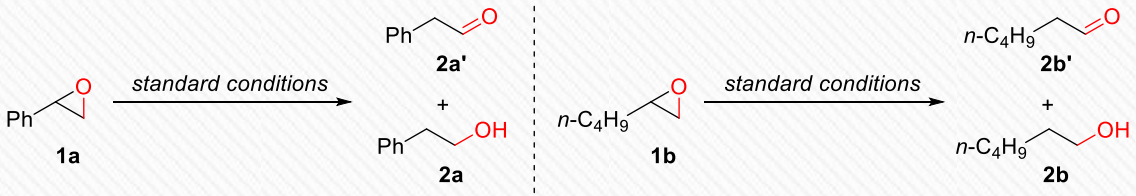
02 Catalytic Anti-Markovnikov Hydrogenation of Epoxides

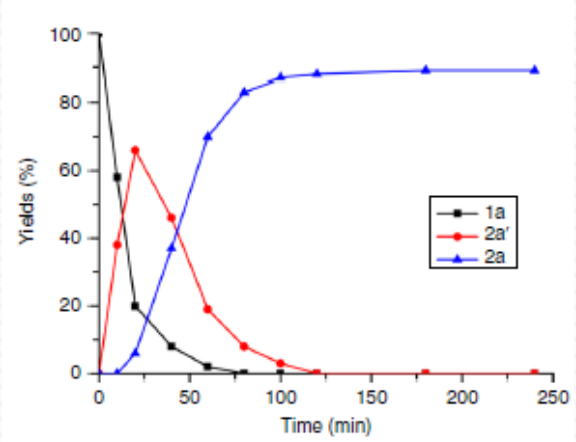
Mercury tests

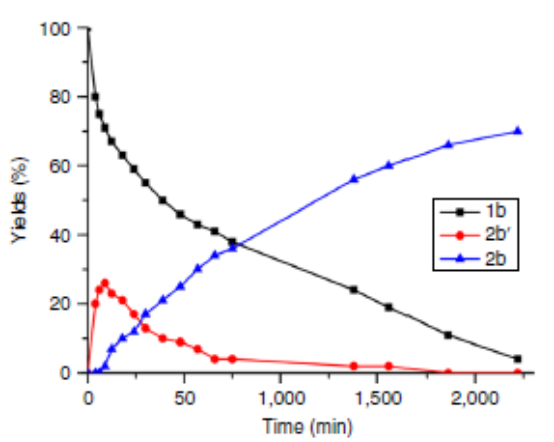


Product	Ph–CH(OH)–CH2	n-C3H7–CH(OH)–CH2	cyclohexanol
Yield	94%	84%	82%
Yield (with Hg)	95%	78%	83%

Kinetic studies





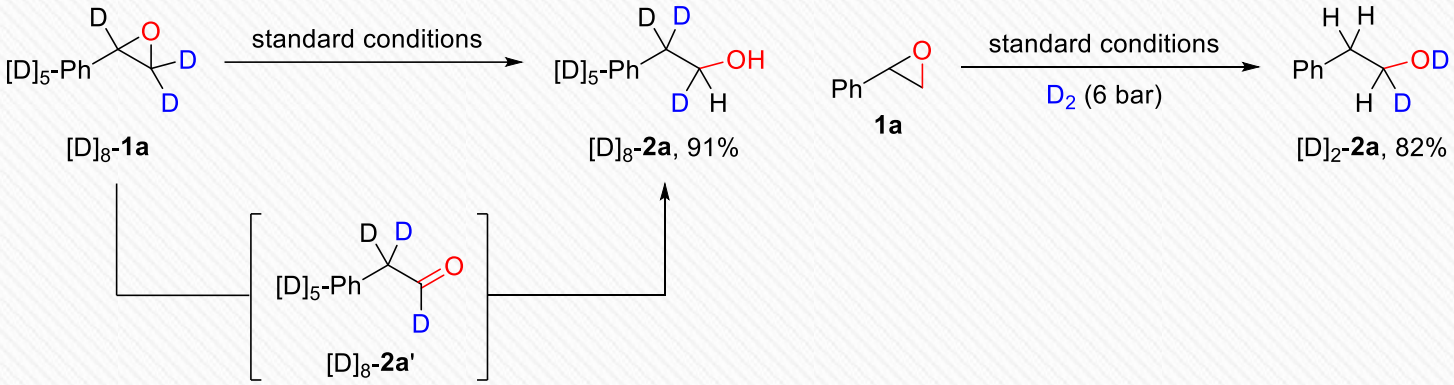


Liu, W.; Li, Wu.; Spannenberg, A.; Junge, K.; Beller, M. *Nat. Catal.* **2019**, *2*, 523.

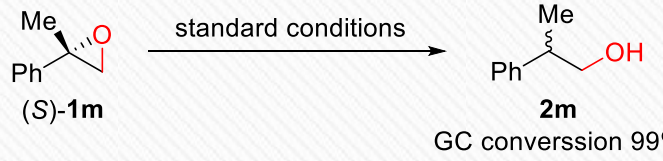
02 Catalytic Anti-Markovnikov Hydrogenation of Epoxides

Control experiments

Deuterium experiments



Racemization investigation



Mechanistic studies

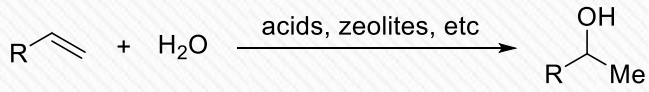
Liu, W.; Li, Wu.; Spannenberg, A.; Junge, K.; Beller, M. *Nat. Catal.* **2019**, *2*, 523.

3 Catalytic Anti-Markovnikov Hydration of Unactivated Alkenes

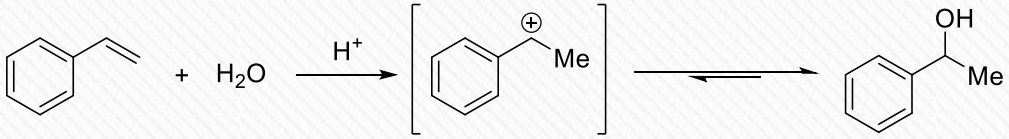
03 Catalytic Anti-Markovnikov Hydration of Unactivated Alkenes

Achieving **anti-Markovnikov hydration of alkenes** under mild conditions has been a dream of synthetic chemists for a long time, and it has been referred to as **one of top ten challenges of catalysis since 1993**.*

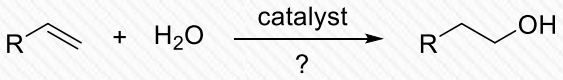
Markovnikov hydration of alkenes



for example:



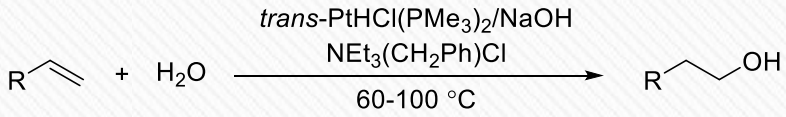
anti-Markovnikov hydration of alkenes

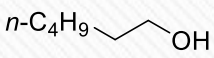


*Haggin, J. *Chem. Eng. News* **1993**, *71*, 23.

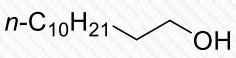
03 Catalytic Anti-Markovnikov Hydration of Unactivated Alkenes

Trogler, 1986:

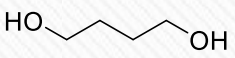




60 °C
rate: 6.9 ± 0.2 turnovers per hour



100 °C
rate: 8.3 ± 0.4 turnovers per hour

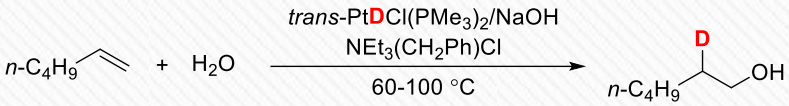


60 °C

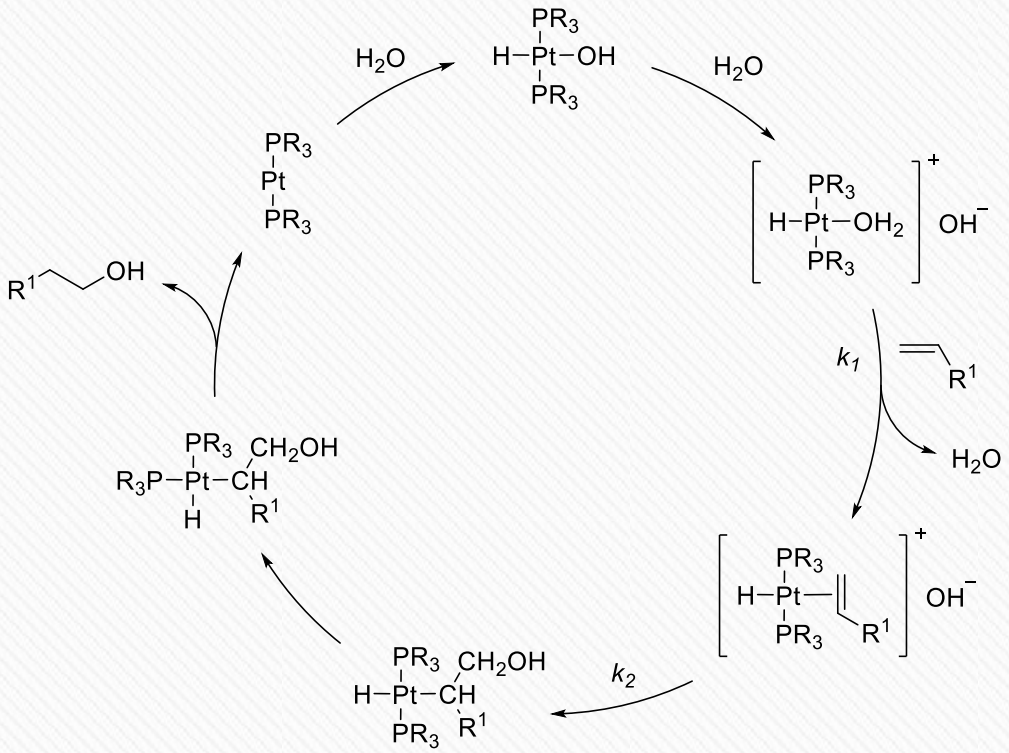
For each example: (1) yield was not given; (2) only trace of branched alcohol (<0.5%) was detected.

Jensen, C. M.; Trogler, W. C. *Science* **1986**, *233*, 1069.

03 Catalytic Anti-Markovnikov Hydration of Unactivated Alkenes



The reaction showed incorporation of lable into the β- C-H bond of the alcohol product.
No deuterium label was detected in the aqueous phase.



Proposed catalytic cycle

Jensen, C. M.; Trogler, W. C. *Science* **1986**, *233*, 1069.

Unfortunately, this work was difficult to reproduce.

Our attempts to hydrate 1-hexene in a basic aqueous medium in the presence of a phase-transfer agent or surfactant and pure trans-$(PMe_3)_2PtHCl$ failed to yield any alcohol products.

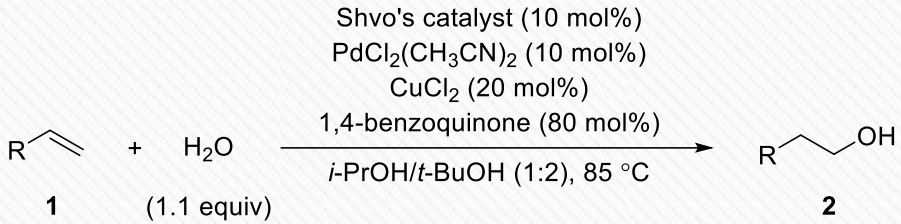
In addition, spectroscopic studies failed to confirm nucleophilic attack of hydroxide ion on coordinated olefins in this system.

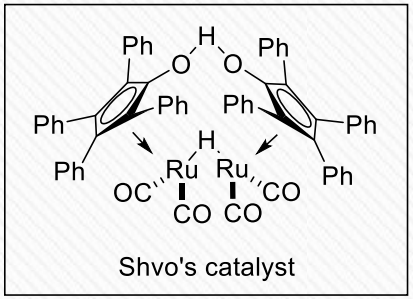
Instead, the predominant reaction under a variety of conditions was olefin isomerization.

Ramprasad, D.; Yue, H. J.; Marsella, J. A. *Inorg. Chem.* **1988**, *27*, 3151.

03 Catalytic Anti-Markovnikov Hydration of Unactivated Alkenes

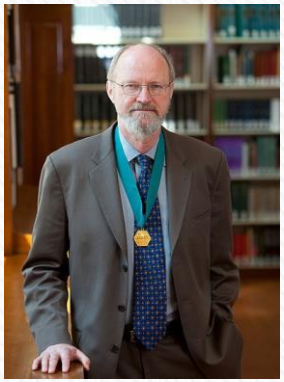
Grubbs, 2011:





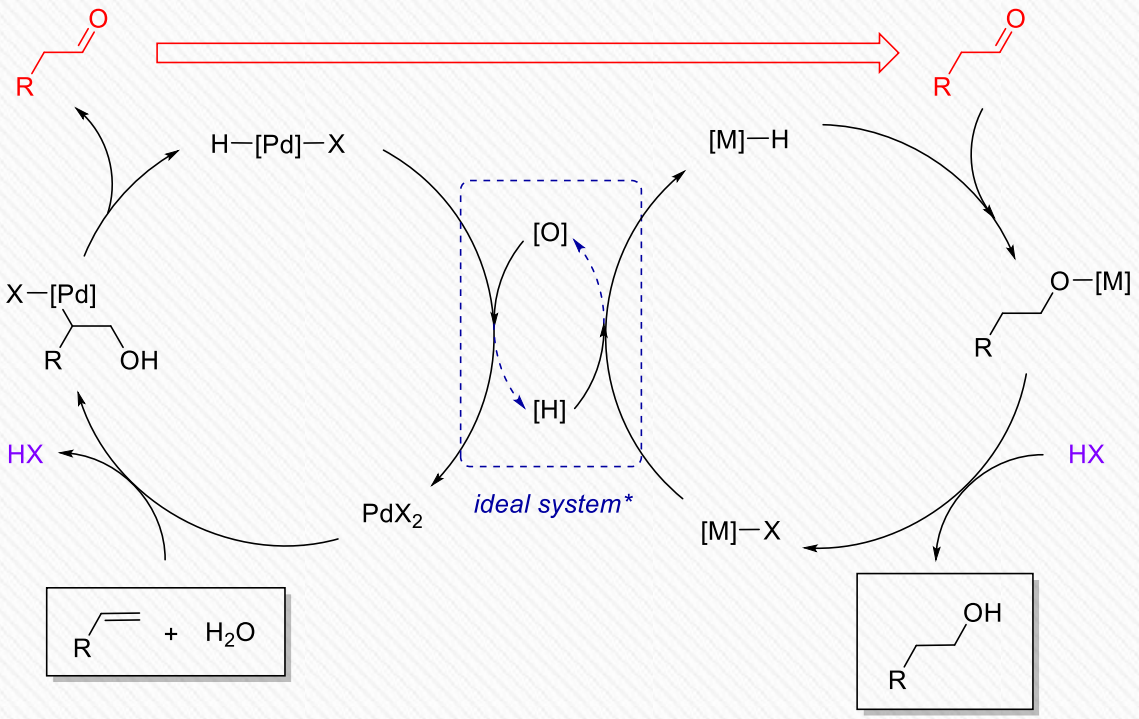
Shvo's catalyst

R = aryl, selectivity (1° OH : 2° OH) ≥ 20:1
R = alkyl, selectivity (1° OH : 2° OH) = 1:1.4 to 1:2.1



Dong, G.; Teo, P.; Wickens, Z. K.; Grubbs, R. H. *Science* **2011**, *333*, 1609.

03 Catalytic Anti-Markovnikov Hydration of Unactivated Alkenes

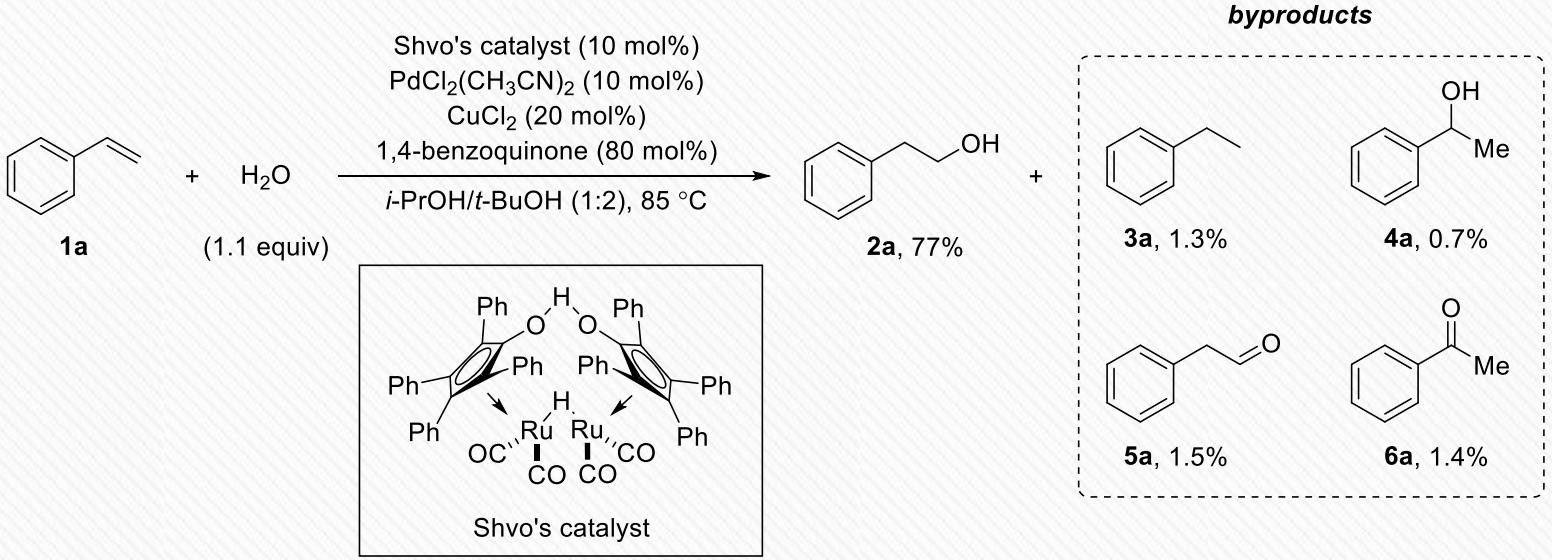


HX: proton sourse; X, anionic ligands, such as chlorides and acetates.

** In the ideal system, either the hydride would be directly transferred from Pd to M or the oxidant [O] and the reductant [H] would be coupled with each other.*

Dong, G.; Teo, P.; Wickens, Z. K.; Grubbs, R. H. *Science* **2011**, *333*, 1609.

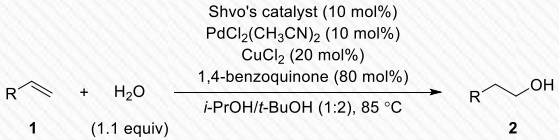
03 Catalytic Anti-Markovnikov Hydration of Unactivated Alkenes



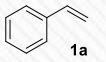
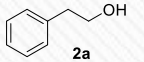
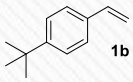
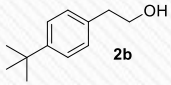
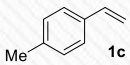
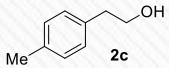
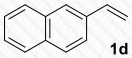
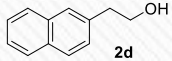
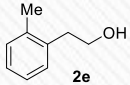
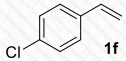
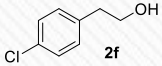
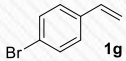
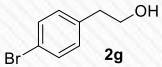
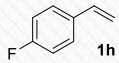
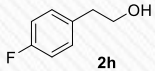
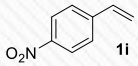
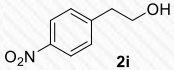
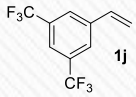
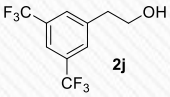
$$\text{anti-Markovnikov selectivity} = \frac{[1^\circ \text{ alcohol}] + [\text{aldehyde}]}{[2^\circ \text{ alcohol}] + [\text{ketone}]} = 38$$

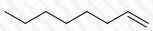
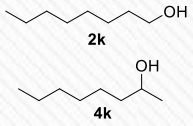
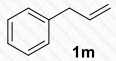
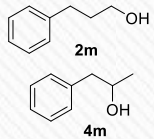
Dong, G.; Teo, P.; Wickens, Z. K.; Grubbs, R. H. *Science* **2011**, *333*, 1609.

03 Catalytic Anti-Markovnikov Hydration of Unactivated Alkenes



1 **2**

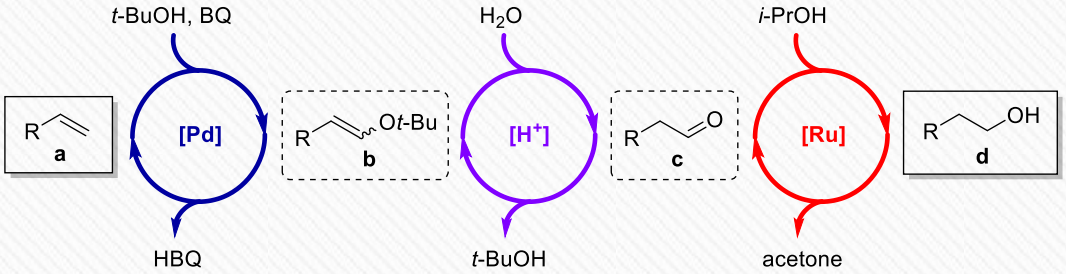
Entry	Substrate	Product	Yield	Selectivity (1° OH : 2° OH)[a]
1	 **1a**	 **2a**	61% (GC yield 65%)[b] 84% (GC yield 83%)[c]	≥ 20:1
2	 **1b**	 **2b**	42%[d]	≥ 20:1
3	 **1c**	 **2c**	61%[d]	≥ 20:1
4	 **1d**	 **2d**	60%[c]	≥ 20:1
5	 **1e**	 **2e**	72%[d]	≥ 20:1
6	 **1f**	 **2f**	75%[c]	≥ 20:1
7	 **1g**	 **2g**	72%[d]	≥ 20:1
8	 **1h**	 **2h**	63%[b] 84%[c]	≥ 20:1
9	 **1i**	 **2i**	83%[c]	≥ 20:1
10	 **1j**	 **2j**	74%[d]	≥ 20:1

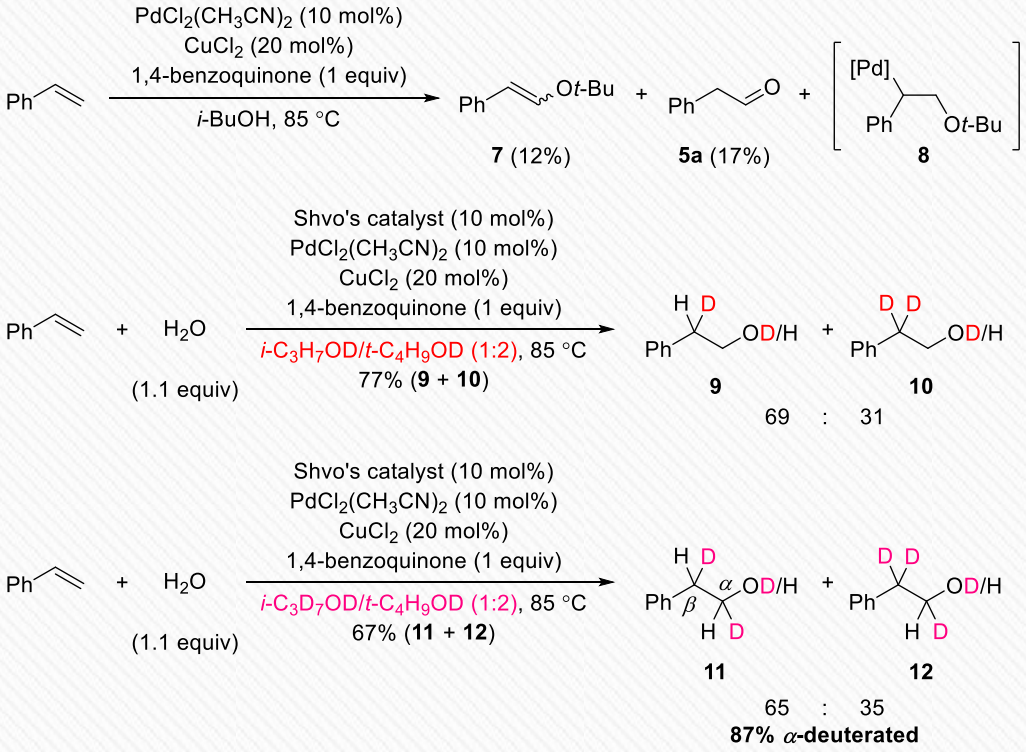
Entry	Substrate	Product	Yield	Selectivity (1° OH : 2° OH)[a]
11	 **1k**	 **2k** **4k**		56%[e,f] (**2k**:**4k** = 1:1.4) 84%[g,f] (**2k**:**4k** = 1:1.9)
12	 **1m**	 **2m** **4m**		12%[c] (**2m**:**4m** = 1:2.1)

[a] The ratio was determined via ^{1}H NMR analysis of the crude reaction mixture. [b] Isolated yield and [C] (initial substrate concentration) = 0.25 M. [c] Isolated yield, [C] = 0.067 M, and 1 equiv of BQ (1,4-benzoquinone) was employed. [d] Isolated yield and [C] = 0.125 M. [e] *i*-PrOH:*t*-BuOH = 1:1, [C] = 0.067 M, and 1 equiv of BQ. [f] Attempted purification through column chromatography; yield was determined via ^{1}H NMR using mesitylene as the internal standard. [g] *i*-PrOH:*t*-BuOH = 1:2, [C] = 0.067 M, and 1 equiv of BQ.

Dong, G.; Teo, P.; Wickens, Z. K.; Grubbs, R. H. *Science* **2011**, *333*, 1609.

03 Catalytic Anti-Markovnikov Hydration of Unactivated Alkenes



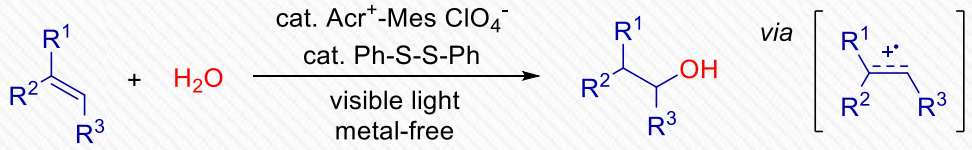


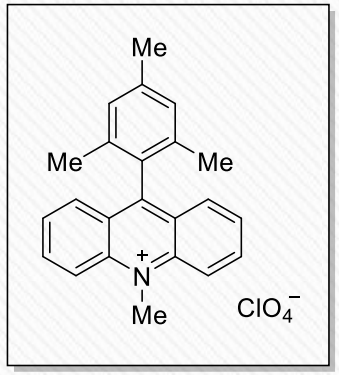
Proposed mechanism and initial mechanistic studies

Dong, G.; Teo, P.; Wickens, Z. K.; Grubbs, R. H. *Science* **2011**, *333*, 1609.

03 Catalytic Anti-Markovnikov Hydration of Unactivated Alkenes

Lei, 2017:





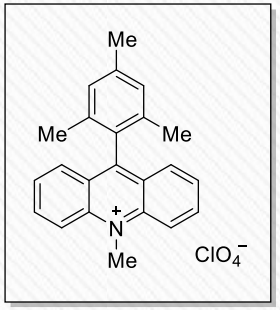
Acr$^+$-Mes ClO_4^-

anti-Markovnikov hydration of alkenes through the radical cation

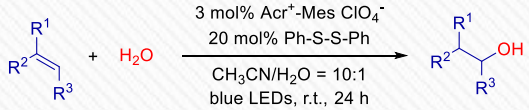
Hu, X.; Zhang, G.; Bu, F.; Lei, A. *ACS Catal.* **2017**, *7*, 1432.

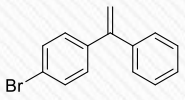
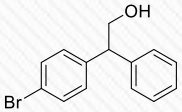
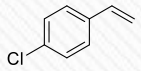
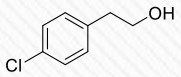
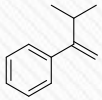
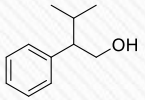
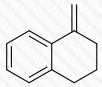
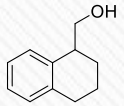
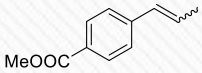
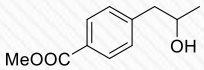
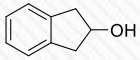
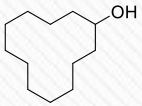
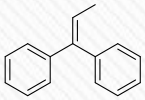
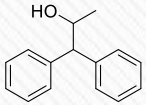
03 Catalytic Anti-Markovnikov Hydration of Unactivated Alkenes

Selected examples:



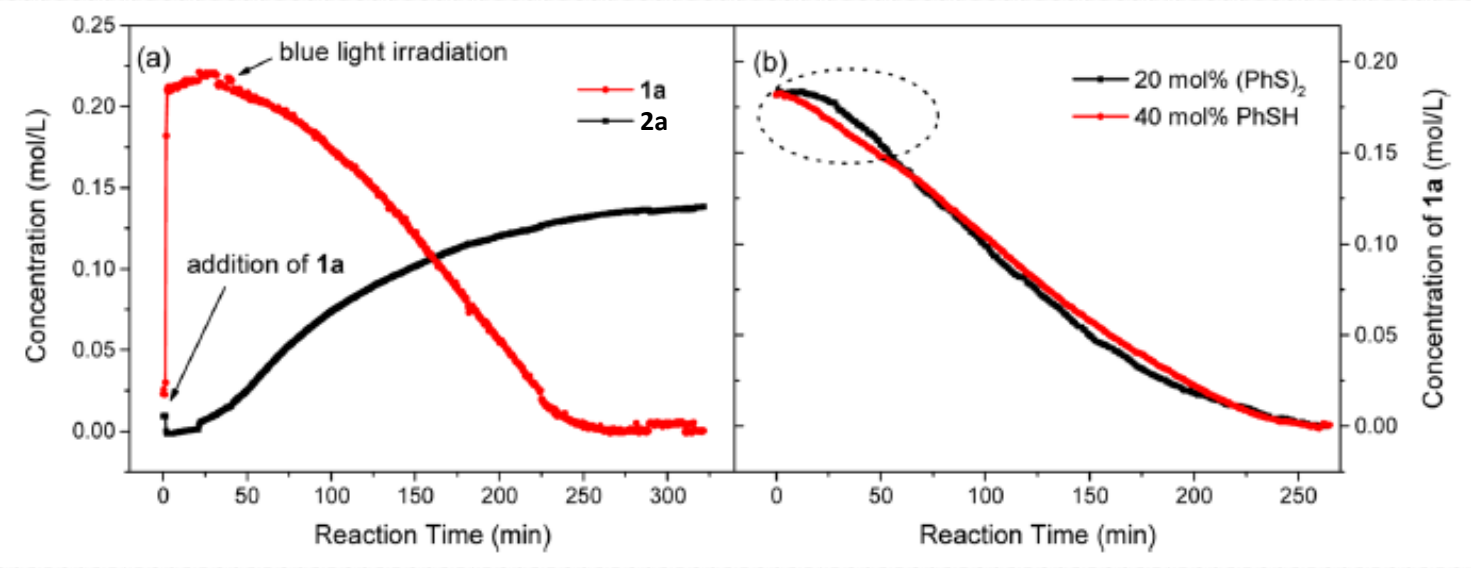
Acr^+-Mes ClO_4^-



Entry	Alkenes	Alcohols	Yield/%
1			74
2			54
3			69
4			41
5			84
6			84
7			84
8			84

Conditions: alkenes **1** (0.3 mmol), photocatalyst **3** (3 mol%), diphenyldisulfane (20 mol%), and 0.2 mL of water in CH_3CN (2 mL) under a nitrogen atmosphere irradiation using 3 W blue LEDs at room temperature for 24 h. Isolated yields were shown.

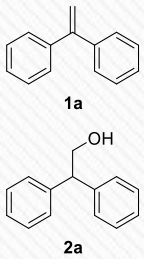
Hu, X.; Zhang, G.; Bu, F.; Lei, A. *ACS Catal.* **2017**, *7*, 1432.

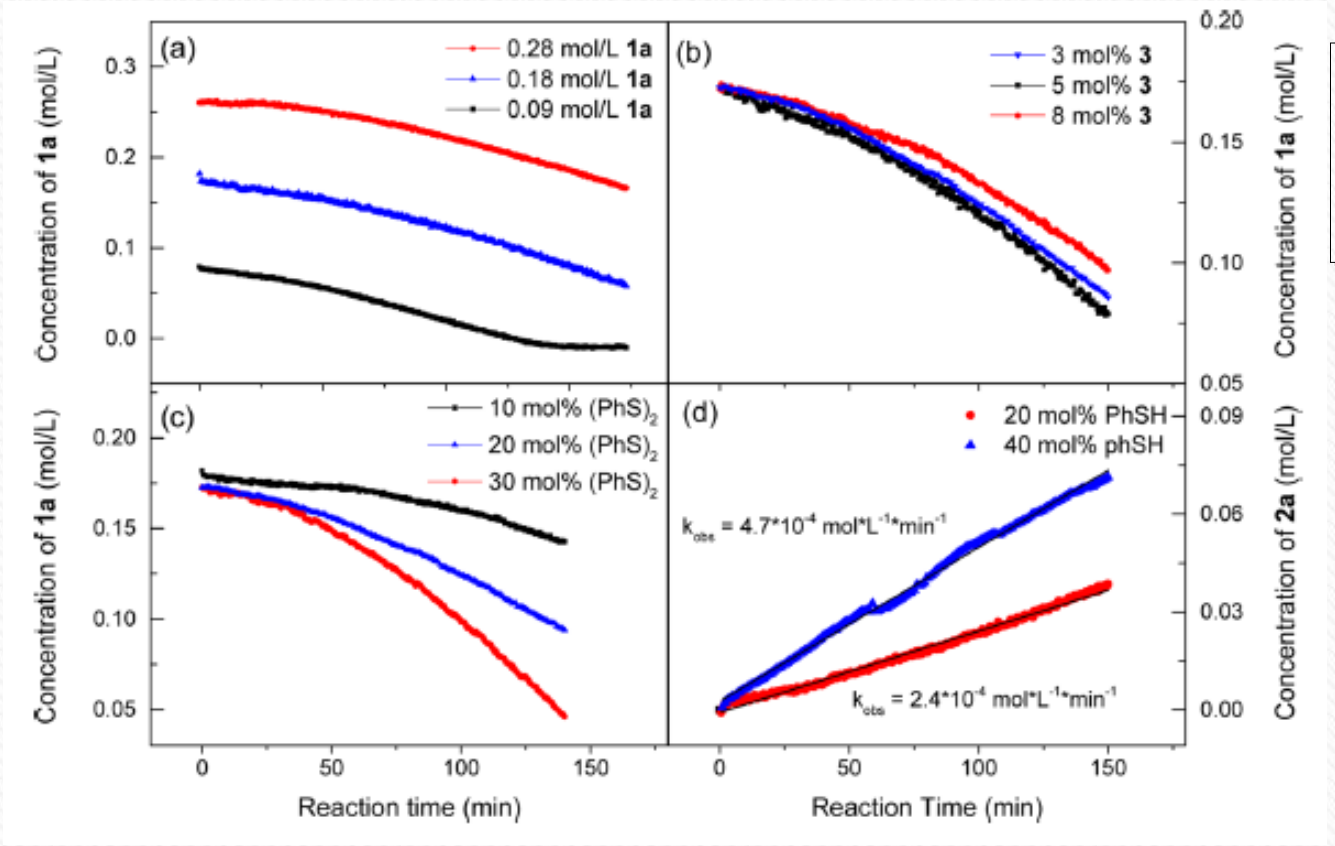


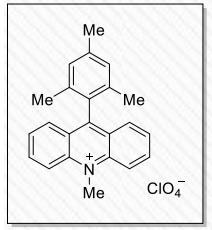
In situ IR investigation for mechanistic insights

Hu, X.; Zhang, G.; Bu, F.; Lei, A. *ACS Catal.* **2017**, *7*, 1432.

Catalytic Anti-Markovnikov Hydration of Unactivated Alkenes







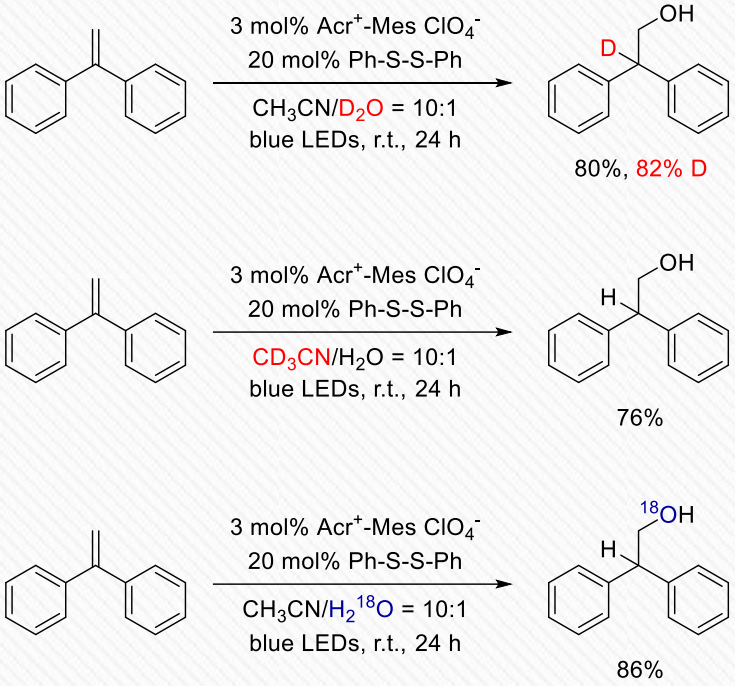
Acr$^+$-Mes ClO_4^- (3)

Kinetic experiments of each component

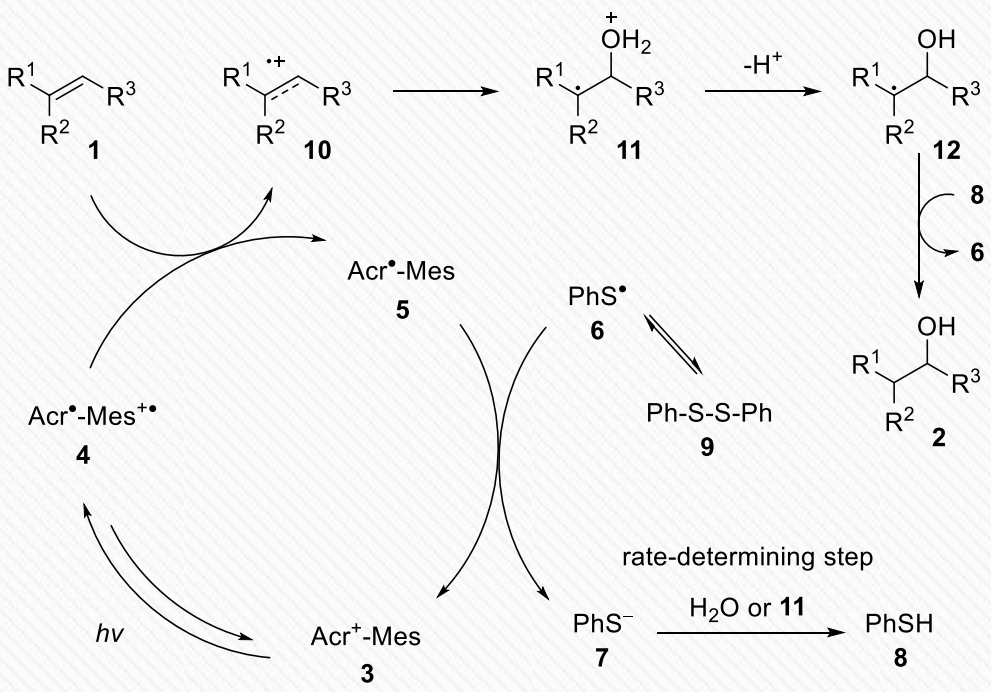
Based on the kinetic data of HAT between PhSH and carbon radical (k = 3.13 × 10^5 M^{-1} S^{-1} for $PhCH_2$· in hexane): (1) the HAT process is expected to be a fast step; (2) the protonation of PhS^- might be the rate-determining step.

Hu, X.; Zhang, G.; Bu, F.; Lei, A. *ACS Catal.* **2017**, *7*, 1432.

03 Catalytic Anti-Markovnikov Hydration of Unactivated Alkenes



Isotope-labeling experiments

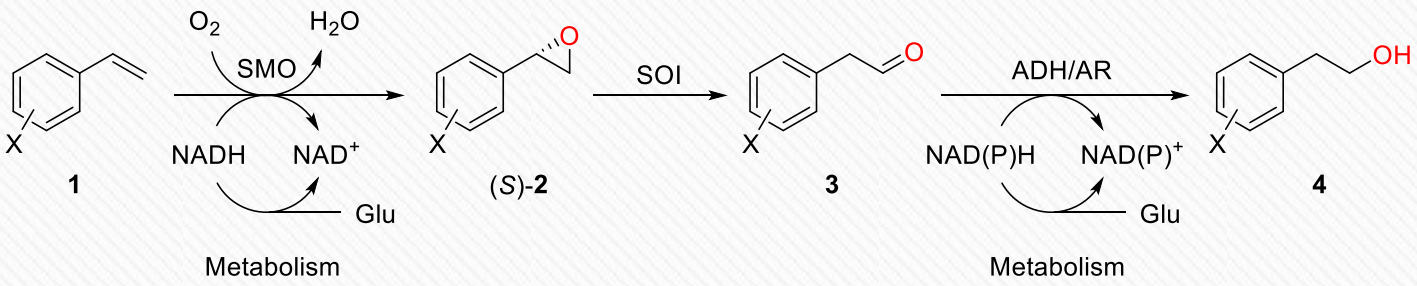


Proposed mechanism

Hu, X.; Zhang, G.; Bu, F.; Lei, A. *ACS Catal.* **2017**, *7*, 1432.

03 Catalytic Anti-Markovnikov Hydration of Unactivated Alkenes

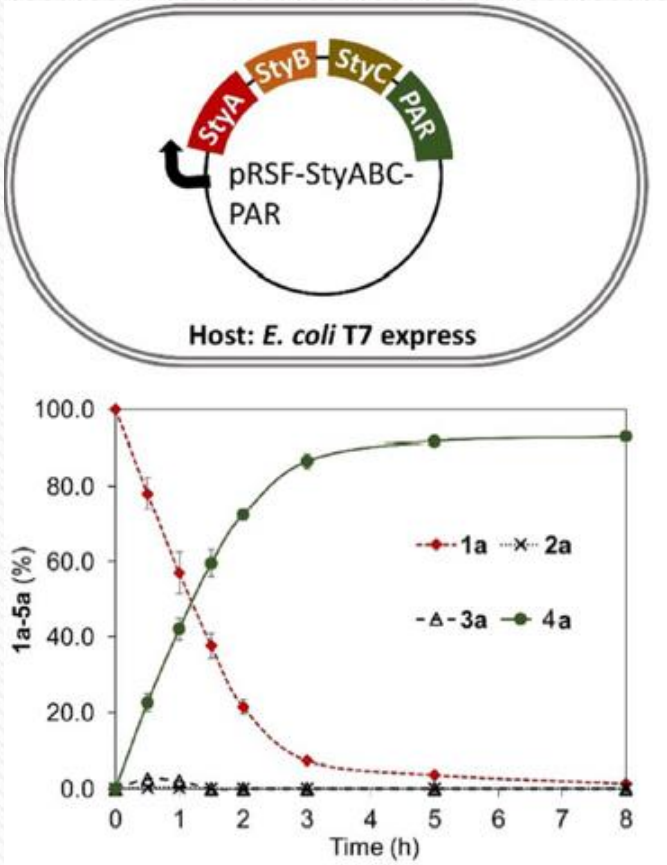
Li, 2017:

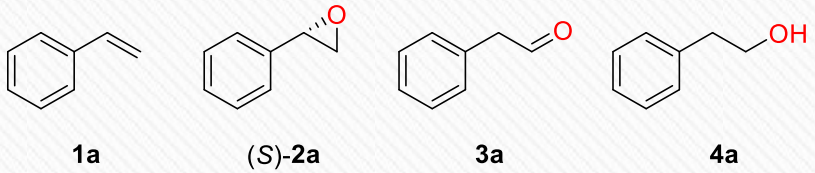


SMO = styrene monooxygenase, SOI = styrene oxide isomerase,
ADH = alcohol dehydrogenase, AR = aldehyde reductase, HLADH = horse liver ADH

Wu, S.; Liu, J.; Li, Z. *ACS Catal.* **2017**, *7*, 5225.

Catalytic Anti-Markovnikov Hydration of Unactivated Alkenes

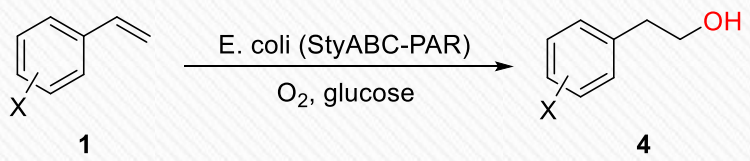




1a **(*S*)-2a** **3a** **4a**

Wu, S.; Liu, J.; Li, Z. *ACS Catal.* **2017**, *7*, 5225.

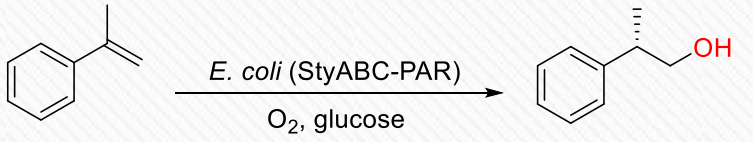
Catalytic Anti-Markovnikov Hydration of Unactivated Alkenes



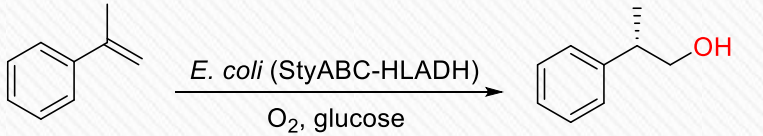
1 **4**

entry	X	conv. to **5** (%)	regioselectivity 2-OH:1-OH
1	H	>99	>99:1
2	*o*-F	90	>99:1
3	*m*-F	94	>99:1
4	*p*-F	98	>99:1
5	*m*-Cl	89	>99:1
6	*p*-Cl	78	>99:1
7	*m*-Br	83	>99:1
8	*p*-Br	60	>99:1
9	*m*-Me	99	>99:1
10	*p*-Me	99	>99:1
11	*m*-OMe	>99	>99:1
12	*p*-OMe	94	>99:1

Reaction conditions: 20 mM styrene **1**, *E. coli* (StyABC-PAR) cells (10 g cdw/L), in KP buffer (200 nM, pH 8, 2% glucose) and *n*-$C_{16}H_{34}$ (1:1) at 30 °C for 10 h, except 24 h for entries 5-12. Regioselectivity was determined by HPLC and GC analysis.



1 (*S*)-**4**
85%, 99:1, 87% ee

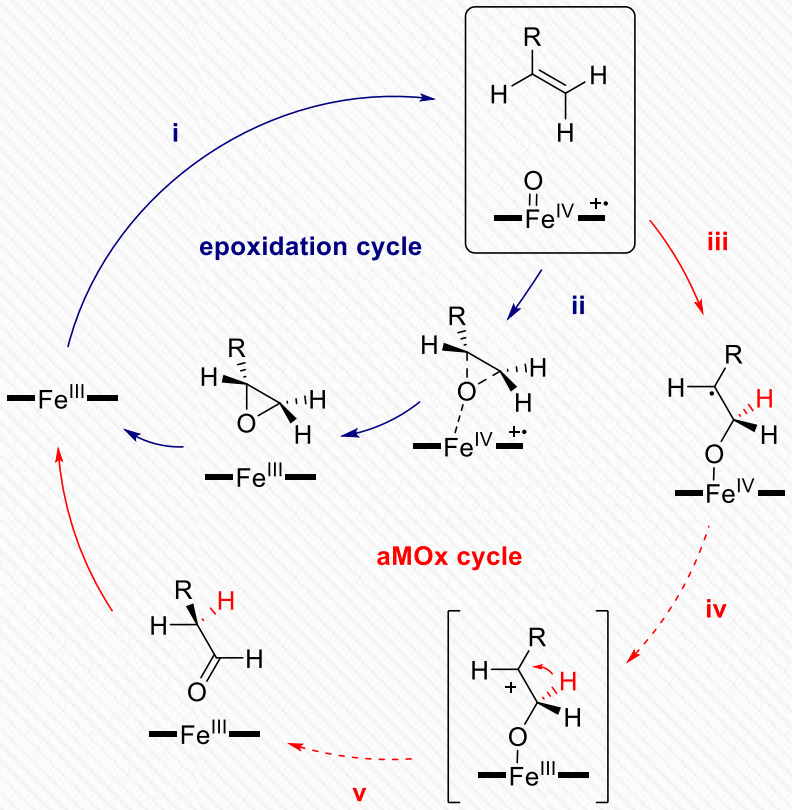


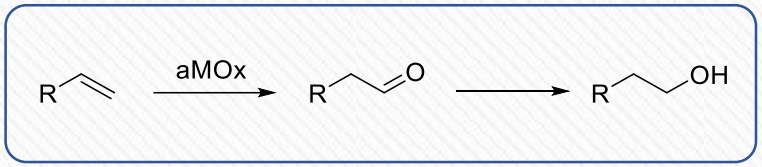
1 (*S*)-**4**
81%, >99:1, 97% ee

Wu, S.; Liu, J.; Li, Z. *ACS Catal.* **2017**, *7*, 5225.

03 Catalytic Anti-Markovnikov Hydration of Unactivated Alkenes

Arnold, 2017:

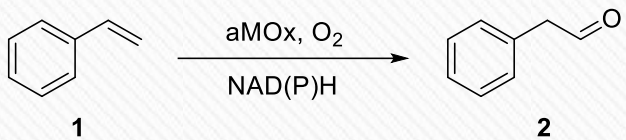


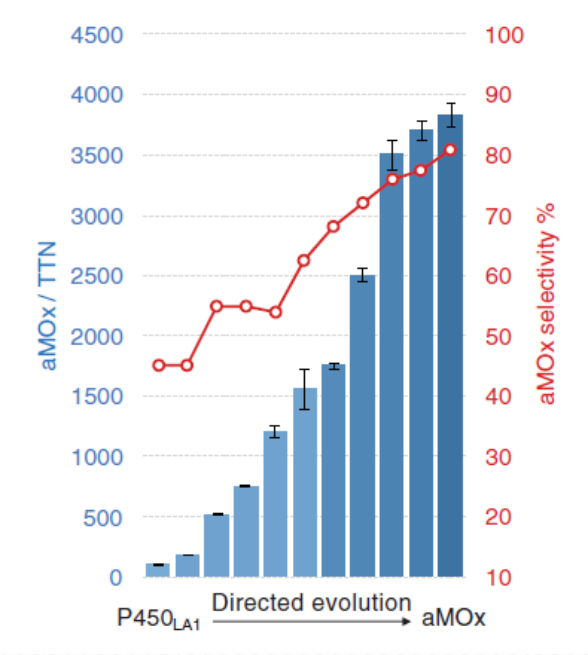


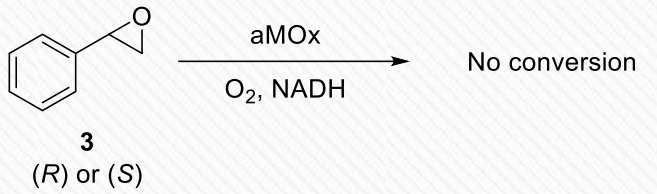
Engineering of a cytochrome P450 enzyme by directed evolution to catalyze metal-oxo–mediated anti-Markovnikov oxidation of styrenes.

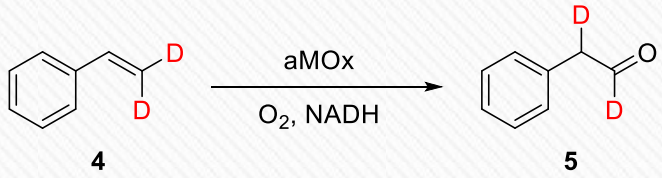
Hammer, S. C.; Kubik, G.; Watkins, E.; Huang, S.; Minges, H.; Arnold, F. H. *Science* **2017**, *358*, 215.

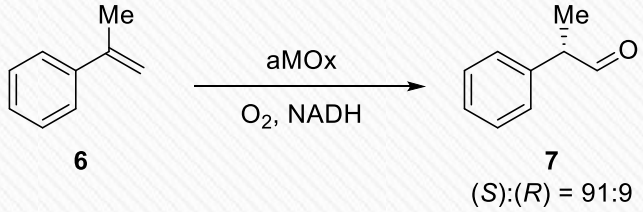
03 Catalytic Anti-Markovnikov Hydration of Unactivated Alkenes

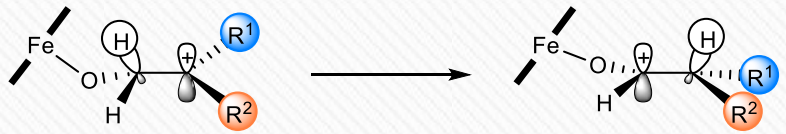








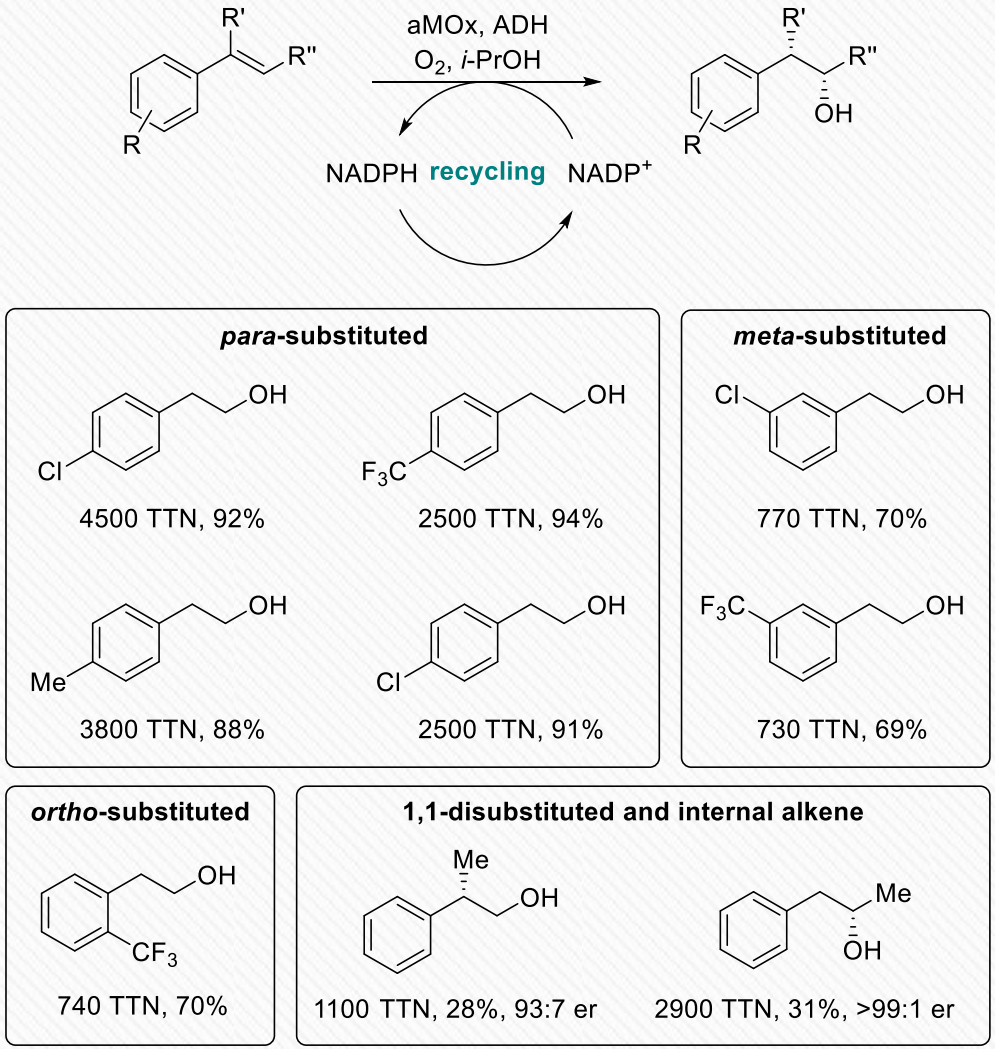




- locked substrate conformation
- enantioselective 1,2-hydride migration

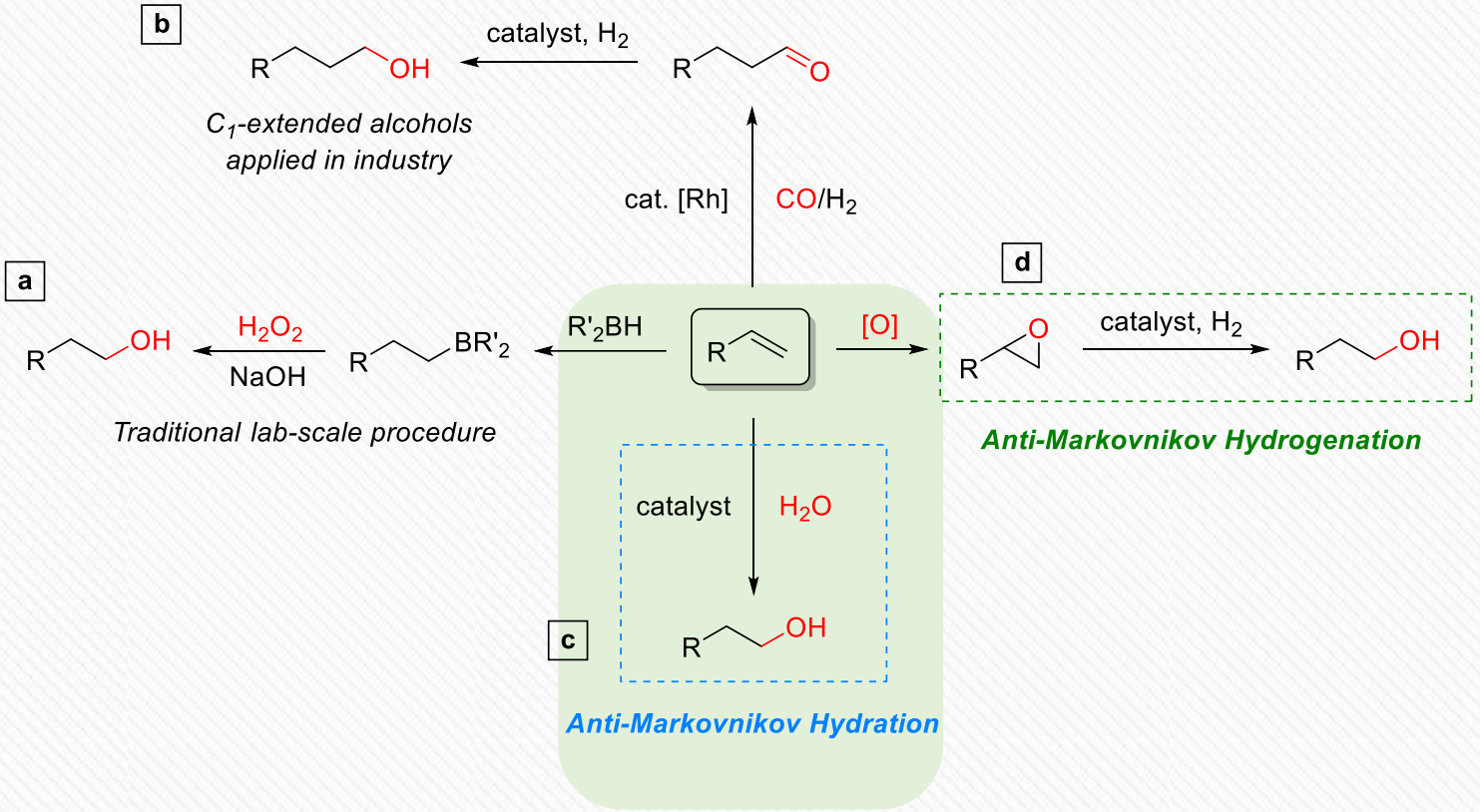
Hammer, S. C.; Kubik, G.; Watkins, E.; Huang, S.; Minges, H.; Arnold, F. H. *Science* **2017**, *358*, 215.

03 Catalytic Anti-Markovnikov Hydration of Unactivated Alkenes



Hammer, S. C.; Kubik, G.; Watkins, E.; Huang, S.; Minges, H.; Arnold, F. H. *Science* **2017**, *358*, 215.

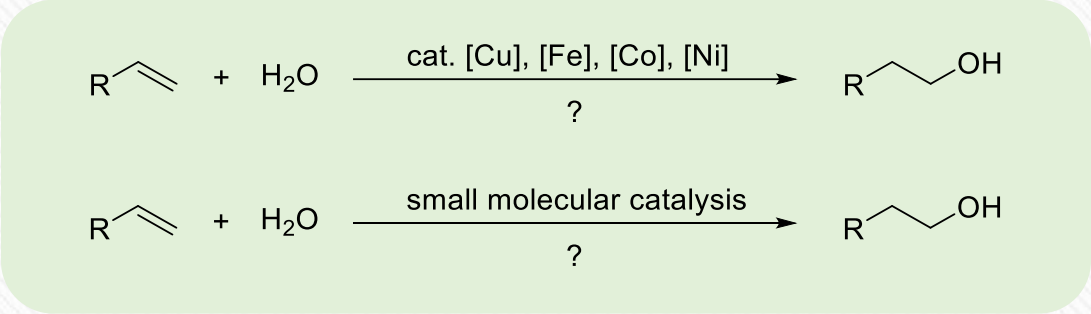
Summary



Directly anti-Markovnikov hydration of alkenes

- **Atomic economy**
  H_2O, without extra additive

- **Novel catalytic system**
  first-raw transition metal; small molecular catalysis



- **Reliable asymmetric catalysis**

- **Computational chemistry – to deeply comprehend mechanisms**

- **Activation of H_2O**

Thanks for your attention!