M2 Seminar
2024.11.16 (Sat.)

The Fundamental Properties and Asymmetric Reactions of Unstable *ortho*-Quinone Methides

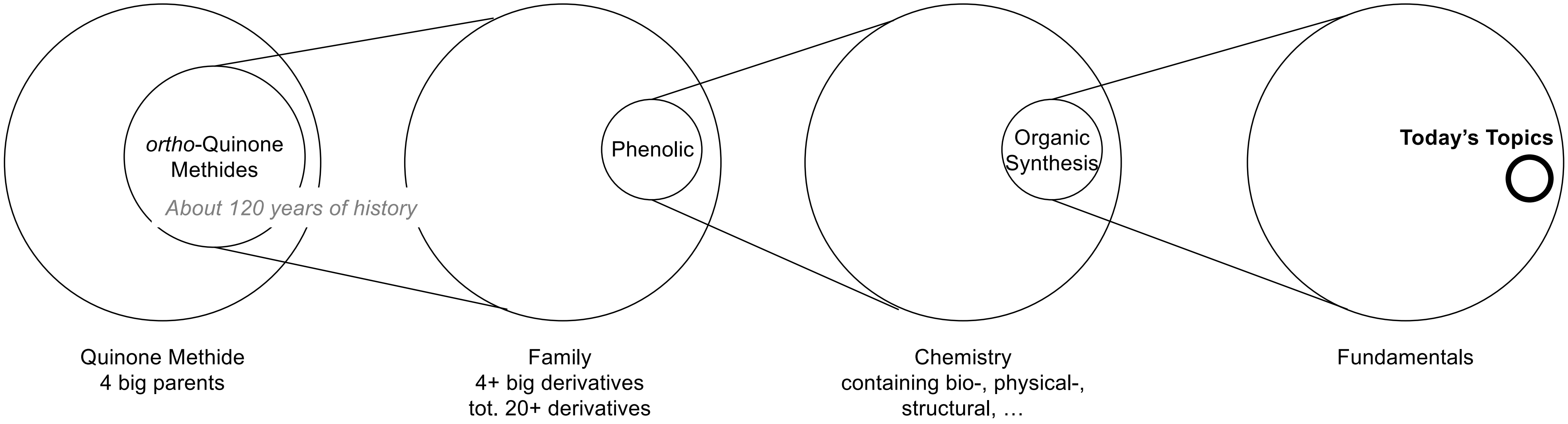
Takaharu MORINO

Before starting, please forgive the following points:

- Many important reports have been omitted due to space and time constraints.

- The chemistry of *ortho*-Quinone Methides is very complex. So, I will explaine with my considerations.

Scopes



Main Topic

Minimum Fundamentals for Asymmetric Reactions of Phenolic "Unstable" *ortho*-Quinone Methide in Organic Synthetic Chemistry

excluded many important, latest & advanced topics.

Table of Contents

nature chemistry

Article | Published: 23 March 2020

Chemoselective oxidative generation of *ortho*-quinone methides and tandem transformations

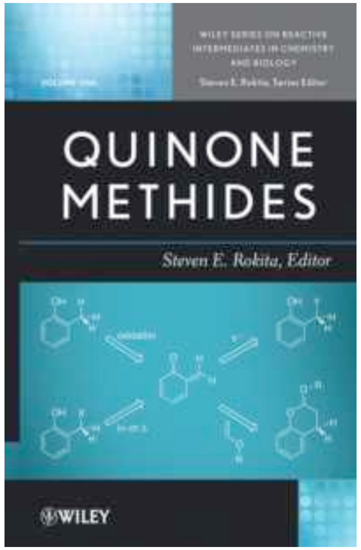
Muhammet Uyanik, Kohei Nishioka, Ryutaro Kondo & Kazuaki Ishihara

Nature Chemistry **12**, 353–362 (2020) | Cite this article

K.ISHIHARA GROUP green catalysis

1. The Fundamental Properties of *ortho*-Quinone Methides

K.ISHIHARA GROUP
green catalysis



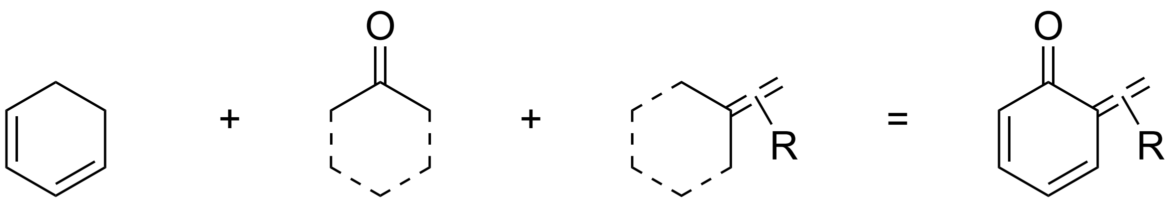
Quinone Methides (Wiley Series of Reactive Intermediates in Chemistry and Biology)

Rokita, S.-E. (editor), 2009.

431 p.

1.1. Structure

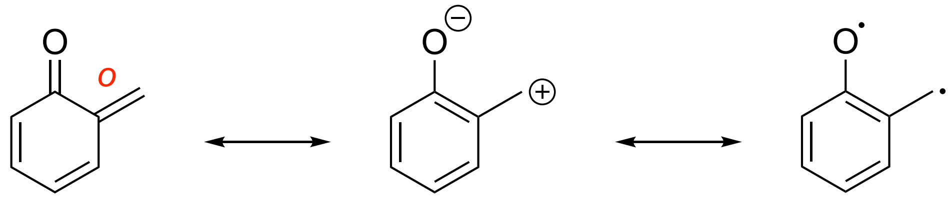
"A quinone methide is a type of conjugated organic compound that contain a **cyclohexadiene** with a **carbonyl** and an **exocyclic methylidene or extended alkene unit**." — wikipedia

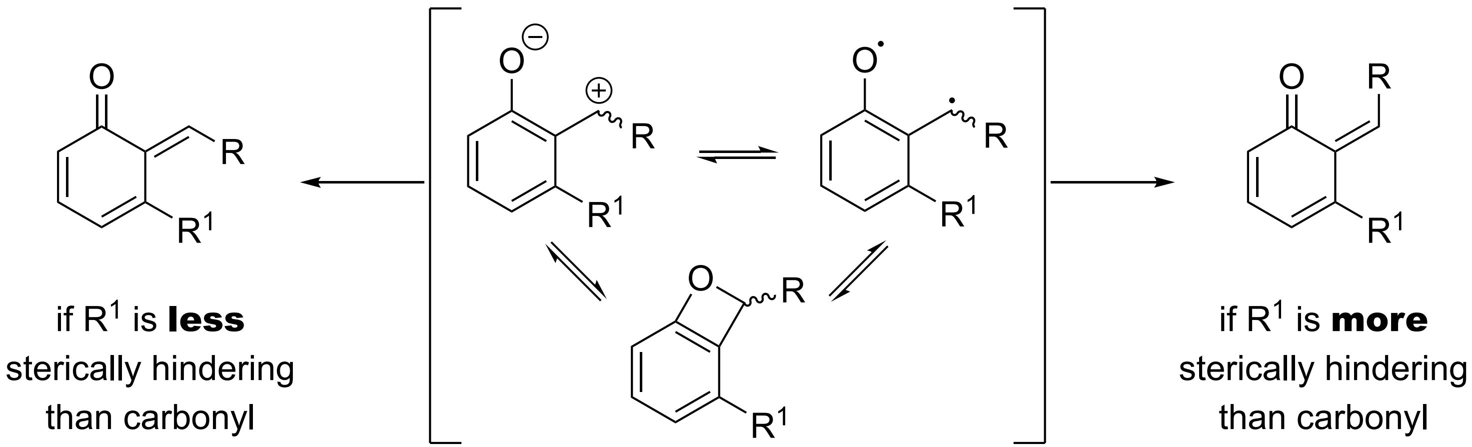


ortho-Quinone Methide
(*o*-QM)

a) wikipedia "Quinone Methide" (ENG), last seeing at 2024/11/5.; b) Rokita, S. E. *Quinone Methide*; John Wiley & Sons, Inc., **2009**.
c) Pettus, T. R. R. *et al. Tetrahedron*, **2002**, *58*, 5367. (very well-organized review of early *o*-QM)

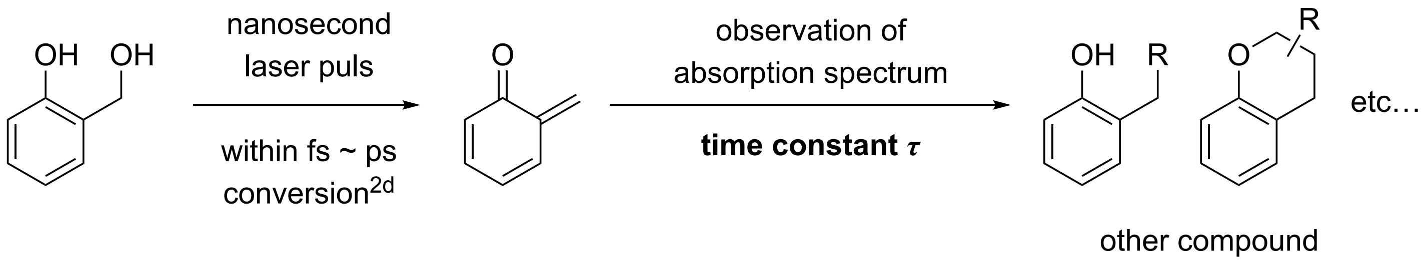
1.2. Equilibrium

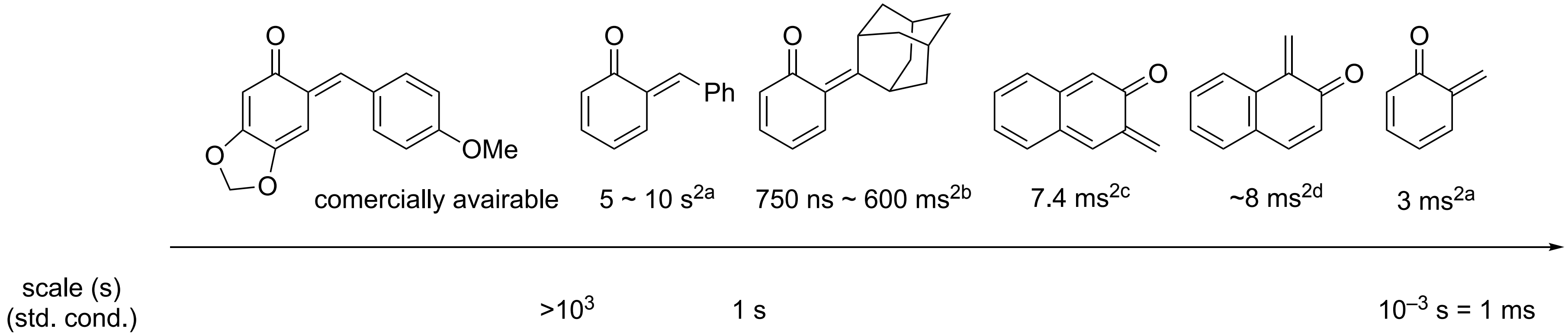




a) wikipedia “Quinone Methide” (ENG), last seeing at 2024/11/5.; b) Rokita, S. E. *Quinone Methide*; John Wiley & Sons, Inc., **2009**.
c) Pettus, T. R. R. *et al. Tetrahedron*, **2002**, *58*, 5367. (very well-organized review of early *o*-QM)

1.3. LFP: Nanosecond Laser Flash Photolysis



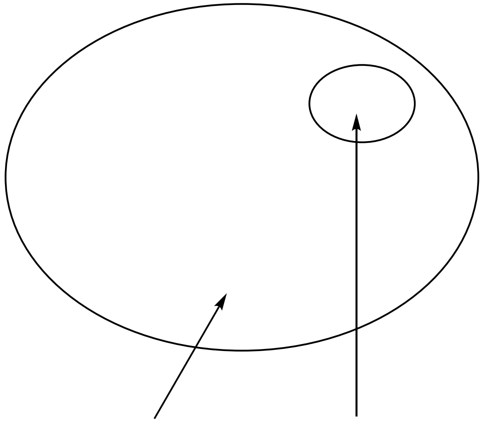


* time constant τ dependeds on leaving group, solvent, λ, atmosphere, trapping reagent, …

1. Rokita, S. E. *Quinone Methide*; John Wiley & Sons, Inc., **2009**. (see chapter 1. for early works and overview)
2. a) Wan, P. *et al. J. Am. Chem. Soc.* ***1995***, *117*, 5369.; b) Vdovic, S. and Cannizzo, A. *et al. Phys. Chem. Chem. Phys.* **2022**, *24*, 4384.
c) Popik, V. V. *et. al. J. Am. Chem. Soc.* **2009**, *131*, 11892.; d) just examples: Ma, J.; Sektor, M.; Basaric, N. and Philips, D. L. *et al. J. Org. Chem.* **2019**, *84*, 8630.
* No data for *o*-PMP-QM, but the this species is much stable than others, so it is listed for convenience to explain.

1.4. Classification and Definition by Stability (My Opinion)

Normal Definitions

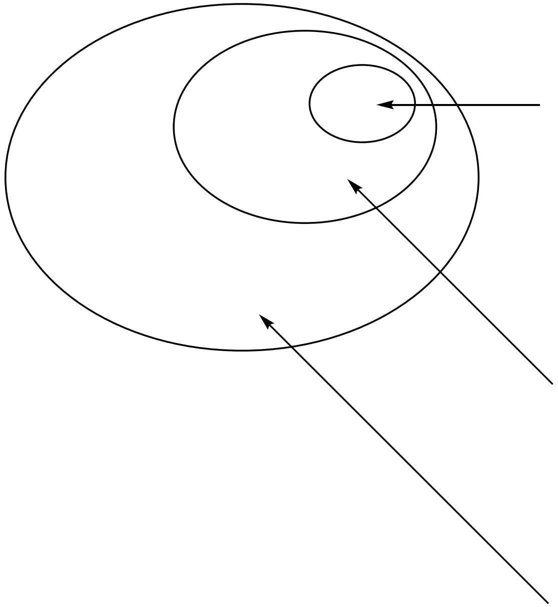


unstable *o*-QM
- unisolatable
- undetectable

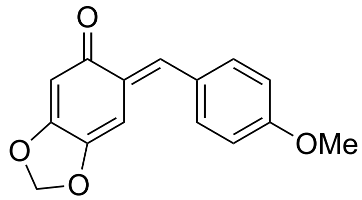
stable *o*-QM
- isolatable
- detectable

TM's Definitions for Today's Convenience

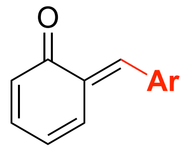
Caution: no literature uses this definition; personal definition



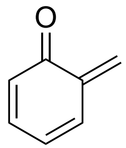
stable *o*-QM
- activation required
- isolatable, detectable

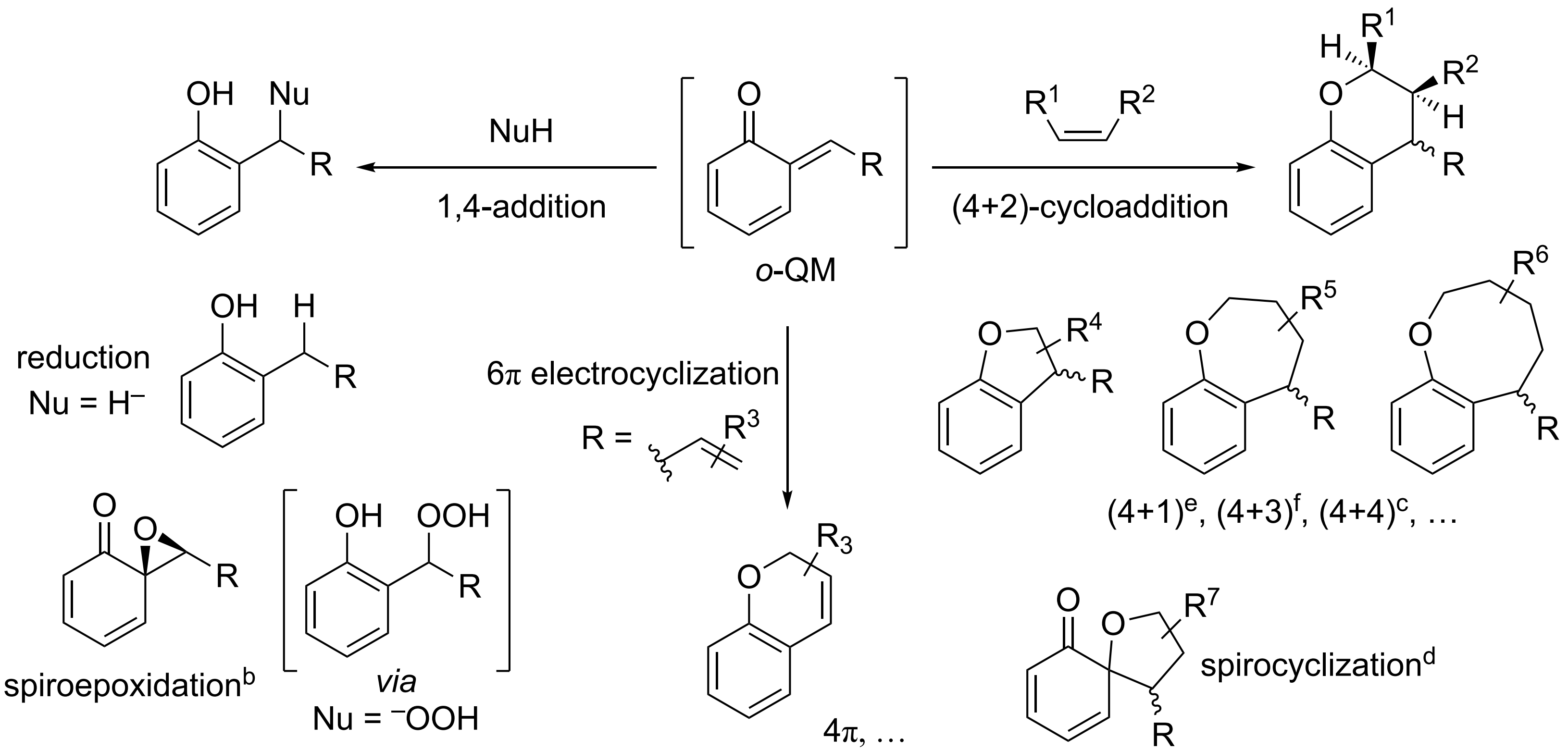


semi-stable *o*-QM
- activation is not necessarily required
  but **can be received due to its rel. long lifetime**
- unisolatable, usually undetectable

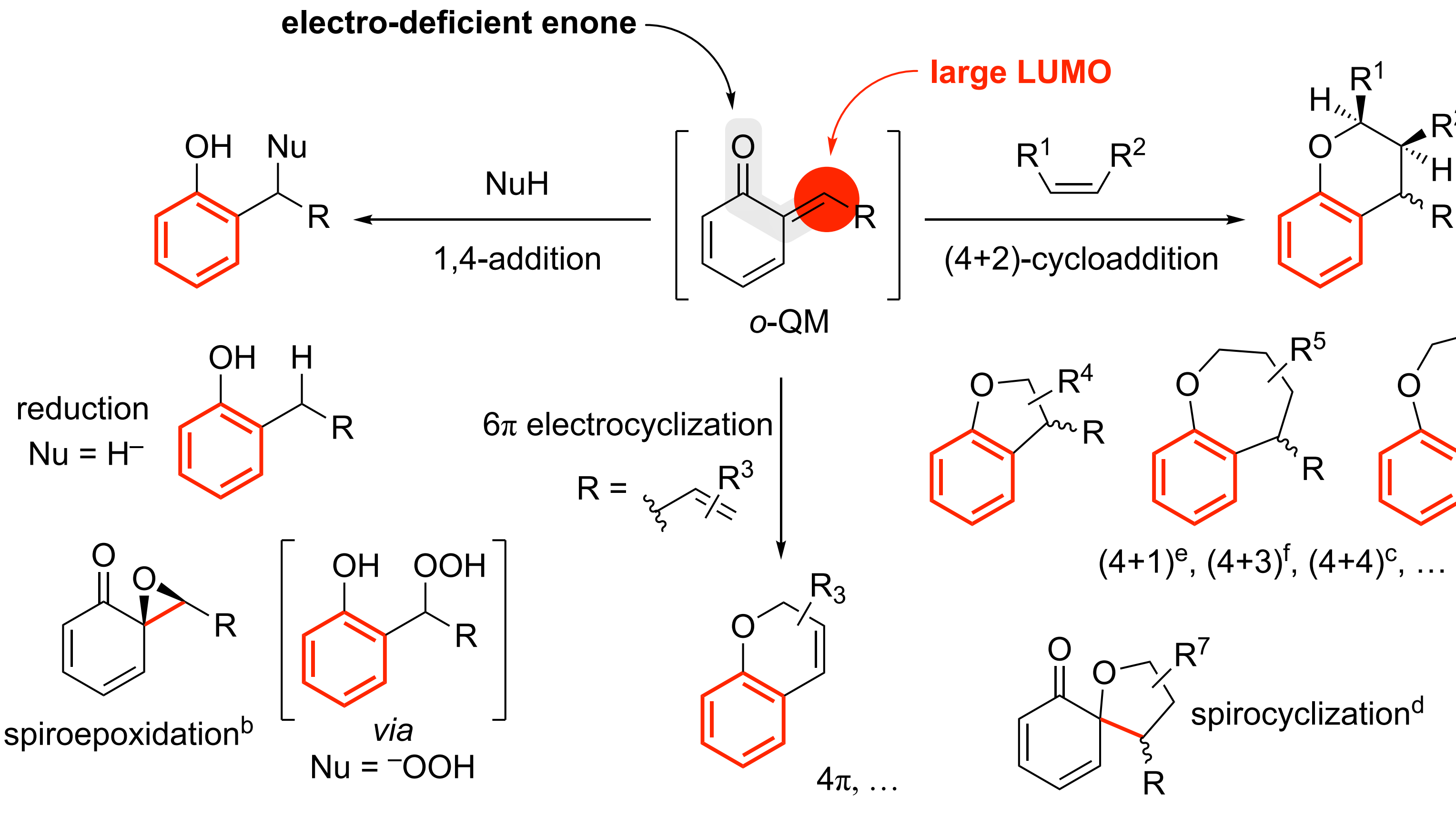


unstable *o*-QM
- dead before activation
- unisolatable, undetectable



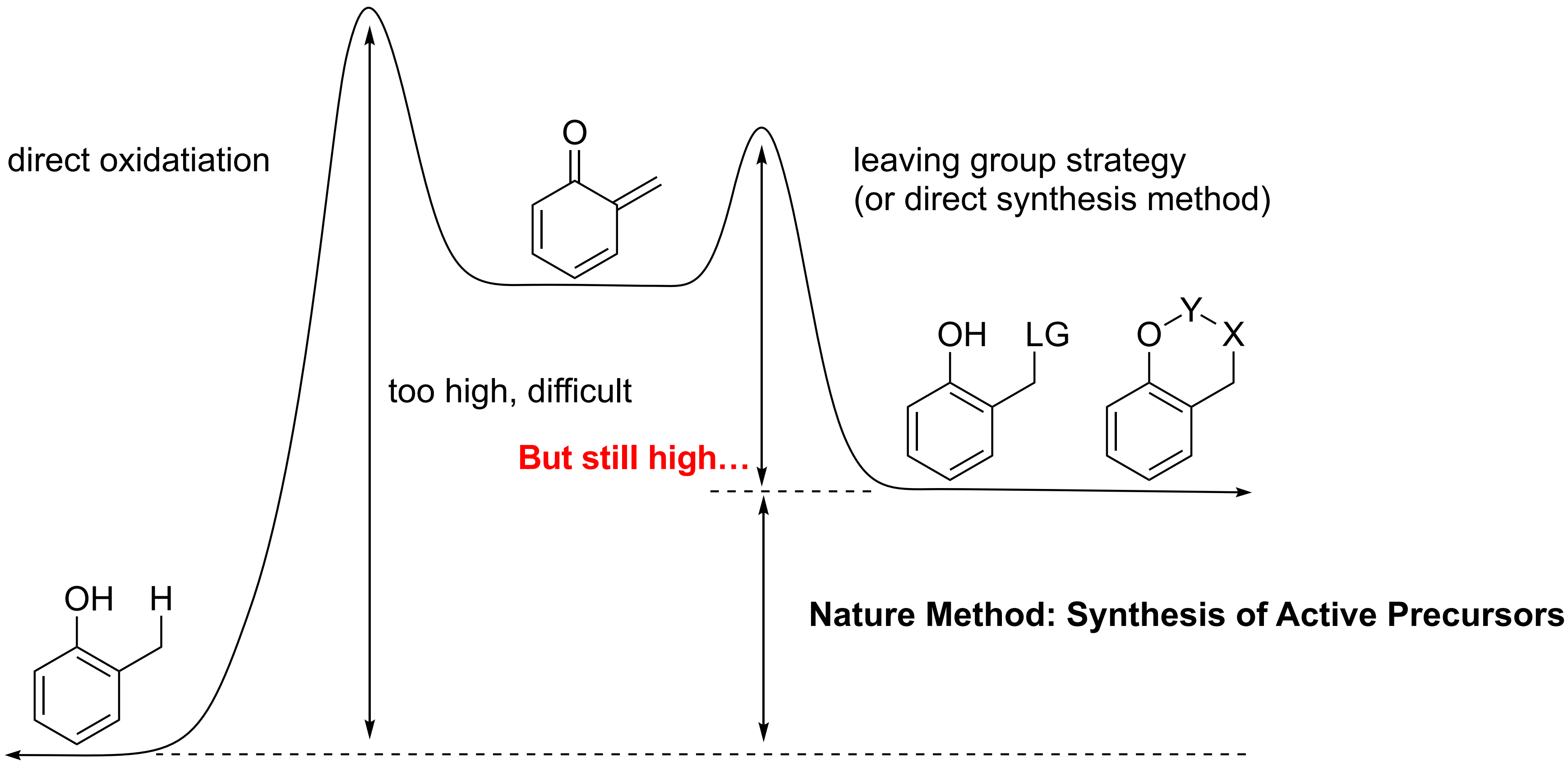


a) Pettus, T. R. R. *et al.* *Tetrahedron*, **2002**, *58*, 5367. (very well-organized review of *o*-QM)
b) Johnson, J. S. *et al.* *J. Am. Chem. Soc.* **2019**, *141*, 2645.; Ishihara, K. *et al.* *Nat. Chem.* **2020**, *12,* 353.
c) Zhou, L. and Xin, L. *et al.* *Org. Biomol. Chem.*, **2024**, *22*, 252.; d) Oguma, T. and Katsuki, T. *Chem. Commum.* **2014**, *50*, 5053.
e) Mai, G. J.; Shi, F. *et al.* *Adv. Synth. Catal.* **2017**, *359*, 3341.; f) Ma, C.-L. *et al.* *Org. Lett.* **2019**, *21*, 465.

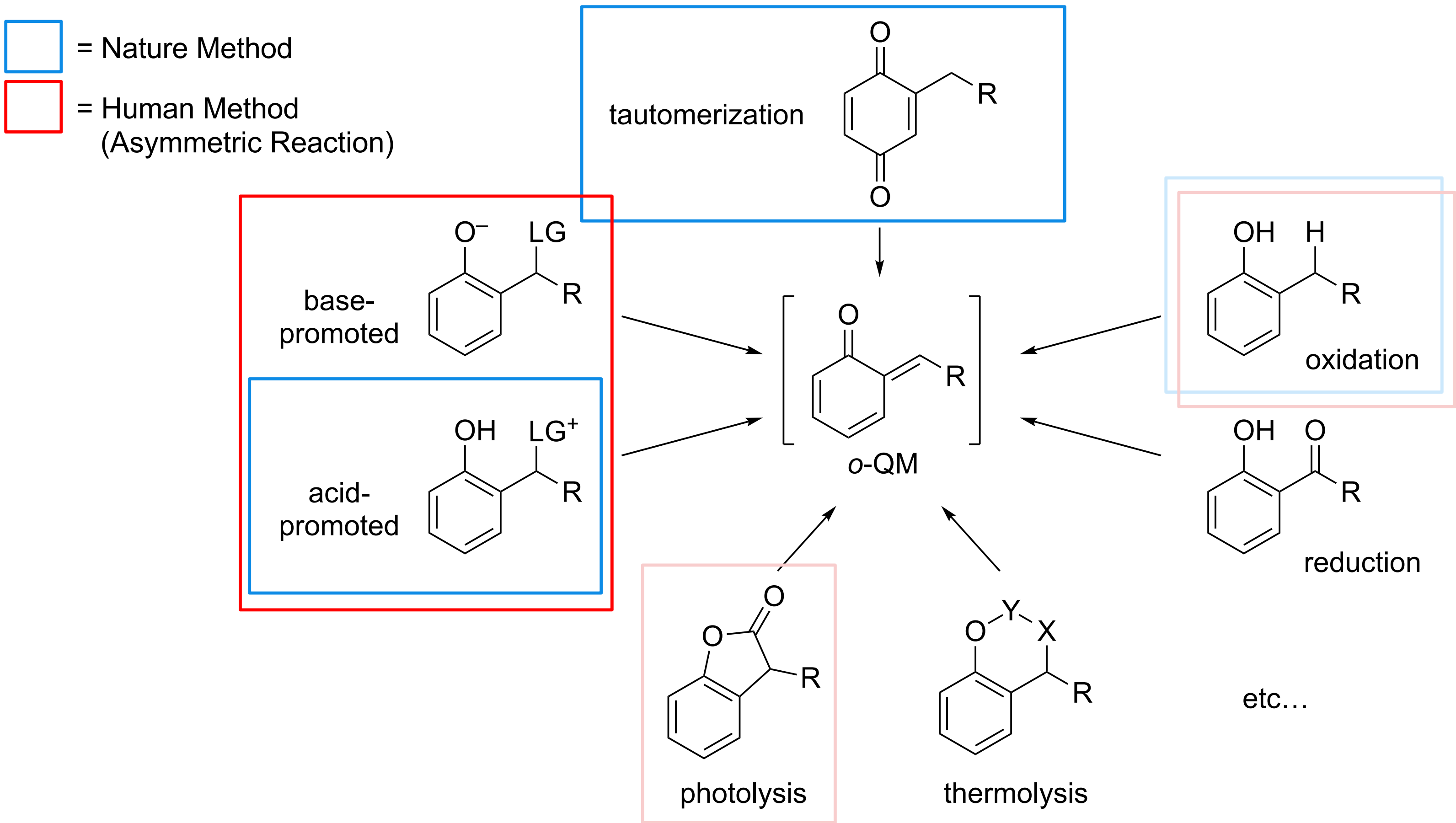


a) Pettus, T. R. R. *et al. Tetrahedron*, **2002**, *58*, 5367. (very well-organized review of *o*-QM)
b) Johnson, J. S. *et al. J. Am. Chem. Soc.* **2019**, *141*, 2645.; Ishihara, K. *et al. Nat. Chem.* **2020**, *12*, 353.
c) Zhou, L. and Xin, L. *et al. Org. Biomol. Chem.*, **2024**, *22*, 252.; d) Oguma, T. and Katsuki, T. *Chem. Commum.* **2014**, *50*, 5053.
e) Mai, G. J.; Shi, F. *et al. Adv. Synth. Catal.* **2017**, *359*, 3341.; f) Ma, C.-L. *et al. Org. Lett.* **2019**, *21*, 465.

1.6. Generation Methods –– Basic Strategy = LG Strategy



1.6. Generation Methods –– Representative Methodology and Substrates



a) Pettus, T. R. R. *et al. Tetrahedron*, **2002**, *58*, 5367. (very well-organized review of *o*-QM); b) Li, S. and Zhou, L. *Org. Lett.* **2023**, *25*, 8700. (recently reported synthetic method)

1.7. What to look for when you see *o*-QM's papers (My Opinion)

K.ISHIHARA GROUP green catalysis

• generation method of *o*-QM (including early methods)

methodology	acid, base, thermo, …, reduction, photo, oxidation →	
handling	easy	difficult
examples	major	minor

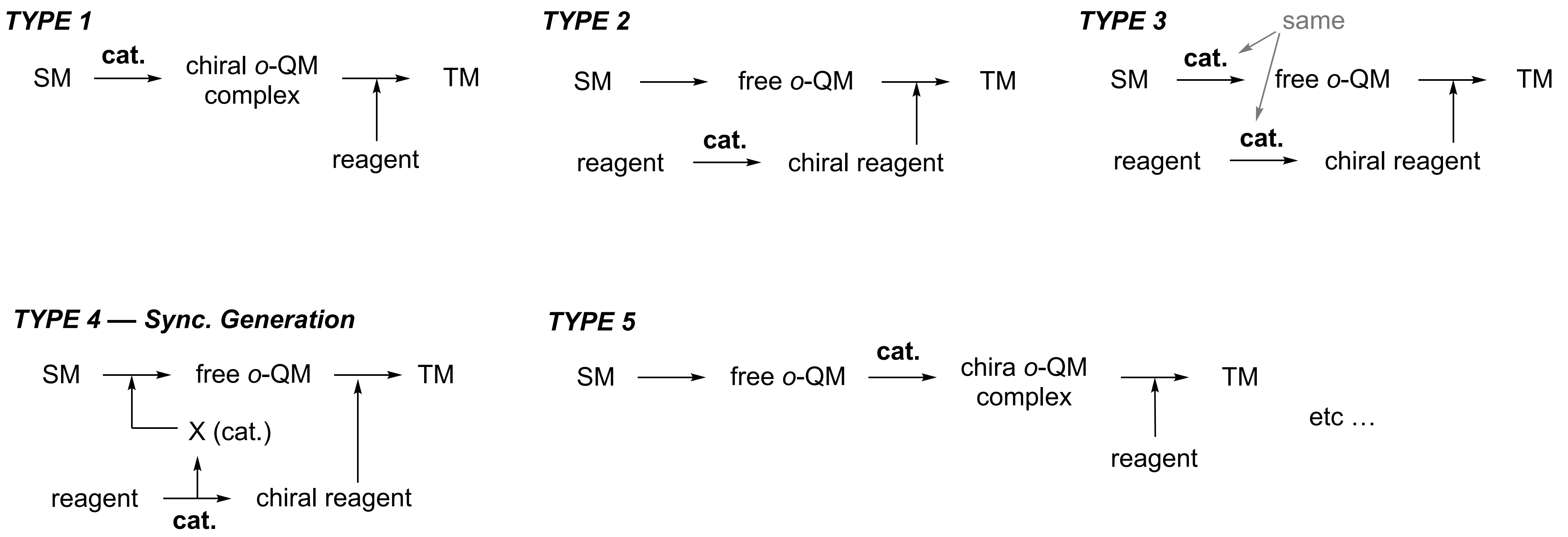
• stability of *o*-QM (stable, semi-stable, unstable o-QM)

stability	stable	semi-stable	unstable
catalytic activation	necessary	not necessary but can take	unnecessary rather no effect
isolatable	yes	usually no	no
examples	a lot	not so many but not so few	a few

• intermolecular or intramolecular

1.7. What to look for when you see *o*-QM's papers (My Opinion)

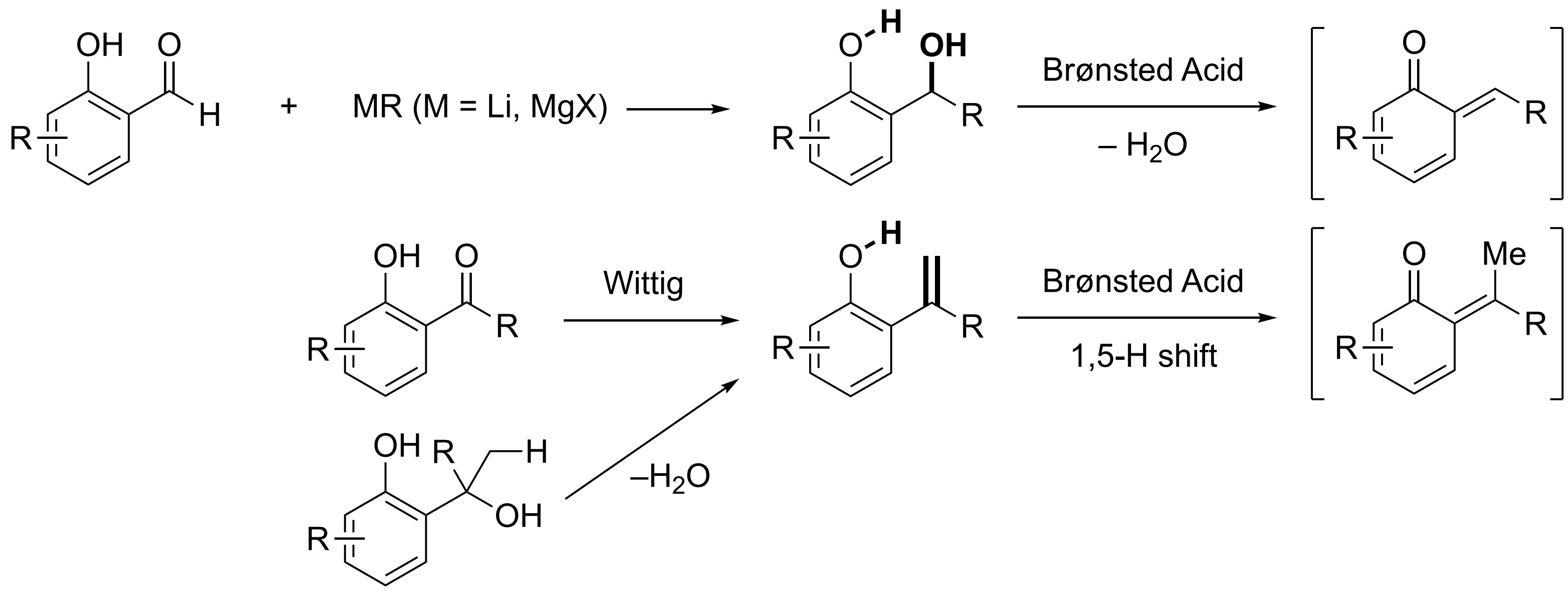
• asymmetric catalysis system



2. The Fundamental Asymmetric Reactions of Unstable *ortho*-Quinone Methides

2.1. Acid-promoted Method

Representative Substrates & Synthesis

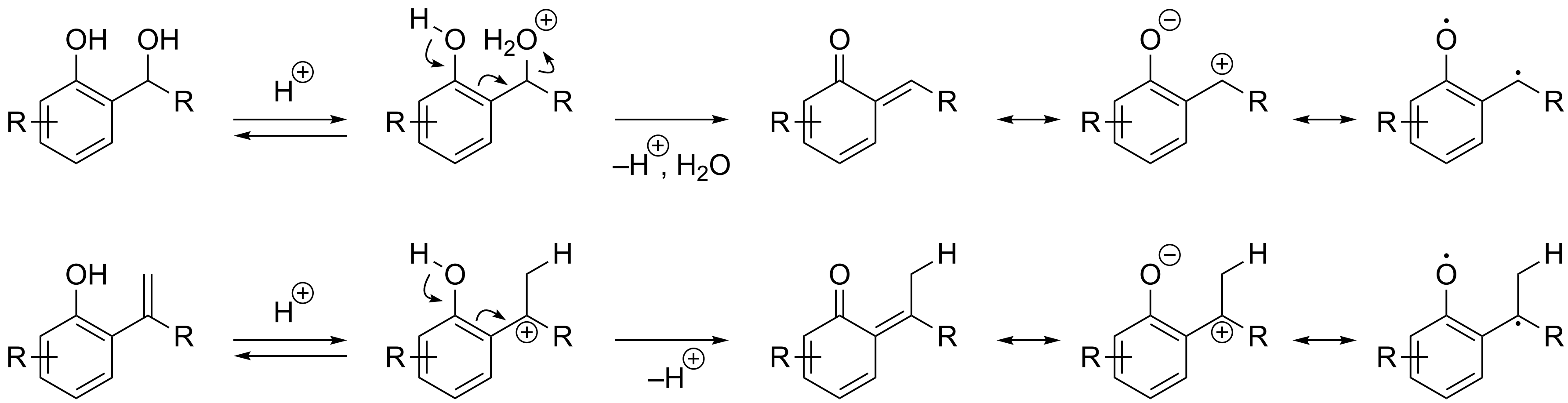


a) Pettus, T. R. R. *et al. Tetrahedron*, **2002**, *58*, 5367.; b) Bernardi, L. and Fochi, M. *Molecules*, **2015**, *20*, 11733.
c) Dorsch, C. and Schneider, C. *Synthesis* **2022**, *54*, 3125. (overview of asymmetric reaction of *o*-QM catalyzed by Brønsted acid)

2.1. Acid-promoted Method (Representative Examples)

Representative Substrates & Synthesis — Possible Generation Mechanism (My Understandings)

R = Ar, … to stabilize carbocation



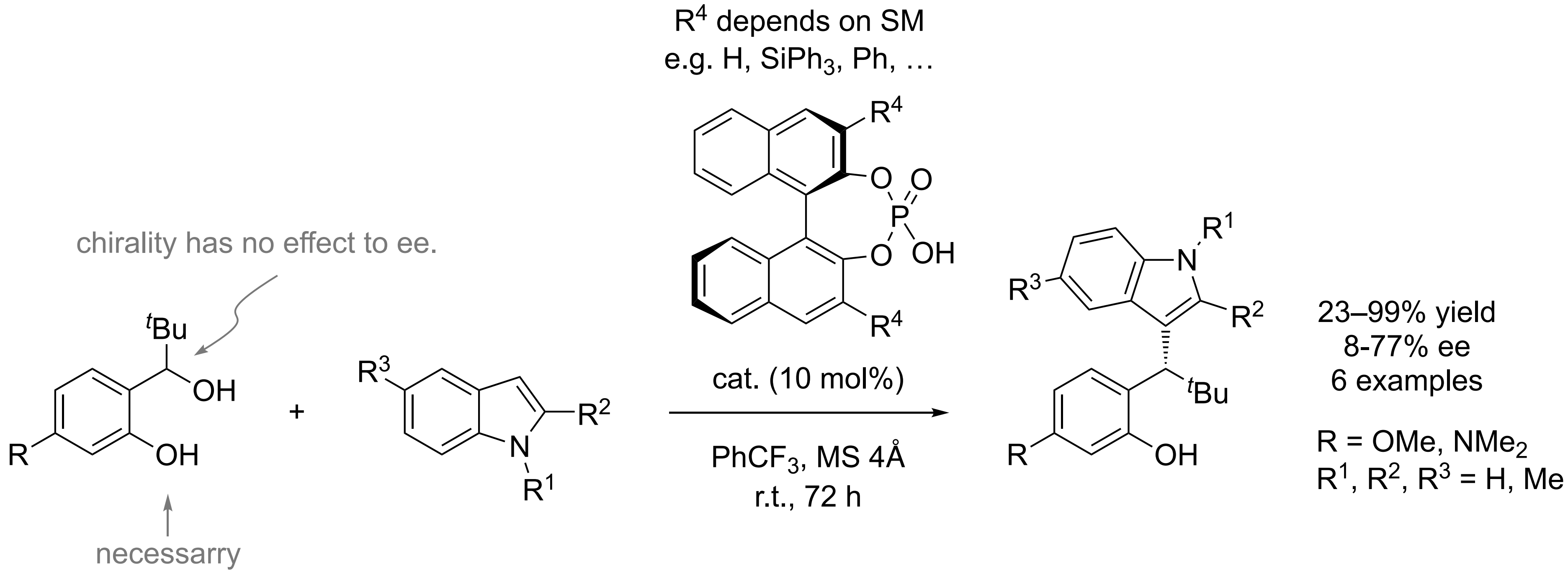
NO resonance stabilization

obtain resonance stabilization

* Stabilization effect for carbocation or forcing generation method is necessary in cat. or mild cond.

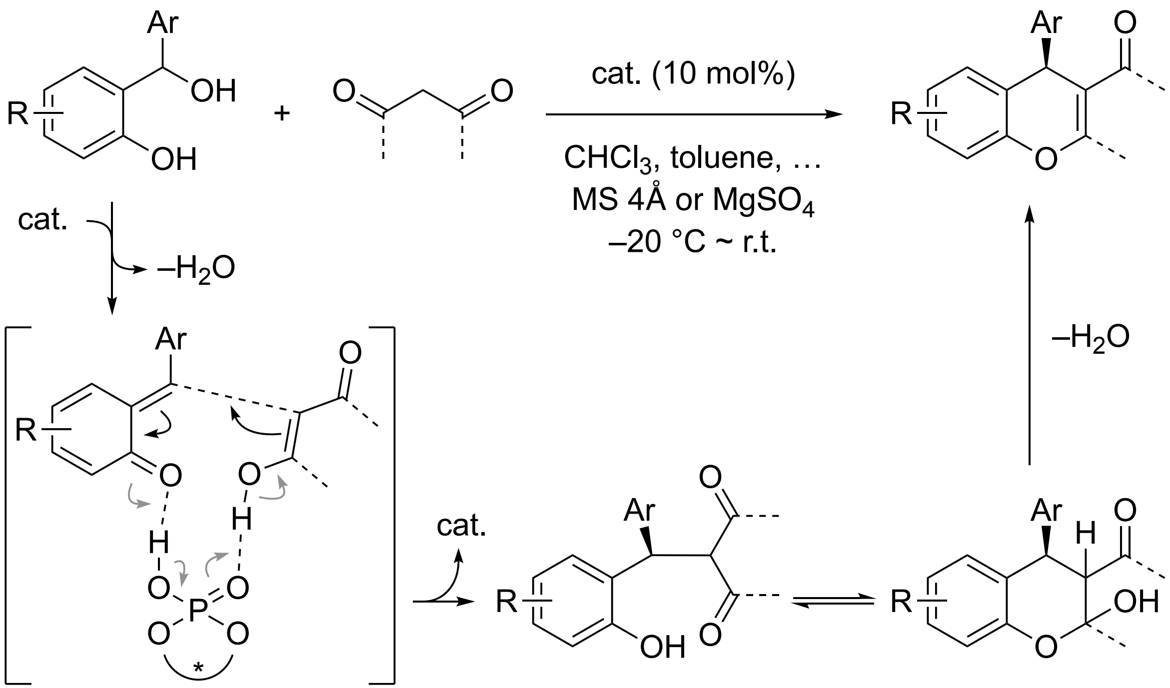
a) Pettus, T. R. R. *et al. Tetrahedron*, **2002**, *58*, 5367.; b) Bernardi, L. and Fochi, M. *Molecules*, **2015**, *20*, 11733.
c) Dorsch, C. and Schneider, C. *Synthesis* **2022**, *54*, 3125. (overview of asymmetric reaction of *o*-QM catalyzed by Brønsted acid)

Bach 2011 — First Example of Asymmetric Reaction of *o*-QM by Brønsted Acid Itself and 1,4-Addition Reaction

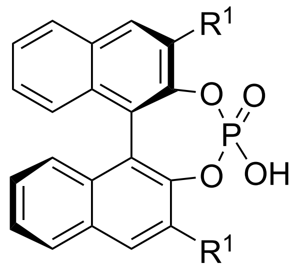


Bach, T. *et al. Synlett* **2011**, 1235.

Schneider, Rueping 2014 — Early Asymmetric 1,4-Addition Reaction



up to 97% yield
up to 98% ee
R = 4-OMe, 4-alkyl, 4-X
Ar = EDG Ar

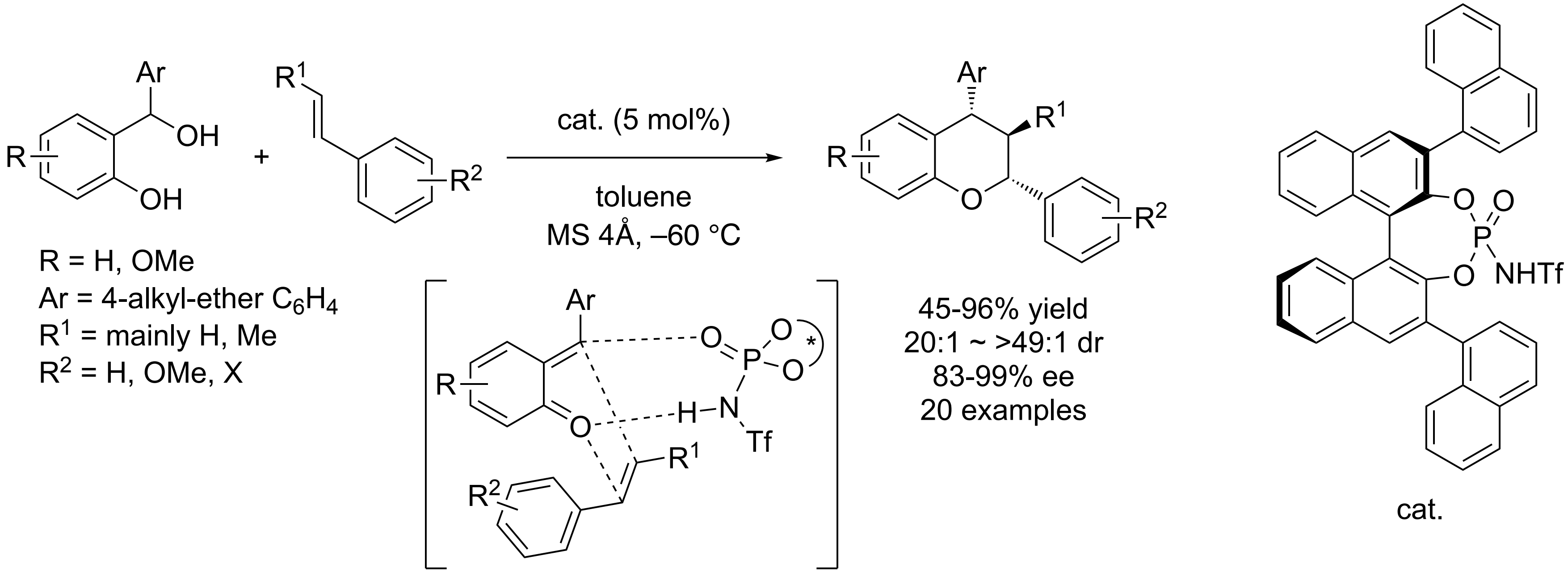


cat.

R^1 = 2,6-Me_2-4-*t*BuC_6H_2,
2-naphthyl, 2,4,6-(*i*Pr)$_3C_6H_2$ (TRIP)

a) Schneider, C. *et al. Angew. Chem. Int. Ed.* **2014**, *53*, 7923.; b) Rueping, M. *et al. Angew. Chem. Int. Ed.* **2014**, *53*, 13258.

Rueping 2015 — (4+2) Cycloaddition with Non-coordinating Styrenes

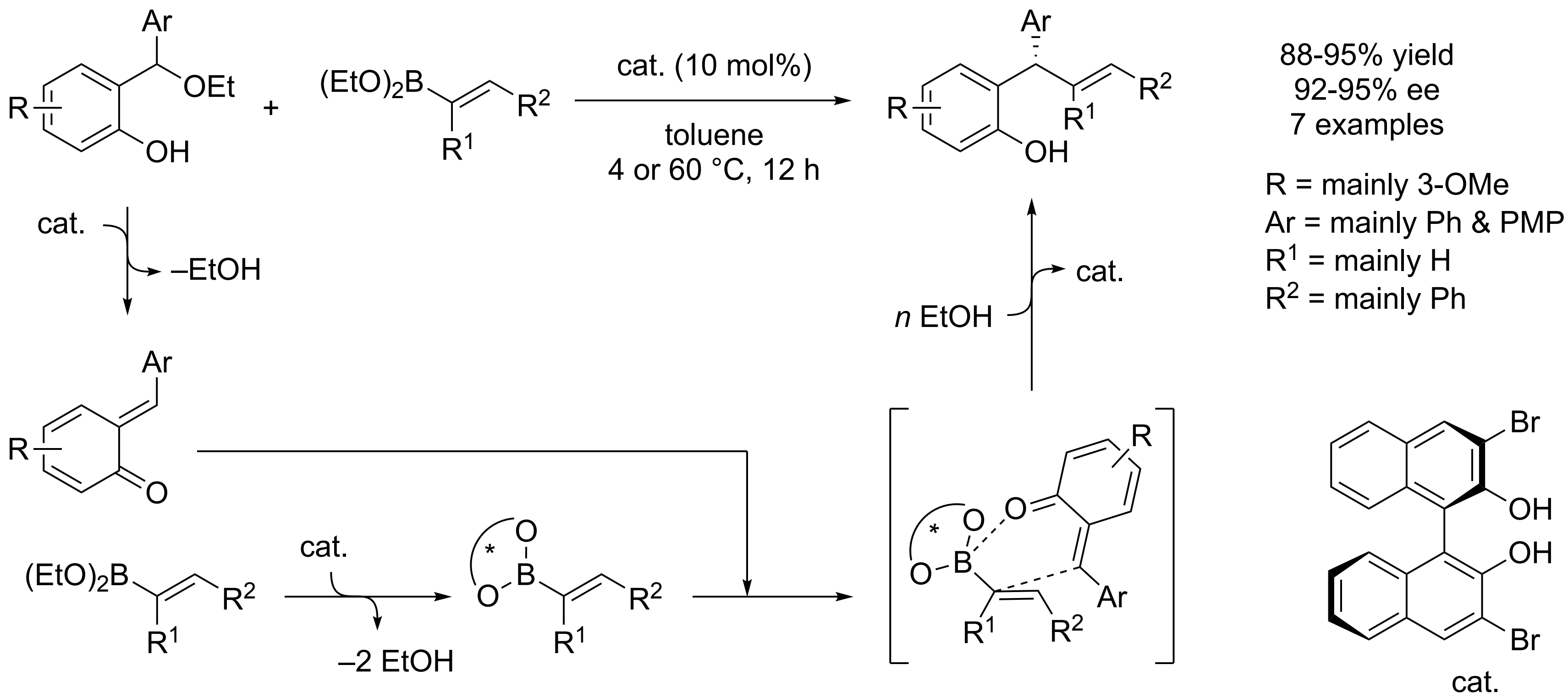


R = H, OMe
Ar = 4-alkyl-ether C_6H_4
R^1 = mainly H, Me
R^2 = H, OMe, X

45-96% yield
20:1 ~ >49:1 dr
83-99% ee
20 examples

Rueping, M. *et al. Angew. Chem. Int. Ed.* **2015**, *54*, 5762.

Schaus 2012 — Addition of Vinyl Boronates to *o*-QM

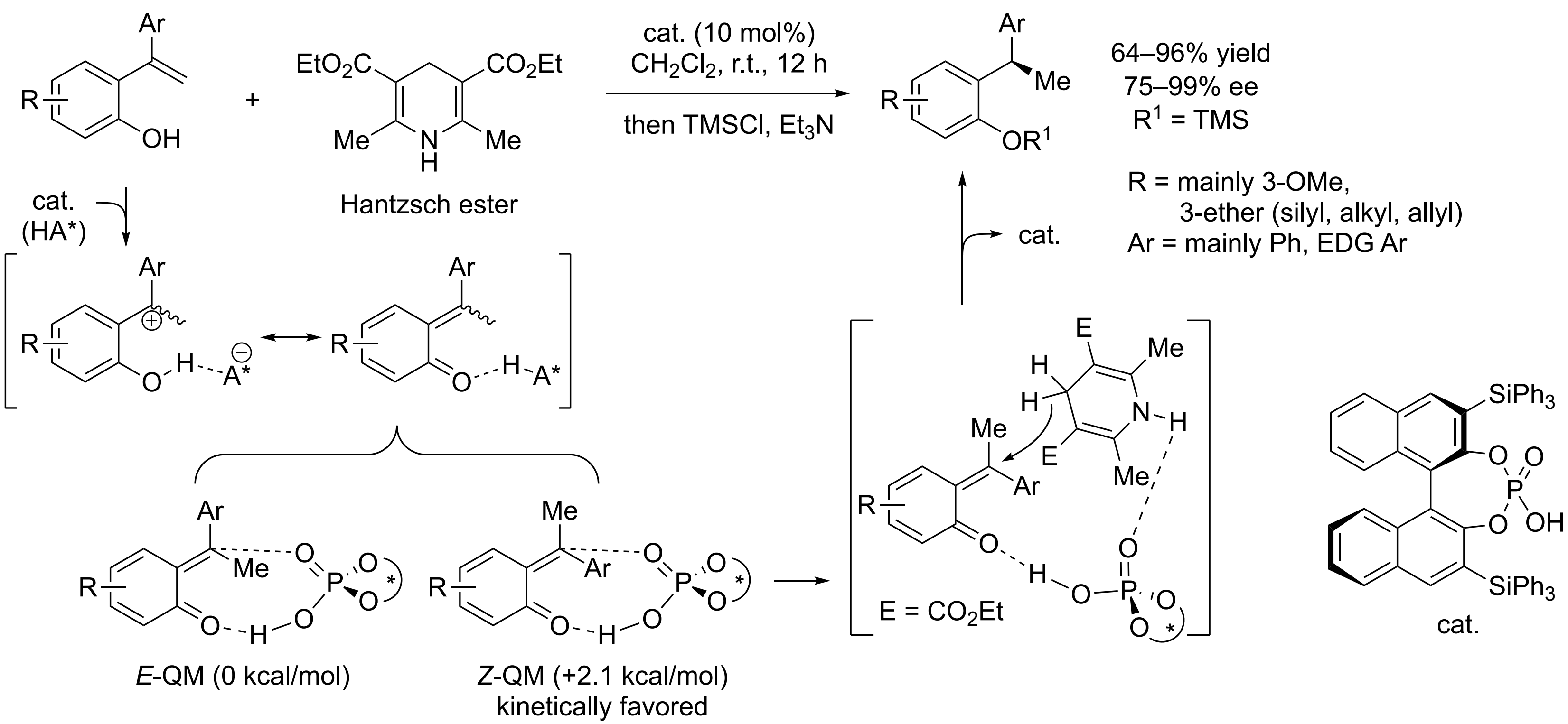


88-95% yield
92-95% ee
7 examples

R = mainly 3-OMe
Ar = mainly Ph & PMP
R^1 = mainly H
R^2 = mainly Ph

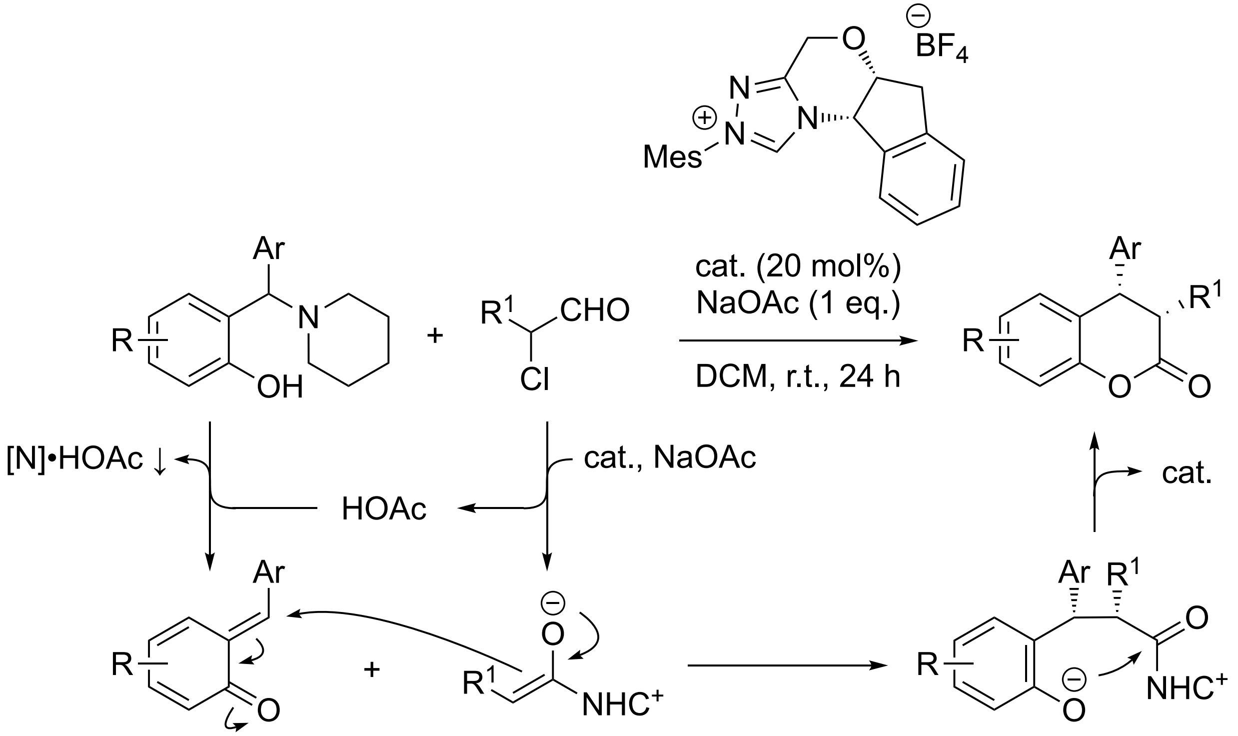
a) Schaus, S. E. *et al. J. Am. Chem. Soc.* **2012**, *134*, 19965.; b) Goodman, J. M. *et al. J. Org. Chem.* **2015**, *80*, 2056. (DFT calc.)

Sun 2015 — Diarylmethanes by Transfer Hydrogenation



Sun, J. *et al. J. Am. Chem. Soc.* **2015**, *137*, 383.

Chi 2017 — Sync. Generation of *o*-QM



36-73% yield
>98% ee
>20:1 dr
8 examples

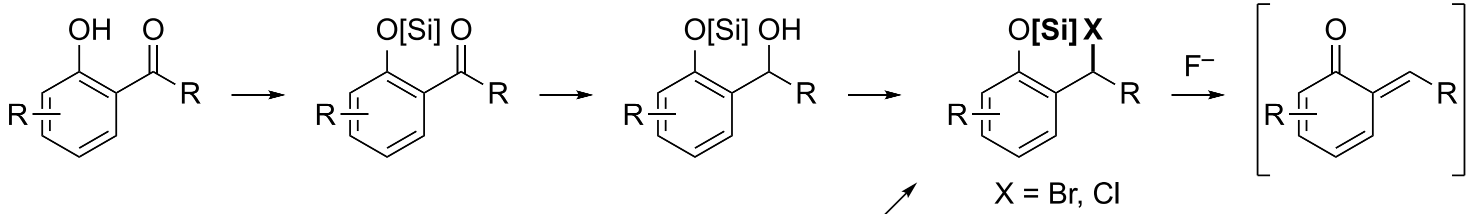
R = 3-NMe_2, OMe, napthol type
Ar = mainly 4-alkyl-ehter-C_6H_4
R^1 = mainly Bn

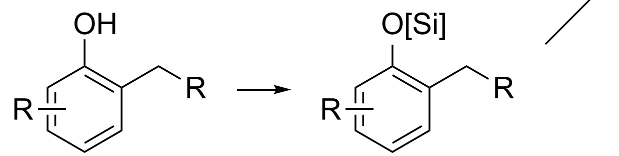
Chi, Y. R. *et al. Org. Lett.* **2017**, *19*, 5892.

2.2. Base-promoted Method

2.2. Base-promoted Method (Representative Examples)

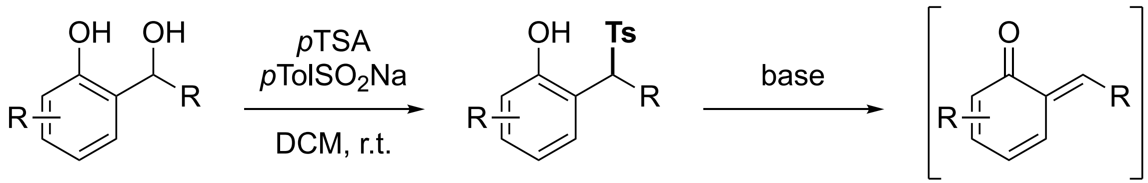
Representative Substrates & Synthesis





* this reagent can be used in acidic conditions[2]

* Rokita found this [Si]-F method during his biochemistry[3]

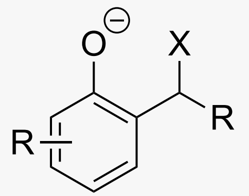


*p*TSA = *para*-Toluenesulfonic Acid

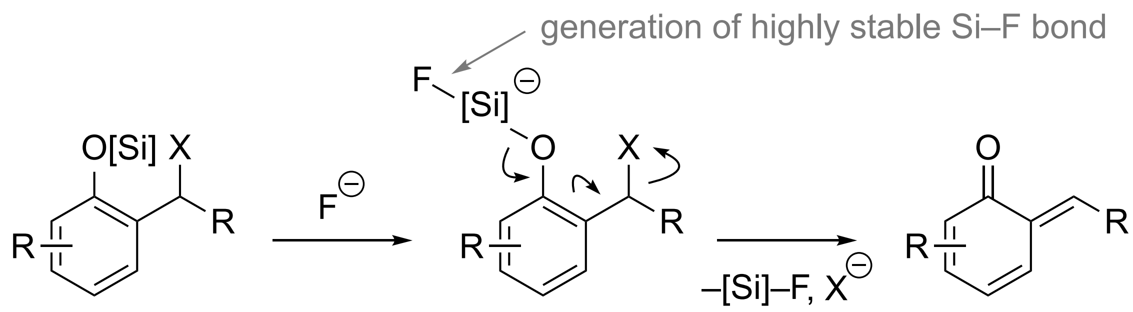
1. a) Pettus, T. R. R. et al. Tetrahedron, 2002, 58, 5367.; b) Bernardi, L. and Fochi, M. Molecules, 2015, 20, 11733.
2. Representative Example: a) Porco, J. A. *et al. Angew. Chem. Int. Ed.* **2012**, *51*, 9348.; b) Jacobsen, E. N. *et al. J. Am. Chem. Soc.* **2014**, *136*, 13614.
3. Rokita, S. E. *et al. J. Am. Chem. Soc.* **1991**, *113*, 7771.

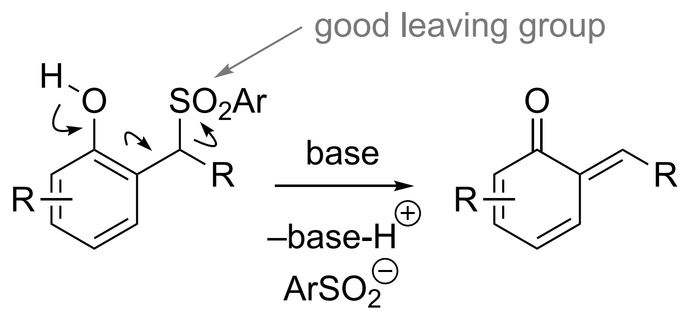
2.2. Base-promoted Method (Representative Examples)

Representative Substrates & Synthesis — Possible Generation Mechanism (My Understandings)



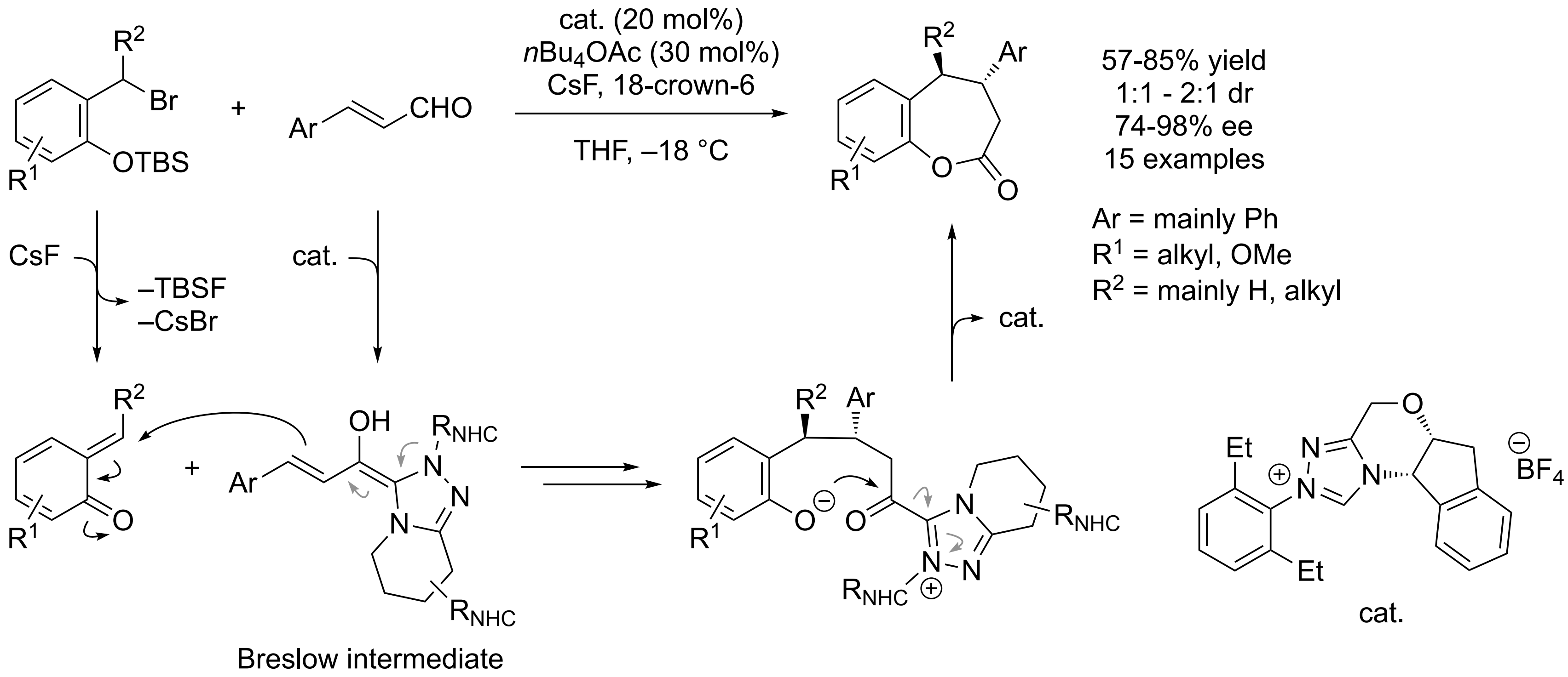
relatively stable
= other driving force is necessary





1. a) Pettus, T. R. R. et al. Tetrahedron, 2002, 58, 5367.; b) Bernardi, L. and Fochi, M. Molecules, 2015, 20, 11733.
2. Representative Example: a) Porco, J. A. *et al. Angew. Chem. Int. Ed.* **2012**, *51*, 9348.; b) Jacobsen, E. N. *et al. J. Am. Chem. Soc.* **2014**, *136*, 13614.
3. Rokita, S. E. *et al. J. Am. Chem. Soc.* **1991**, *113*, 7771.

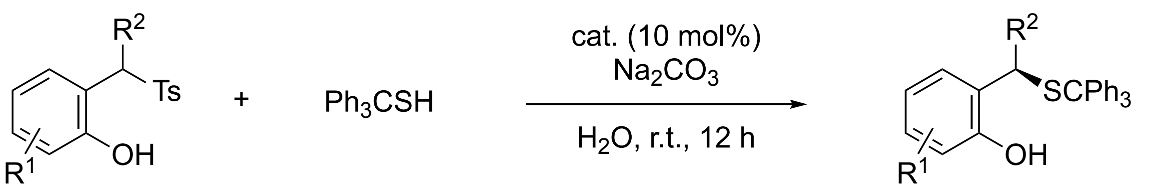
Scheidt 2013 — First Example of Asymmetric Annuration Reaction with NHC Catalysis

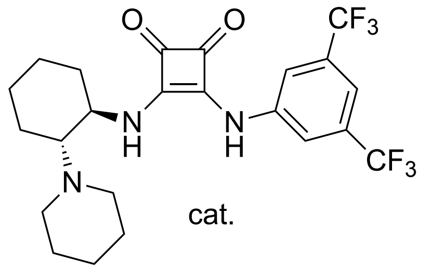


Scheidt, K. A. *et al. J. Am. Chem. Soc.* **2013**, *135*, 10634.

2.2. Base-promoted Method (Representative Examples)

Zhou, Li, Bernardi 2015 — Brønsted Base Catalysis and PTC System

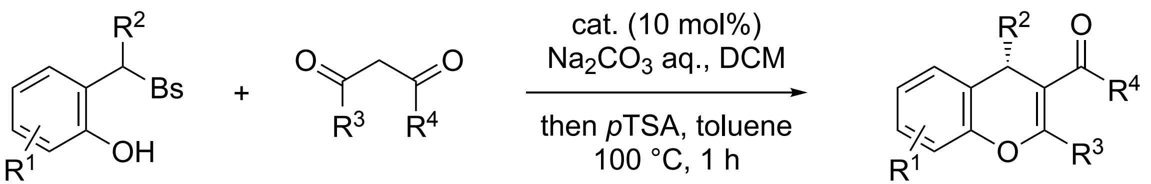


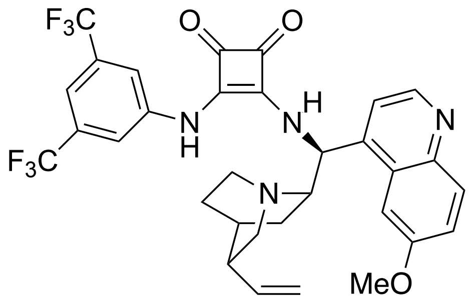


cat.

R^1 = mainly nothing, X
R^2 = Ar (EWG, EDG), alkyl

72-97% yield
82-94% ee
16 examples





cat.

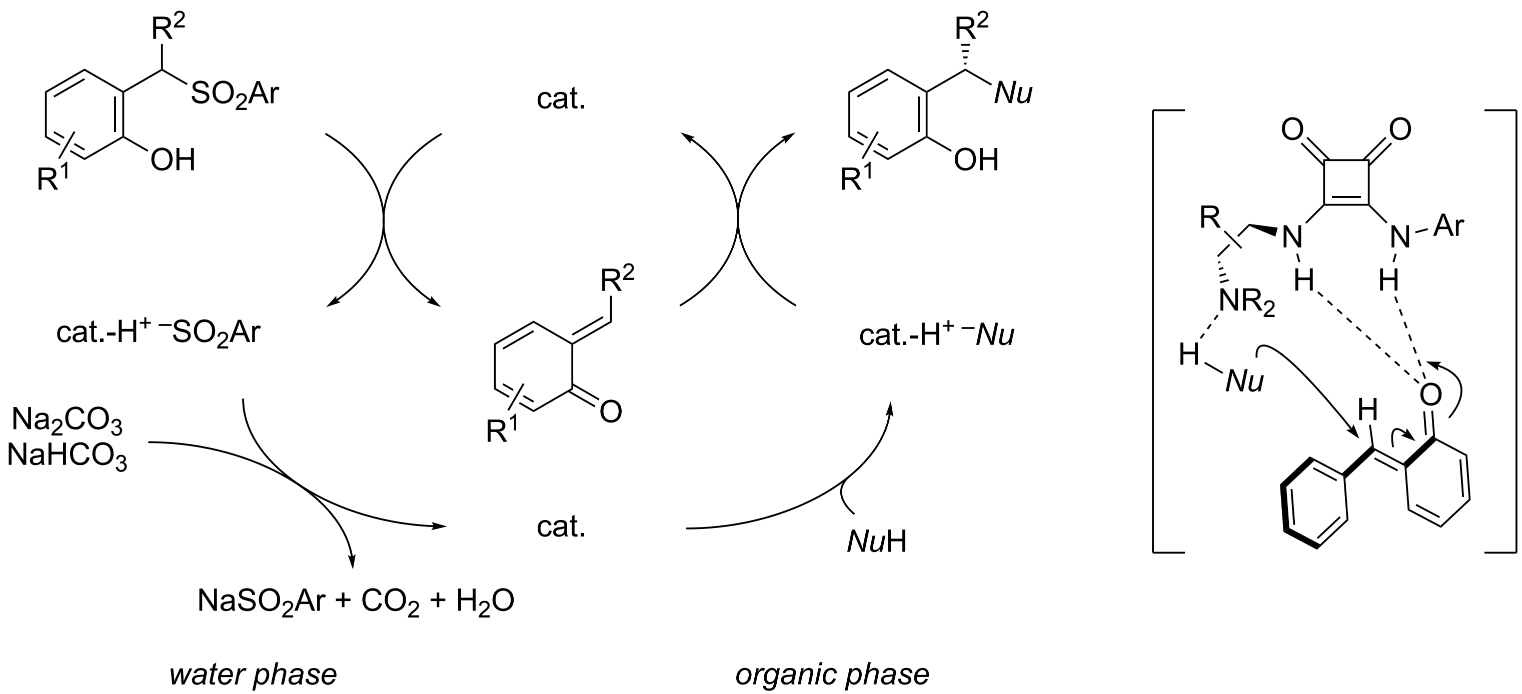
R^1 = mainly 3-OMe
R^2 = manly Ph
R^3, R^4 = alkyl (1,3-di-ketone), OR (1,3-keto-ester)
Bs = SO_2Ph

+ 2 reaction (tot. 10 example)
72-97% yield
82-94% ee

a) Zhou, Y. G. *et al. Tetrahedron Lett.* **2015**, *56*, 1135. (first example but only one low enantio-purity example)
b) Li, C. *et al. Angew. Chem. Int. Ed.* **2015**, *54*, 4522.; c) Bernardi, L. *et al. Chem. Eur. J.* **2015**, *21*, 6037.

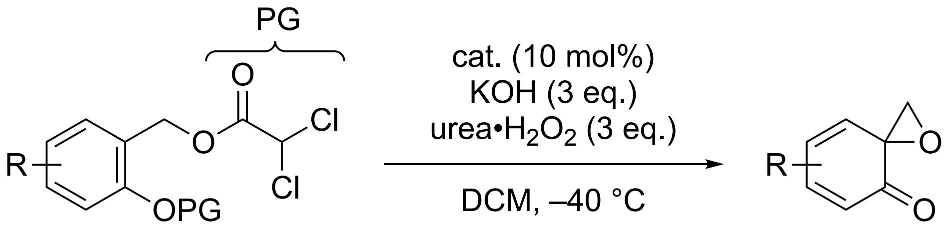
2.2. Base-promoted Method (Representative Examples)

Zhou, Li, Bernardi 2015 — Brønsted Base Catalysis and PTC System



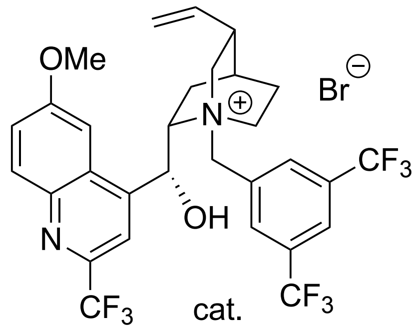
a) Zhou, Y. G. *et al. Tetrahedron Lett.* **2015**, *56*, 1135. (first example but only one low enantio-purity example)
b) Li, C. *et al. Angew. Chem. Int. Ed.* **2015**, *54*, 4522.; c) Bernardi, L. *et al. Chem. Eur. J.* **2015**, *21*, 6037.

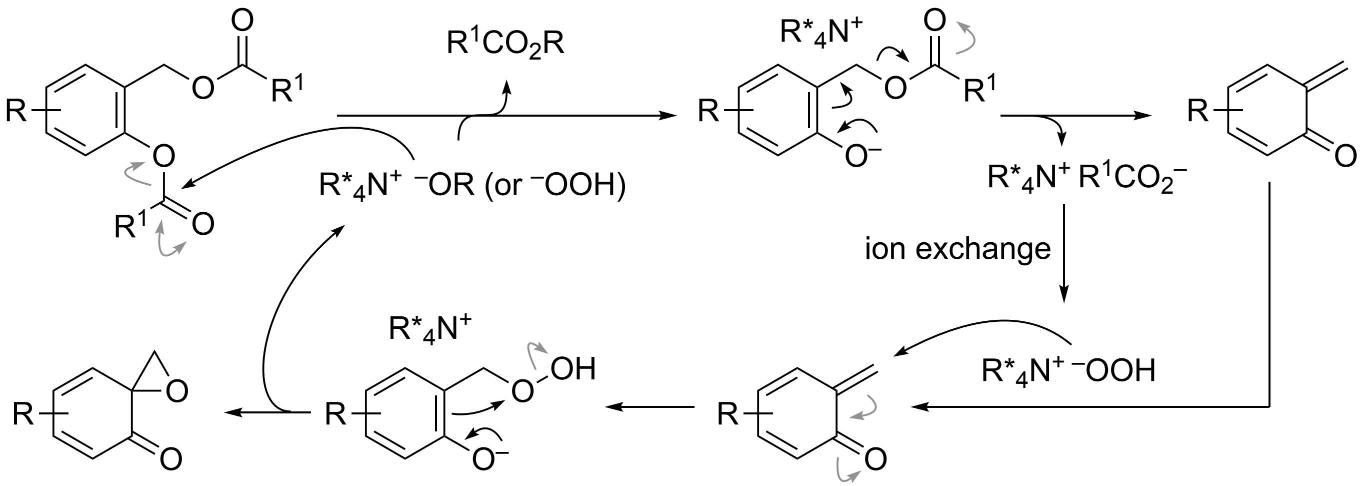
Johnson 2019 — Enantioselective Spiroepoxidation



6 examples
15-85% yield
racemi-80% ee
R = mainly alkyl

* 12 examples (w/o cat.*)



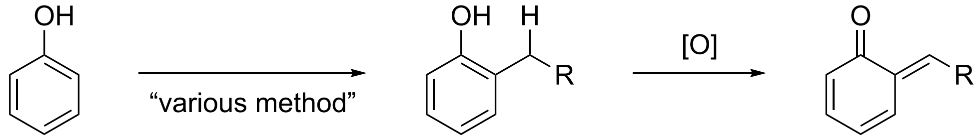


Johnson, J. S. *et al. J. Am. Chem. Soc.* **2019**, *141*, 2645.

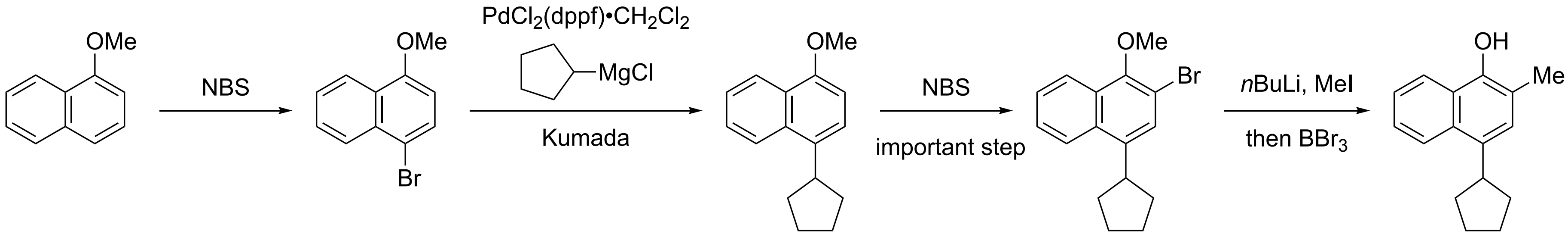
2.3. Oxidative Generation

2.3. Oxidative Generation (Representative Examples)

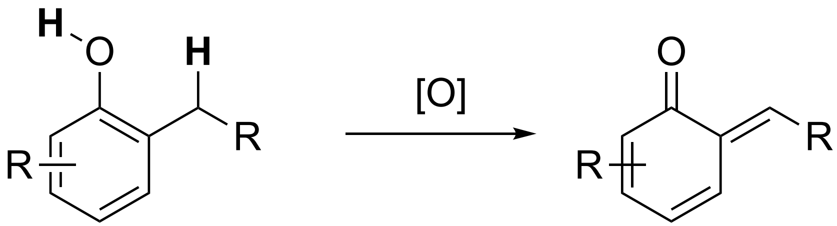
Representative Substrates — JUST a alkyl phenol



Typical Synthetic Procedure (Ishihara's work)



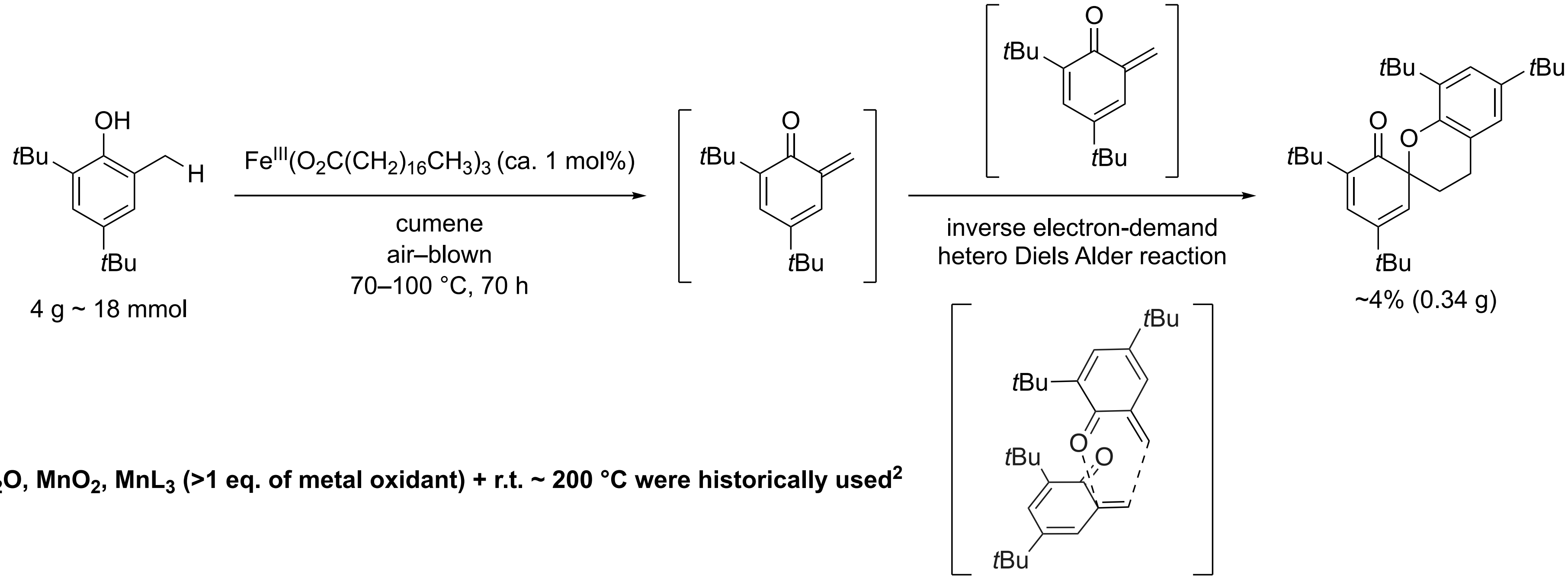
Uyanik, M.; Nishioka, K.; Kondo, R.; Ishihara, K. *Nat. Chem.* ***2020***, *12*, 353.
* NBS = N-bromosuccinimide



How to oxidize?
What is the driving force to generate unstable species?

2.3. Oxidative Generation (Representative Examples)

Water 1954[1]

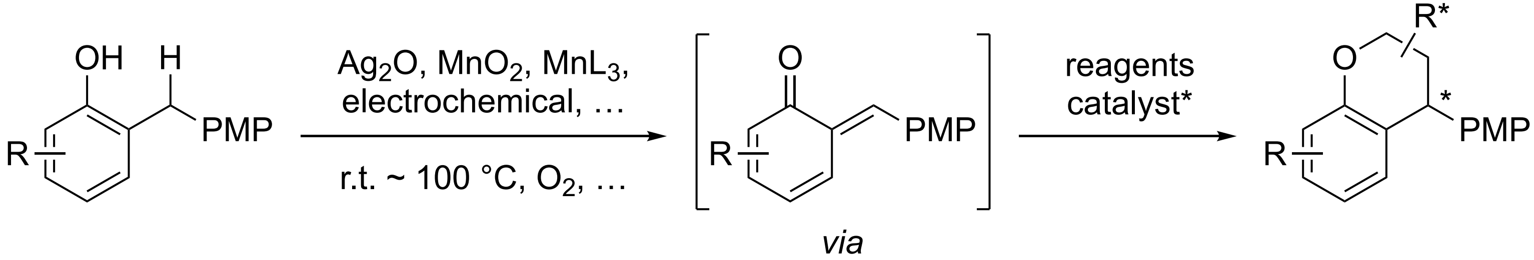


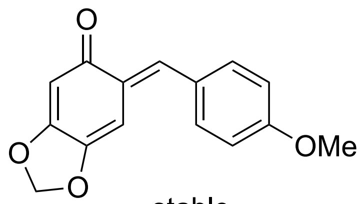
*** Ag_2O, MnO_2, MnL_3 (>1 eq. of metal oxidant) + r.t. ~ 200 °C were historically used[2]**

1. Moore, R. F. & Waters, W. A. *J. Chem. Soc.* **1954**, 243.; 2. Pettus, T. R. R. *et al. Tetrahedron*, **2002**, *58*, 5367.

2.3. Oxidative Generation (Representative Examples)

Zhou, Sun, Schneider and so on … — Asymmetric Reaction with Oxidatively Generated Stable *o*-QM

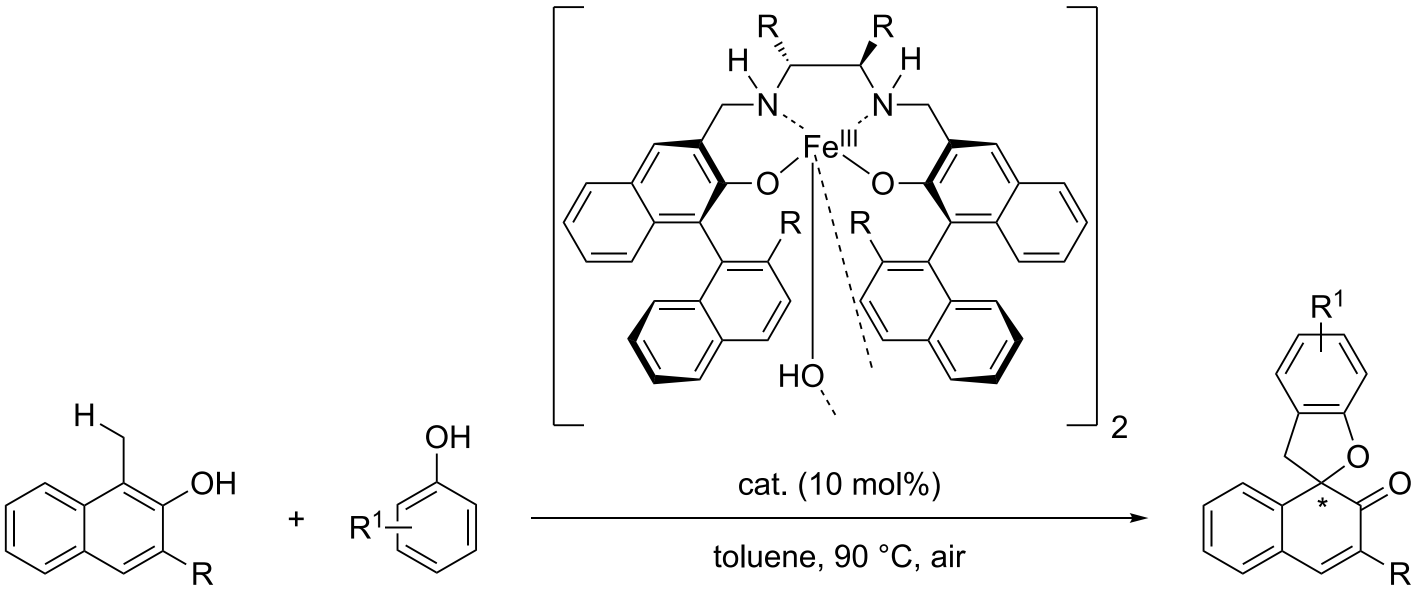




stable
isolatable
(commercially available)

a) Zhou, Y.-G. *et al. Org. Lett.* **2015**, *17*, 6134.; b) Sun, J. *et al. Tetrahedron*, **2016**, *72*, 2748.
c) Schneider, C. *et al. Org. Lett.* **2017**, *19*, 4588.; d) Kim, D.-Y. *et al. Asian J. Org. Chem.* **2020**, *11*, e202200486.; and so on …

Katsuki 2014 — Fe catalyzed Oxidatively Generation of *o*-QM and Asymmetric Spirocylization

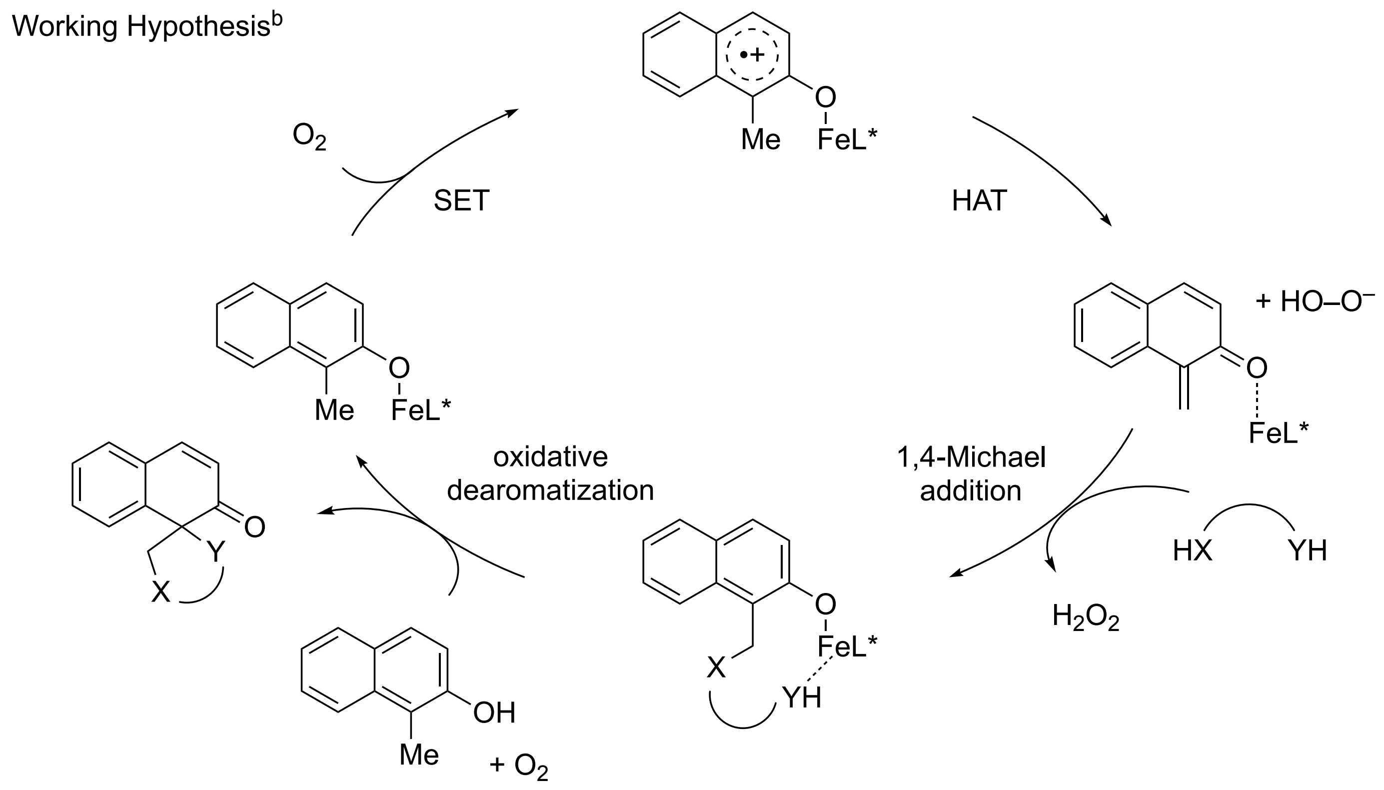


61-95% yield
78–93% ee
13 examples

R = mainly Me
R^1 = X, CO_2Me, CN, alkyl

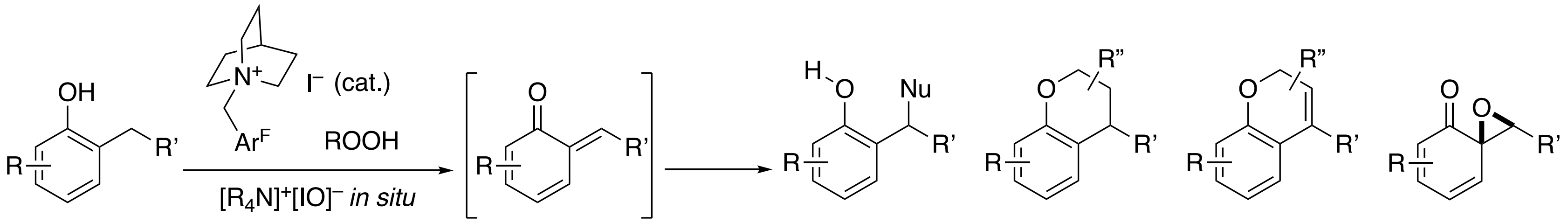
a) Katsuki, T. *et al. Chem. Commun.* **2014**, *50*, 5053.; b) Katsuki, T. *et al. Asian J. Org. Chem.* **2020**, *9*, 404.

Katsuki 2014 — Fe catalyzed Oxidatively Generation of *o*-QM and Asymmetric Spirocylization



a) Katsuki, T. *et al. Chem. Commun.* **2014**, *50*, 5053.; b) Katsuki, T. *et al. Asian J. Org. Chem.* **2020**, *9*, 404.

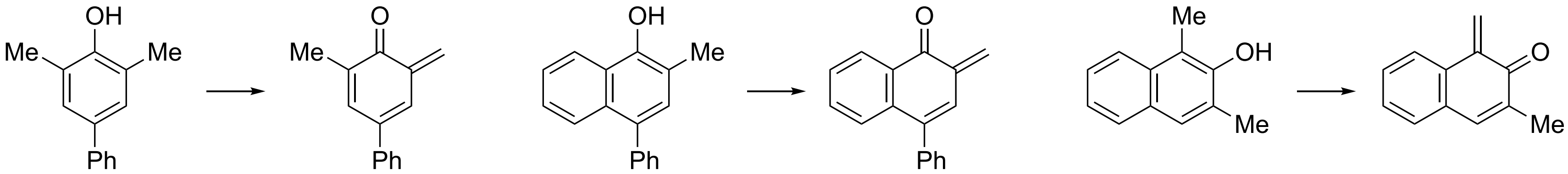
Ishihara 2020 — Hypoiodite Catalyzed Oxidative Generation of *o*-QM and Its Tandem Reaction



R = mainly EDG or EDG + X
R' = mainly alkyl
R" = mainly stem from EVE
Nu = N_3, OAc, …

tot. >30 examples
~40 ~ 99% yield
>20:1 ~ single diastereomer dr.

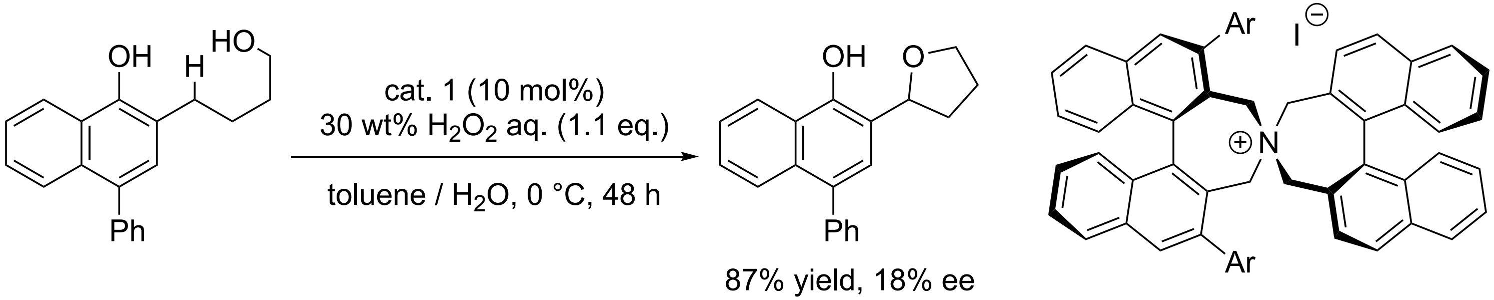
e.g.

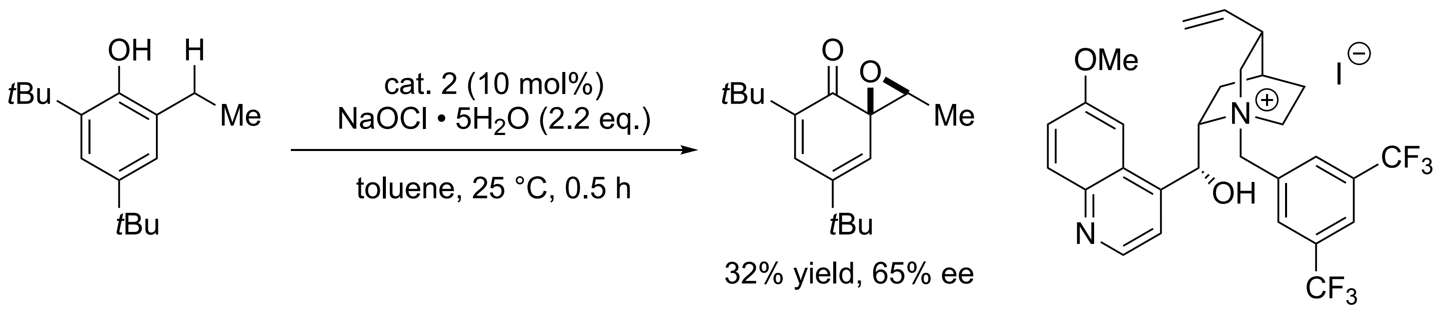


Uyanik, M.; Nishioka, K.; Kondo, R.; Ishihara, K. *Nat. Chem.* **2020**, *12*, 353.

2.3. Oxidative Generation (Representative Examples)

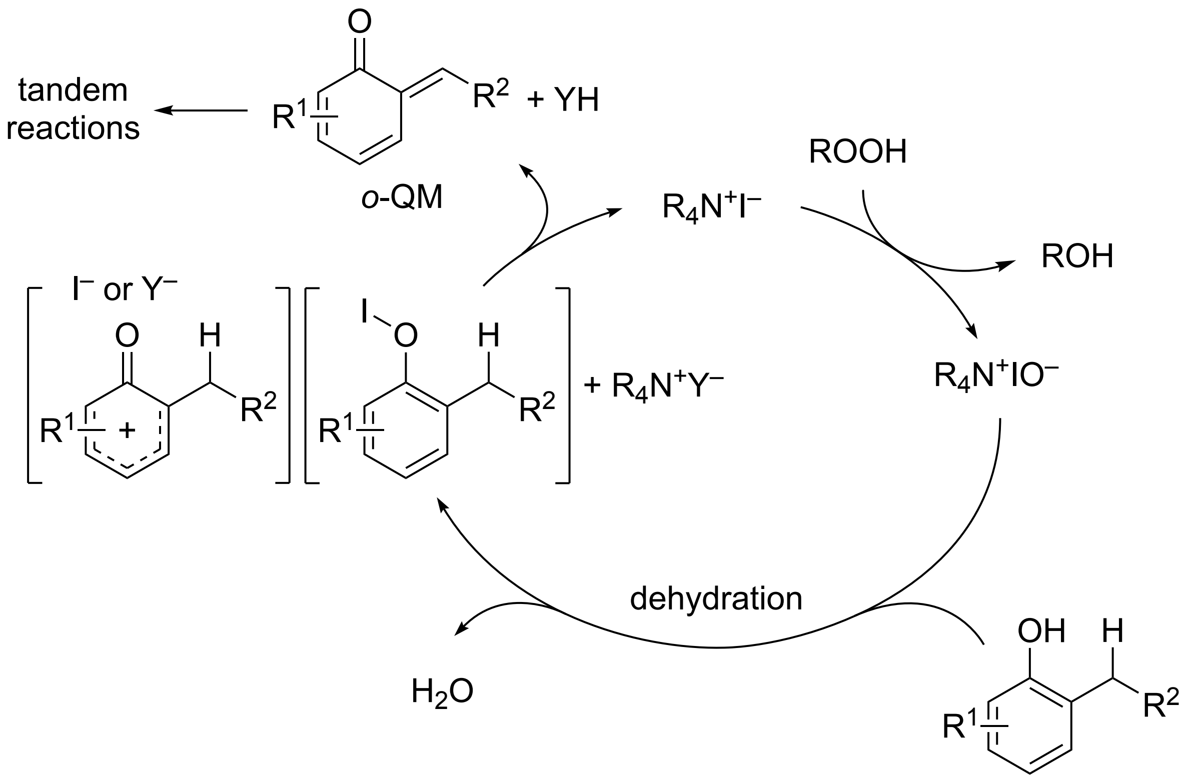
Ishihara 2020 — Hypoiodite Catalyzed Oxidative Generation of *o*-QM and Its Tandem Reaction





Uyanik, M.; Nishioka, K.; Kondo, R.; Ishihara, K. *Nat. Chem.* **2020**, *12*, 353.

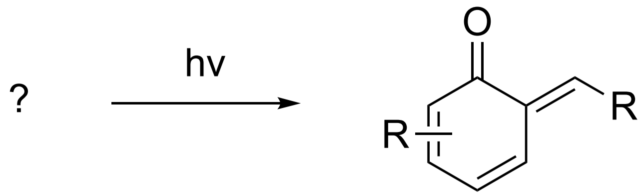
Ishihara 2020 — Hypoiodite Catalyzed Oxidative Generation of *o*-QM and Its Tandem Reaction



Uyanik, M.; Nishioka, K.; Kondo, R.; Ishihara, K. *Nat. Chem.* **2020**, *12*, 353.

2.4. Photochemical Generation

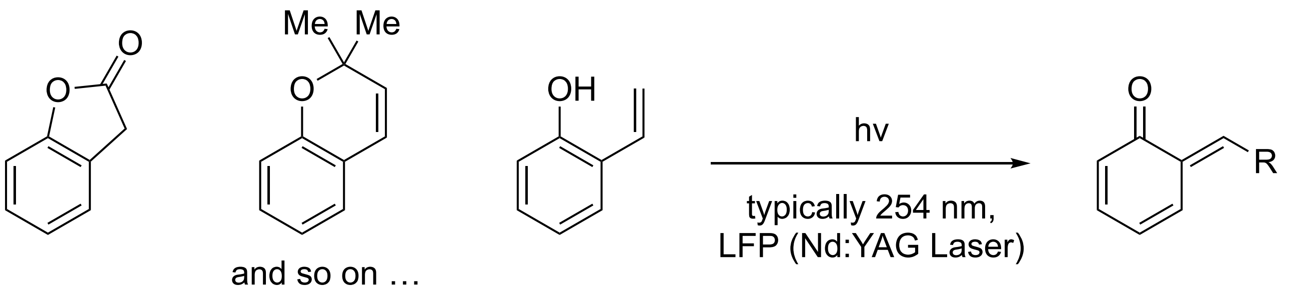
2.4. Photochemical Generation (Representative Examples)

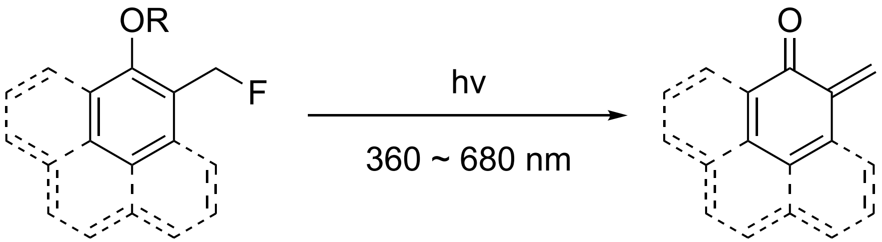


How?

2.4. Photochemical Generation (Representative Examples)

Representative Substrates & Synthesis — case by case but most of them are for racemic reaction





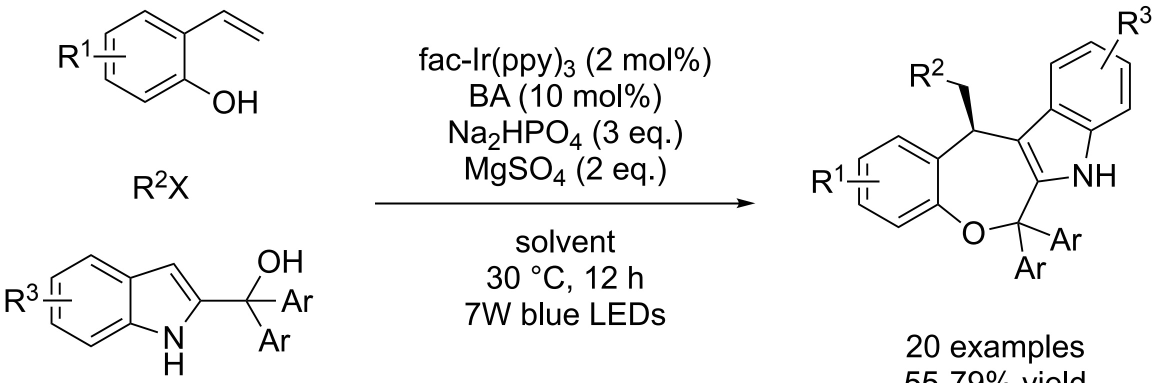
R = H, PG, …

e.g.) for protein labeling[a,c]

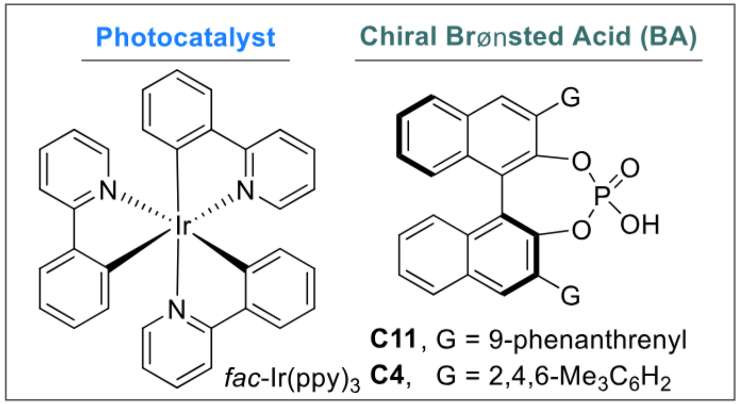
a) Pettus, T. R. R. *et al. Tetrahedron*, **2002**, *58*, 5367. (early generation methods); Rokita, S. E. *Quinone Methide*; John Wiley & Sons, Inc., **2009**.
b) personally interesting reactions: Freccero, M. *et al. J. Org. Chem.* **2006**, *71*, 3889.; Ooi, T. *et al. Chem. Sci.* **2021**, *12*, 2778.
c) Noguchi, K. *et al. Bioconjugate Chem.* **2020**, *31*, 1740. (just a selected example of CLAMP for protein labeling; numerous other probes and methods have been developed.)

Liang 2024 — First Example[?] for Photochemical Generation of Unstable *o*-QM and its Reaction

* many examples in aza *o*-QM



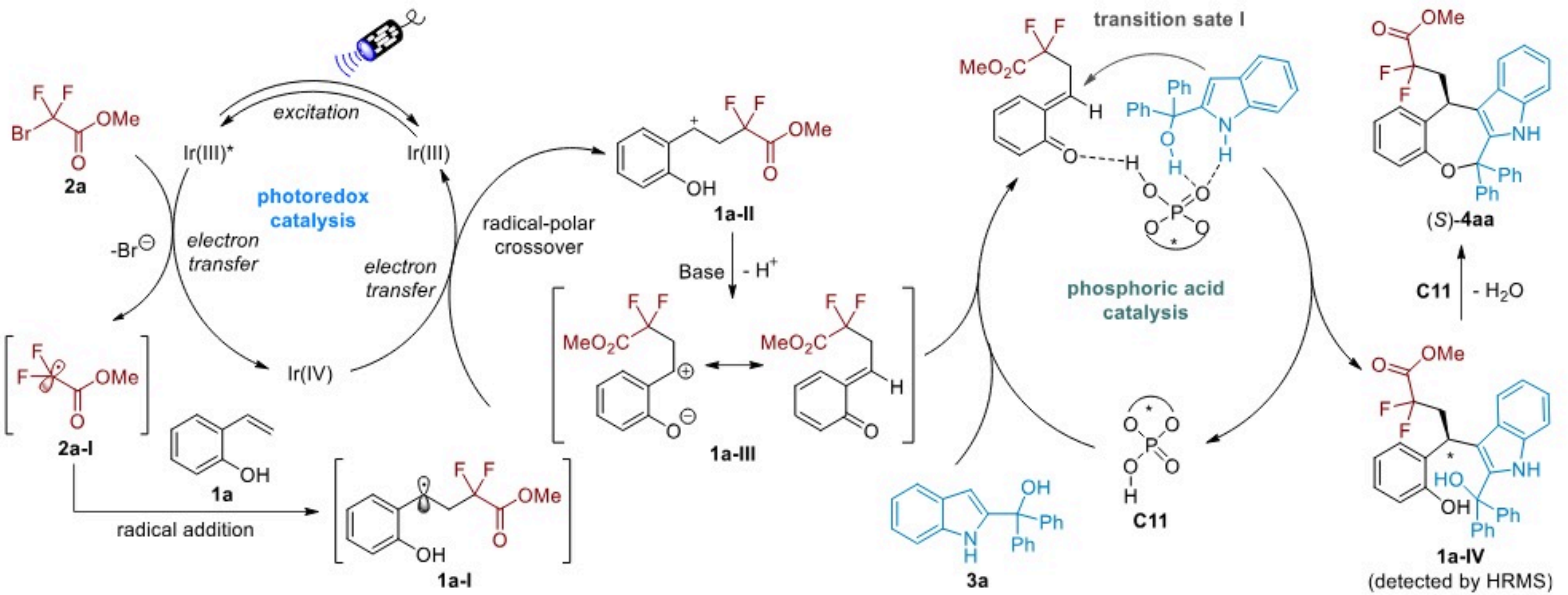
20 examples
55-79% yield
76-92% ee



R^1 = mainly nothing, X
R^2 = mainly F_2BrCO_2-Alkyl, 2-halo-1,3-diester
R^3 = mainly nothing
Ar = mainly Ph, 4-X

Liang, D. *et al. Green Synthesis and Catalysis* **2024**, https://doi.org/10.1016/j.gresc.2024.01.002

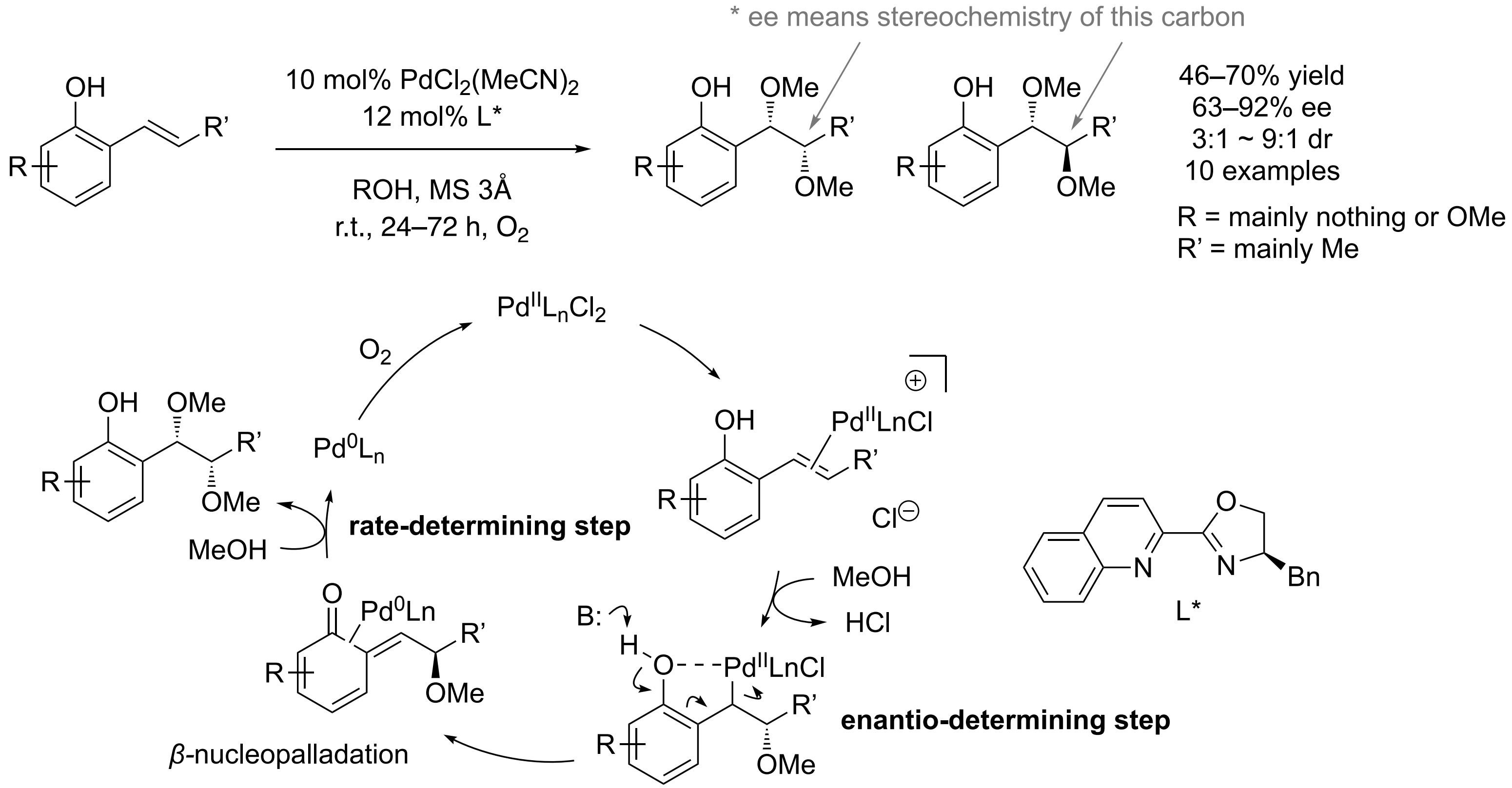
Liang 2024 — First Example? for Photochemical Generation of Unstable *o*-QM and its Reaction



Liang, D. *et al. Green Synthesis and Catalysis* **2024**, https://doi.org/10.1016/j.gresc.2024.01.002

2.5. Metal Method

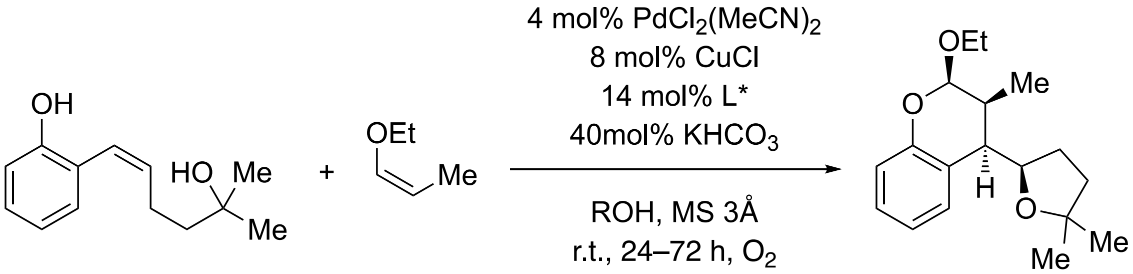
Sigman 2007 — Pd Catalyzed Enantioselective Aerobic Dialkoxylation *via* metal *o*-QM complex



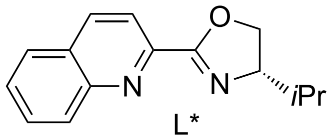
a) Sigman, M. S. *et al. J. Am. Chem. Soc.* **2007**, *129*, 3076.; b) Sigman, M. S. *et al. J. Org. Chem.* **2011**, *76*, 9210. (review: overview of Sigman's research)

Sigman 2010 — Pd Catalyzed Enantioselective Aerobic Dialkoxylation *via* metal *o*-QM complex

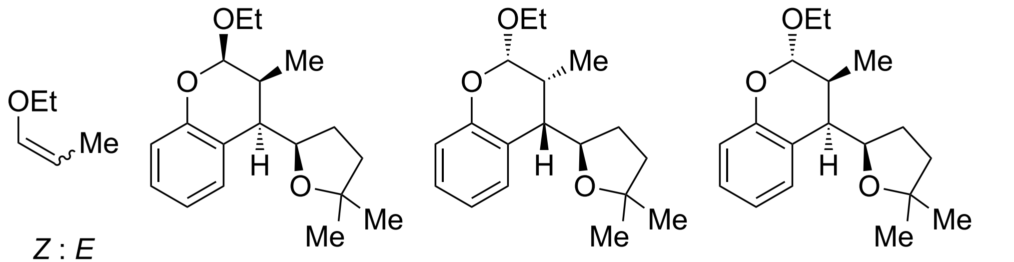
Picked Up Example of (4+2) Cycloaddition



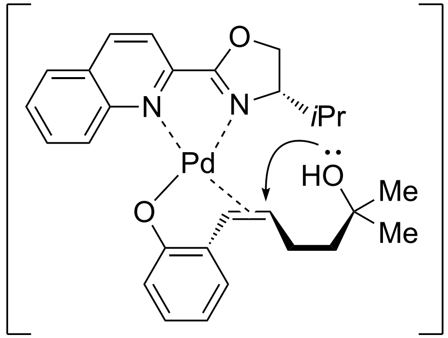
72% yield
86% ee



L*



Z : *E*			
10 : 1	7.1	1	0.3
4.8 : 1	8.5	1	0.5
1.6 : 1	8.7	1	1.4



a) Sigman, M. S. *et al. J. Am. Chem. Soc.* **2010**, *132*, 17471.; b) Sigman, M. S. *et al. J. Org. Chem.* **2011**, *76*, 9210. (review: overview of Sigman's research)

2.6. Summary

2.6. Summary

Methodology	Acid-promoted	Base-promoted	Oxidative, Photochemical	other
Examples	many	some	a few	a few
Catalytic TYPE	1 ~ 4	2, 4	2, 4	–
Stability of *o*-QM	semi-stable	semi-stable ~ unstable	unstable	unstable
Reaction Type (Starting Point)	1,4-addition, cycloaddition electrocylization	1,4-addition	1,4-addition	–

Catalytic Asymmetric Reaction of Unstable *o*-QM is Difficult