Literature Report IV

Catalytic Asymmetric Deoxygenative Cyclopropanation Reactions by a Chiral Salen-Mo Catalyst

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Checker: Han Wang
Date: 2023-03-06

Cao, L.-Y., Zhuo, C.-X. *J. Am. Chem. Soc*. **2023**, *145,* 2765.

CV of Prof. Chun-Xiang Zhuo (卓春祥)

Research Interest:

- Asymmetric Catalysis
- Organic Synthesis Methodology
- Synthesis of Active Natural Products and Pharmaceutical Molecules

Background:

- **2005-2009** B.S., Hunan University
- **2009-2014** Ph.D., Shanghai Institute of Organic Chemistry, CAS
- **2014-2019** Postdoc., Max-Planck-Institut für Kohlenforschung
- **2019-now** Professor, Xiamen University

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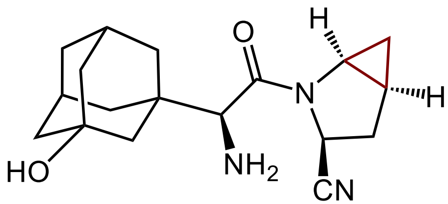
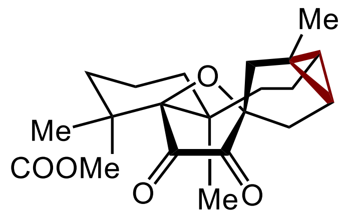
Introduction

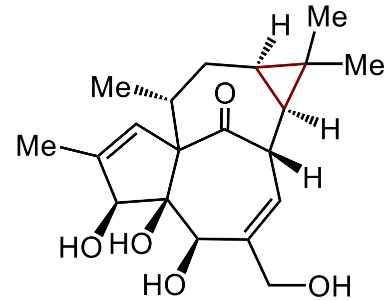
Selected Examples of Pharmaceutical Agents Containing the Cyclopropyl Core



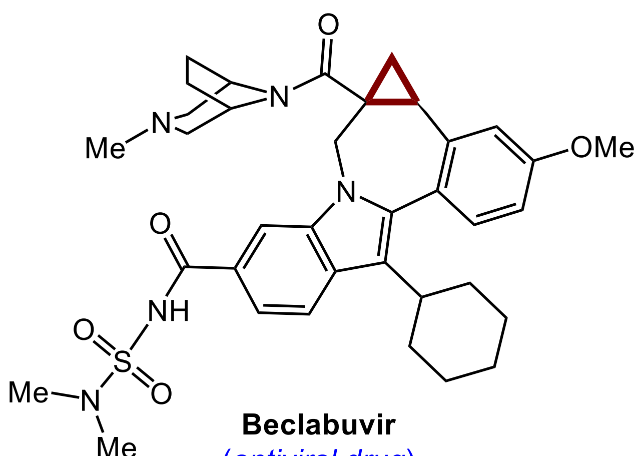
Saxagliptin
(*blood glucose drug*)



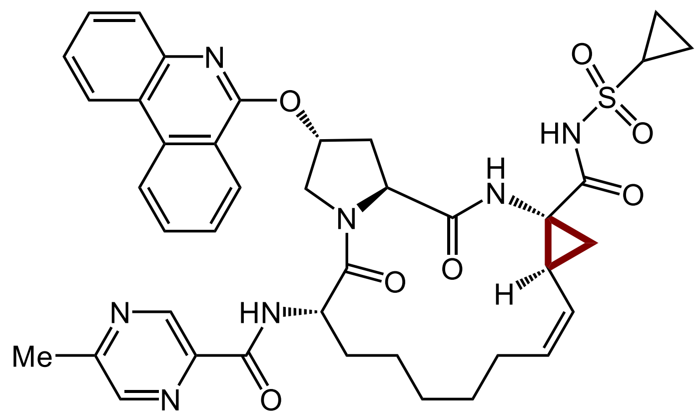
Mitrephorone A
(*antibacterial*)



Ingenol
(*anti-cancer drug*)



Beclabuvir
(*antiviral drug*)

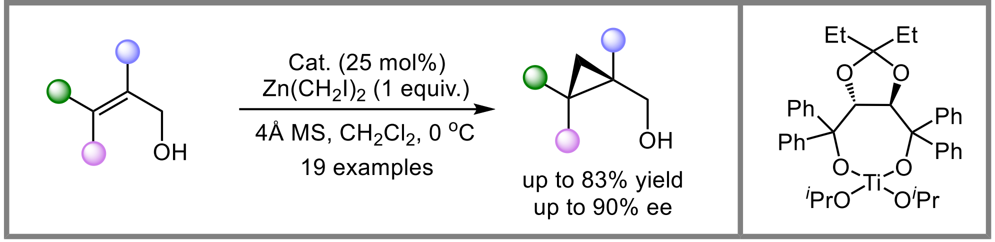


Paritaprevir
(*antiviral drug*)

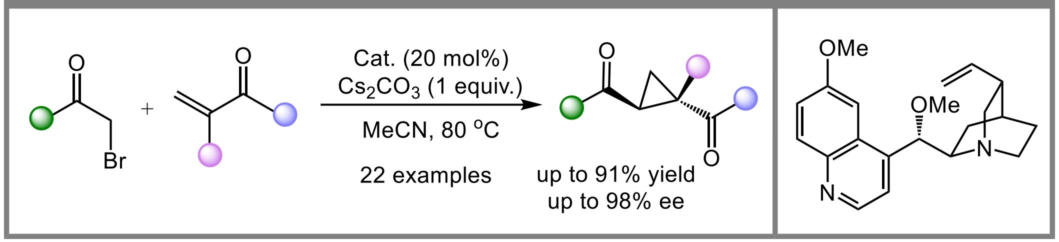
Ebner, C., Carreira, E. M. *Chem. Rev*. **2017**, *117*, 11651.

Introduction

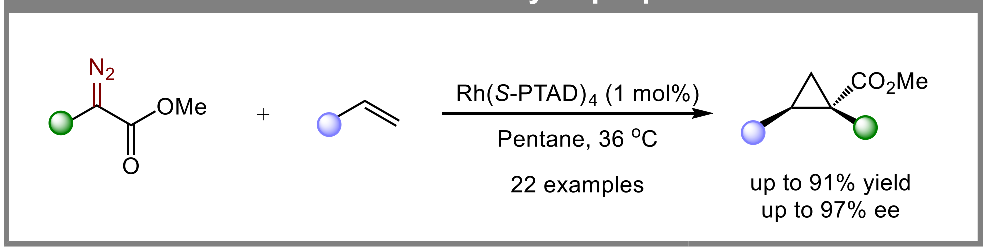
Simmons-Smith Cyclopropanation Reaction



Corey-Chaykovsky Cyclopropanation Reaction



Metallocarbenoid-Mediated Cyclopropanation Reaction



Charette, A. B., Brochu, C. *J. Am. Chem. Soc.* **2001**, *123,* 12168.
Papageorgiou, C. D., Gaunt, M. J. *Angew. Chem. Int. Ed.* **2004**, *43,* 4641.
Wang, H. B., Davies, H. M. L. *Chem. Sci*. **2013**, *4*, 2844.

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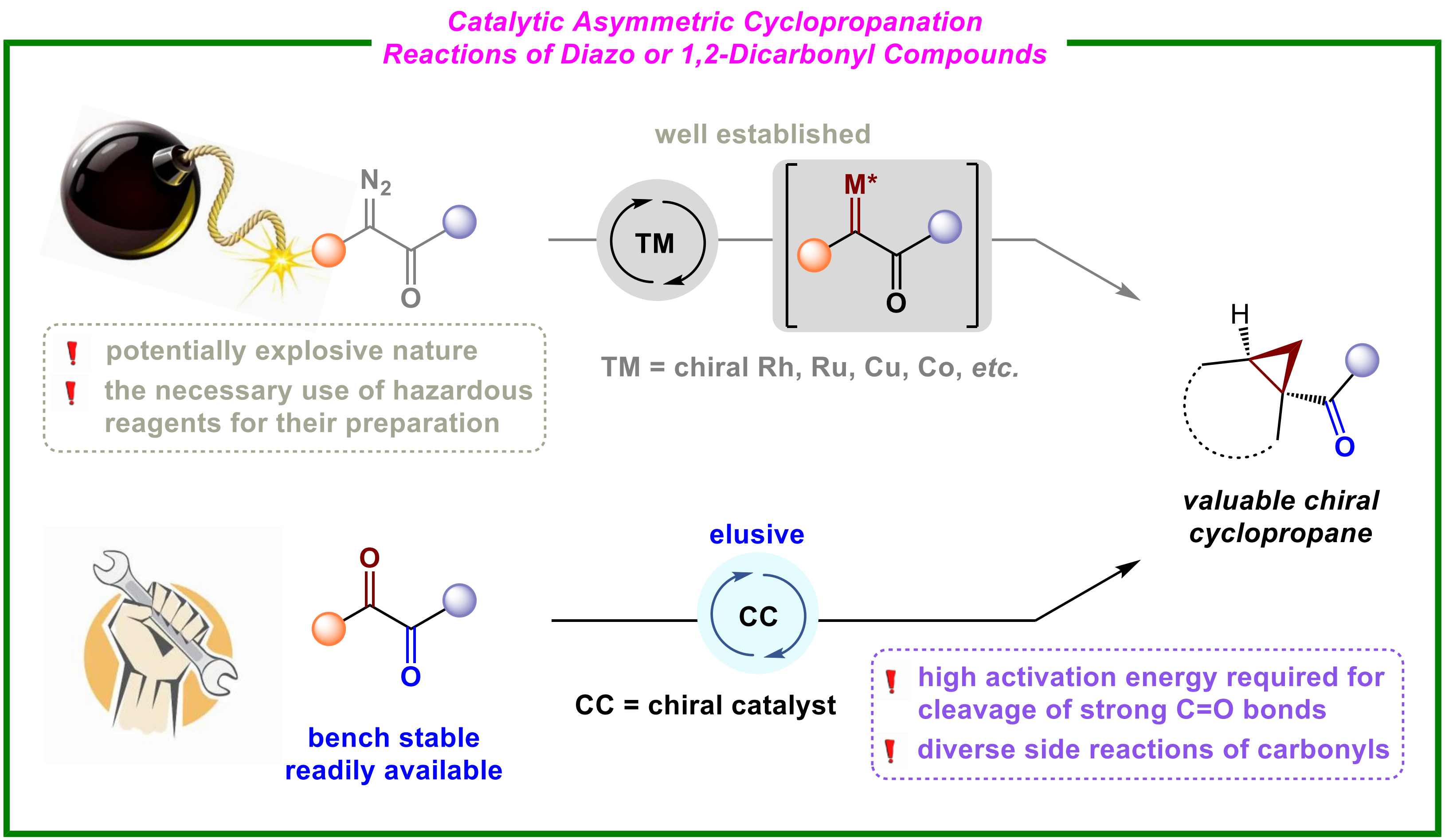

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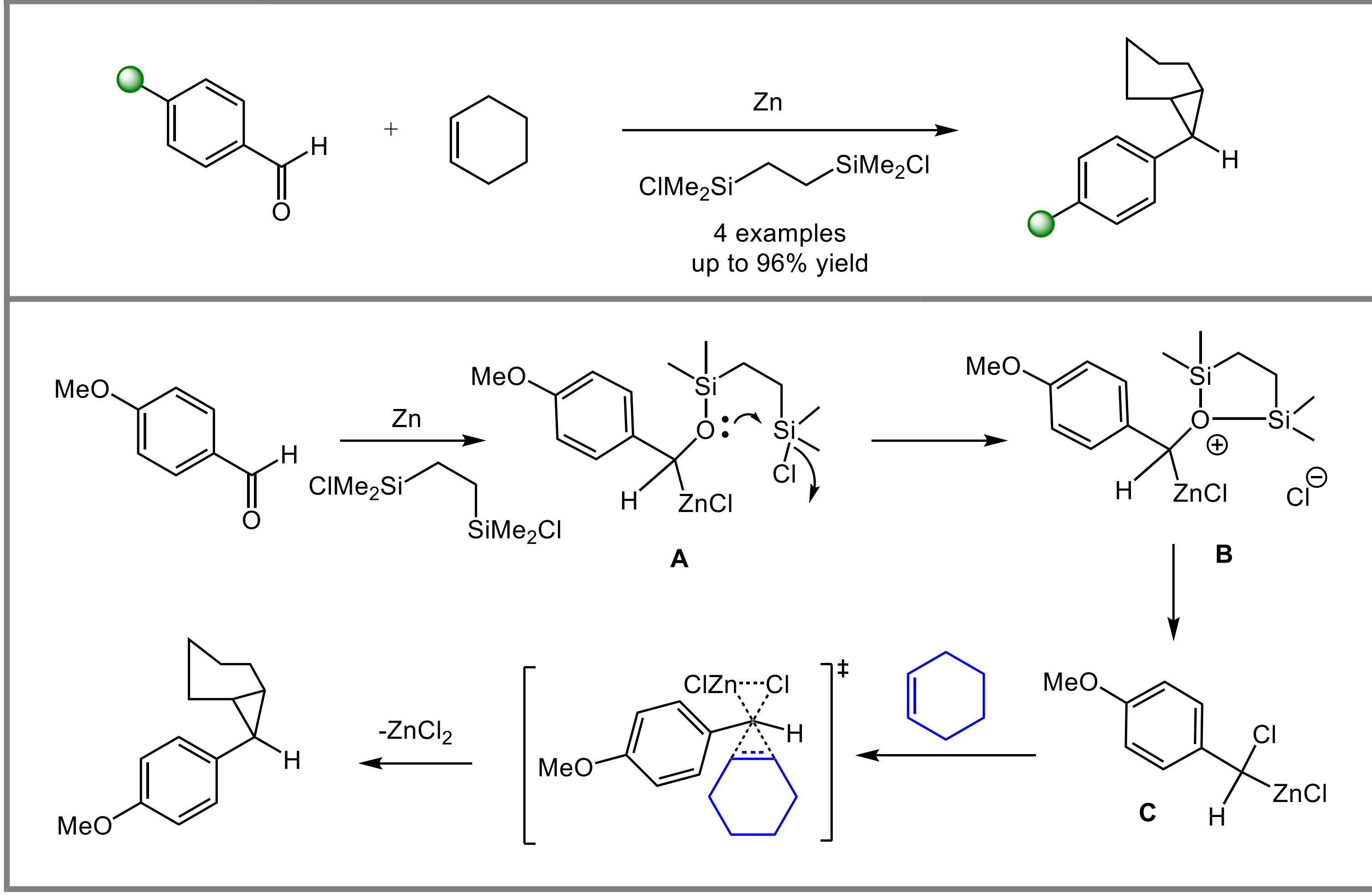
Cyclopropanation with Organozinc Carbenoid

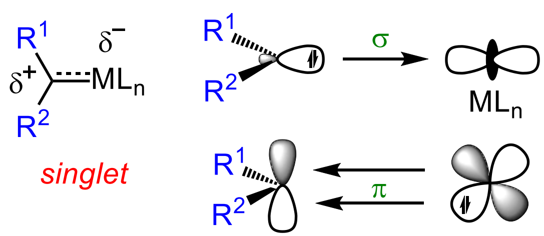


Motherwell, W. B. *J. Organomet. Chem.* **2001**, *624*, 41.

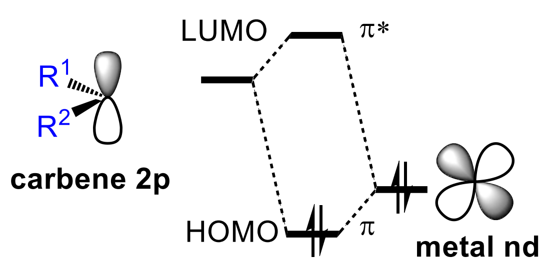
Introduction

Metal Carbene: Fisher-Type and Schrock-Type

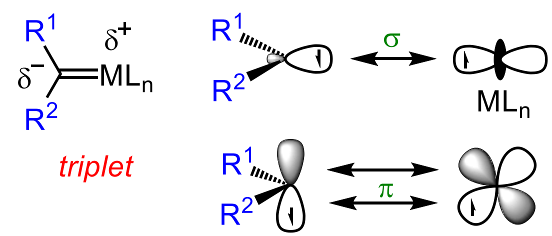
Fisher-Type



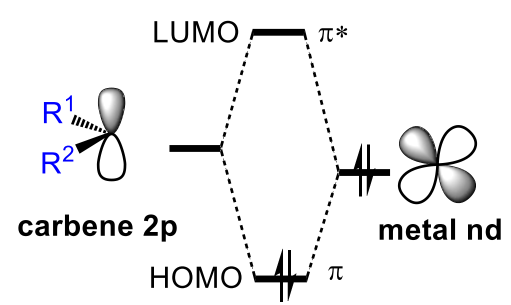
R1 = alkyl, Ar, alkenyl, alkynyl;
R2 = O, N, S;
M = low oxidation states, 18e,
late transition metals;
L: π-acceptor (CO)



Schrock-Type



R1/R2 = H, alkyl, Ar;
M = high oxidation states; 10-18e,
early transition metals;
L: σ/π-donor (Cp, Cl, alkyl)



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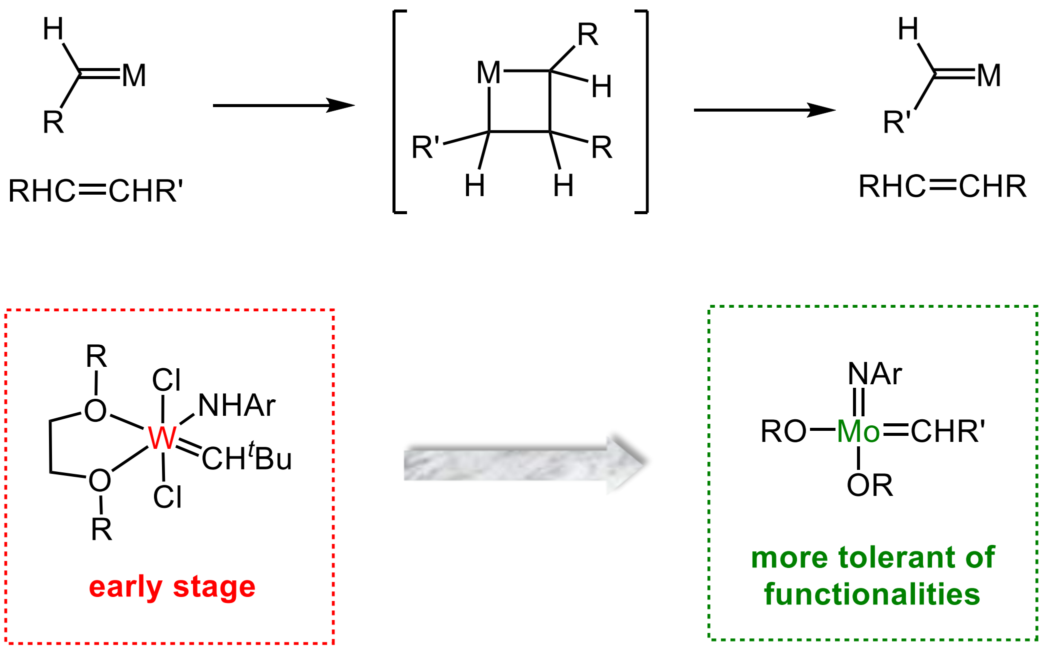
Development of Schrock-Type Carbene



Schrock, R. R. *Chem. Rev.* **2009**, *109*, 3211.
Schrock, R. R., Liu, A. H. *J. Am. Chem. Soc.* **1988**, *110,* 1423.

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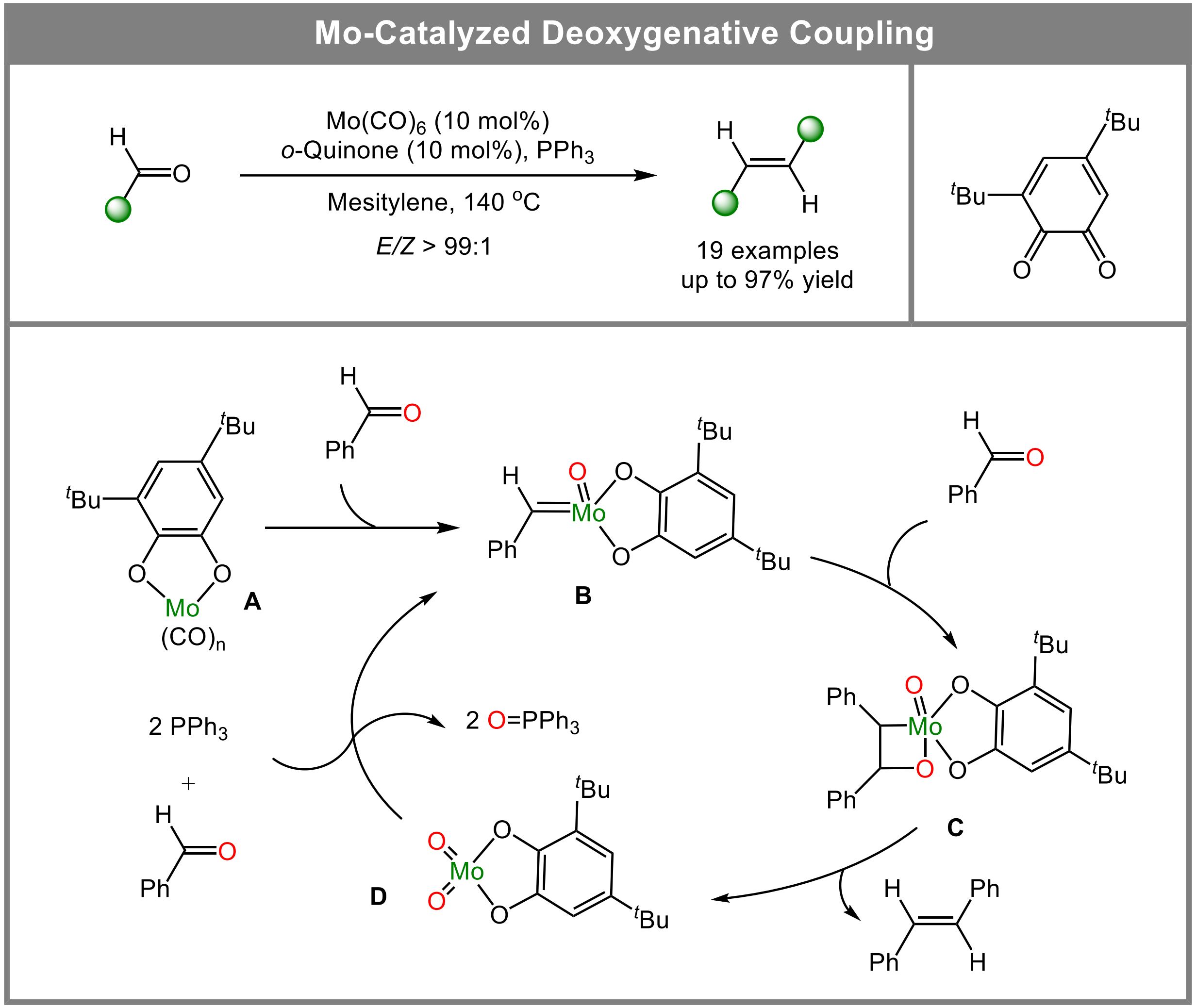

Banerjee, S., Ilies, I. *Org. Lett.* **2022**, *24*, 7242.

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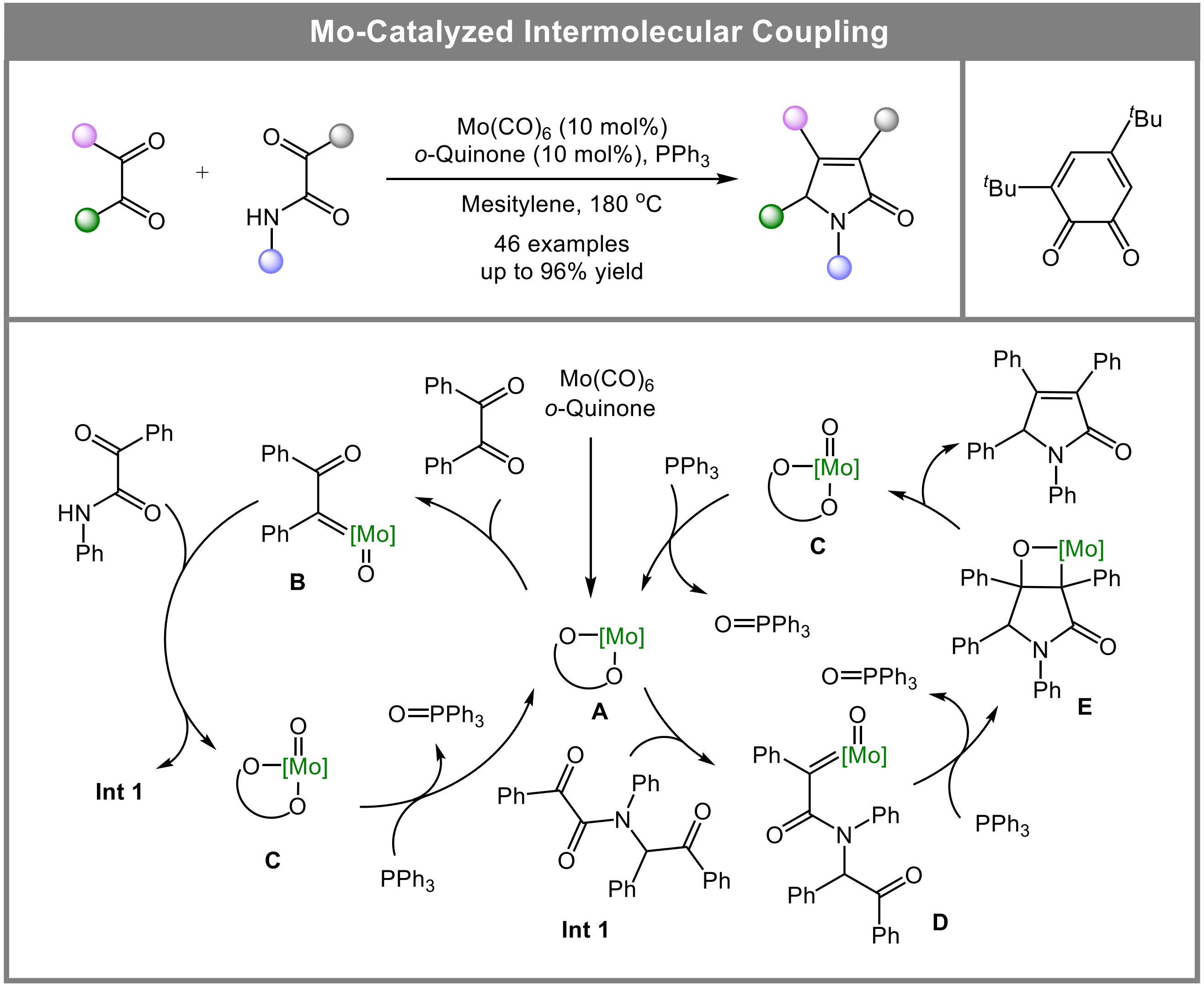

Dong, Y.-Q., Zhuo, C.-X. *ACS Catal*. **2022**, *12*, 11428.

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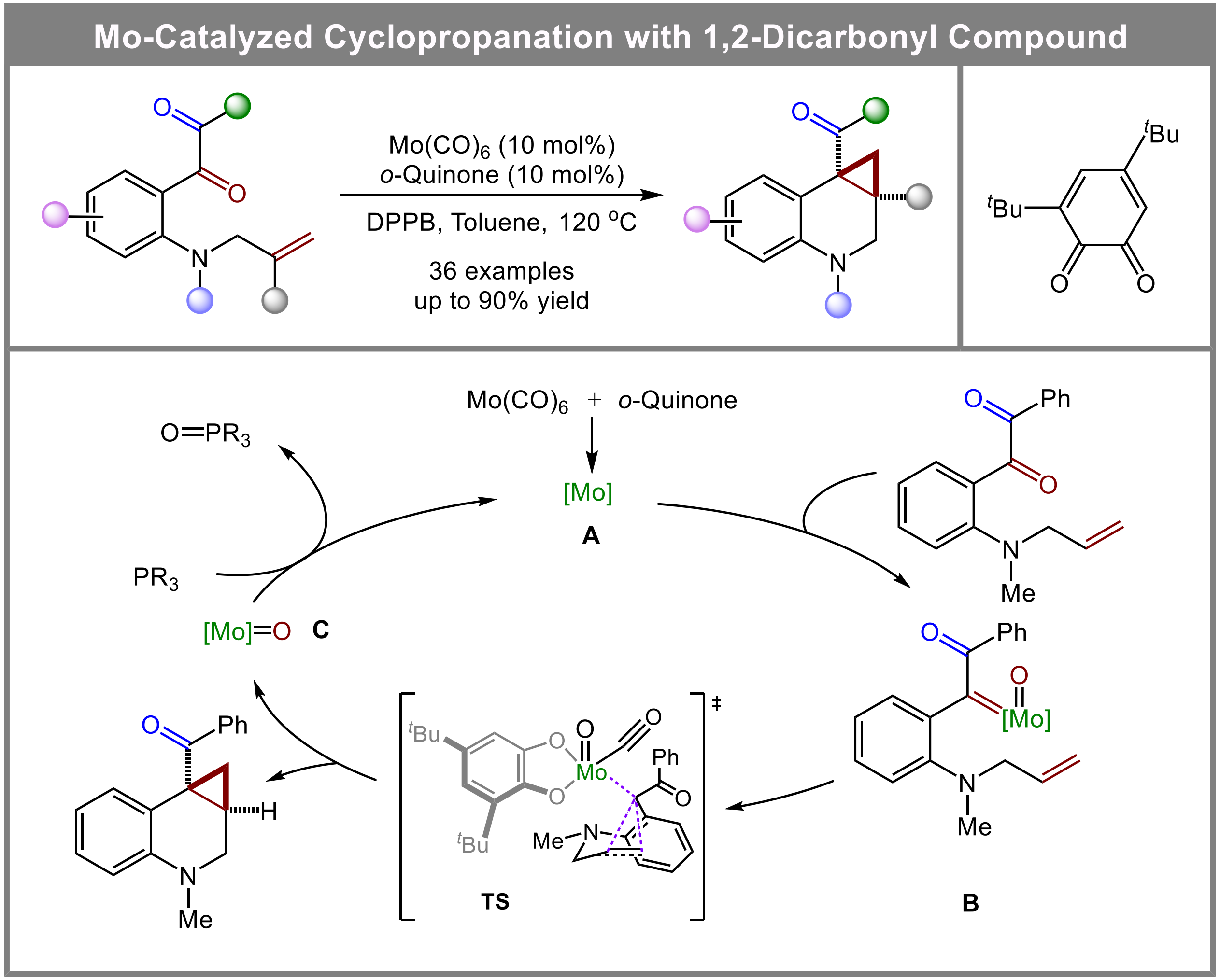
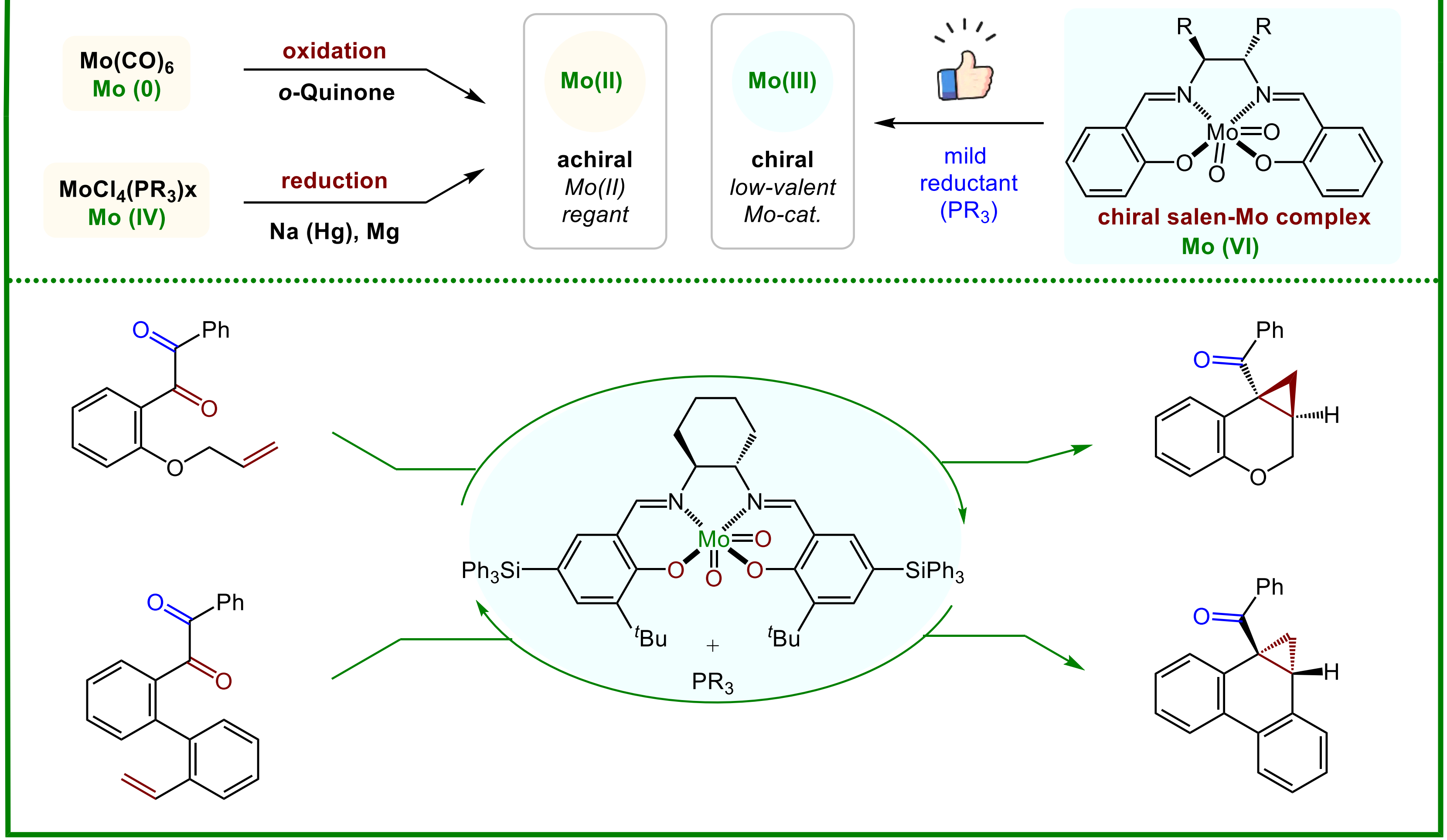


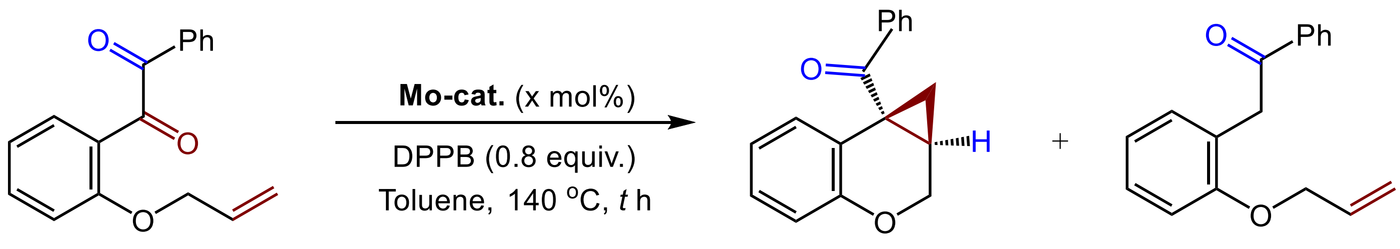
Cao, L.-Y., Zhuo, C.-X. *Angew. Chem. Int. Ed.* **2021**, *60*, 15254.

Salen-Mo Catalytic Cyclopropanation Reaction

The Generation of Low-Valent Mo-Species
for The Deoxygenation of Carbonyls

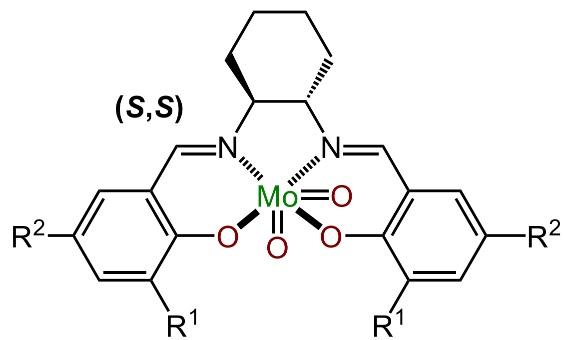


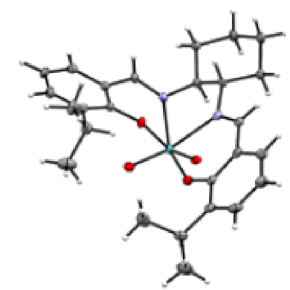
Optimization of Cyclopropanation Reaction



1a 2a B1

Mo-1: R[1] = ^{t}Bu, R[2] = ^{t}Bu
Mo-2: R[1] = H, R[2] = ^{t}Bu
Mo-3: R[1] = ^{t}Bu, R[2] = H
Mo-4: R[1] = ^{i}Pr, R[2] = H
Mo-5: R[1] = ^{t}Bu, R[2] = CN
Mo-6: R[1] = ^{t}Bu, R[2] = Br
Mo-7: R[1] = ^{t}Bu, R[2] = CF_3
Mo-8: R[1] = ^{t}Bu, R[2] = Ph
Mo-9: R[1] = ^{t}Bu, R[2] = 2,4,6-$Me_3C_6H_2$
Mo-10: R[1] = ^{t}Bu, R[2] = $SiPh_3$





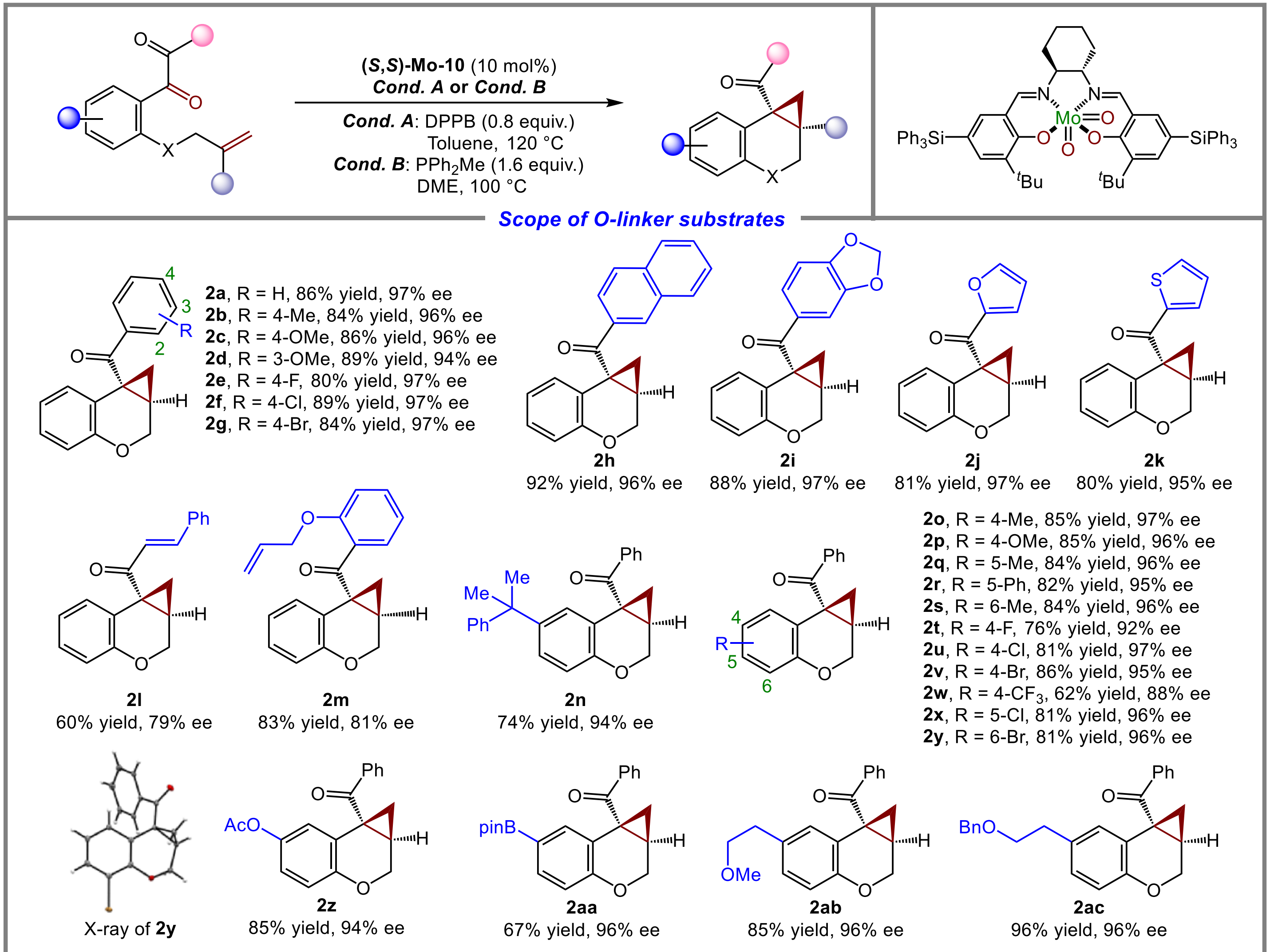
X-ray of **Mo-4**

Optimization of Cyclopropanation Reaction

Entry	Mo-cat.	x (mol %)	*t* (h)	Yield[a] (%) 2a	ee[b] (%) 2a	Yield[a] (%) B1
1	**Mo-1**	20	23	84	92	13
2	**Mo-2**	20	23	87	81	11
3	**Mo-3**	20	23	89	93	11
4	**Mo-4**	20	9	90	91	10
5	**Mo-5**	20	10	90	89	10
6	**Mo-6**	20	16	80	90	15
7	**Mo-7**	20	10	89	92	11
8	**Mo-8**	20	16	88	93	10
9	**Mo-9**	20	20	89	94	11
10	**Mo-10**	20	12	89	95	10
11	**Mo-10**	10	16	91	94	9
12	**Mo-10**	5	80	86	93	14
13[c]	**Mo-10**	10	55	91(86)	97	9

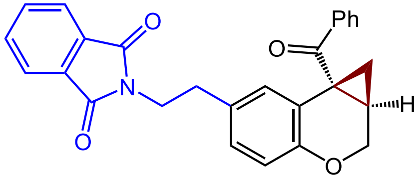
[a]The reaction was performed on 0.1 mmol (entries 1-12) or 0.2 mmol (entry 13) scale, and yield was determined by ^{1}H NMR analysis using CH_2Br_2 as internal standard. [b]Determined by HPLC analysis on a chiral stationary phase. [c]At 120 ^{o}C. Isolated yield in the parentheses.

Substrate Scope

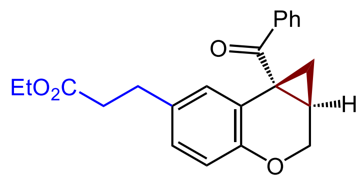


Substrate Scope

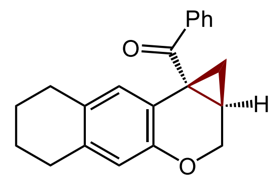
Scope of O-linker substrates



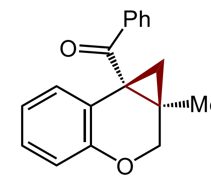
2ad
83% yield, 95% ee



2ae
72% yield, 94% ee

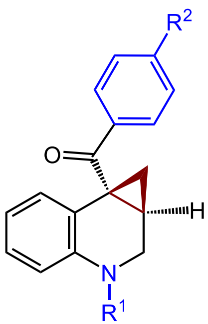


2af
81% yield, 95% ee

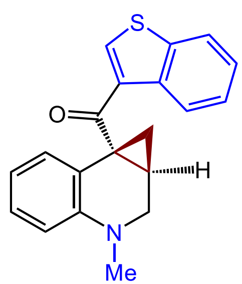


2ag
68% yield, 84% ee

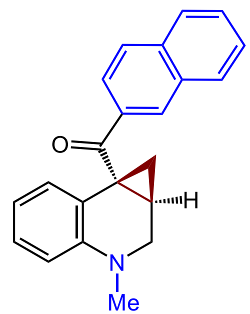
Scope of the N, S, or C-linker substrates



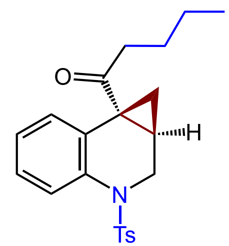
2ah, R^1 = Me, R^2 = H, 76% yield, 93% ee
2ai, R^1 = Me, R^2 = Me, 76% yield, 92% ee
2aj, R^1 = Me, R^2 = OMe, 74% yield, 90% ee
2ak, R^1 = Me, R^2 = F, 70% yield, 92% ee
2al, R^1 = Me, R^2 = Br, 71% yield, 91% ee
2am, R^1 = Ts, R^2 = H, 97% yield, 98% ee
2an, R^1 = Ts, R^2 = Br, 78% yield, 94% ee



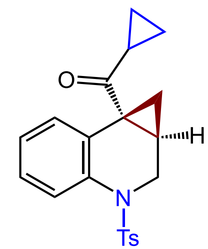
2ap
62% yield, 80% ee



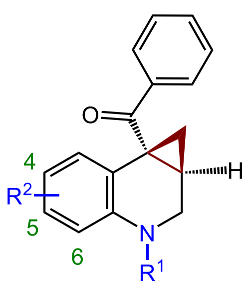
2ao
71% yield, 92% ee



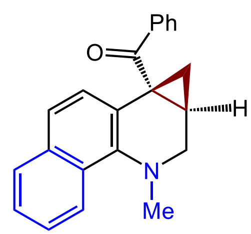
2aq
92% yield, 93% ee



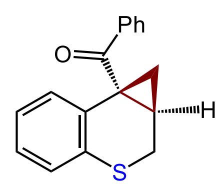
2ar
92% yield, 82% ee



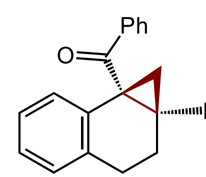
2as, R^1 = Me, R^2 = 4-Me, 74% yield, 90% ee
2at, R^1 = Me, R^2 = 5-Cl, 73% yield, 91% ee
2au, R^1 = Ts, R^2 = 4-Me, 93% yield, 97% ee
2av, R^1 = Ts, R^2 = 5-Me, 89% yield, 95% ee
2aw, R^1 = Me, R^2 = 4-Cl, 94% yield, 97% ee
2ax, R^1 = Ts, R^2 = 5-Br, 80% yield, 94% ee



2ay
62% yield, 90% ee



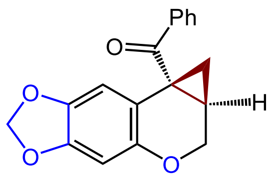
2az
60% yield, 89% ee



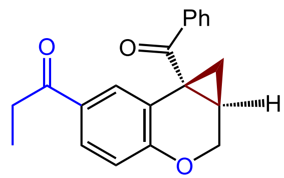
2ba
75% yield, 91% ee

Substrate Scope

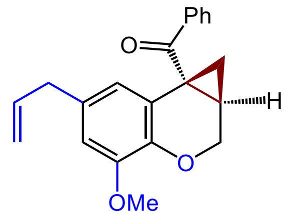
Derivatization of bioactive molecules



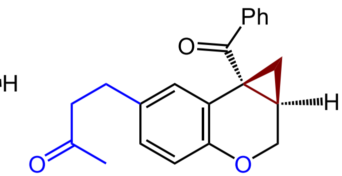
from sesamol, **2bb**
92% yield, 95% ee



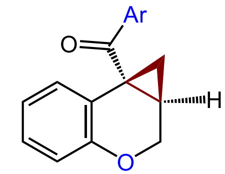
from paroxypropione, **2bc**
85% yield, 96% ee



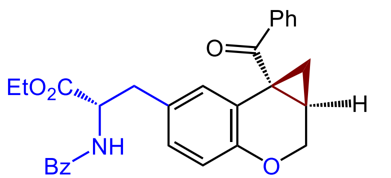
from eugenol, **2bd**
60% yield, 90% ee



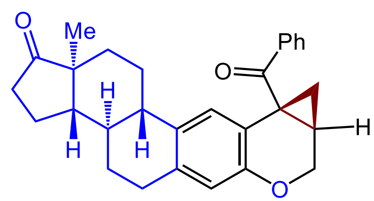
from raspberry ketone, **2be**
90% yield, 97% ee



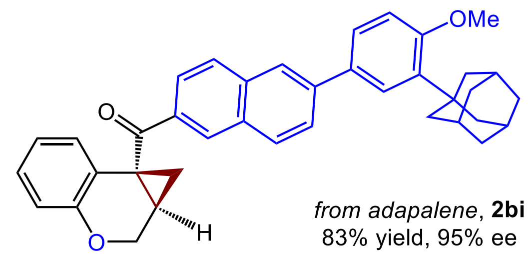
Ar = 4-$SO_2N(^nPr)_2$-C_6H_4
from probenecid, **2bf**
61% yield, 95% ee



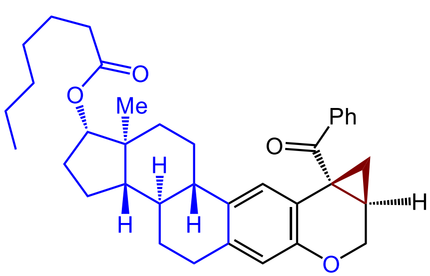
from ethyl N-benzoyl-L-tyrosinate, **2bg**
88% yield, >20/1 dr



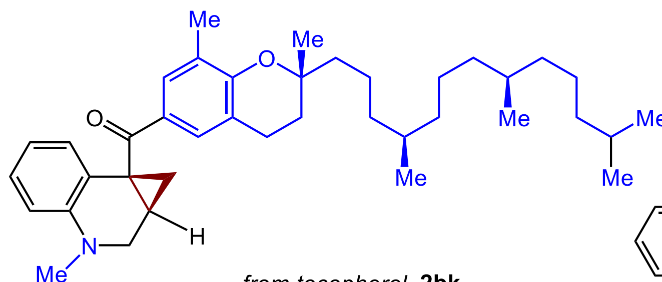
from estrone, **2bh**
84% yield, >20/1 dr



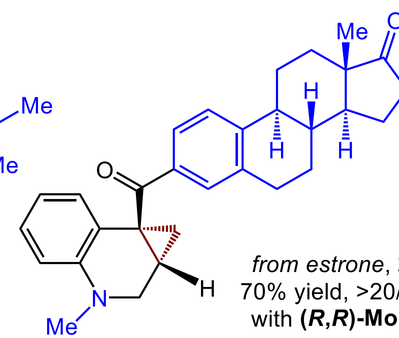
from adapalene, **2bi**
83% yield, 95% ee



from oestradiol 17-heptanoate, **2bj**
91% yield, >20/1 dr

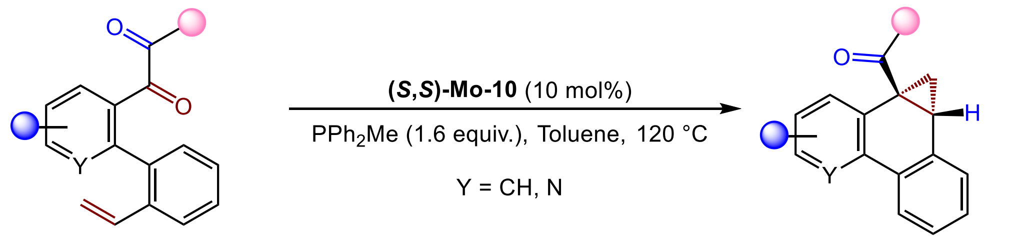


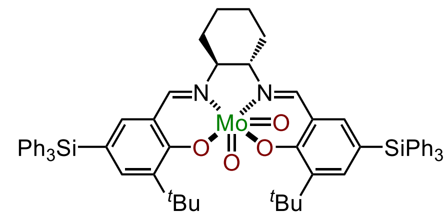
from tocopherol, **2bk**
73% yield, >20/1 dr



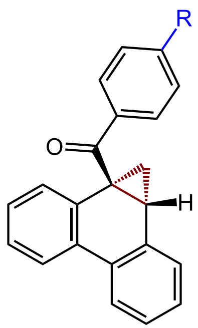
from estrone, **2bl**
70% yield, >20/1 dr
with **(*R*,*R*)-Mo-10**

Substrate Scope

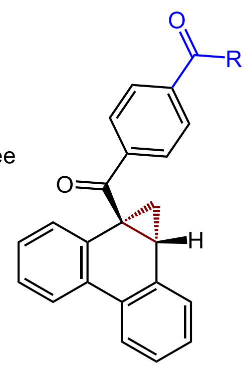




Scope of Styrene Derivatives

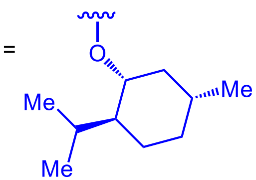


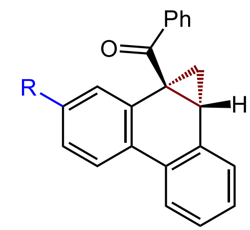
4a, R = H, 82% yield, 91% ee
4b, R = OMe, 75% yield, 88% ee
4c, R = F, 75% yield, 92% ee
4d, R = Cl, 80% yield, 92% ee



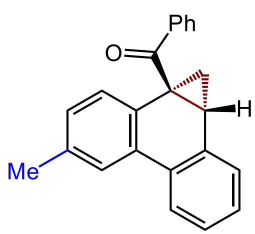
4e, R = OMe, 77% yield, 86% ee
4f, 43% yield, 14/1 dr

R =

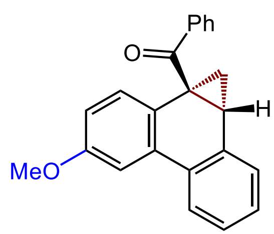




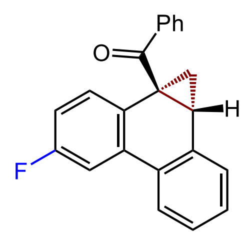
4g, R = Me, 72% yield, 89% ee
4h, R = CF_3, 65% yield, 91% ee
4i, R = F, 75% yield, 92% ee



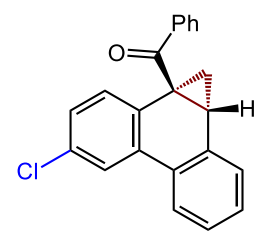
4j, 84% yield, 90% ee



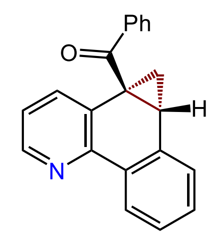
4k, 77% yield, 87% ee



4l, 72% yield, 89% ee

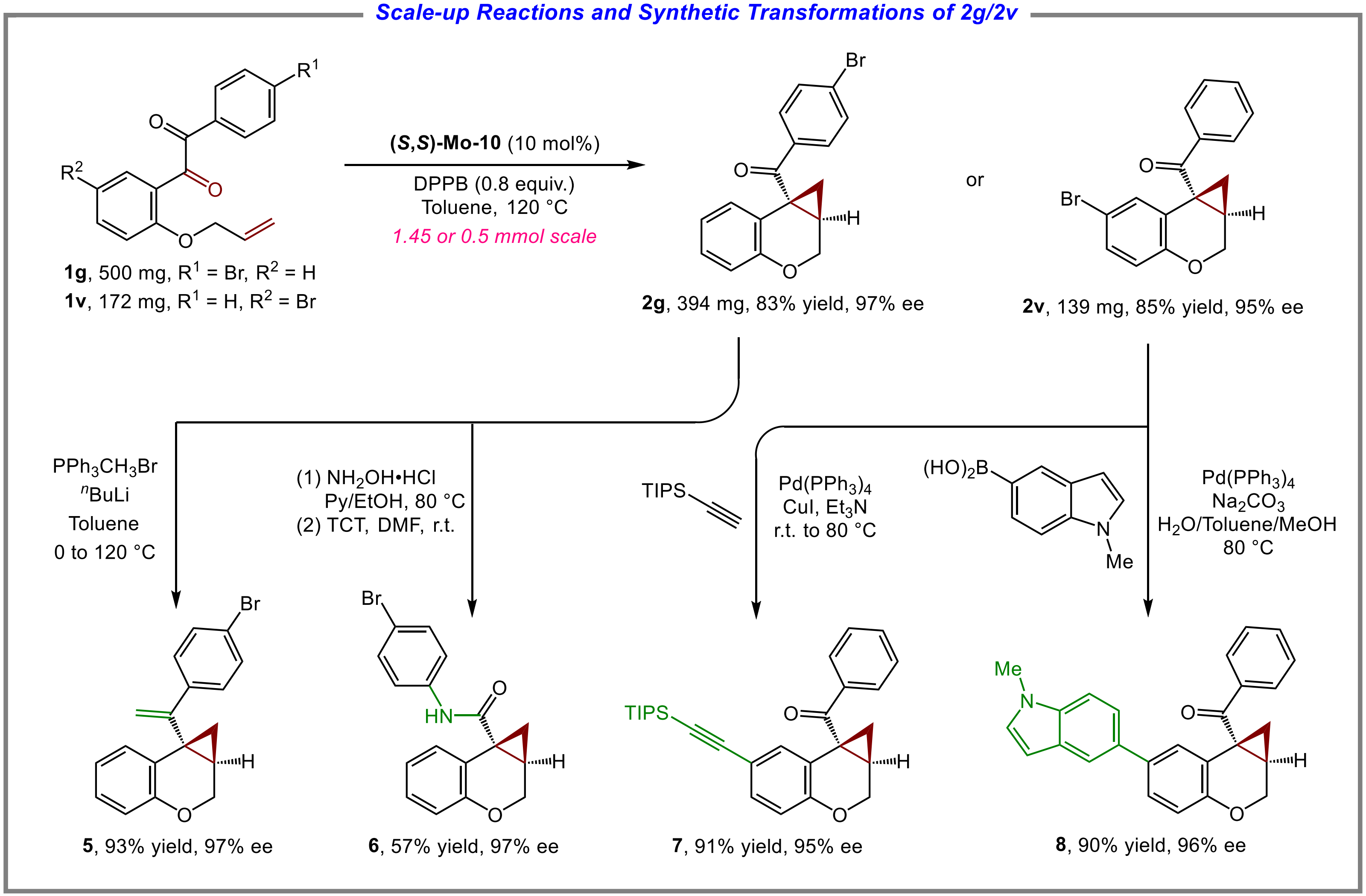


4m, 70% yield, 90% ee



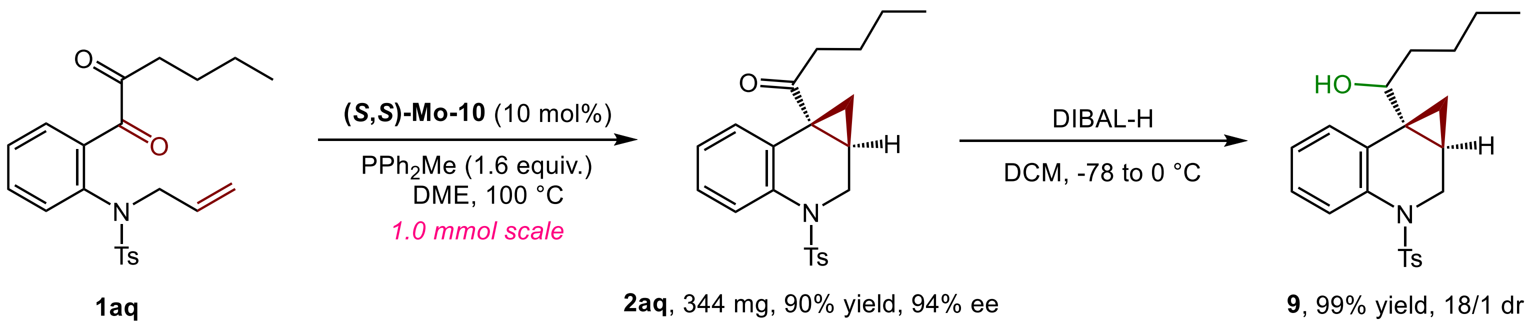
4n, 50% yield, 80% ee

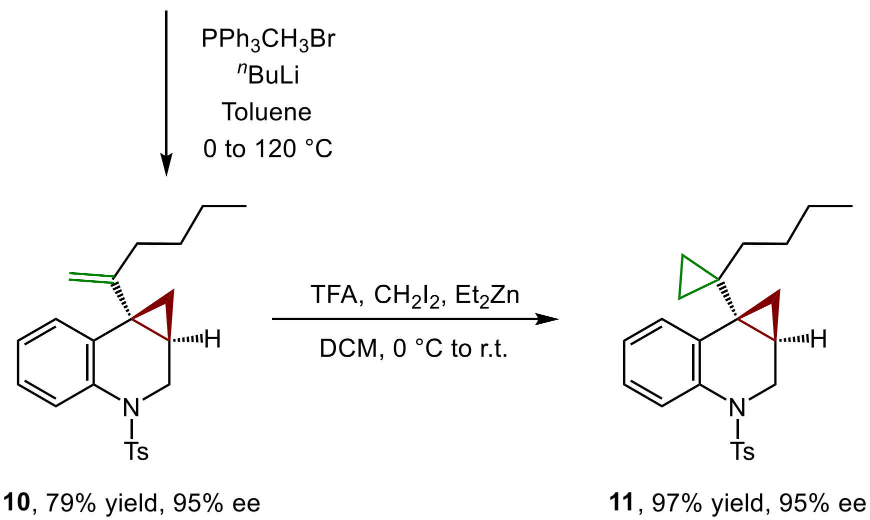
Scale-up Reactions and Synthetic Applications



Scale-up Reactions and Synthetic Applications

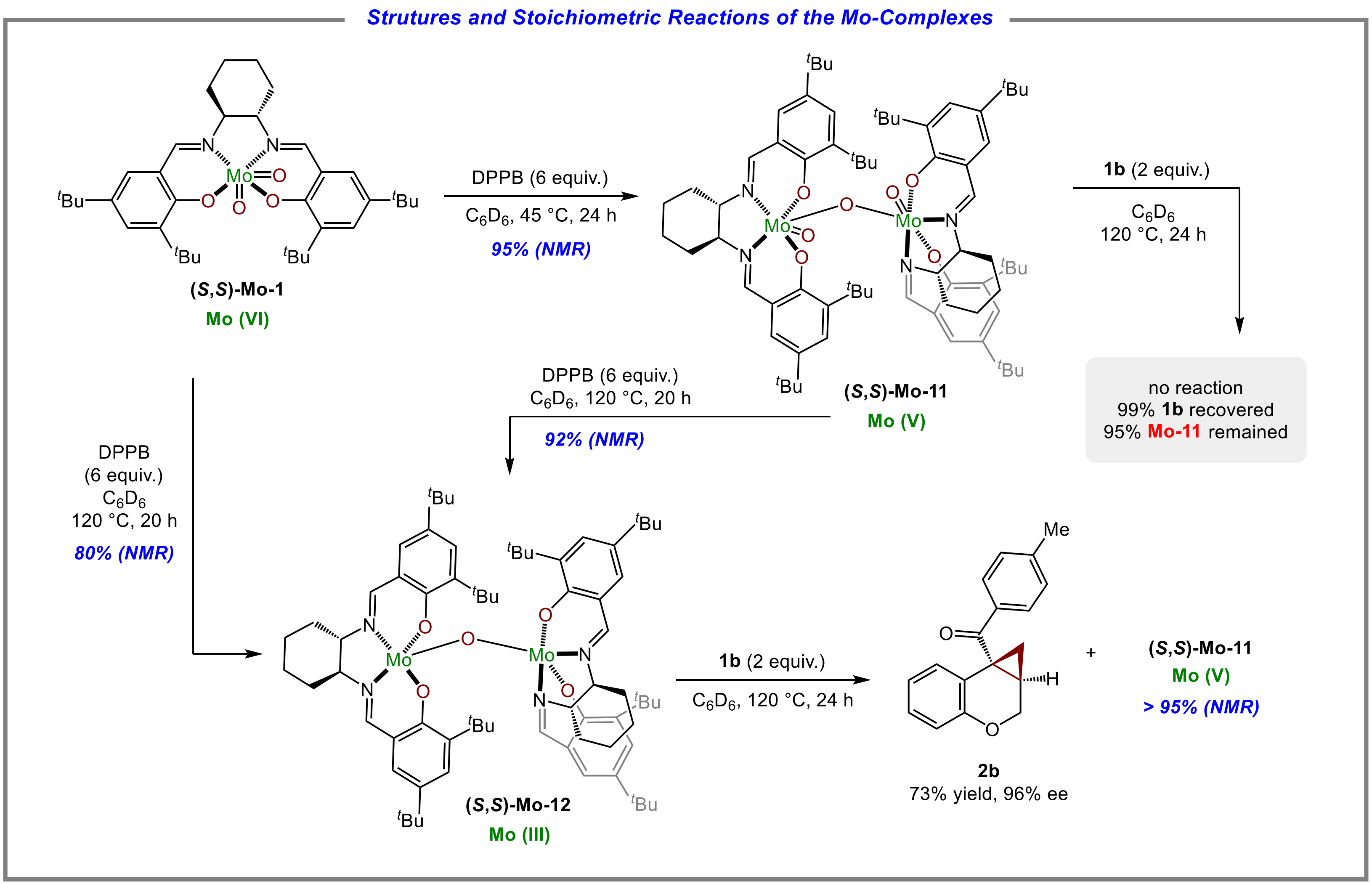
Scale-up Reactions and Synthetic Transformations of 2aq



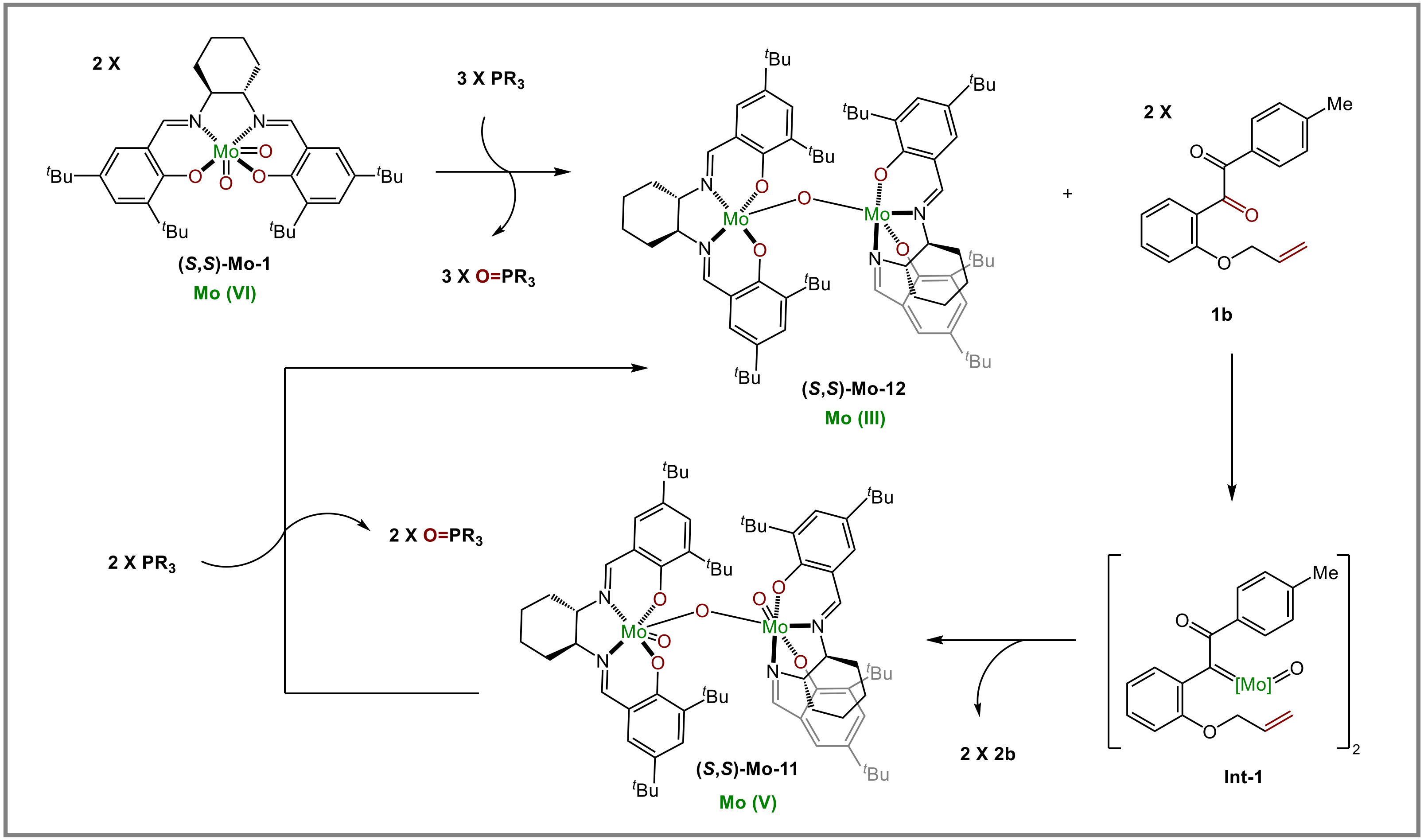


- readily prepared on a several hundred millig-ram scale
- the cyclopropane ring could be well tolerated
- easily accessed through several downstream transformations of the cyclopropane products
- the enantiomeric purities of the chiral starting materials were all well preserved

Experimental Mechanistic Studies

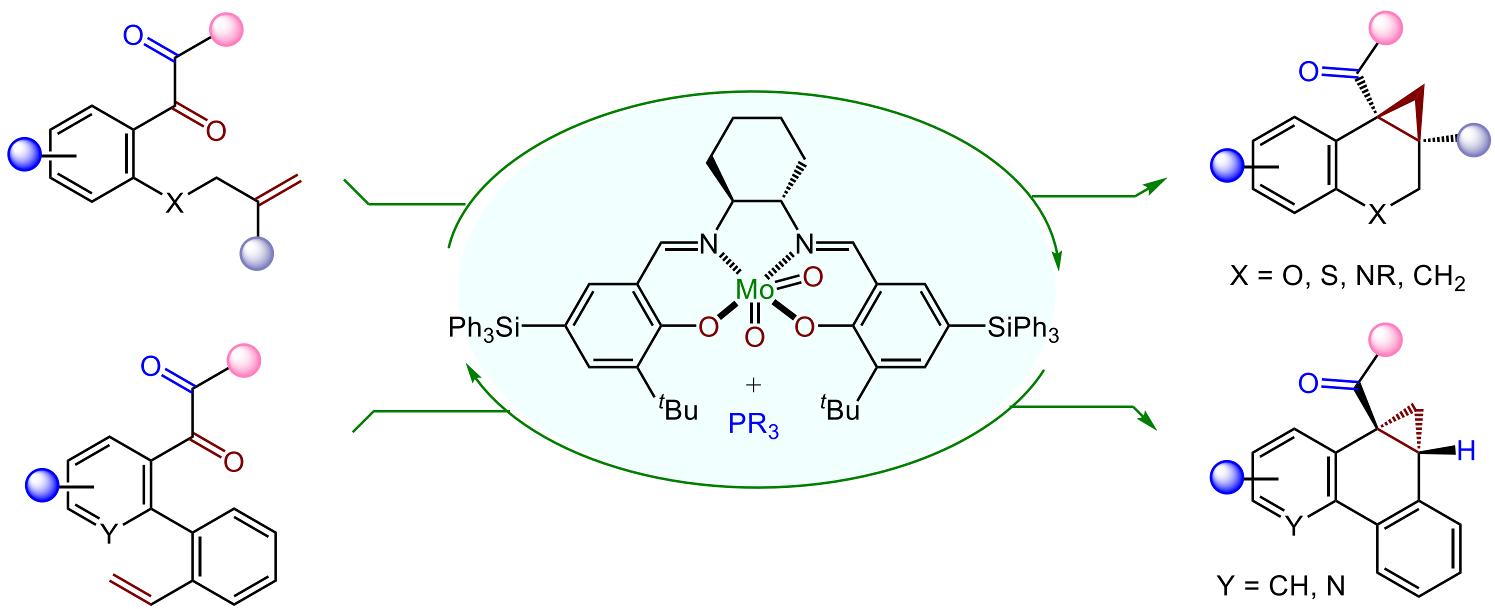


Proposed Mechanism



Summary

Salen-Mo Catalytic Asymmetric Deoxygenative Cyclopropanation Reactions



- 80 Examples, good to excellent enantioselectivities and yields
- Phosphine as both the oxygen acceptor and a mild reductant
- An array of valuable chiral cyclopropanes was readily accessed
- Efficiently generate the catalytically active low-valent chiral salen-Mo species

Writing Strategy

☐ The First Paragraph

Importance of chiral cyclopropane motif

- ✓ The chiral cyclopropane motif is widely distributed in an array of natural products and approved drugs. The unique properties of cyclopropanes make them appealing candidates in drug discovery, especially in their optically pure form.

Traditional synthetic methods

- ✓ Among the many methods used to achieve this goal, the transition-metal-catalyzed asymmetric cyclopropanation reaction of alkenes with chiral metal carbene intermediates, derived from diazo compounds and chiral metal complexes, was found to be one of the most straightforward, powerful, and useful methods.

Limitations of traditional methods

- ✓ Unfortunately, the handling of diazo compounds requires special care due to their potentially explosive nature and the necessary use of hazardous reagents for their preparation.

Writing Strategy

◻ The Last Paragraph

Summary
of this work

- ✓ In summary, a class of chiral salen-Mo catalysts was described for the direct catalytic asymmetric deoxygenative cyclopropanation reaction of 1,2-dicarbonyl compounds.

Advantages of
the current method

- ✓ The key to success included the discovery of a novel approach to efficiently generate the catalytically active low-valent chiral salen-Mo species as well as the use of phosphine as both the oxygen acceptor and a mild reductant for catalyst generation.

Outlook
of this work

- ✓ We anticipate that this work can become a stepping stone to uncovering the potency of chiral salen-Mo catalysts as efficient chiral catalysts for the increasingly appealing catalytic deoxygenative functionalization reactions of carbonyl compounds.

Representative Examples

To date, only a handful of examples relying on the power of either stoichiometric metal reagents and reductants or low-valent transition-metal complexes have been reported. (一小撮，很少)

This seemingly simple conceptual design posed great challenges. (概念上的)

Several scale-up reactions and synthetic transformations were carried out to showcase (展示) the potential of this methodology. (进行了几个放大反应和合成转化，以展示该方法的潜力)

Thanks
for your attention