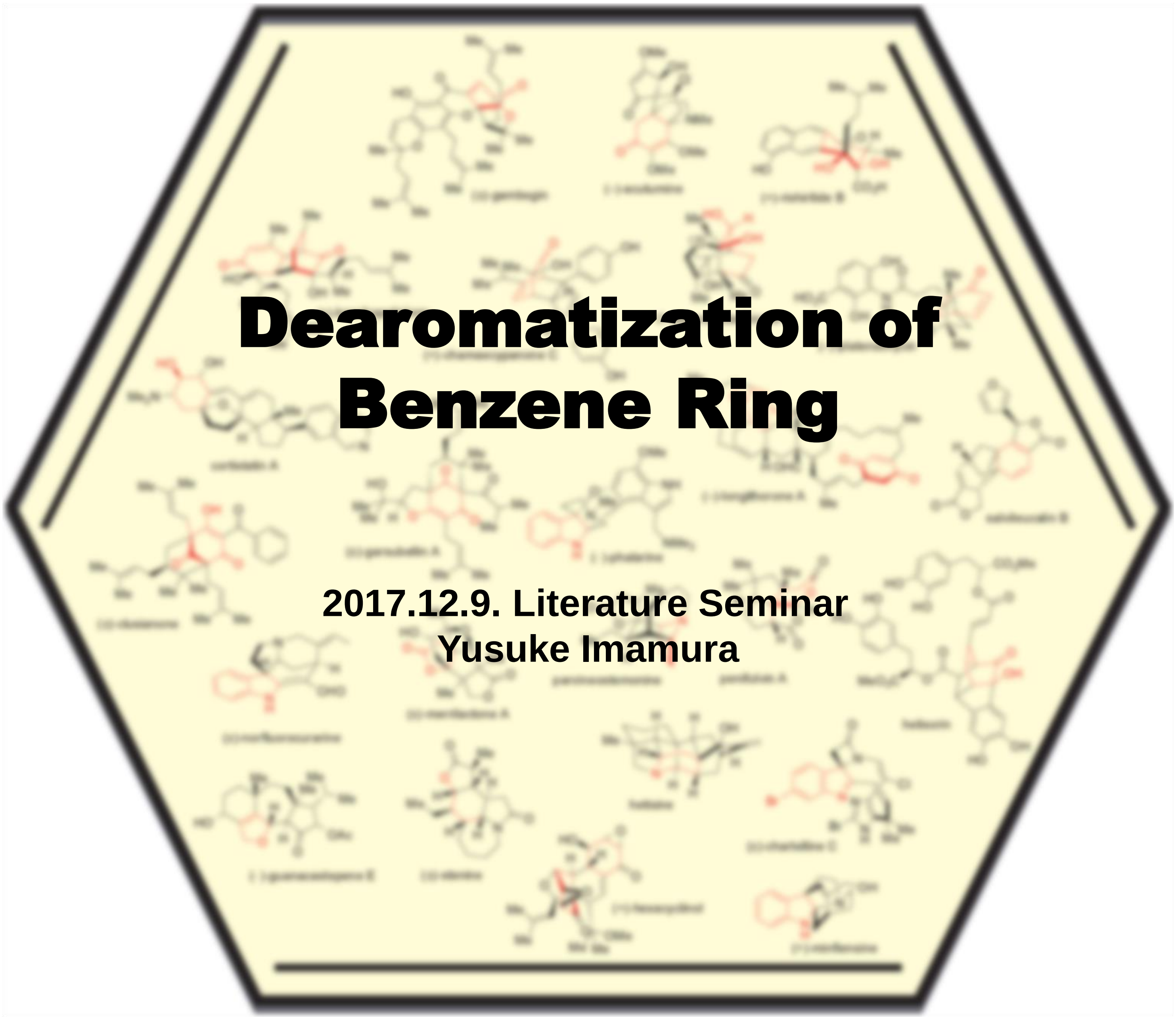
Dearomatization of Benzene Ring

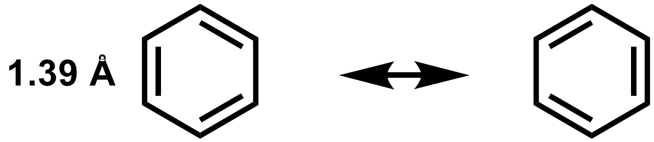


2017.12.9. Literature Seminar

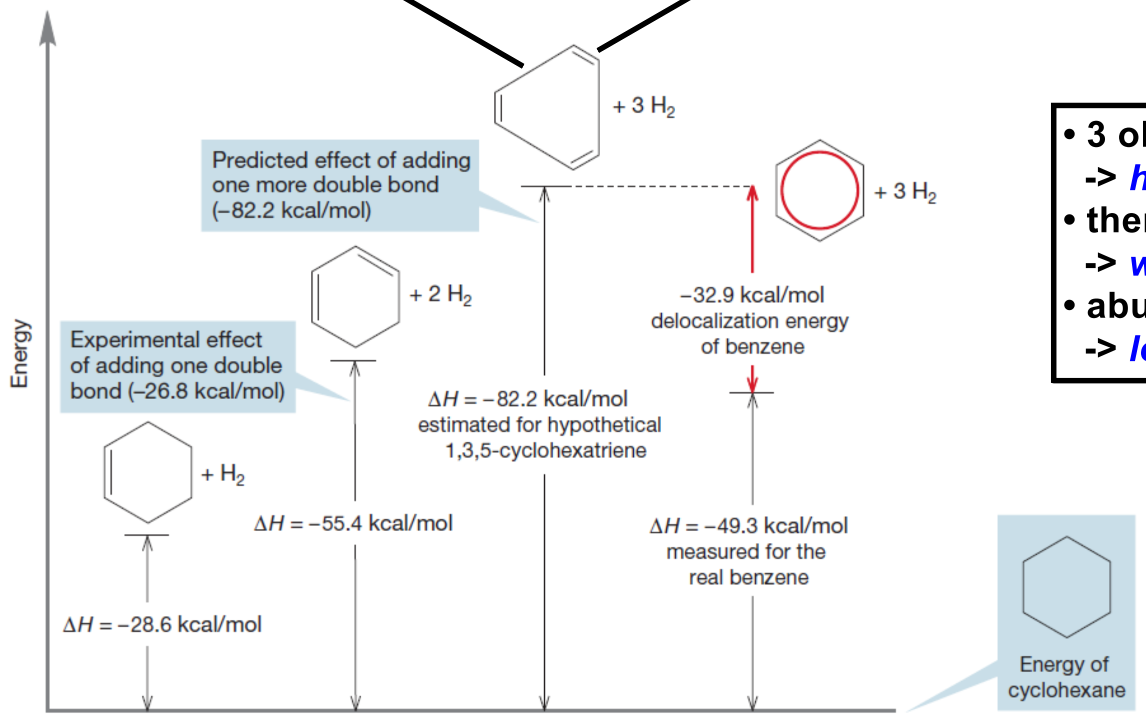
Yusuke Imamura

Contents

Benzene Ring



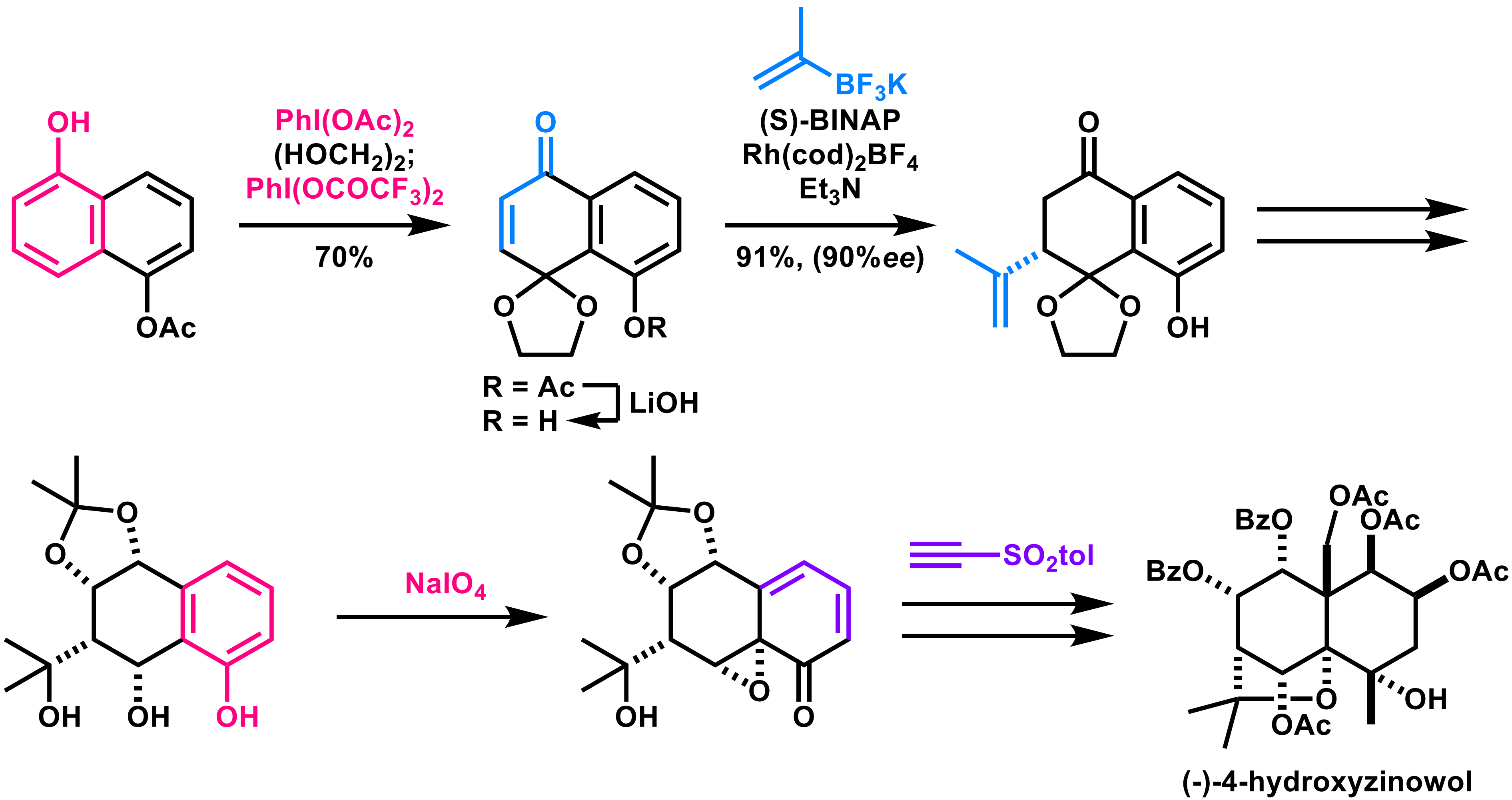
normal single bonds: 1.47 Å **normal doble bonds: 1.33 Å**



- **3 olefins**
  -> ***high oxidation level***
- **thermaly stable**
  -> ***wide compatibility***
- **abundant source**
  -> ***low cost***

1) Jones, M, Fleming, S. A. *Organic Chemistry*

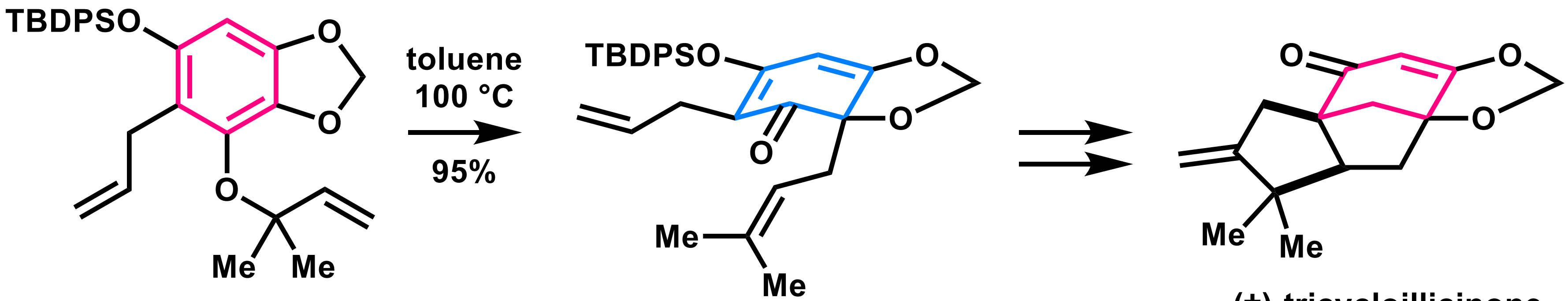
Dearomatization in Our Lab



1) Todoroki, H.; Iwatsu, M.; Urabe, D.; Inoue, M. *J. Org. Chem,* **2014**, *79*, 8835.

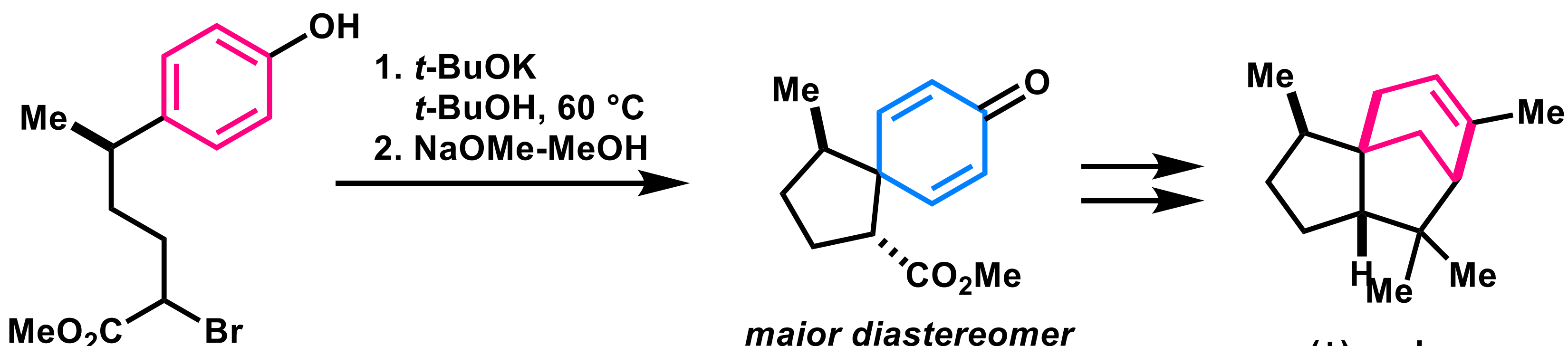
Dearomatization in Total Syntheses

1. Aromatic Claisen rearrangement [1)]



(±)-tricycloillicinone

2. Alkylative dearomatization of phenols [2)]



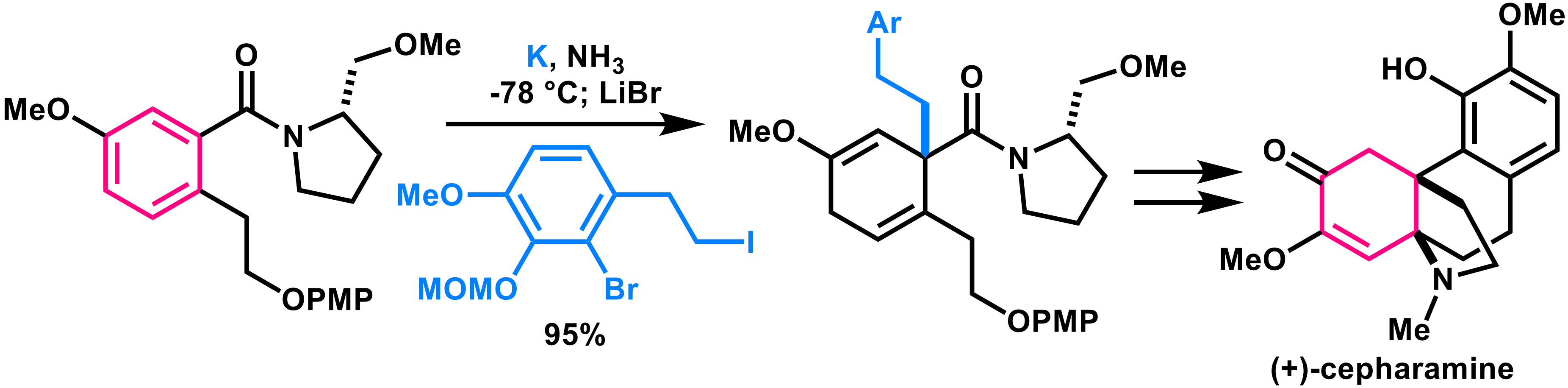
major diastereomer

(±)-cedrene

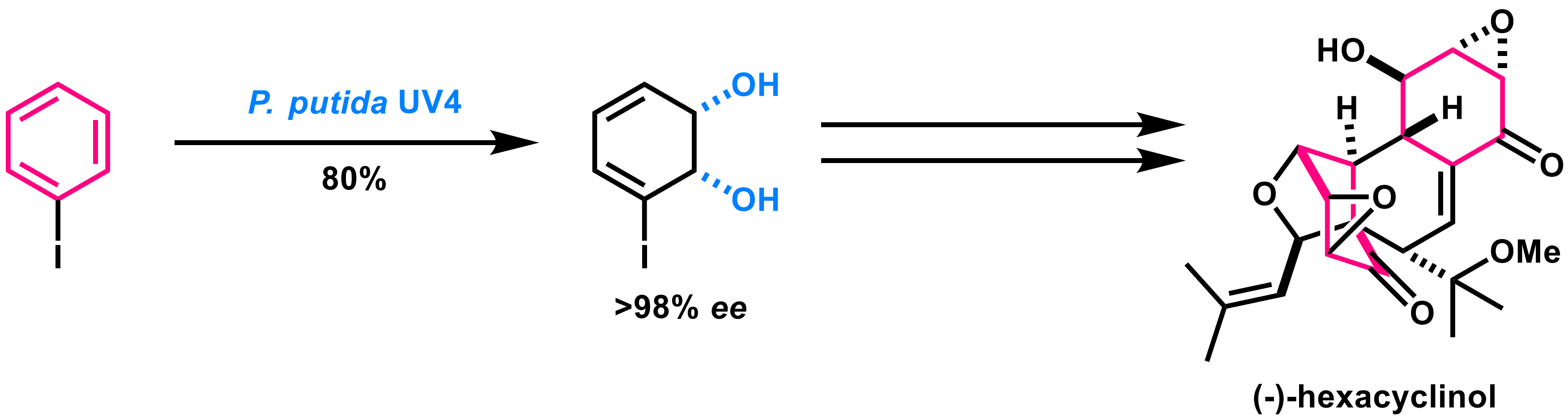
1) Pettus, T. R. R.; Chen, X.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1998**, *120*, 12684.
2) Corey, E. J.; Girota, N. N.; Mathew, C. T. *J. Am. Chem. Soc.* **1969**, *91*, 1557.

Dearomatization in Total Syntheses

3. Alkylative Birch-reduction[1)]



4. Enzymatic dearomative dihydroxylation [2)]



1) Schultz, A. G.; Wang, A. *J. Am. Chem. Soc.* **1998**, *120*, 8259.
2) Pinkerton, D. M.; Banwell, M. G.; Willis, A.C. *Org. Lett.* **2009**, *11*, 4290.

David Sarlah

-2006	Bachelor in Chem. University of Ljubljana (Prof. Roman Jerala, Synthtic biology)
2006 – 2011	Ph.D. The Scripps Research Institute, CA (Prof. K. C. Nicolaou, Total synthesis of complex natural product)
2011 – 2014	Postdoc. ETH Zürich (Prof. E. M. Carreira, Asymmetric catalyst)
2014 -	Assistant Professor of Chemistry, UIUC

Research Topics:
✔ Natural Products Chemistry and Synthesis
✔ Synthetic Methods
✔ Chemical Biology and Medicinal Chemistry

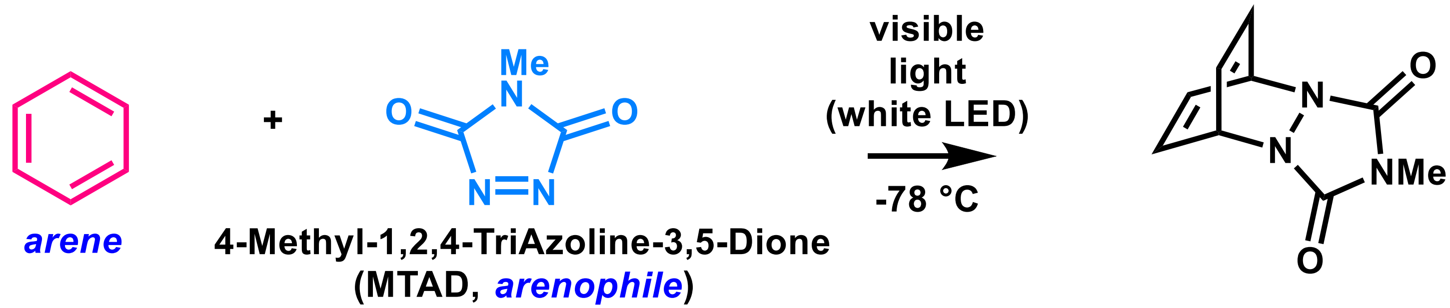
Contents

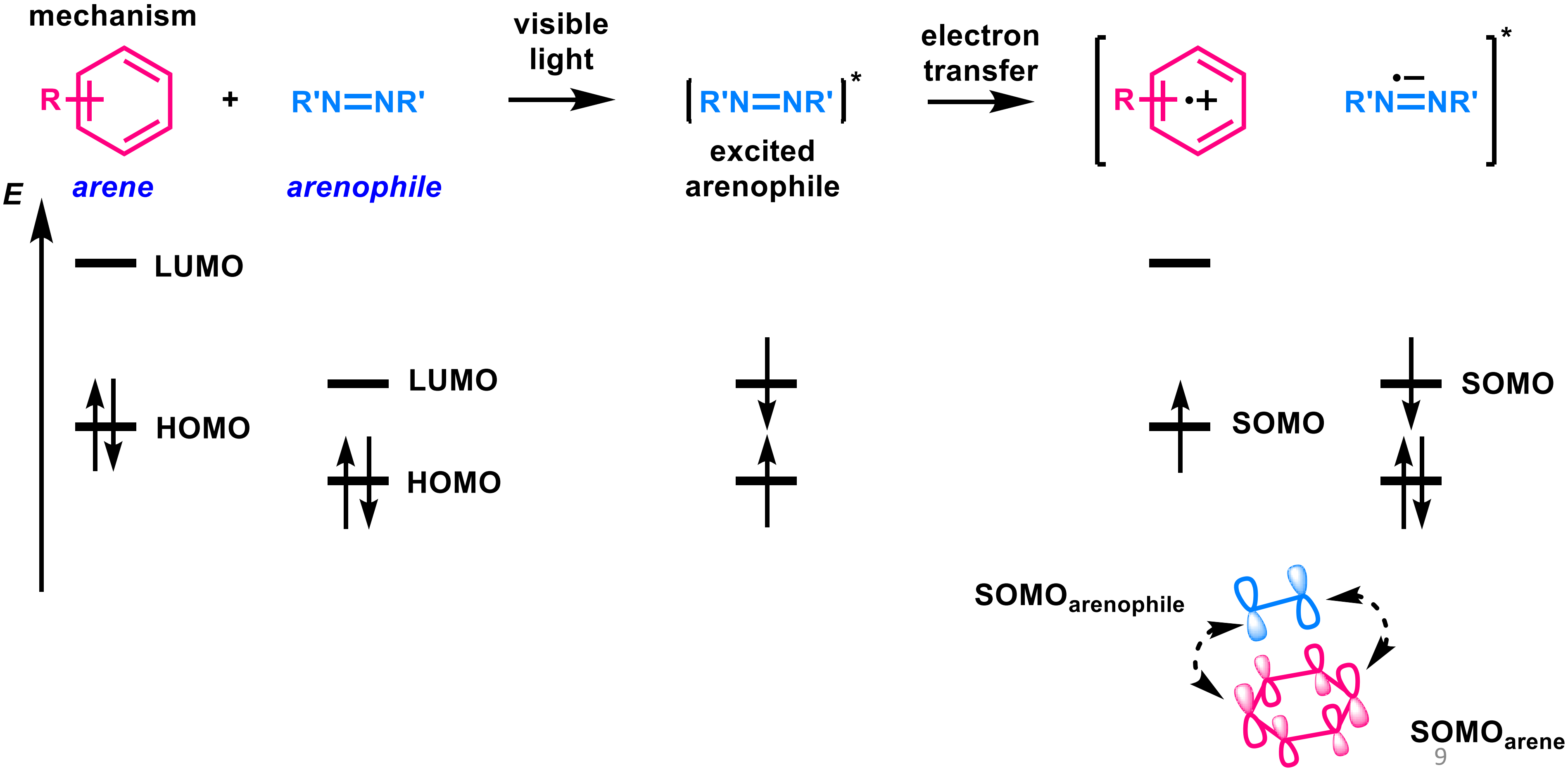
ARTICLES
PUBLISHED ONLINE: 22 AUGUST 2016 | DOI: 10.1038/NCHEM.2594
nature chemistry

Dearomative dihydroxylation with arenophiles

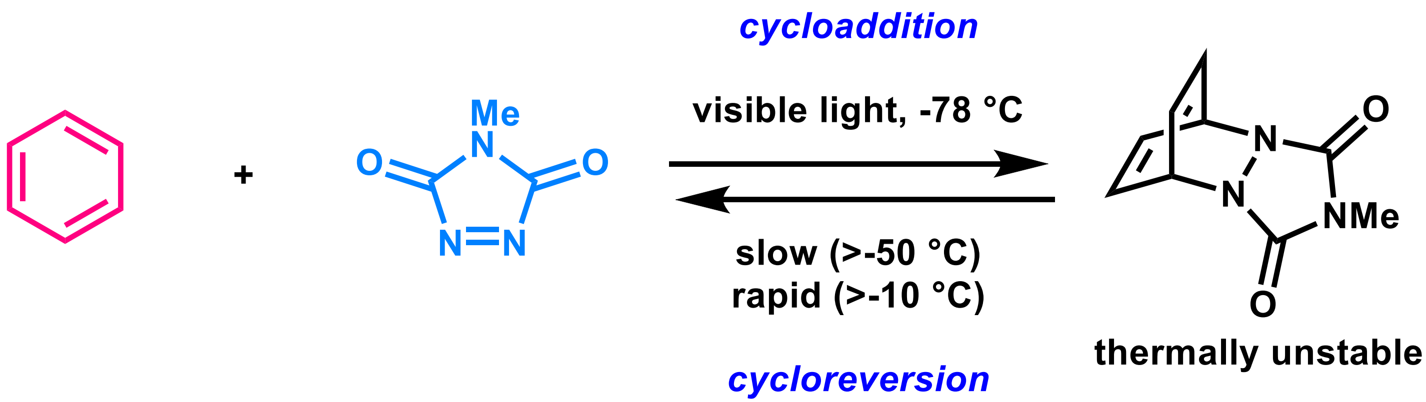
Emma H. Southgate†, Jola Pospech†, Junkai Fu, Daniel R. Holycross and David Sarlah*

Formation of Bicyclic-ring



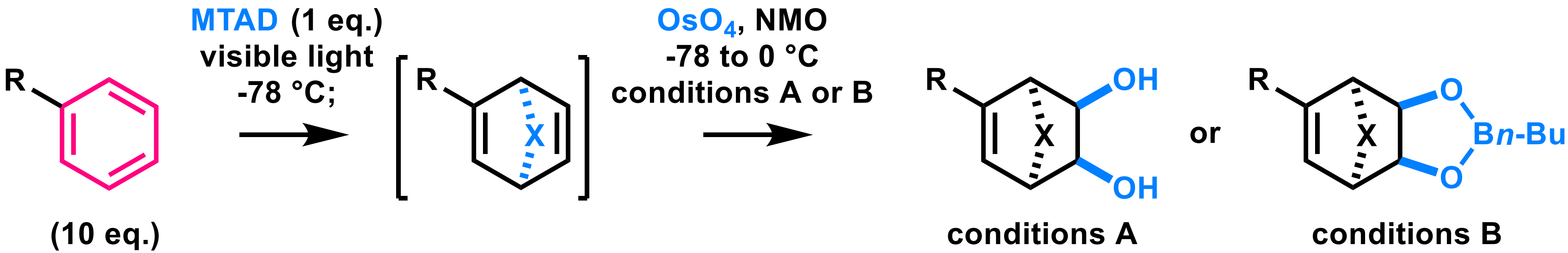


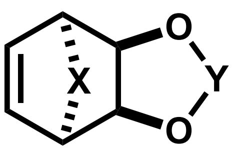
Problem to Application



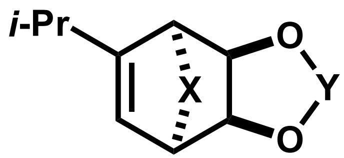
-> Cycloadduct must be used for next reaction *in situ*.

Dearomative Dihydroxylation

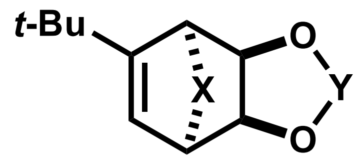




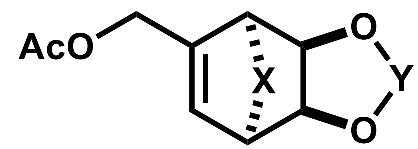
A: 56%
B: 65%



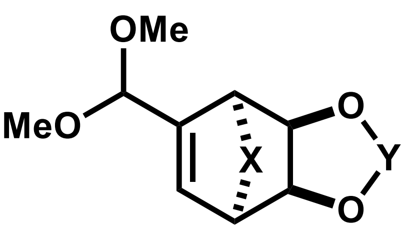
A: 39%
B: 28%



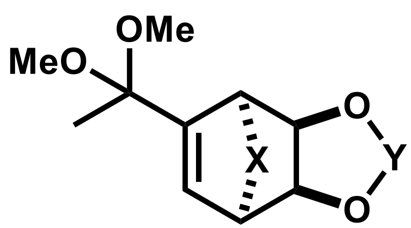
A: 70%
B: 28%



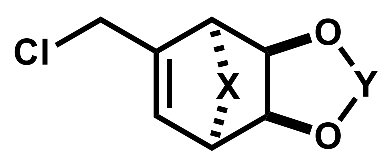
A: 48%
B: 55%



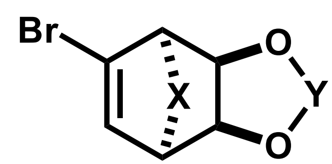
A: 23%
B: 61%



A: 58%
B: 64%



A: 44%
B: 64%

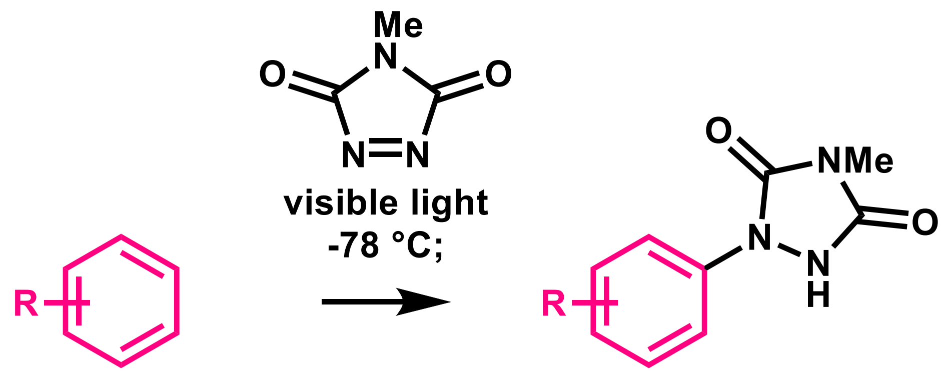


A: 24%
B: 40%

Condition A: OsO_4 (5 mol%), NMO (1.2), *p*-$TsNH_2$ (1.2), H_2O (20), acetone (0.1 M)
Condition B: OsO_4 (5 mol%), NMO (1.2), *n*-$BuB(OH)_2$ (1.2), CH_2Cl_2
***Isolated yields of the purified material based on MTAD.**

Substrate Limitation
Incompatible Substrate

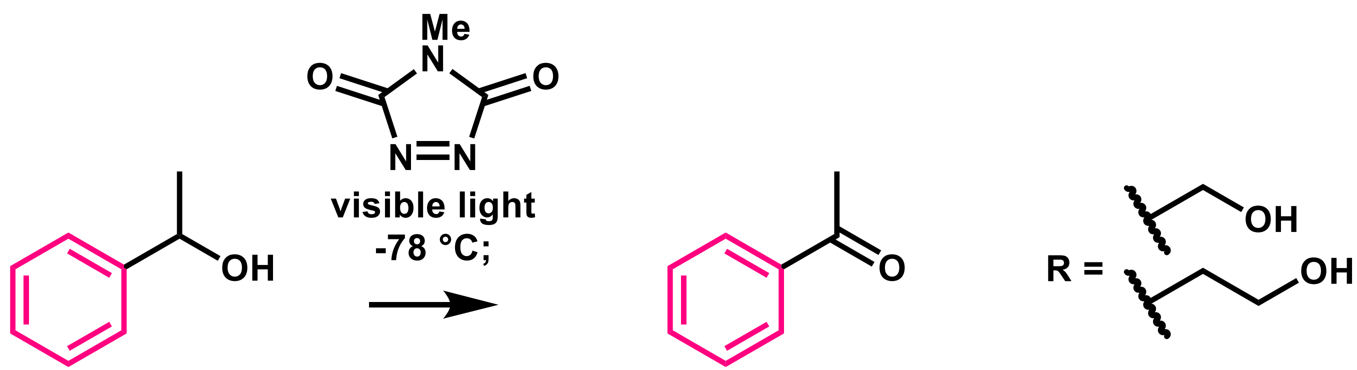
- **phenol and aniline derivatives**



R = OH, OMe, OMs
NH_2, NHAc, phth

Friedel-Crafts-type reaction

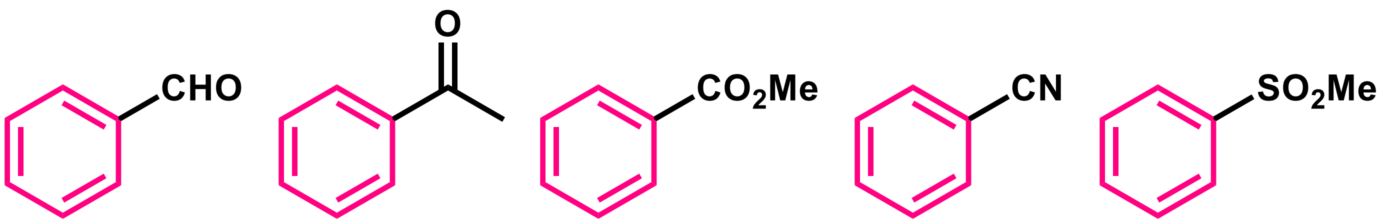
- **alcohols**



Oxidation
-> acetyl protection worked well

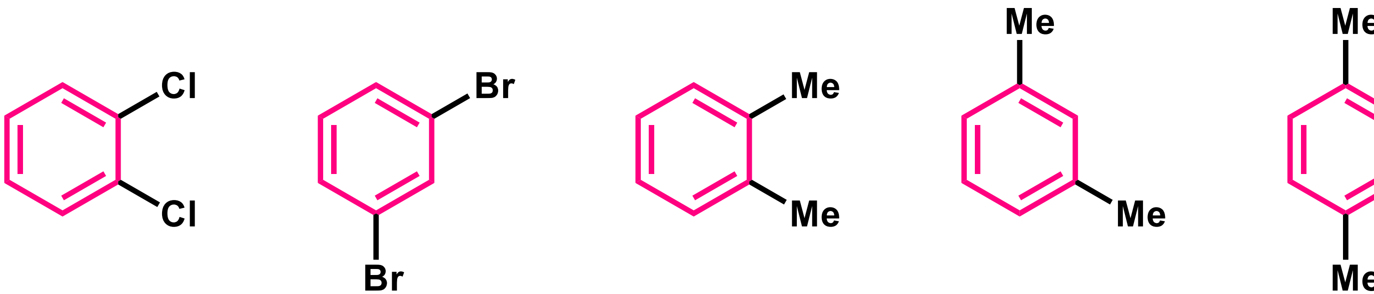
Substrate Limitation
Unreacted Substrate

• electron deficient arenes



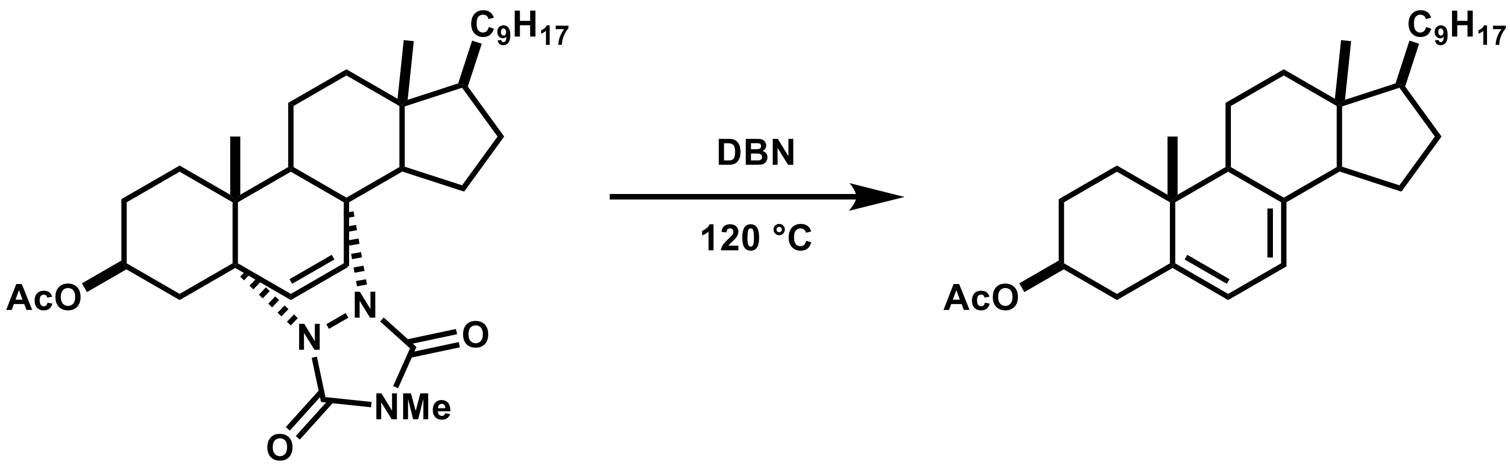
Corresponding methoxy protected acetal worked well.

• disubstituted arenes

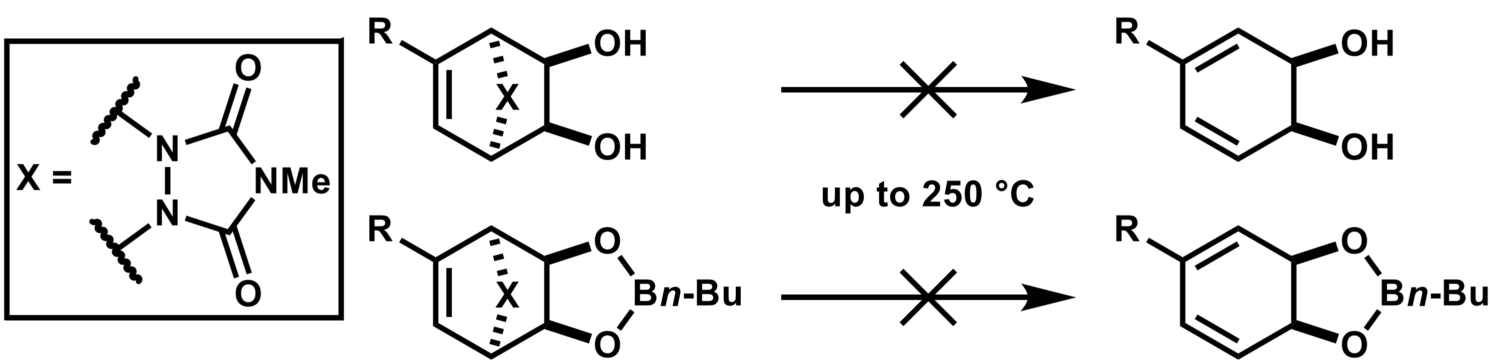


Attempts to Cycloreversion

Previous Research [1]

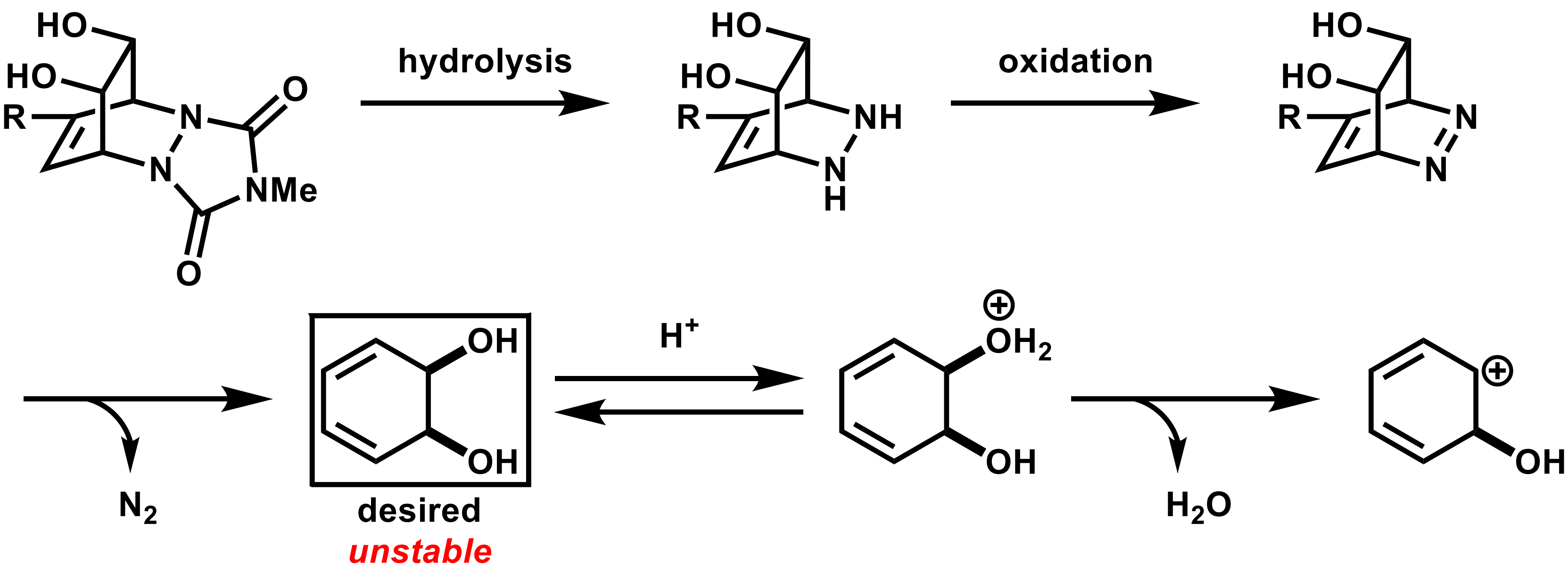


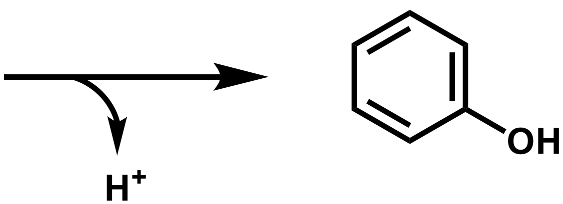
Attempted Cycloreversion



1) Rickborn, B. The retro-Diels–Alder reaction. Part II. Dienophiles with one or more heteroatoms. *Org. React.* 1998, *53*, 223.

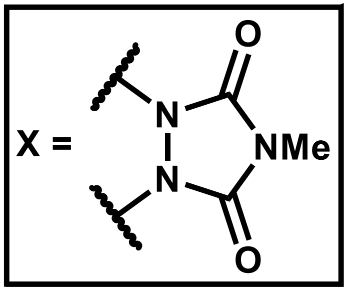
Attempts to Cycloreversion





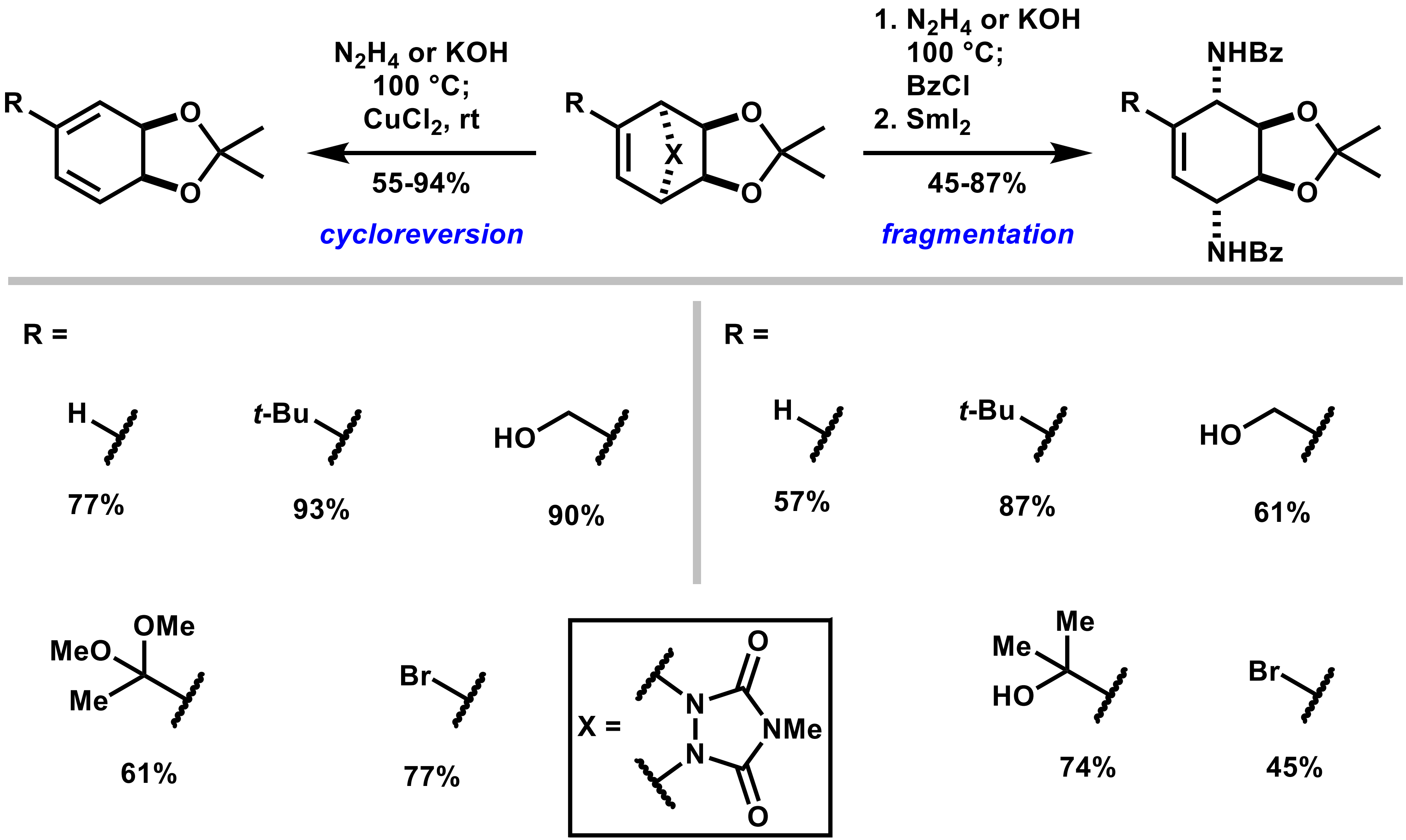
- phenol detected at oxidation step

-> protecting groups and oxidation conditions examined

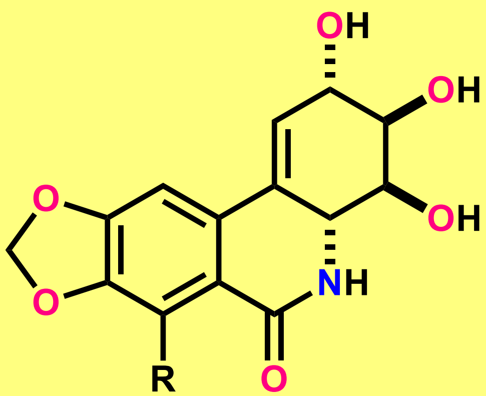


1) Lawlor, D. A.; Kudavalli, J. S.; MacCormac, A. C.; Coyne, D. A.; Boyd, D. R.; O'Ferrall, R. A. M. *J. Am. Chem. Soc.* **2011**, *133*, 19718.

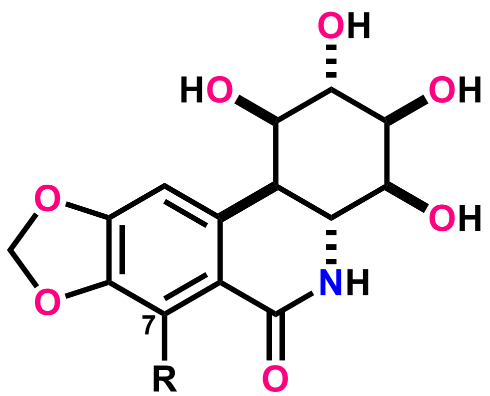
Conversion of Cycloadduct



Isocarbostyril Alkaloids



R = H: lycoricidine
R = OH: narciclasine

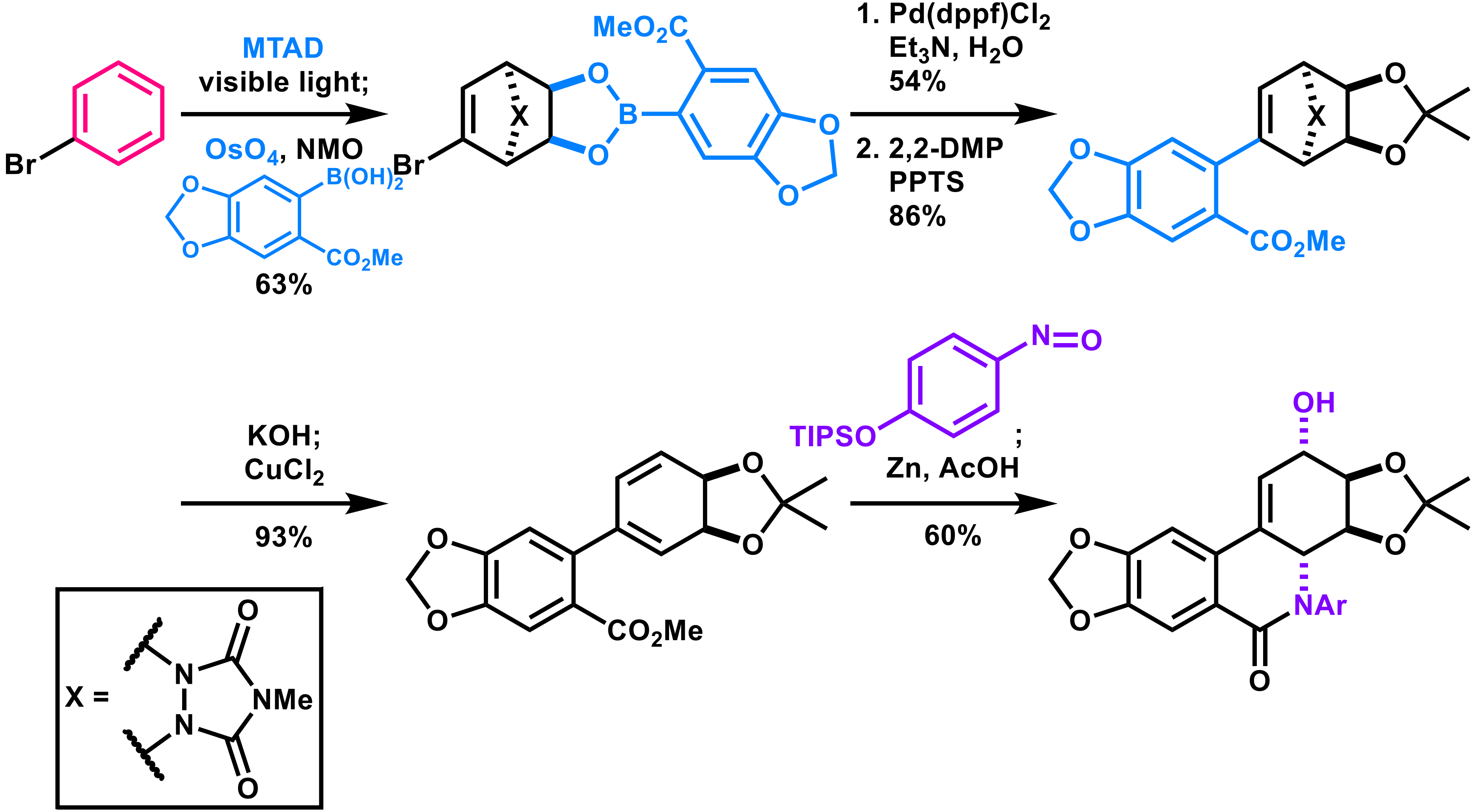


R = H: 7-deoxypancratistatin
R = OH: pancratistatin

Isolation	**Amaryllidaceae family of plants**
Bioactivity	**submicromolar inhibitory activity [1)] against multiple cancer cell lines**
Total synthesis	**lycoricidine: 15 total syntheses narciclasine: 6 total syntheses 7-deoxypancratistatin: 11 total syntheses pancratistatin:13 total syntheses**

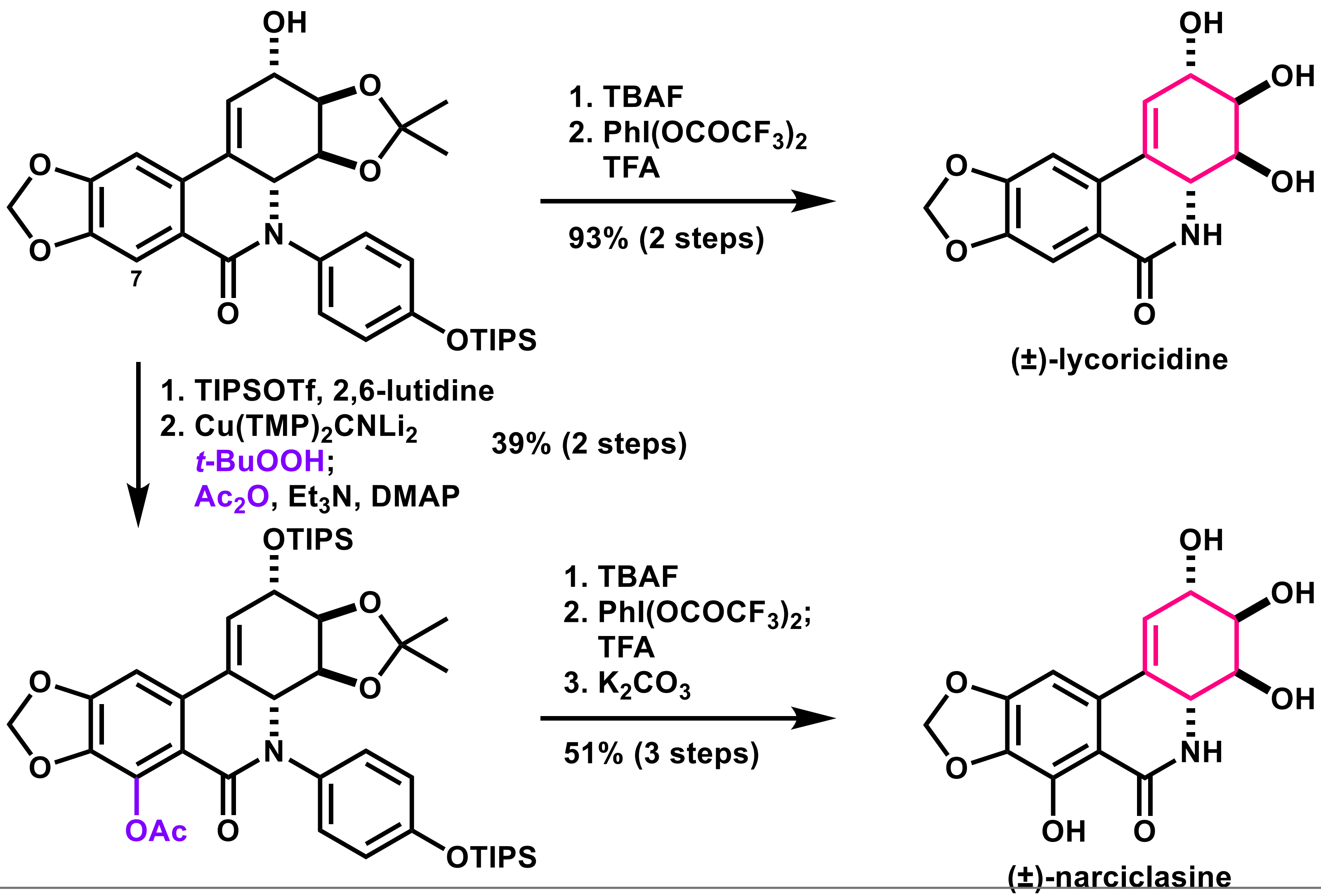
1) a) Kornienko, A.; Evidente, A. *Chem. Rev.* **2008**, *108*, 1982.
b) Ingrassia, F. Lefranc, V. Mathieu, F. Darro, R. Kiss, *Transl. Oncol.* **2008**, *1*, 1.

Application to Total Synthesis



1) Southgate, E. H.; Holycross, D. R.; Sarlah, D. *Angew. Chem. Int. Ed.* **2017**, *56*, 15049.

Total Synthesis of Lycoricidine and Narciclasine



1) Southgate, E. H.; Holycross, D. R.; Sarlah, D. *Angew. Chem. Int. Ed.* **2017**, *56*, 15049.

Contents

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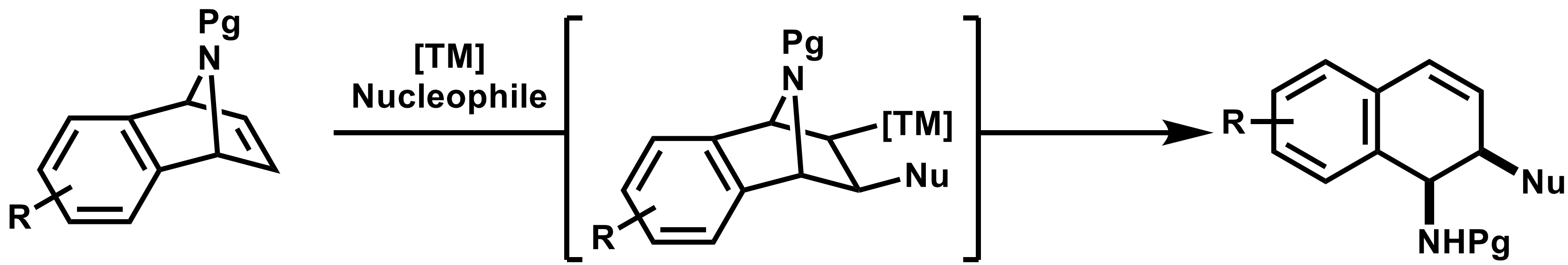
Palladium-Catalyzed Dearomative *syn*-1,4-Carboamination

Mikiko Okumura, Alexander S. Shved, and David Sarlah*

Reactions of Heterobicyclic Alkene

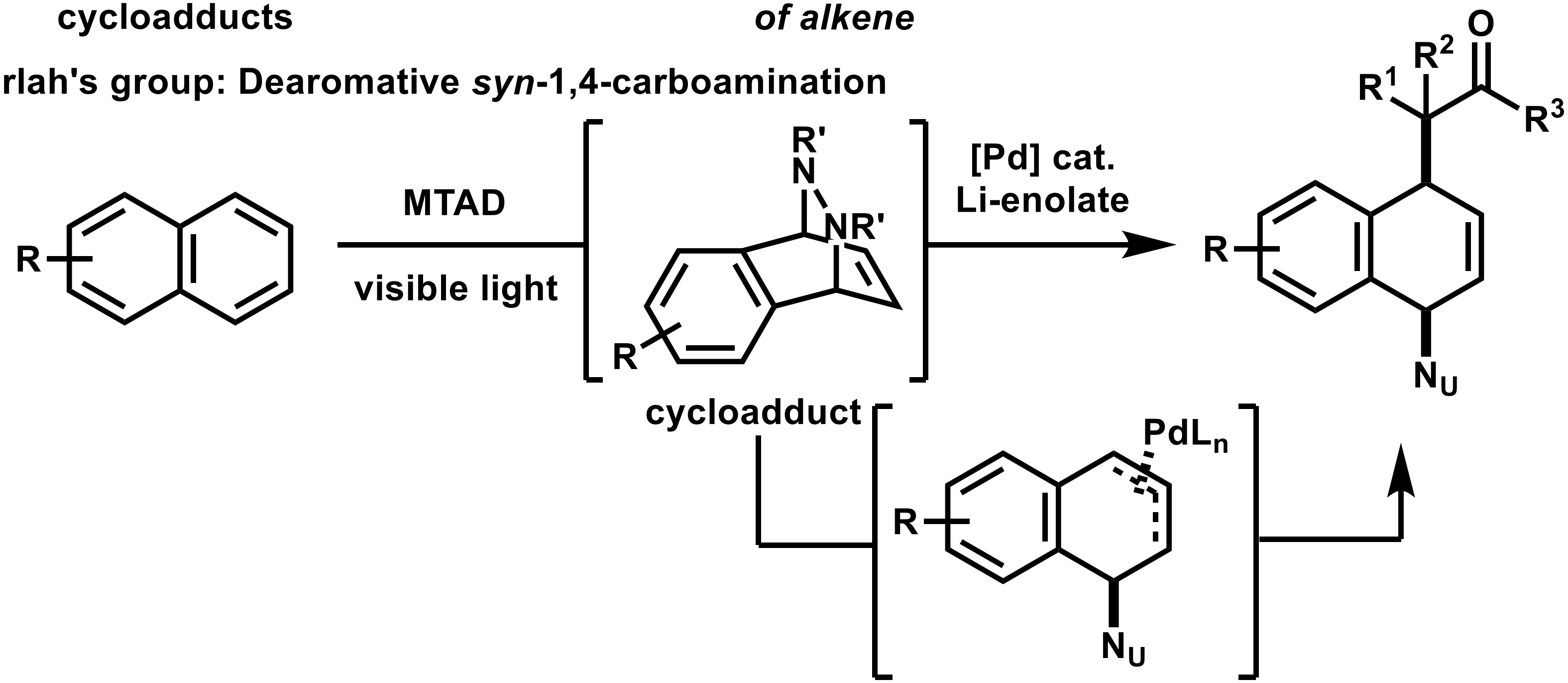
- Previous work: Formal dearomative *syn*-1,2-aminofunctionalization [1)]



benzyne-pyrrole cycloadducts

via nucleometalation of alkene

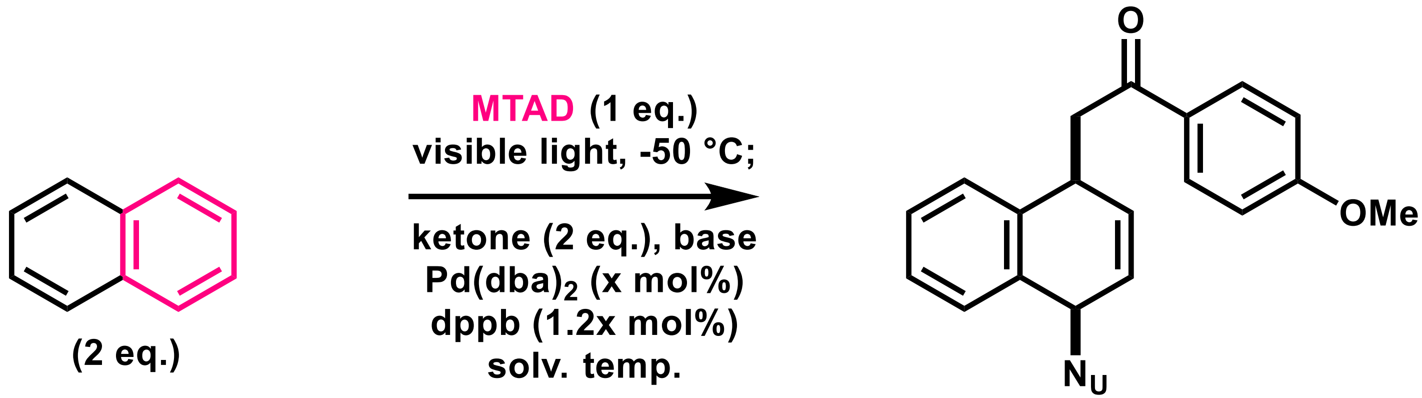
- Sarlah's group: Dearomative *syn*-1,4-carboamination



via Pd-cat. nuclephilic substitution

1) Lautens, M.; Fagnou, K.; Hiebert, S. *Acc. Chem. Res.* **2003**, *36*, 48.

Dearomative Carboamination

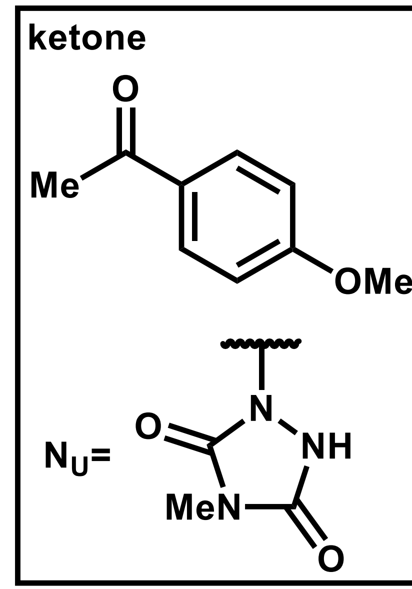


entry	[Pd] (mol%)	base	solv.	temp. (°C)	yield (%)[a]
1	5.0	LDA	CH_2Cl_2	-50	43
2	5.0	LDA	CH_2Cl_2	-30	72
3	5.0	LDA	CH_2Cl_2	-10	47
4	5.0	LiTMP	CH_2Cl_2	-30	44
5	5.0	LiHMDS	CH_2Cl_2	-30	58
6	5.0	LDA	EtCN	-30	85
7	2.5	LDA	EtCN	-50 to 0	91 (92)
8	2.5	LDA	EtCN	-50 to 0	82
9	2.5	LDA	EtCN	-50 to 0	85

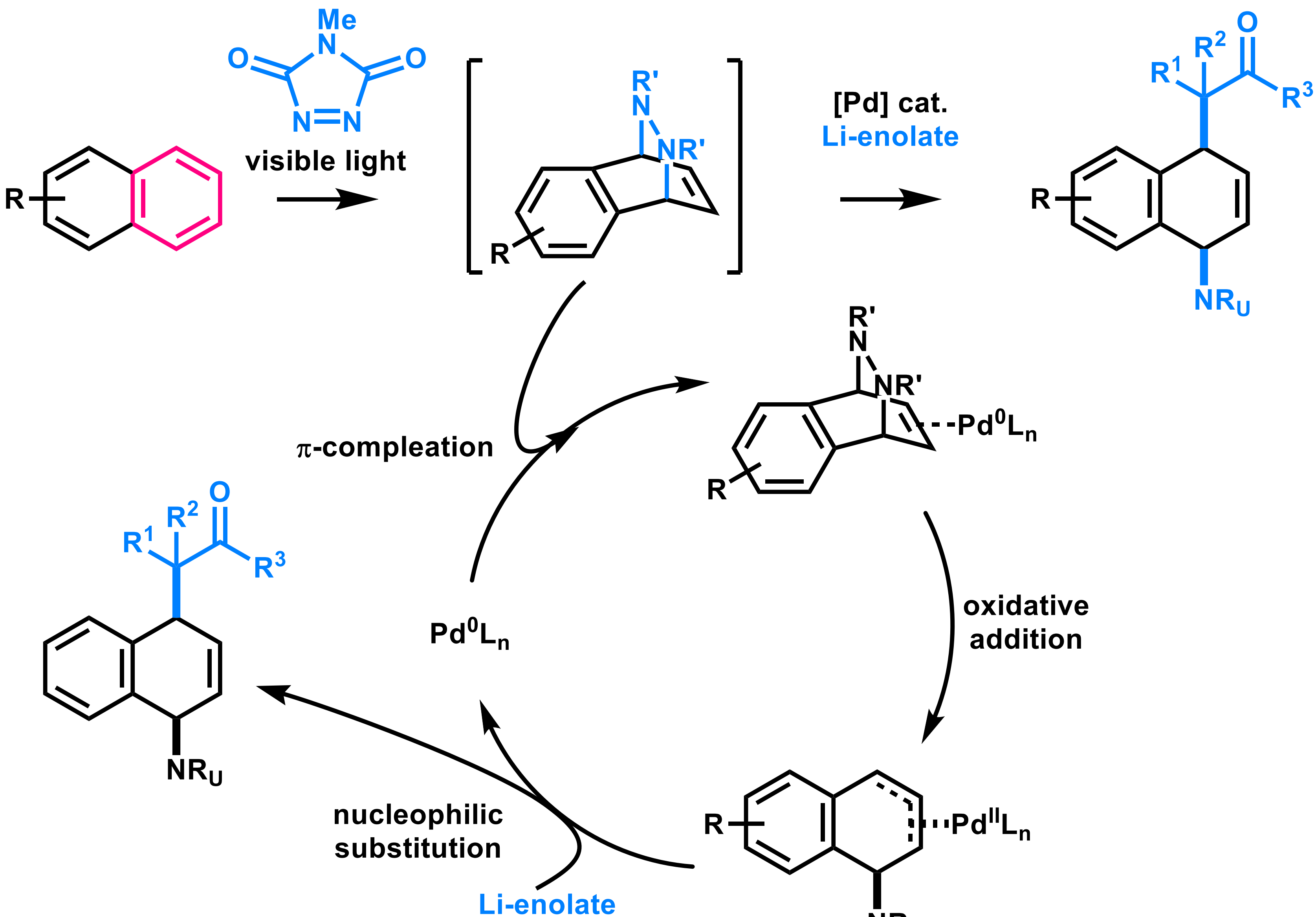
[a]NMR yield (isolated yield)

*enolate 1.4 eq. (entry 8)

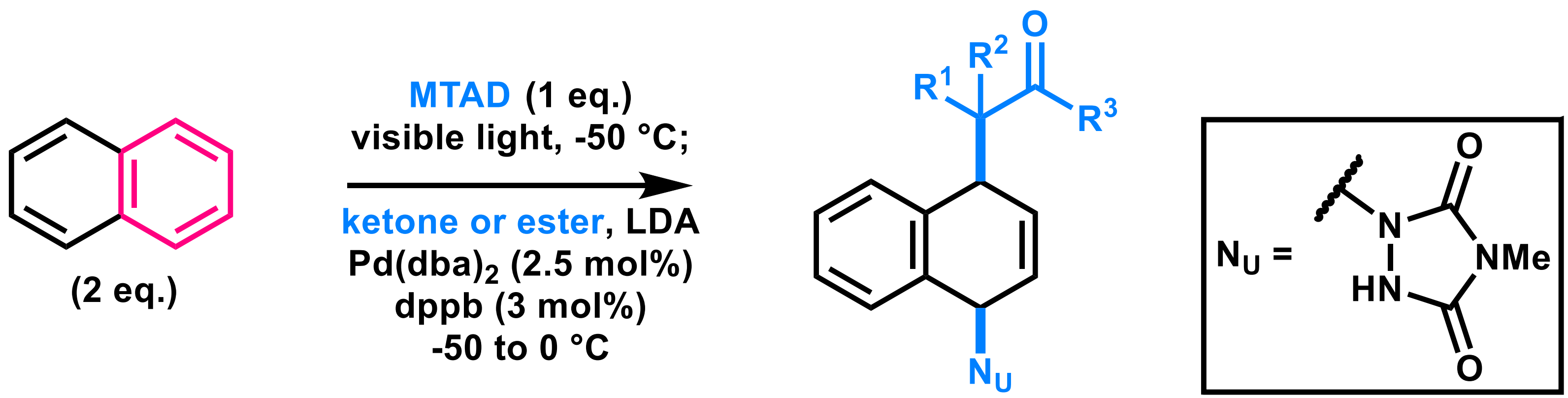
*naphthalene 1.5 eq. (entry 9)

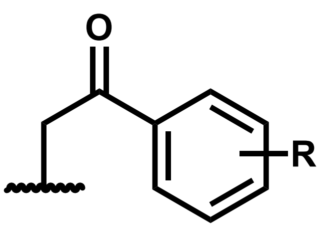


Reaction Mechanism

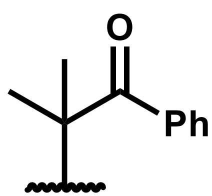


Ketone and Ester Scope

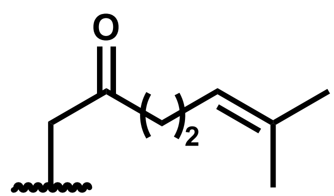




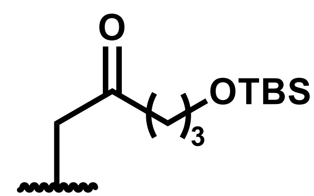
(R = *p*-OMe), 92%
(R = H), 81%
(R = *p*-I), 73%
(R = *p*-Br), 79%
(R = *p*-Cl), 80%
(R = *p*-CF$_3$), 80%
(R = *o*-Me), 85%



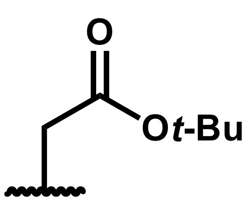
57%



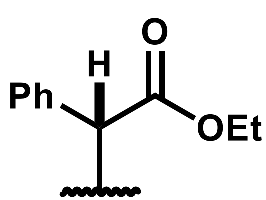
69%



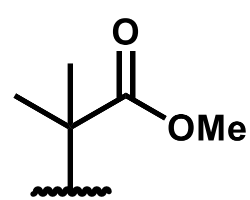
69%



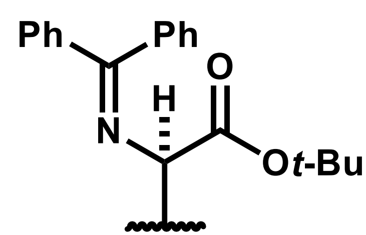
55%



75%, 6.3:1 dr

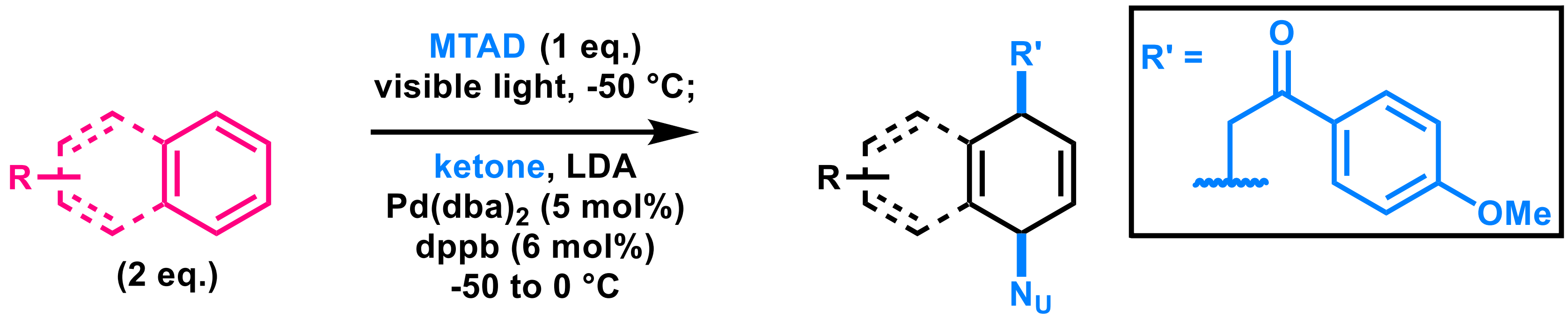


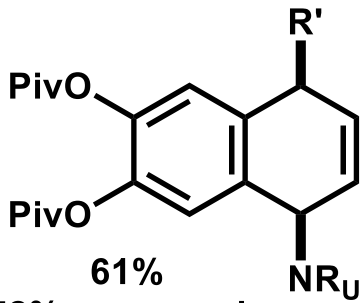
72%



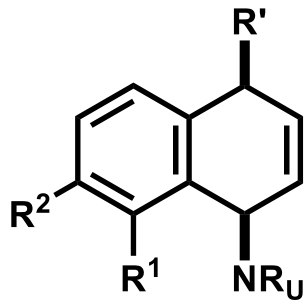
54%, 3:1 dr

Arene Scope

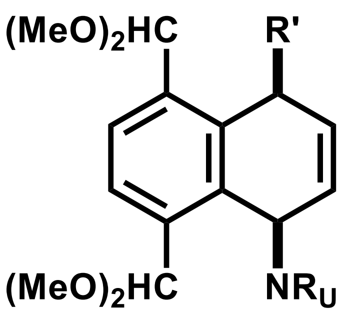




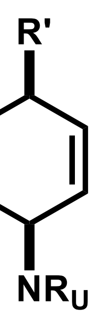
61%
52% gram scale



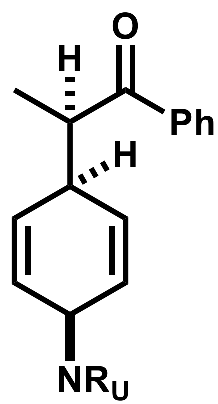
R^1 = *p*-CF_3-C_6H_4, R^2 = H, 62%. (2:1)
R^1 = TMS, R^2 = H, 42%. (1.4:1)
R^1 = CF_3, R^2 = H, 74%. (2:1)
R^1 = OPiv, R^2 = H, 54%. (3:1)
R^1 = H, R^2 = OPiv, 57%. (1:1)
R^1 = Br, R^2 = OPiv, 62%. (3:1)



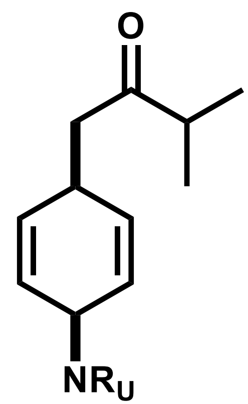
54%



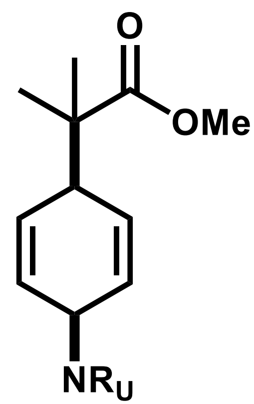
80%



86%
20:1 dr

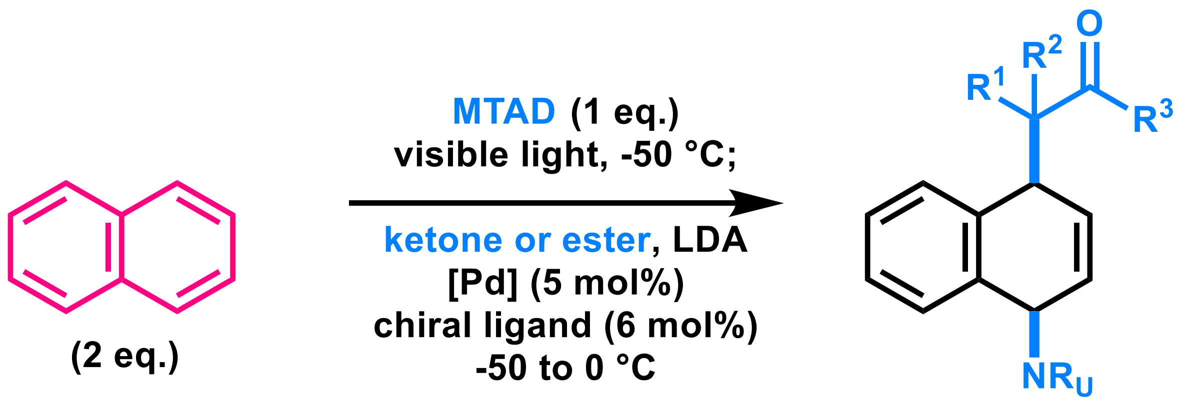


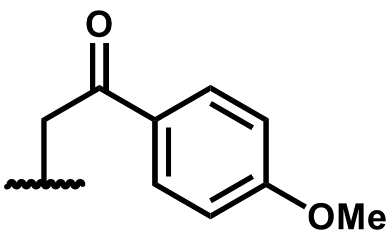
74%



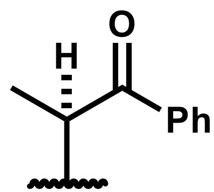
75%

Enantioselective Reaction

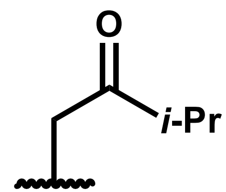




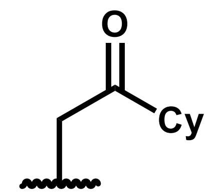
75%, 95:5 er



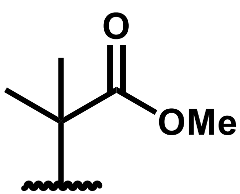
60%, 82:18 er
20:1 dr



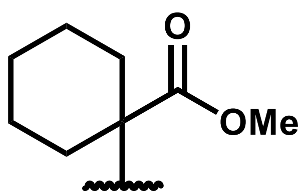
45%, 95:5 er



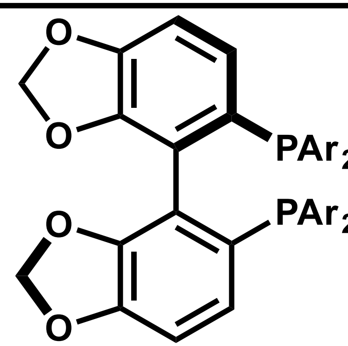
68% 97:3 er



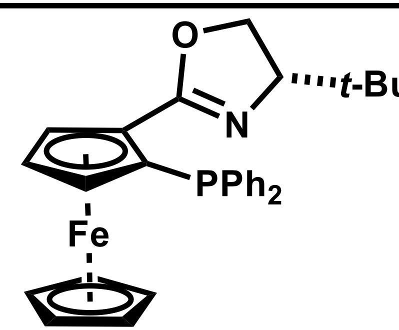
61% 95:5 er



72% 95:5 er

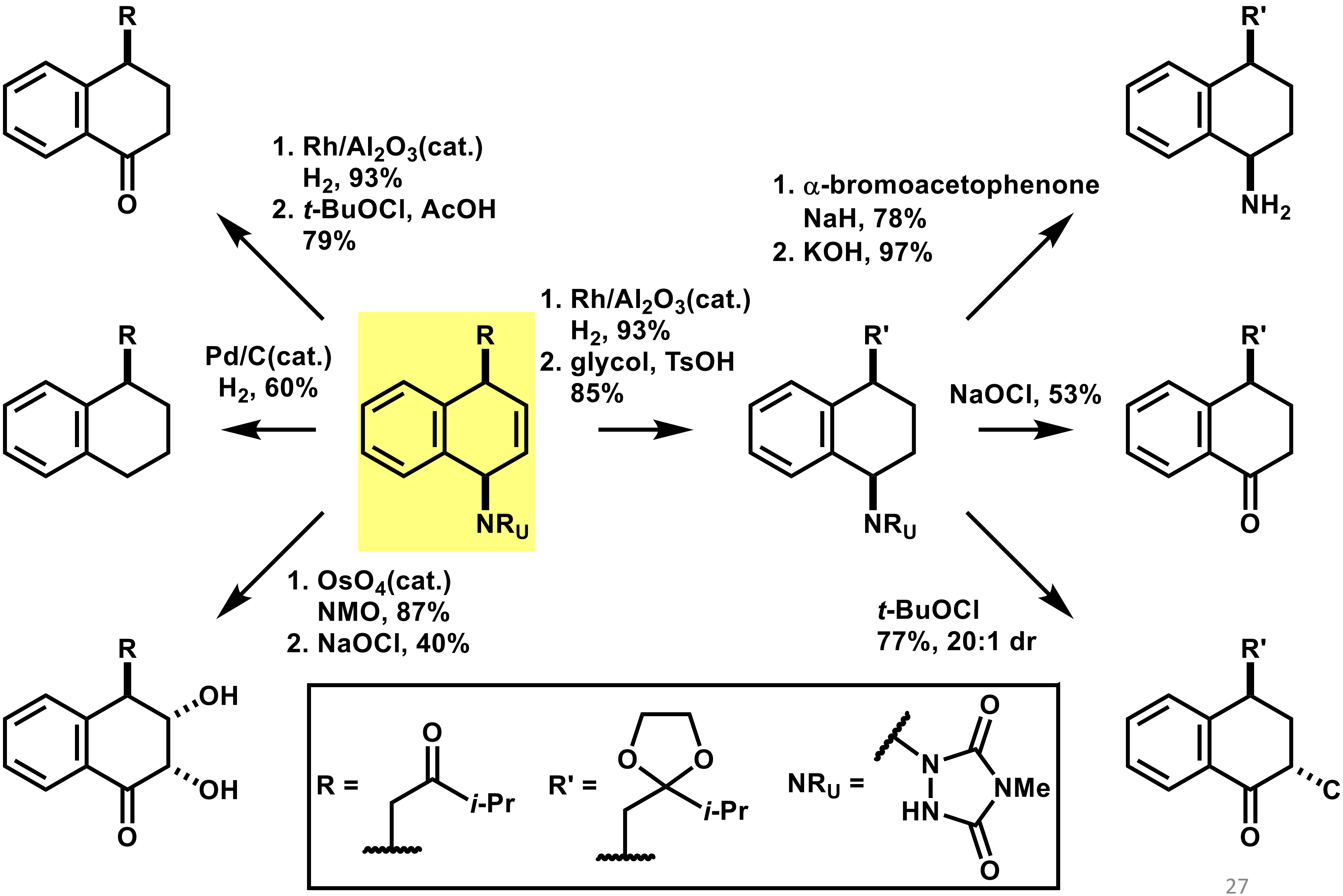


(*R*)-DTBM-SEGPHOS
for ester
(Ar = 3,5-di-*t*-Bu-4-OMe-C_6H_2)

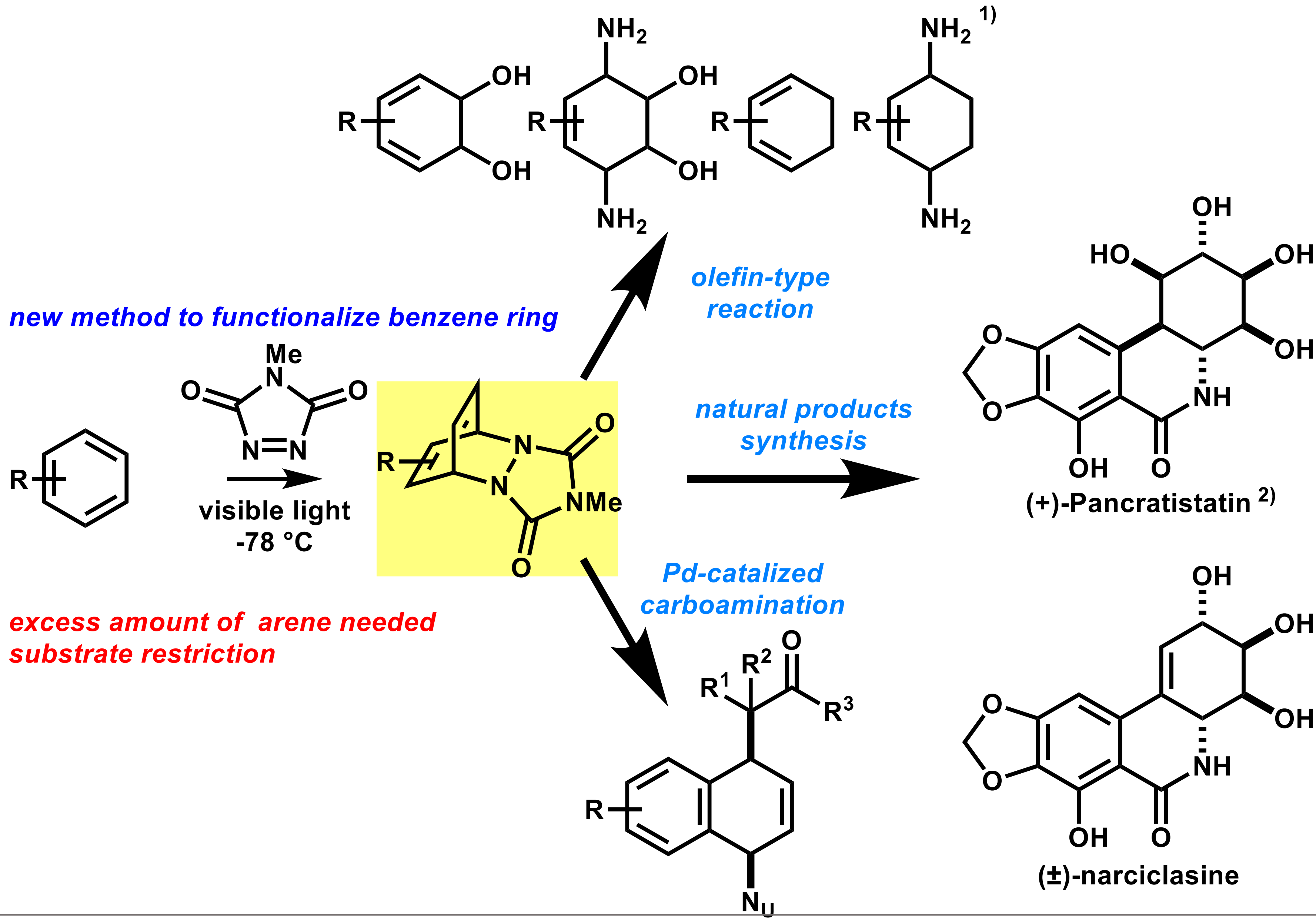


(S, S_p)-*t*-Bu-Phosferrox
for ketone

Application of Dearomative Carboamination



Summary

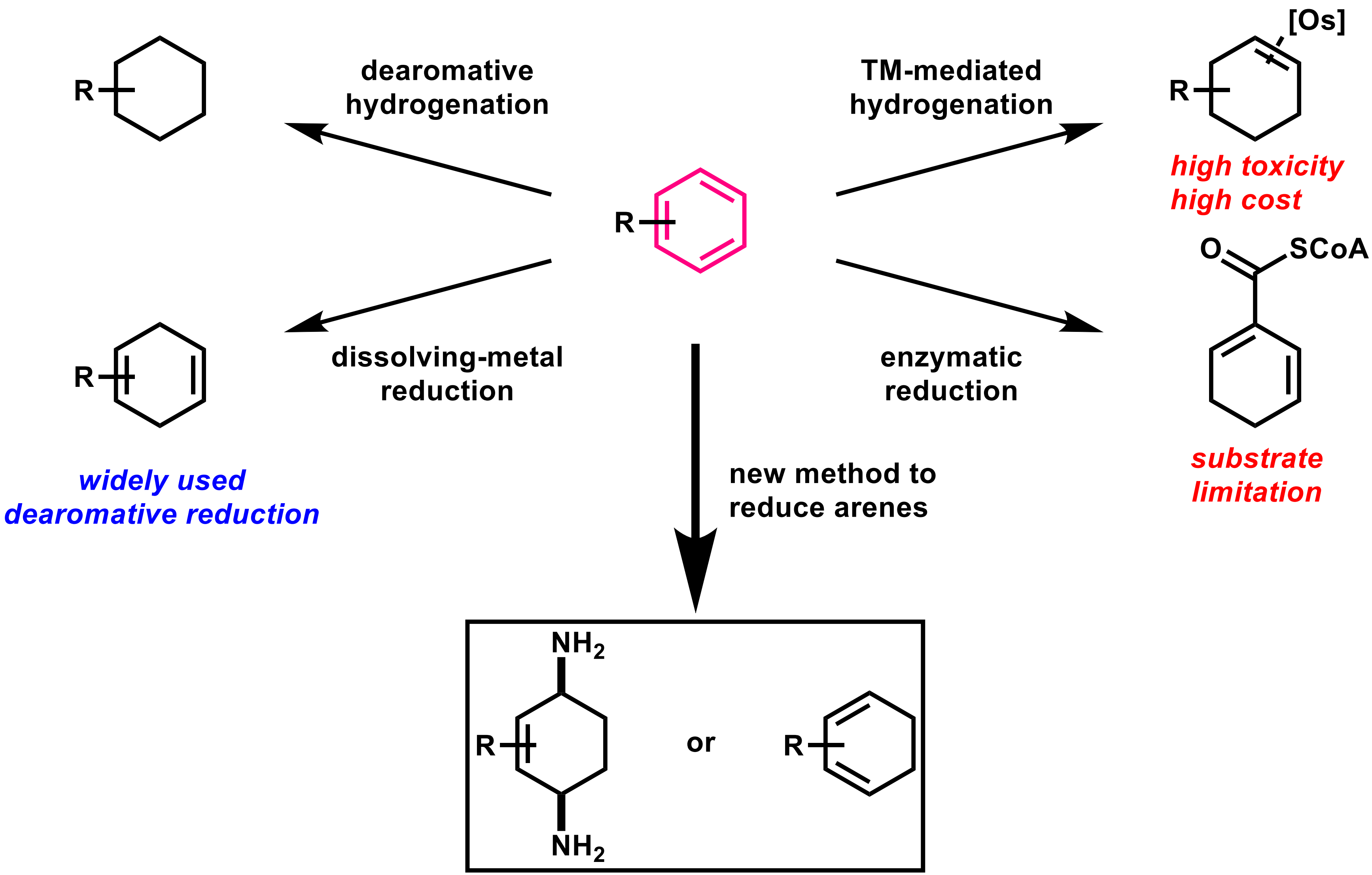


1) Okumura, M.; Huynh, S. M. N.; Pospech, J.; Sarlah, D. *Angew. Chem. Int. Ed.* **2016**, *55*, 15910.

2) Hernandez, L. W.; Pospech, J.; Klockner, U.; Bingham, T. W.; Sarlah, D. *J. Am. Chem. Soc.* **2017**, *139*, 15656

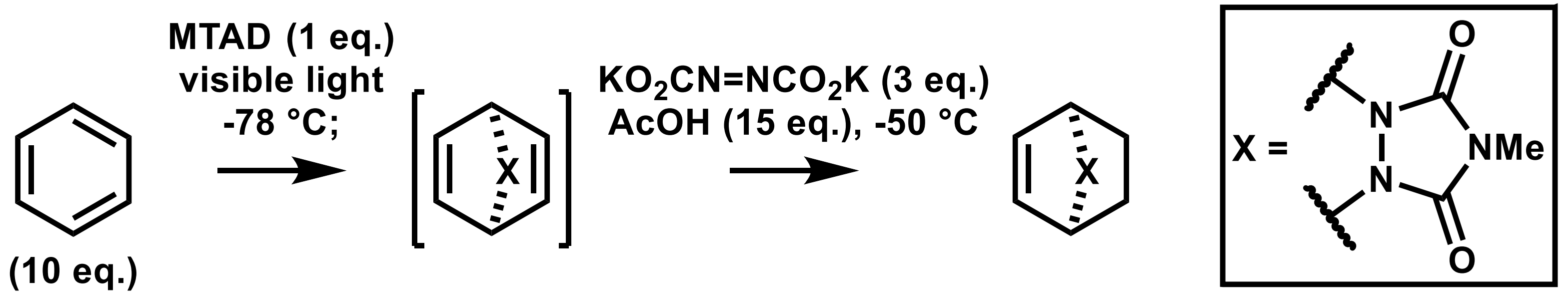
Appendix

Dearomative Reduction



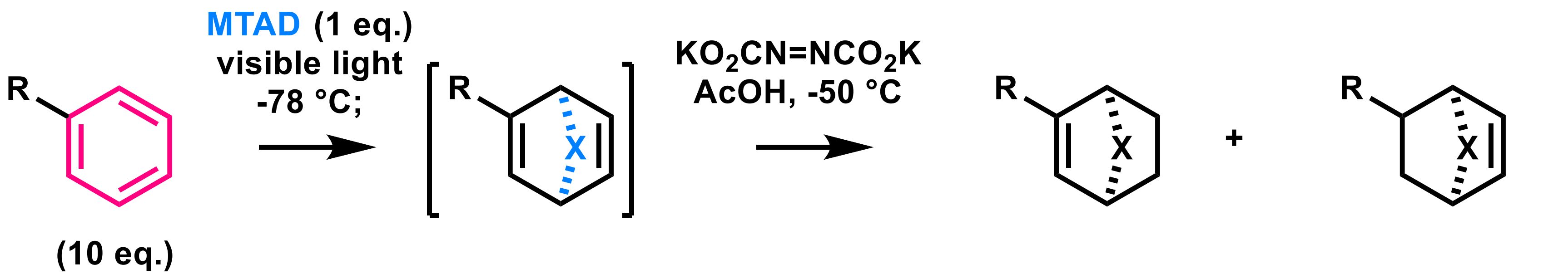
1)

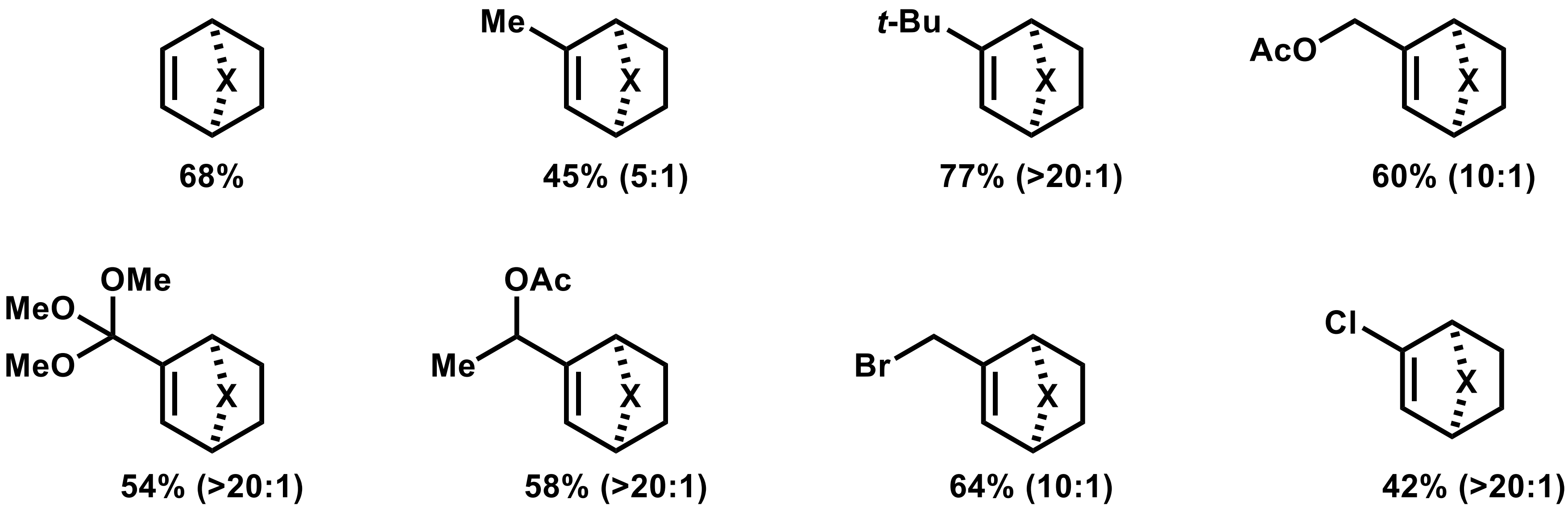
Dearomative Reduction



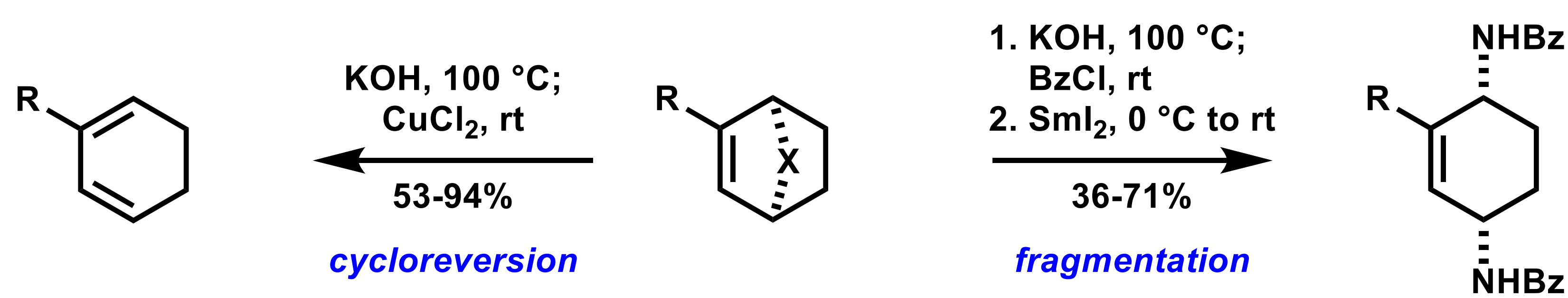
entry	deviation from standard conditions	yield (%)
1	none	65
2	diimide reduction at -78 °C	36
3	CH_2Cl_2 was used instead of EtOAc	61
4	acetone was used instead of EtOAc	31
5	EtCN was used instead of EtOAc	55
6	*o*-NO_2-C_6H_4-SO_2Cl, $N_2H_4 \cdot H_2O$ were used instead of $KO_2CN{=}NCO_2K$, AcOH	10
7	HCO_2H was used instead of AcOH	61
8	TFA was used instead of AcOH	16
9	with 10 eq. of AcOH	26
10	with 2 eq. of $KO_2CN{=}NCO_2K$	48

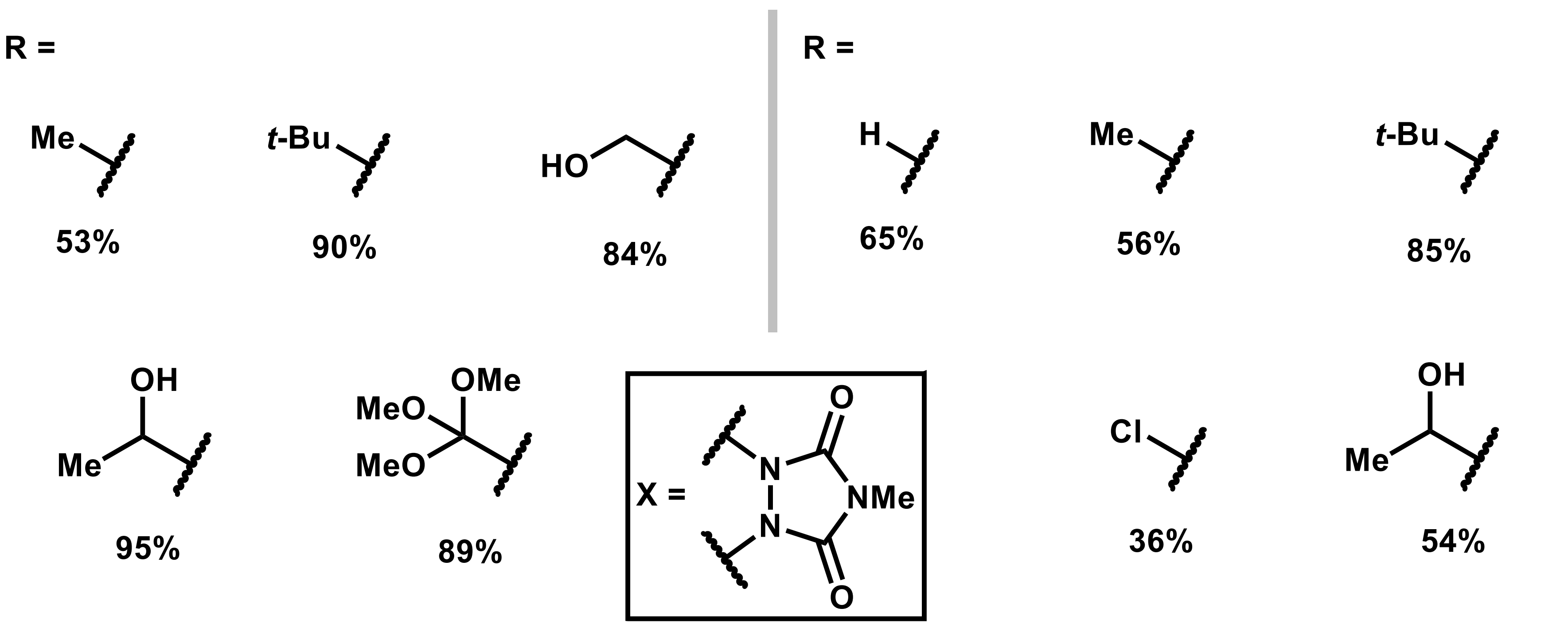
Dearomative Reduction



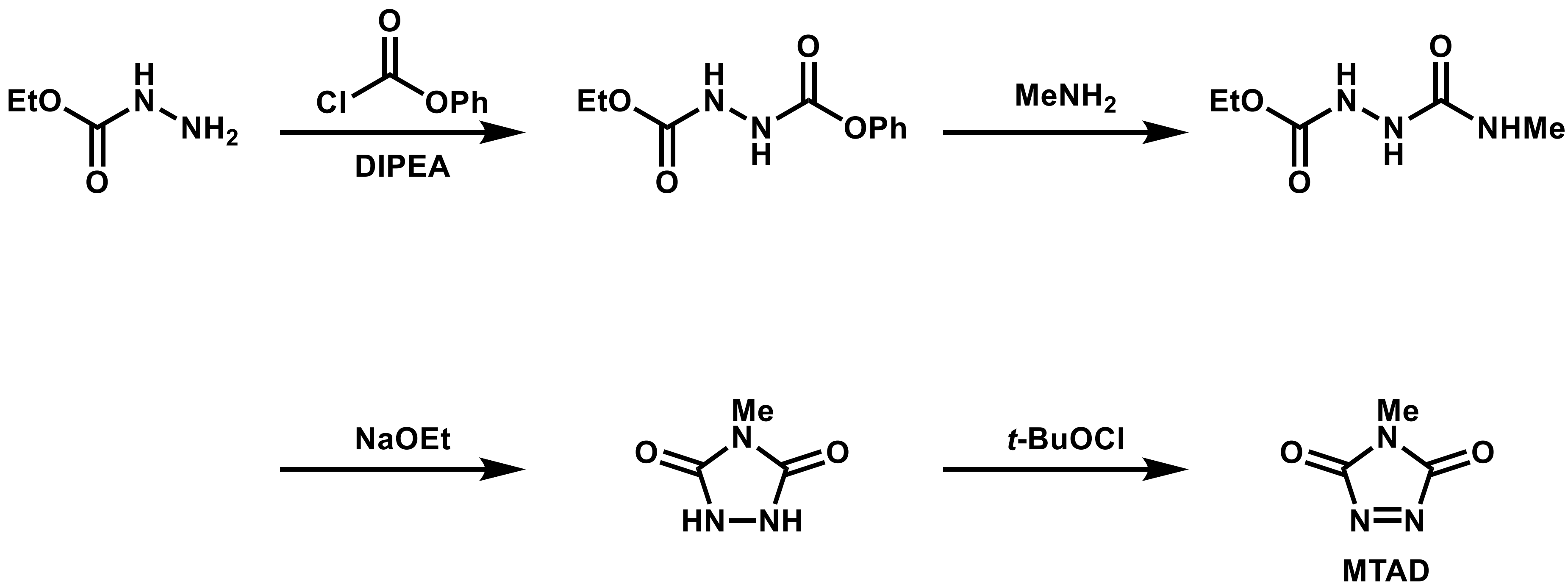


Conversion of Cycloadduct

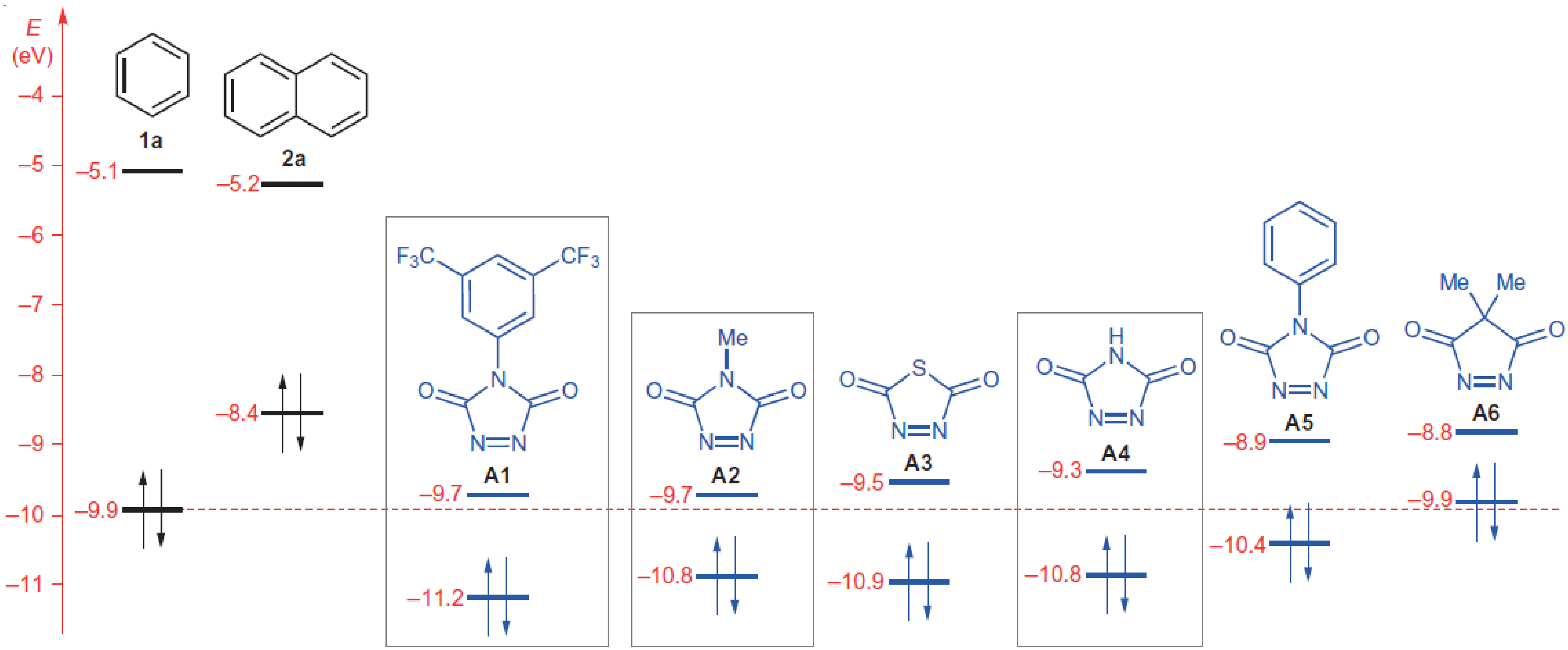




Preparation of MTAD



Caluclulation



Calculations were performed at University of Illinois using Gaussian 09 at the B3LYP level of density functional theory with the 6-31G(d) basis set.

All structures were fully optimized [B3LYP/6-311+G(d,p)] and verified to be local minima by the existence of no imaginary frequencies.

Frontier molecular orbital (FMO) energies were calculated using the DFT-based method that includes empirical linear correction factors to improve the accuracy of computed values.

Photoreaction

Figure 1. Large scale reaction

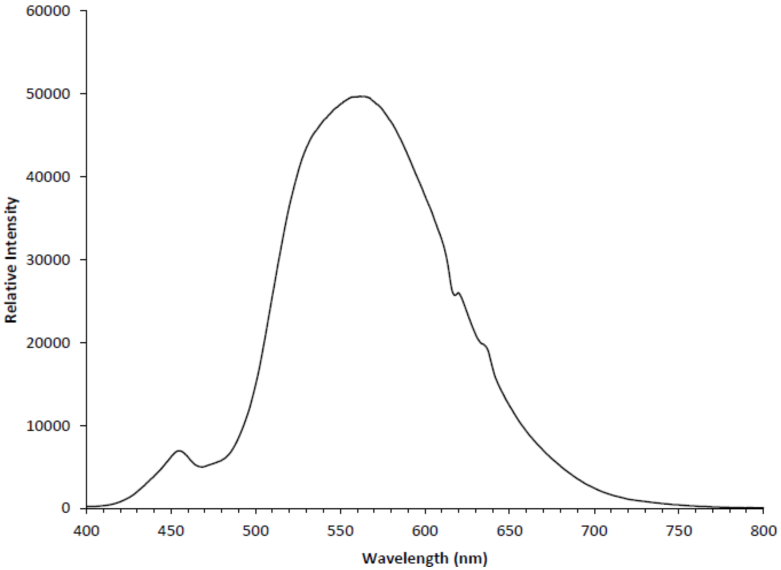


Figure 2. Spectrum of LED bulb

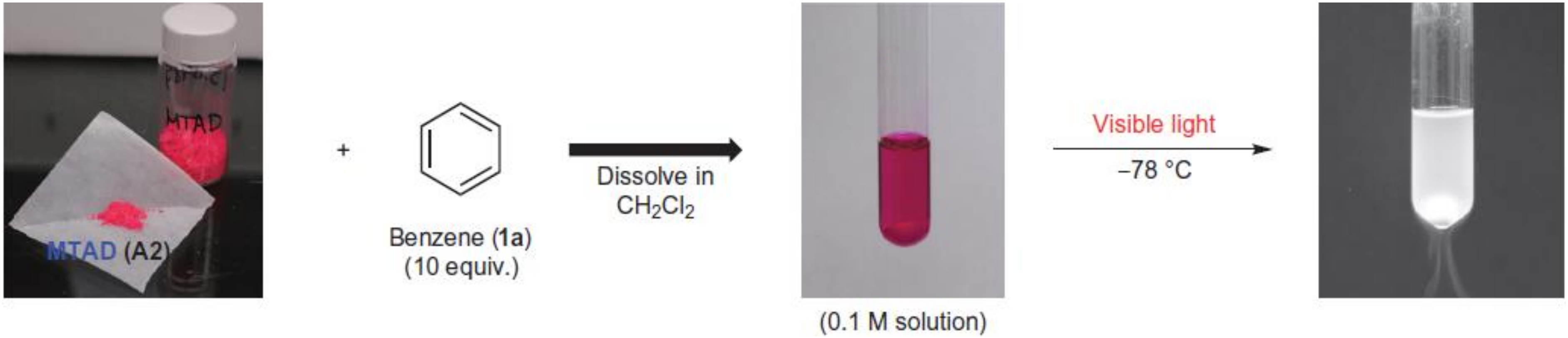
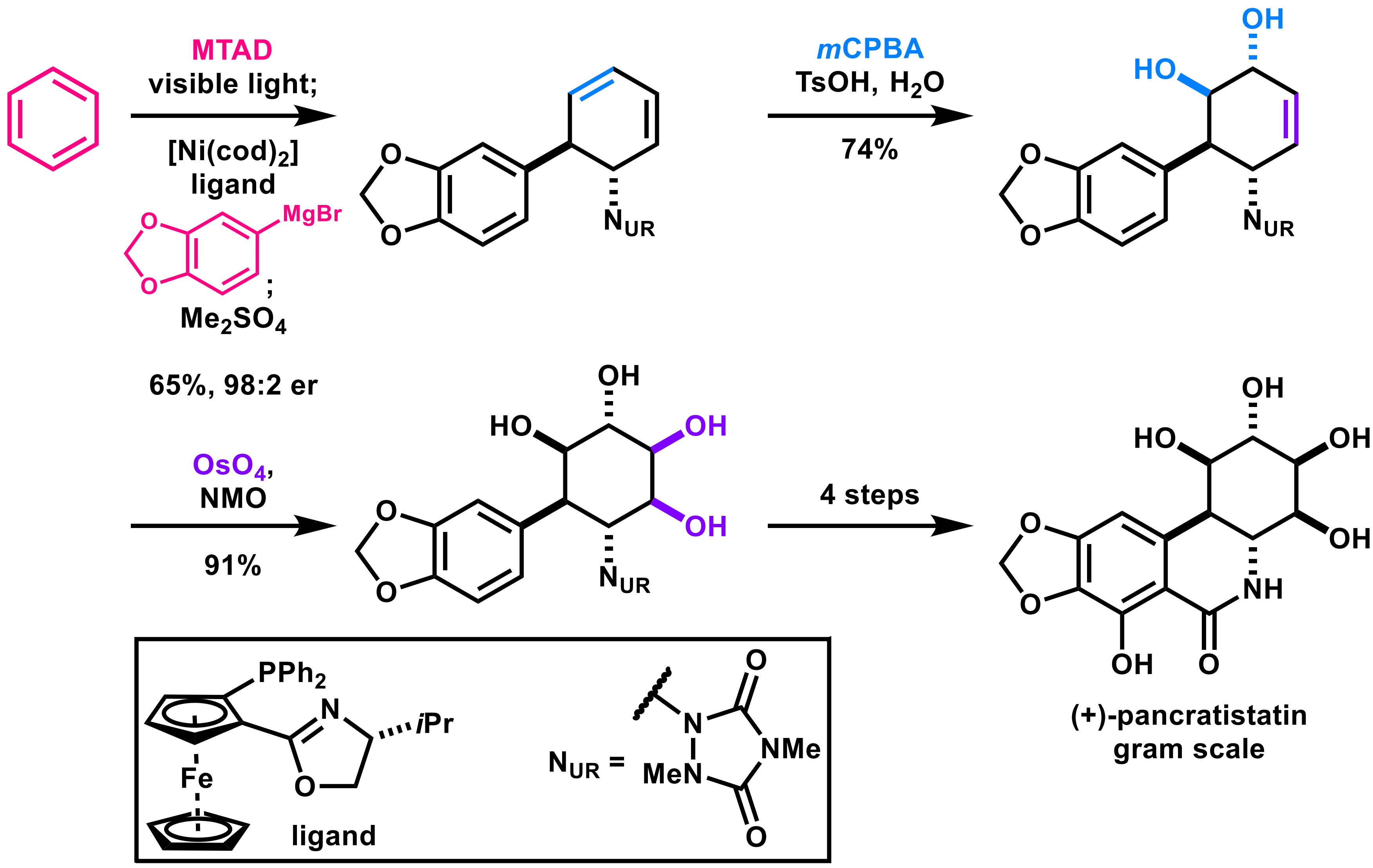
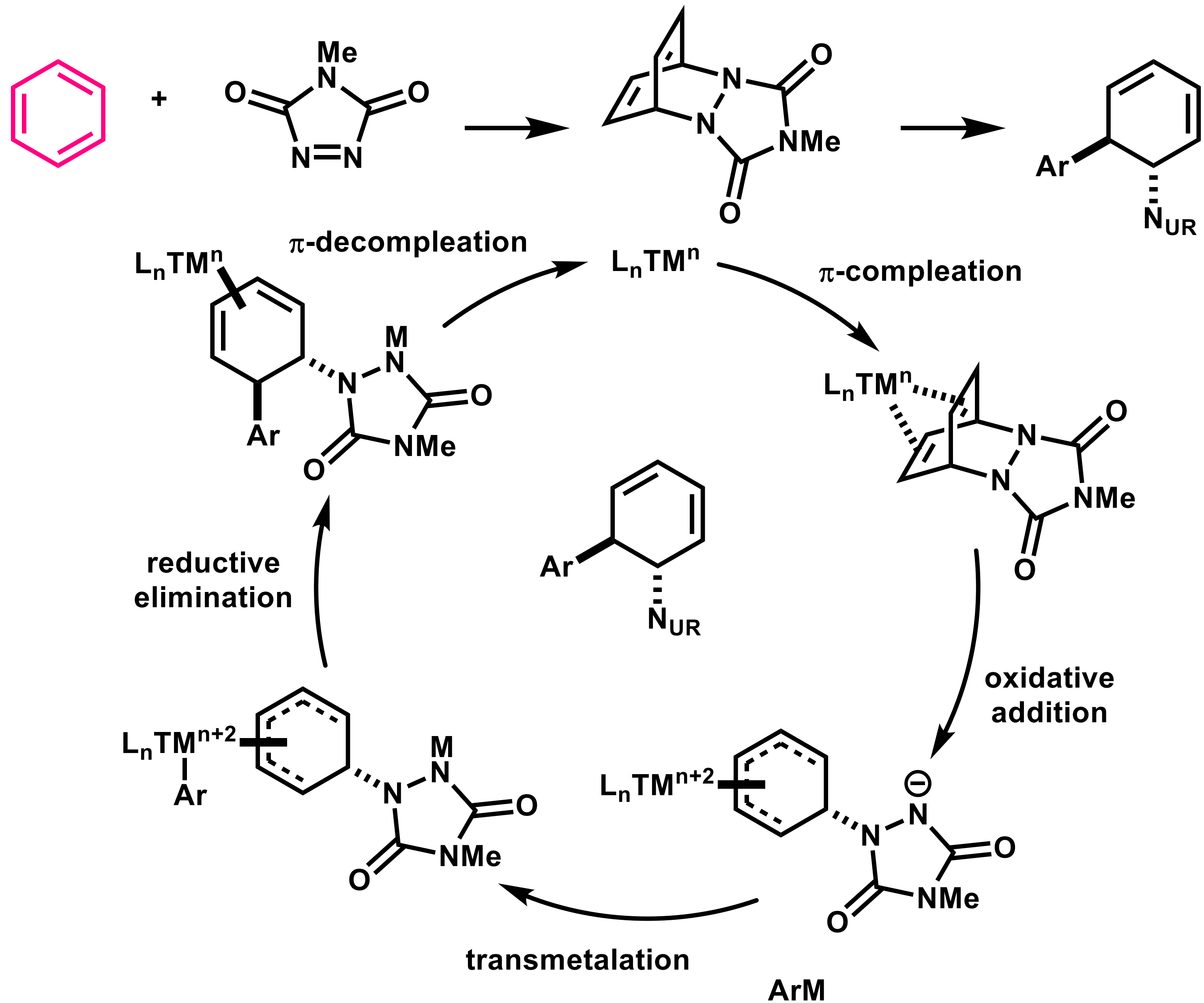


Figure 3. Before-after of photoreaction

Total Synthesis of (+)-Pancrastistatin



Carboamination



Application of Dearomative Reduction