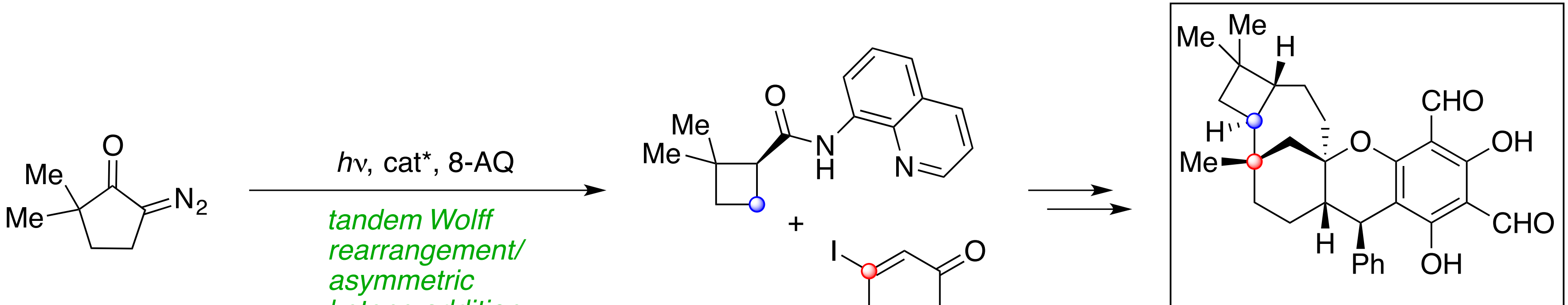
Enantioselective Total Synthesis of (+)-Psiguadial B



(+)-psiguadial B
HepG2 IC_{50} = 46 nM

L. M. Chapman, J. C. Beck, L. Wu, S. E. Reisman

J. Am. Chem. Soc. **2016**, *138,* 9803–9806

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Samuel Rieder, 9. Jan. 2017

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1997-2001	B.A. Conneticut College, New London, CT Supervisor: **Prof. Timo V. Ovsaka**
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2006-2008	NIH Postdoctoral Fello, Harvard University Cambridge, MA Supervisor: **Prof. Eric N. Jacobson**
2008-2014	Assistant Professor, CalTech, Pasadena, CA
2014-	Professor of Chemistry, CalTech

Research Interest
Natural Product Synthesis, Methods Development
Nickel Catalysis

http://reismangroup.caltech.edu/index.html

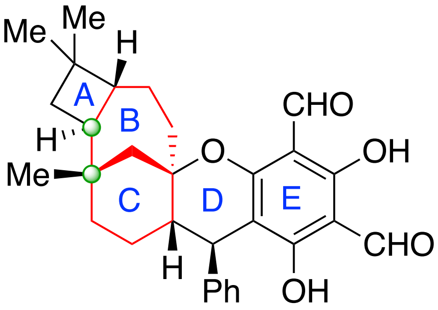
(+)-Psiguadial B

Information; Biosynthesis

- First enantioselective total synthesis
- Isolated by Shao in 2010 from *Psidium guajava*
- Exhibits potent antiproliferative activity against human hepatoma cells (HepG2 IC_{50} = 46 nM)

- *Hepatoma: Cancer originating in the liver, in liver cells. More often called hepatocarcinoma or hepatocellular carcinoma.*

- Biosynthesis → β-caryophyllene (sesquiterpenoid)
- Key Challenges
  - Bicyclo[4.3.1]decane *trans*-fused to cyclobutane
  - Synthesis of A–B–C ring system
  - Strategic formation of C1–C2 bond
  - Control of enantioselectivity

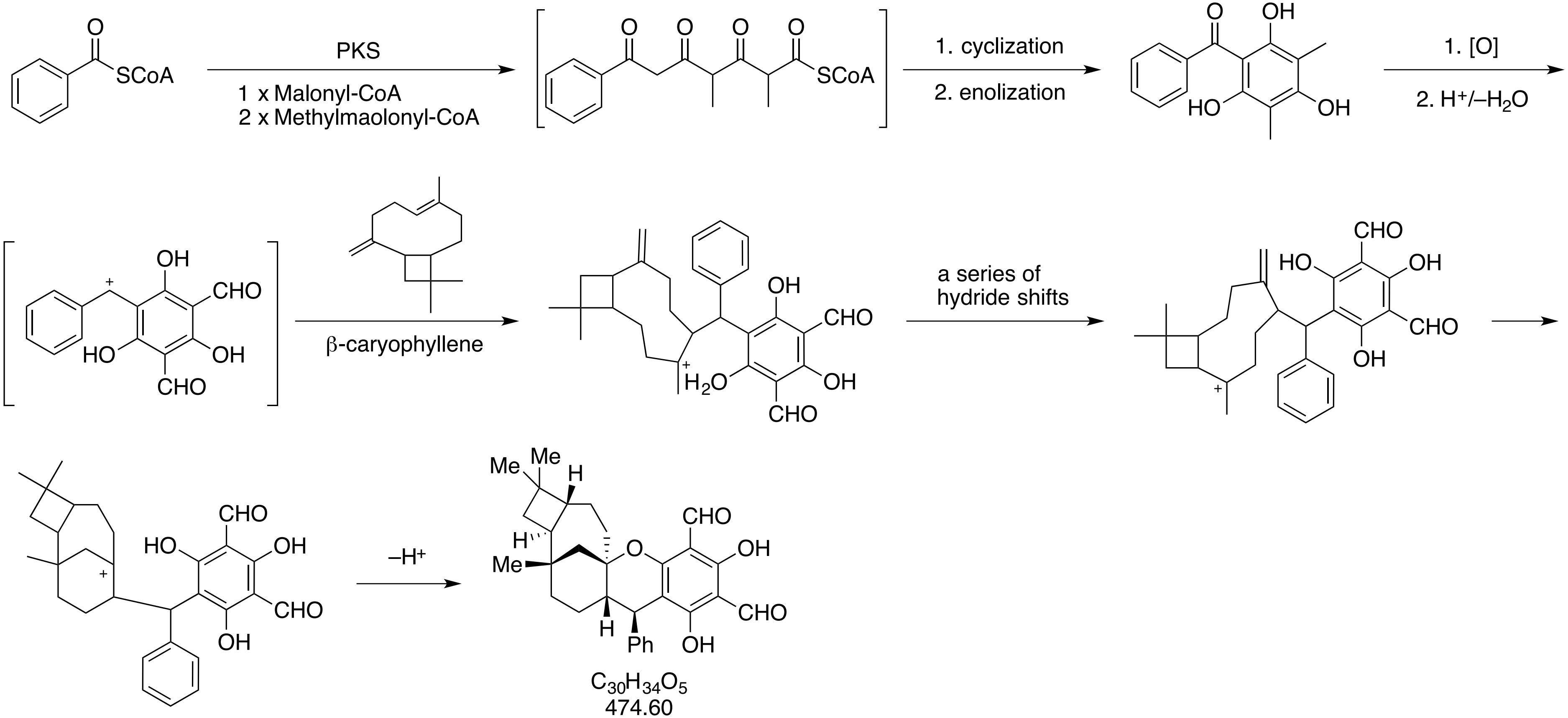


$C_{30}H_{34}O_5$
474.60

M. Shao, et al., *Org. Lett.* **2010**, *12*, 5040–5043

(+)-Psiguadial B

Biosynthesis

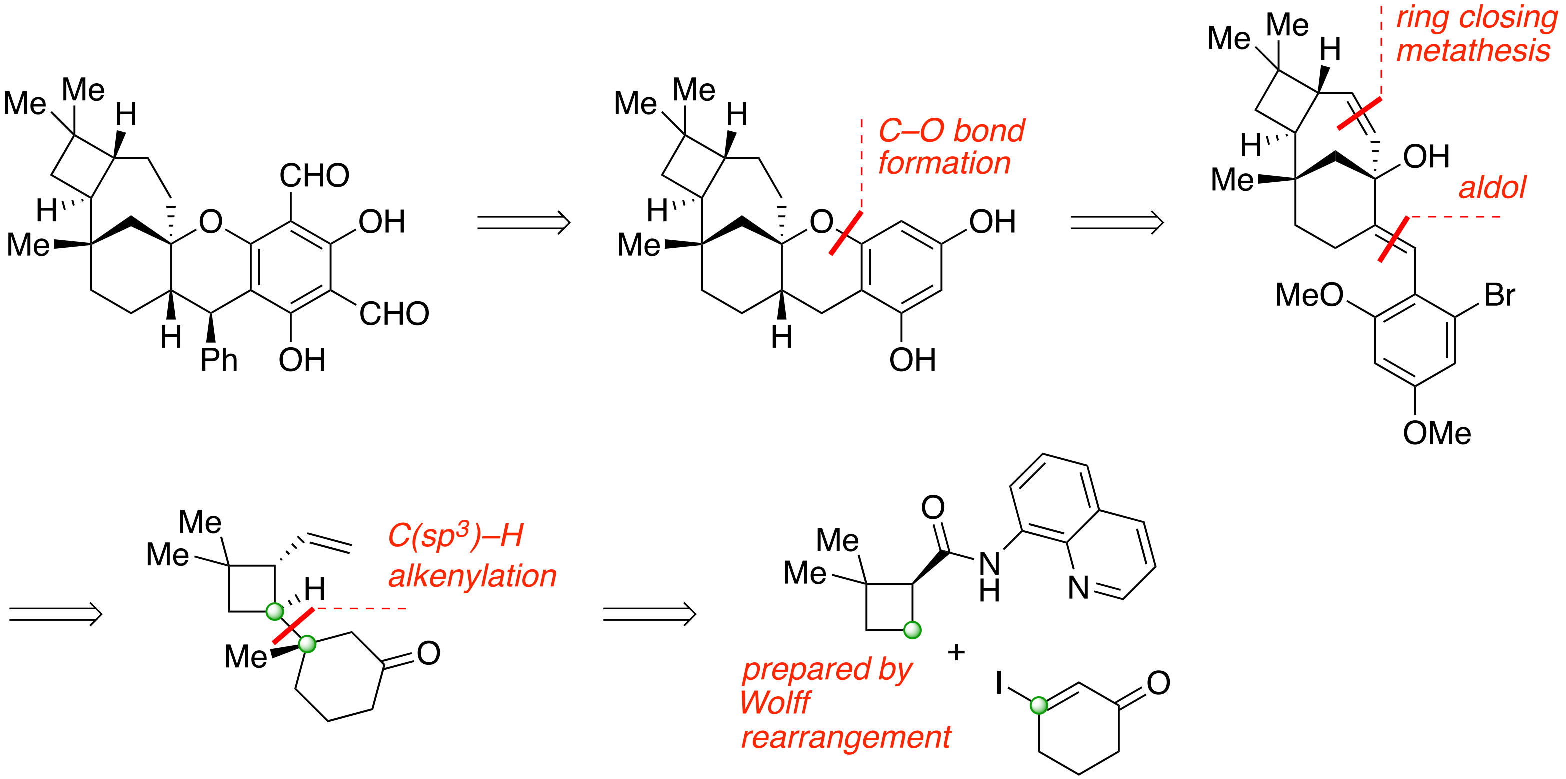


$C_{30}H_{34}O_5$
474.60

M. Shao, et al., *Org. Lett.* **2012**, *14*, 5262–5265.

(+)-Psiguadial B

Retrosynthetic Analysis



C–O bond formation

ring closing metathesis

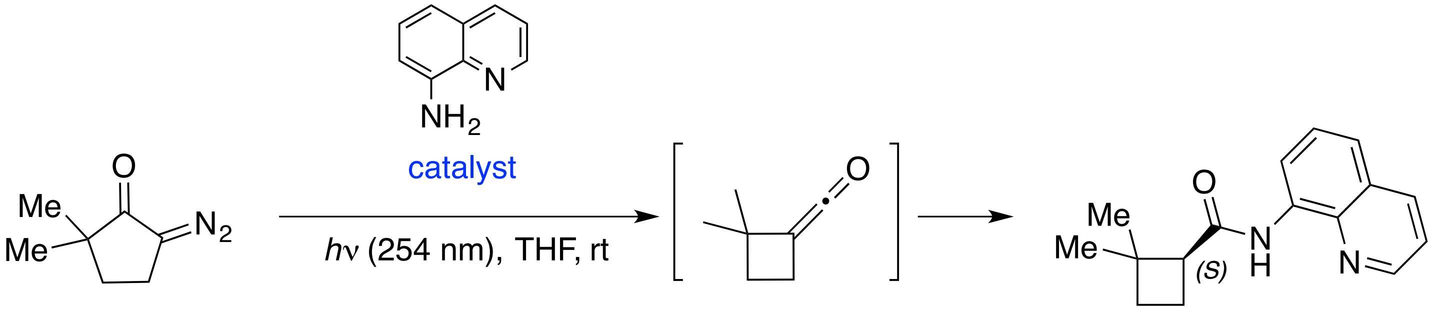
aldol

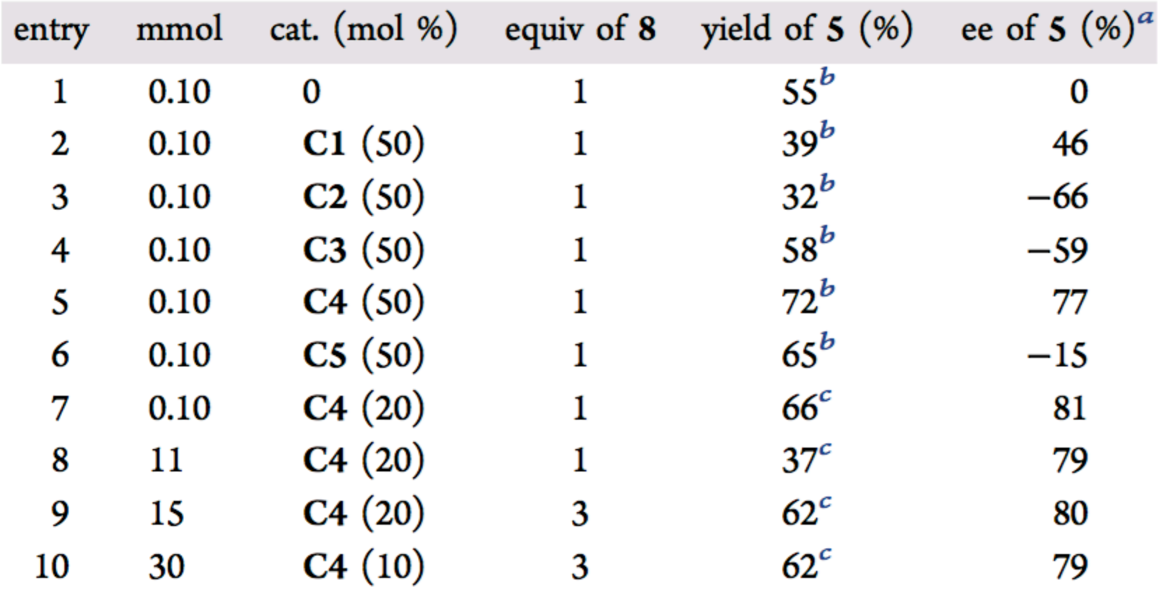
C(sp^3)–H alkenylation

prepared by Wolff rearrangement

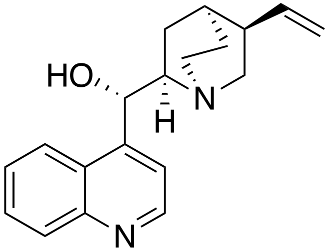
Synthesis I

Optimisation of the Tandem Wolff Rearrangement





entry	mmol	cat. (mol %)	equiv of **8**	yield of **5** (%)	ee of **5** (%)[a]
1	0.10	0	1	55[b]	0
2	0.10	C1 (50)	1	39[b]	46
3	0.10	C2 (50)	1	32[b]	−66
4	0.10	C3 (50)	1	58[b]	−59
5	0.10	C4 (50)	1	72[b]	77
6	0.10	C5 (50)	1	65[b]	−15
7	0.10	C4 (20)	1	66[c]	81
8	11	C4 (20)	1	37[c]	79
9	15	C4 (20)	3	62[c]	80
10	30	C4 (10)	3	62[c]	79

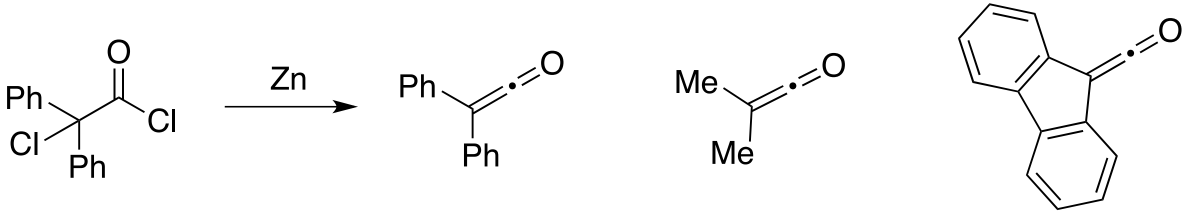


(+)-cinchonine (C4)

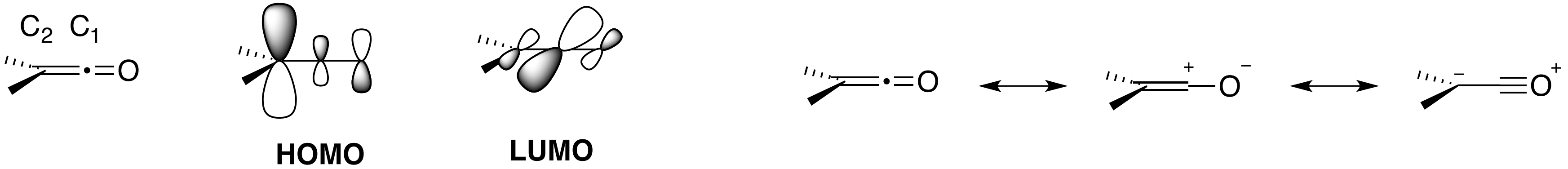
M. Shao, et al., *Org. Lett.* **2012**, *14*, 5262–5265.

Side-Discussion on Ketenes
History; Properties

- Hermann Staudinger



- Reactivity

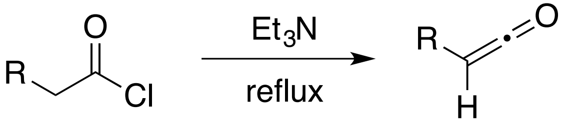


- Electrophile (at C_2 or O): perpendicular to the ketene plane
- Nucleophile (at C_1): in ketene plane

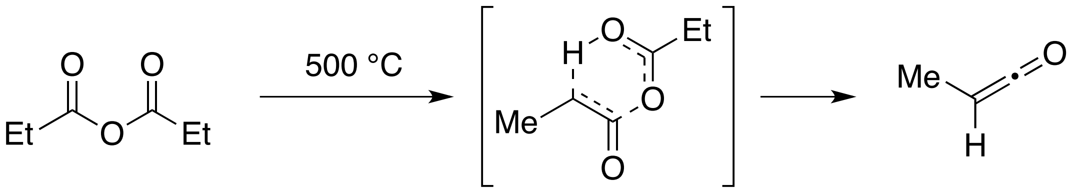
T. T. Tidwell, *Ketenes II*, John Wiley & Sons, Inc., Hoboken, NJ, USA, **2006**.

Side-Discussion on Ketenes
Preparation from Carboxylic Acid Derivatives

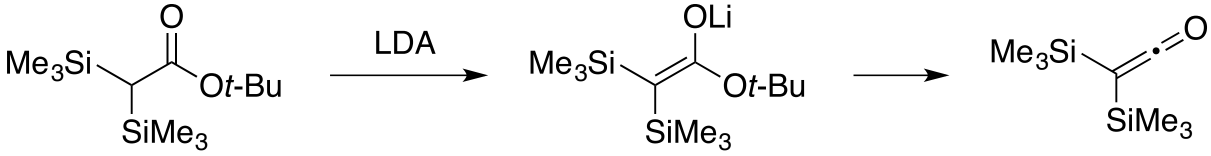
- α-halo carboxylic derivatives (Staudinger)
- Acyl chlorides (Wedekind)



- Anhydrides



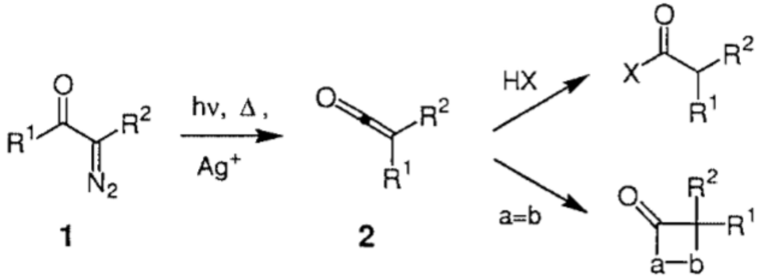
- Esters (E1cB)



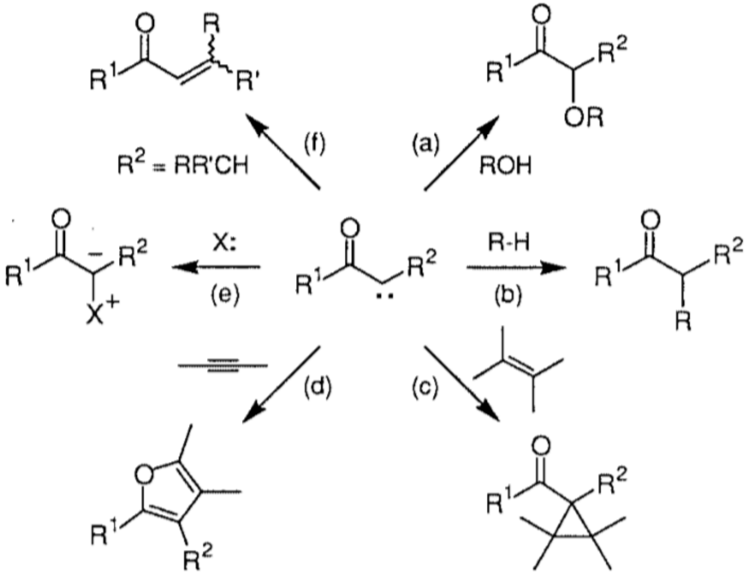
Side-Discussion on Ketenes

Wolff Rearrangement

- Ludwig Wolff (**1902**)



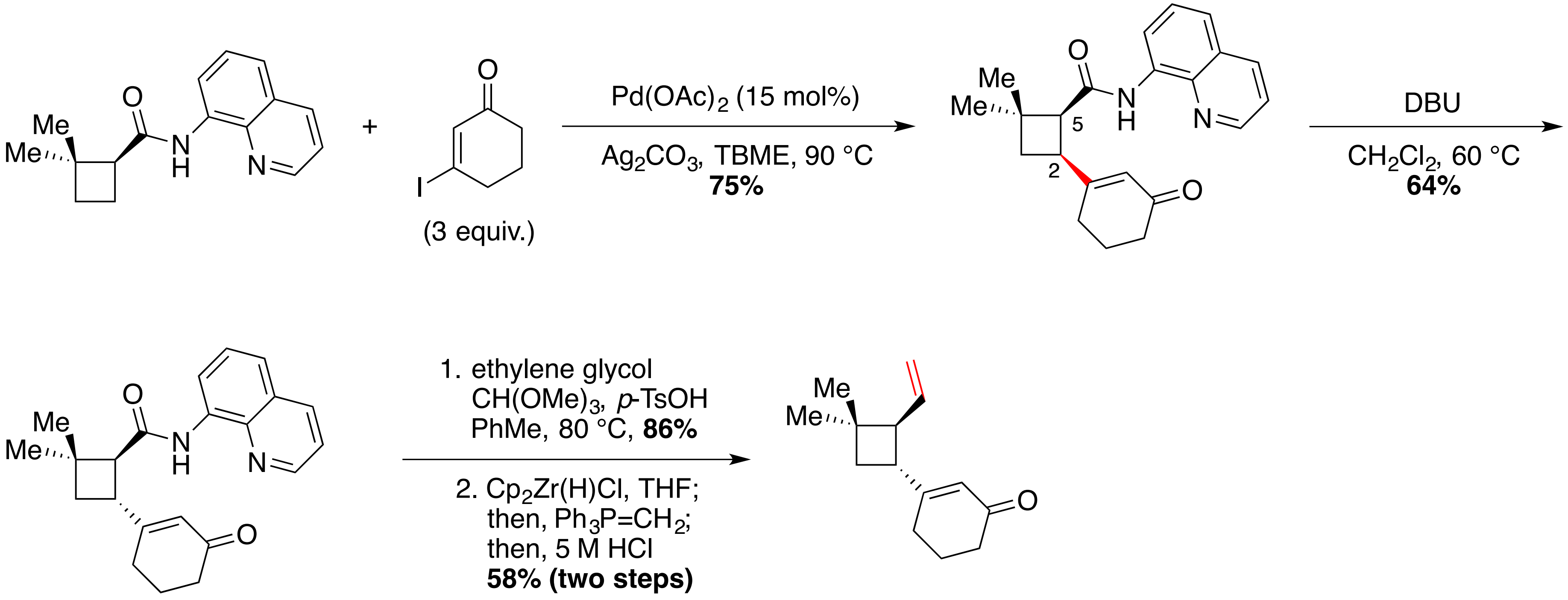
- Reactions of carbonylcarbenes that can compete with the Wolff rearrangement



W. Kirmse, *Eur. J. Org. Chem.* **2002**, *2002*, 2193.

Synthesis II

C(sp^3)-alkenylation; Epimerization I



$Pd(OAc)_2$ (15 mol%)
Ag_2CO_3, TBME, 90 °C
75%

DBU
CH_2Cl_2, 60 °C
64%

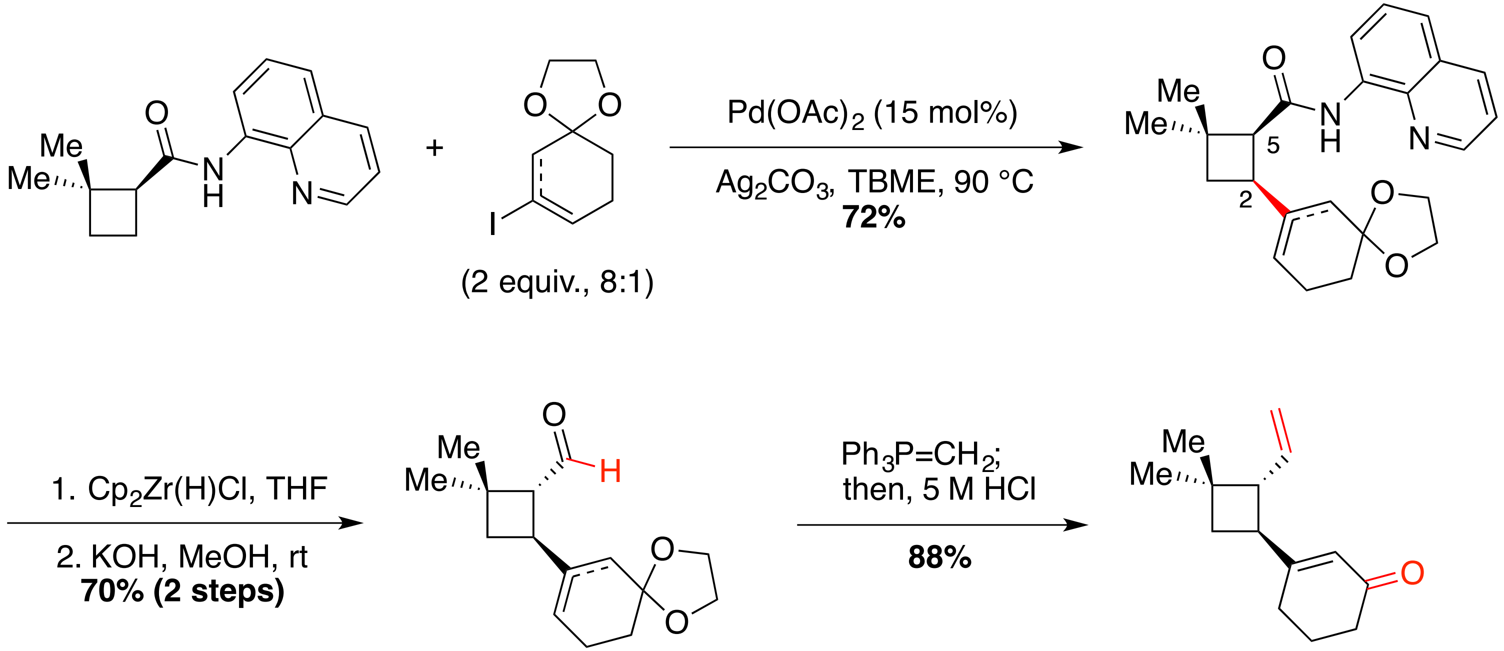
1. ethylene glycol
   $CH(OMe)_3$, *p*-TsOH
   PhMe, 80 °C, **86%**
2. $Cp_2Zr(H)Cl$, THF;
   then, $Ph_3P{=}CH_2$;
   then, 5 M HCl
   58% (two steps)

- **Undesired** enantiomer is obtained
- **(–)-cinchonine** did not help
    - *Pseudoenantiomeric* catalyst *ent*-product with 58% *ee*

D. J. A. Schedler, J. Li, B. Ganem, *J. Org. Chem.* **1996**, *61*, 4115–4119.

Synthesis III

C(sp^3)-alkenylation; Epimerization II



(2 equiv., 8:1)

Pd(OAc)$_2$ (15 mol%)

Ag$_2$CO$_3$, TBME, 90 °C

72%

1. Cp$_2$Zr(H)Cl, THF

2. KOH, MeOH, rt

70% (2 steps)

Ph$_3$P=CH$_2$;
then, 5 M HCl

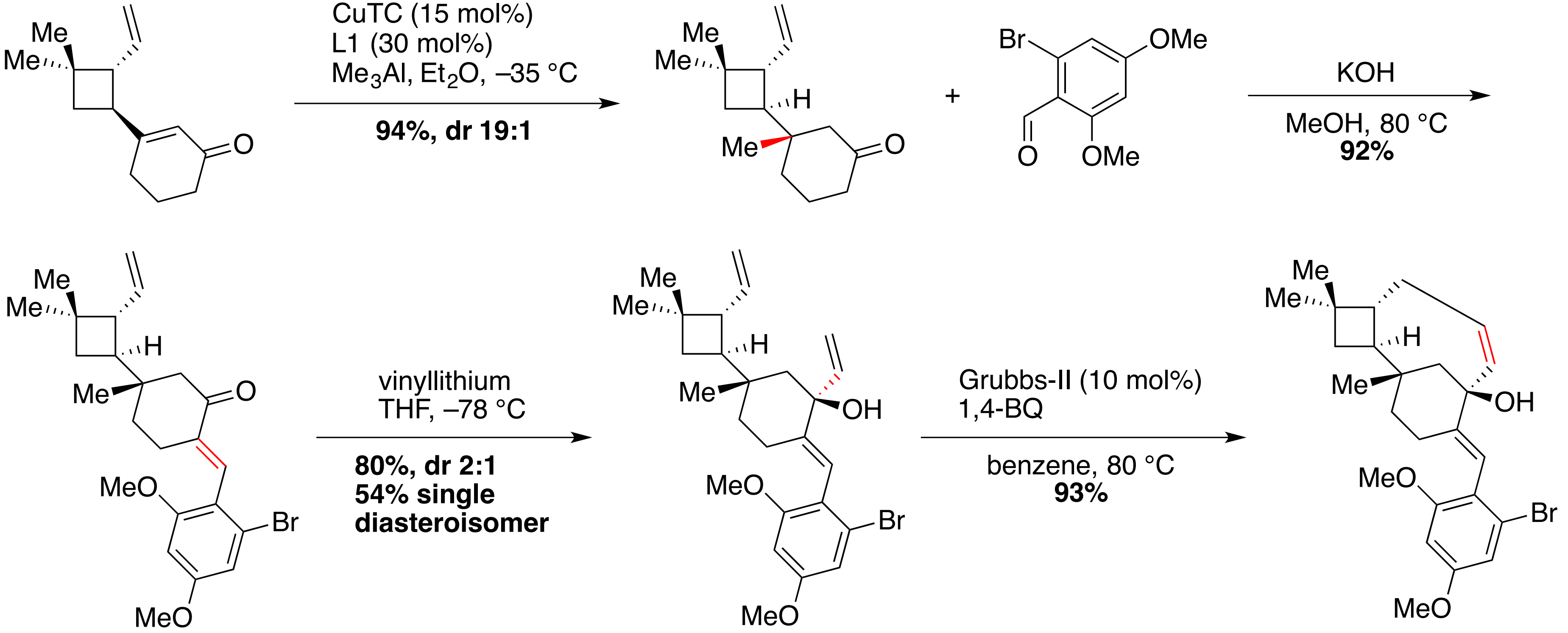
88%

- **Desired** enantiomer obtained
- Acetal as coupling partner → **elimination** of linear protection step

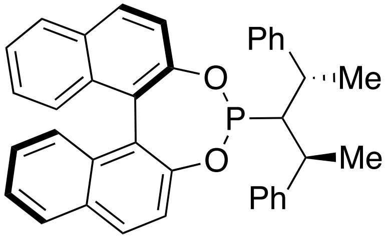
D. J. A. Schedler, J. Li, B. Ganem, *J. Org. Chem.* **1996**, *61*, 4115–4119.

Synthesis IV

Completion of the Synthesis I

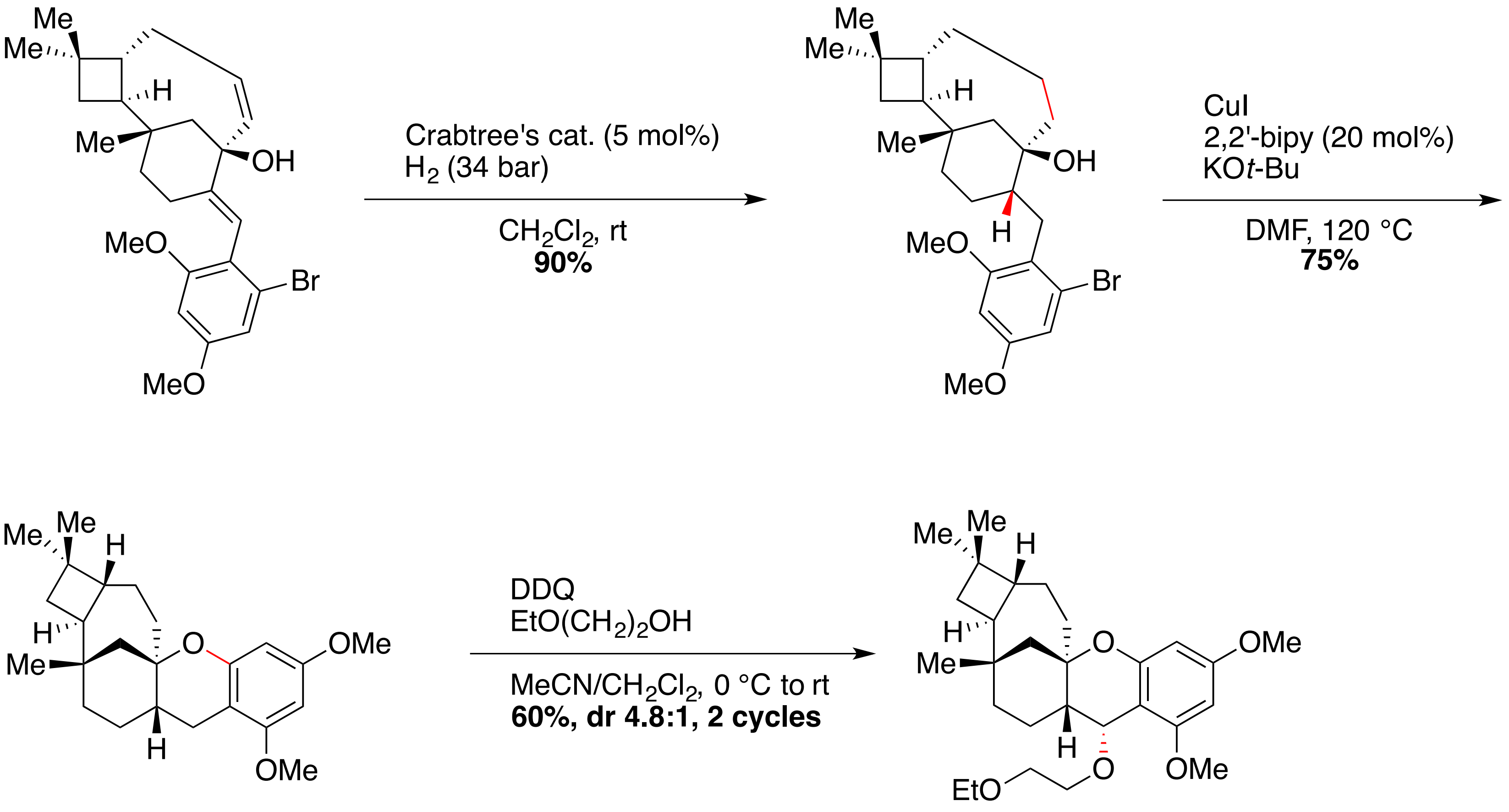


- **Gilman's** reagent furnished product in moderate yield (dr 3:1)
- Extensive experimentation to **improve dr** unsuccessful



Synthesis V

Completion of the Synthesis II



Crabtree's cat. (5 mol%)
H_2 (34 bar)

CH_2Cl_2, rt
90%

CuI
2,2'-bipy (20 mol%)
KO*t*-Bu

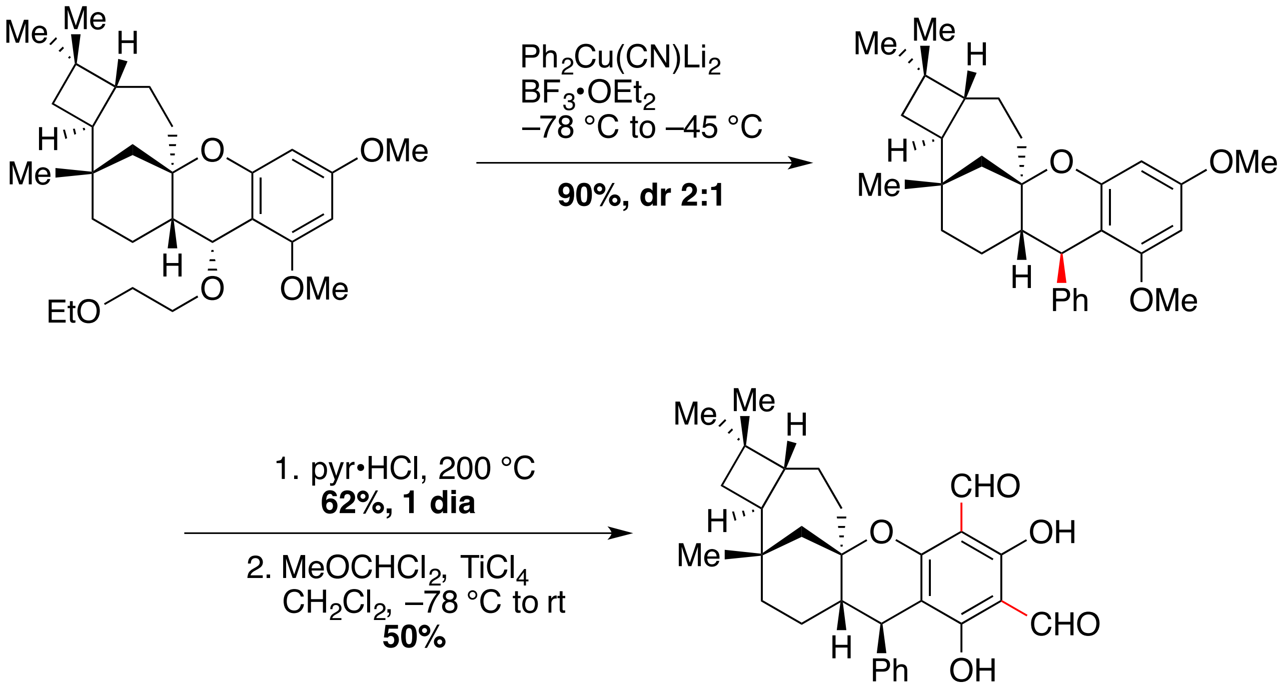
DMF, 120 °C
75%

DDQ
$EtO(CH_2)_2OH$

$MeCN/CH_2Cl_2$, 0 °C to rt
60%, dr 4.8:1, 2 cycles

Synthesis VI

Completion of the Synthesis III



$Ph_2Cu(CN)Li_2$
BF_3•OEt_2
–78 °C to –45 °C

90%, dr 2:1

1. pyr•HCl, 200 °C
62%, 1 dia

2. $MeOCHCl_2$, $TiCl_4$
CH_2Cl_2, –78 °C to rt
50%

(+)-psiguadial

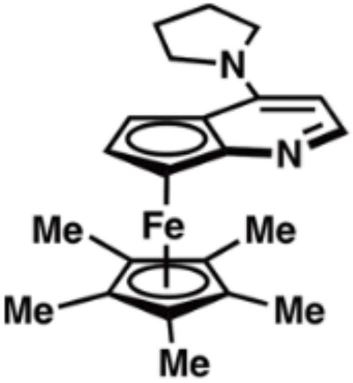
Conclusion

- (+)-psiguadial obtained in **15 steps** from diazoketone
- Spectroscopically **identical** with natural sample reported by Shao
- De novo construction **of trans-fused cyclobutane** ring
- Pd-catalyzed C(sp^3)–H alkenylation
- Expansion of sequence scope to other cyclobutanes ongoing

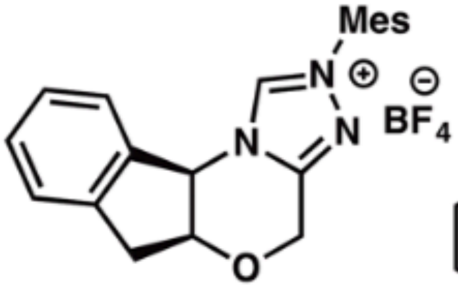
Thank you for your attention

Backup-Slide I

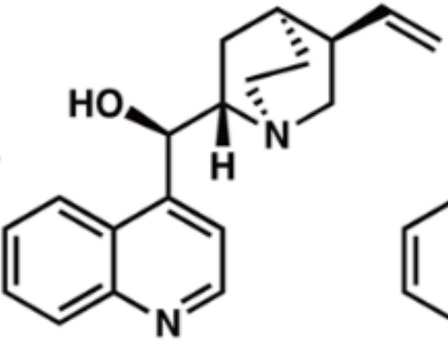
Screened Catalysts for the Wolff Rearrangement



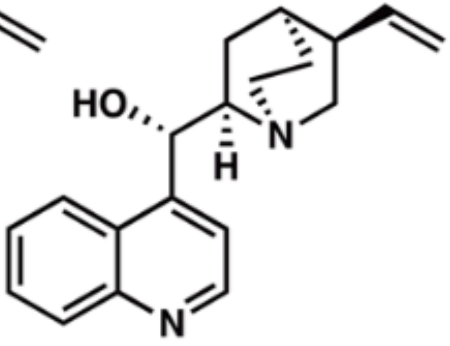
PPY-Me* (C1)



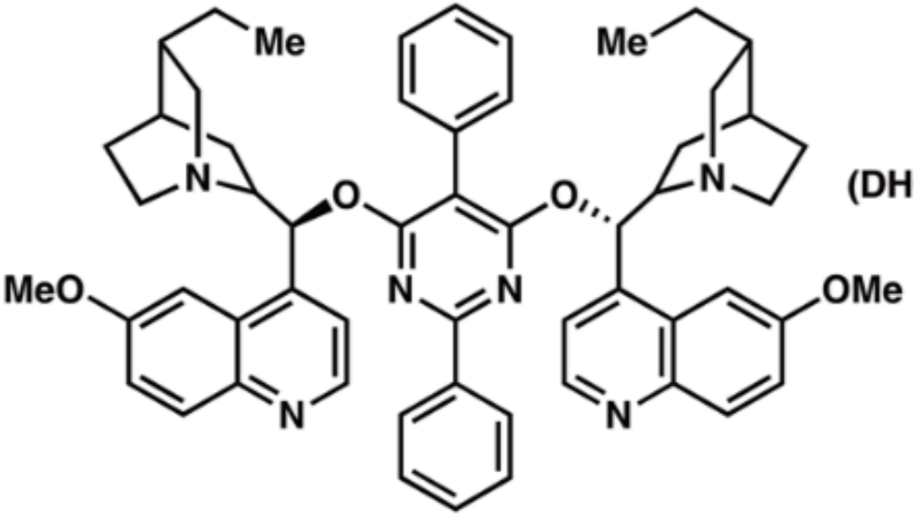
Indanyl-NHC (C2)



(–)-cinchonidine (C3)



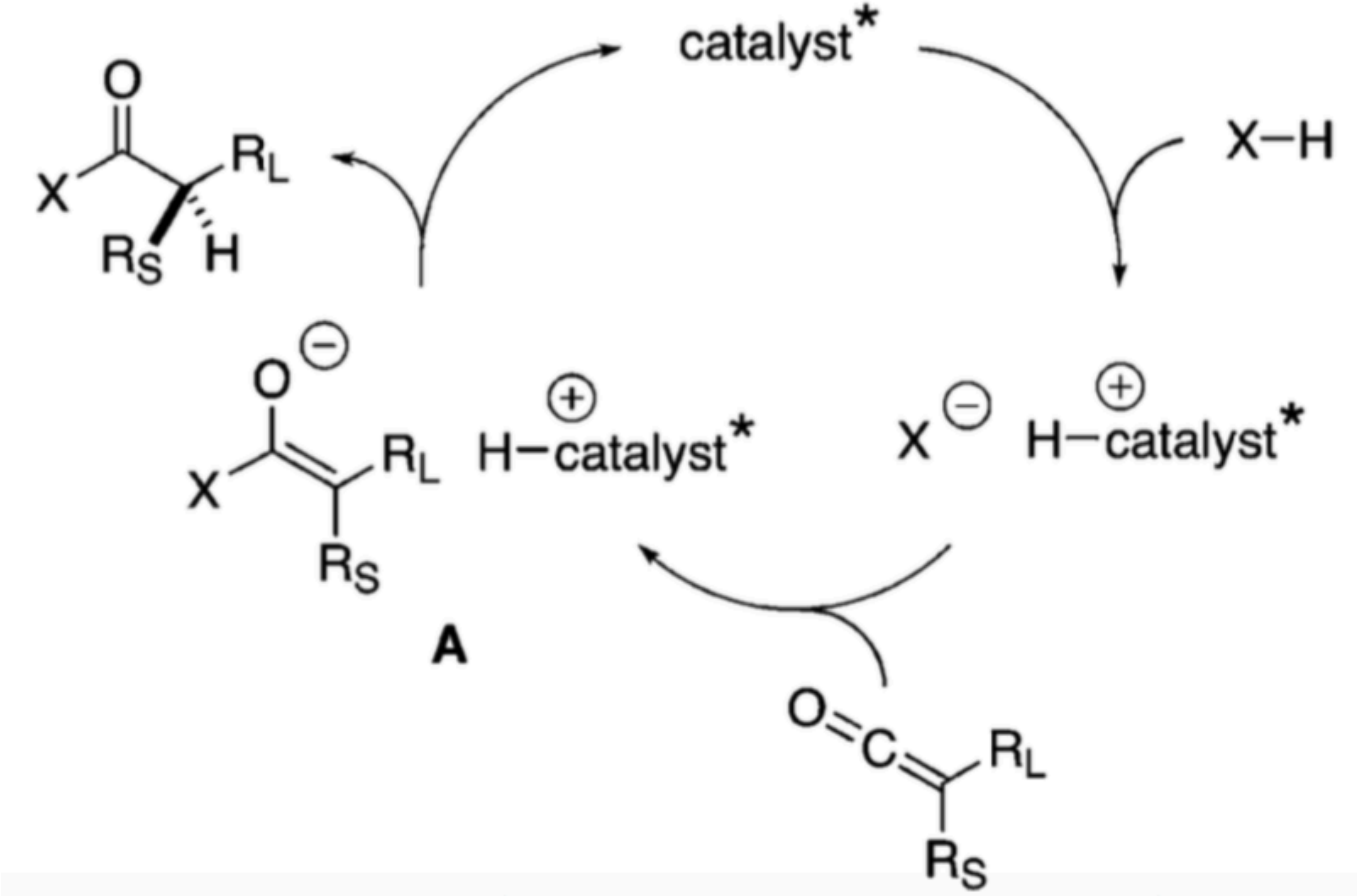
(+)-cinchonine (C4)



(DHQD)$_2$PYR (C5)

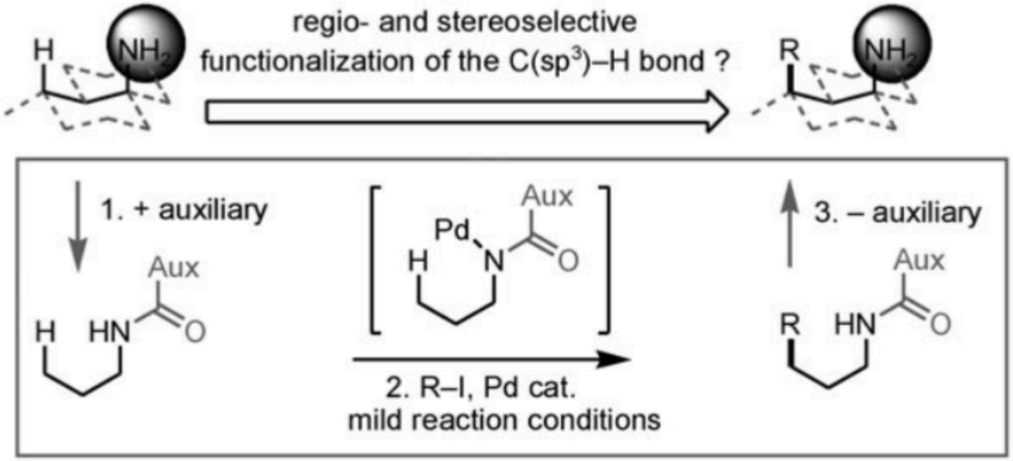
Backup-Slide II

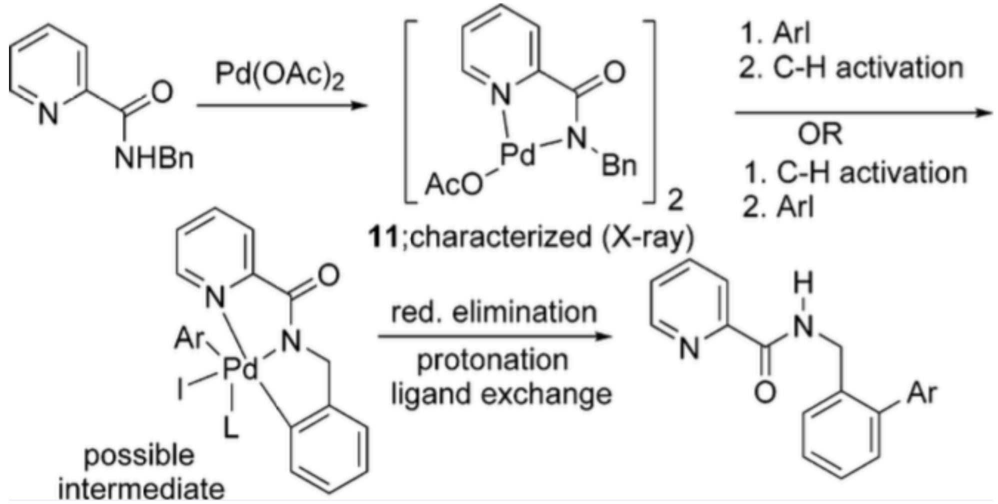
Asymmetric Catalysis of Amide Formation

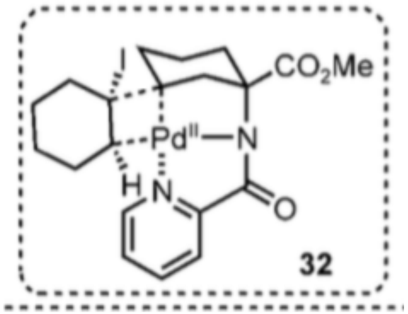


Backup-Slide III

Coupling with Pd(OAc)2







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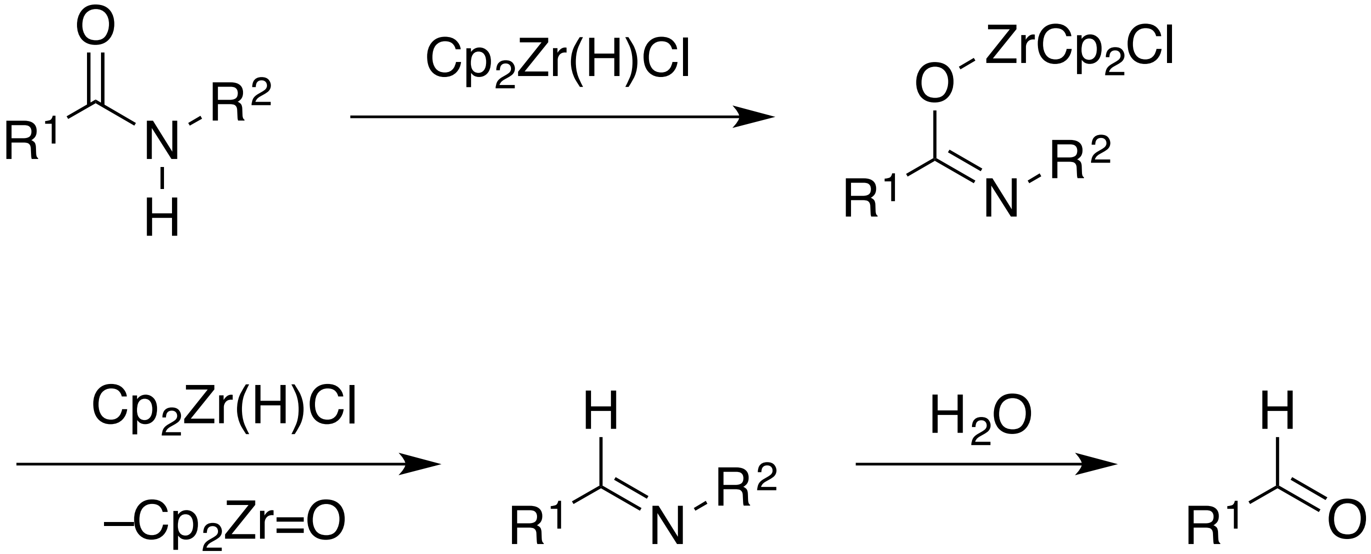
G. He, G. Chen, *Angew. Chem. Int. Ed.* **2011**, *50*, 5192–5196
V. G. Zaitsev, D. Shabashov, O. Daugulis, *J. Am. Chem. Soc.* **2005**, *127*, 13154–13155.

Backup-Slide IV

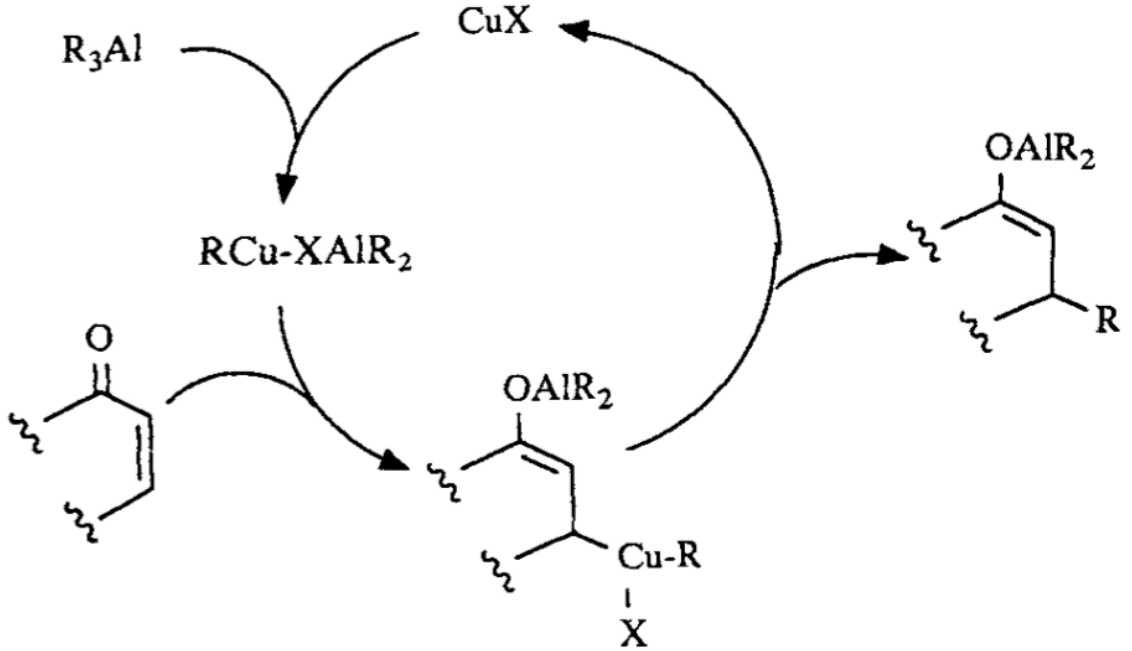
Schwartz Reduction



D. J. A. Schedler, J. Li, B. Ganem, *J. Org. Chem.* **1996**, *61*, 4115–4119.

Backup-Slide V

Copper Catalyzed Alkylation

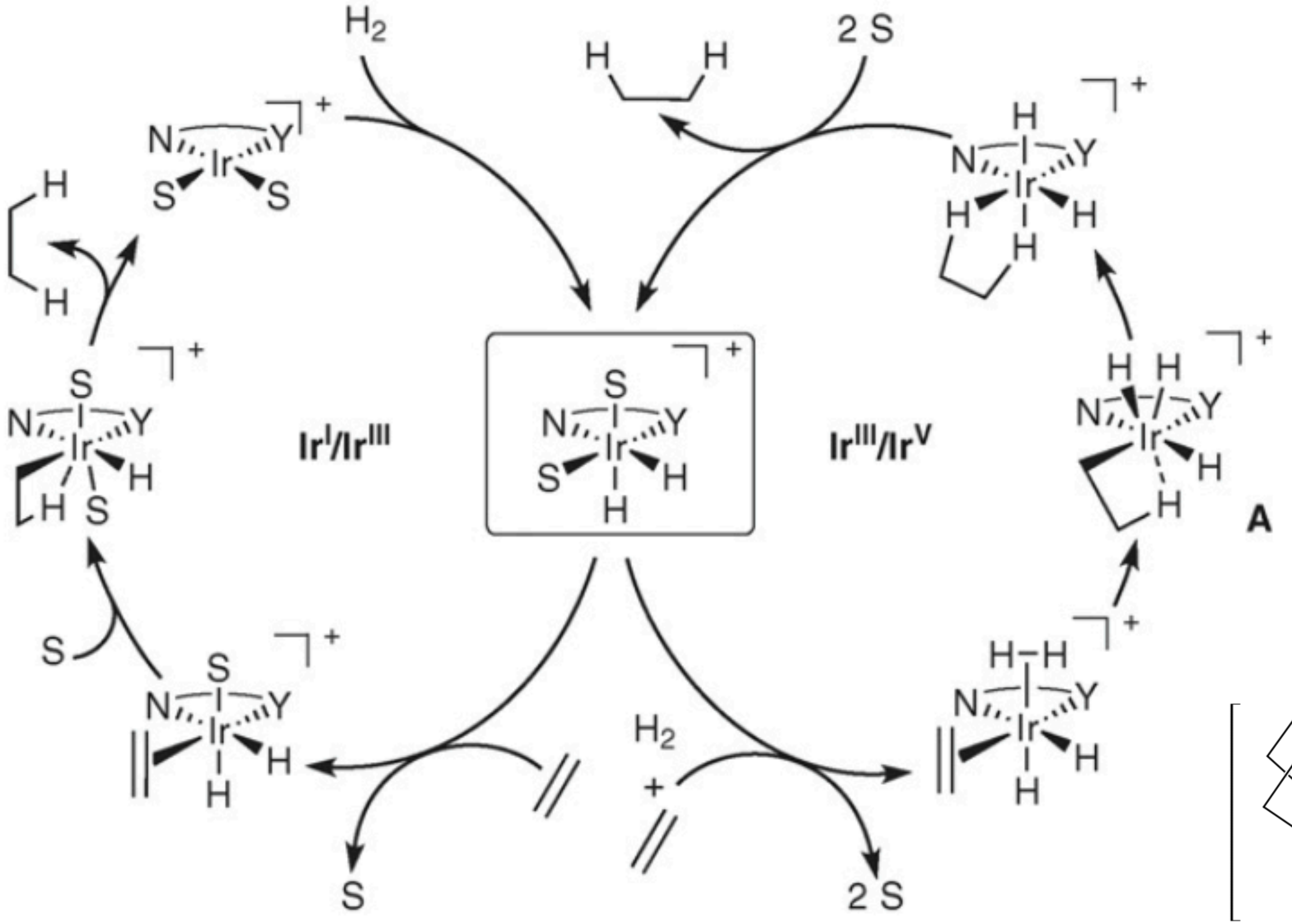


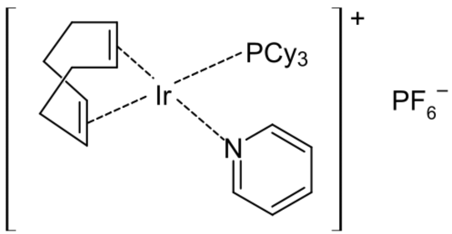
- **stronger coordinating solvents** are used than with dialkylzinc reagents (Et_2O or THF instead of toluene or CH_2Cl_2) as this allows the **cleavage of the AlR_3 dimeric species**, thus increasing its reactivity
- 18 h at –30 °C; more rapidly at higher temperatures but decrease in *ee*

J. Westermann, K. Nickisch, *Angew. Chem. Int. Ed.* **1993**, *32*, 1368–1370
M. d'Augustin, L. Palais, A. Alexakis, *Angew. Chem. Int. Ed.* **2005**, *44*, 1376–1378

Backup-Slide VI

Crabtree’s Catalyst

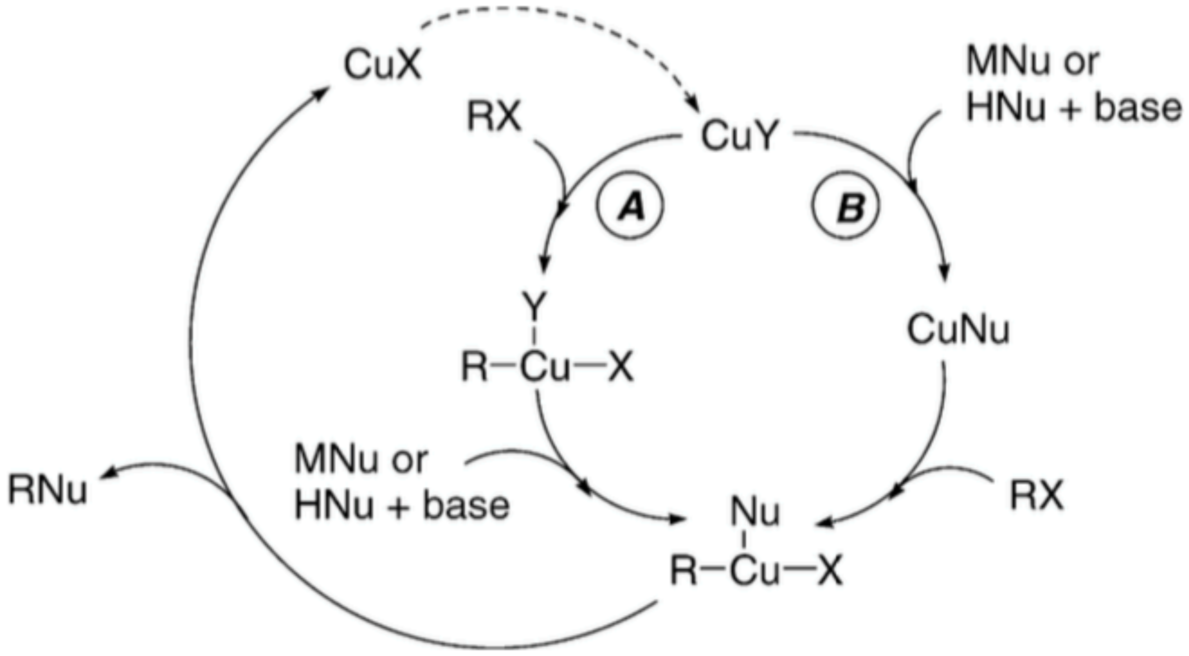




T. L. Church, P. G. Andersson, *Coord. Chem. Rev.* **2008**, *252*, 513–531

Backup-Slide VII

Copper Catalyzed *O*-arylation; Ullmann



I. P. Beletskaya, A. V. Cheprakov, *Coord. Chem. Rev.* **2004**, *248*, 2337–2364.