Construction of contiguous quaternary carbon

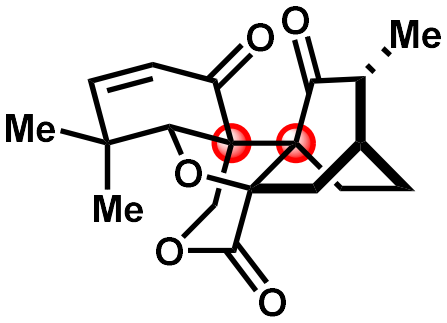
LS 2016/12/17 Yusuke Imamura

Today's contents

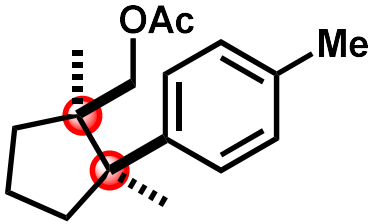
- 1. Introduction
- 2. Prof. Garcia-Garibay's approach
- 3. Prof. Xie's approach (main paper)

Contents

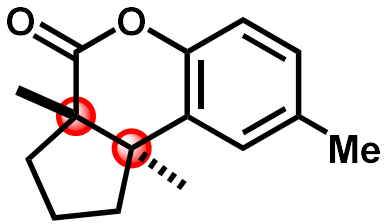
Natural products containing contiguous quaternary carbon



maoecrystal V



tochuinyl acetate

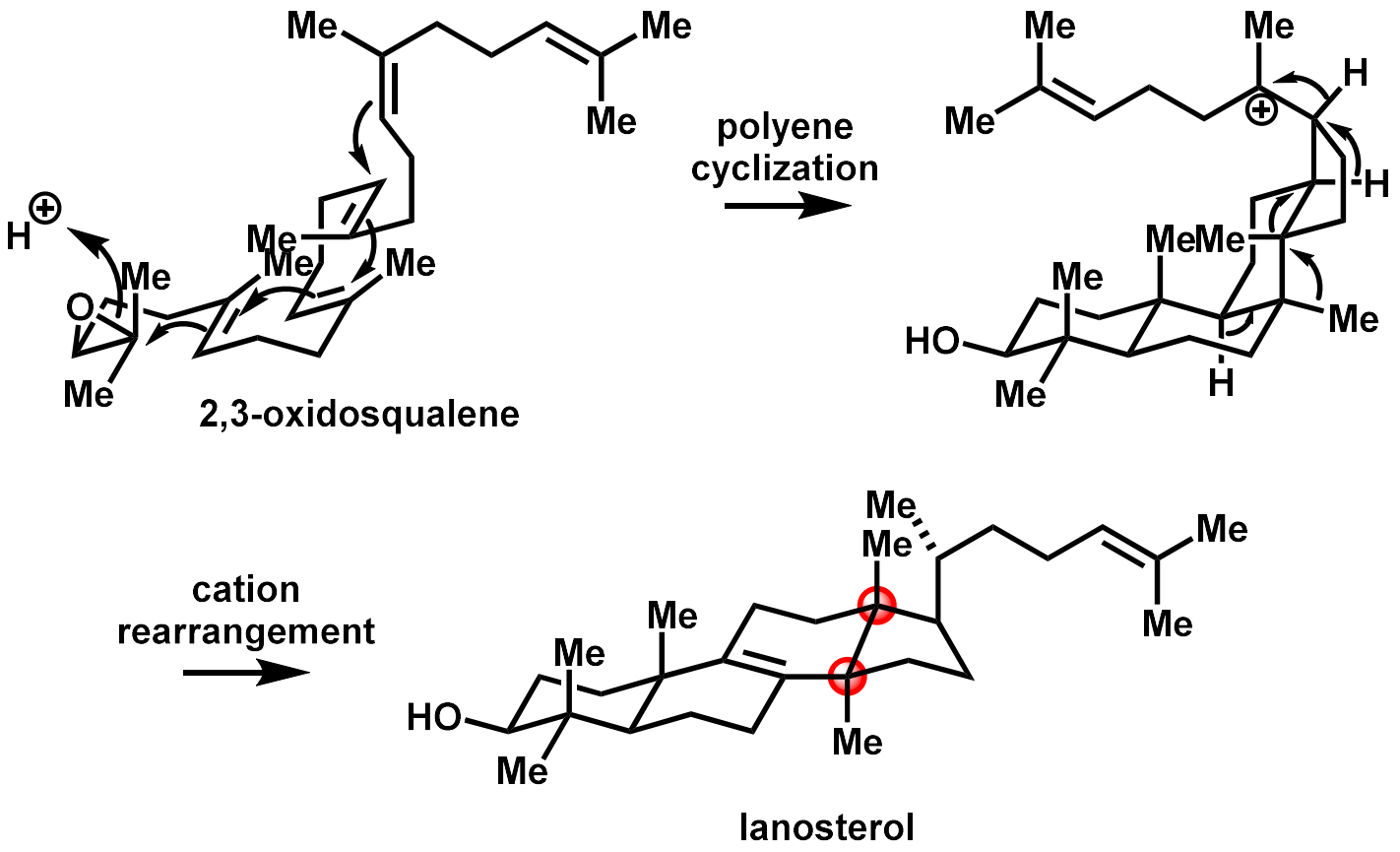


herbertenolide

…quaternary carbon atoms on one or more stereogenic centers, which when embedded within the core structure of an intended target molecule presents a formidable challenge to a synthetic chemist.

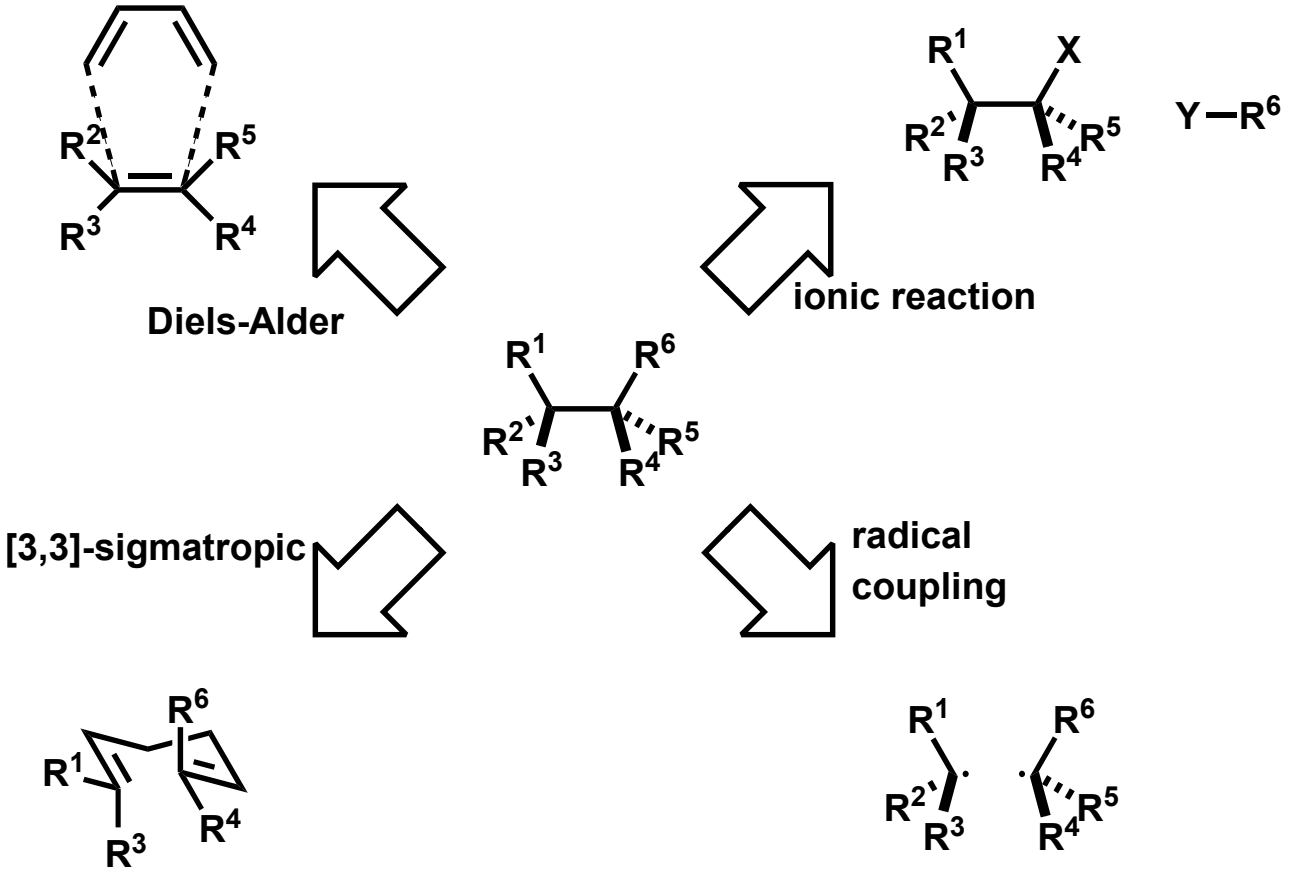
Overman, L. E. et al. *Angew. Chem. Int. Ed.* **2016**, *55*, 4156.

Biosynthetic way to construct vicinal quaternary carbon

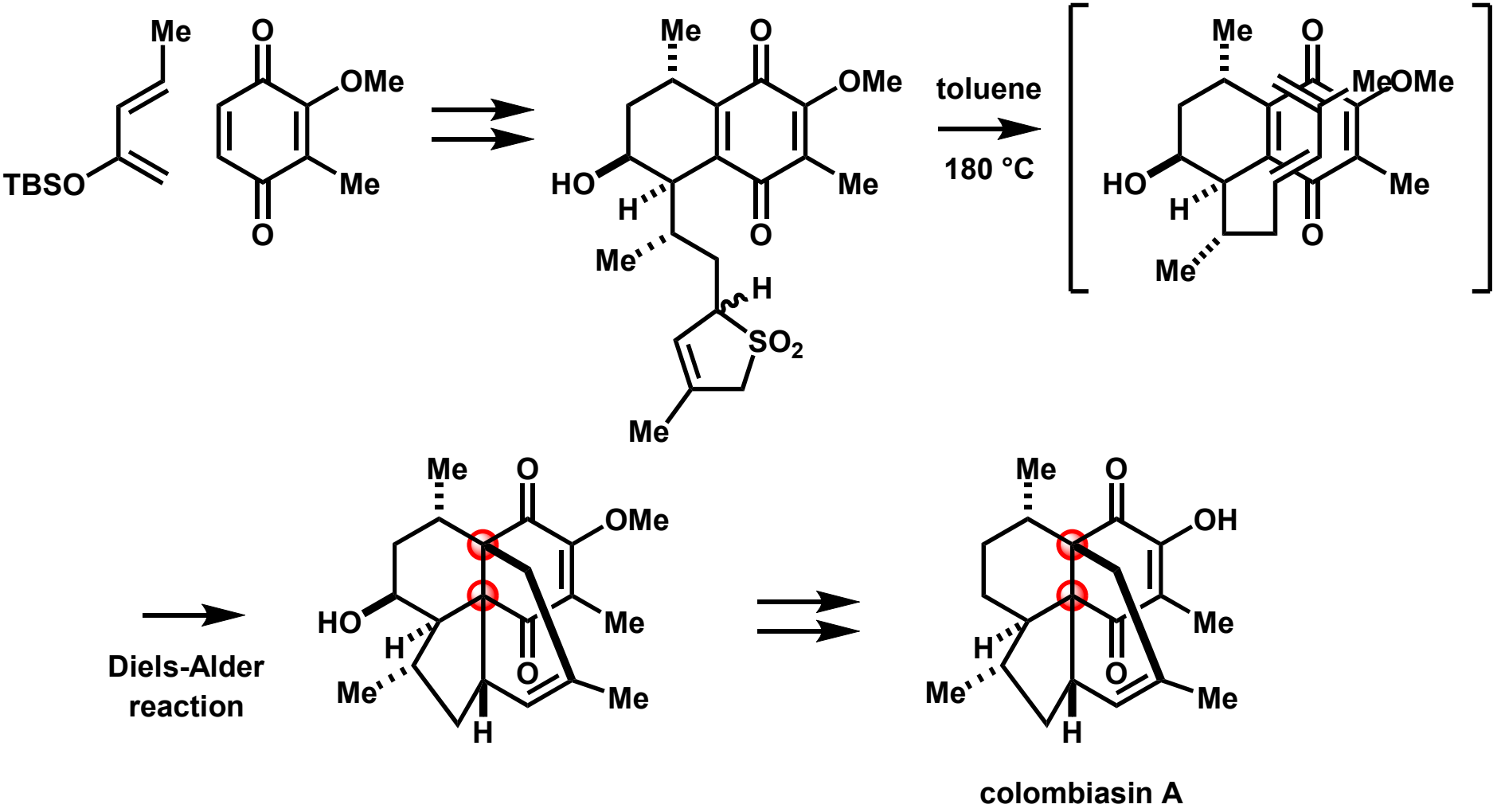


Ruf, A. et al. *Nature*, **2004**, *432*, 118.

General approach to construct vicinal quaternary carbon

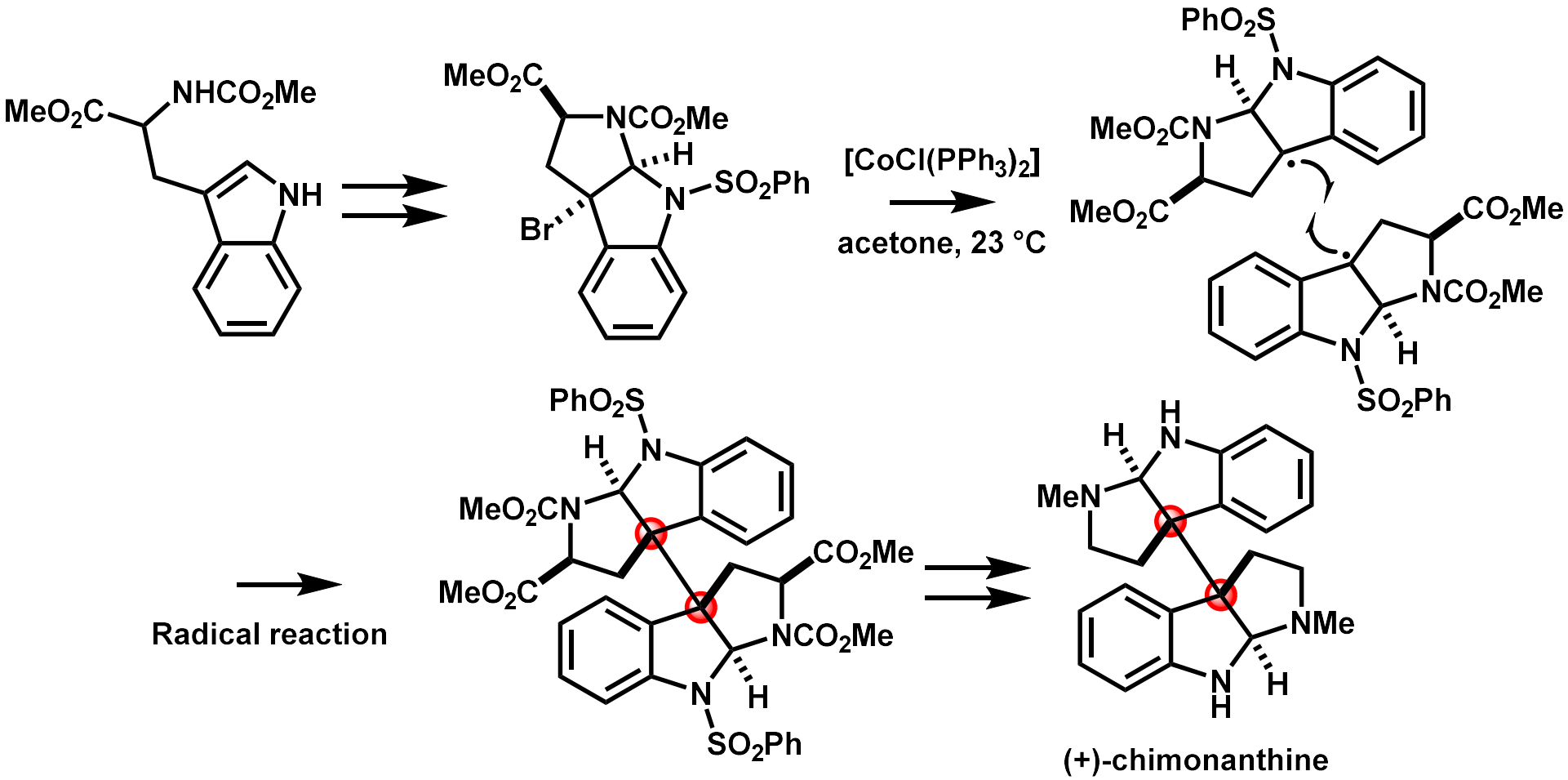


Diels-Alder reaction



Kranich, R. et al. *Angew. Chem. Int. Ed.* **2001**, *40*, 2482.

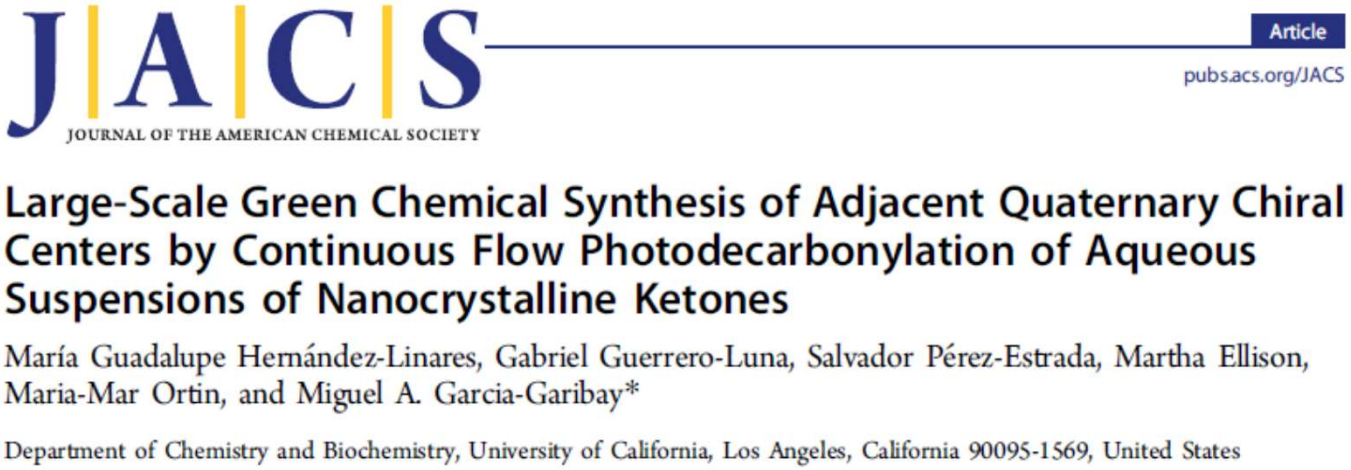
Radical reaction



Movassaghi, M. Schmidt, M. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 3725.

Contents

- 1. introduction about quaternary carbon
- **2. Prof. Garcia-Garibay's approach**
- 3. Prof. Xie's approach (main paper)



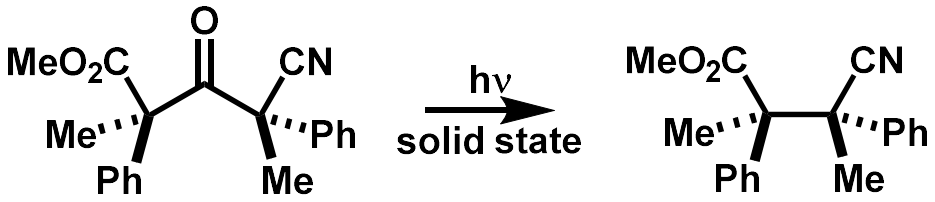
JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Article
pubs.acs.org/JACS

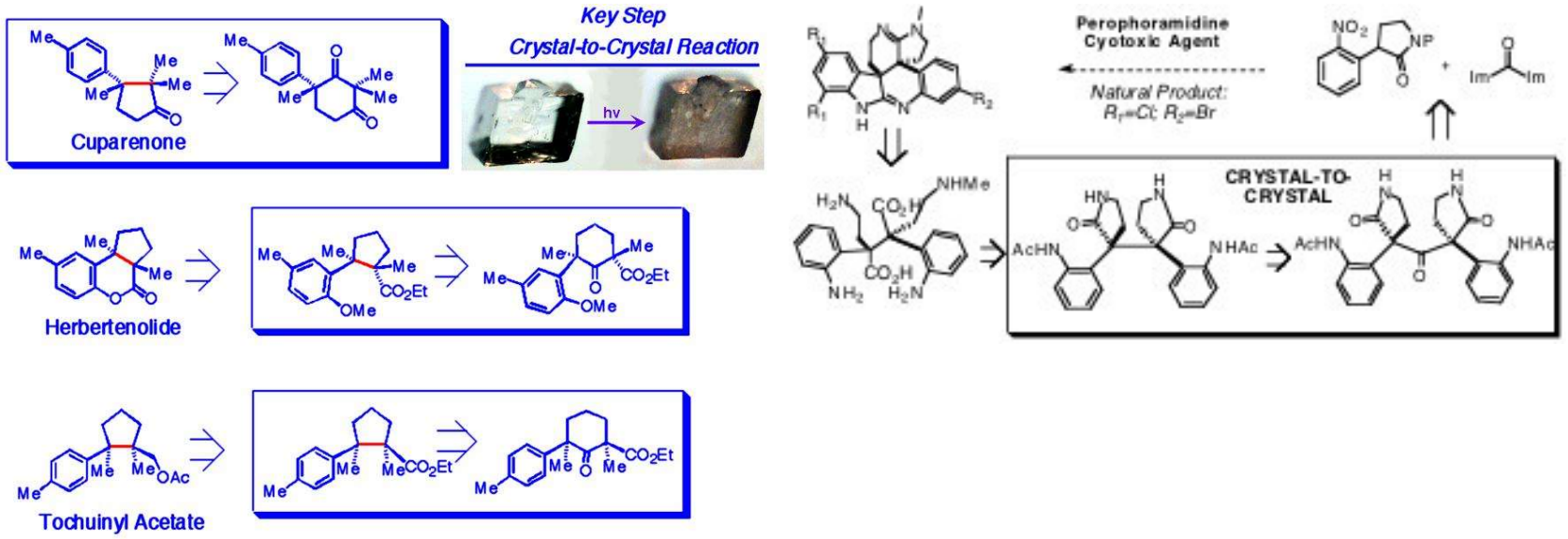
Large-Scale Green Chemical Synthesis of Adjacent Quaternary Chiral Centers by Continuous Flow Photodecarbonylation of Aqueous Suspensions of Nanocrystalline Ketones

María Guadalupe Hernández-Linares, Gabriel Guerrero-Luna, Salvador Pérez-Estrada, Martha Ellison, Maria-Mar Ortin, and Miguel A. Garcia-Garibay*

Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095-1569, United States

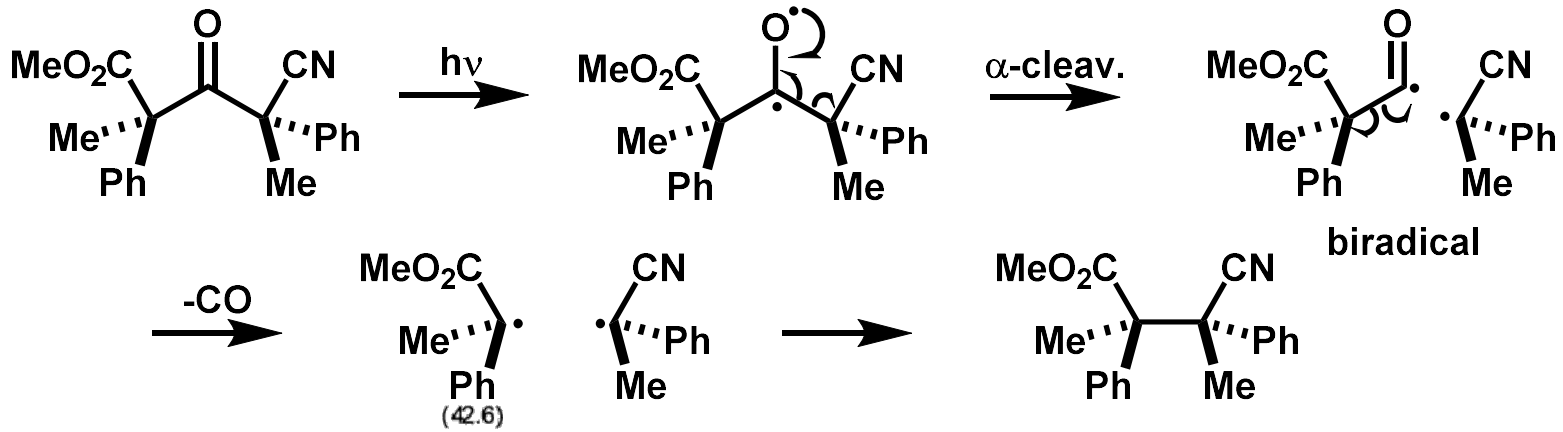
Photodecarbonylation

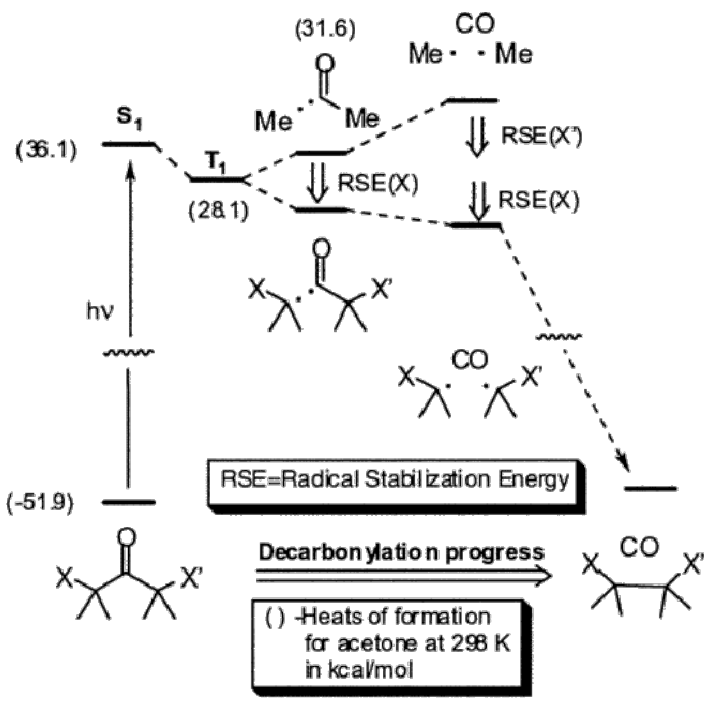




Quinkert, G. et al. *Tetrahedron Lett.* **1963**, *27*, 1863.
Garcia-Garibay, M. A. et al. *J. Am. Chem. Soc.* **2015**, *137*, 1679.
For detail see:110917_LS_Tamaki HOSHIKAWA

Reaction mechanism



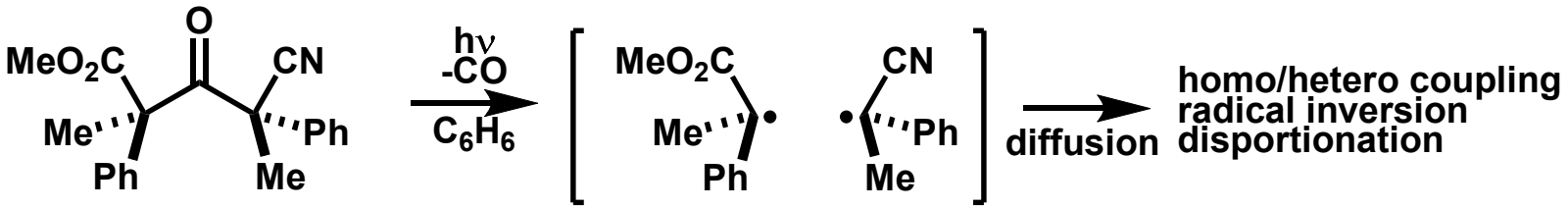


Substituents with Radical Stabilization Energy (RSE) >11 kcal/mol are required to form biradical.

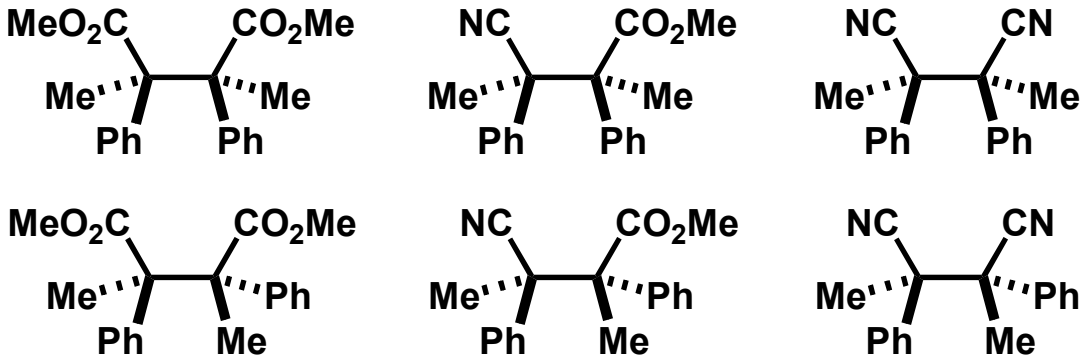
RSE…The gap between energy to form $^{\cdot}CH_3$ from CH_4 and energy to form the radical from the hydride form.

Garcia-Garibay, M. A. et al. *J. Org. Chem.* **2002**, *67*, 3749.

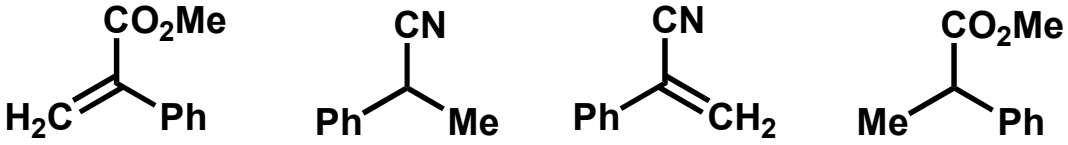
Photodecarbonylation in solution



free radicals



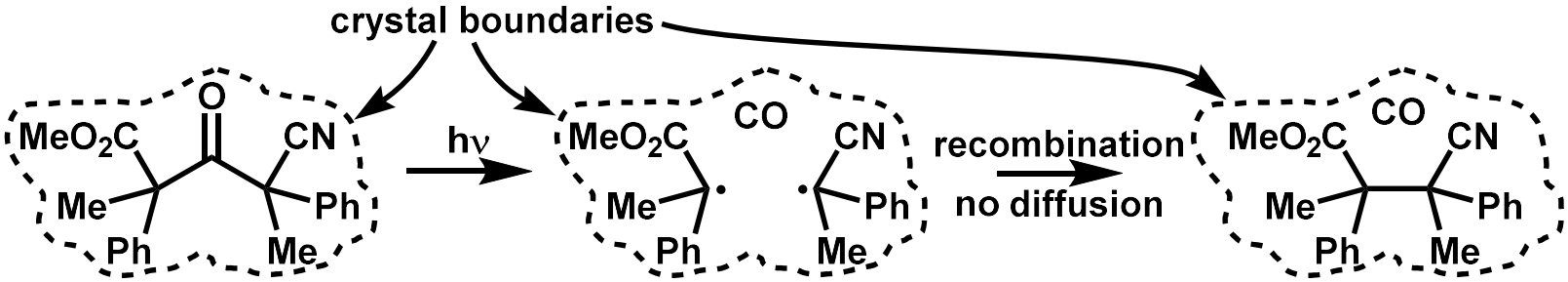
6 combination products (4 racemic compounds)



4 disproportionation products

Garcia-Garibay, M. A. et al. *J. Am. Chem. Soc.* **2015**, *137*, 1679.
For detail see:110917_LS_Tamaki HOSHIKAWA

Photodecarbonylation in solid



The reaction proceed highly stereo-selectively.

But this method has several problem…

1. Substrate restriction

Substrate must have radical stabilizing group at α-position

Substrate must be solid

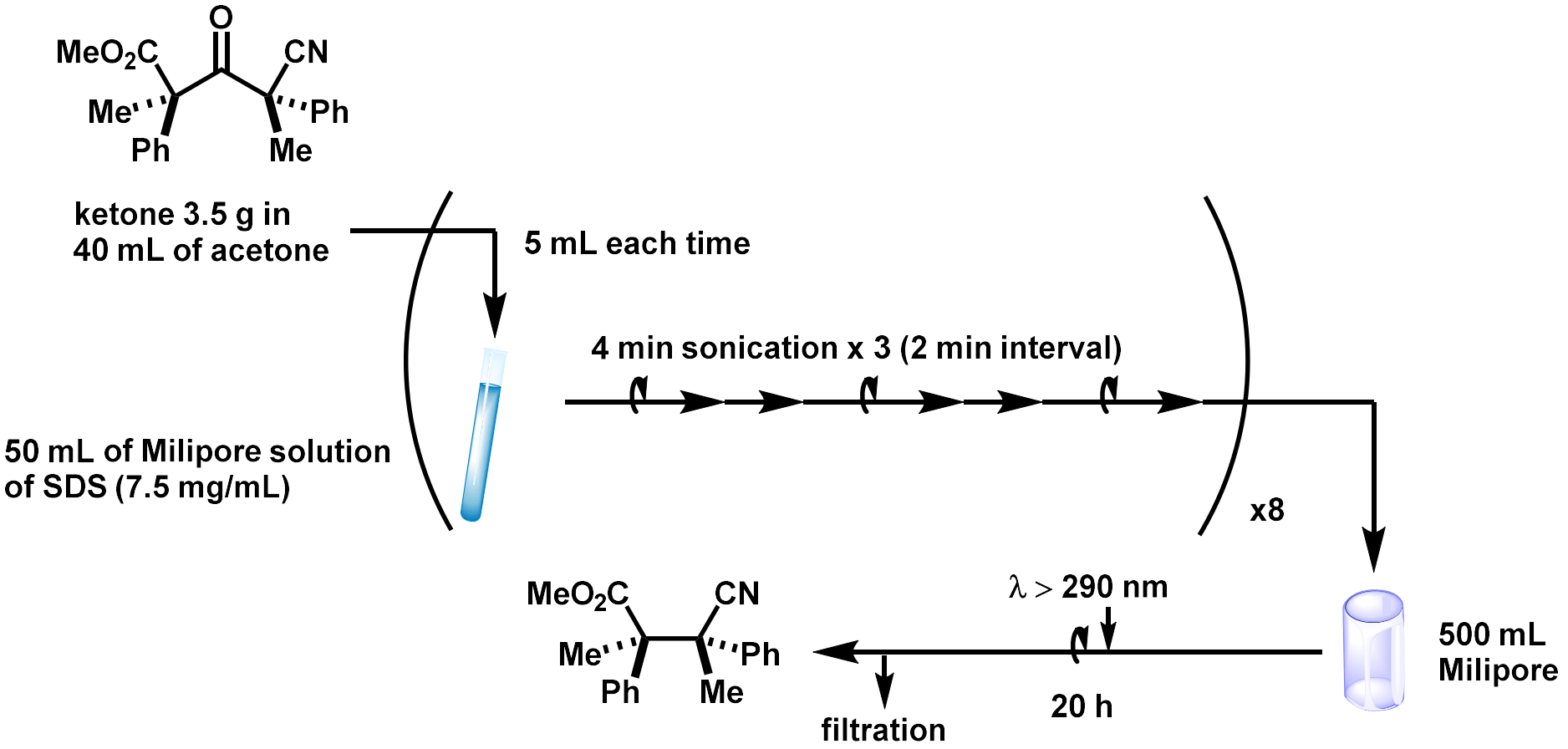
2. Scalability

Only the surface of the solid was exposed by light

Garcia-Garibay, M. A. et al. *J. Am. Chem. Soc.* **2015**, *137*, 1679.
For detail see:110917_LS_Tamaki HOSHIKAWA

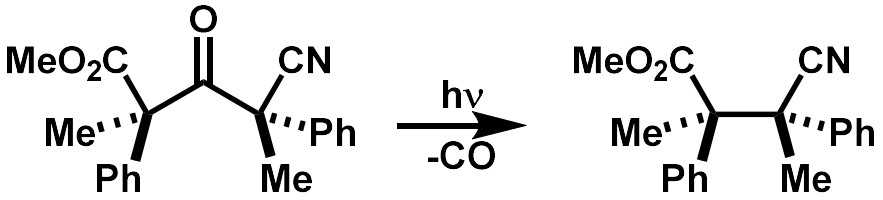
Nanocrystalline method

Nanocrystal…crystal in the range of ca. 200-500 nm



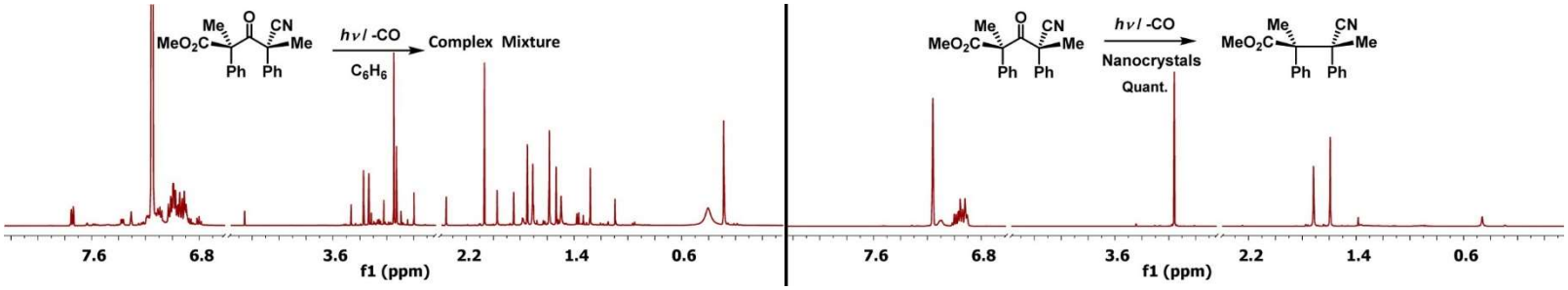
Garcia-Garibay, M. A. et al. *J. Am. Chem. Soc.* **2015**, *137*, 1679.

Nanocrystalline method



entry	medium	conversion(%)	yield[a](%)	dr (% ee[b])
1	(±)Solution	100	18	1.3:1 (0)
2	(+)Solution	100	18	1.3:1 (77)
3	(±)Dry solid	90	91	10:1 (0)
4	(+)Dry solid	62	96	24:1 (100)
5	(+)Nanocrystalline Suspention	100	100	100:0 (100)

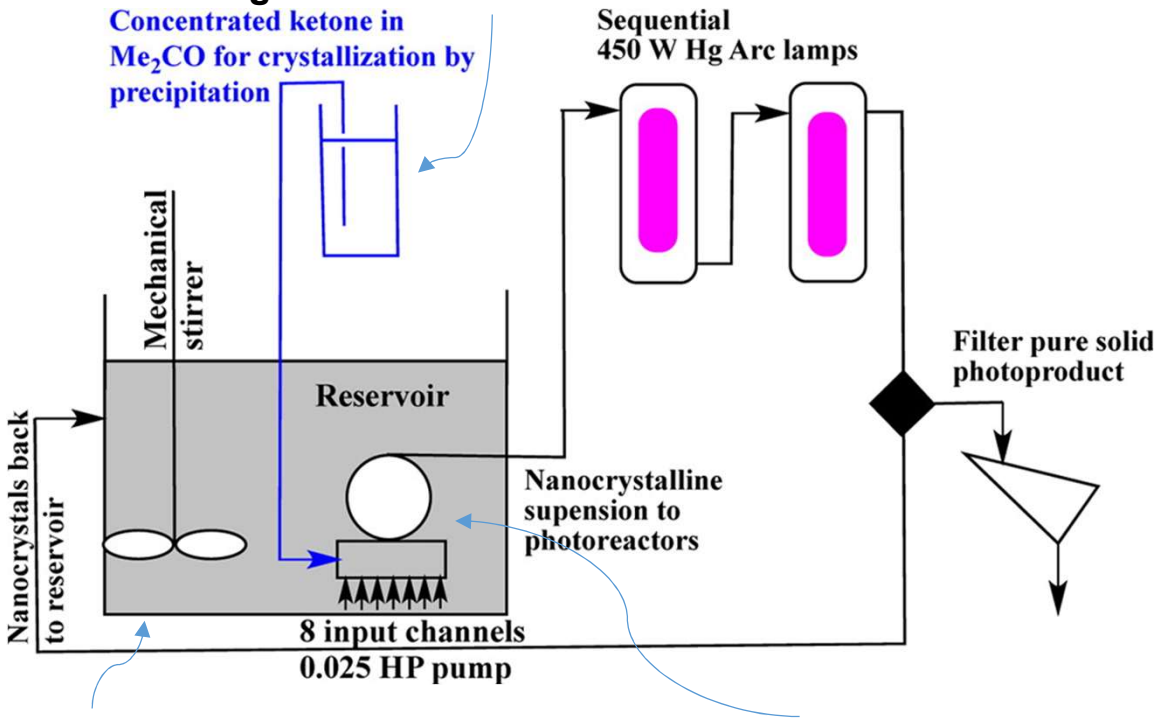
[a]ratio of combination products
[b]ditermined by ^{1}H NMR



Garcia-Garibay, M. A. et al. *J. Am. Chem. Soc.* **2015**, *137*, 1679.

Large scale synthesis

1. ketone 4.0 g in 50 mL of acetone

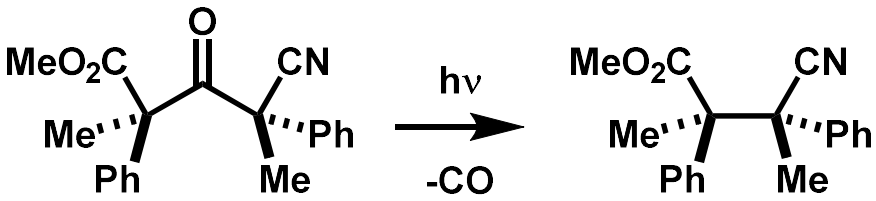


2. SDS 375 mg in 2 L of Millipore

3. mixed in mixing chamber(12 mL)

Garcia-Garibay, M. A. et al. *J. Am. Chem. Soc.* **2015**, *137*, 1679.

Short summary



advantage

stereo-selectively

No need for extraction, concentration, or purification

Scale up synthesis(~15 g)

disadvantage

~~**Scalability**~~

Substrate and products must have high melting point

Substrate must have radical stabilizing group

Garcia-Garibay, M. A. et al. *J. Am. Chem. Soc.* **2015,** *137*, 1679.

Contents

- 1. introduction about quaternary carbon
- 2. Prof. Garcia-Garibay's approach
- **3. Prof. Xie's approach (main paper)**

GDCh Communications Angewandte International Edition Chemie

Ring Contraction

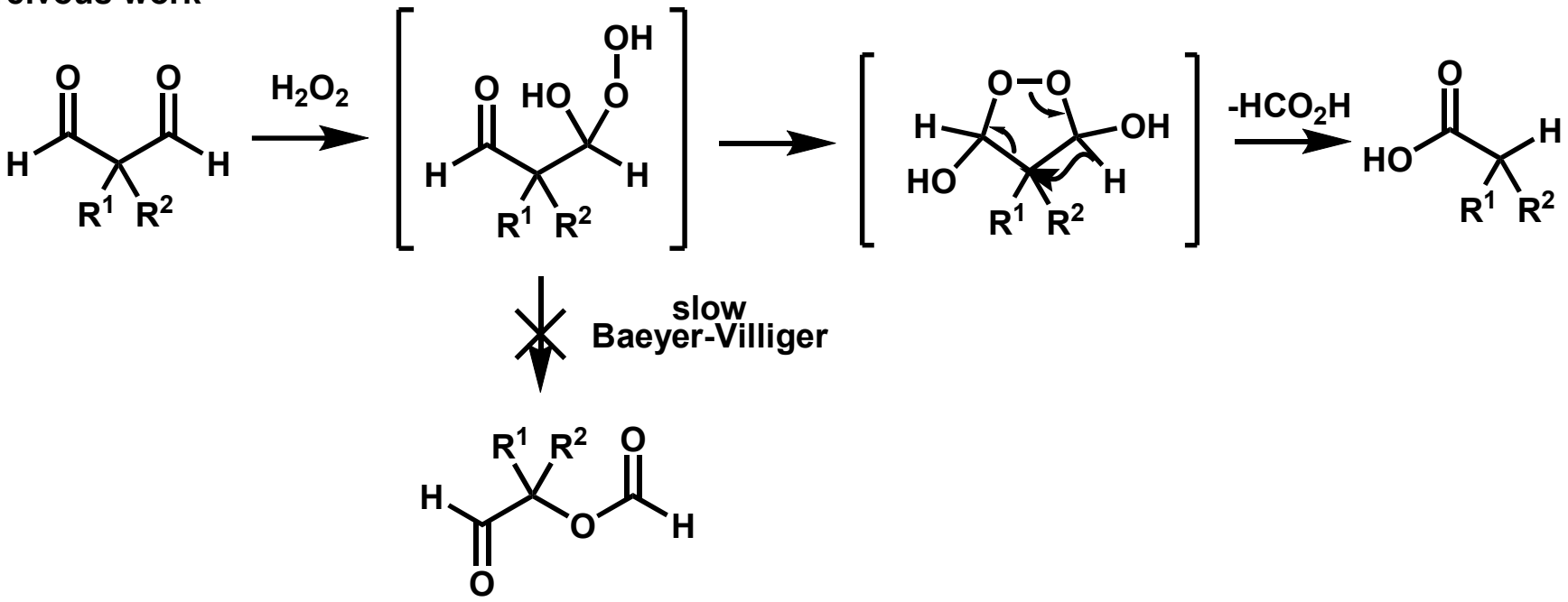
International Edition: DOI: 10.1002/anie.201609975
German Edition: DOI: 10.1002/ange.201609975

Stereospecific Construction of Contiguous Quaternary All-Carbon Centers by Oxidative Ring Contraction

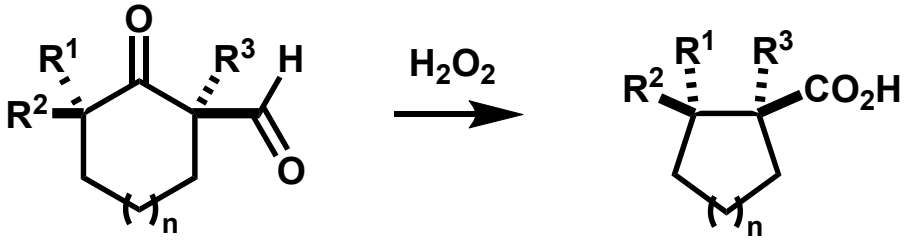
*Xin Yu[+], Jiadong Hu[+], Zhigao Shen, Hui Zhang, Jin-Ming Gao, and Weiqing Xie**

Oxidative rearrangement

Preivous work

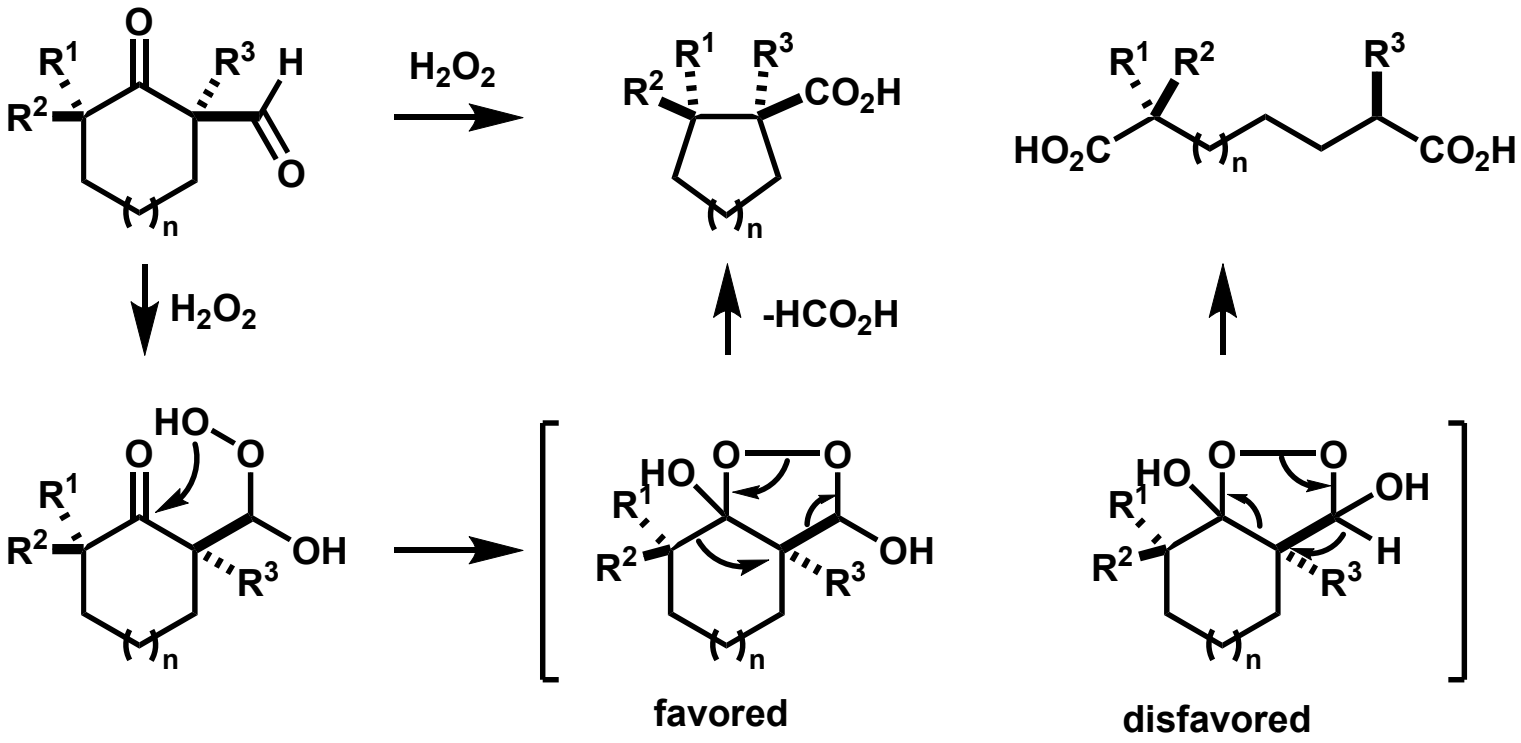


This work

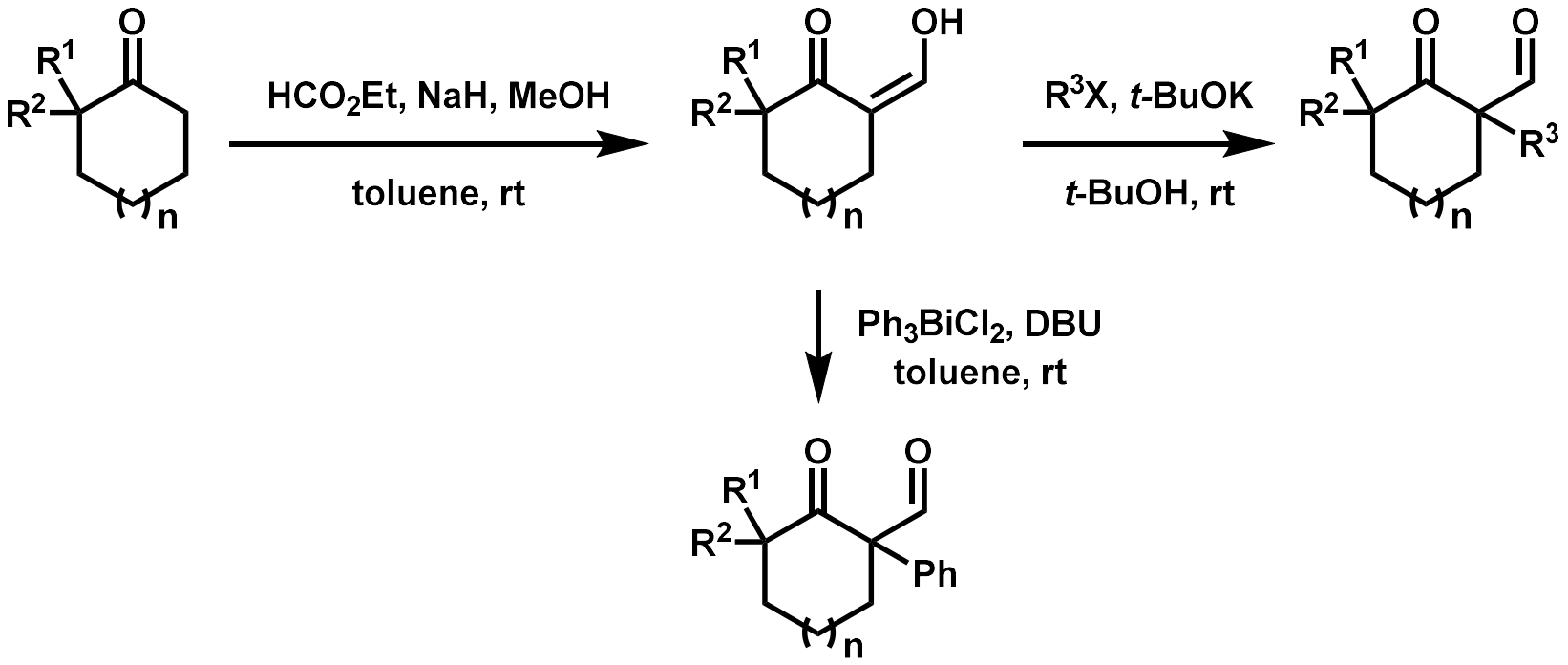


Xie, W. et al. *RSC Adv.* **2014**, *4*, 53397.

Reaction mechanism

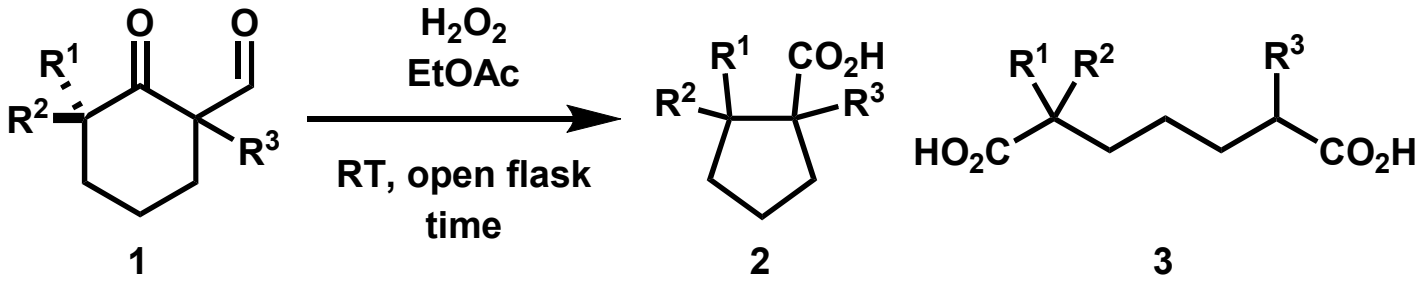


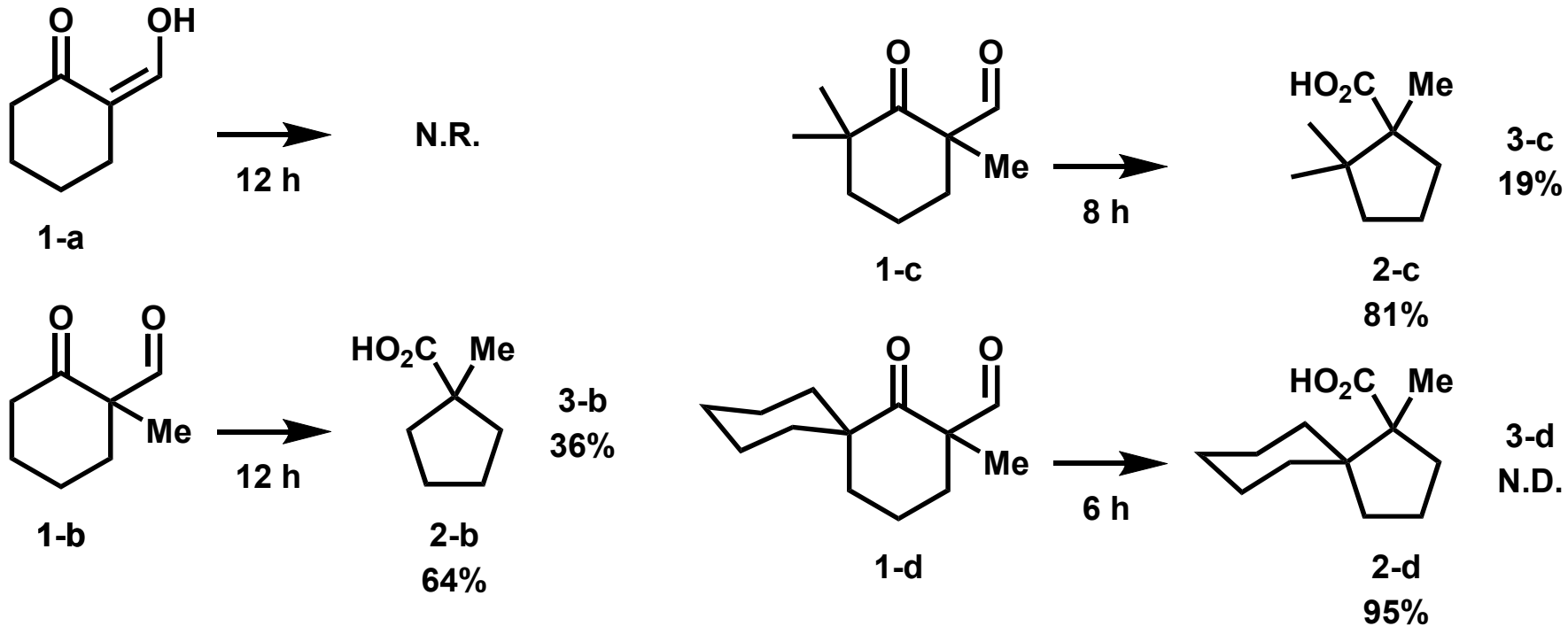
Preparation of substrate



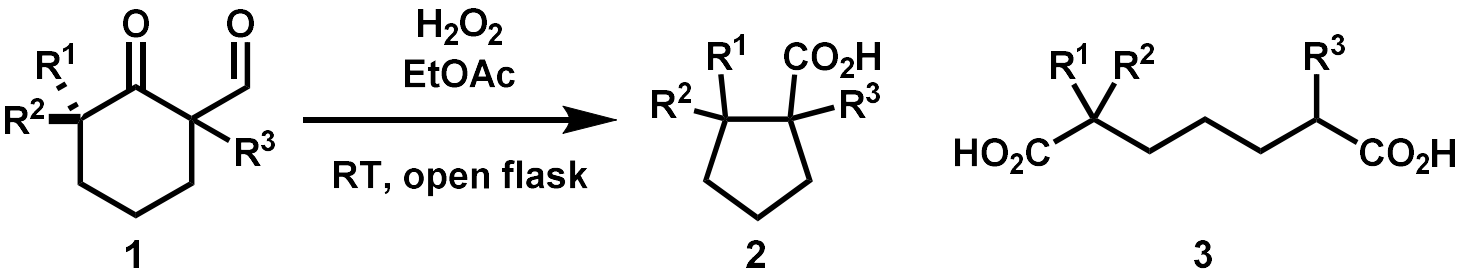
Easy introduction of substituent with rich enolate chemistry.

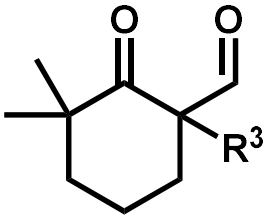
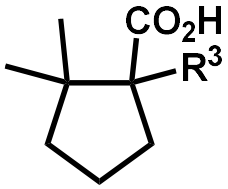
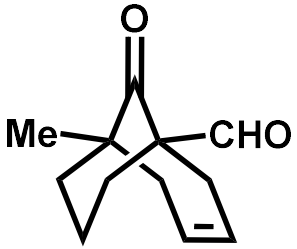
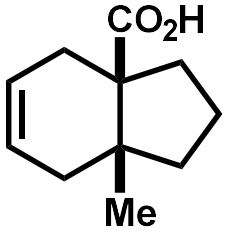
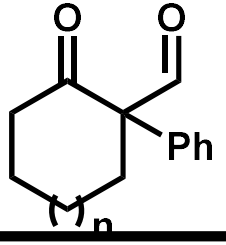
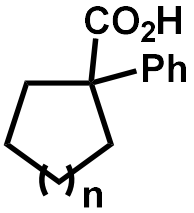
Substrate scope



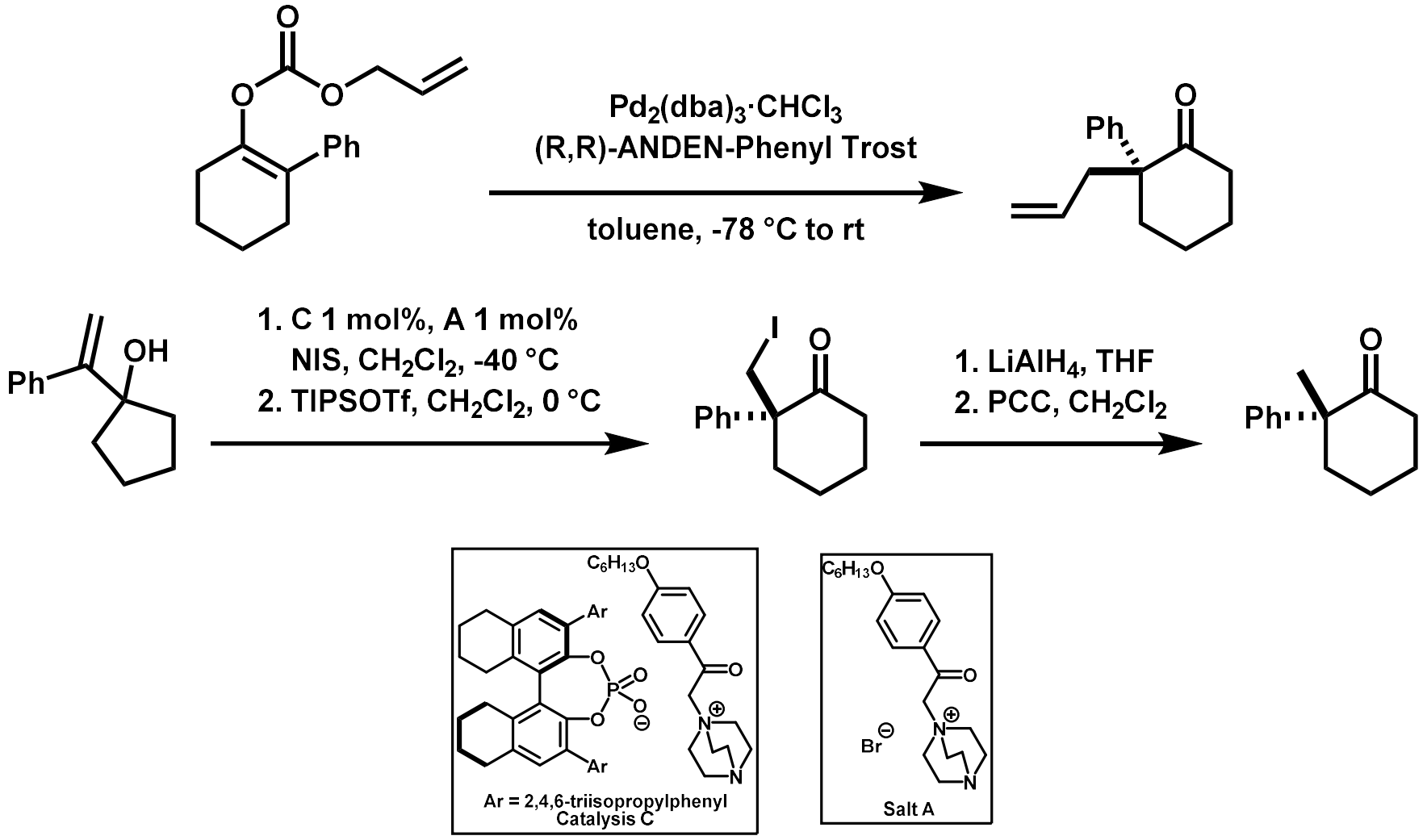


Substrate scope



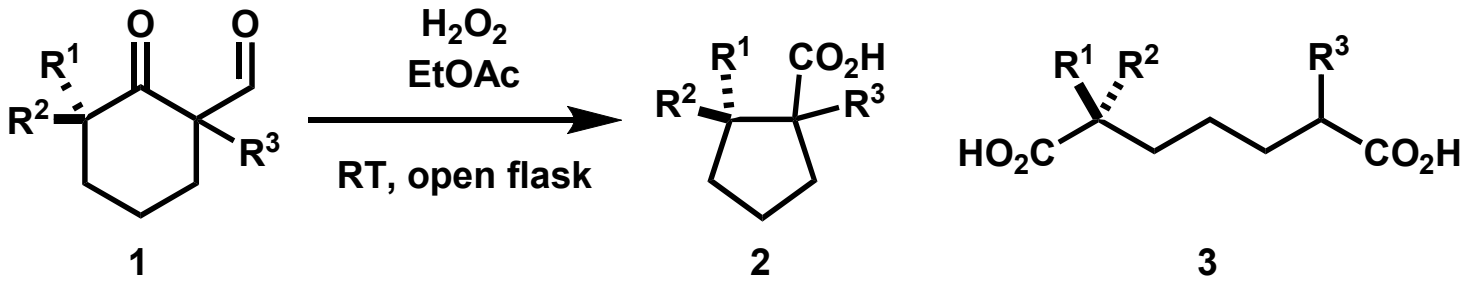
substrate	product		2 (%)	ratio(2:3)
		R^3 = Me	81	4.2:1
		R^3 = Allyl	83	4.9:1
		R^3 = Bn	84	5.2:1
			95	>99:1
		n = 1	92	>99:1
		n = 2	91	>99:1
		n = 3	92	>99:1
		n = 7	66	1.9:1

Preparation of enantioenriched substrate



Trost, B. M. et al. *J. Am. Chem. Soc.* **2009**, *131*, 18343.
Xie, W. et al. *Chem. Sci.* **2015**, *6*, 6986.

Substrate scope



1 2 3

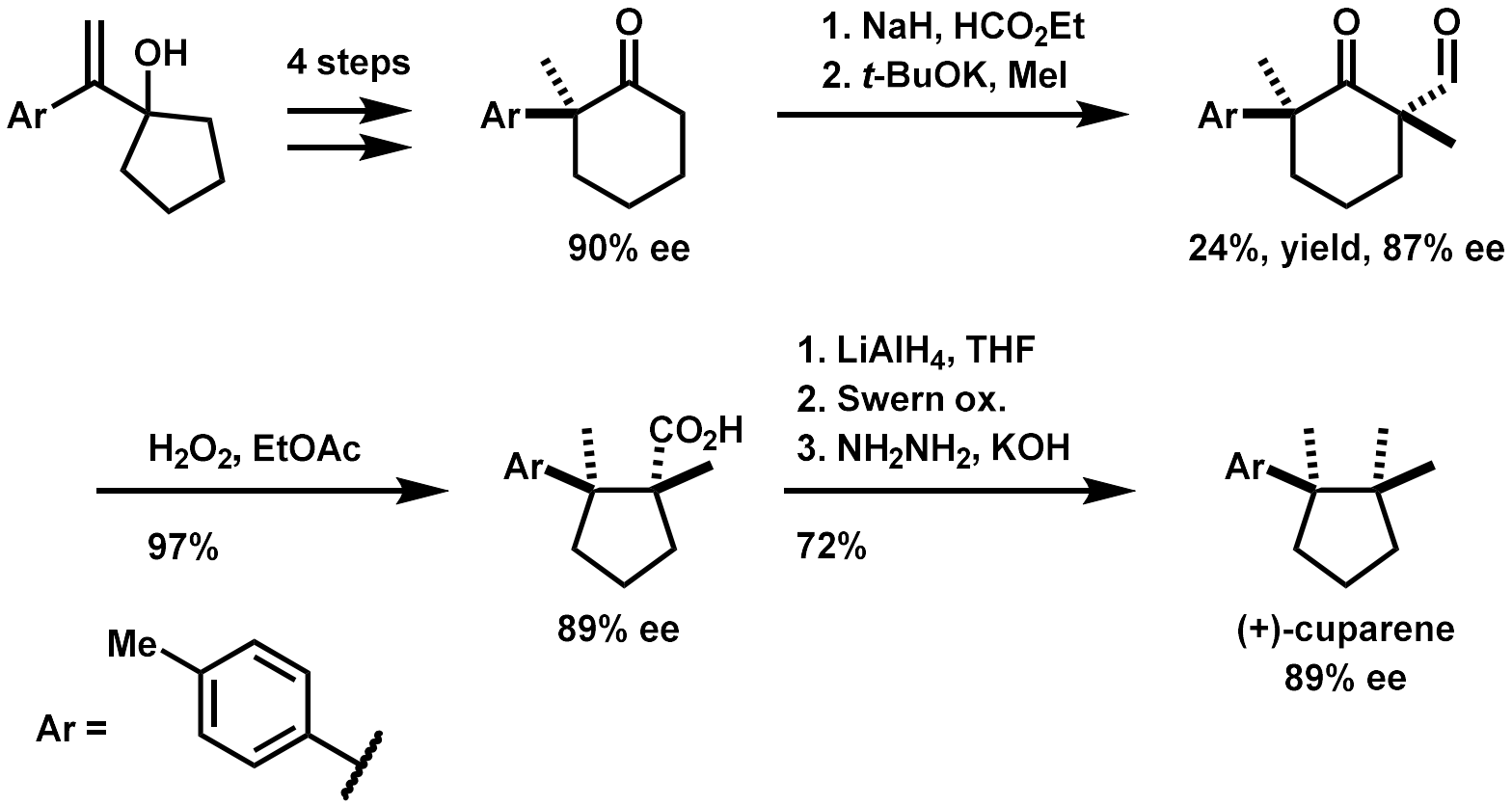
84% ee — 98%, 85% ee; 2:3 = >99:1

84% ee — 80%, 85% ee; 2:3 = >99:1

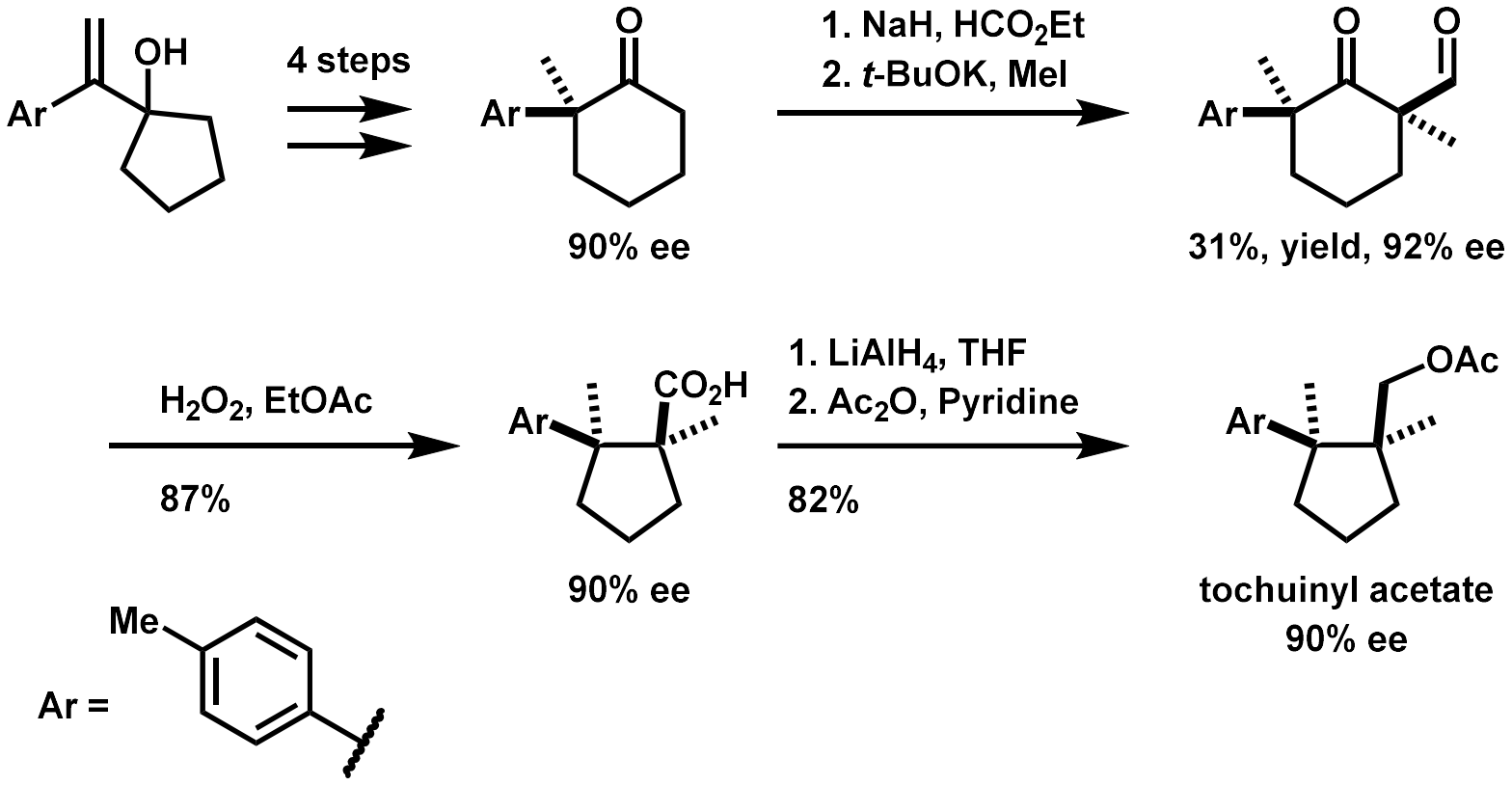
93% ee — 98%, 93% ee; 2:3 = >99:1

93% ee — 97%, 93% ee; 2:3 = >99:1

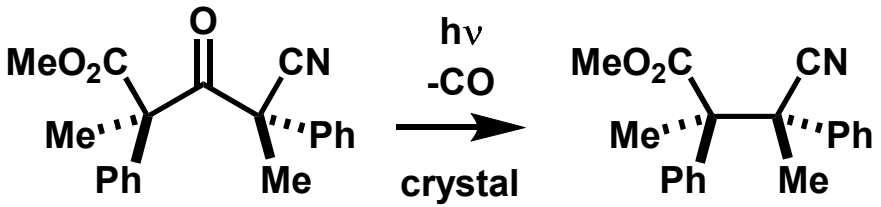
Application for total synthesis (+)-cuparene



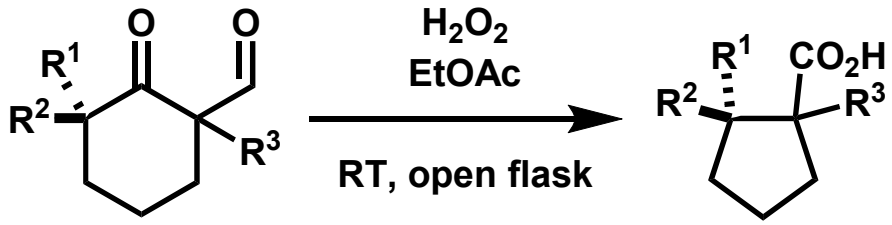
Application for total synthesis tochuinyl acetate



Summary

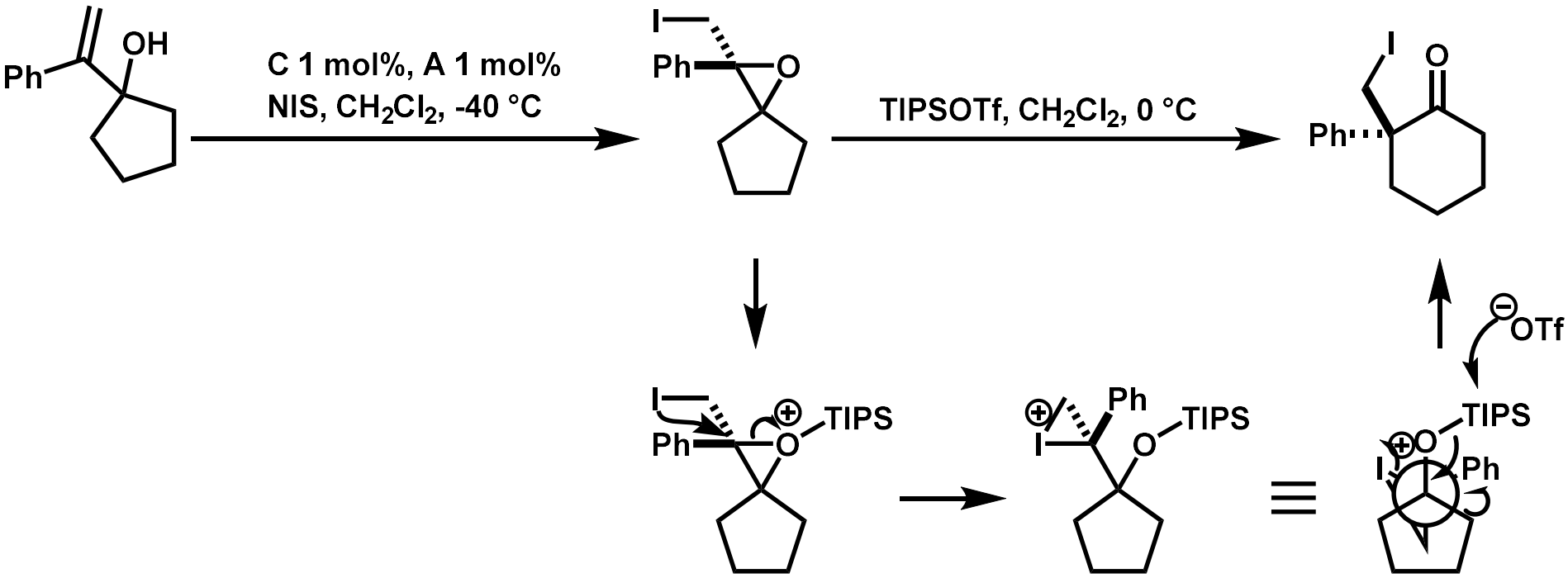


Substrate restriction



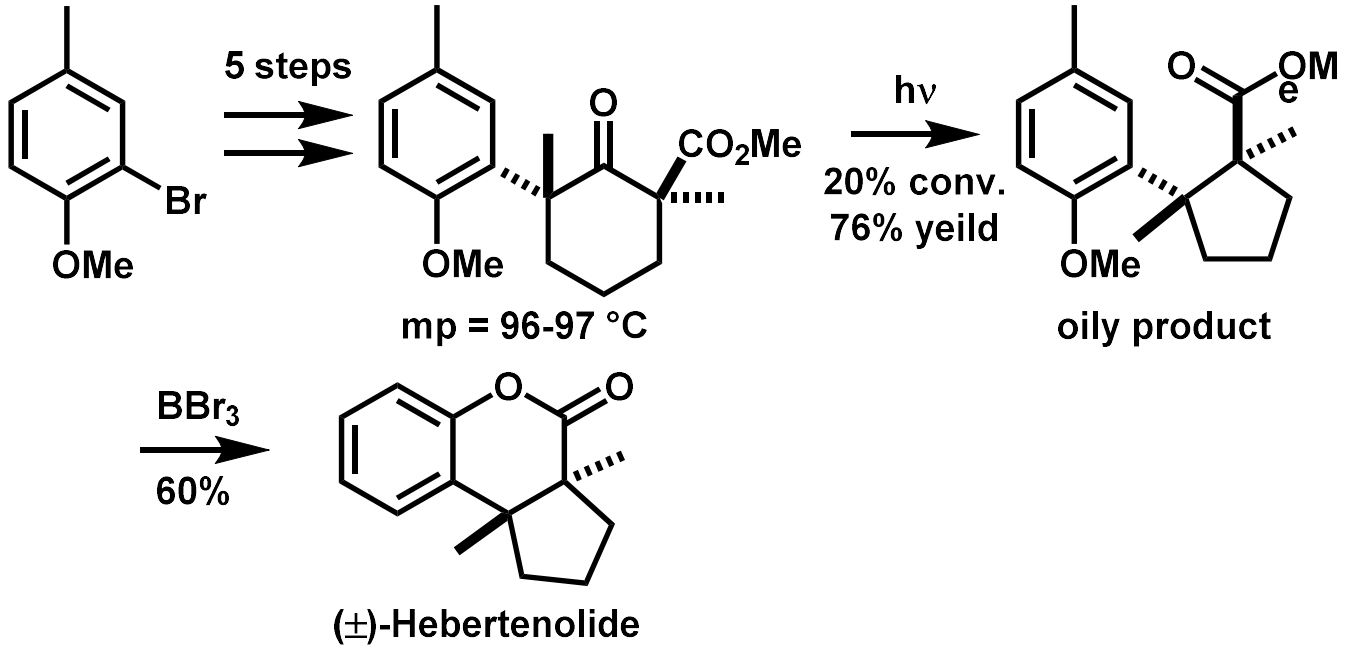
high stereo- selectivity
easy introduction of substituent

Preparation of enantioenriched substrate



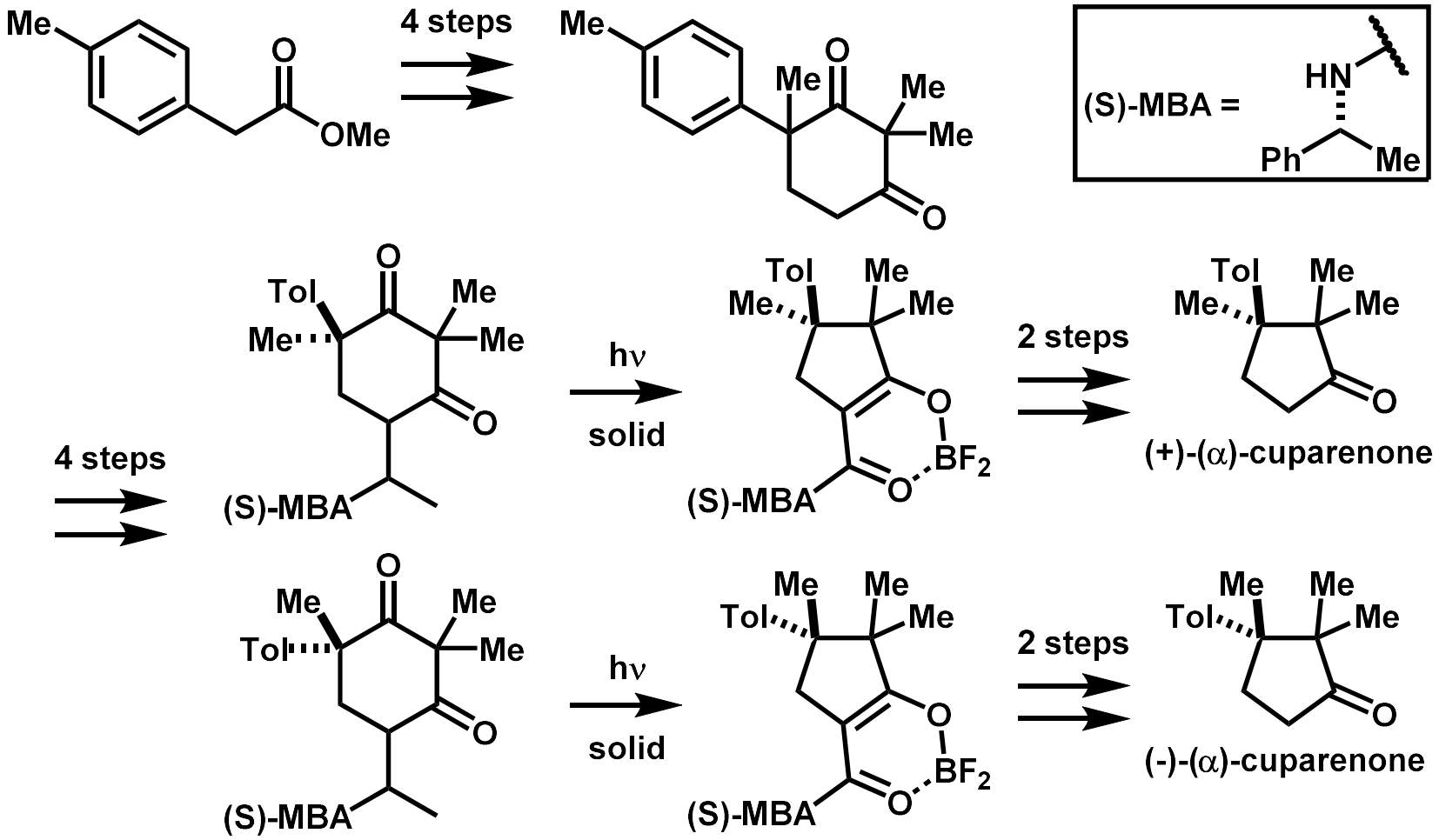
Xie, W. et al. *Chem. Sci.,* **2015,** *6,* 6986
Xie, W. et al. *Angew. Chem. Int. Ed.,* **2016,** *55*

Application for total synthesis Herbertenolide



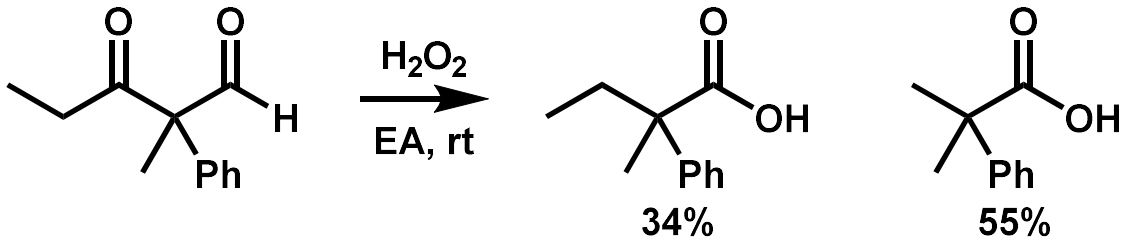
Garcia-Garibay, M. A. et al., *Org. Lett.,* **2004,** *6,* 645

Application for total synthesis (α)-cuparenone



Garcia-Garibay, M. A. et al., *Angew. Chem.,* **2007, *119,*** 6605

Linear dicarbonyl



hydride shift product was obtained in linear substrate

Garcia-Garibay, M. A. et al., *Angew. Chem.,* **2007, *119,*** 6605