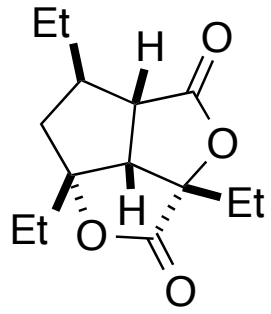
Total Synthesis of Gracilioether F: Development and Application of Lewis Acid Promoted Ketene-Alkene [2+2] Cycloadditions and Late Stage C-H Oxidation

Christopher M. Rasik and M. Kevin Brown

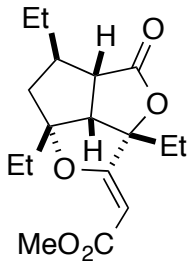
Angew. Chem. Intd. Ed. **2014**, *53*, 1-6



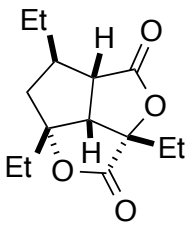
Gracilioether F

Introduction

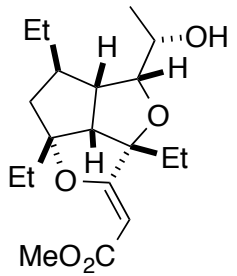
- Isolated from marine sponge *Plakinastrella mamillaris* in 2012
- No known biological activity
- Other members show antimalarial activity
- No prior syntheses of any members



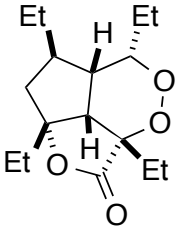
Gracilioether E



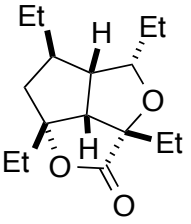
Gracilioether F



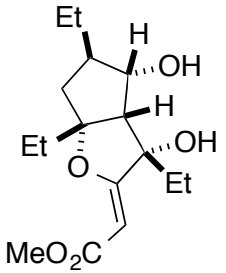
Gracilioether G



Gracilioether H



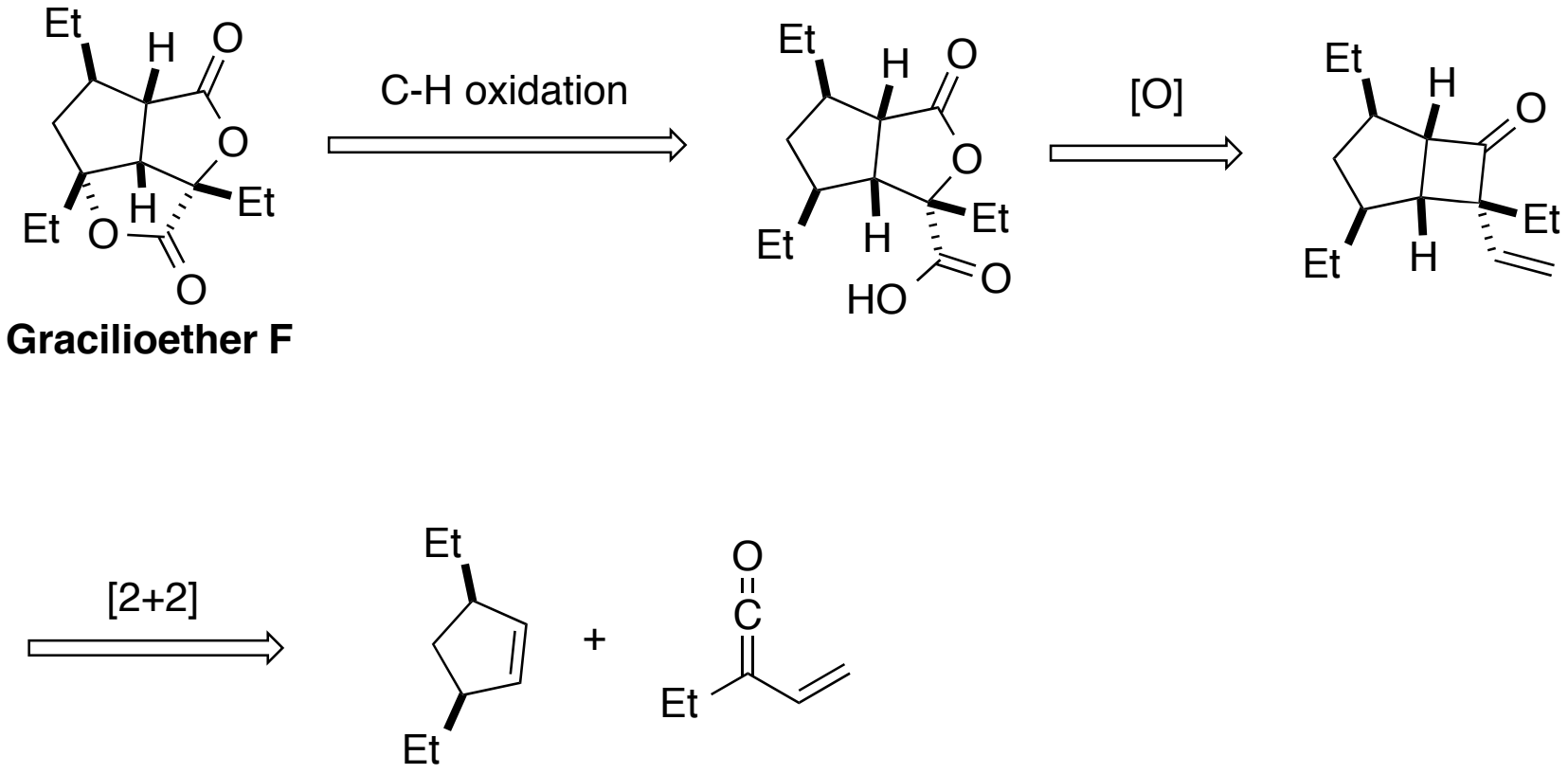
Gracilioether I



Gracilioether J

Tetrahedron **2012**, *68*,10157-10163

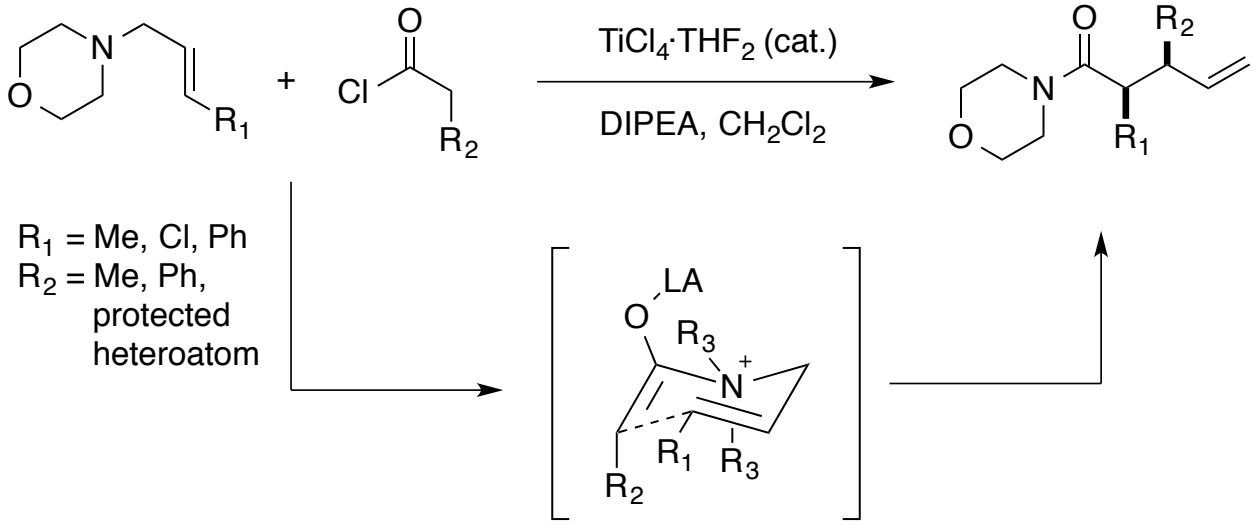
Retrosynthesis

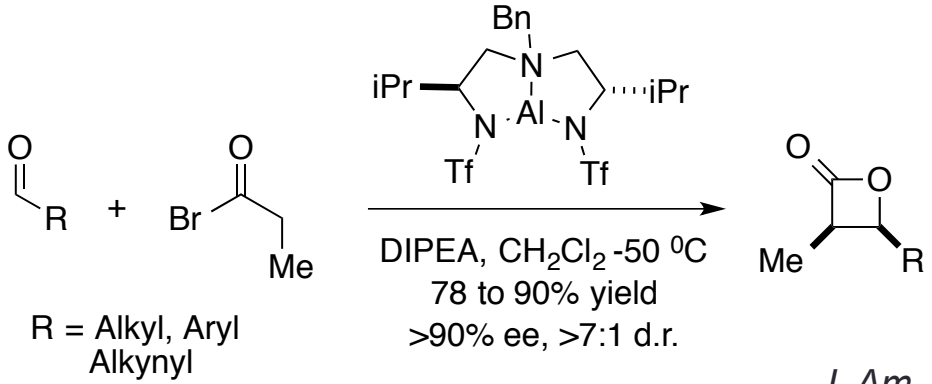


Gracilioether F

Angew. Chem. Intd. Ed. **2012**, *68*, 10157-10163

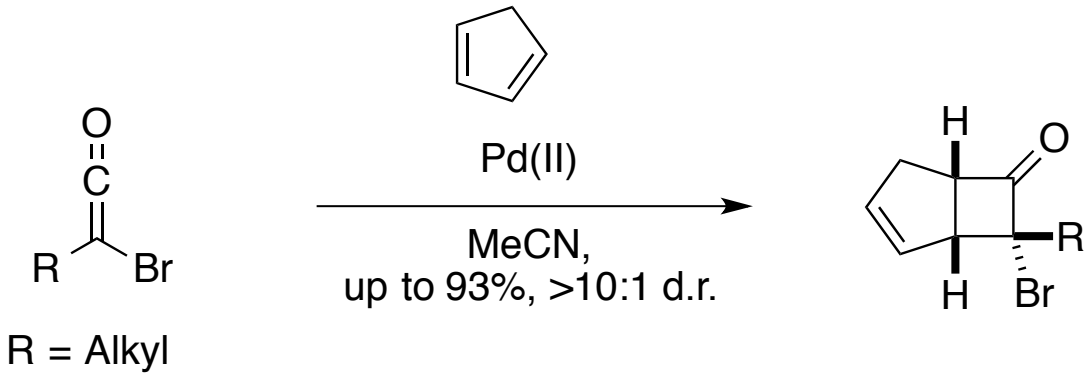
Previous Generation of Ketenes in Presence of Lewis Acids





J. Am. Chem. Soc. **1999,** *121,* 9726-9727
Org. Lett. **2000**, 2, 1883-1886

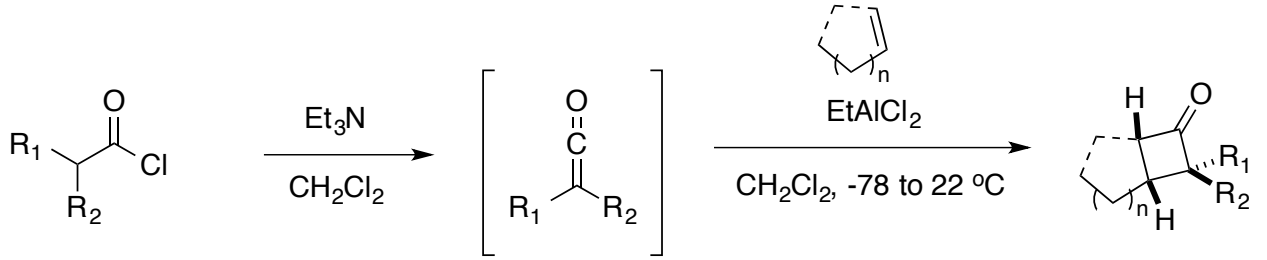
Pd-Mediated Ketene-Alkene [2+2]



- Significant improvement in yield over thermal reaction
- Opposite diastereomer of thermal reaction
- Very limited scope

Tetrahedron. **2001**, *57*, 2237-2246

Previous [2+2] Ketene-Alkene Cycloadditions



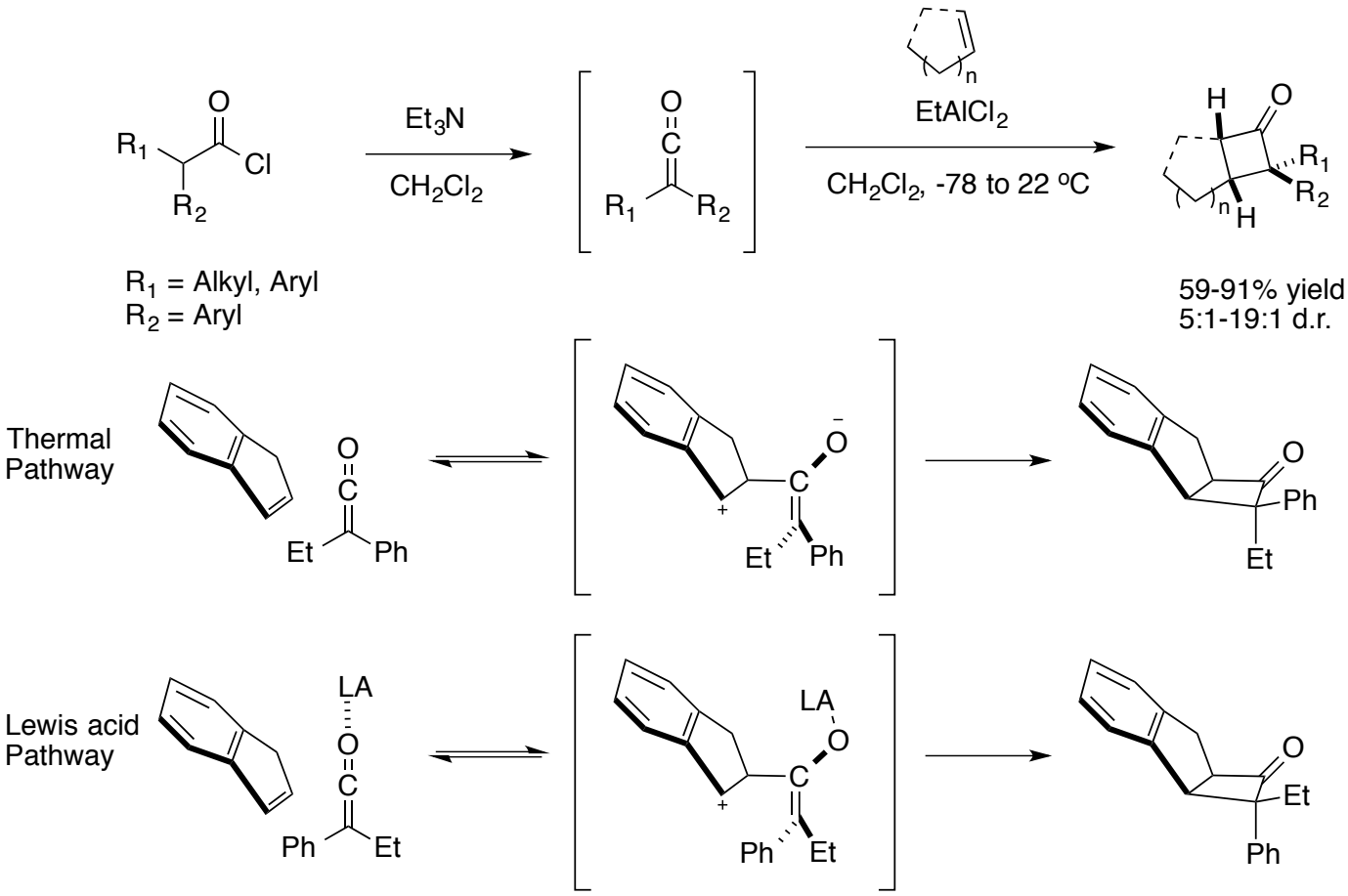
R_1 = Alkyl, Aryl
R_2 = Aryl

59-91% yield
5:1-19:1 d.r.

- $Sc(OTf)_3$, $Zn(OTf)_2$, $FeCl_3$, $SnCl_4$, $SiCl_4$, BCl_3, AgOTf, $Sn(OTf)_2$, $Mg(ClO_4)_2$, CuOTf, $AgClO_4$, $In(OTf)_3$, $AlMe_3$ all gave no product
- Opposite diastereomer from thermal [2+2]

J. Am. Chem. Soc. **2013**, *135*, 1673-1676

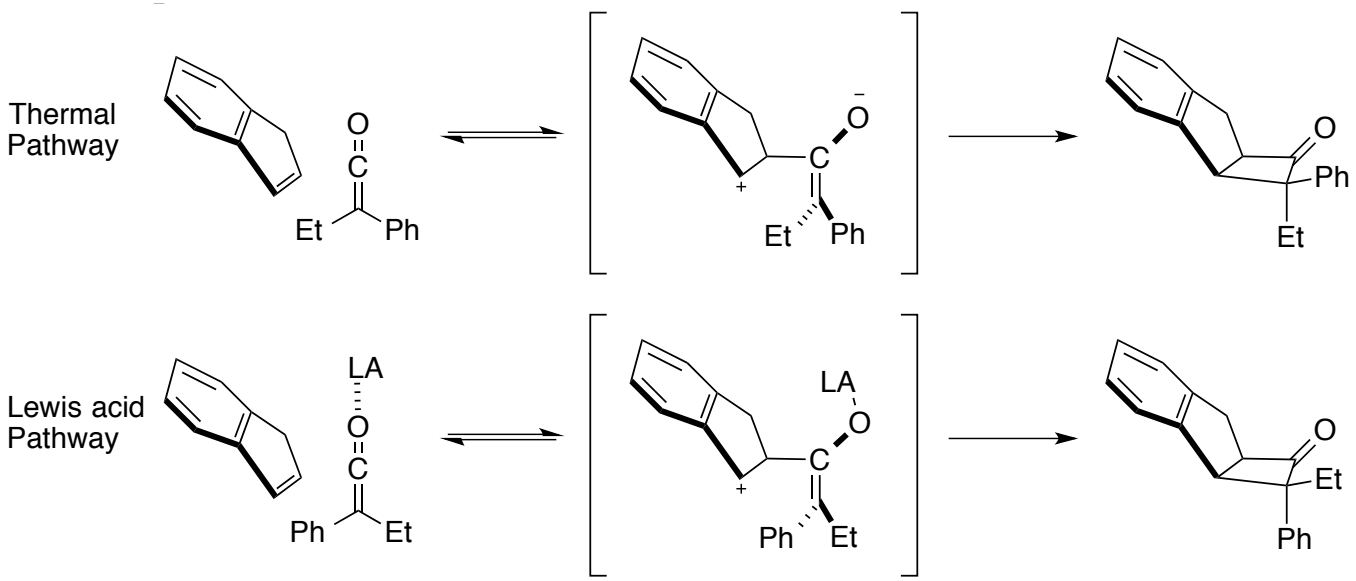
Previous [2+2] Ketene-Alkene Cycloadditions



J. Am. Chem. Soc. **2013**, *135*, 1673-1676
Org. Lett. **2014**, *16*, 5168-5171

Previous [2+2] Ketene-Alkene Cycloadditions

- Alkene from less hindered side in thermal reaction
- Lewis acid has steric clash with Ph; leads to selectivity
- Rotational barrier for Ph-ketene bond reduced from 3.6 to 1.7 kcal/mol



J. Am. Chem. Soc. **2013**, *135*, 1673-1676
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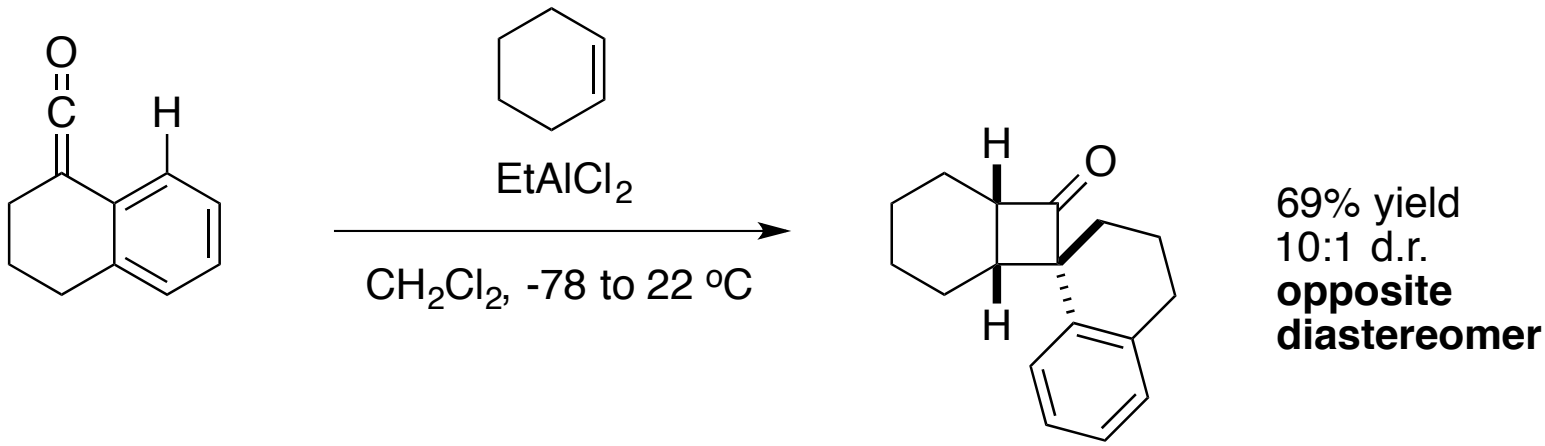
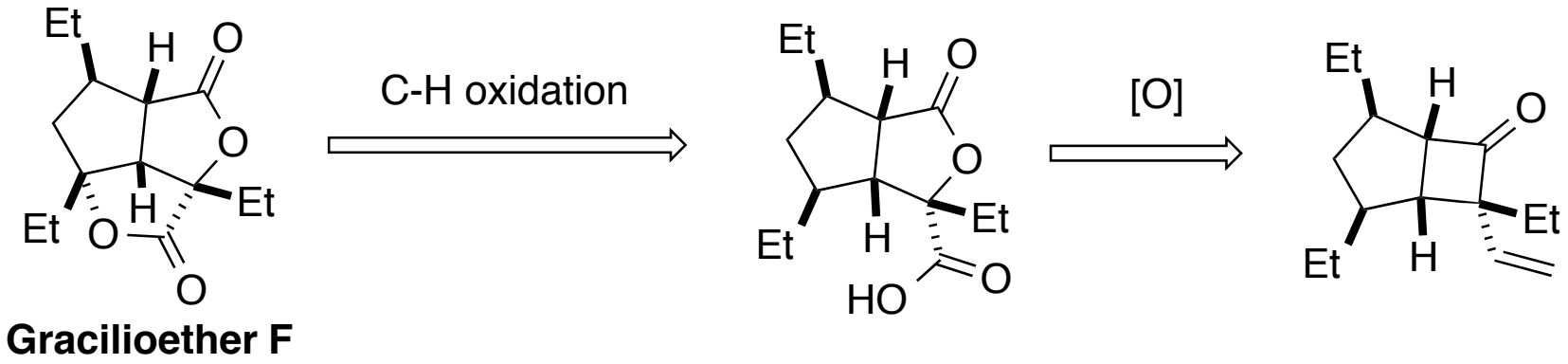


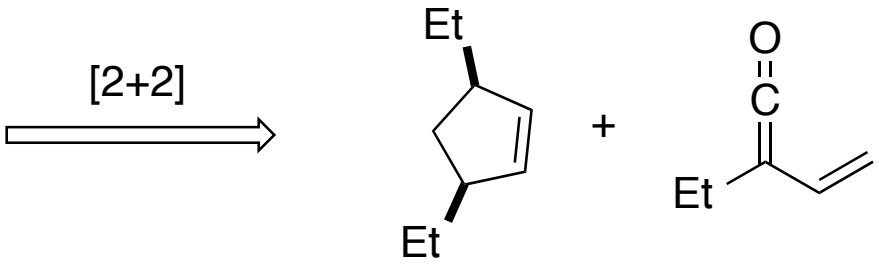
69% yield
10:1 d.r.
opposite diastereomer

J. Am. Chem. Soc. **2013**, *135*, 1673-1676
Org. Lett. **2014**, *16*, 5168-5171

Retrosynthesis

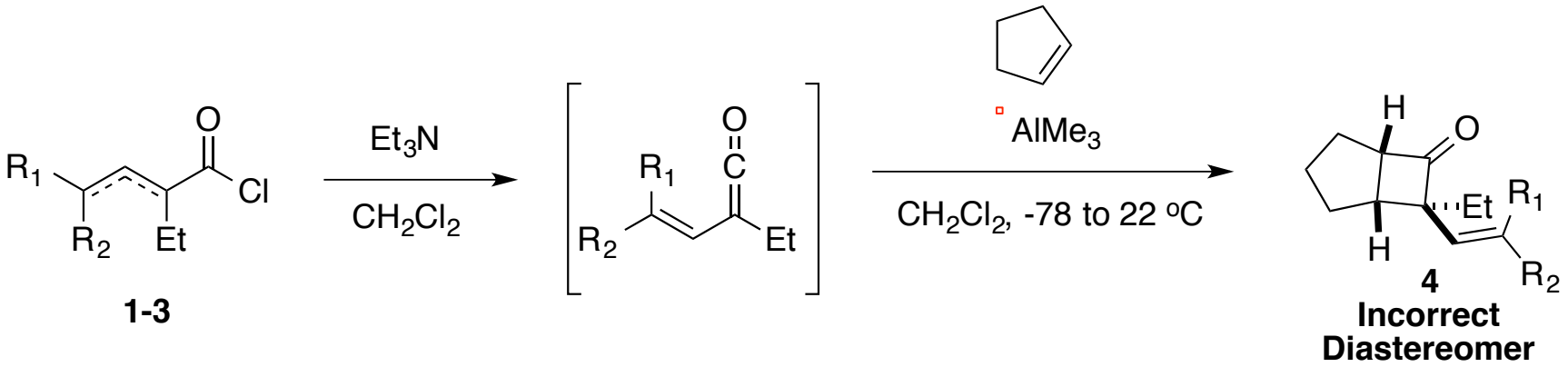


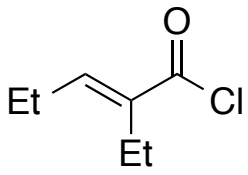
Gracilioether F



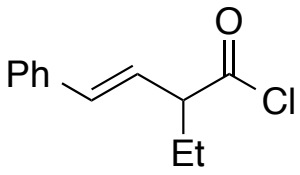
Angew. Chem. Intd. Ed. **2012**, *68*, 10157-10163

Development of [2+2] for Gracilioether F

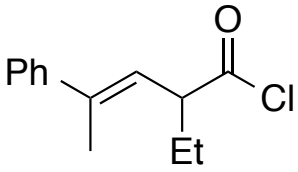




1
<2% yield



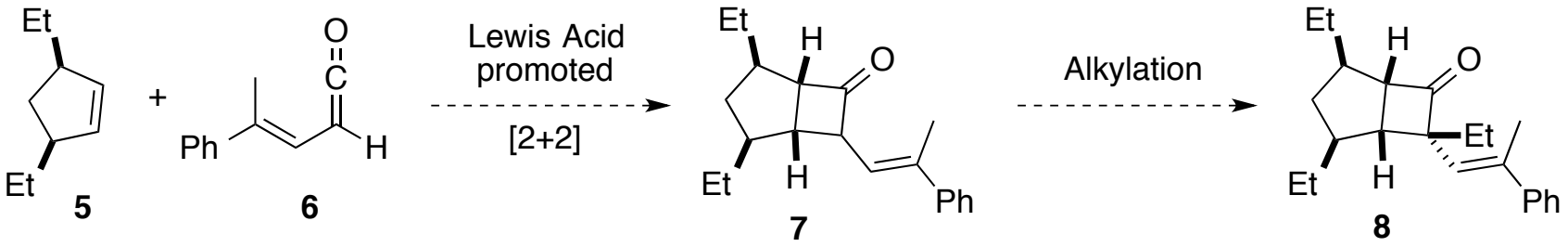
2
42% yield
7:1 d.r.



3
61% yield
3:1 d.r.

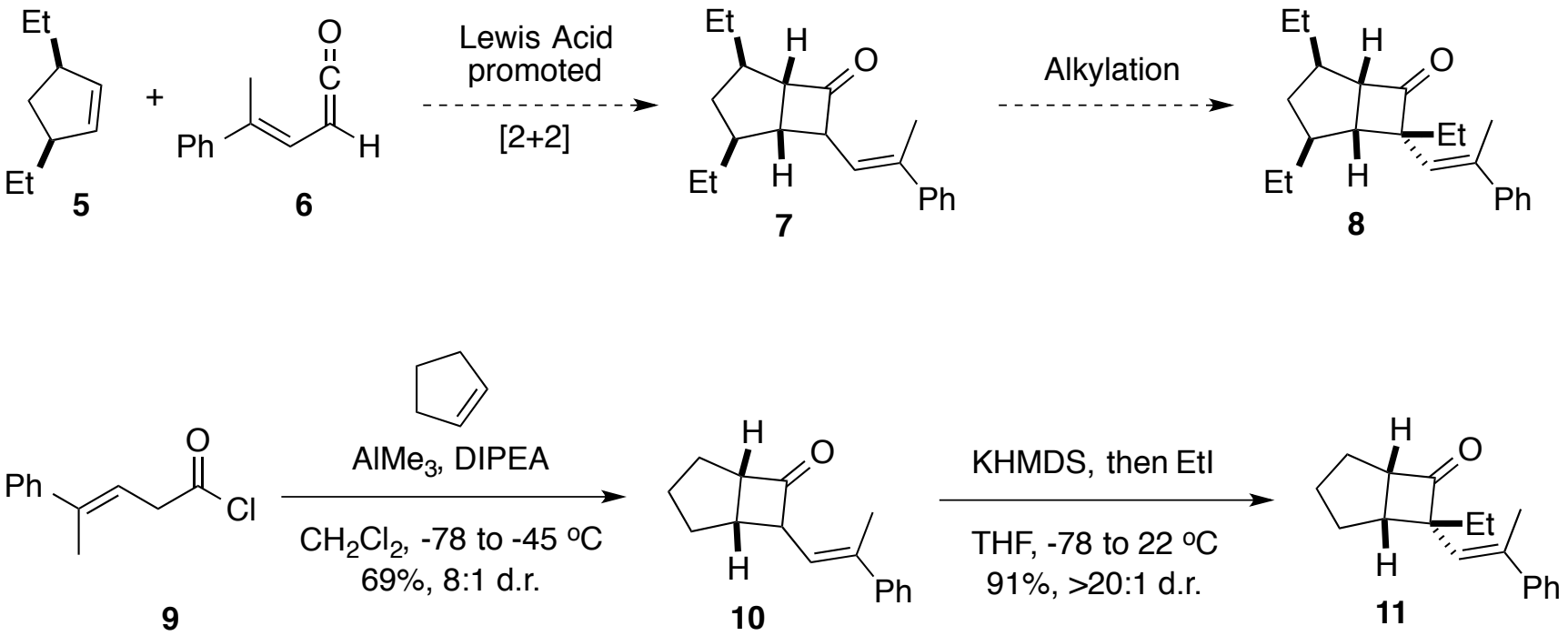
Angew. Chem. Intd. Ed. **2012**, *68*, 10157-10163

New Strategy for [2+2]



Angew. Chem. Intd. Ed. **2012**, *68*, 10157-10163

New Strategy for [2+2]



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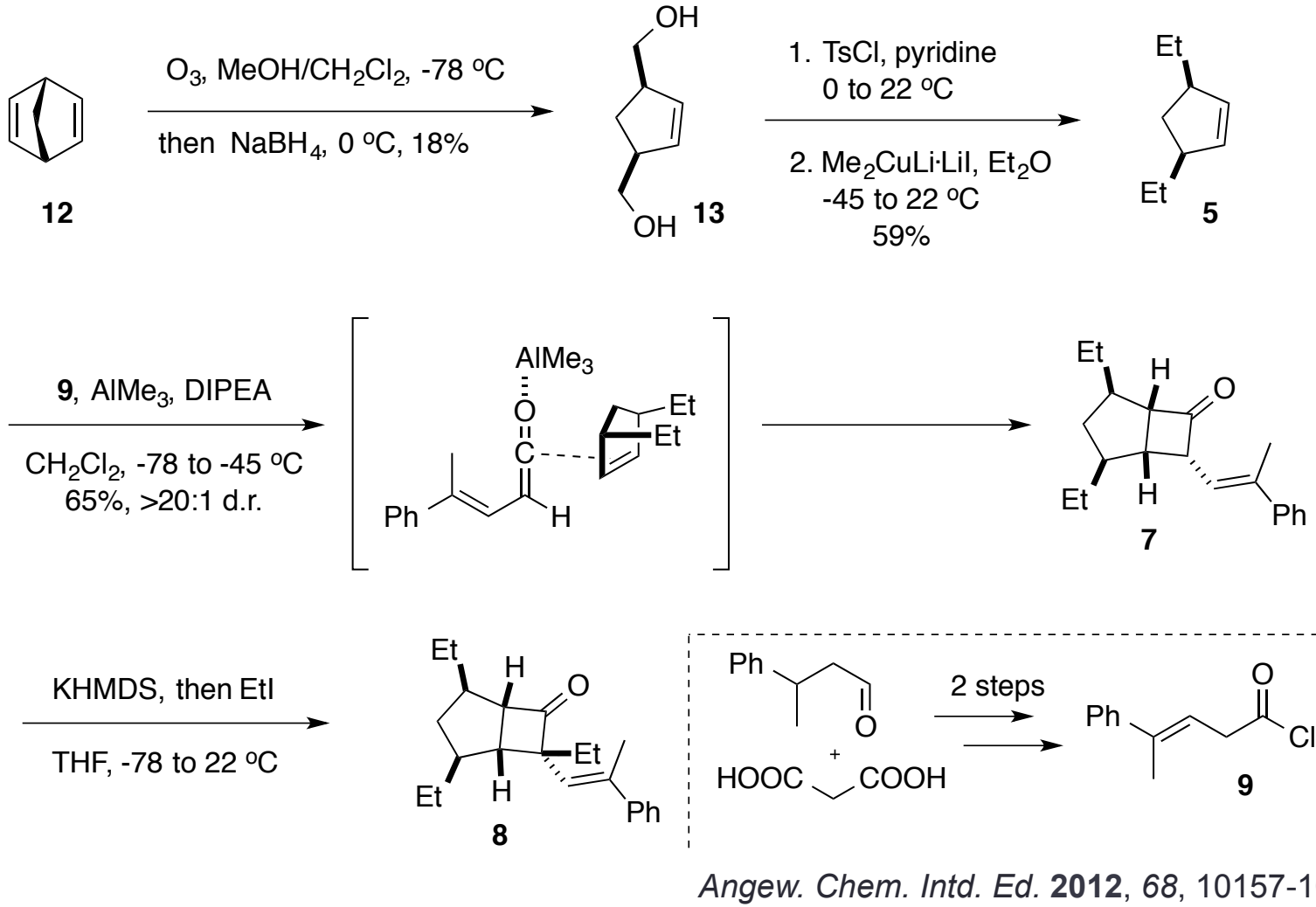
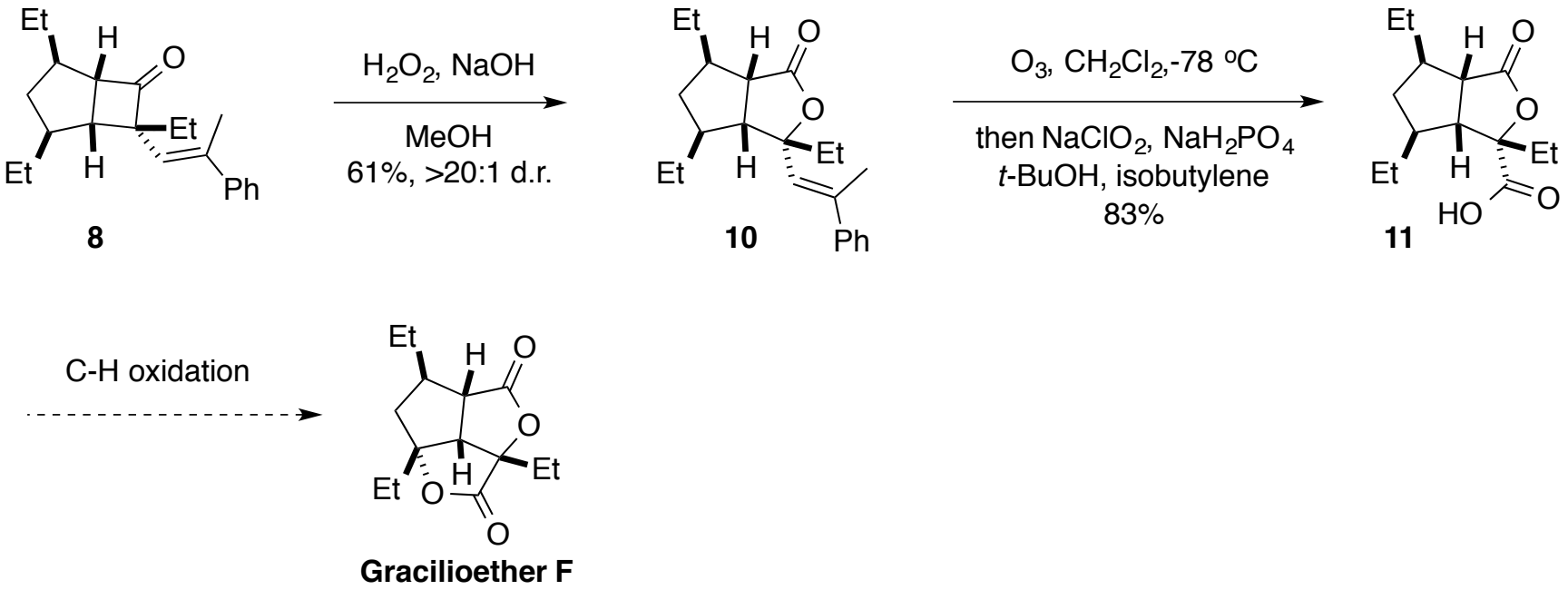
Synthesis



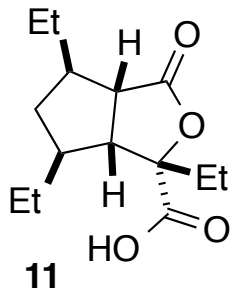
Angew. Chem. Intd. Ed. **2012**, *68*, 10157-10163

Synthesis (cont'd.)



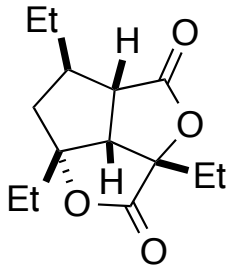
Angew. Chem. Intd. Ed. **2012**, *68*, 10157-10163

C-H Oxidation Development

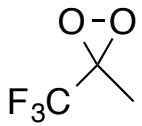


11

Conditions

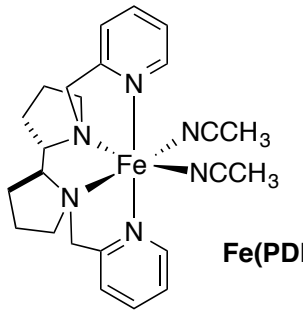


Gracilioether F



TFDO

Entry	Conditions	Yield (%)	RSM (%)
1	$RuCl_3$, $KBrO_3$, pyridine MeCN/H_2O	<2	---
2	TFDO, CH_2Cl_2, -45 to 22 °C	<2	>90
3	Fe(PDP) (20 mol%), H_2O_2,MeCN	9	48
4	$Fe(OAc)_2$, H_2O_2,MeCN	<2	~80
5	$Mn(OAc)_2$, H_2O_2,MeCN	<2	~80
6	$Cu(OAc)_2$, H_2O_2,MeCN	15	51
7	$Cu(OAc)_2$, H_2O_2,MeCN, 0 °C	10	88
8*	$Cu(OAc)_2$, H_2O_2,MeCN, 0 °C	<2	>90

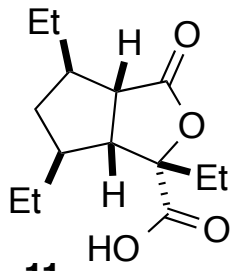


Fe(PDP)

*using Me ester of **11**

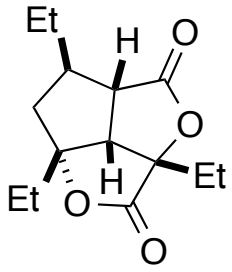
Angew. Chem. Intd. Ed. **2012**, *68*, 10157-10163

C-H Oxidation Development



11

Conditions



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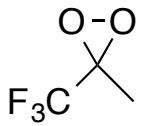

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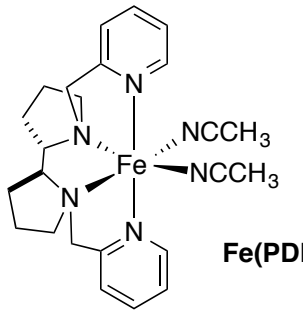

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Conclusions

- Gracilioether F was synthesized in 8 steps in 0.35% yield
- Features a unique Lewis acid promoted ketene-alkene [2+2] cycloaddition and a late stage C-H oxidation
- Yield is disappointing
- C-H oxidation is very impractical