Total Synthesis of Resveratrol-Based Natural Products
&
Nucleophilic Carbene and HOAt Relay Catalysis in an Amide Bond Coupling

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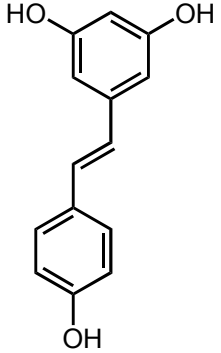
Group Meeting

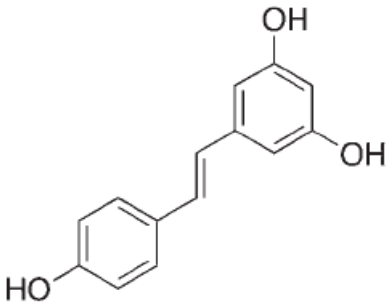
12/14/2007

Resveratrol

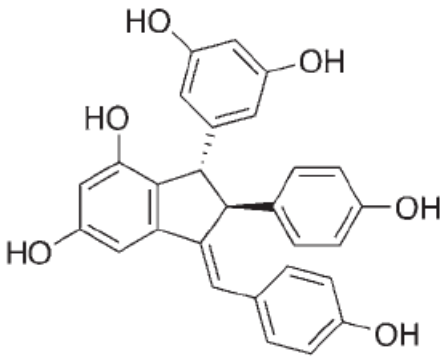
- A phytoalexin(antibiotics) produced naturally by several plants when under attack by bacteria or fungi.
- *In vivo* and *in vitro* activity against inflammation, heart disease, aging, and cancer.
- Found in the skin of red grapes and is a constituent of red wine (~ 100µM).
- Absent in white wine and grape juice.
- Popular notion: it is supporter of " French Paradox".
  (the observation that the French suffer relatively low incidence of coronary heart disease, despite having a diet relatively rich in saturated fats.)



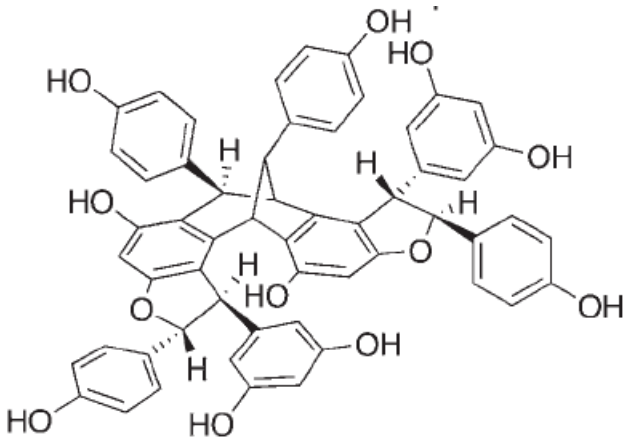
Resveratrol- Based Natural Products



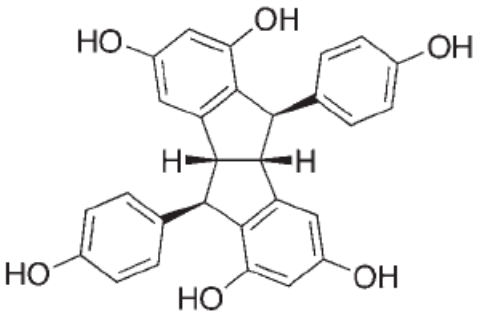
1: resveratrol



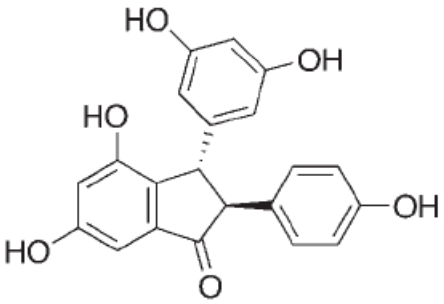
2: ampelopsin D



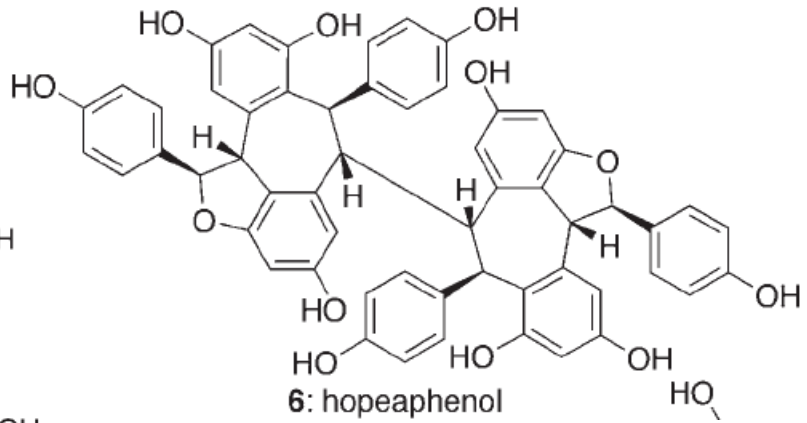
5: vaticanol C



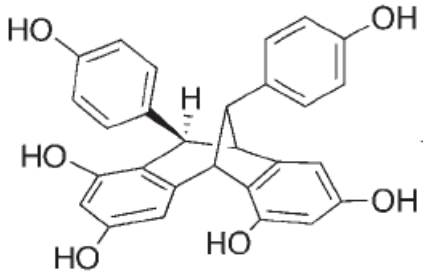
3: pallidol



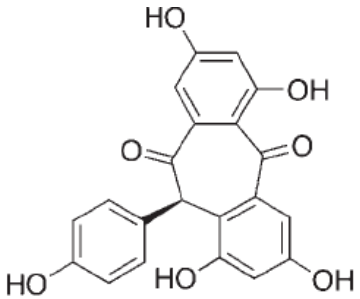
7: paucifloral F



6: hopeaphenol

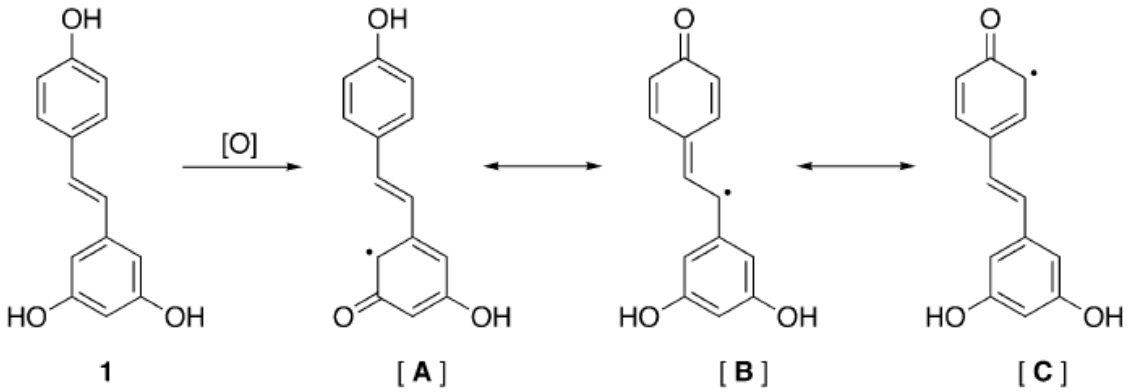


4: ampelopsin F



8: diptoindonesin A

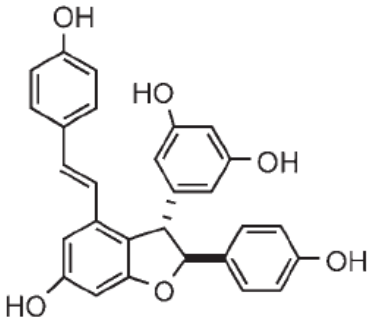
Earlier Approaches



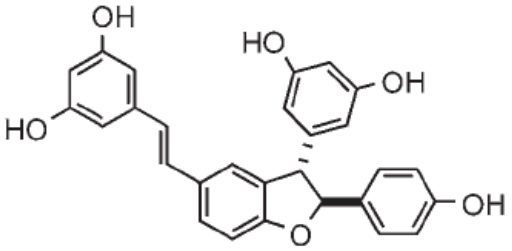
[A] + [B] ⟶ ε-viniferin

[B] + [B] ⟶ pallidol

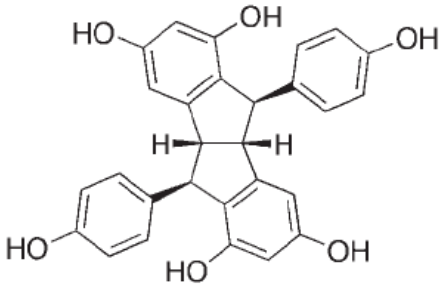
[B] + [C] ⟶ resveratrol-*trans*-dehydrodimer



ε-viniferin (**8**)



resveratrol *trans*-dehydrodimer (**9**)



3: pallidol

Niwa *et.al.*, *Tetrahedron* **2005,** *61*, 10285

Earlier Approaches

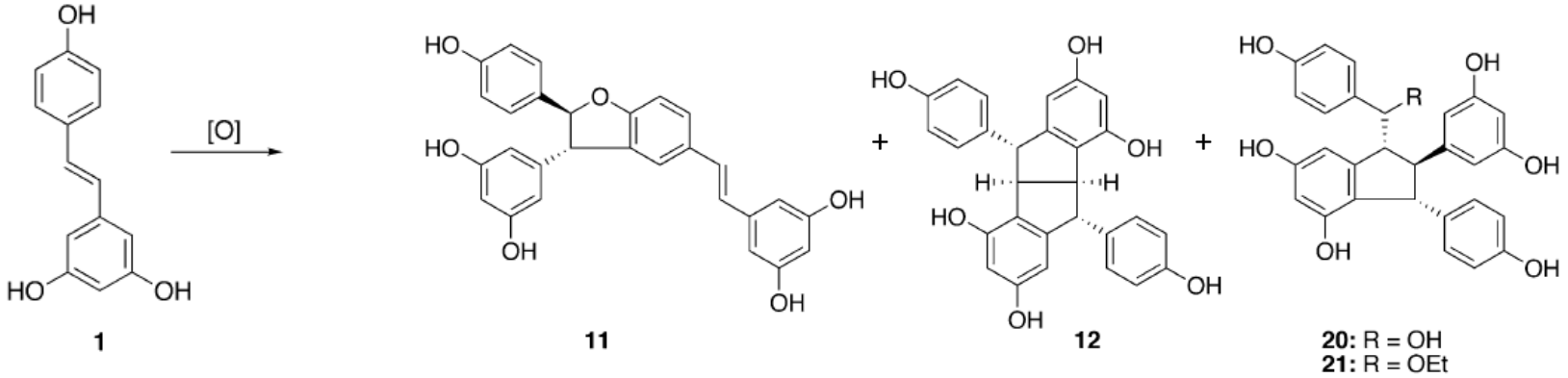


Table 2. Diversity of the products obtained by the treatment of resveratrol (**1**) with peroxidases

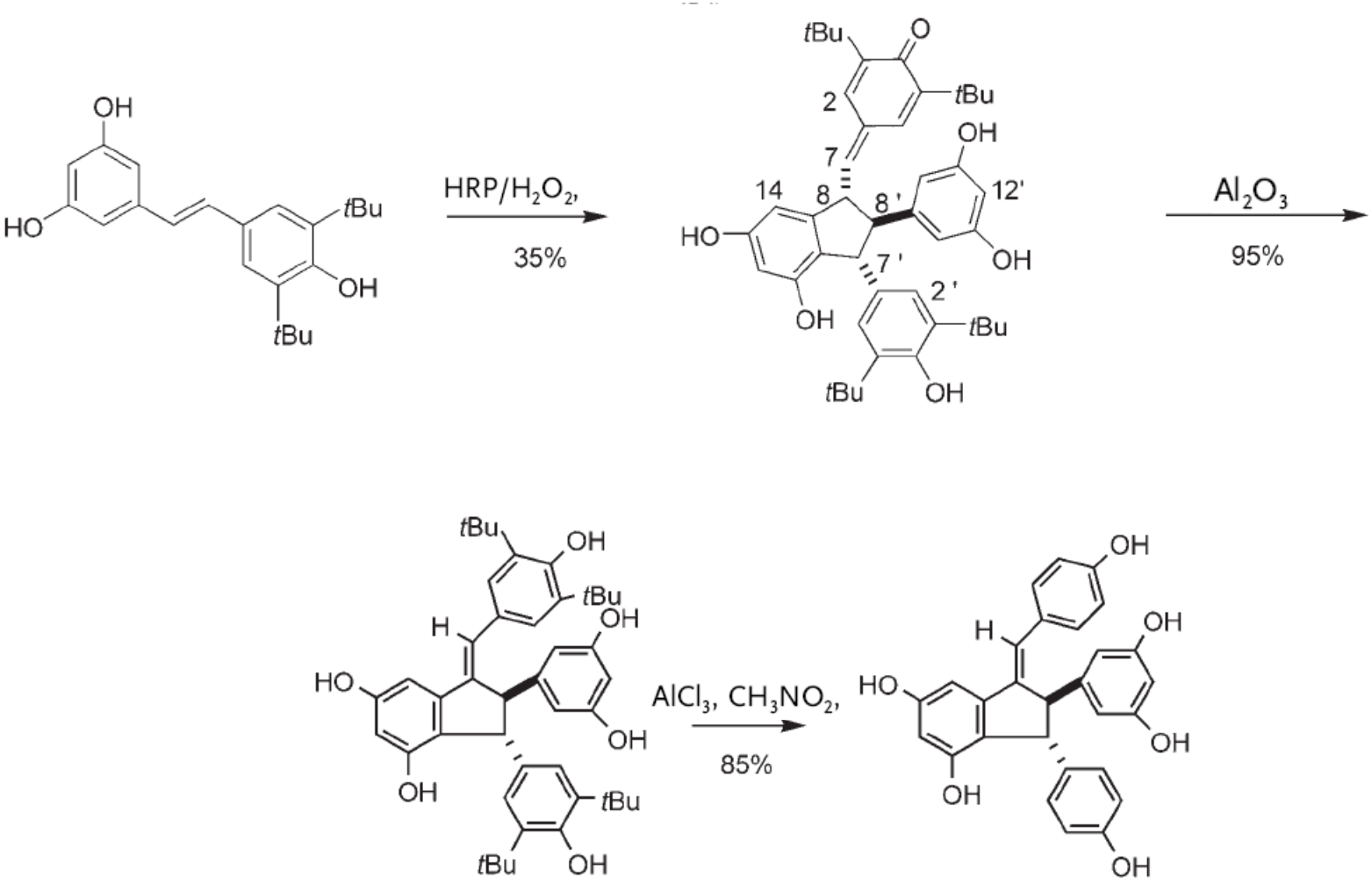
Origins of peroxidases	Solvent	**11** (%)	**12** (%)	**20** (%)	**21** (%)
Glycine max	aq Acetone	21.4	7.2	1.8	—
Arthromyces ramosus	aq Acetone	18.4	7.4	4.6	—
Horseradish	aq Acetone	12.6	10.2	—	—
Glycine max	aq EtOH	12.1	9.5	5.2	8.6
Arthromyces ramosus	aq EtOH	13.1	5.0	4.6	8.2

The percentage in this table means the 'degree of transformation (%DT)'. See Section 3.

Low yields and Low selectivity

Niwa *et.al.*, *Tetrahedron* **2005,** *61*, 10285

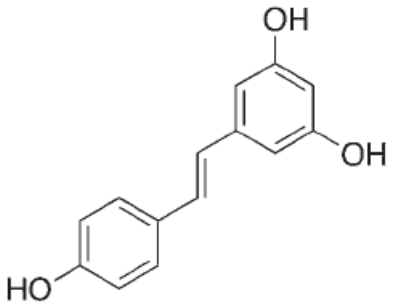
Earlier Approaches



Quardrangularin A

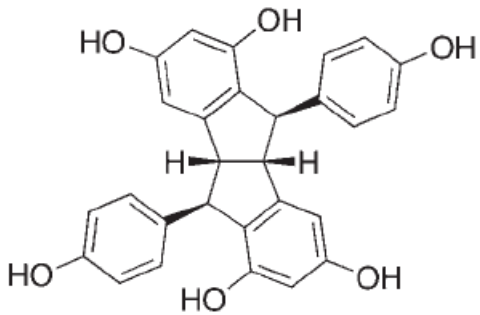
Hou *et.al.*, *ACIEE* **2006,** *45,* 7609

Solution to Chemoselectivity Problem

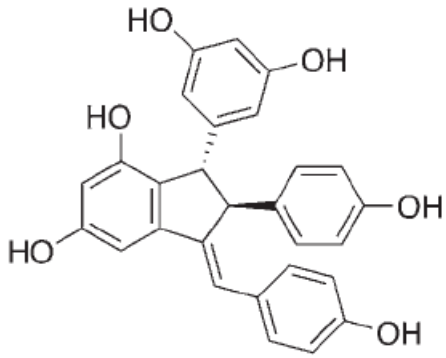


1: resveratrol

Direct
oligomerization



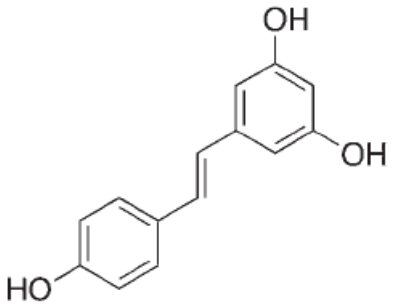
3: pallidol



2: ampelopsin D

Snyder *et.al.* *ACIEE* **2007,** *46*, 8186

Solution to Chemoselectivity Problem



1: resveratrol

Direct
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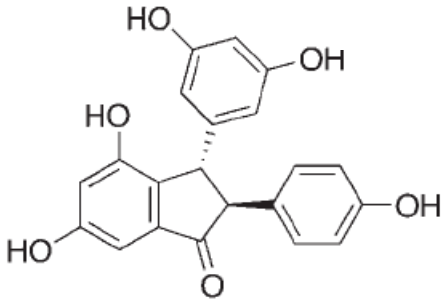
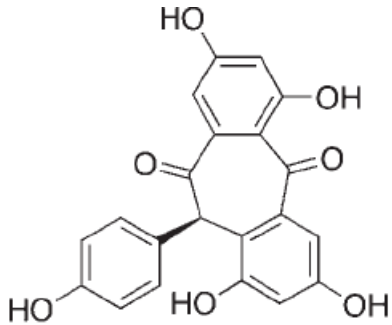
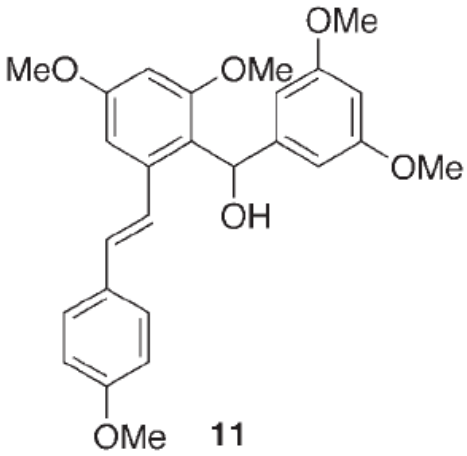


7: paucifloral F



8: diptoindonesin A

Hypothesis: Tri-aryl precursors can be lead to every family member(may be by altering the reagents and reaction conditions)



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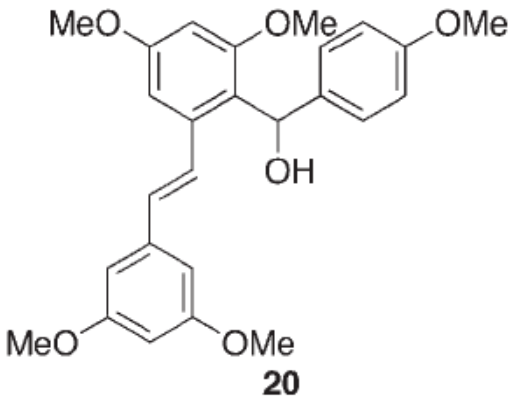
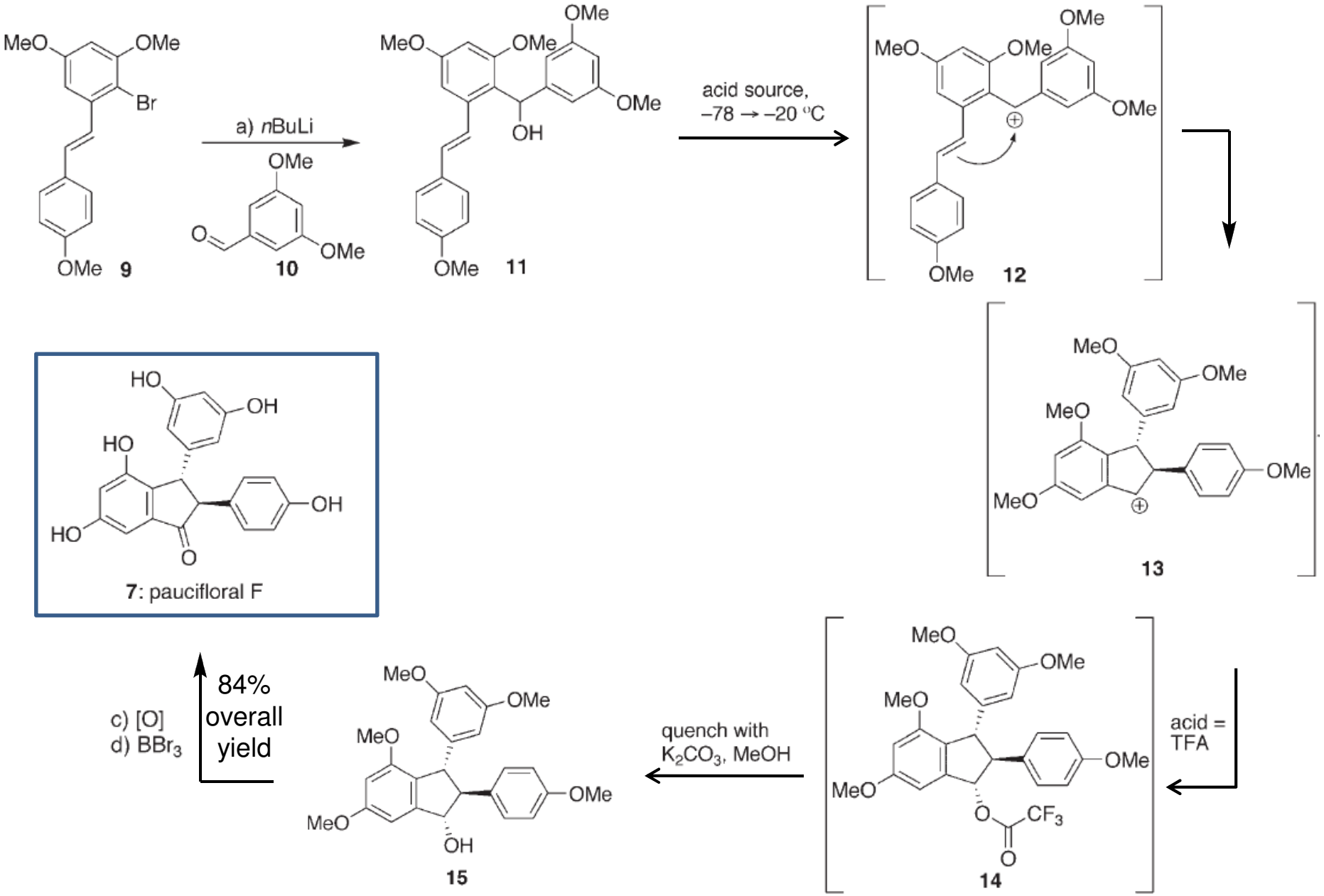


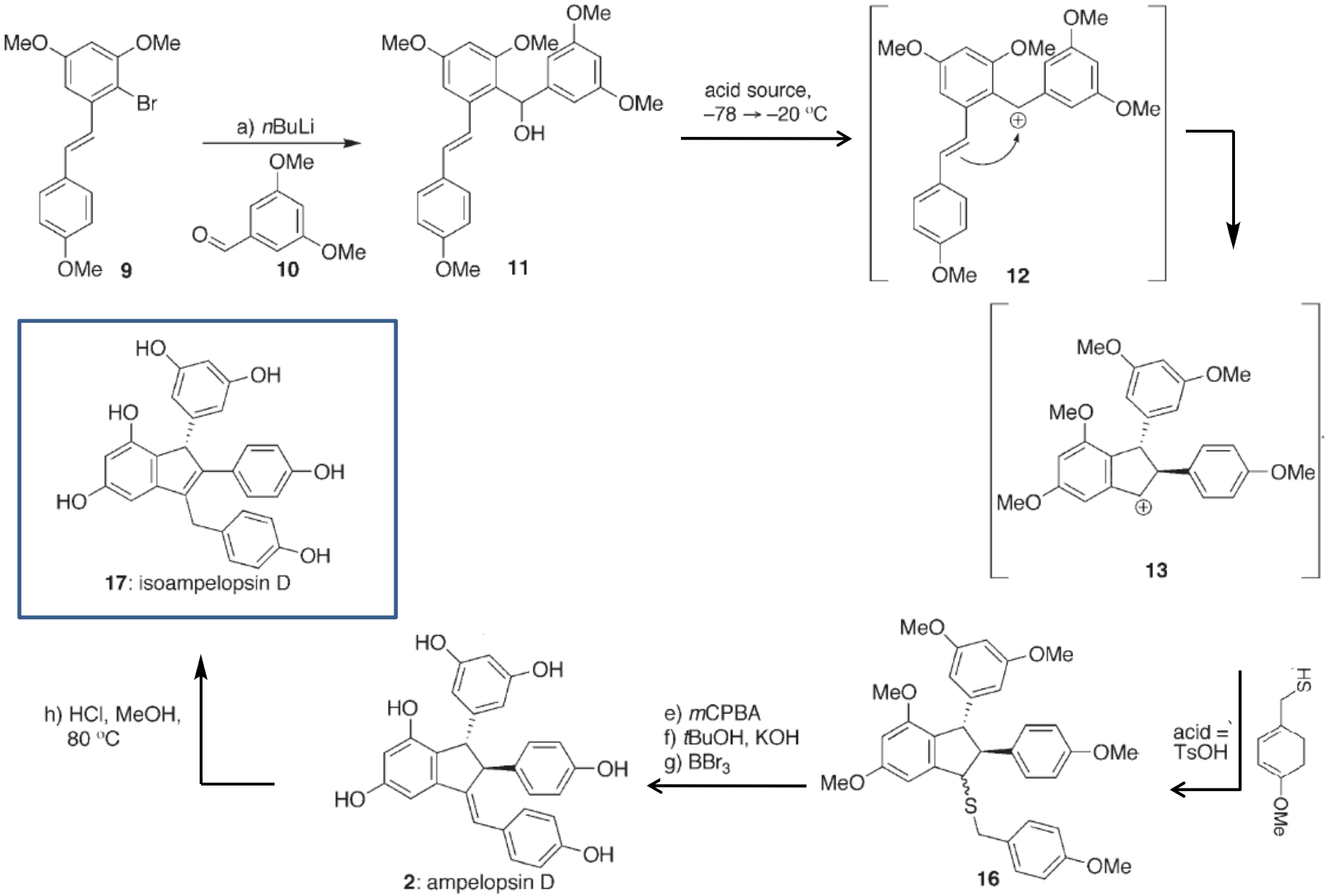
20

Snyder *et.al.* *ACIEE* **2007,** *46*, 8186

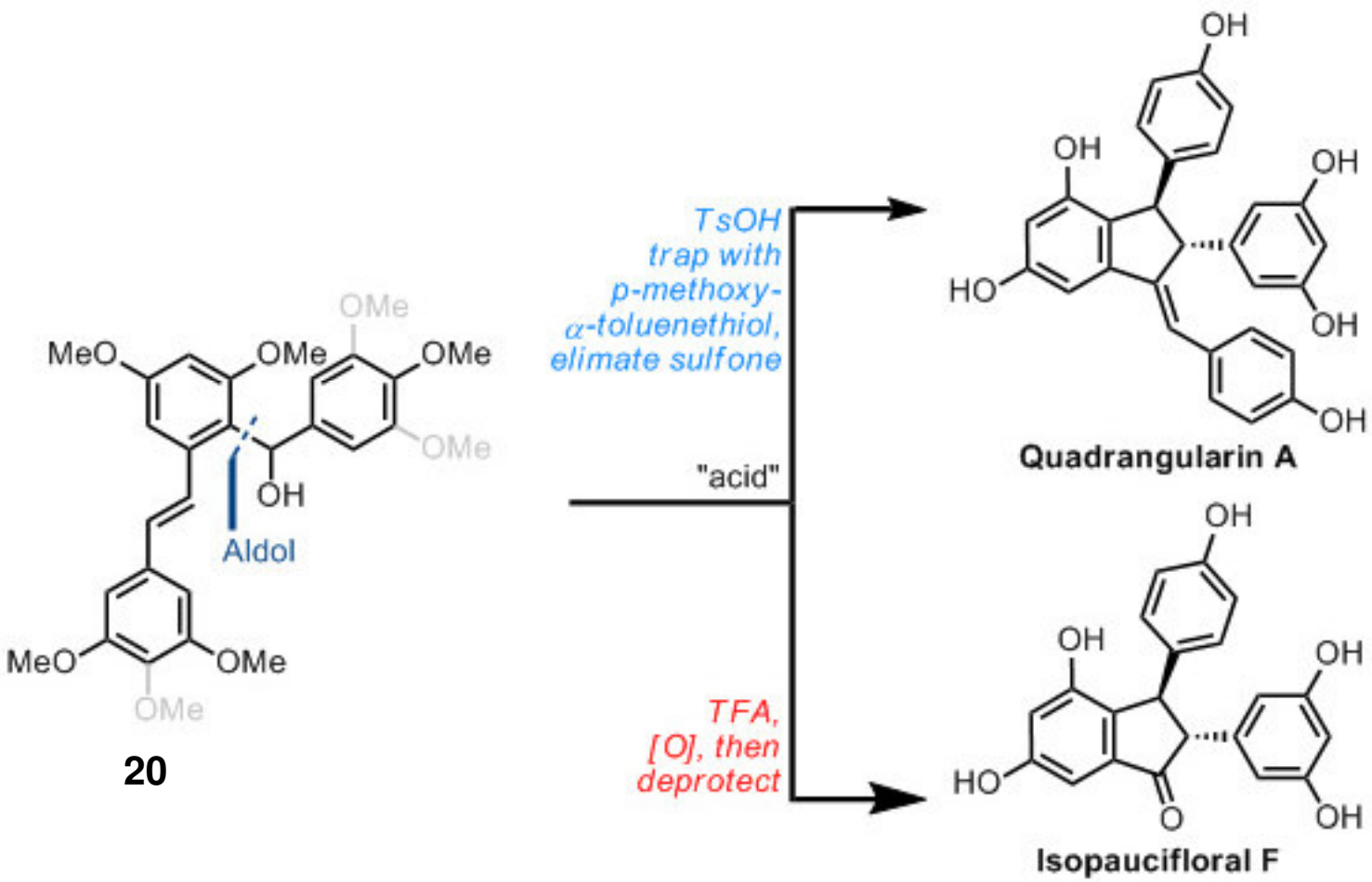
Total Synthesis of Paucifloral F



Total Synthesis of Ampelosin D & Isoampelopsin D

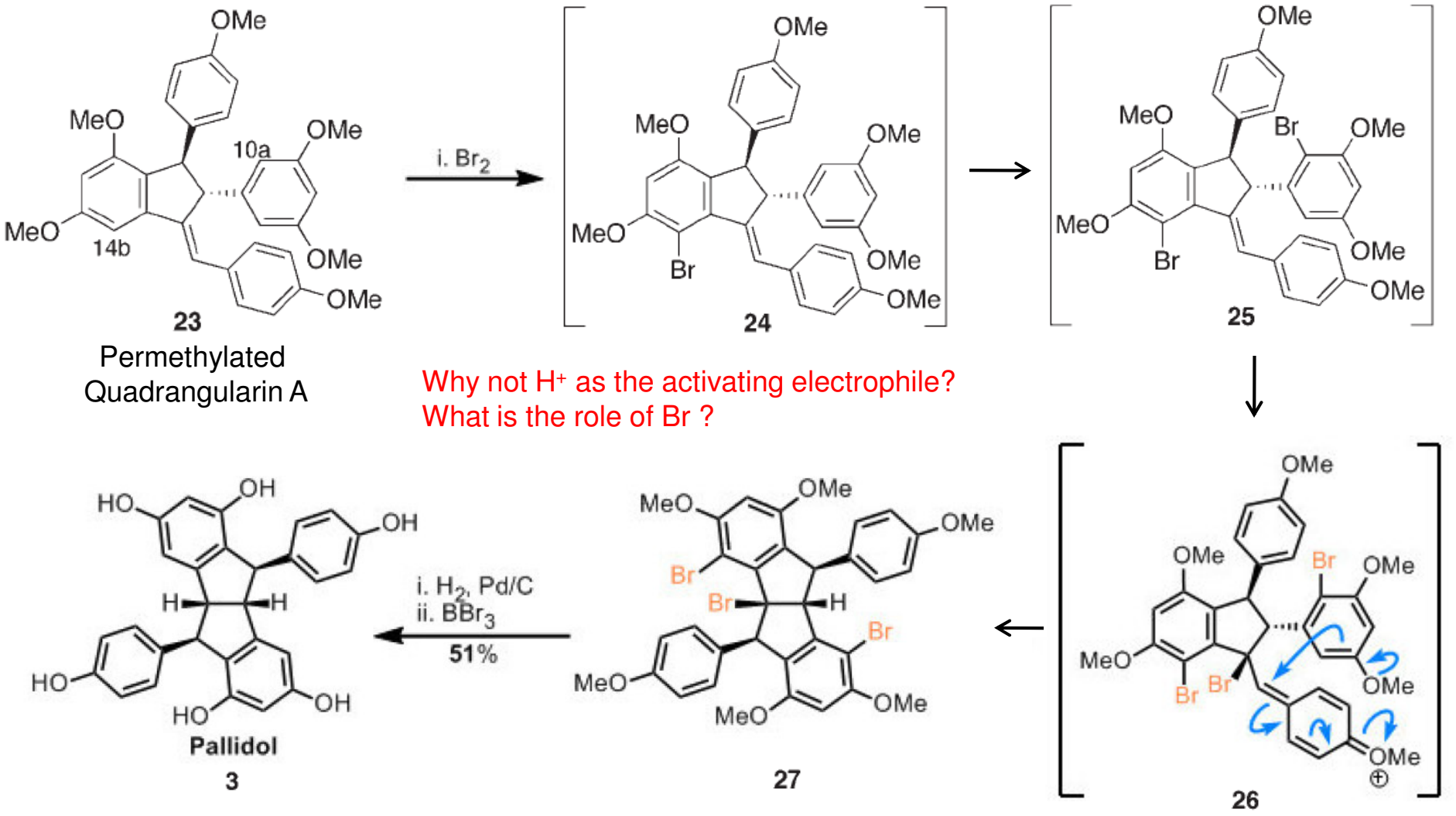


Total Synthesis of quadrangularin A and Isopaucifloral F



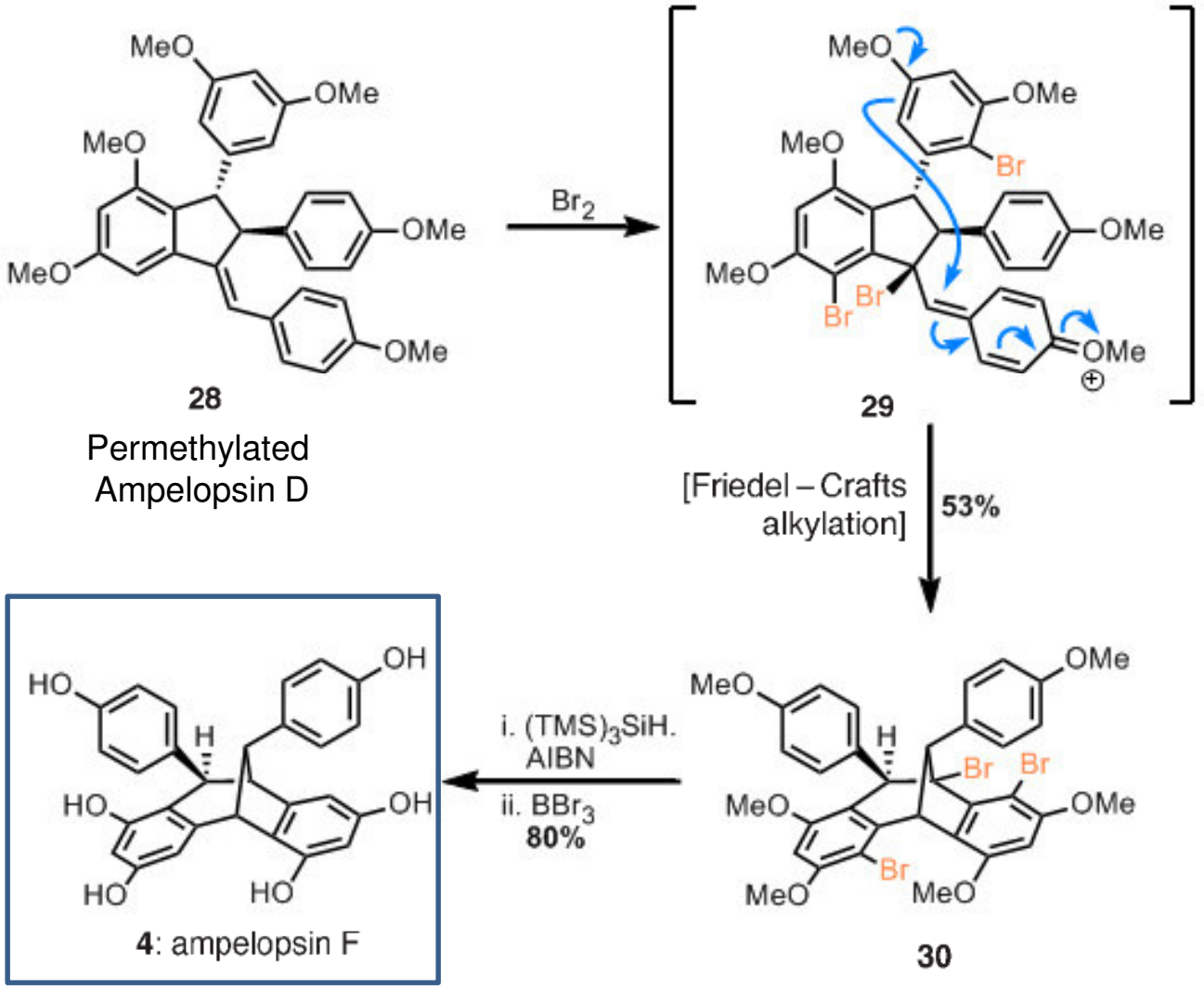
Snyder *et.al.* *ACIEE* **2007,** *46*, 8186

Total Synthesis of Pallidol



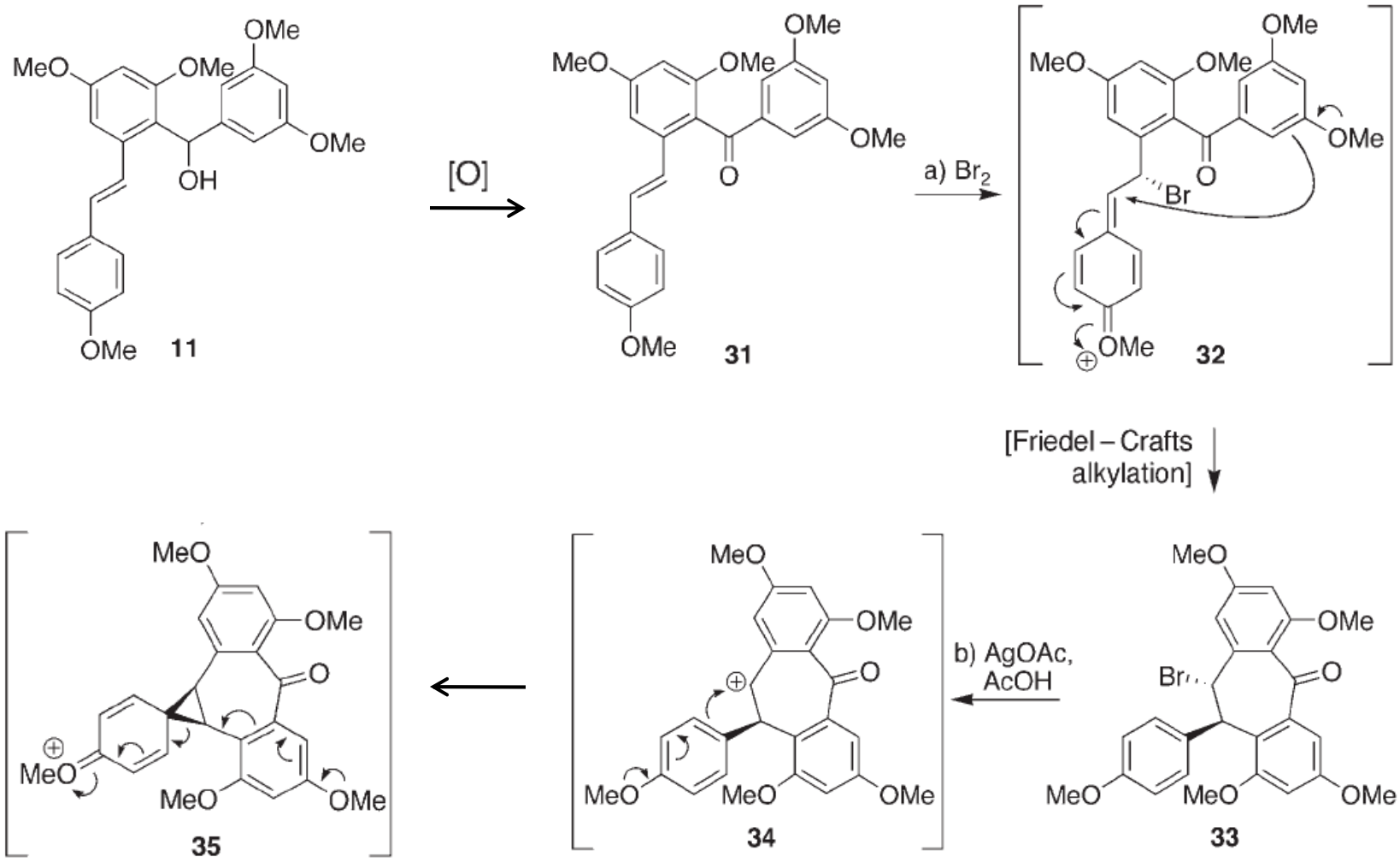
Snyder *et.al.* *ACIEE* **2007,** *46*, 8186

Total Synthesis of Ampelopsin F



Snyder *et.al.* *ACIEE* **2007,** *46*, 8186

Total Synthesis of analogue of Hemsleyanol E



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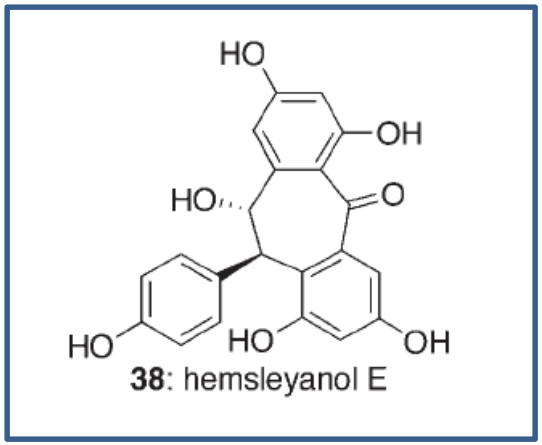
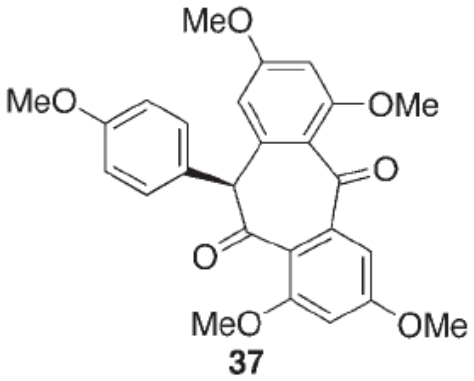
Total Synthesis of analogue of Hemsleyanol E

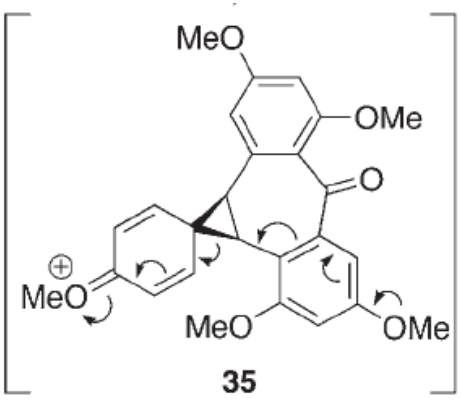


38: hemsleyanol E



37

c) K_2CO_3, MeOH
d) [O]



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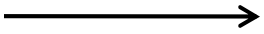
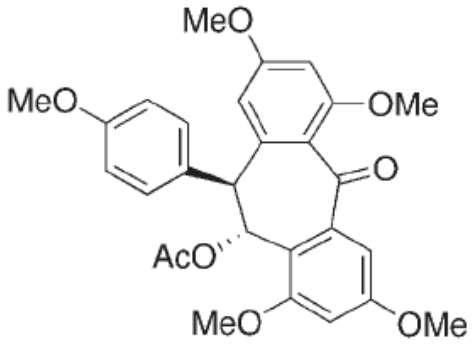


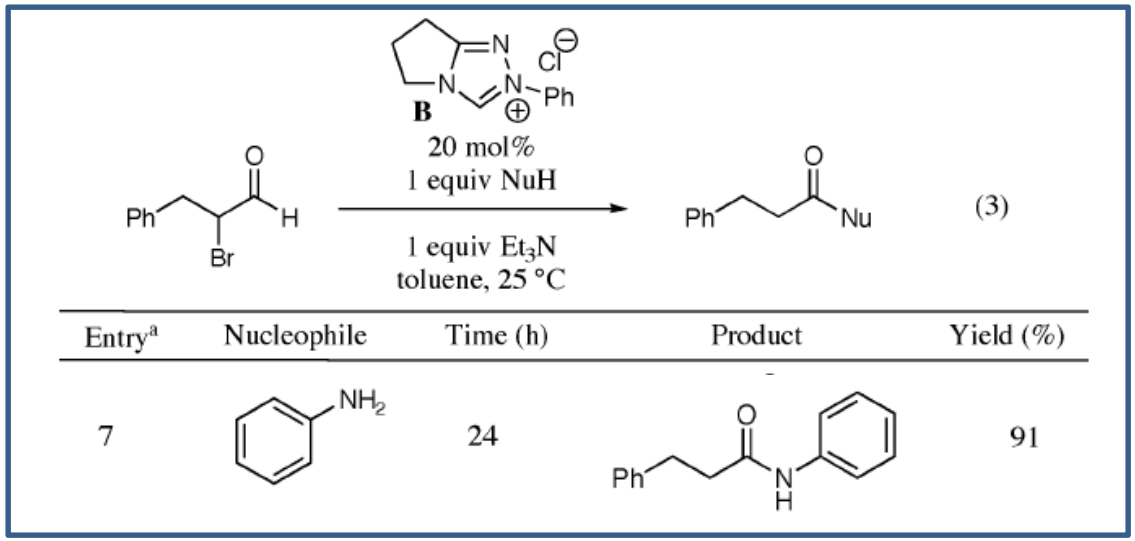


36 [confirmed by X-ray crystallograph]

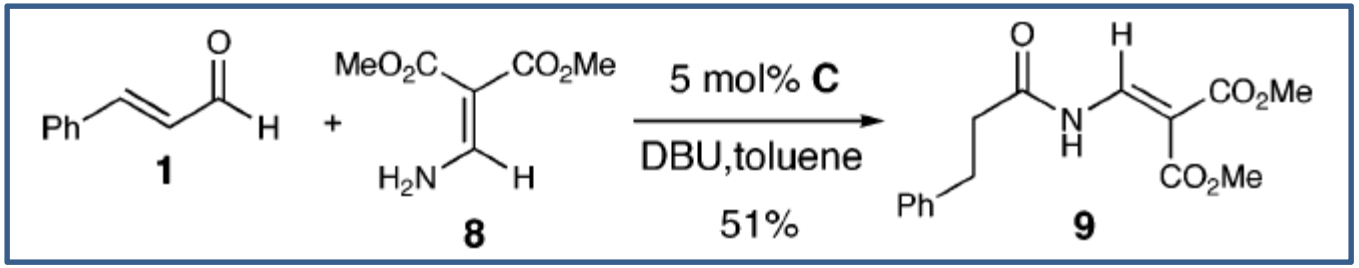
Snyder *et.al.* *ACIEE* **2007,** *46*, 8186

Nucleophilic Carbene and HOAt Relay Catalysis in an Amide Bond Coupling

- Conventional amide bond formation utilizes acids and amines as coupling partners and relies on stoichiometric activating agents for the acid functionality.
- Only two amines are reported so far for catalytic amidation using NHCs as catalyst.



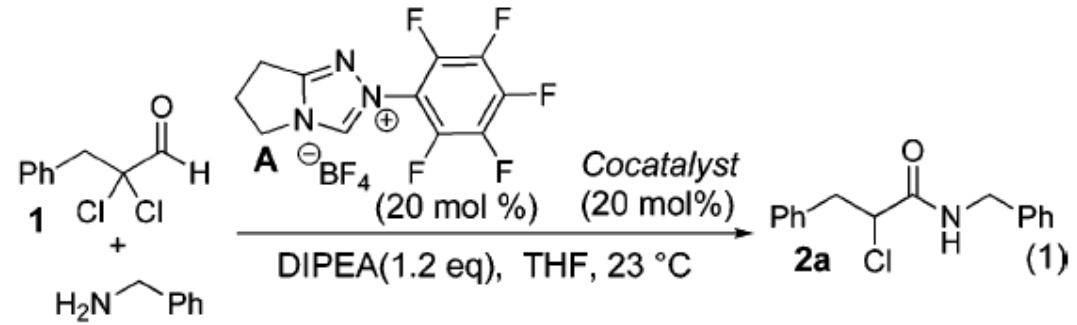
Entry[a]	Nucleophile	Time (h)	Product	Yield (%)
7		24		91



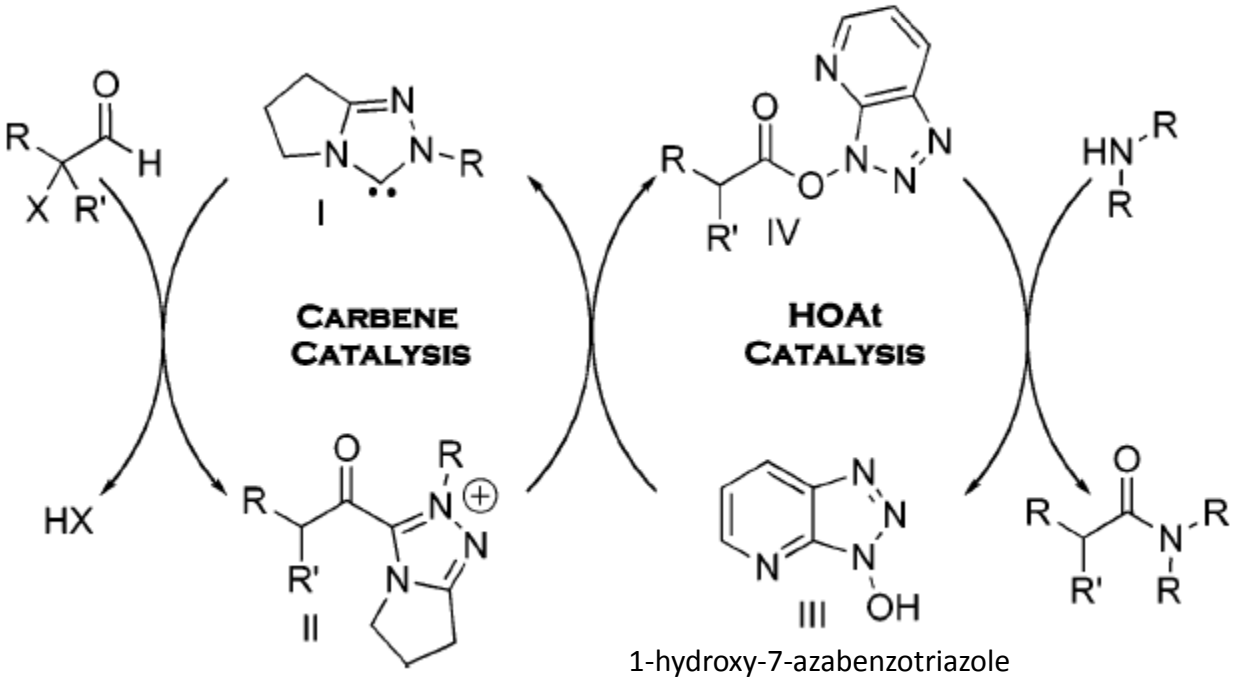
Reynolds, N. T.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2004,** *126*, 9518.

Scheidt, K. A. *Org. Lett.* **2005,** *7*, 905.

Reaction and its Proposed Catalytic Cycle



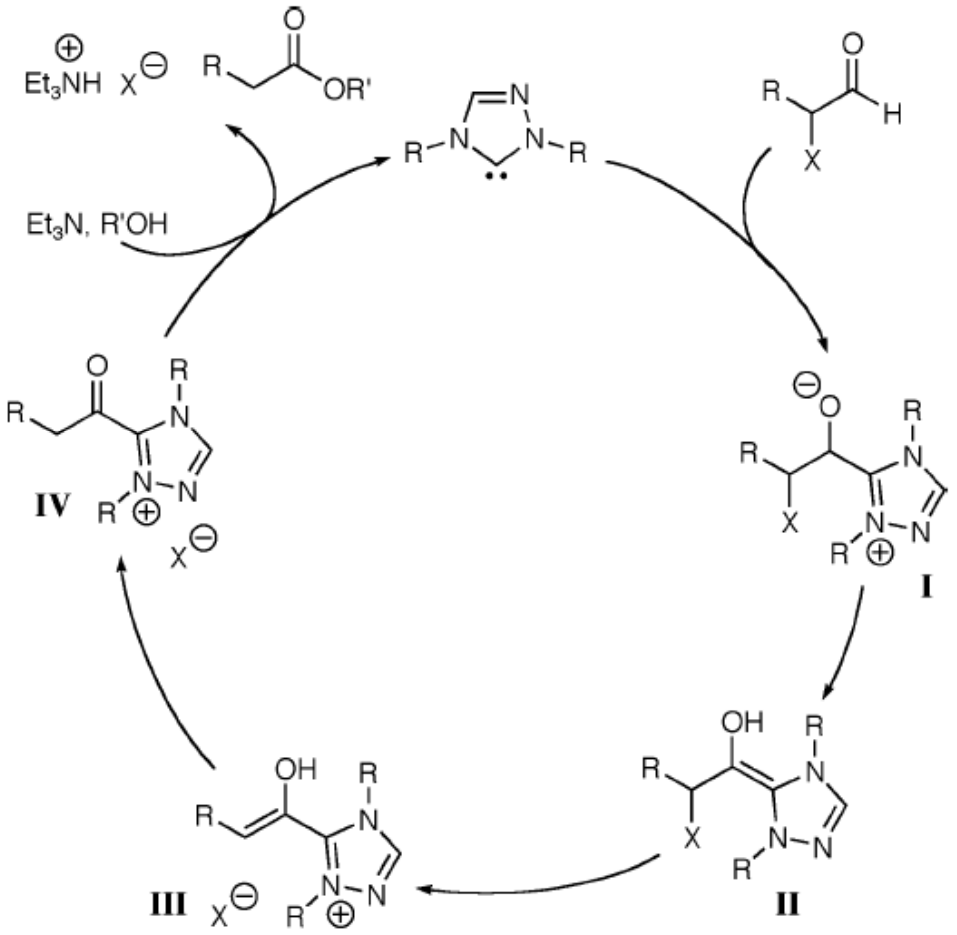
Cocatalyst:	None	HOBt	HOAt	DMAP	Imidazole	PFPOH
Yield (%)	**30**	**92**	**93**	**90**	**85**	**88**



1-hydroxy-7-azabenzotriazole

Rovis, T.; Vora, H. U. *J. Am. Chem. Soc.* **2007,** *129*, 13796.

Carbene Mechanism



Reynolds, N. T.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2004,** *126*, 9518.

Amine and α-haloaldehyde Substrate Scope

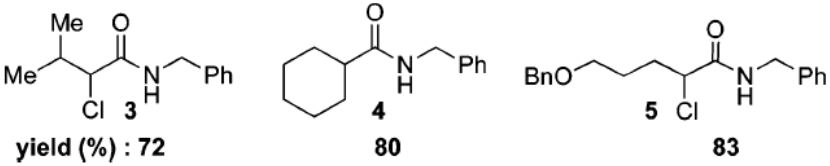
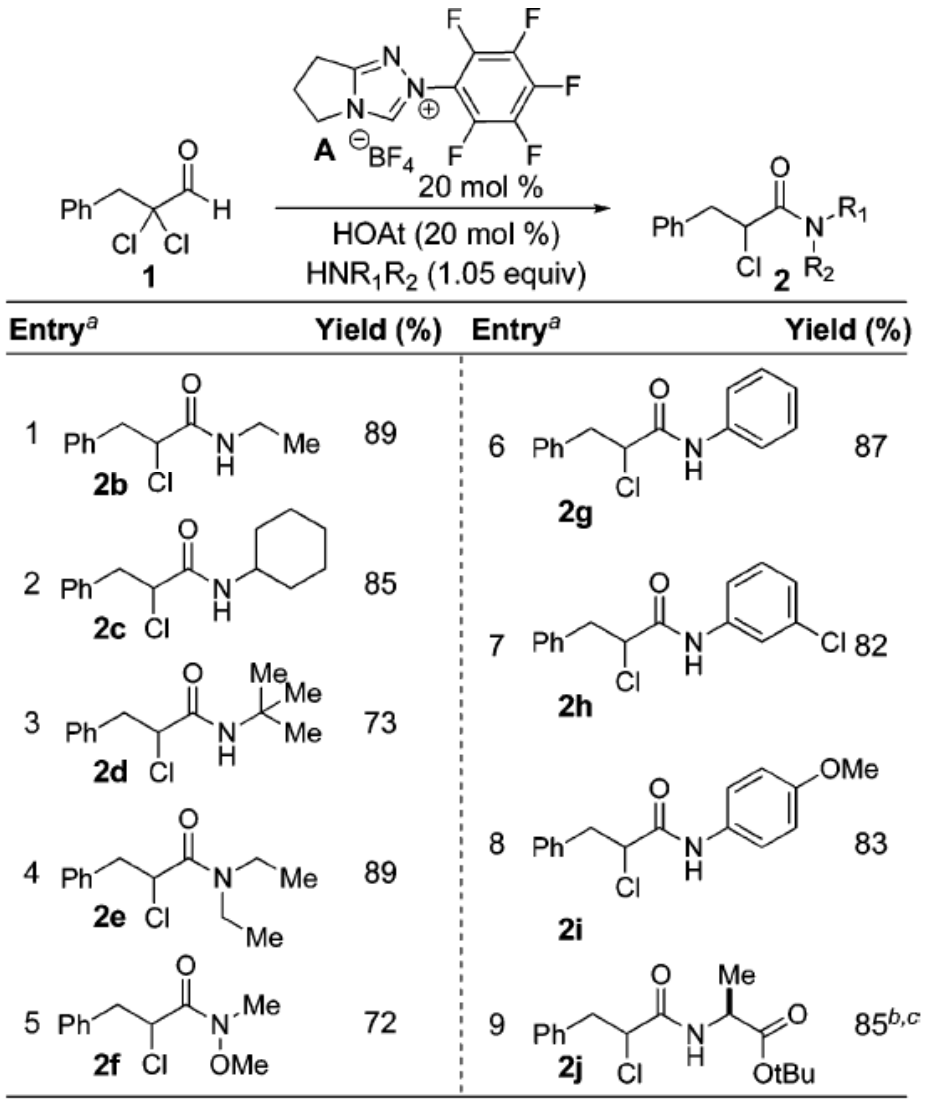


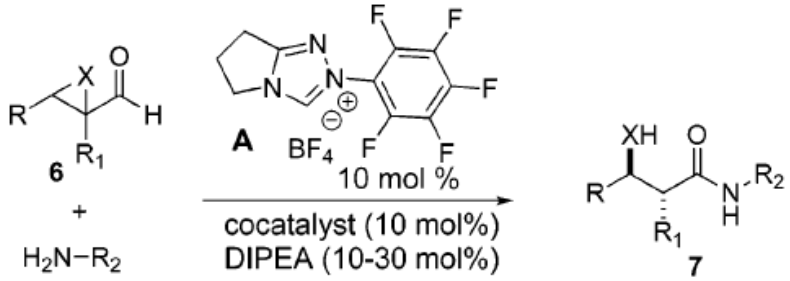
Figure 1. α-Haloaldehyde substrate scope.

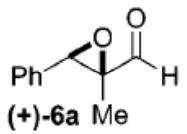
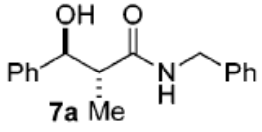
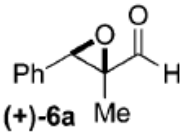
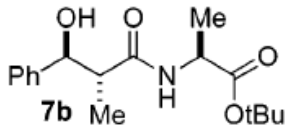
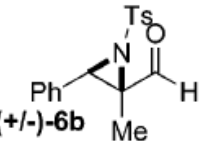
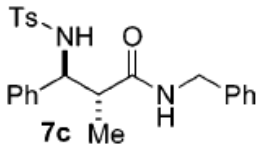
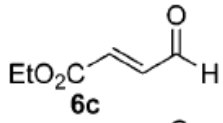
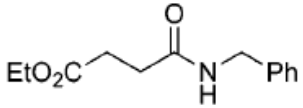
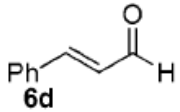
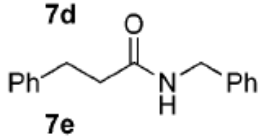


Rovis, T.; Vora, H. U. *J. Am. Chem. Soc.* **2007,** *129*, 13796.

Atom-Economical Amidation

Table 2. Atom-Economical Amidation

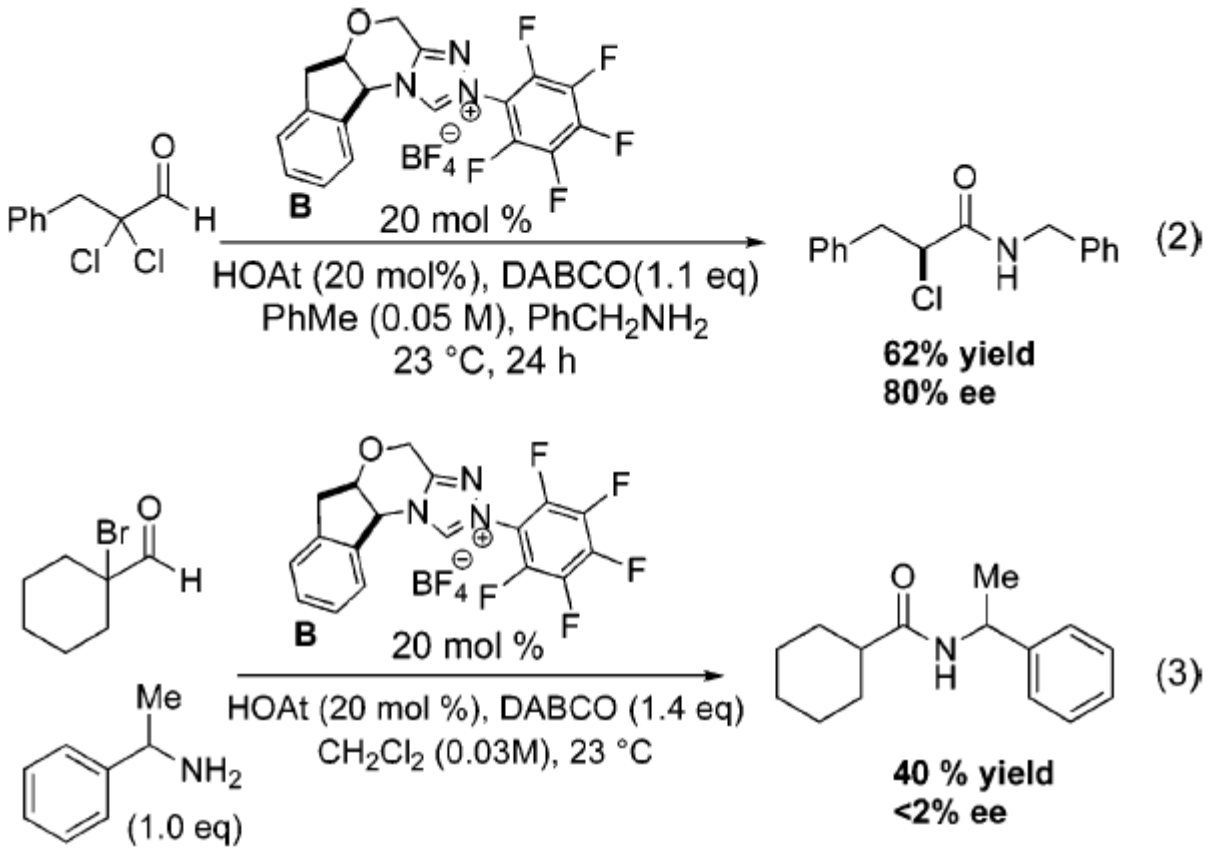


Entry	Substrate	Product	Yield (%)	dr
1	 **(+)-6a**	 **7a**	86[a]	>19:1
2	 **(+)-6a**	 **7b**	75[a]	15:1
3	 **(+/-)-6b**	 **7c**	72[a]	>19:1
4	 **6c**	 **7d**	80[b]	-
5	 **6d**	 **7e**	82[b]	-

Base is used
in catalytic Amount

Rovis, T.; Vora, H. U. *J. Am. Chem. Soc.* **2007,** *129*, 13796.

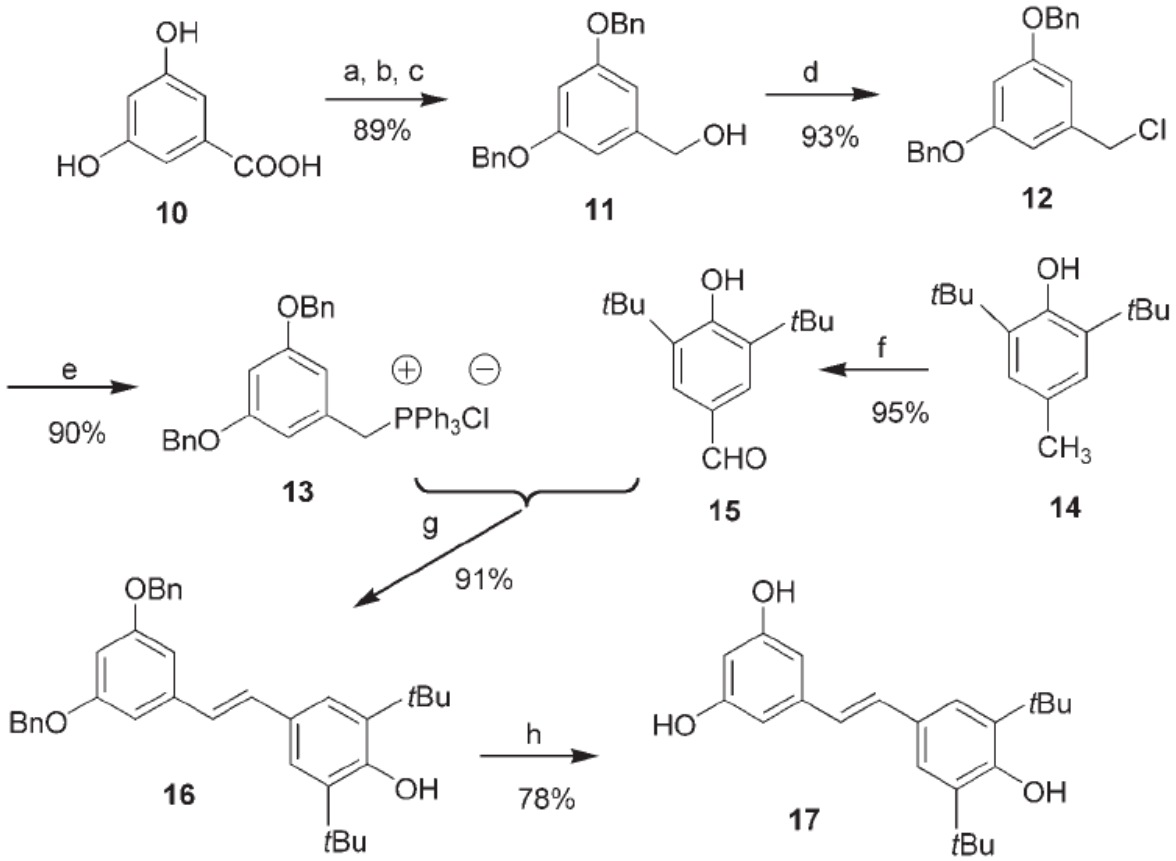
Proof of Mechanism: Use of Chiral Carbenes



Rovis, T.; Vora, H. U. *J. Am. Chem. Soc.* **2007,** *129*, 13796.

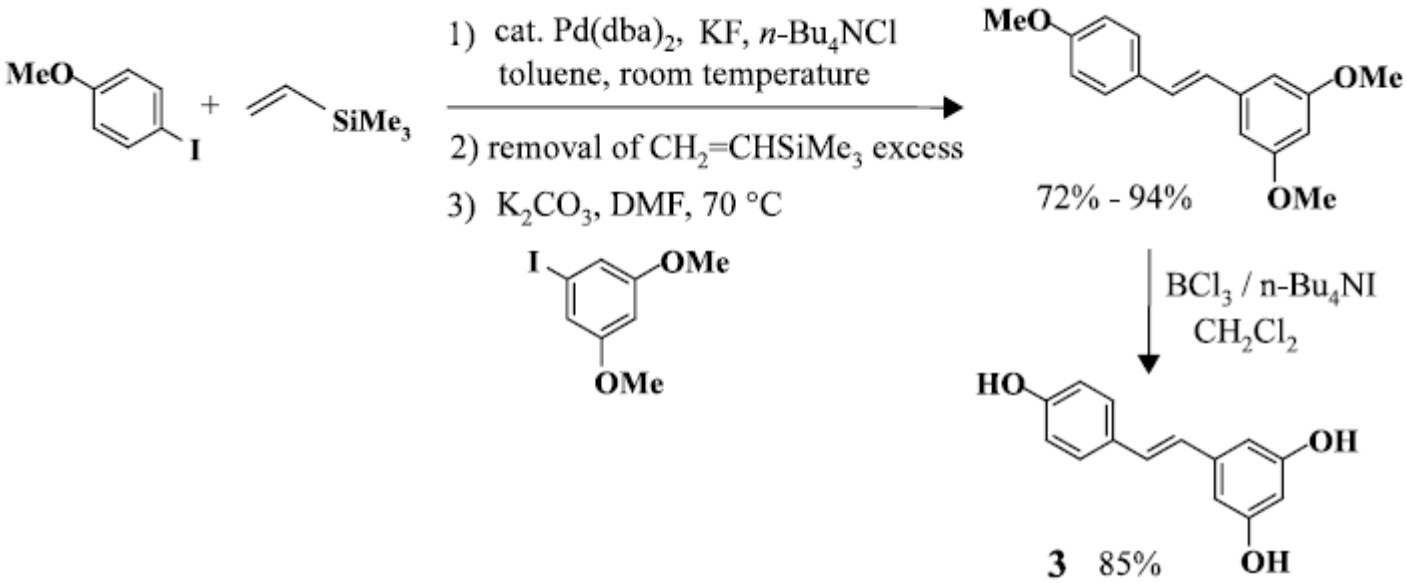

Red Wine Grapes
Seeds of Change

Earlier Approaches



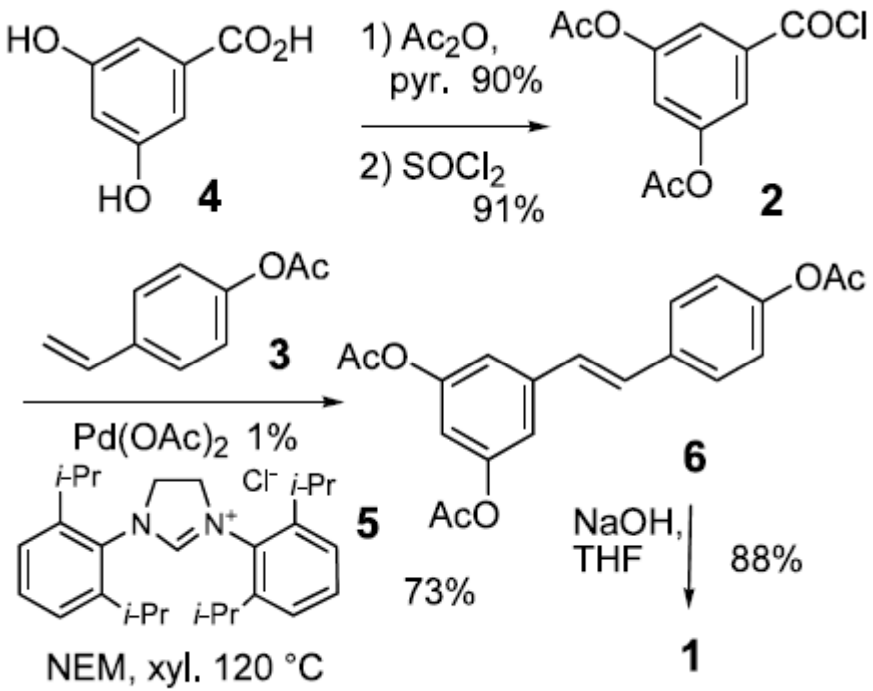
a) CH_3OH, H_2SO_4,
reflux; b) $PhCH_2Br$, K_2CO_3, DMF, RT; c) $LiAlH_4$, Et_2O, RT; d) $SOCl_2$, Et_3N, benzene, 0°C→RT; e) PPh_3, xylene, reflux; f) Br_2, *tert*-butanol, RT; g) *n*BuLi, toluene, RT→ reflux; h) $AlCl_3$, $PhNMe_2$, CH_2Cl_2, 0°C

Synthesis of resveratrol



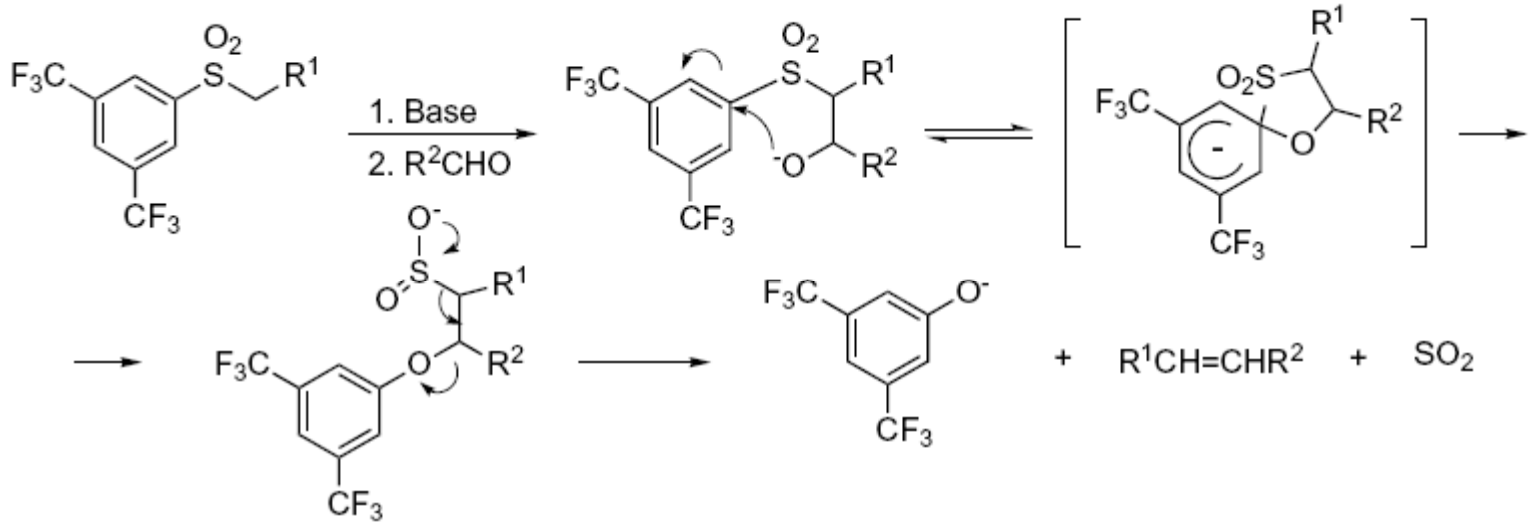
Jeffery *et.al. Tetrahedron Lett.* **2003**, *44*, 193

Synthesis of resveratrol



Andrus *et.al. Tetrahedron Lett.* **2003**, *44*, 4819

Synthesis of resveratrol



Najera *et.al. Tetrahedron Lett.* **2004**, *45*, 573