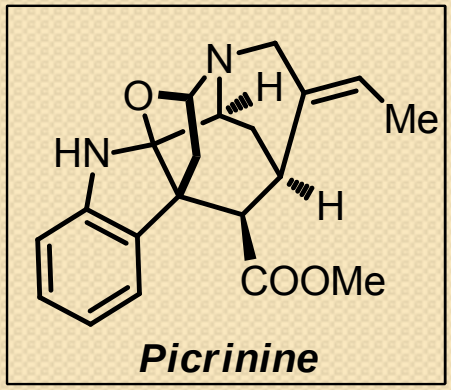
Total Synthesis of the Akuammiline Alkaloid Picrinine

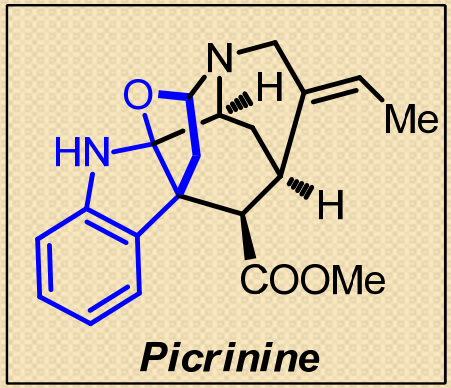
J. M. Smith, J. Moreno, B. W. Boal and N. K. **Garg**,
J. Am. Chem. Soc., 2014, **136**, 4504-4507.



Picrinine

Current literature
Gong Xu
10.04.2014

About Picrinine

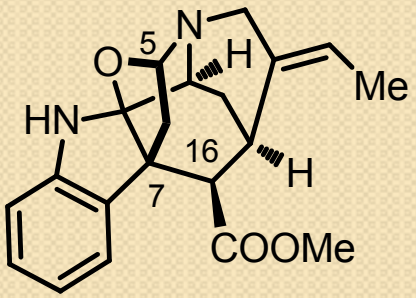


Picrinine

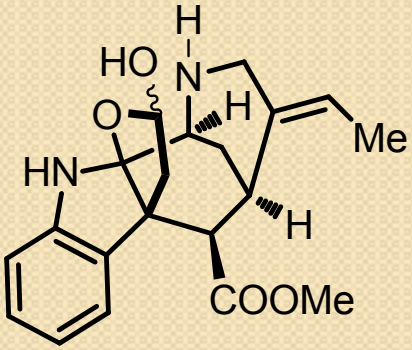
- Belonging to the **akuammiline** family;
- First discovered in 1965 from the leaves of ***Alstonia scholaris***;
- **Structural features**:
  Highly complex, cage-like molecule that contains a **furoindoline core** fused to a densely functionalized cyclohexyl ring; The central cyclohexyl ring is part of a **bridged [3.3.1]-azabicyclic** framework; six stereogenic centers, five of which are contiguous, and contains two **N,O-acetal linkages**.
- **Anti-inflammatory** activity through inhibition of the 5-lipoxygenase enzyme.

Chatterjee, A.; Mukherjee, B.; Ray, A. B.; Das, B. *Tetrahedron Lett.* **1965**, 6, 3633−3637.

Retrosynthesis

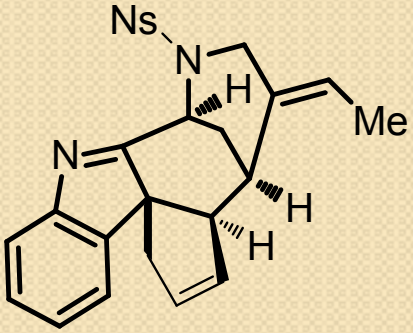


***Picrinine* 1**



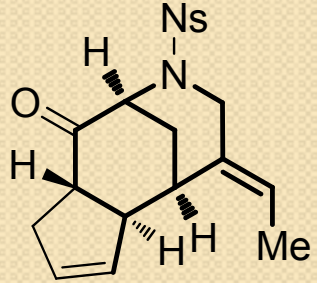
aminolactol **2**

[O]



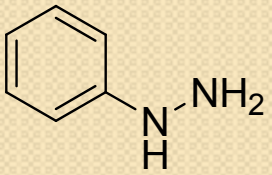
cyclopentene **3**

Fischer Indolization

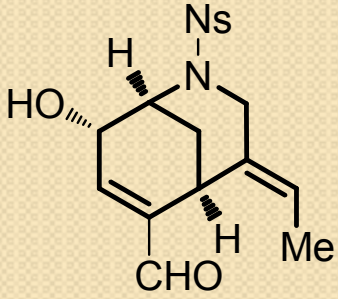


tricyclic cyclopentene **4**

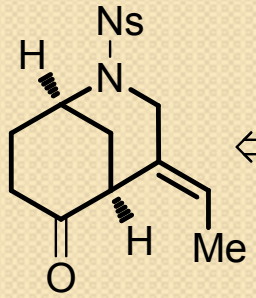
+



phenylhydrazine

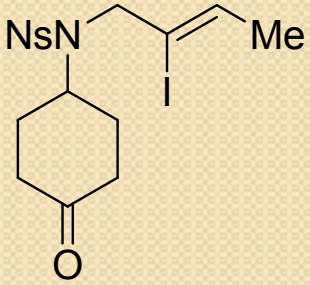


enal **5**



[3.3.1]-azabicycle **6**

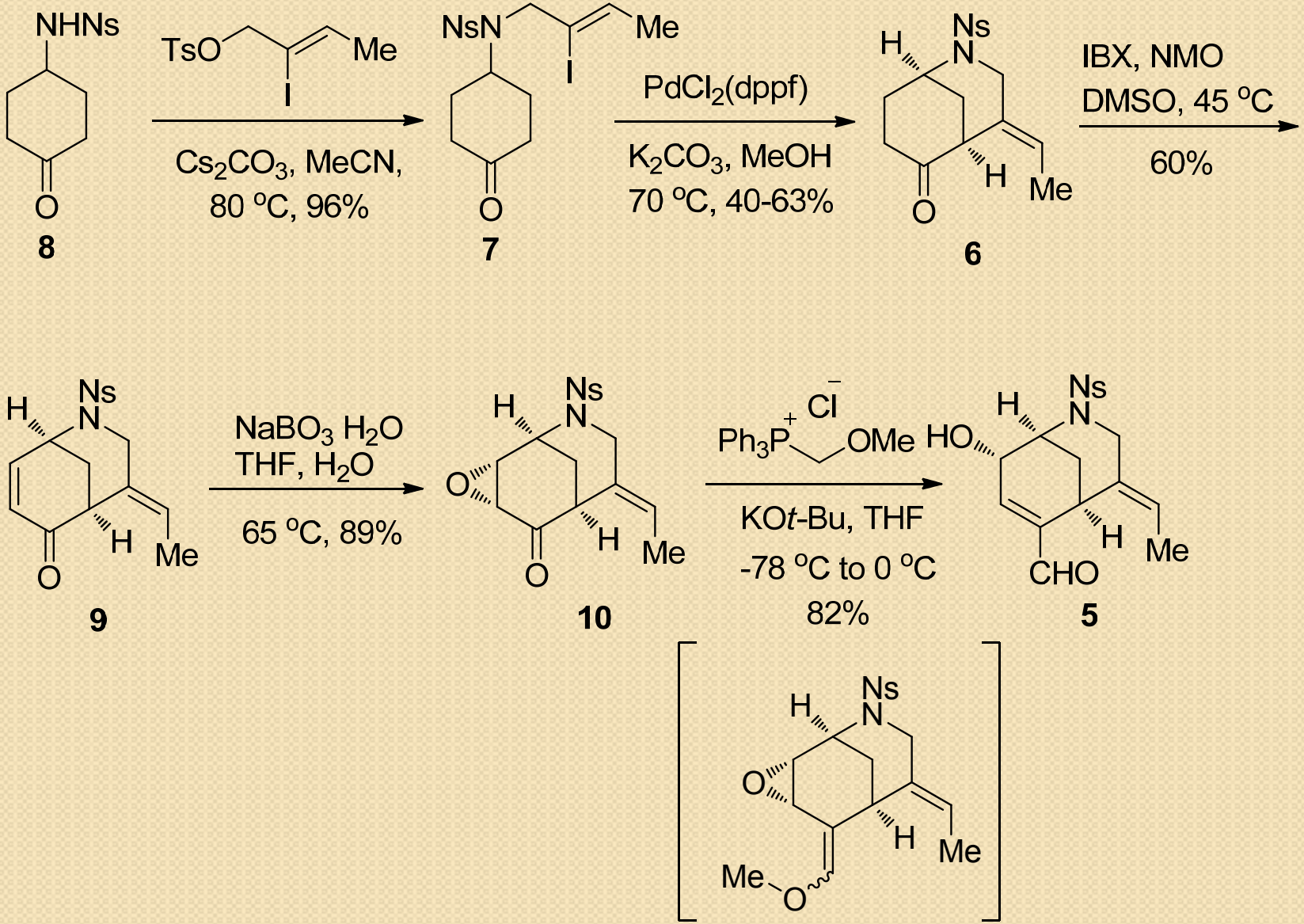
Pd-Enolate cyclization



vinyl iodide **7**

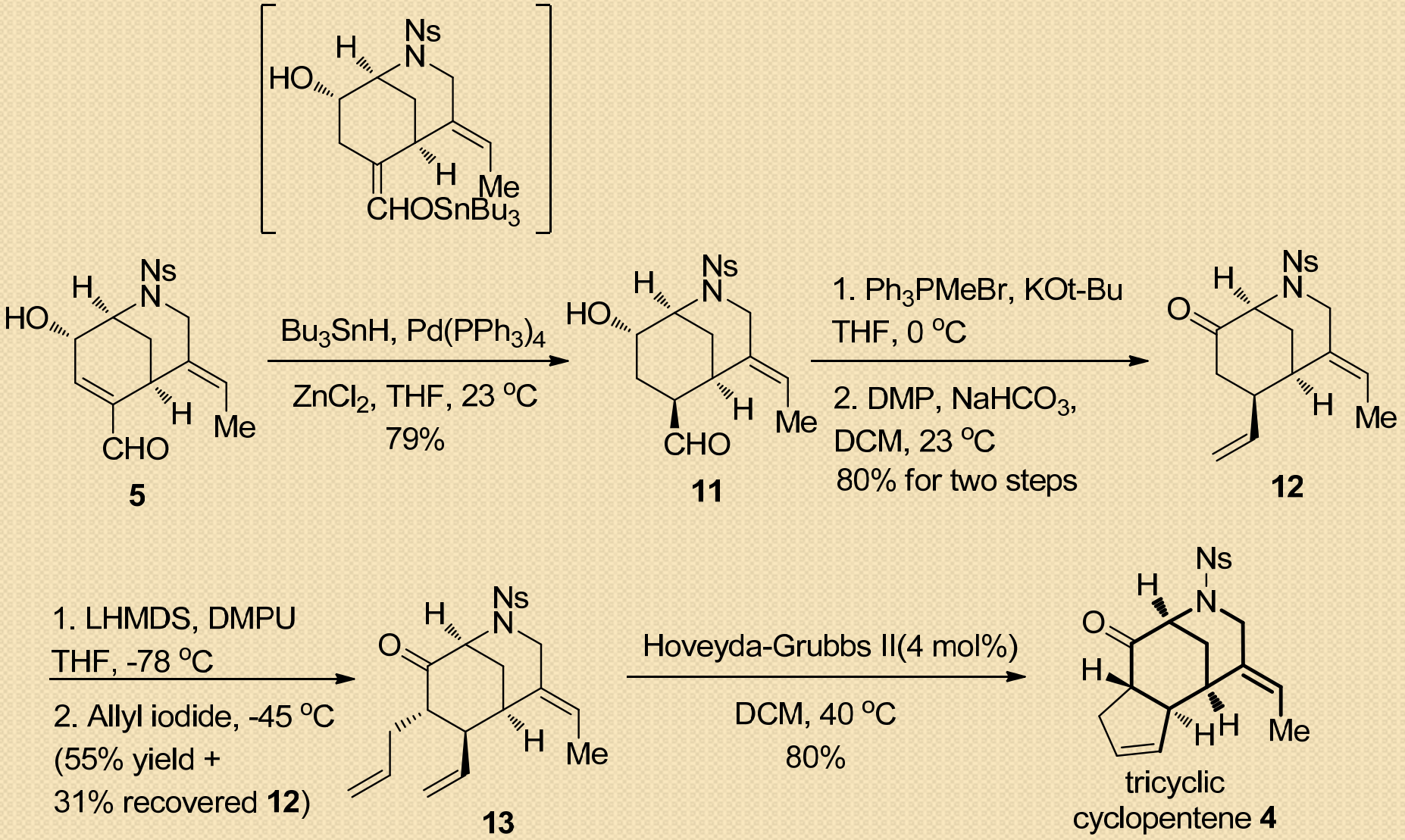
J. M. Smith, J. Moreno, B. W. Boal and N. K. **Garg**,
J. Am. Chem. Soc., 2014, **136**, 4504-4507.

Preparation of enal 5



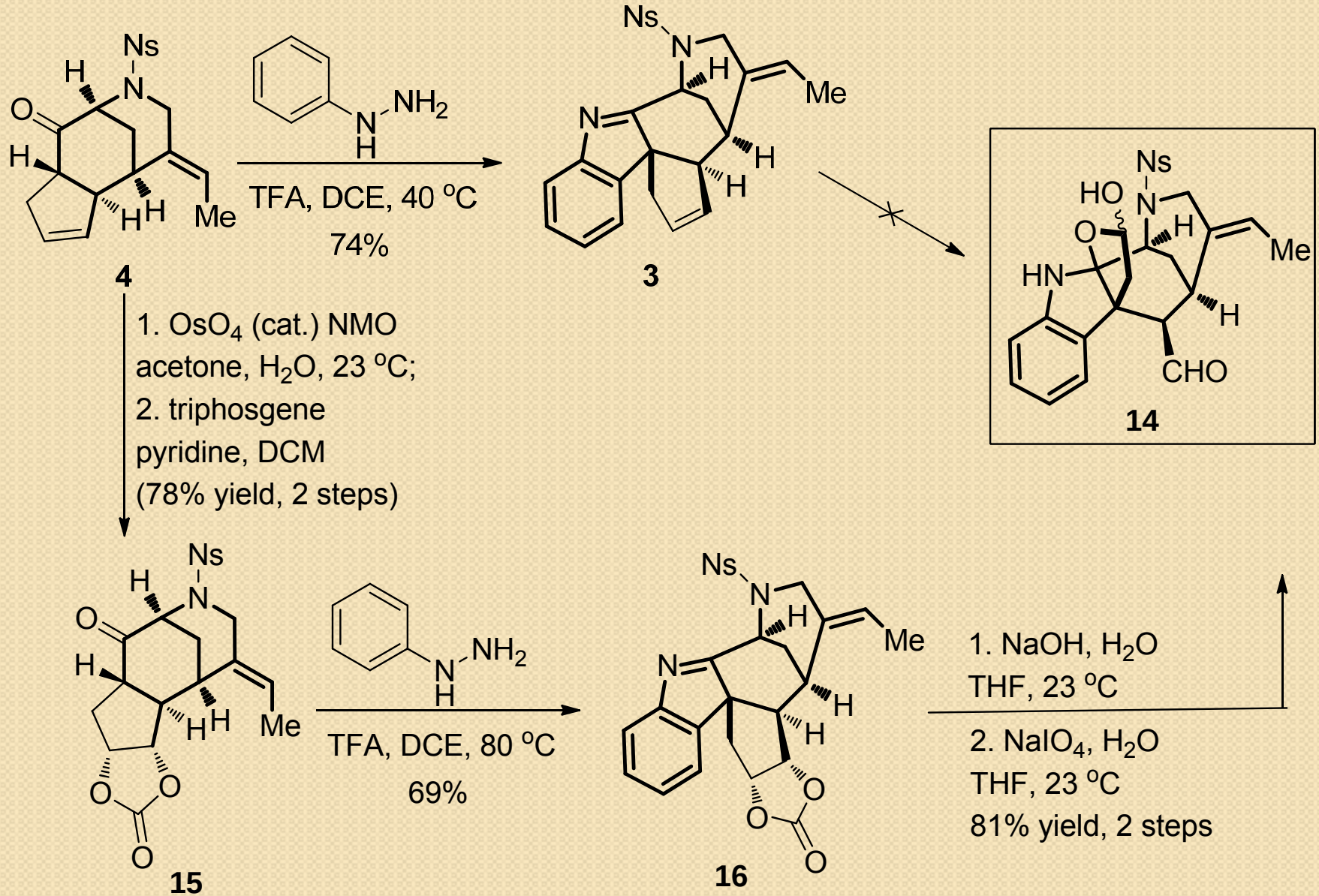
J. M. Smith, J. Moreno, B. W. Boal and N. K. **Garg**, *J. Am. Chem. Soc.*, 2014, **136**, 4504-4507.

Preparation of tricyclic cyclopentene 4



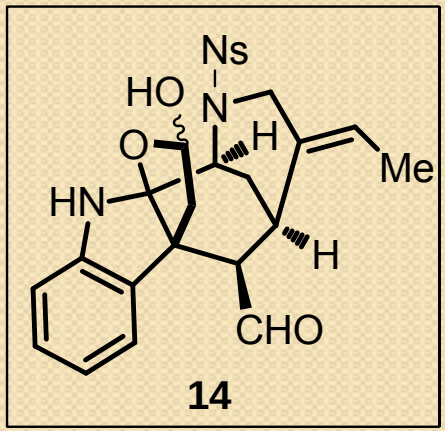
J. M. Smith, J. Moreno, B. W. Boal and N. K. **Garg**, *J. Am. Chem. Soc.*, 2014, **136**, 4504-4507.

Fischer indolization and Furoindoline formation



J. M. Smith, J. Moreno, B. W. Boal and N. K. **Garg**, *J. Am. Chem. Soc.*, 2014, **136**, 4504-4507.

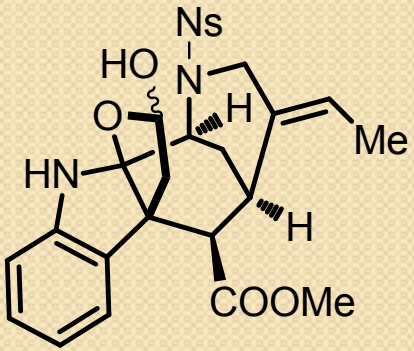
Furnish picrinine



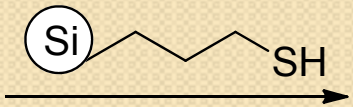
14

1. $NaClO_2$, NaH_2PO_4
2-methyl-2-butene
t-BuOH, H_2O, 23 °C;

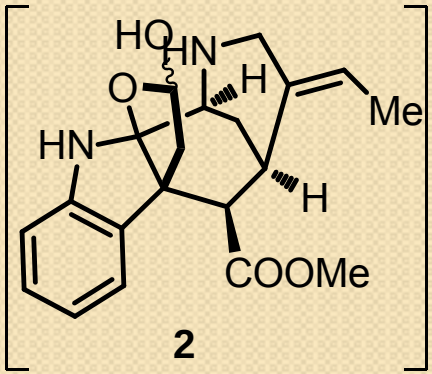
2. Me_3SiCHN_2
MeOH, THF, 23 °C
58% yield for two steps



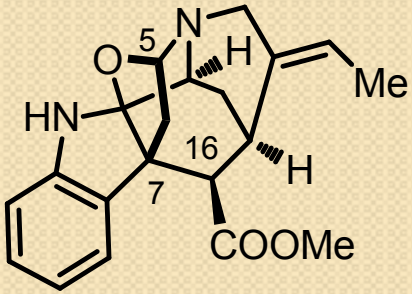
15



Cs_2CO_3, MeCN,
65 °C, 75%



2



***Picrinine* 1**

J. M. Smith, J. Moreno, B. W. Boal and N. K. **Garg**, *J. Am. Chem. Soc.*, 2014, **136**, 4504-4507.

Summary

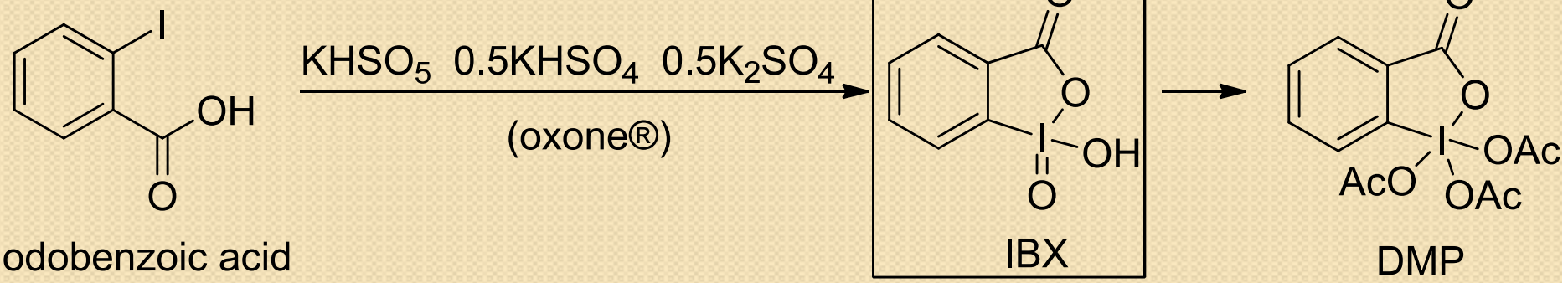
- the first total synthesis of the akuammiline alkaloid picrinine (**18 steps** from known ketone 8).
- Features:

a concise assembly of the **[3.3.1]-azabicyclic core**;

a key **Fischer indolization** reaction to forge the natural product's carbon framework,

a series of delicate late-stage transformations to complete the total synthesis.

IBX

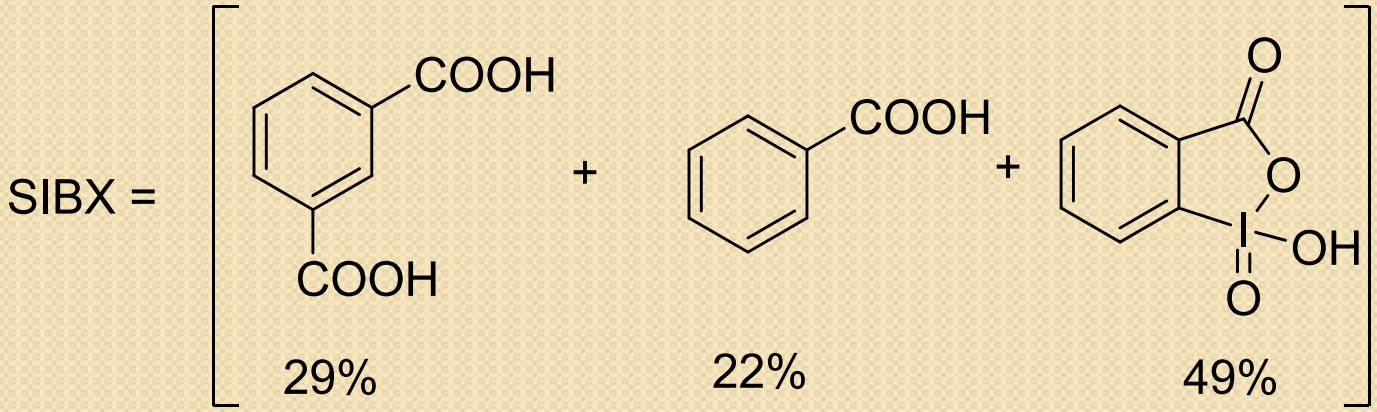


2-iodobenzoic acid

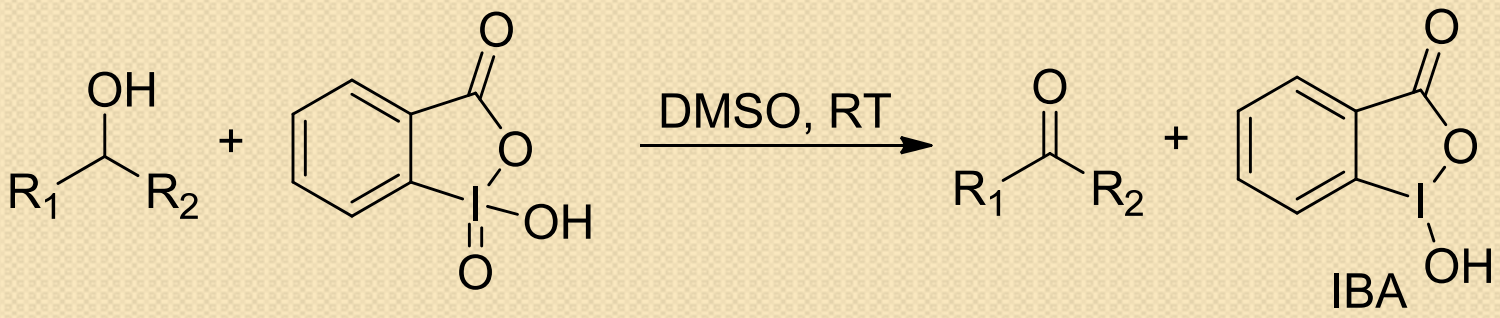
2-iodoxybenzoic acid

Limitation in industrial applications:

DMP and IBX **decompose violently** under impact and/or heating (>200°C)

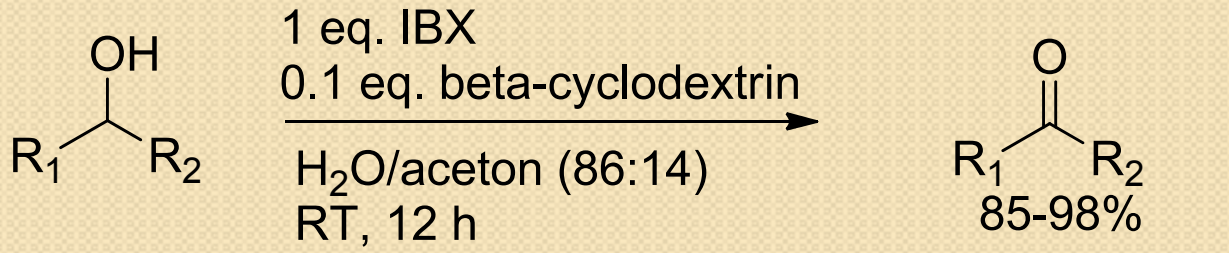


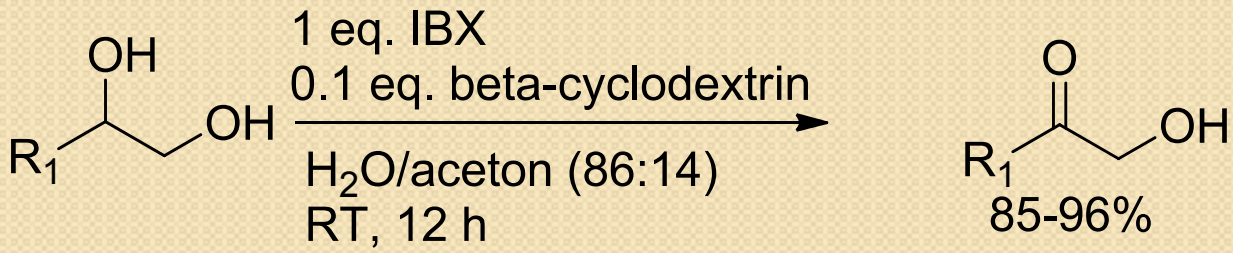
Developed by
SIMAFEX (a French company)



Problem: the **limited solubility** of IBX

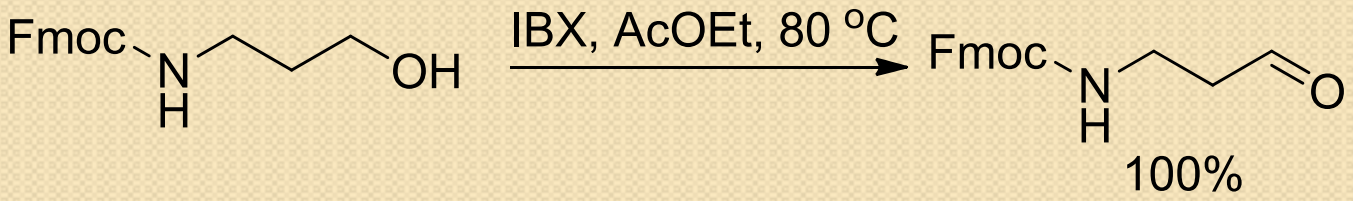
o-iodoxybenzoic acid (IBX) is catalyzed by **β-cyclodextrin** in a water/acetone mixture through the formation of host-guest complexes by noncovalent bonding



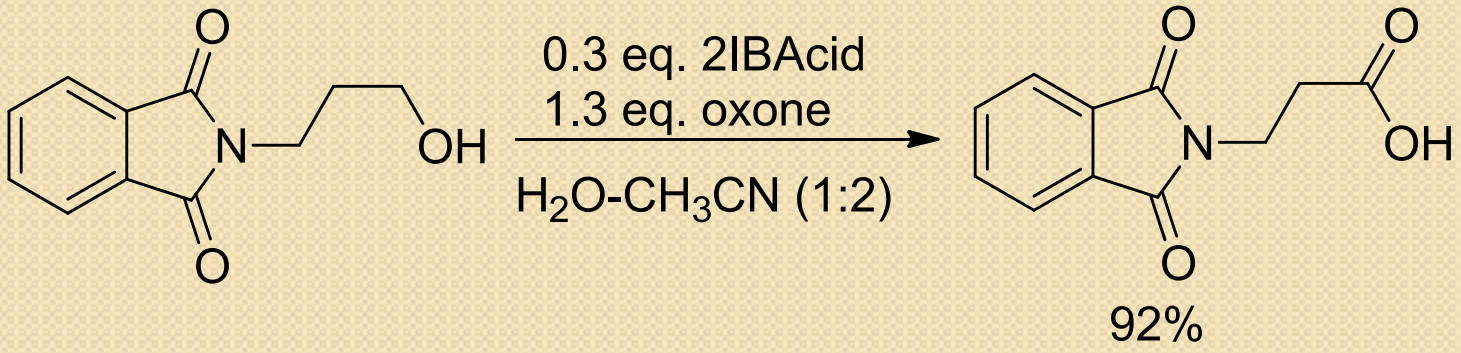


K. Surendra, N. Srilakshmi Krishnaveni, M. Arjun Reddy, Y. V. D. Nageswar, K. Rama Rao, J. Org. Chem., 2003, 68, 2058-2059.

- At elevated temperature, IBX is soluble in most solvents to carry on oxidation of alcohols. Best results were obtained with **EtOAc or DCE** as solvent: byproducts are insoluble at RT and therefore removed by simple filtration.

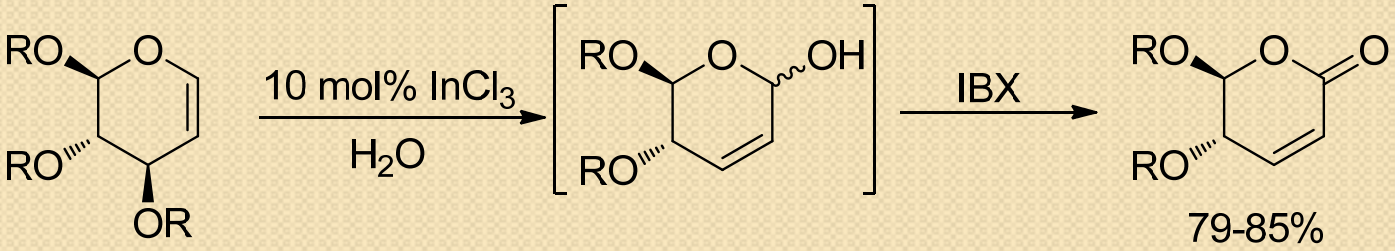


- *In situ* generation of IBX from catalytic amounts of 2IBAcid in the presence of oxone® as co-oxidant.



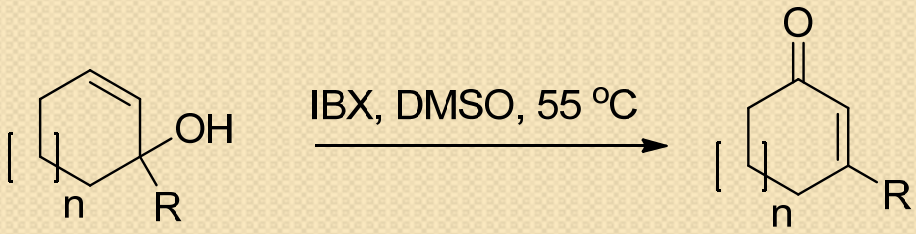
A. P. Thottumkara, M. S. Bowsher, T. K. Vinod, Org. Lett. 2005, 7, 2933-2936.

❖ Conversion of glycols into α,β-unsaturated δ-lactones was efficiently carried out using IBX with a catalytic amount of $InCl_3$.



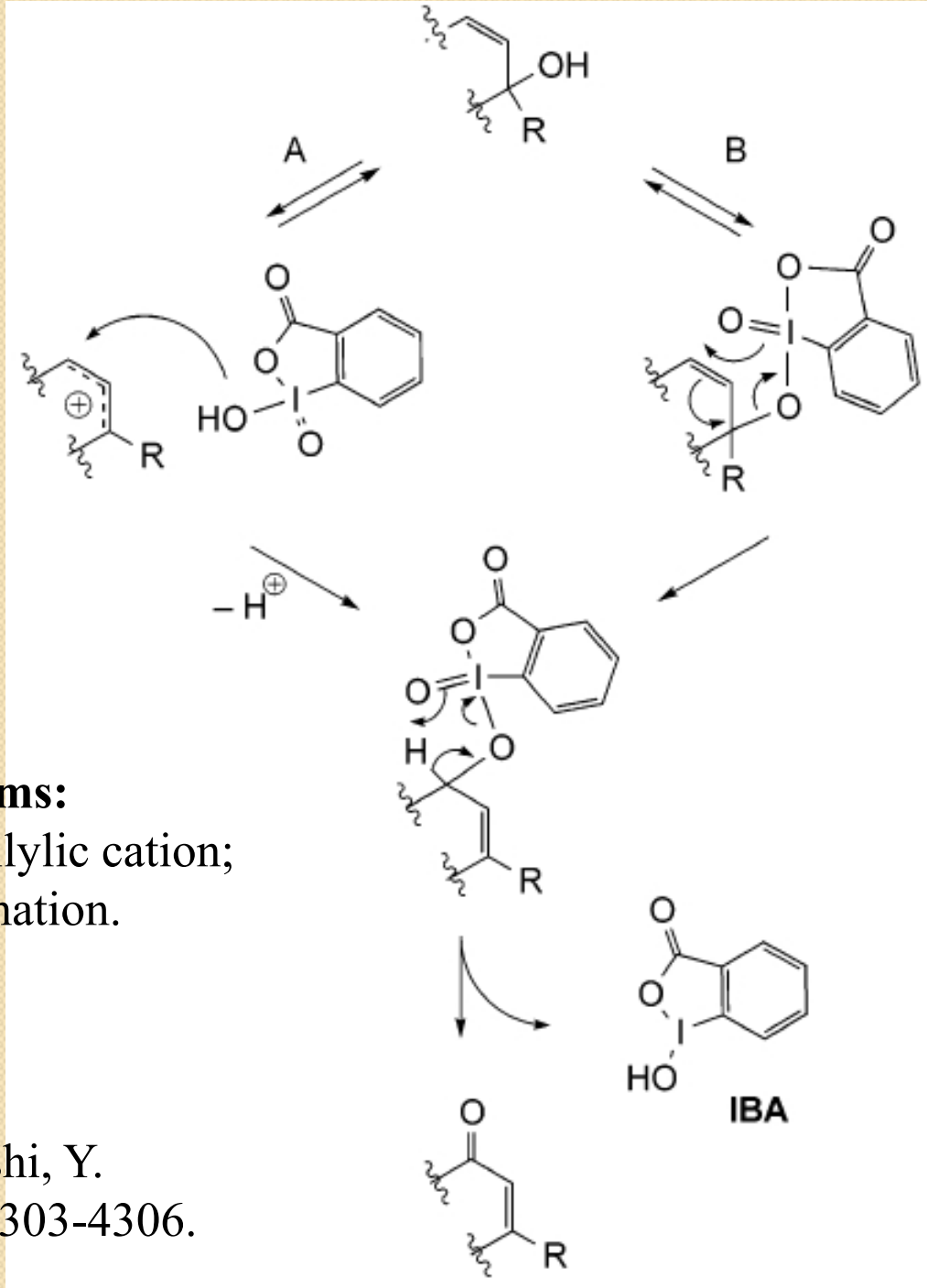
J. S. Yadav, B. V. Subba. Reddy, Ch. Suresh Reddy, Tetrahedron Lett. 2004, 45, 4583-4585.

❖ Oxidative rearrangement of five- and six-membered cyclic tertiary allylic alcohols was performed with IBX.



R = alkyl, aryl; n = 0, 1

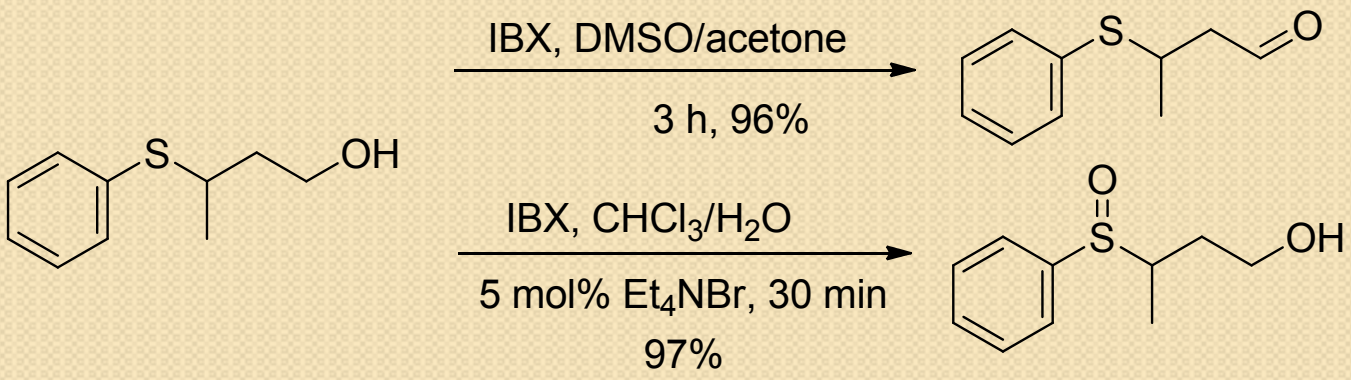
M. Shibuya, S. Ito, M. Takahashi, Y. Iwabuchi, Org. Lett. 2004, 6, 4303-4306.



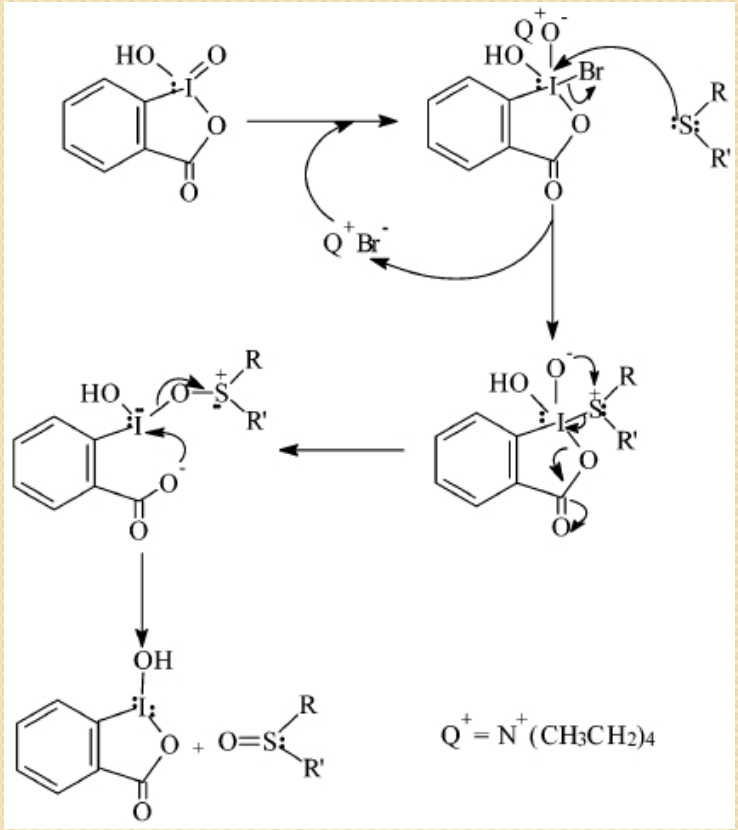
Plausible Reaction Mechanisms:
Path A: tertiary alcohol to an allylic cation;
Path B: tertiary iodic ester formation.

M. Shibuya, S. Ito, M. Takahashi, Y. Iwabuchi, Org. Lett. 2004, 6, 4303-4306.

❖ Chemoselectively oxidation with IBX

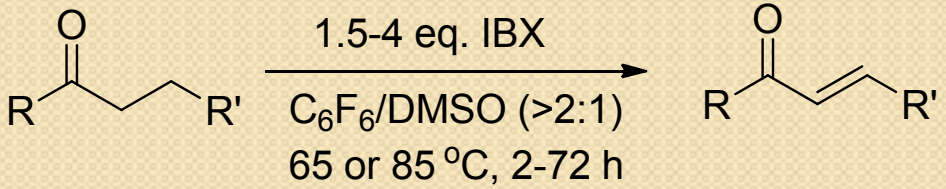


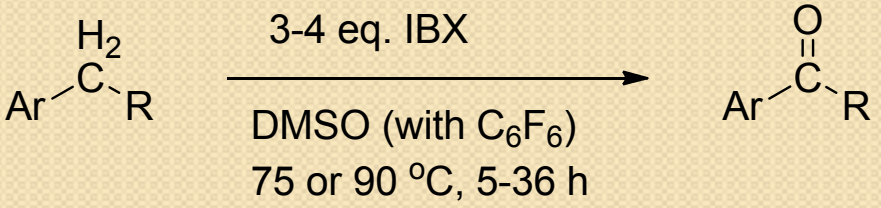
V. G. Shukla, P. D. Salgaonkar, K. G. Akamanchi, J. Org. Chem. 2003, 68, 5422-5425.



The oxidation may involve the initial **polarization of the I=O bond by TEAB** then a nucleophilic attack of sulfur on the hypervalent iodine(V) center followed by a concerted oxygen transfer to give sulfoxides.
Over-oxidation to sulfones does not occur and this could be attributed to the low nucleophilicity of sulfoxide.

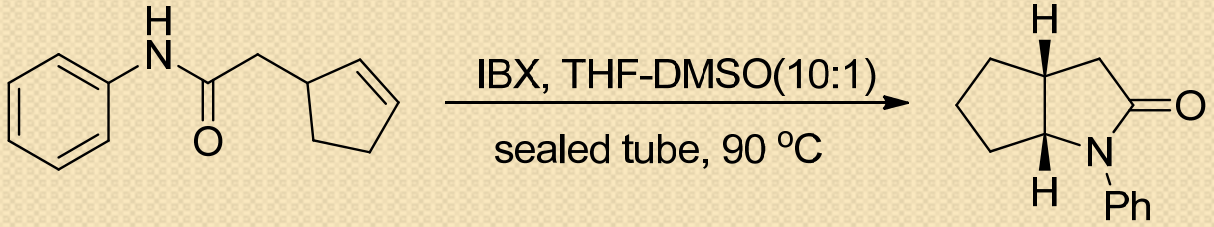
❖ o-Iodoxybenzoic Acid as a Chemospecific Tool for **Single Electron Transfer-Based Oxidation** Processes





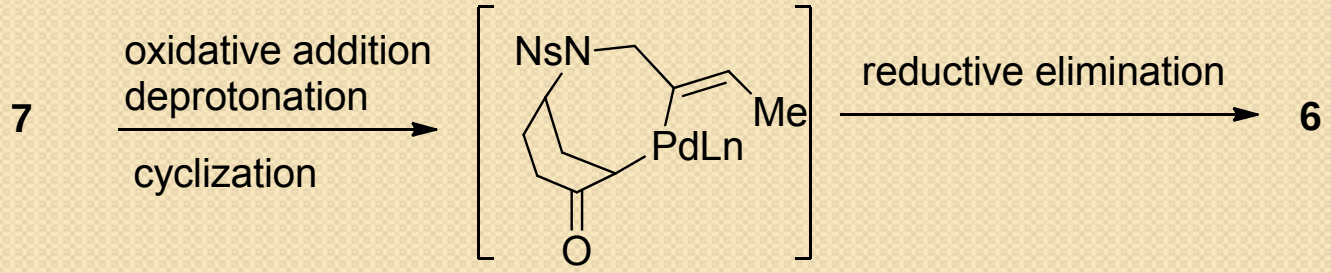
K. C. Nicolaou, T. Montagnon, P. S. Baran, Y.-L. Zhong, J. Am. Chem. Soc., 2002, 124, 2245-2258

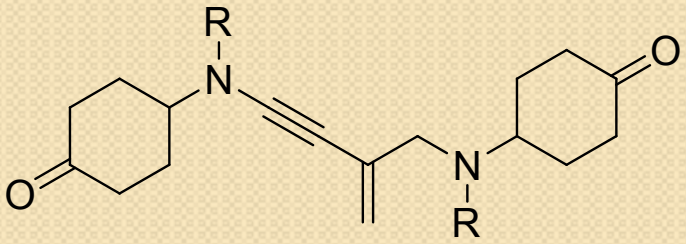
❖ o-IodoxybenzoIBX-mediated radical cyclization of unsaturated N-aryl amides and unsaturated alkoxyamine *via* **N-centered radicals** involving a single electron transfer (SET) mechanism.



K. C. Nicolaou, P. S. Baran, Y.-L. Zhong, S. Barluenga, K. W. Hunt, R. Kranich, J. A. Vega, J. Am. Chem. Soc. 2002, 124, 2233-2244

Pd-catalyzed ketone enolate cyclization

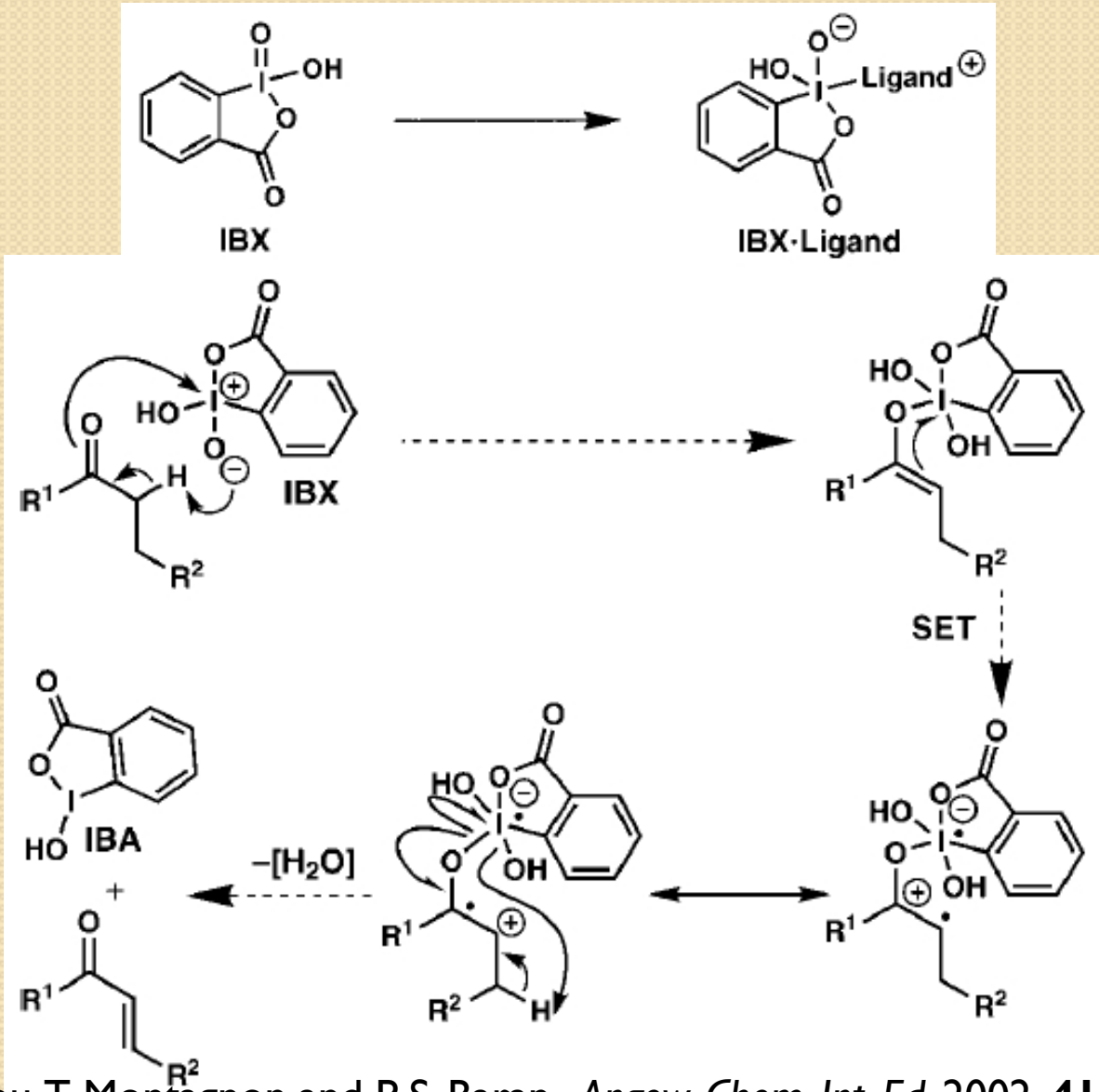




dimer as major byproduct

Solé, D.; Piedró, E.; Bonjoch, J. Org. Lett. 2000, 2, 2225−2228.

IBX-mediated dehydrogenation of ketones and aldehydes to α, β-unsaturated carbonyl compounds.



K. C. Nicolaou, T. Montagnon and P. S. Baran, *Angew. Chem. Int. Ed.* 2002, **41**, 993-996.