Catalytic Asymmetric Total Synthesis of (−)-Actinophyllic Acid

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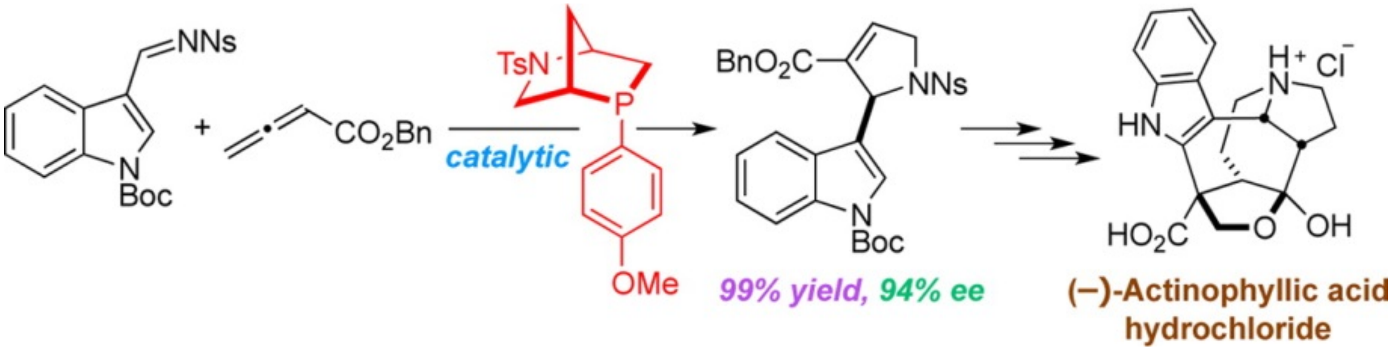
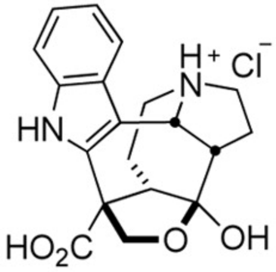


A chiral phosphine-catalyzed [3 + 2] annulation

Liming Cao
Wipf Group Current Literature
3/12/2015

(–)-Actinophyllic Acid from *Alstonia actinophylla*

- Firstly isolated by Quinn, Caroll, at al. from the leaves of the tree *Alstonia actinophylla* in Cape York Peninsula, Far North Queensland, Australia.



(–)-Actinophyllic acid hydrochloride

- The cage-like scaffold: five contiguous stereogenic centers, one of which is a quaternary carbon, bridged by a tetrahydrofuran lactol

- Therapeutic agents for the treatment of cardiovascular disorder:
  - a potent inhibitor of the zinc-dependent carboxypeptidase U (CPU), with an IC_{50} of 0.84 μM.

- Carboxypeptidase U (CPU): an endogenous inhibitor of fibrinolysis, the breakage of fibrin clots.

- Inhibitors of CPU can facilitate fibrinolysis and inhibit the blood clot formation that is a cause of various cardiovascular disorders.

- No subsequent biological studies reported because of the scarcity, due to low isolation yield (0.0072%); syntheses should benefit exploration of its biomedical potential.

Alstonia actinophylla

http://bie.ala.org.au/species/urn:lsid:biodiversity.org.au:apni.taxon:259314

J. Am. Chem. Soc., DOI:10.1021/jacs.6b00567

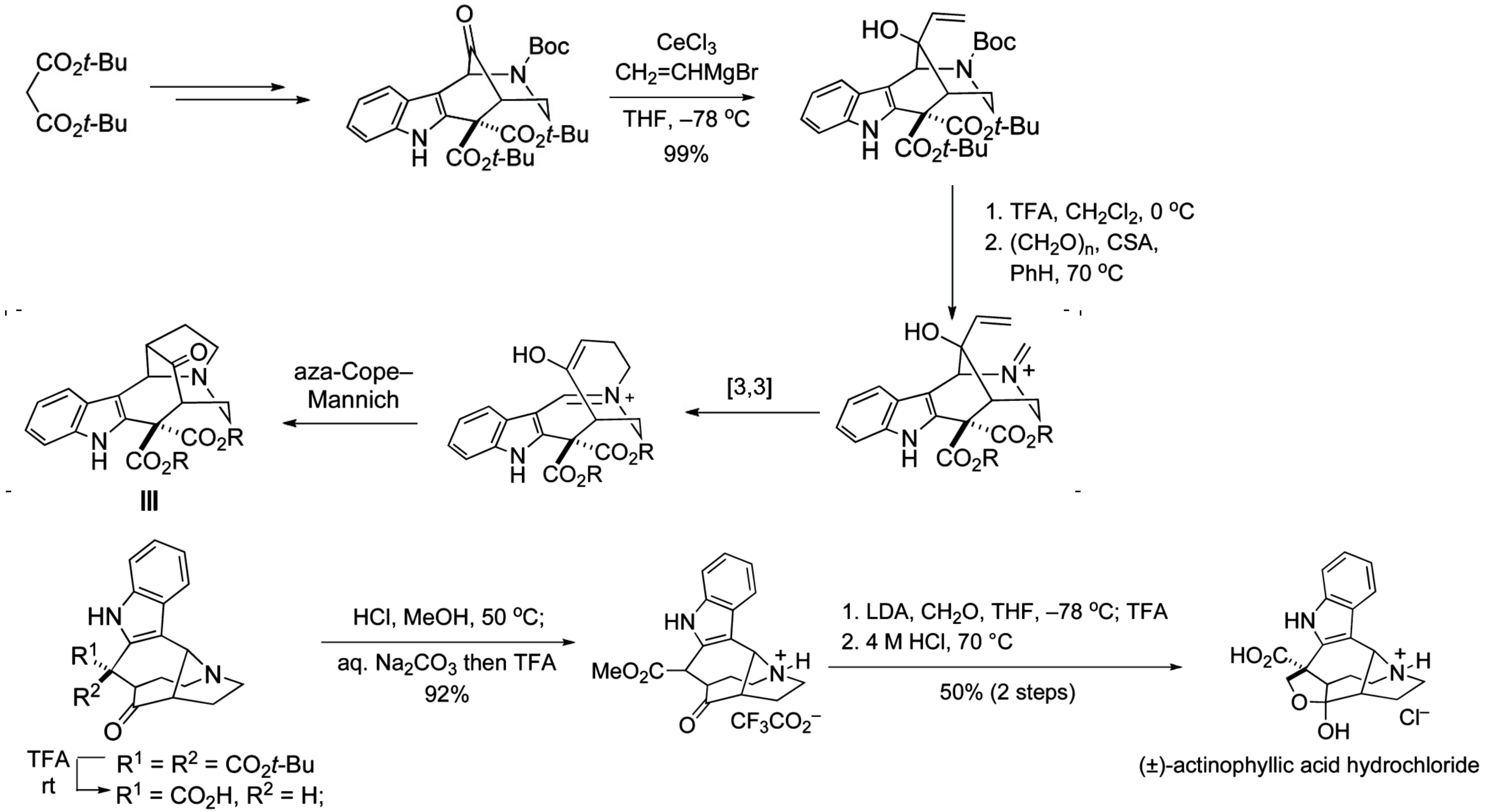
J. Thromb. Haemostasis **2004**, *2*, 416; *Bioorg. Med. Chem.* **2004**, *12*, 1151;

Thromb. Haemostasis **2005**, *94*, 417;

Hemostasis and Thrombosis: Basic Principles and Clinical Practice, 6th ed, Lippincott Williams & Wilkins: Philadelphia, **2013**

Previous Studies

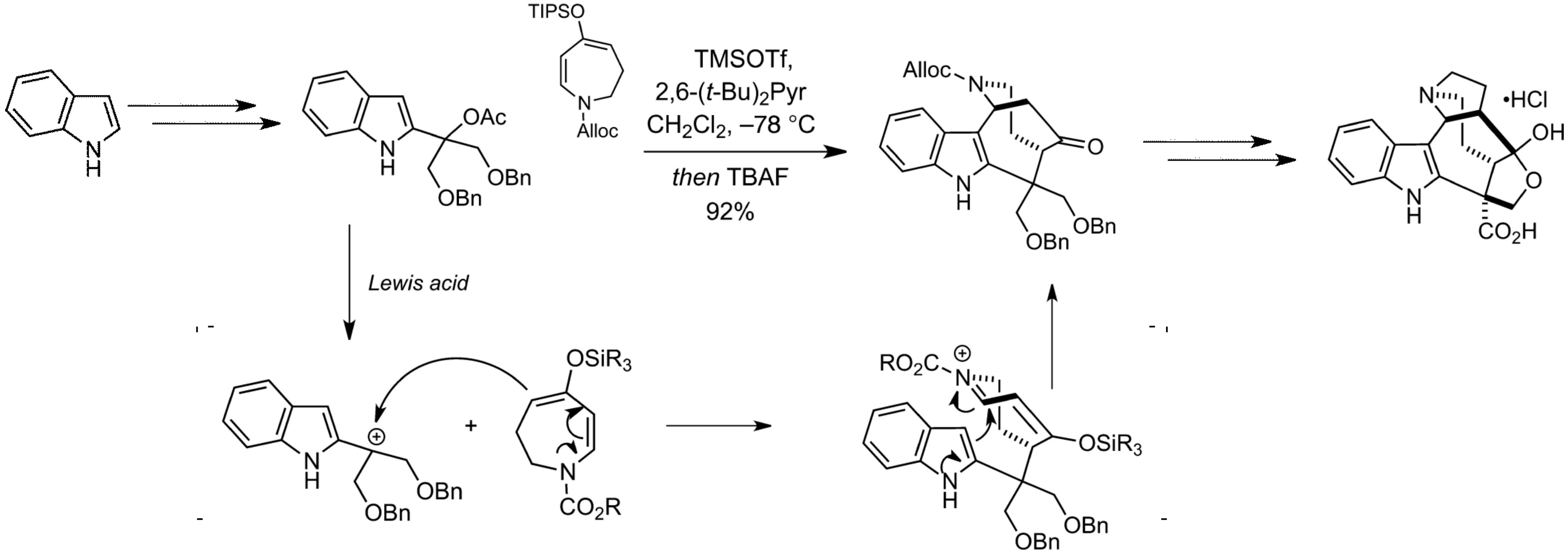
- Overman: total synthesis of (±)- Actinophyllic Acid: aza-Cope/ Mannich strategy



J. Am. Chem. Soc. **2008**, *130*, 7568
J. Am. Chem. Soc., **2010**, 132, 4894

Previous Studies

- Martin: total synthesis of (±)- Actinophyllic Acid: a cascade reaction between a seven-membered ring dienamine and a tertiary 2-indolyl acetoxylate

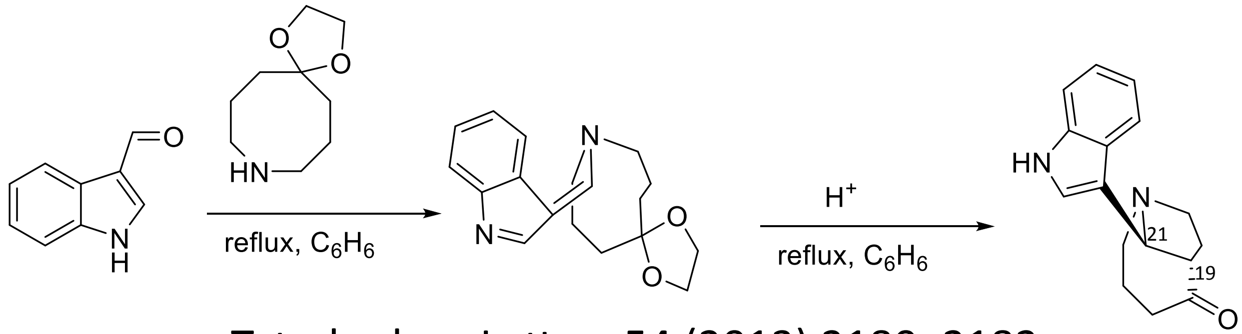


The geometric constraints guarantee formation of a single stereo-isomeric product.

J. Am. Chem. Soc., **2013**, *135* , 12984
Tetrahedron , **2014**, *70*, 4094

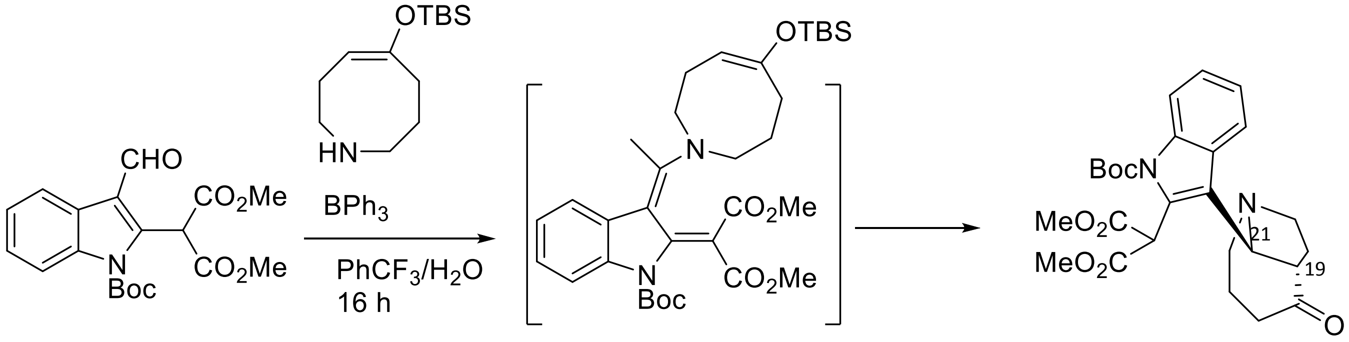
Previous Studies

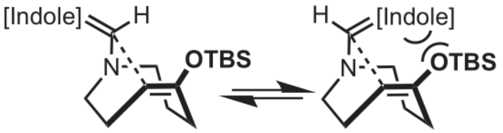
- Maldonado:



- Coldham:

Tetrahedron Letters 54 (2013) 2180–2182



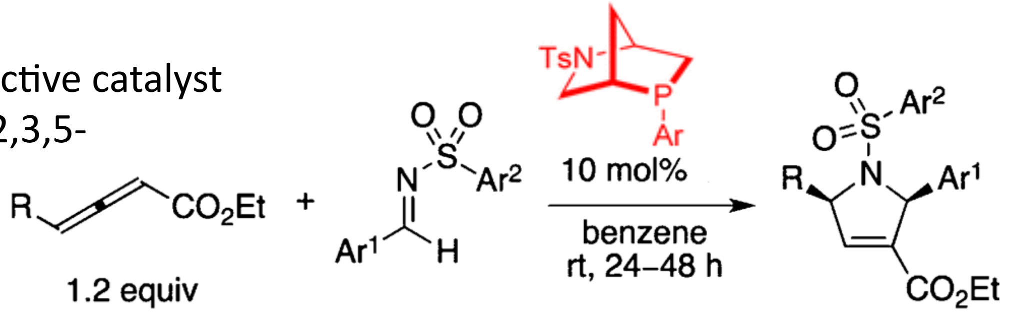


C19 and 21: trans stereochemistry incorrect due to steric congestion

Tetrahedron Lett . **2013**, *54*, 2180
Tetrahedron Lett. **2014**, *55*, 1255

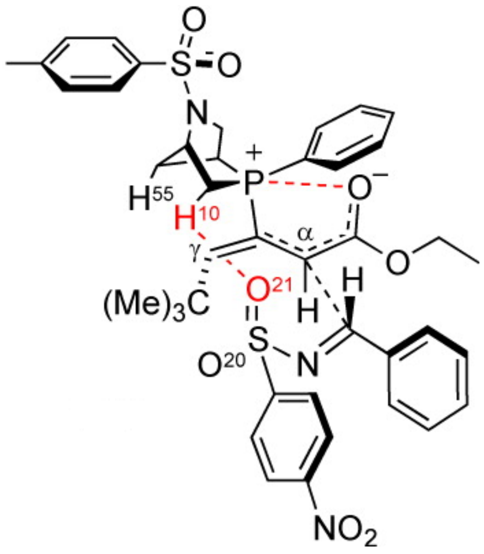
Previous Studies

- Enantioselective allene−imine [3 + 2] annulations;
- A new class of rigid chiral [2.2.1] bicyclophosphine that is highly effective catalyst for the asymmetric syntheses of 1,2,3,5-substituted pyrrolines.



76-99% yield, 71-99% ee

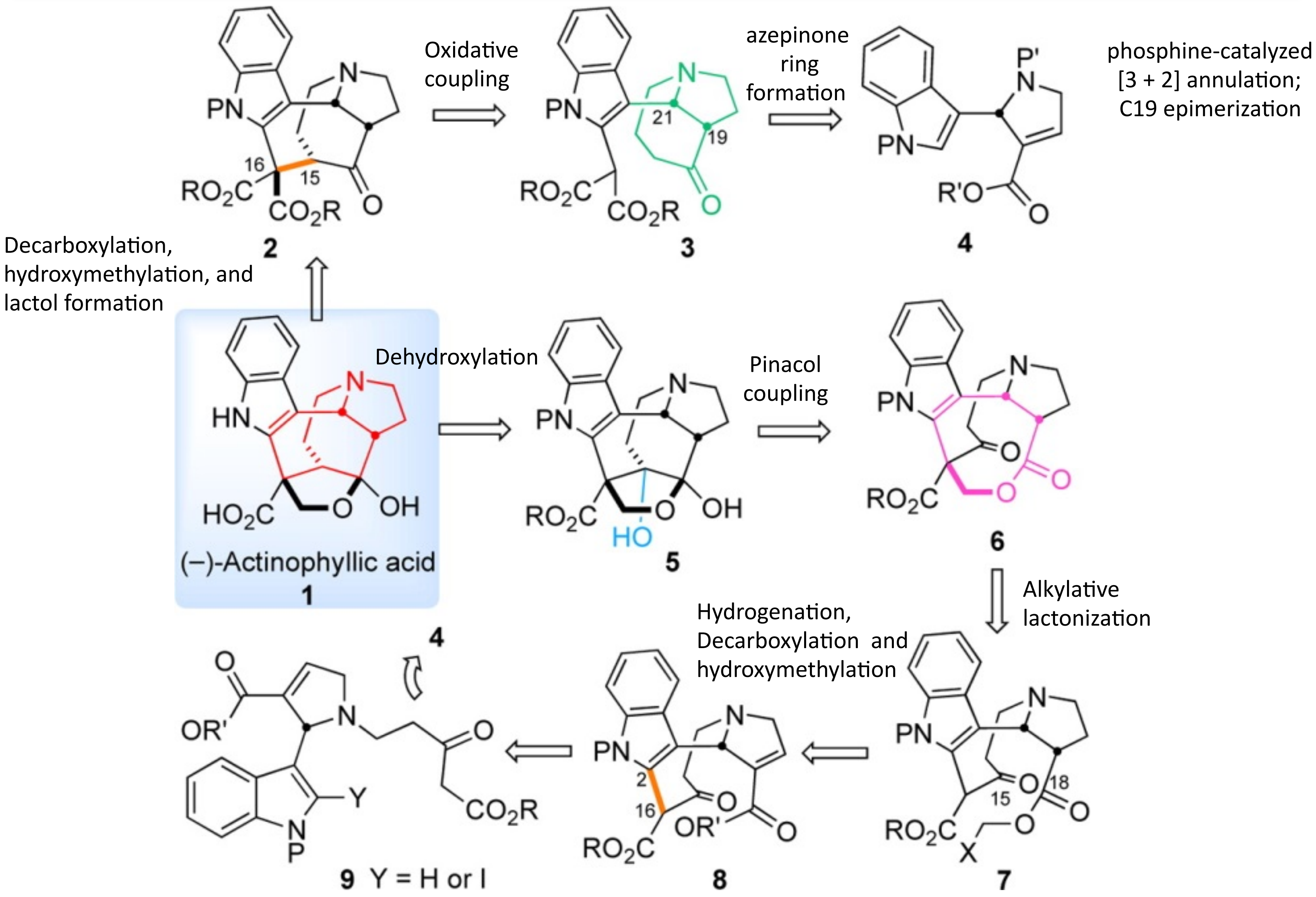
Transition State:



- Transition states features the lowest possible number of unfavorable van der Waals contacts of *P*-phenyl group.
- Two stabilizing factors for the $C_{\alpha}\cdots C_{imine}$ bond-formation:
    - a hydrogen bond between imine-sulfonyl O and bicyclic ring H
    - a favorable Coulombic interaction between allenoate $C{=}O$ O and P
- The catalyst blocked the *Re* face of the phosphonium dienolate, resulting in a (2*S*)-stereofacial imine addition

J. Am. Chem. Soc., **2014**, *136*, 11890

Retrosynthetic Analysis



Oxidative coupling

azepinone ring formation

phosphine-catalyzed [3 + 2] annulation; C19 epimerization

Decarboxylation, hydroxymethylation, and lactol formation

Dehydroxylation

Pinacol coupling

Alkylative lactonization

Hydrogenation, Decarboxylation and hydroxymethylation

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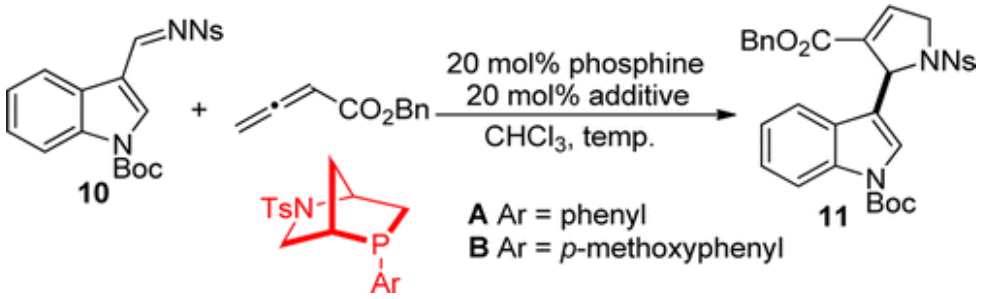
Phosphine-Catalyzed Pyrrolidine Synthesis



:

entry	cat.	temp. (°C)	additive	time (h)	yield (%)[a]	ee (%)[b]
1	PPh_3	rt		6	99	
2	A	rt		5	97	75
3	B	rt		5	99	83
4	B	0		5	99	91
5	B	0	phenol	2	99	91
6	B	0	biphenol	2	99	91
7	B	0	s-BINOL	2	99	94
8	B	0	r-BINOL	2	99	94

- The more nucleophilic phosphine B and lower temperature 0 °C improved the enantioselectivity.
- Hydrogenbondingwouldfacilitate the proton-transfer steps and rigidify the transition-state assembly, improving the enantioselectivity and decreasing the reaction time.

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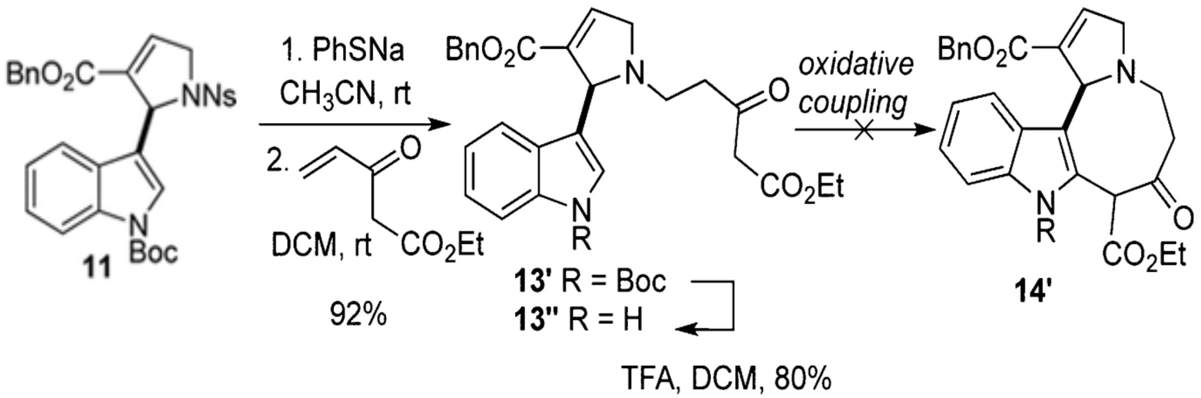
Attempted Oxidative Coupling

- Formation of hexahydroazocinone ring through oxidative coupling



- Oxidants including Fe^{3+}, Cu^{2+}, Mn^{3+}, Co^{2+}, Ag^{+}, and I_2 failed to facilitate the oxidative coupling of the substrate 13’ and 13”.

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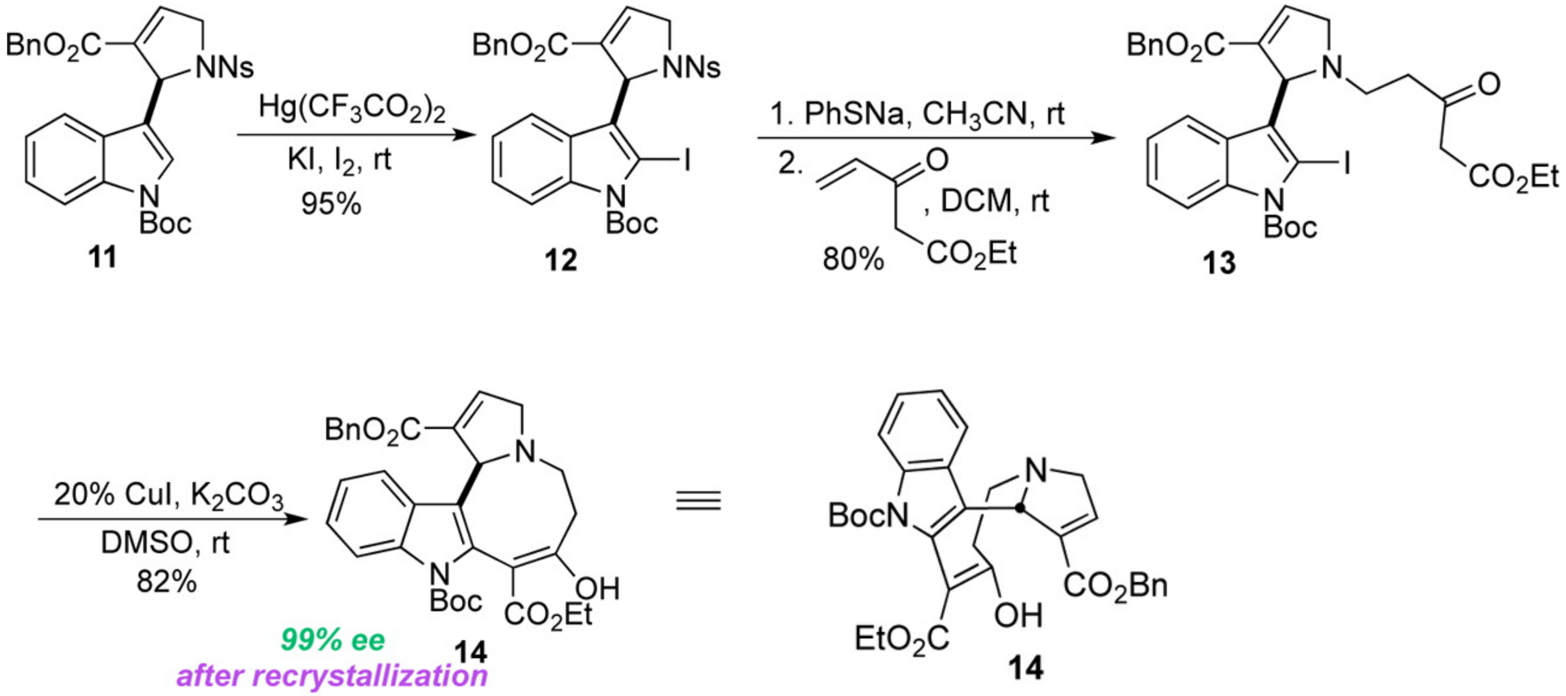
Redox-Neutral Coupling Approach



99% ee
after recrystallization

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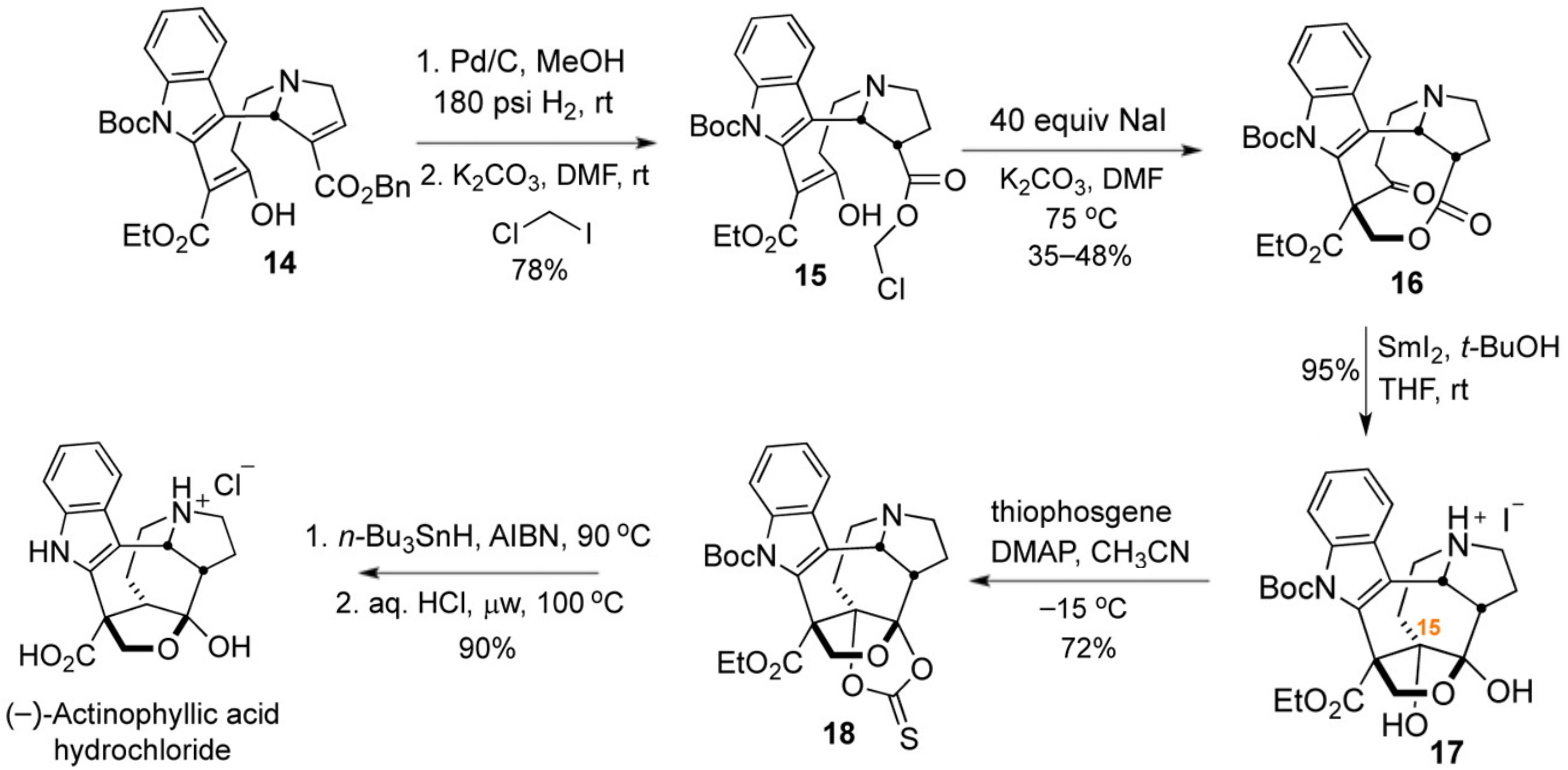
Total Synthesis



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Conclusion

- The total synthesis of (−)-actinophyllic acid as accomplished in 13 steps from a known aldehyde in 12.4% yield.
- The key steps include:
  - chiral phosphine-catalyzed [3 + 2] annulation between an allenoate and an indole imine;
  - CuI-catalyzed coupling between a 2-iodoindole and a ketoester to assemble a hexahydro-1H-azocino[4,3-b]indole system;
  - intramolecular alkylative lactonization to form a tetrahydrooxocine ring;
  - highly efficient pinacol coupling between a ketone and a lactone to form the caged scaffold of (−)-actinophyllic acid;
  - regioselective removal of a tertiary alcohol by taking advantage of a vicinal hemiketal.