New Methods of Indole Formations and Applications in Total Synthesis

Palladium-Catalyzed Synthesis of 2-(Aminomethyl)indoles from Ethyl 3-(o-Trifluoroacetamidophenyl)-1-Propargyl Carbonate
Ilaria Ambrogio, Sandro Cacchi and Giancario Fabrizi
Org. Lett., 2006, ASAP

and

A New Modular Indole Synthesis. Construction of the Highly Strained CDEF Parent Tetracycle of Nodulisporic Acids A and B
Amos B. Smith, III, László Kürti and Akin H. Davulcu
Org. Lett., 2006, ASAP

Erick B. Iezzi, PhD
Current Literature
May 6, 2006

Why are these articles significant?

- New routes to functionalized indoles:
  - significant for natural product and pharmaceutical drug synthesis

- Cacchi's group developed a simple approach to 2-(aminomethyl)indoles and the important class of 2-(piperazin-1-ylmethyl)indoles

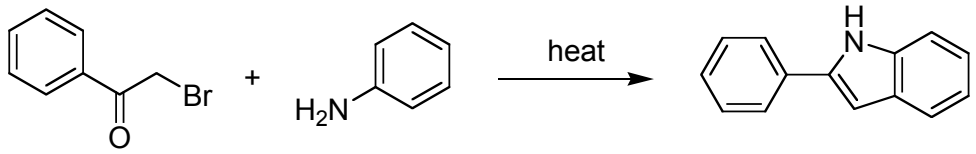
- Smith's group developed a new synthesis of tetracyclic indoles via a Stille cross-coupling/Buckwald-Hartwig union/cyclization

Synthesis and Functionalization of Indoles

• Classical methods (over last 100 years):

- Fisher synthesis
- Gassman synthesis
- Madelung cyclization
- Bischler synthesis

Bischler-Möhlau synthesis

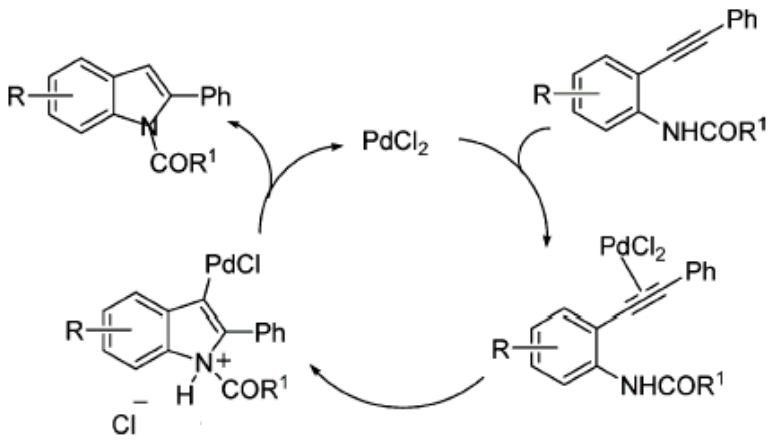


• Palladium-catalyzed syntheses (over last 40 years):

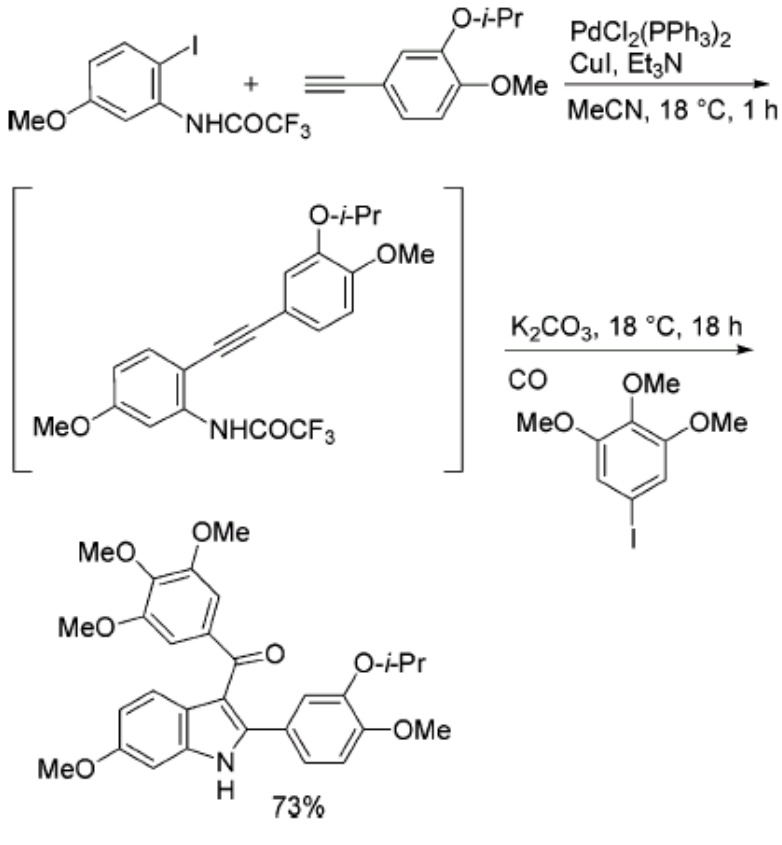
- industrial synthesis of acetaldehyde from ethylene ($PdCl_2$ and $CuCl_2$) launched a new area of research
  - fewer steps, less waste, etc.

Alkyne-Based Palladium-Catalyzed Assembly of Indoles

Mechanism



Example



Cacchi and Fabriz. *Chem. Rev.* **2005**, *105*, 2873

Alkene-Based Palladium-Catalyzed Assembly of Indoles

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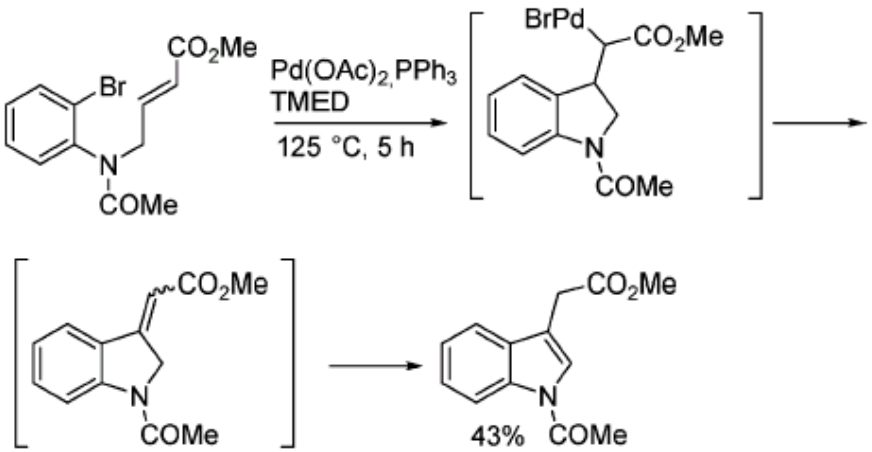
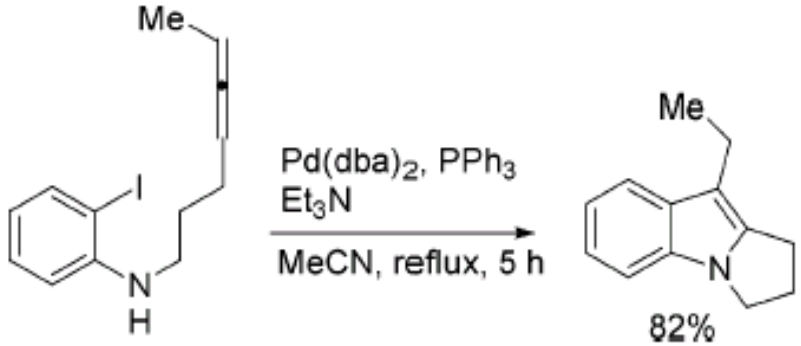


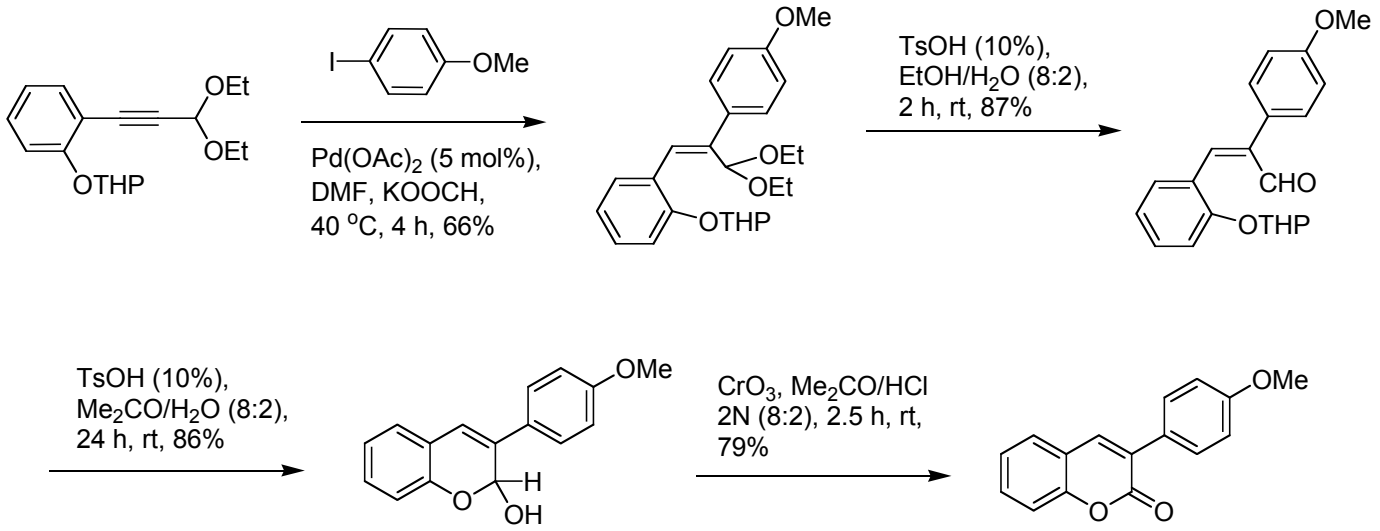
Example



Cacchi and Fabriz. *Chem. Rev.* **2005**, *105*, 2873

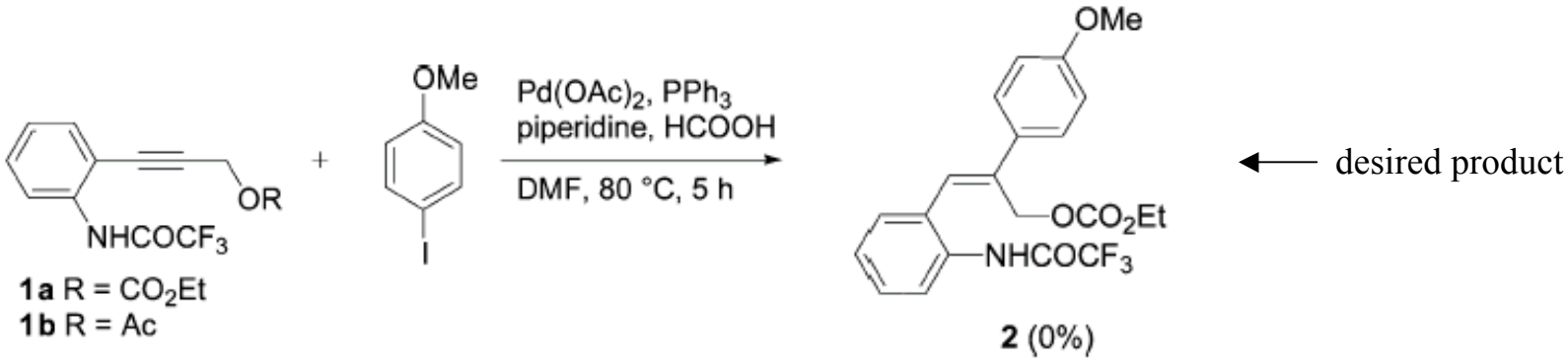
Palladium-catalyzed hydroarylation/cyclization of alkynes (Cacchi's methodology)

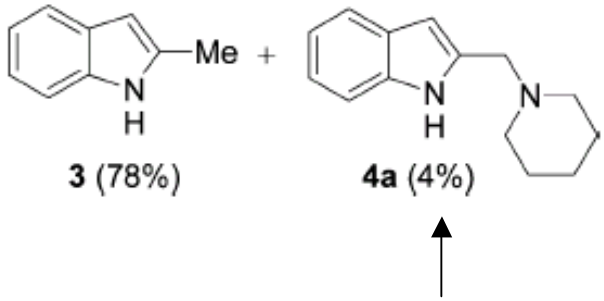
- Used to construct heterocyclic rings:
  - butenolides
  - quinolines
  - chromenes
  - coumarins
  - chromanols



Cacchi, et al. *Synlett.* **1997**, 1367

Palladium-Catalyzed Synthesis of 2-(Aminomethyl)indoles (Cacchi et al., ASAP)

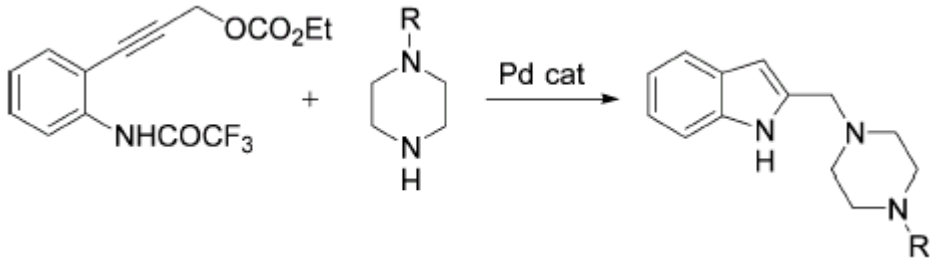




* A new palladium-catalyzed cyclization of an acyclic alkyne to a free N-H functionalized indole!

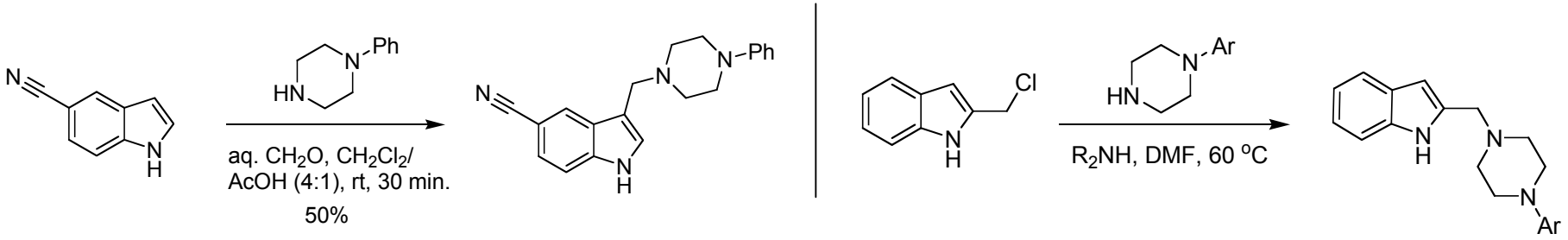
Synthesis of 2-(piperazin-1-ylmethyl)indoles (Cacchi et al., ASAP)

- 2 privileged structures (indole and piperazine nuclei)
  - significant components in pharmaceutical chemistry (i.e., Clozapine)
  - formed in a single step



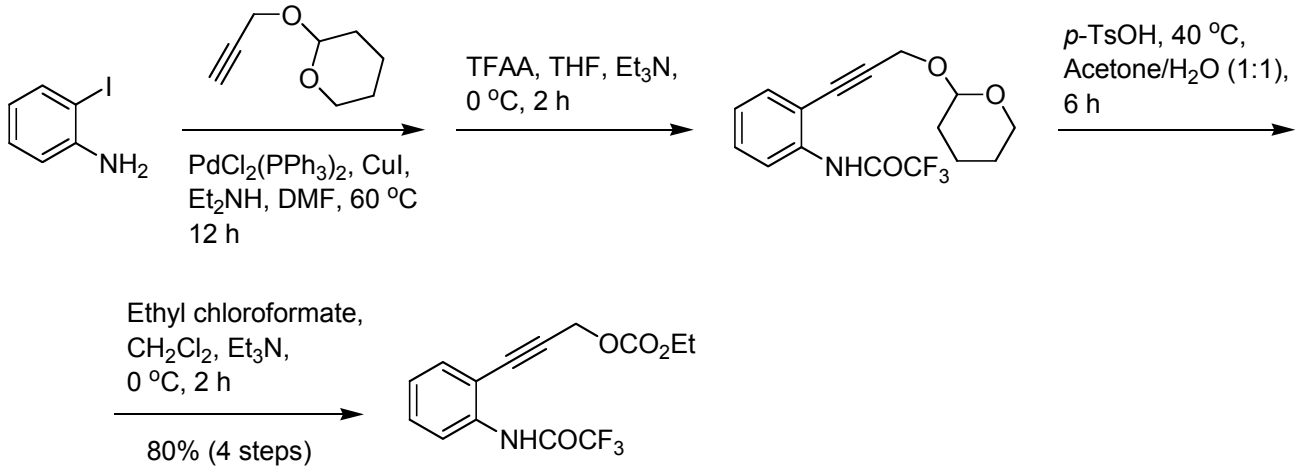
Two C-N bonds formed in a single operation

- Stepwise pathways (2 & 3 positions)



Gmeiner, et al. *J. Med. Chem.* **2000**, *43*, 4563

Synthesis of Starting Materials and Evaluation of Conditions for 2-(Piperazin-1-ylmethyl)indole Formation



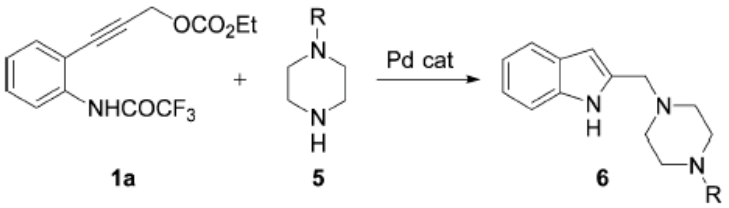
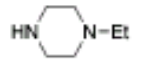
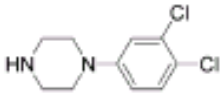
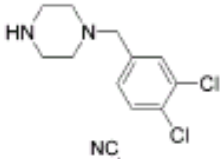
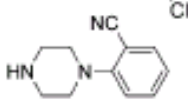
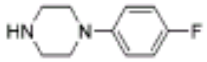
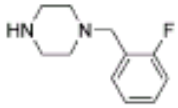
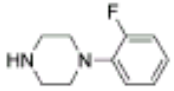
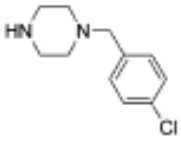
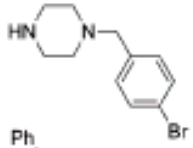
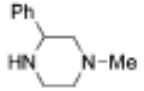
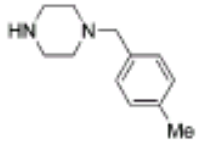
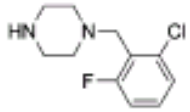
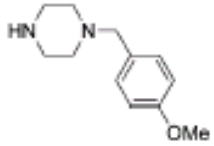
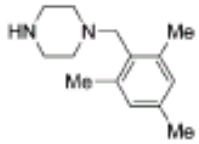
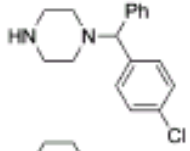
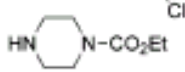


Table 1. Examination of the Reaction of Ethyl 3-(*o*-Trifluoroacetamidophenyl)-1-propargyl Carbonate **1a** with *N*-Ethylpiperazine **5a**[a]

entry	catalyst system	solvent	time (h)	yield % of **6a**[b]
1	$Pd(OAc)_2$, PPh_3	THF	6	52
2	$Pd_2(dba)_3$, PPh_3	THF	6	58
3	$Pd(PPh_3)_4$	MeCN	6	57[c]
4	$Pd(PPh_3)_4$	DMF	6	54[c]
5	$Pd(PPh_3)_4$	THF	1.5	91
6	$Pd_2(dba)_3$, dppf	THF	6	85
7	$Pd_2(dba)_3$, dppe	THF	24	50
8	$PdCl_2(2\text{-furyl})_2$	THF	24	33

[a] Unless otherwise stated, reactions were carried out on a 0.159 mmol scale in 1 mL of solvent under argon at 80 °C by using 1 equiv of **1a**, 3 equiv of **5a**, 0.05 equiv of [Pd], 0.1 equiv of PPh_3, or 0.05 equiv of bidentate phosphine ligand. [b] Yields are given for isolated products. [c] With 0.05 equiv of $Pd(PPh_3)_4$.

Evaluation of Functional Groups in 2-(Piperazin-1-ylmethyl)indole Formations

entry	piperazine **5**	time (h)	yield % of **6**[b]
1	 **5a**	1.5	**6a** 91
2	 **5b**	2	**6b** 96
3	 **5c**	24	**6c** 80
4	 **5d**	3	**6d** 98
5	 **5e**	6	**6e** 96
6	 **5f**	6	**6f** 98
7	 **5g**	2.5	**6g** 97
8	 **5h**	3	**6h** 92
9	 **5i**	3	**6i** 94
10	 **5j**	6	**6j** 58
11	 **5k**	4	**6k** 85
12	 **5l**	12	**6l** 78
13	 **5m**	4	**6m** 81
14	 **5n**	4	**6n** 80
15	 **5o**	8	**6o** 92
16	 **5p**	20	**6p** 88

[a] Reactions were carried out on a 0.159 mmol scale in 1 mL of THF under argon at 80 °C by using 1 equiv of **1a**, 3 equiv of **5**, and 0.05 equiv of $Pd(PPh_3)_4$. [b] Yields are given for isolated products.

Evaluation of Secondary Amines and Proposed Reaction Mechanism

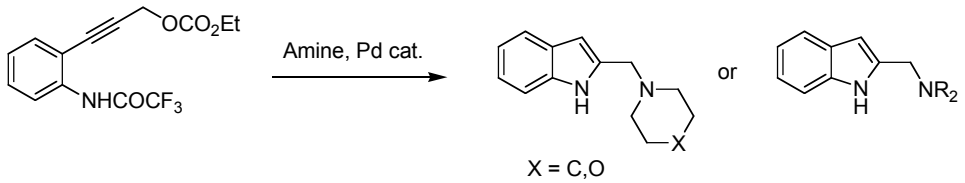
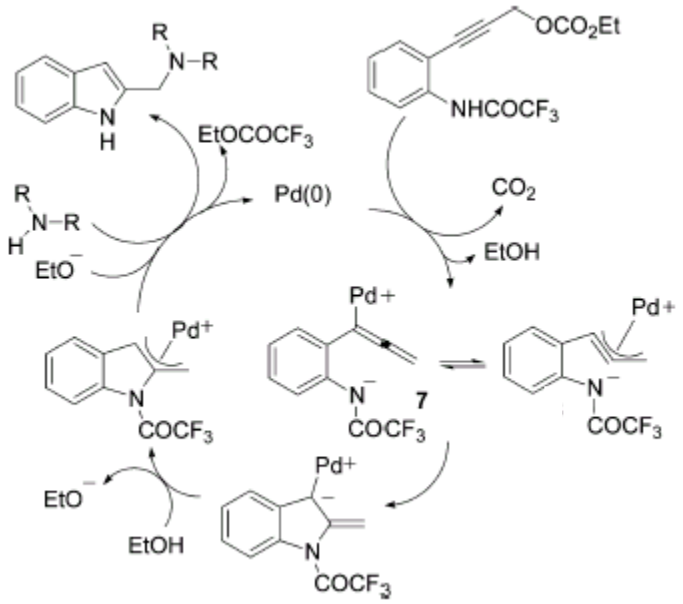
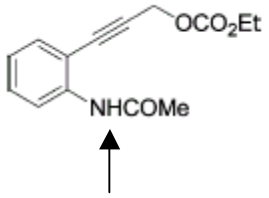


Table 3. Palladium-Catalyzed Reaction of Ethyl 3-(*o*-Trifluoroacetamidophenyl)-1-propargyl Carbonate **1a** with Secondary Amines[a]

entry	amine	time (h)	yield % of **4**[b]
1		1	**4a** 94[c]
2		1	**4b** 98
3	Et_2NH	2	**4c** 60[d]
4	$(i\text{-}Pr)_2NH$	4	**4d** 45

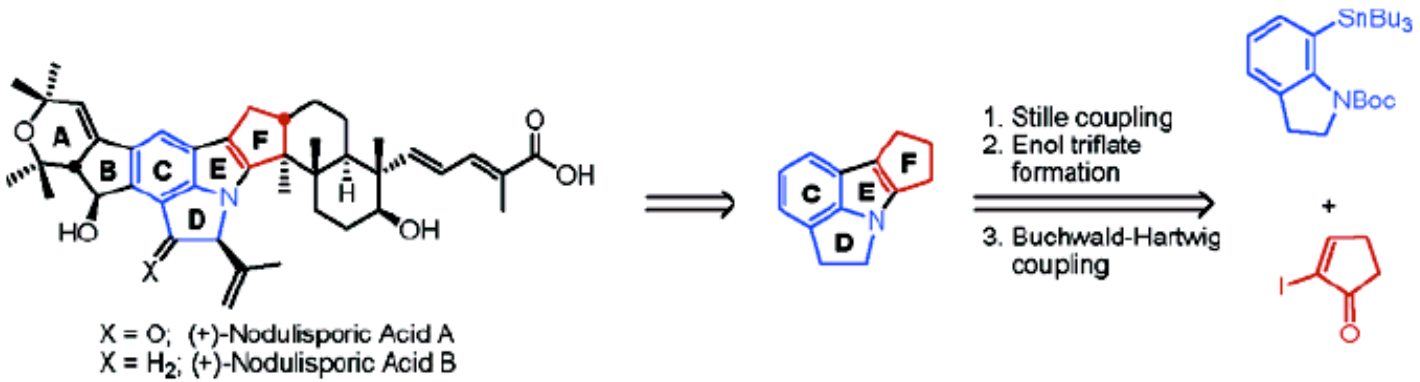
Proposed mechanism





Not acidic enough

A New Modular Indole Synthesis. Construction of the Highly Strained CDEF Parent Tetracycle of Nodulisporic Acids A & B (Smith et al., ASAP)



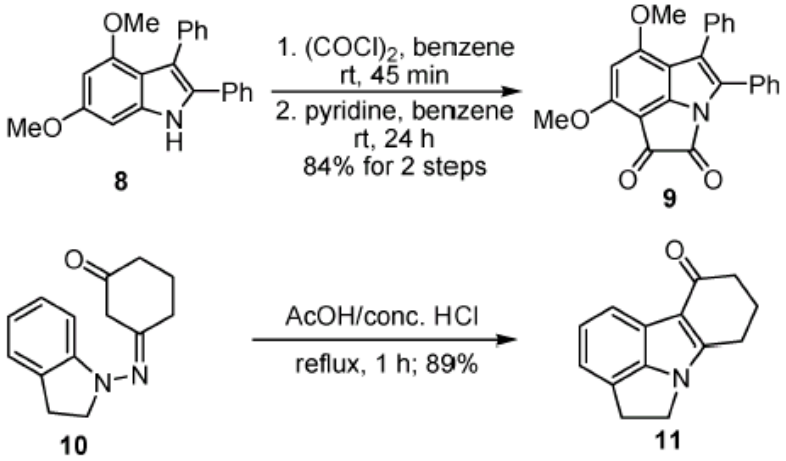
Nodulisporanes:

- a novel class of indole diterpene alkaloids
- display potent insecticidal properties (i.e., fleas and ticks)
  - modulation of the invertebrate-specific glutamate-gated chloride ion channels

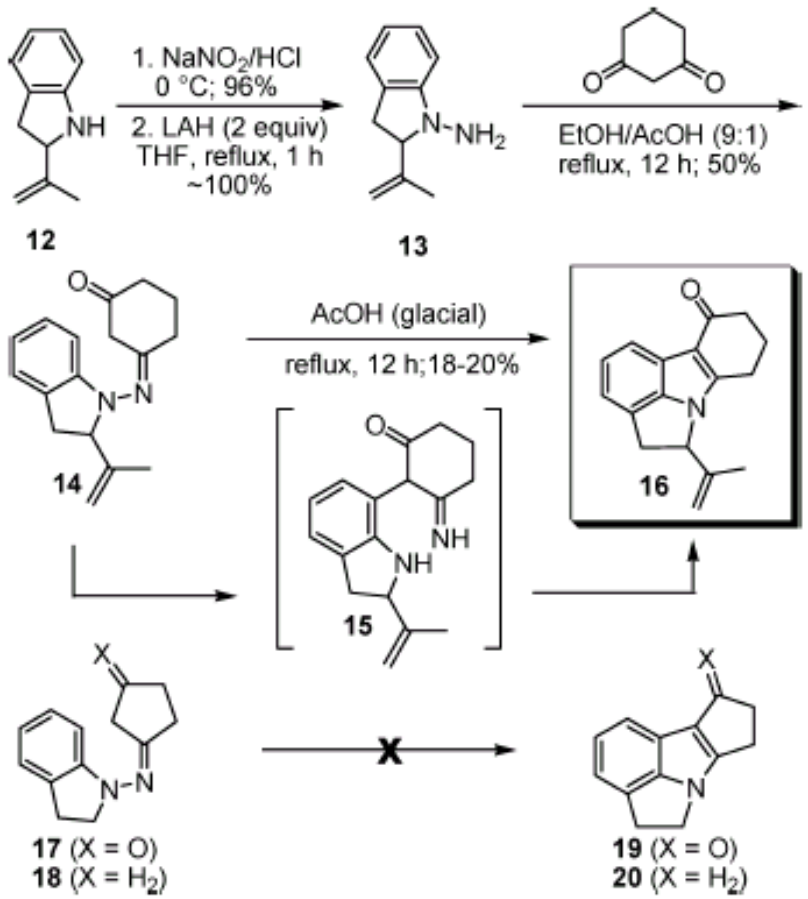
- Nodulisporic acid A – first reported by Merck in 1997 as a lead compound
  (potentcy, stability and pharmacokinetic profile was not optimal!)

Attempts to Synthesize the CDE Core via Known Indole Formations (Smith et al., ASAP)

Reported approaches to CDE tricycle

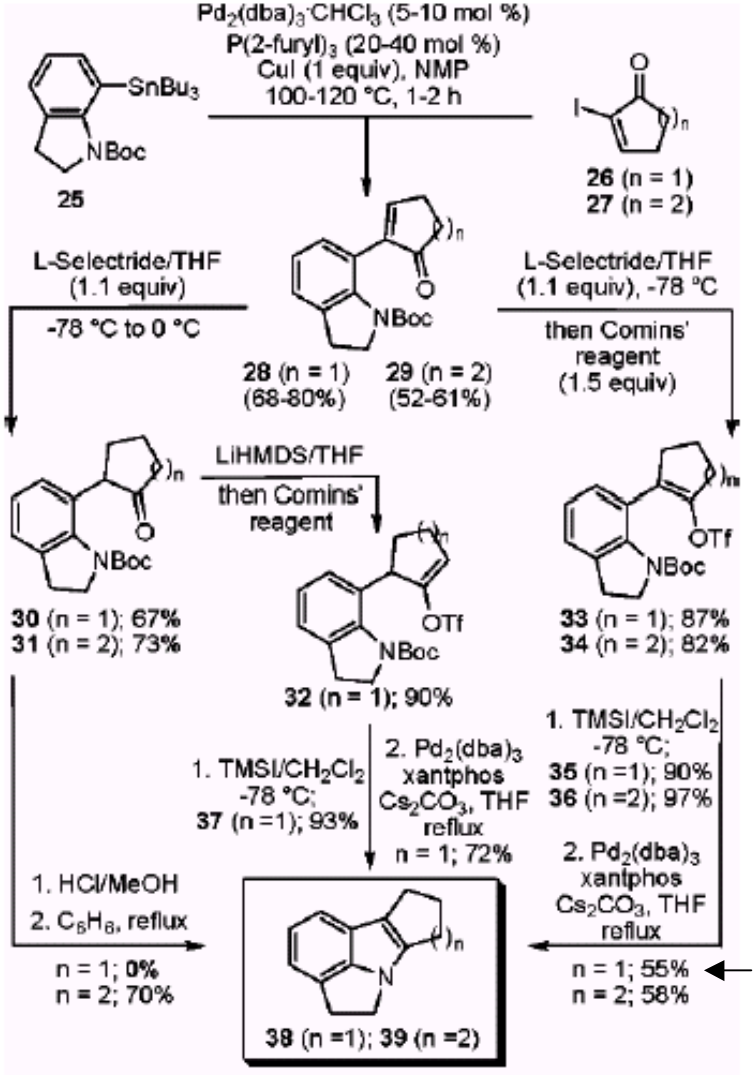


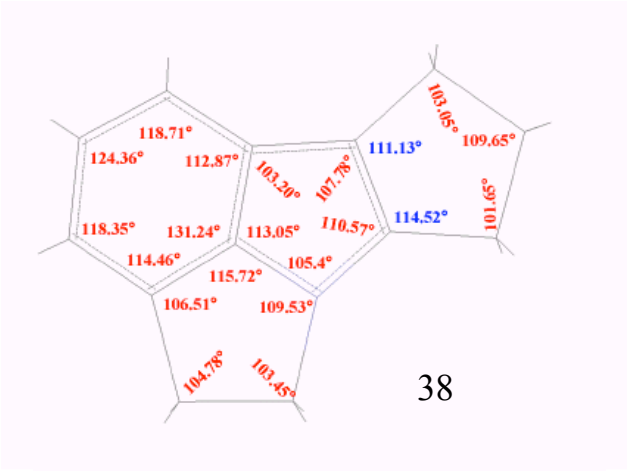
Application of the Fisher Indole Synthesis



High strain in five-membered system!

Stille Cross-Coupling/Buchwald-Hartwig Union/Cyclization Tactic (Smith et al., ASAP)





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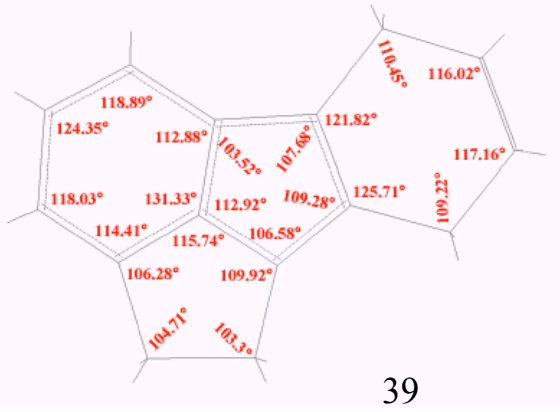

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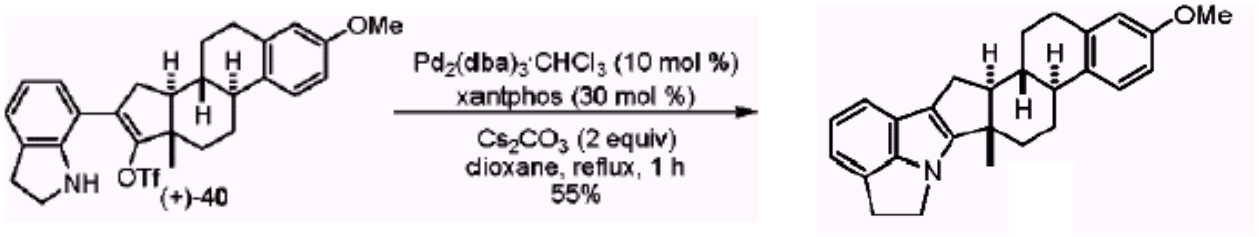
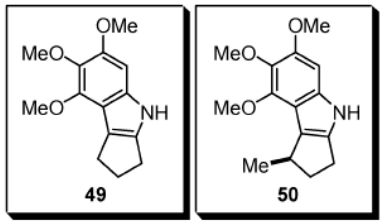
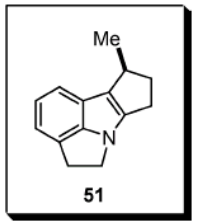
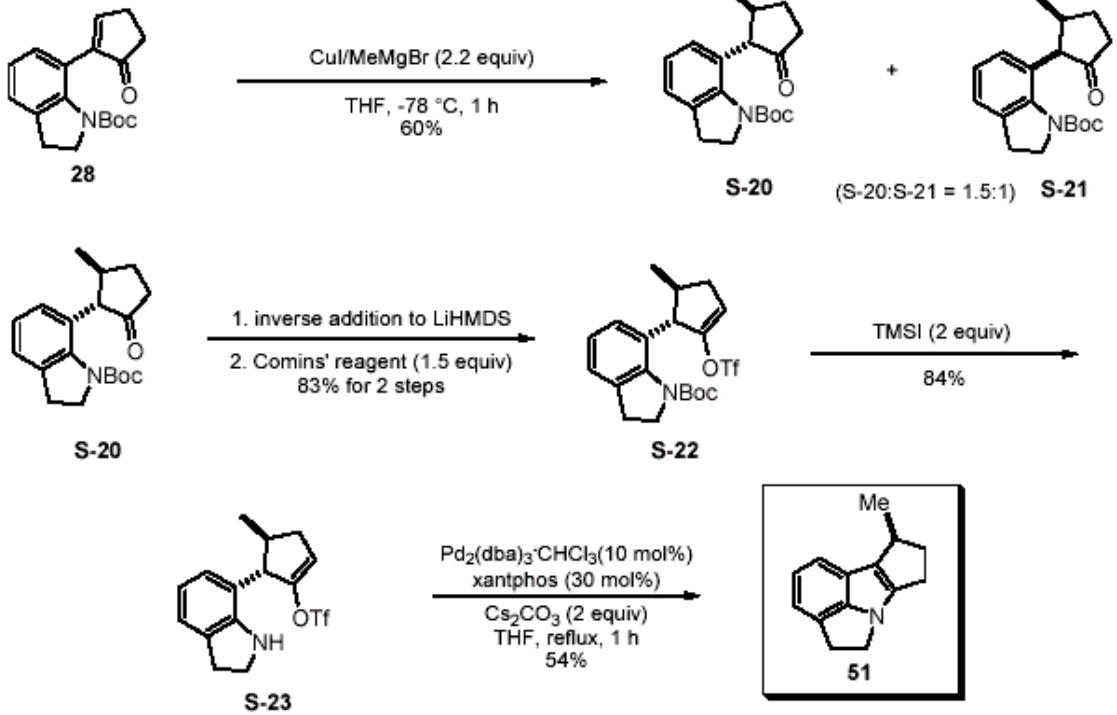
No reaction with 2.5 mol% cat.

Preparation of a Highly Substituted and Strained Indole Derived from (+)-Estrone and Construction of Diverse Indoles









Summary of New Indole Methodologies

- Cacchi's group developed a simple approach to 2-(aminomethyl)indoles and 2-(piperazin-1-ylmethyl)indoles under mild conditions in a single operation
  - high product yields
  - application to functionalized indoles

- Smith's group developed a new indole synthesis via a Stille/Hartwig-Buchwald coupling using mild conditions
  - application to structurally diverse indoles, especially novel tricyclic systems