

## Practical Organic Synthesis in Pharmaceutical Industry

- I. Heterocycle Syntheses
- II. Asymmetric Syntheses

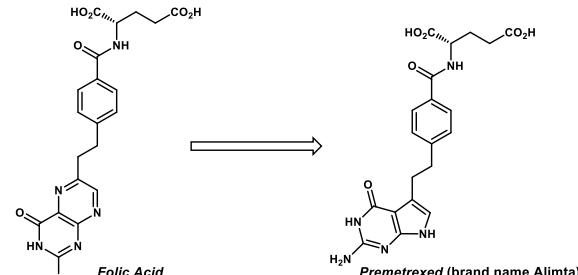
Cheng Yi Chen, Ph. D.  
IASOC, Sept. 22-25, 2018  
Naples, Italy

Art credit: Close-up of the inhibitor binding site of the colony-stimulating factor-1 receptor kinase domain.



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Professor Edward (Ted) C. Taylor (1923-2017)



Growth-promoting compound

Growth-inhibiting compound

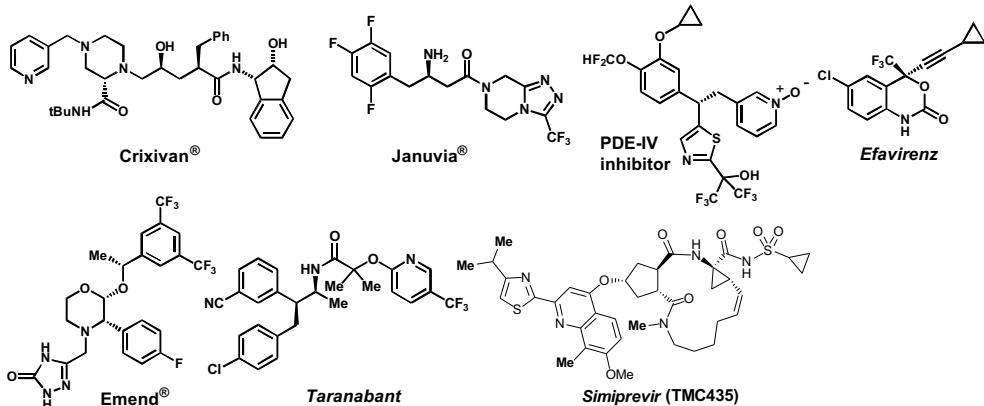
Collaboration with Lilly: 1984

Drug Launch: 2004

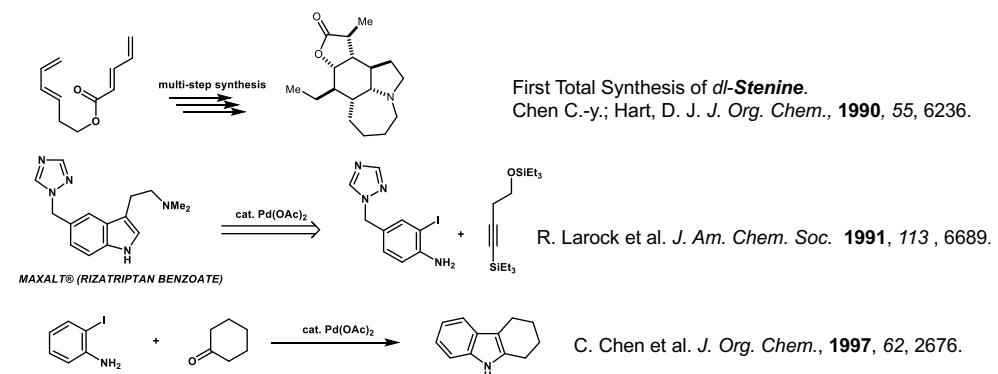


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## Examples of Complex Pharmaceutical Agents



## Synthesis of Indoles via Pd-catalyzed Coupling Reaction



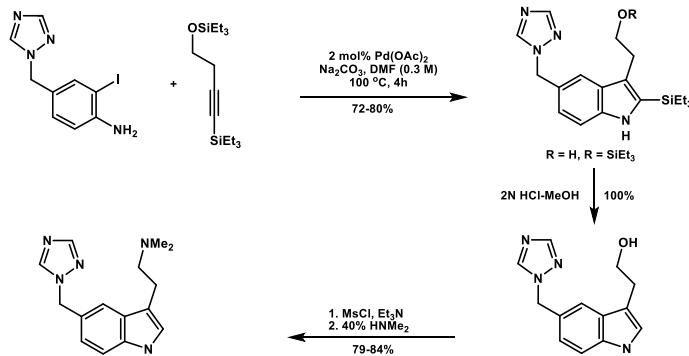
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### The Manufacturing Process for Rizatriptan



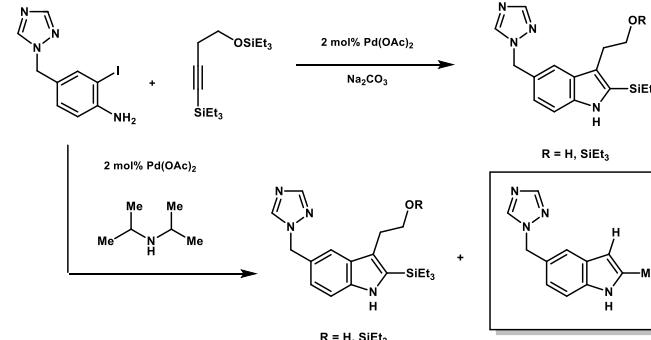
MAXALT® (RIZATRIPTAN)

C. Chen et al. *Tetrahedron Lett.* 1994, 38, 6981.

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### Unexpected Formation of 2-Methylindole

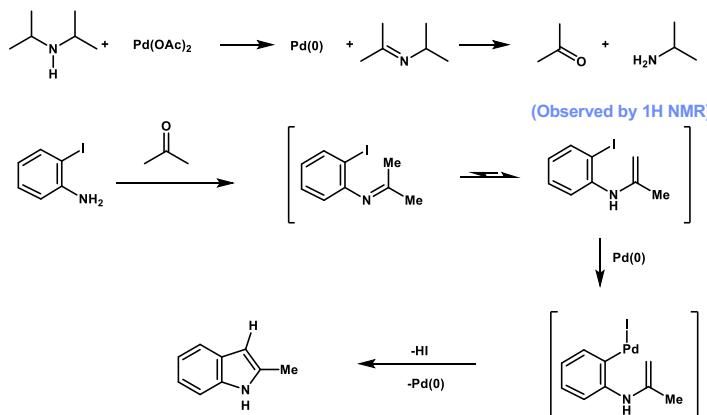


Where does the 2-Me indole come from?

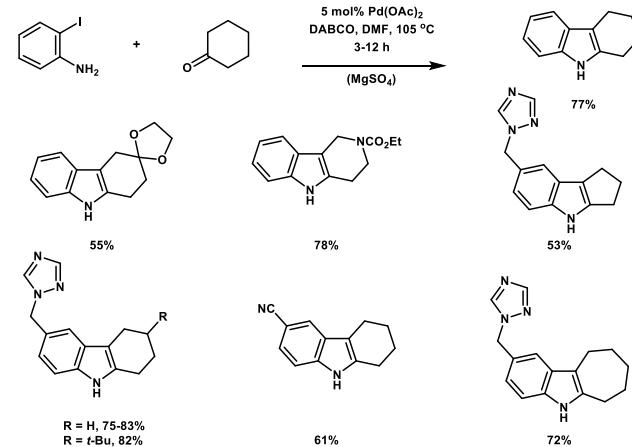
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### Proposed Mechanism for the Formation of 2-Methylindole



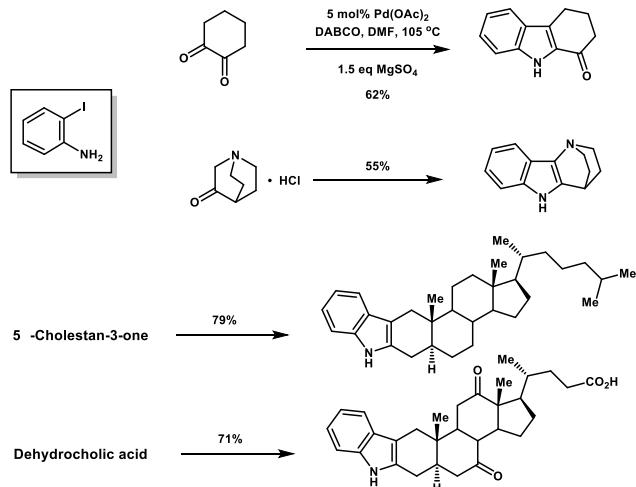
### Synthesis of Indoles via Pd-catalyzed Coupling



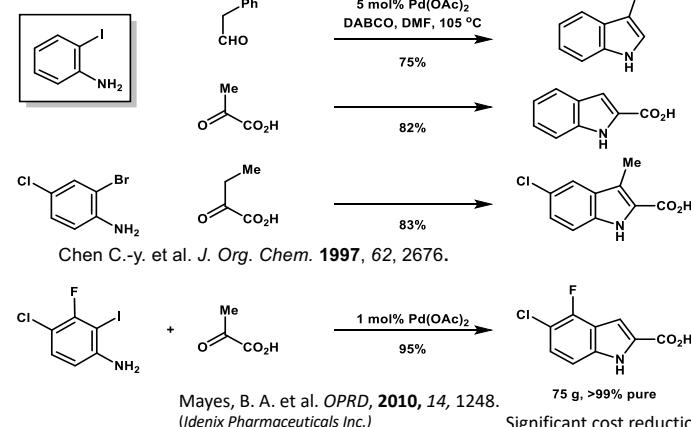
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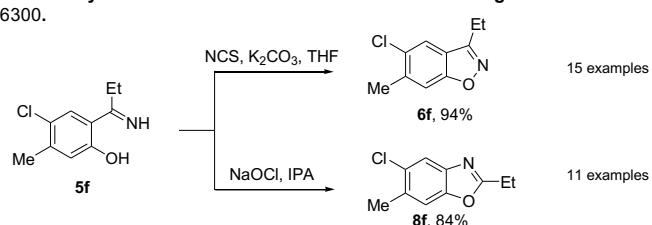
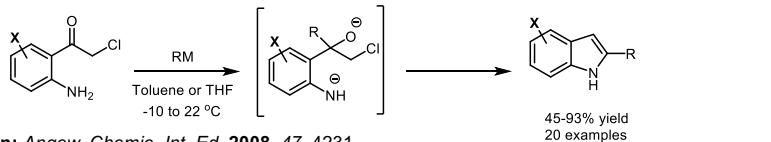




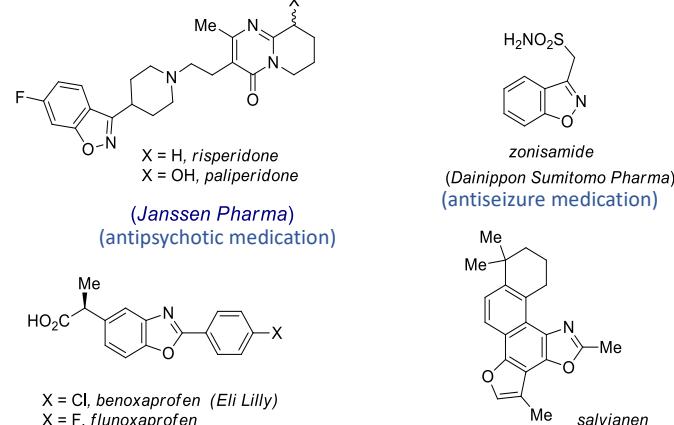
## More Indole Syntheses and Applications



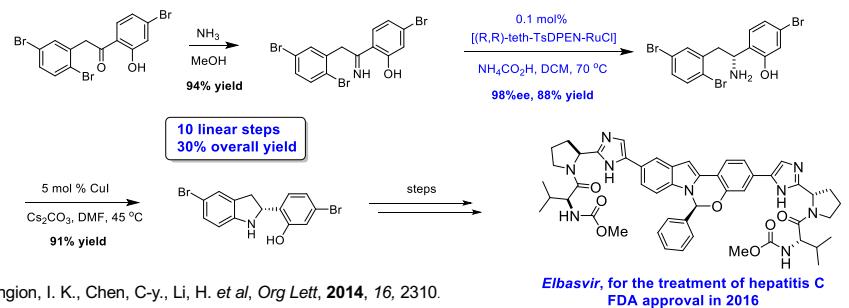
## Other Heterocyclic Chemistry



## Benzisoxazole and Benzoxazole in Drugs and Natural Products

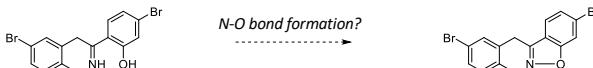


## Enantioselective Synthesis of Elbasvir



Mangion, I. K., Chen, C.-y., Li, H. et al, *Org Lett*, 2014, 16, 2310.

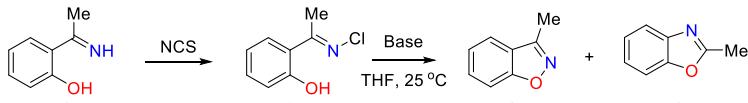
A research idea:



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## Survey of Bases

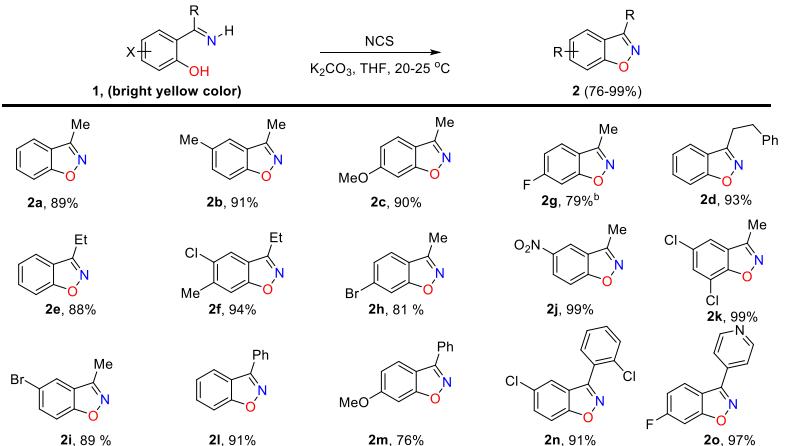


Base	2	3	4
Pyridine	100%		
DABCO		92%	8%
KOt-Bu		94%	4%
K <sub>2</sub> CO <sub>3</sub>		93%	7%
aq K <sub>2</sub> CO <sub>3</sub>	20%	50%	30%
aq NaOCl			91% yield

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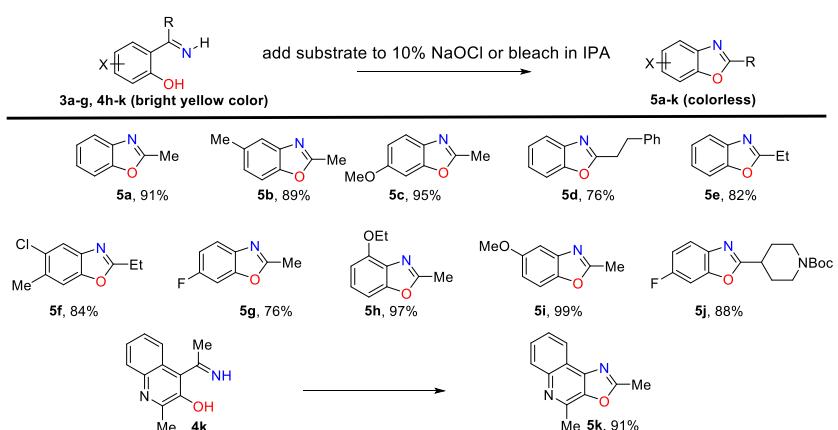
## Synthesis of Benzisoxazoles



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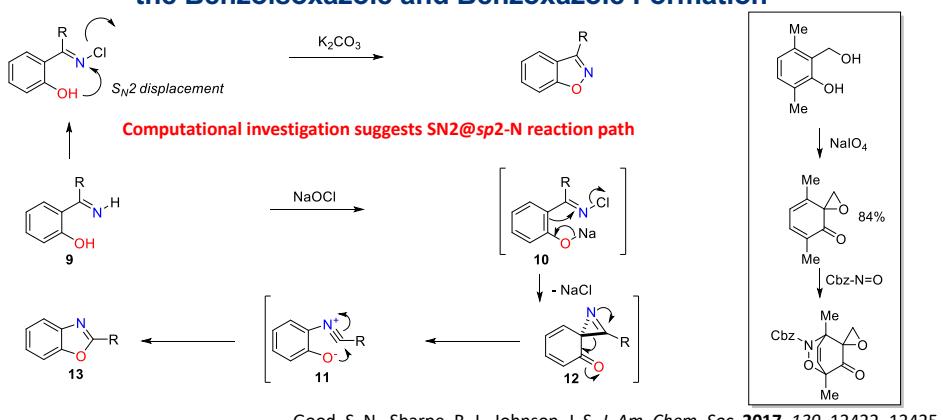
## Synthesis of Benzoxazoles



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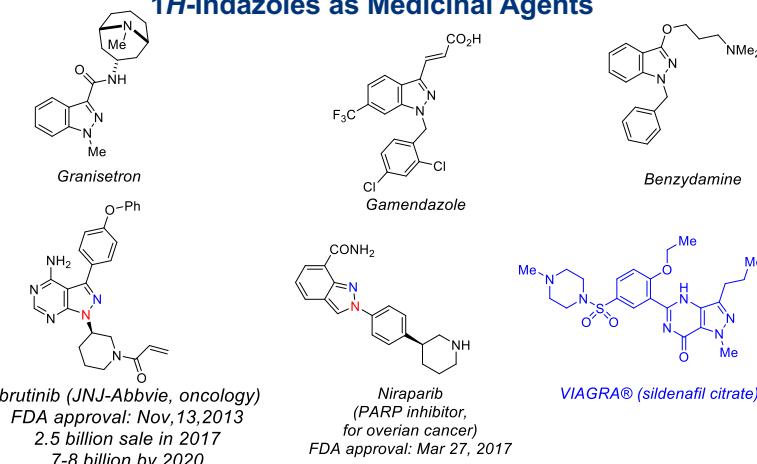
## Proposed Reaction Paths for the Benzoisoxazole and Benzoxazole Formation



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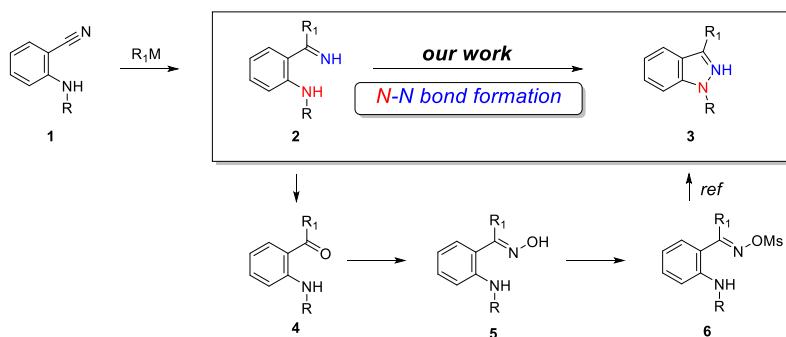
## 1*H*-Indazoles as Medicinal Agents



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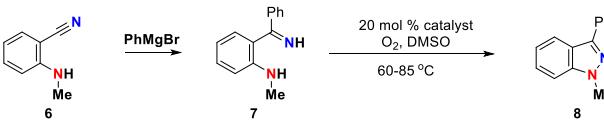
## Synthesis of 1*H*-Indazoles via N-N Bond Formation



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## Copper salts screening

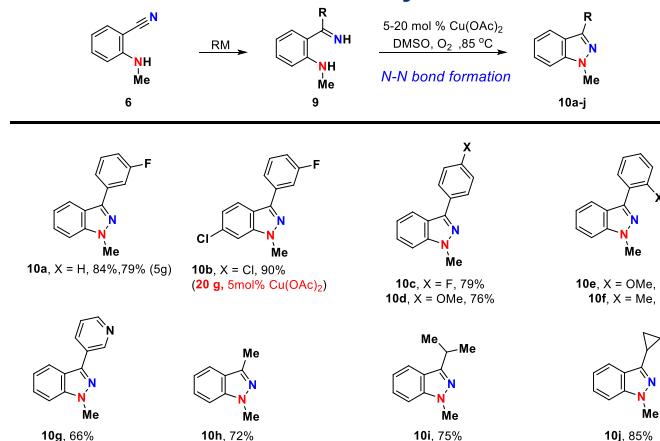


Entry	Catalyst	Yield (%)
1	$Cu(OAc)_2$	77.8
2	$Cu(OTf)_2$	42.5
3	$CuBr_2$	53.3
4	$CuCl$	69.4
5	$CuI$	58.6
6	$CuBr$	68.7
7	$CuO$	30.7
8	$Pd(OAc)_2$	1.0
9	$Ni(dppe)Cl_2$	--
10	$Pd(dppf)Cl_2/PPh_3$	--

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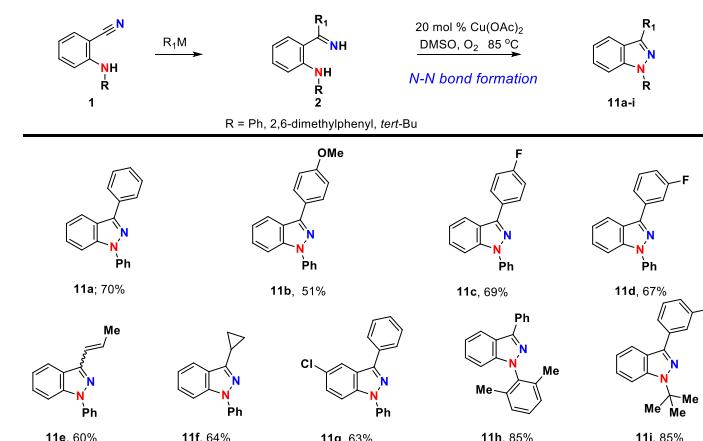
### 1*H*-Indazoles from 2-Methylaminobenzonitriles



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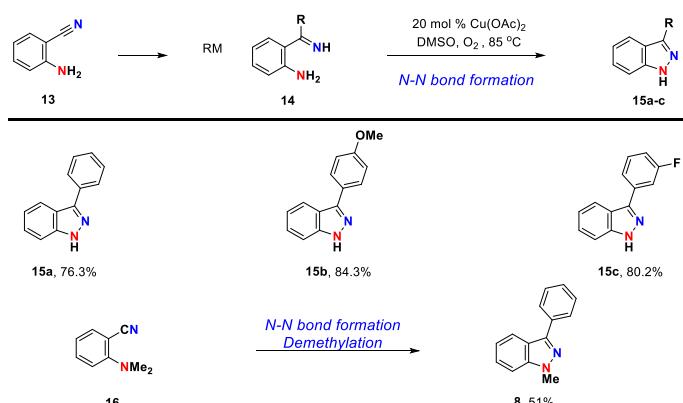
### 1*H*-Indazoles from 2-Aminobenzonitriles



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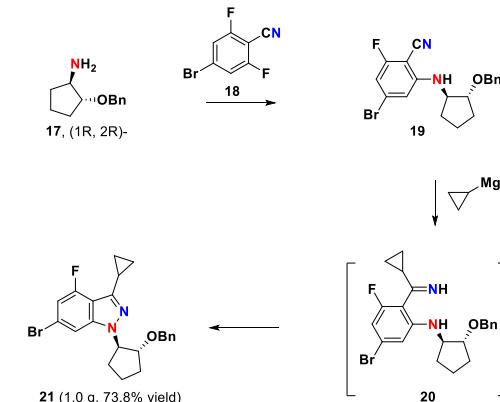
### 1*H*-Indazoles from 2-Aminobenzonitriles and 2-Dimethylaminobenzonitrile



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### Preparation of Chiral 1*H*-Indazole



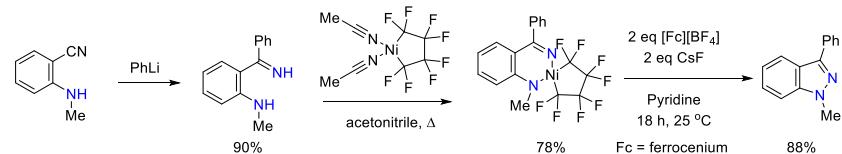
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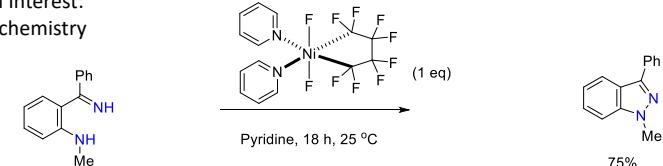
## A Critique on the Cu-catalyzed N-N Bond Formation



## Nitrogen–Nitrogen Bond Formation via a Substrate-Bound Anion at a Mononuclear Nickel Platform



Professor Vicic's Research Interest:  
Ni, F, one-electron redox chemistry



Kosobokov M. D.; Sandleben, A.; Vogt, N.; Klein, A.; Vicic, D. A.\* *Organometallics*, **2018**, *37*, 521.

## Nitrogen–Nitrogen Bond Formation via a Substrate-Bound Anion at a Mononuclear Nickel Platform

Kosobokov M. D.; Sandleben, A.; Vogt, N.; Klein, A.; Vicic, D. A.\* *Organometallics*, **2018**, *37*, pp 521.  
(listed as one of the “most-read” article in Feb 2018)

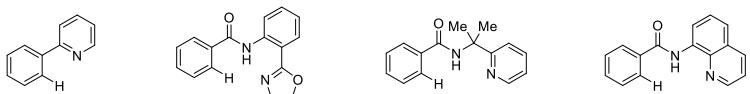
“The reaction described in equation 1 formally involves the loss of two electrons and two protons and can be used to prepare indazoles bearing a variety of functional groups and chiral centers. **Unfortunately, no metal-containing intermediates were isolated or studied, making an understanding of this reaction extremely limited.**”

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## Directing Groups in C-H Activation

### 1. Common DGs for copper-mediated/catalyzed *ortho*-hydroxylation of C(sp<sup>2</sup>)-H bond



### 2. Tandem transformation of C(sp<sup>2</sup>)-H Hydroxylation/N-N bond formation

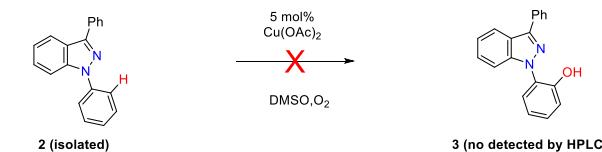
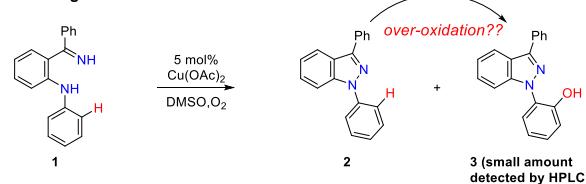


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## Unexpected *ortho*-Hydroxylation via C-H activation

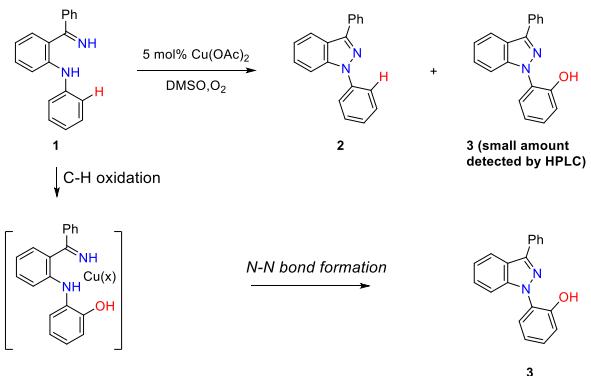
20 g reaction:



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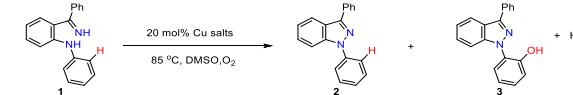
## A proposed path for the sequential C-H oxidation and N-N bond formation



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## Copper salt screening for the C-H hydroxylation and N-N bond formation

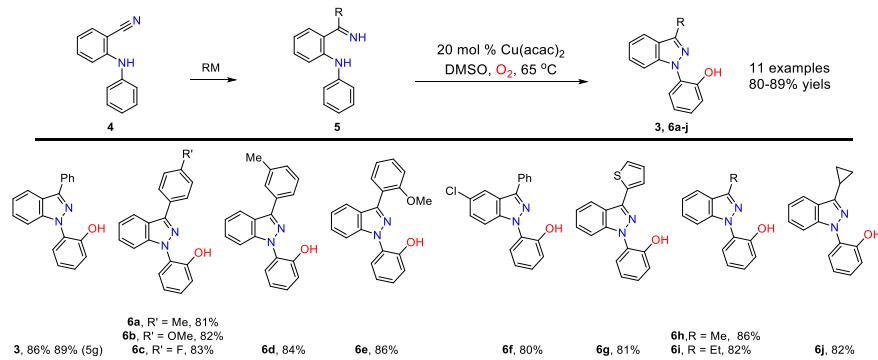


Entry	Cu salt	mol/%	ratio of 2:3 (isolated yield of 3)
1	Cu(OAc) <sub>2</sub>	20	10.7 : 1
2	CuI	40	6.0 : 1
3	CuBr	40	3.7 : 1
4	CuCl	40	2.5 : 1
5	CuBr <sub>2</sub>	40	3.2 : 1
6	Cu(OTf) <sub>2</sub>	40	1 : 2.0
7	Cu(NO <sub>3</sub> ) <sub>2</sub>	40	1 : 2.8
8	CuSO <sub>4</sub>	40	1 : 3.3
9	CuO	40	1 : 10 (65%)
10	Cu(acac) <sub>2</sub>	40	1 : 12.5 (67%)
11 (65 °C)	Cu(acac) <sub>2</sub>	20	1 : 15.9 (86%)

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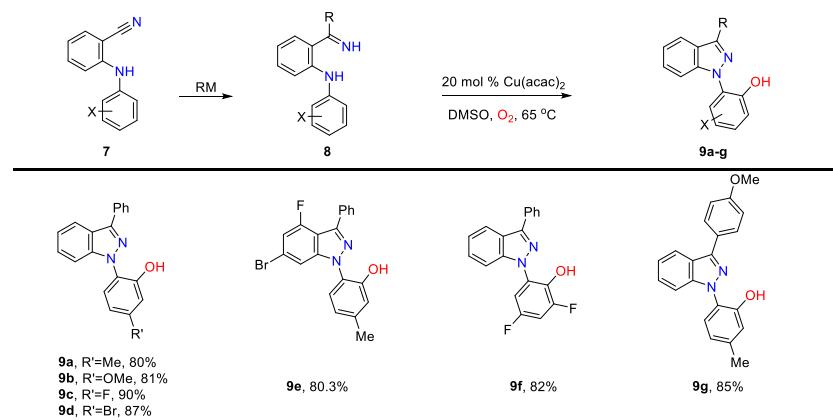
## ortho-Hydroxylaryl 1*H*-Indazoles from 2-Phenylaminobenzonitriles



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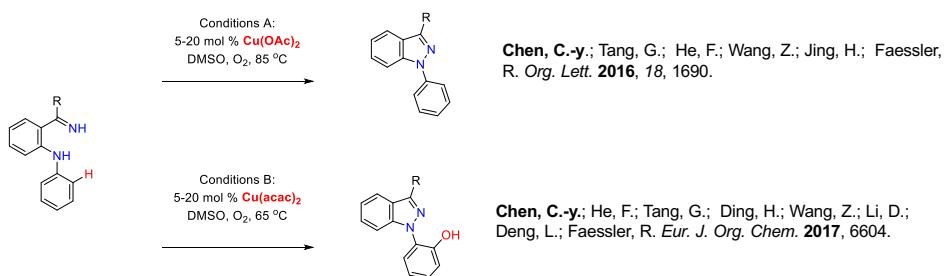
## ortho-Hydroxylaryl 1*H*-Indazoles from 2-Arylamino Benzonitriles



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## Summary on N-N Bond Formation to Indazole



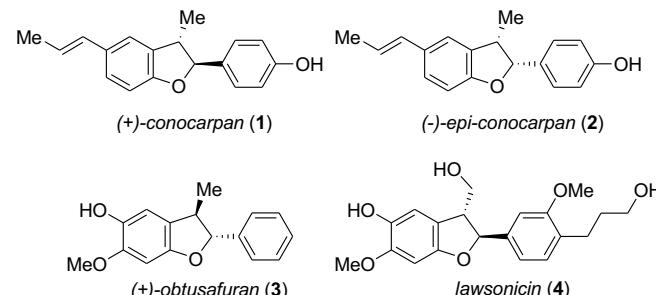
Highlight: Victor Snieckus; Marzieh Miranzadeh (Snieckus Innovations and Tarbiat Modares University, Tehran, Iran) *Synfacts* 2018; 14, 131.

1<sup>st</sup> review on the N-N bond formation: Q. Guo; Z. Lu *Synthesis* 2017, 49, 3835. (only 66 references cited)

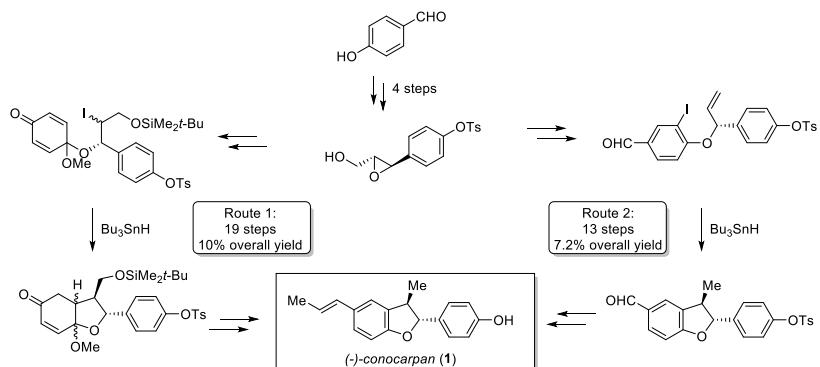


## Syntheses of Natural Products via DKR

### 8, 5-Neolignans with *trans*-Dihydrobenzofuran



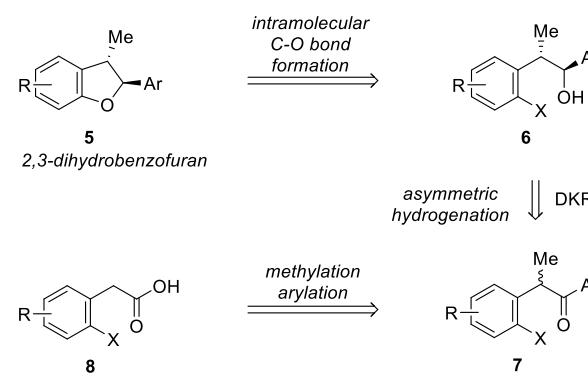
## D. Clive's Syntheses of (-)-Conocarpan



This synthetic work established the absolute configuration of (+)-conocarpan.

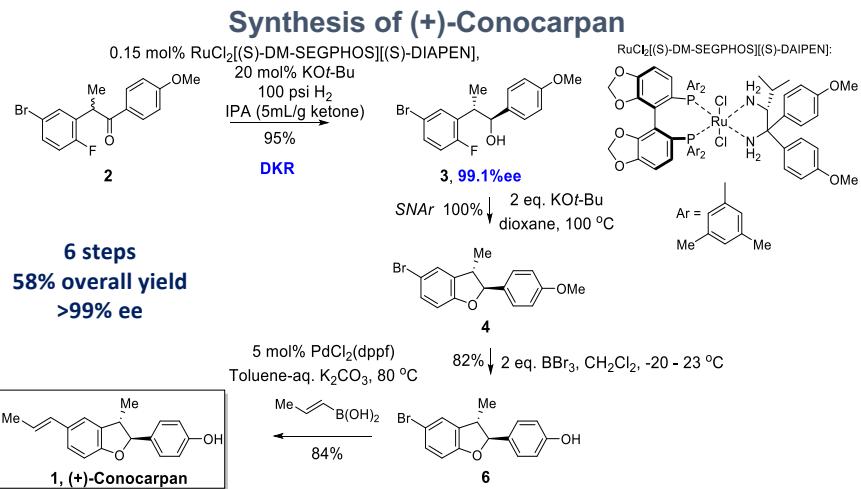


## Synthetic Strategy for *trans*-Dihydrobenzofuran



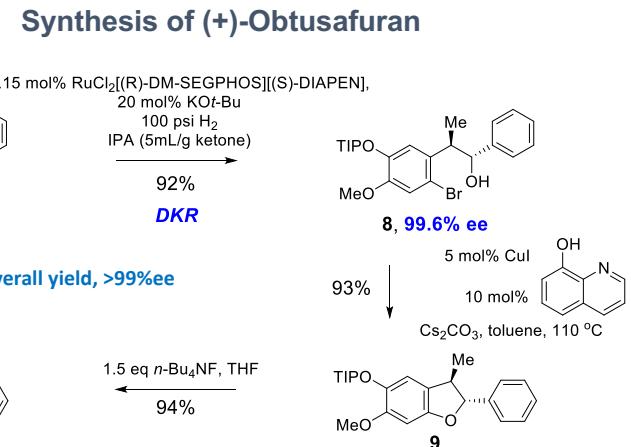
Weisel and Chen *Synlett* 2013, 24, 189-192





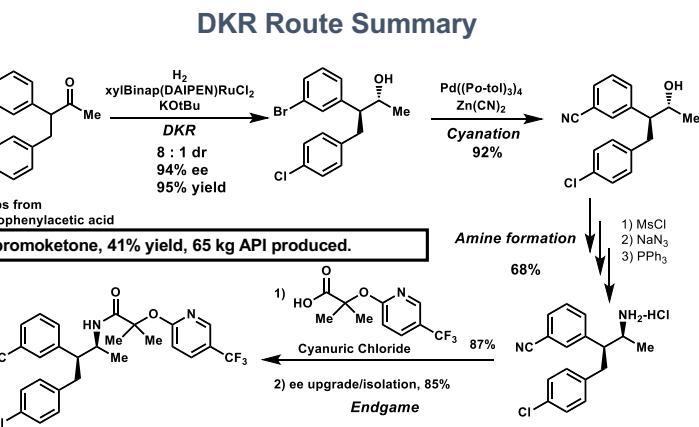
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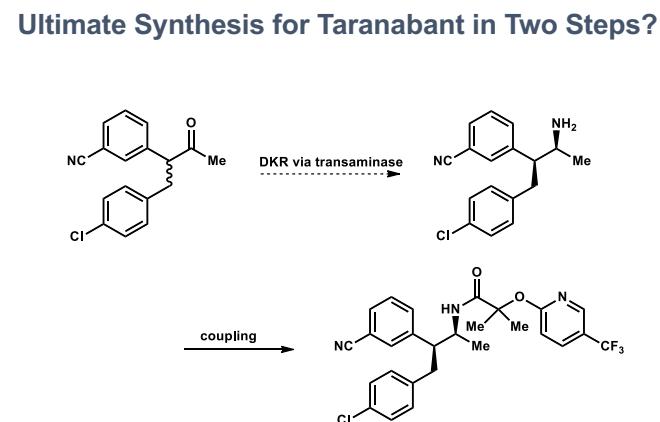
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