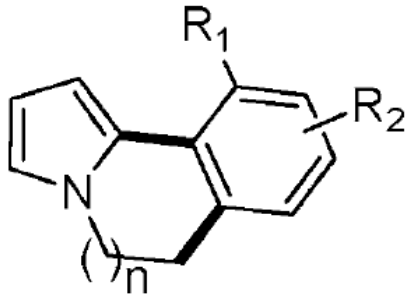
Preparation of Annulated Nitrogen Containing Heterocycles via a One-Pot Palladium-Catalyzed Alkylation/Direct Arylation Sequence



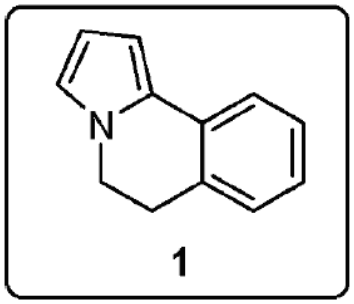
Christophe Blaszykowski, Evangelos Aktoudianakis, Cyril Bressy, Dino Alberico and Mark Lautens, *Org. Lett.* ASAP

University of Toronto

Dhanalakshmi Kasi

6 May 2006

Natural Products Containing Tricyclic Structure 1



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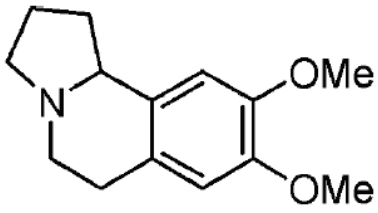
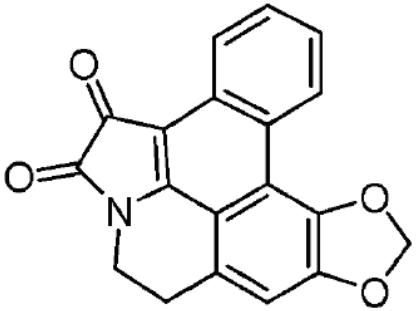
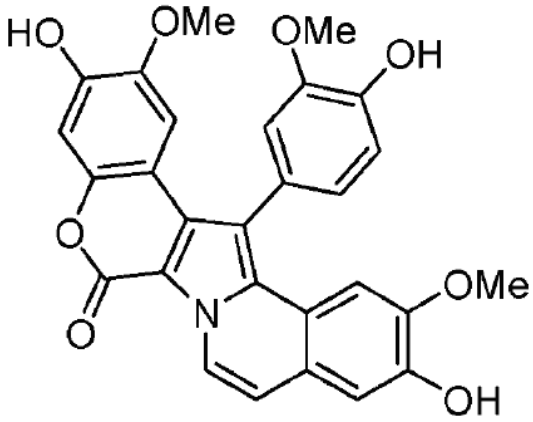


Crispine A : **2**



Lettowianthine : **3**



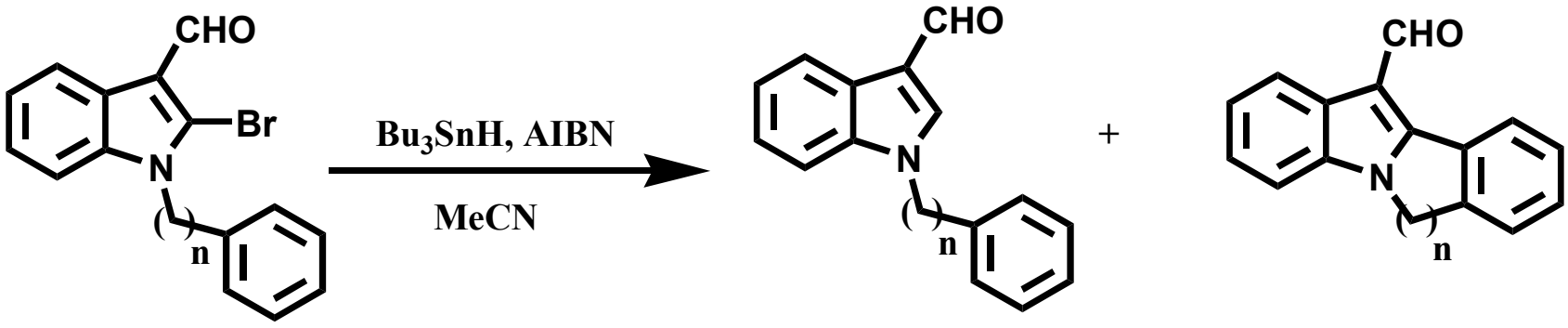
Lamellarin D : **4**

Crispine A: Isolated from *Carduus crispus* –cyctotoxic activity

Lettowianthin: Isolated from *Lettowianthus stellatus*

Lammelarin D: Marine Alkaloid, potent cytotoxic.

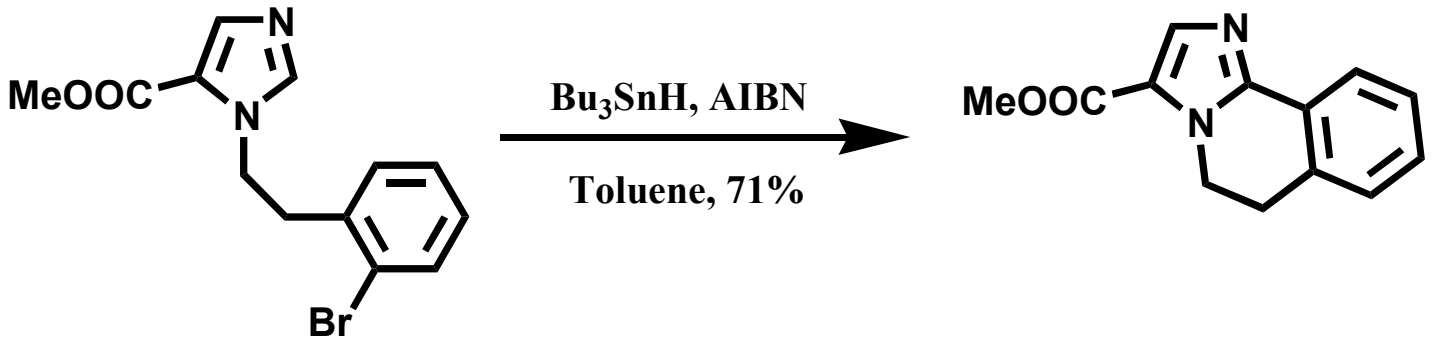
Annulation of Indole via Indole Radicals: Addition of the 2-Indolyl Radical to Aromatic Rings



n = 1	**55%**	**25%**
n = 2	**20%**	**65%**
n = 3	**32%**	**37%**

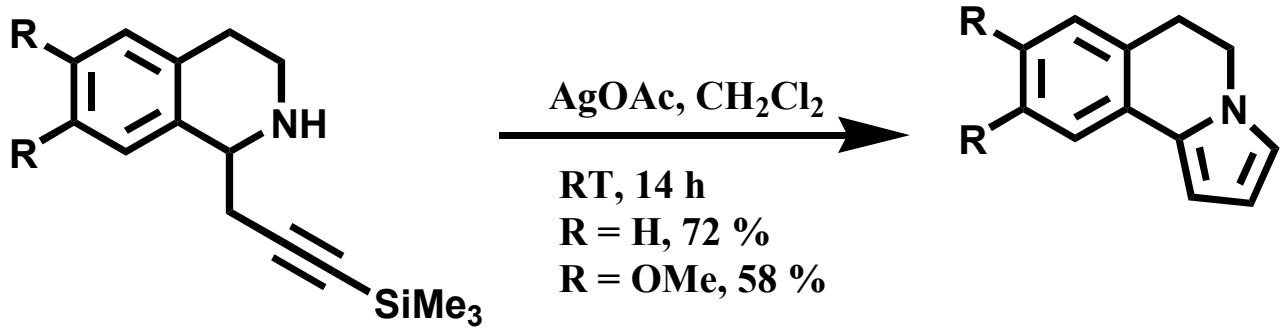
Fiumana, A.; Jones, K. *Tet. Lett.* **2000**, *41*, 4209-4211

Synthetic Applications of Aryl radical Building Blocks for Cyclization onto Azoles



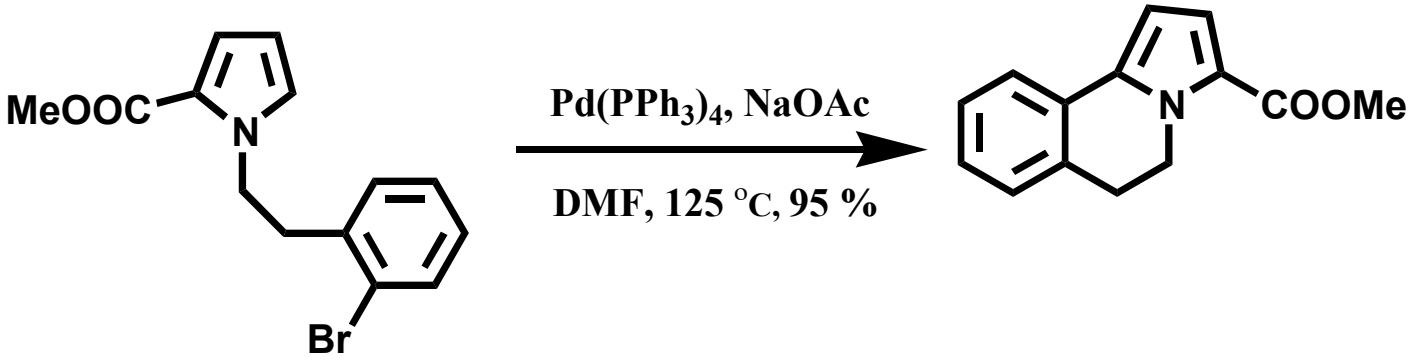
Allin, S.M.; Bowman, W.R.; Elsegood, M.R.J.; McKee, V.; Karim, R.; Rahman, S.S. *Tetrahedron* **2005**, *61*, 2689-2696.

Total Synthesis of the Antitumor Active Pyrrolo[2,1-a]isoquinoline Alkaloid (±)-Crispine A Silver(I) Promoted Oxidative Cyclization



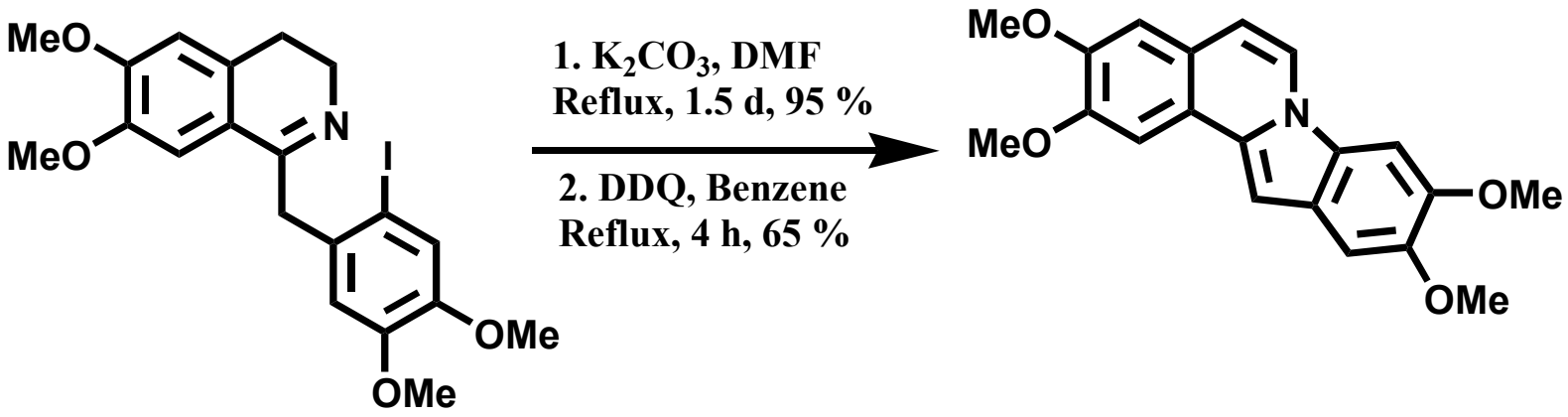
Knolker, H.; Agarwal, S. *Tet. Lett.* **2005**, *46*, 1173-1175.

5,6-Dihydropyrrolo[2,1-b]isoquinolines as Scaffolds for Synthesis of Lamellarin Analogues Intramolecular Heck Reaction



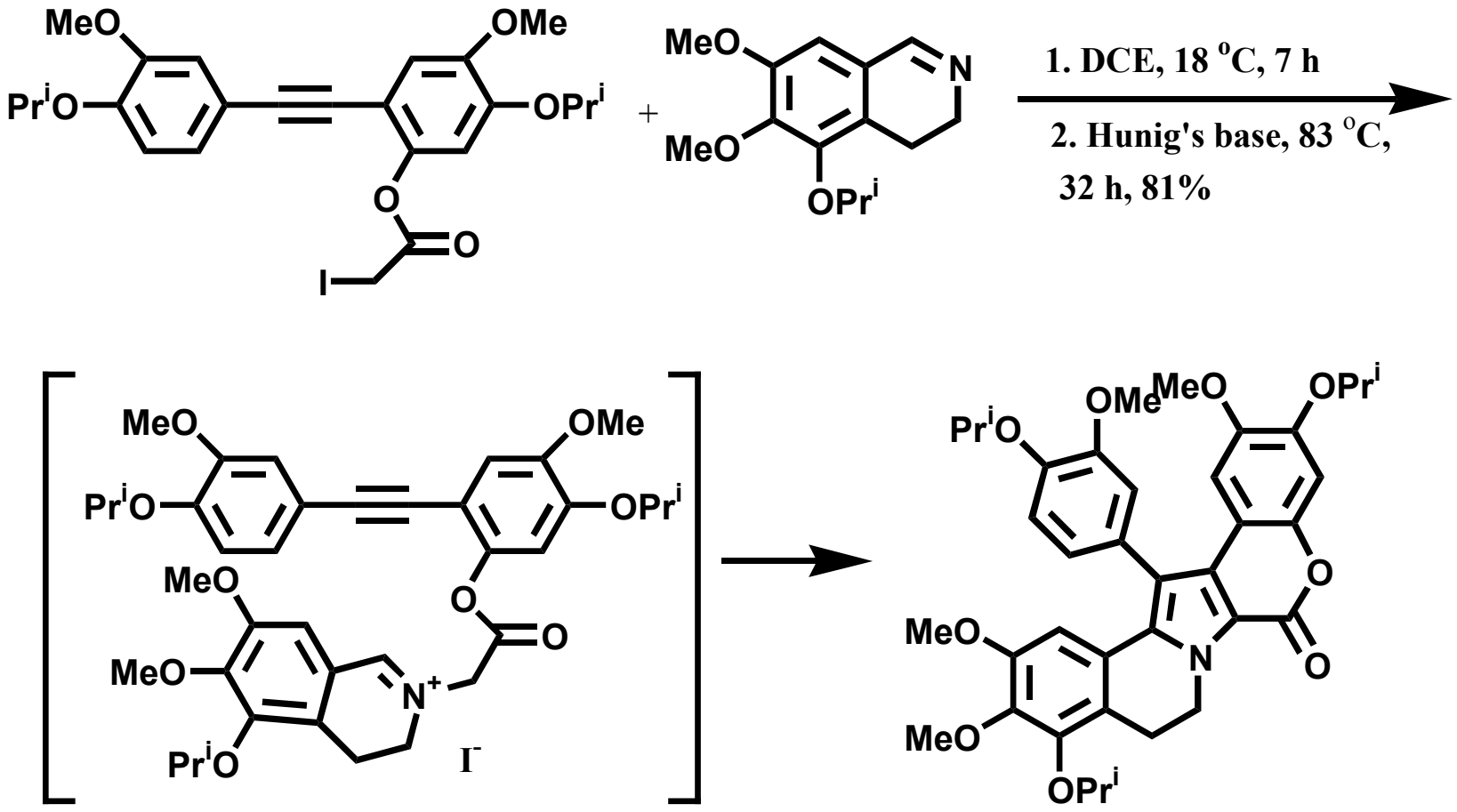
Olsen, C.A.; Parera, N.; Albericio, F.; Alvarez, M. *Tet. Lett.* **2005**, *46*, 2041-2044.

A Facile Route to Indolo[2,1-a]isoquinolines and Dibenzopyrrocoline Alkaloids



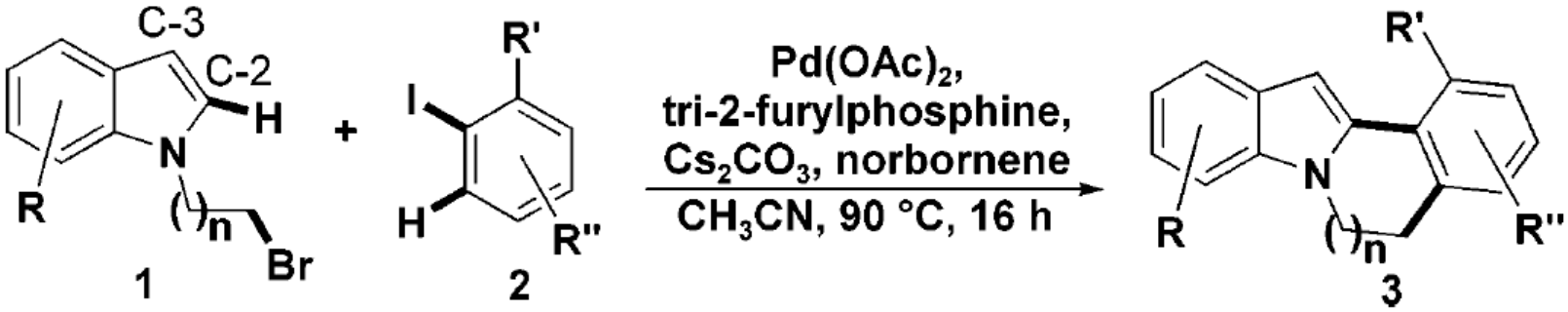
Orito, K.; Harada, R.; Uchiito, S.; Tokuda, M. *Org. Lett.* **2000**, *2*, 1799-1801.

Convergent Total Synthesis of Lamellarin K
Intramolecular [3+2] Cycloaddition



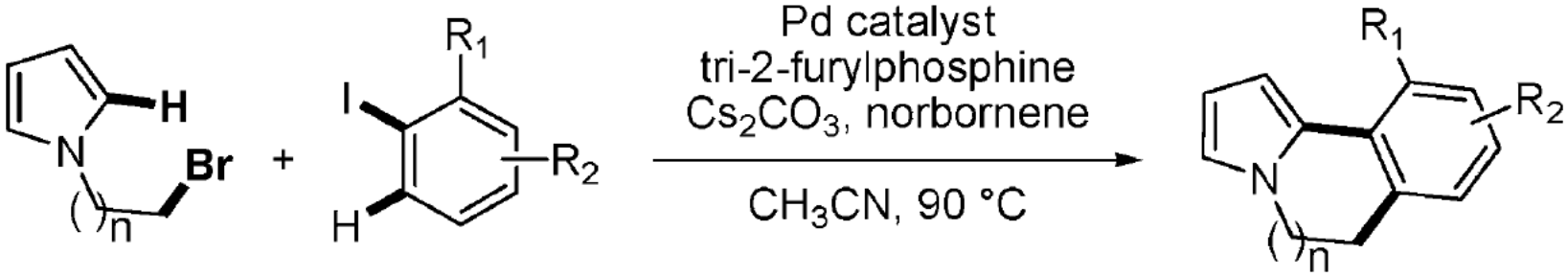
Banwell, M.; Flynn, B.; Hockless, D. *Chem. Commun.* **1997**, 2259-2260.

Synthesis of Annulated Indoles



Bressy, C.; Alberico, D.; Lautens, M. *J. Am. Chem. Soc.* **2005**, *127*, 13148-13149..

Synthesis of 5,6-Dihydro-pyrrolo[2,1-a]isoquinoline Derivatives



Reaction Conditions

Iodoarene: 1 equiv

Bromoalkylpyrrole: 2 equiv

Cs_2CO_3: 2 equiv

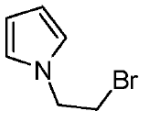
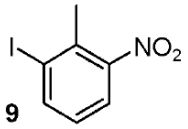
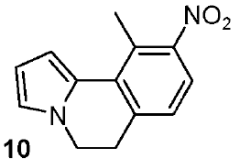
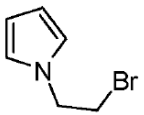
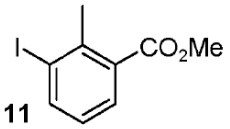
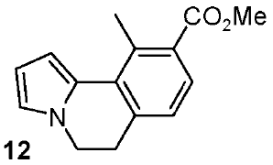
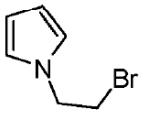
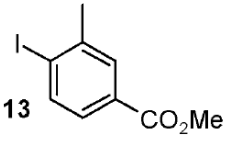
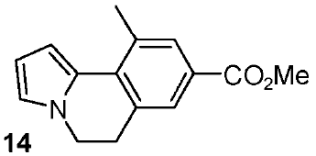
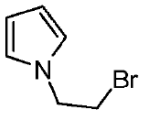
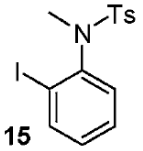
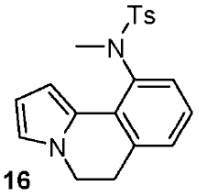
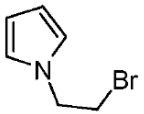
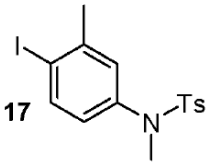
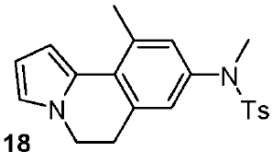
$PdCl_2$: 10 mol %

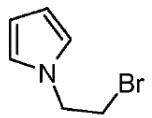
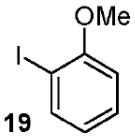
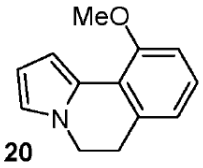
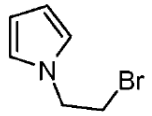
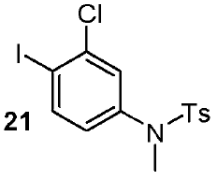
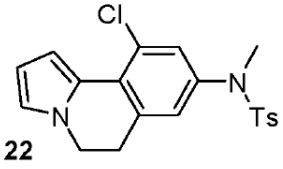
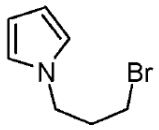
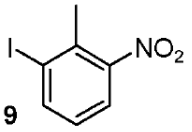
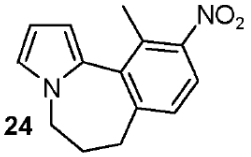
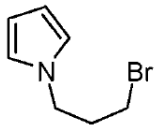
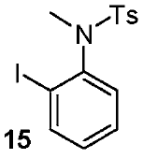
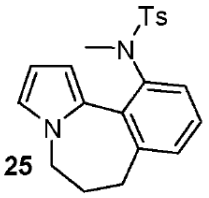
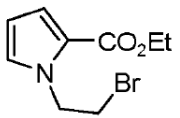
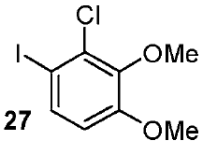
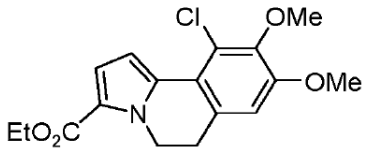
Tri-2-furylphosphine: 22 mol %

Norbornene: 2 equiv

CH_3CN: 0.1M

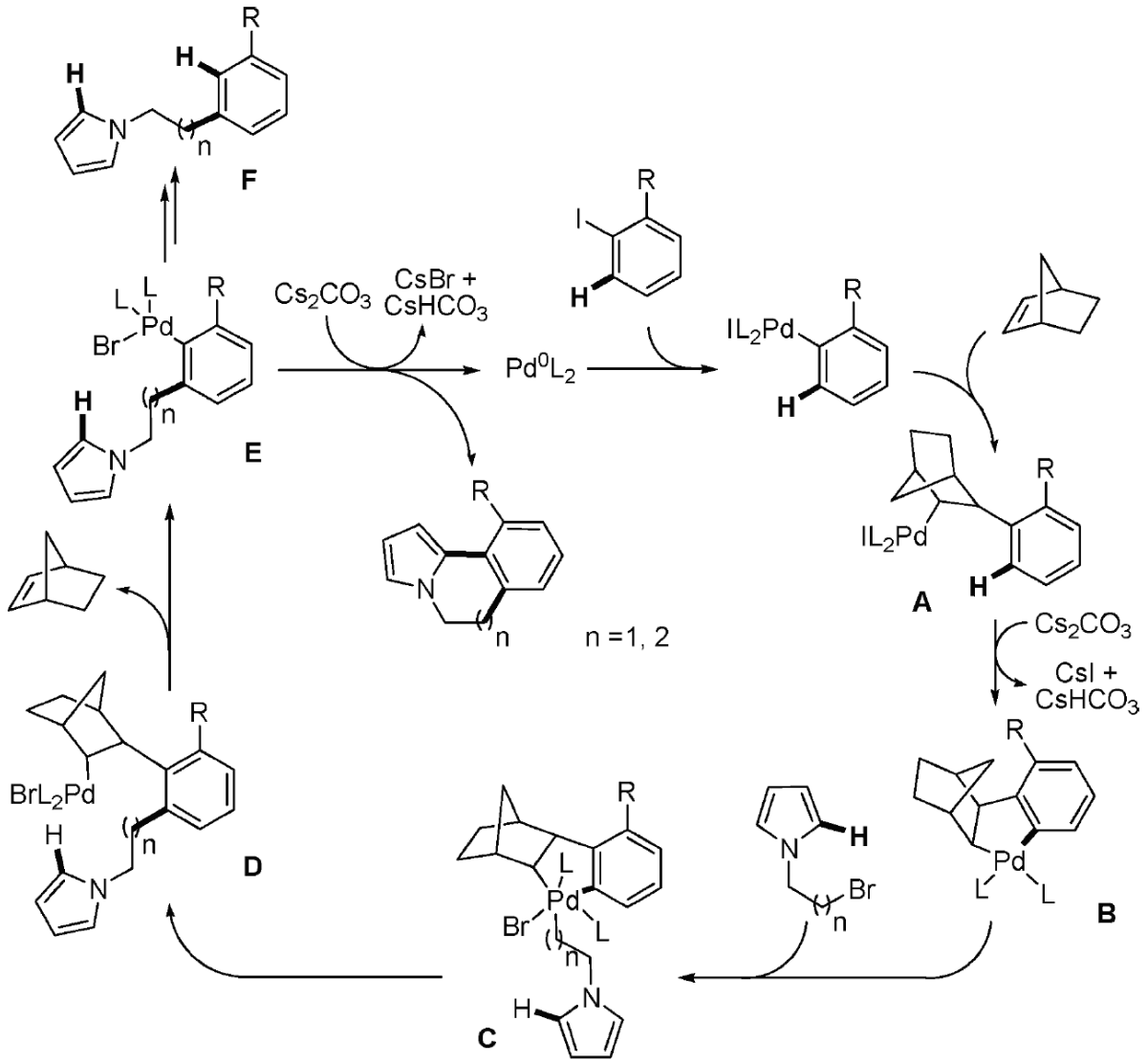
Synthesis of Annulated Pyrroles

entry	pyrrole	iodide	product	yield (%)[b]
1	**8** 	 **9**	 **10**	77
2	**8** 	 **11**	 **12**	67
3	**8** 	 **13**	 **14**	91
4	**8** 	 **15**	 **16**	73
5	**8** 	 **17**	 **18**	84

6	**8** 	 **19**	 **20**	59
7	**8** 	 **21**	 **22**	75
8	**23** 	 **9**	 **24**	74[c]
9	**23** 	 **15**	 **25**	69[c]
10	**26** 	 **27**	 **28**	59[d]

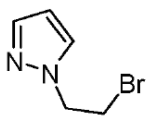
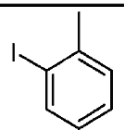
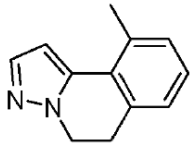
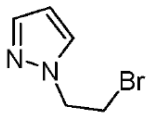
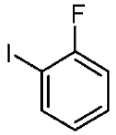
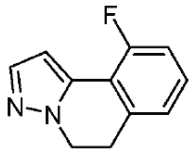
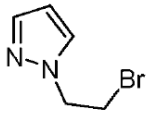
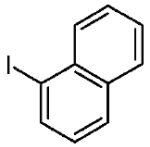
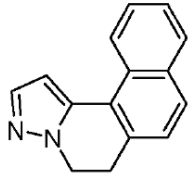
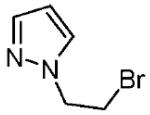
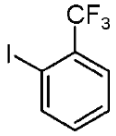
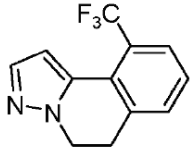
[a] Unless otherwise noted, all reactions were run under the following conditions: iodoarene (0.20 mmol, 1 equiv), $PdCl_2$ (10 mol %), tri-2-furylphosphine (22 mol %), Cs_2CO_3 (2 equiv), norbornene (2 equiv), and bromoalkyl pyrrole (2 equiv) in acetonitrile (2 mL) were heated in a sealed tube at 90 °C for 23 h (conditions A). [b] Isolated yield. [c] $Pd(OAc)_2$ was used as the catalyst. [d] Reaction run on a 2 mmol scale.

Proposed Mechanism for the Synthesis of Annulated Pyrroles



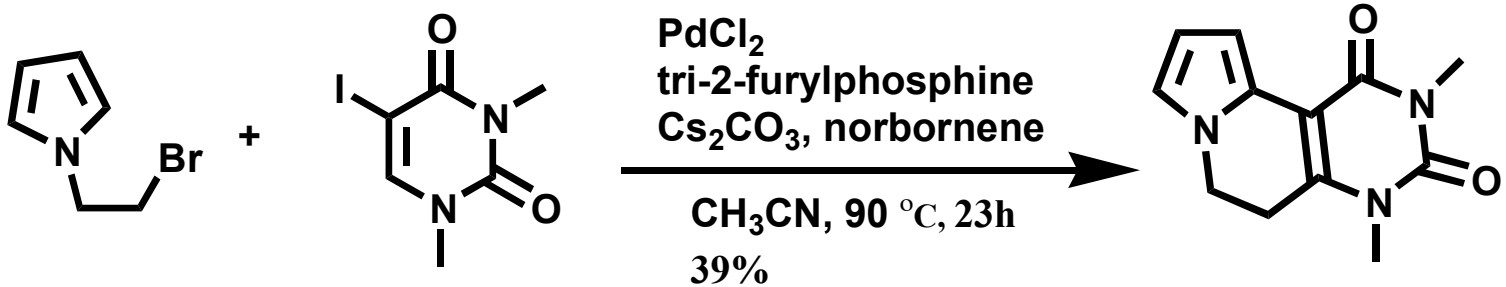
Catellani, M.; Frignani, F.; Rangoni, A. *Angew. Chem.Int. Ed. Engl.* **1997**, *36*, 119-122.

Synthesis of Annulated Pyrazole

entry	pyrazole	iodide	product	yield (%)[b]
1	 **29**	 **30**	**31** 	54
2	 **29**	 **32**	**33** 	49
3	 **29**	 **34**	**35** 	51
4	 **29**	 **36**	**37** 	42

[a] All reactions were run under the following conditions: at 90 °C, to a MeCN (2 mL) solution of iodoarene (0.60 mmol, 1.5 equiv), $Pd(OAc)_2$ (10 mol %), tri-2-furylphosphine (22 mol %), Cs_2CO_3 (2 equiv), and norbornene (2 equiv) was added dropwise (20 h addition) bromoalkyl pyrazole (1 equiv) in MeCN (2 mL) using a syringe pump. [b] Isolated yield.

Reaction with Iodouracil



Summary

- One pot synthesis of six and seven membered annulated pyrroles was achieved in very good yields.
- The reaction sequence involves the formation of alkyl-aryl and a heteroaryl-aryl bond in one step.
- Convenient stratergy for synthesis of other heteroaromatics like annulated pyrazoles and uracil.