Two Titanium-Catalyzed Reaction Sequences for Syntheses of Pyrroles from (*E/Z*)*-Chloroenynes or α-Haloalkynols*

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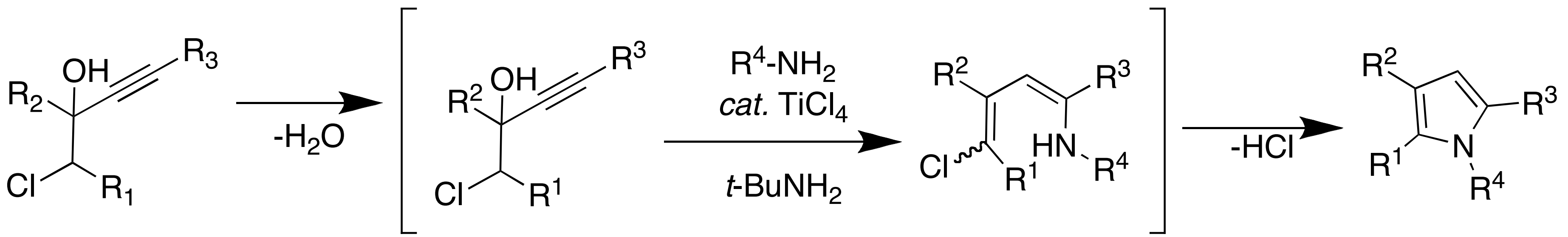
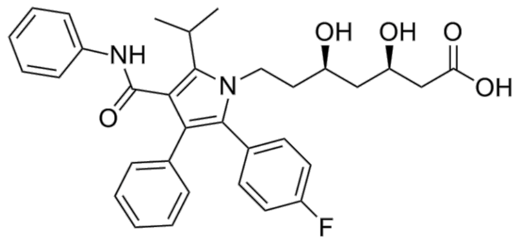


Jared Hammill
Wipf Group Current Lit
4/11/09

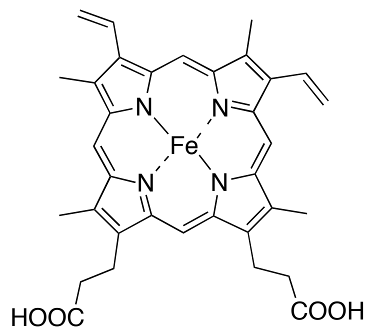
Biological Importance of Pyrroles

Pharmaceuticals:
-Lipitor is the largest selling drug in the world (2006 $12.9 billion)

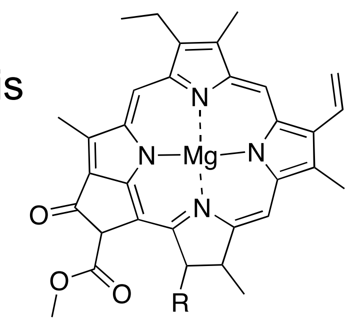


Biology:
-Porphyrins (Heme, Chlorophyl, and Vitamin B_{12})

Hemoproteins:
-transport diatomic gases
-chemical catalysis
-diatomic gas detection
-electron transfer



Chlorophyl:
-vital to photosynthesis



Material Science:
-Polypyrrole
-fast-charging and discharging batteries
-bio-sensors for metals (such as Li)

^ Loftus, Peter (2007-08-16). "Pfizer's Lipitor Patent Reissue Rejected". The Wall Street Journal Online. http://online.wsj.com/article/SB118730255664700229.html.
http://www.greencarcongress.com/2006/09/brown_universit.html#more

History of Pyrrole

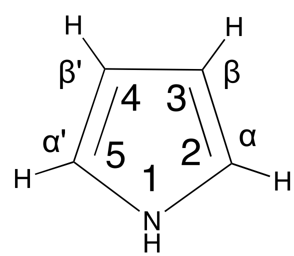
- 1834, Runge noted that a component of coal tar and bone oil imparted a red color to pine splinters which had been moistened with mineral acid, naming the compound pyrrole (from the greek meaning red oil)

- 1857, Anderson isolates the pure compound via distillation of bone oil

- 1870, Beyer determines its structural formula

- 1884, Paal and Knorr almost simultaneously report sythesis of pyrrole from 1,4-diketones

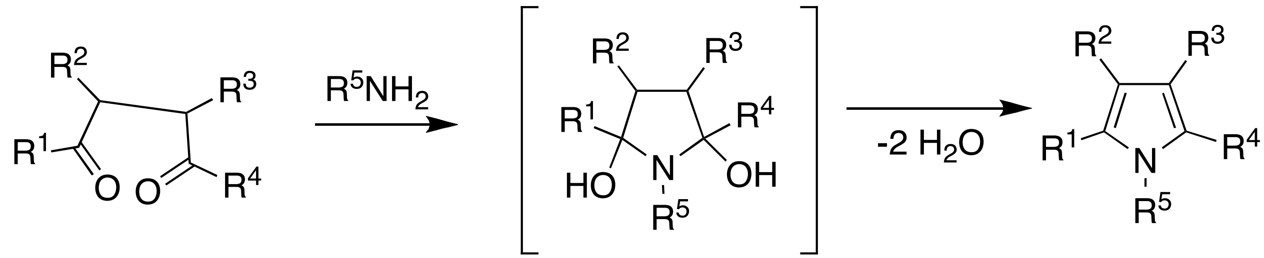
- Useful nomenclature



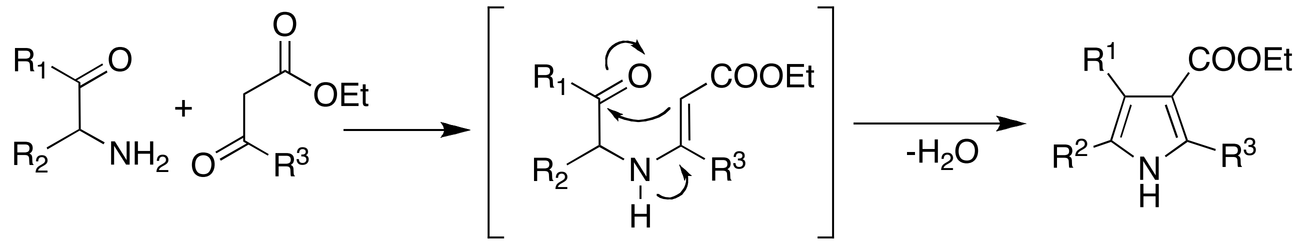
Bean, Alan, R. and Gerritt Jones. The Chemistry of Pyrroles. Academic press, 1977

Classical Syntheses

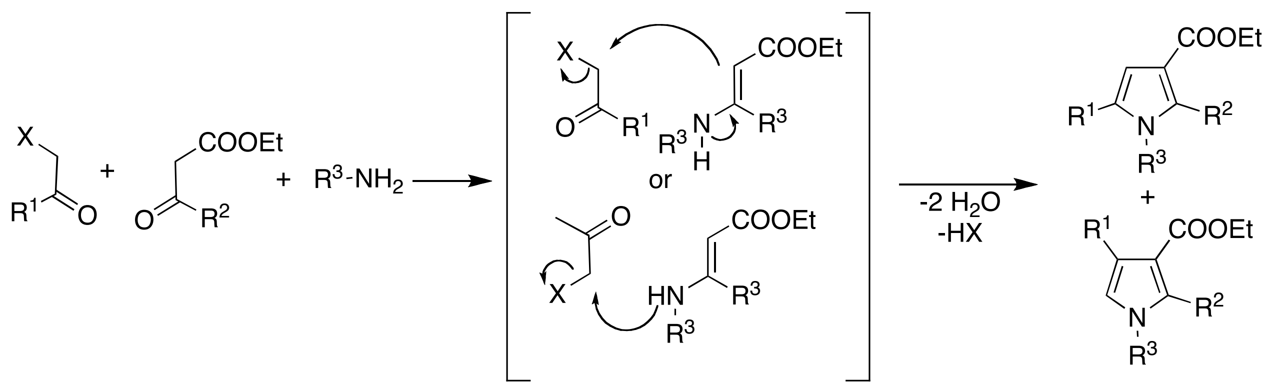
- Paal-Knorr Pyrrole Synthesis (1884)



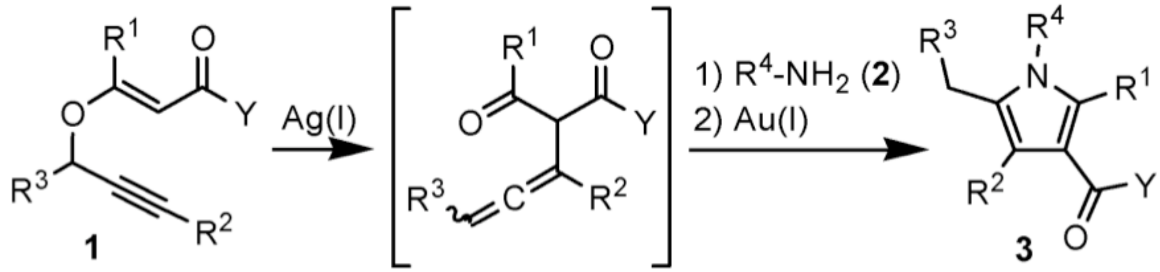
- Knorr Synthesis (1886)



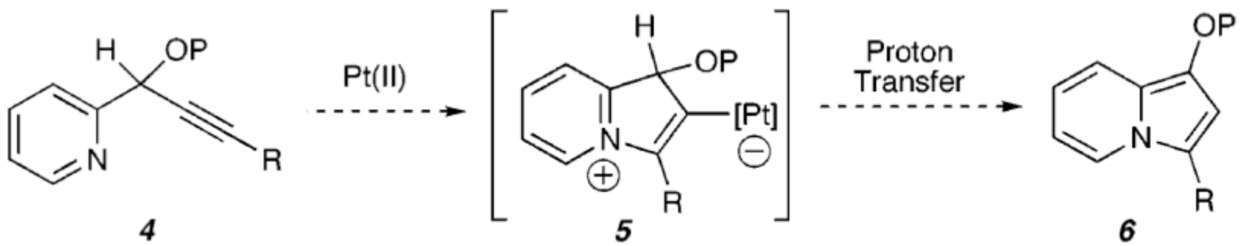
- Hantzsch Pyrrole Synthesis (1890)



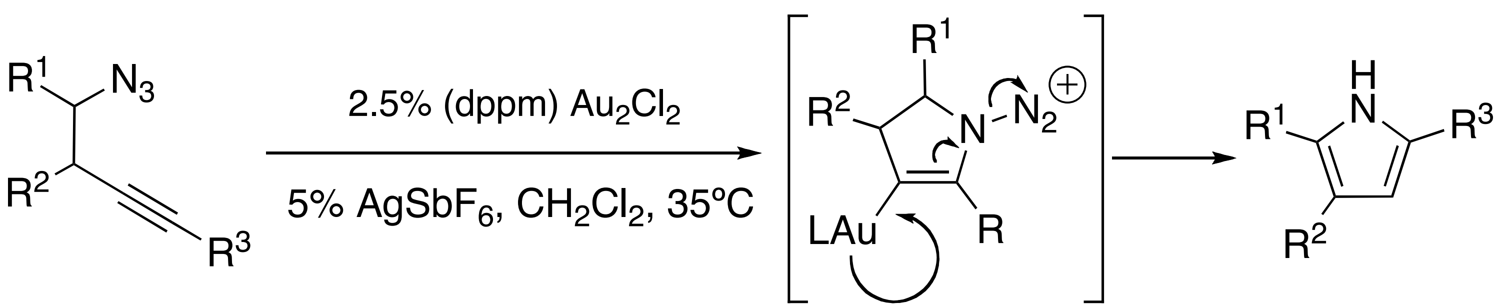
T.M. Catalyzed C-N Bond Formation



Kirsch, *Org. Lett.*, **2006**, 8, 2151-2153

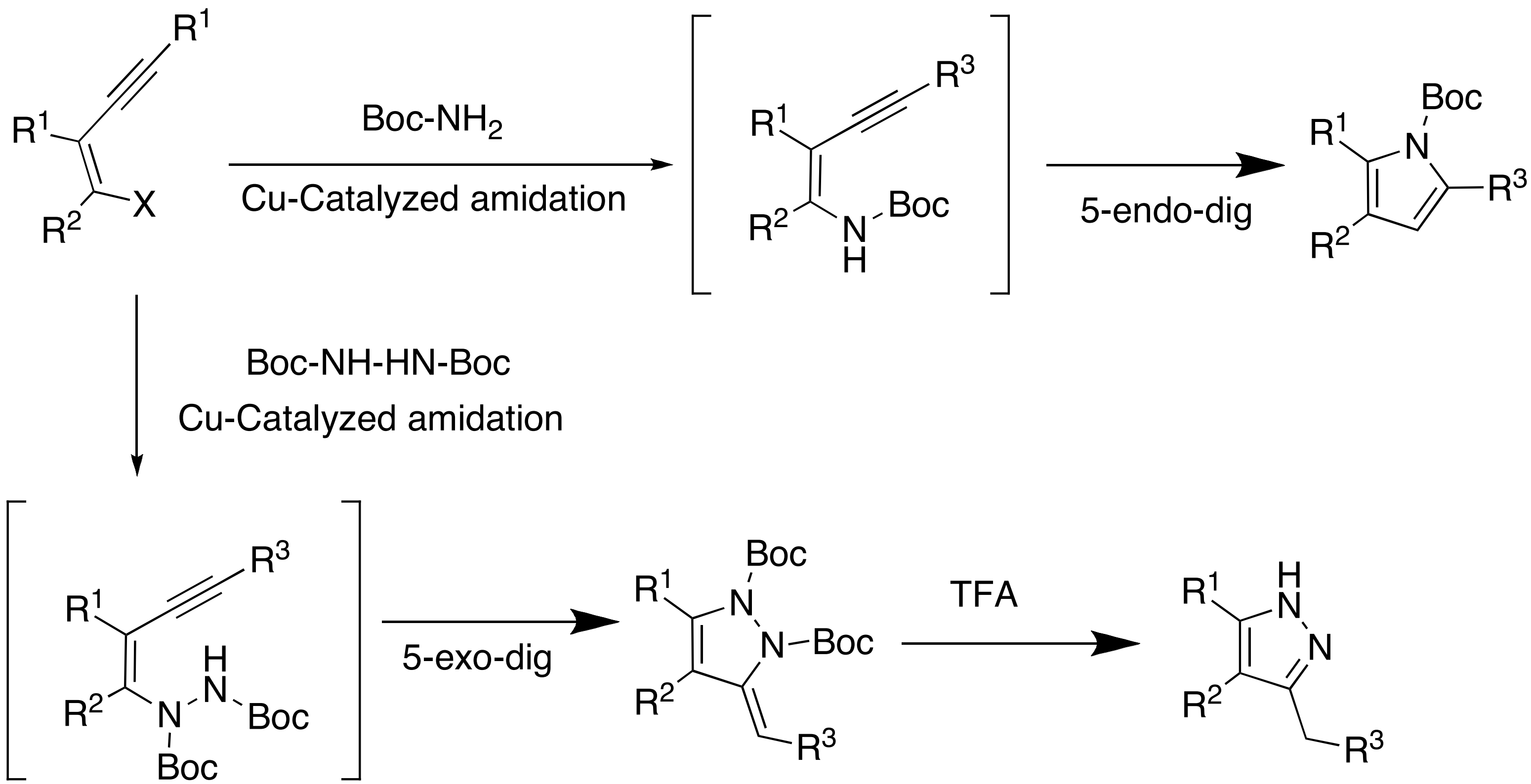


Sarpong, *Org. Lett.*, **2007**, 9, 1169-1171



Toste, *JACS.*, **2005**, 127, 11260-11261

Previous Work

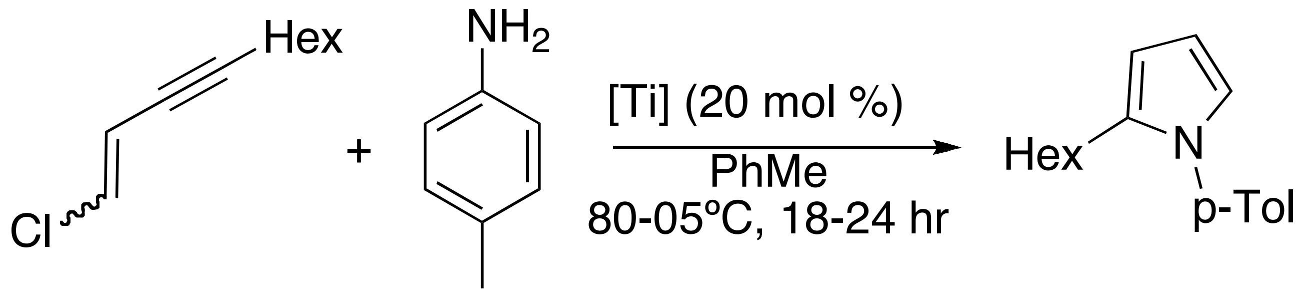


-Pittfalls:

1) requires diastereomerically pure (Z)-iodo or (Z)-bromo enynes
2) requires less basic N-nucleophile Boc-NH_2 or Boc-NH-NH-Boc

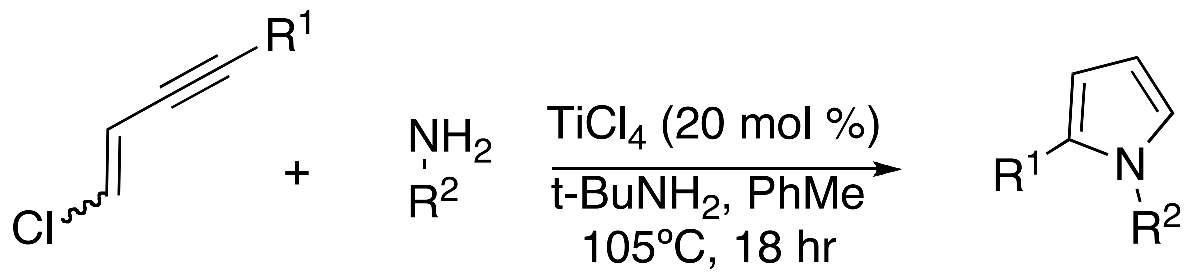
Buchwald, ACIE, **2006**, 45, 7079-7082

Optimization

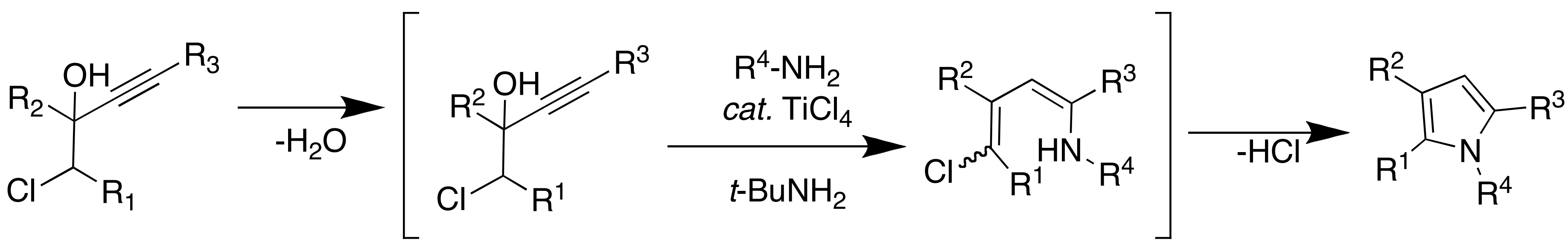


Diastereomer	[Ti]	T (°C)	Yield (%)
Z	$TiCl_4$/t-$BuNH_2$	105	80
E	$TiCl_4$/t-$BuNH_2$	105	83
E/Z	$TiCl_4$/t-$BuNH_2$	105	86
E/Z	$TiCl_4$	105	22
E/Z	$Ti(NMe_2)_4$	105	82
E/Z		105	
E/Z	$TiCl_4$/t-$BuNH_2$	80	84
E/Z	$TiCl_4$/t-$BuNH_2$	25	

New Reactions

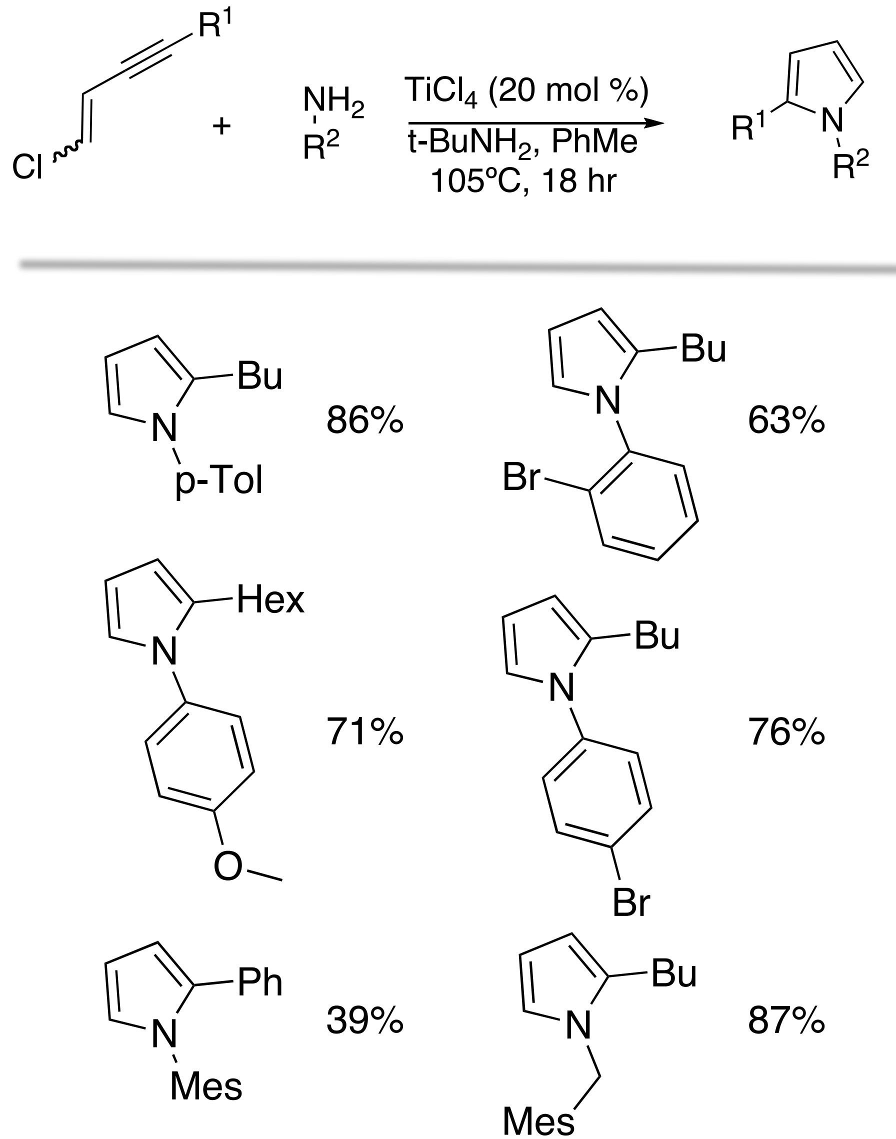


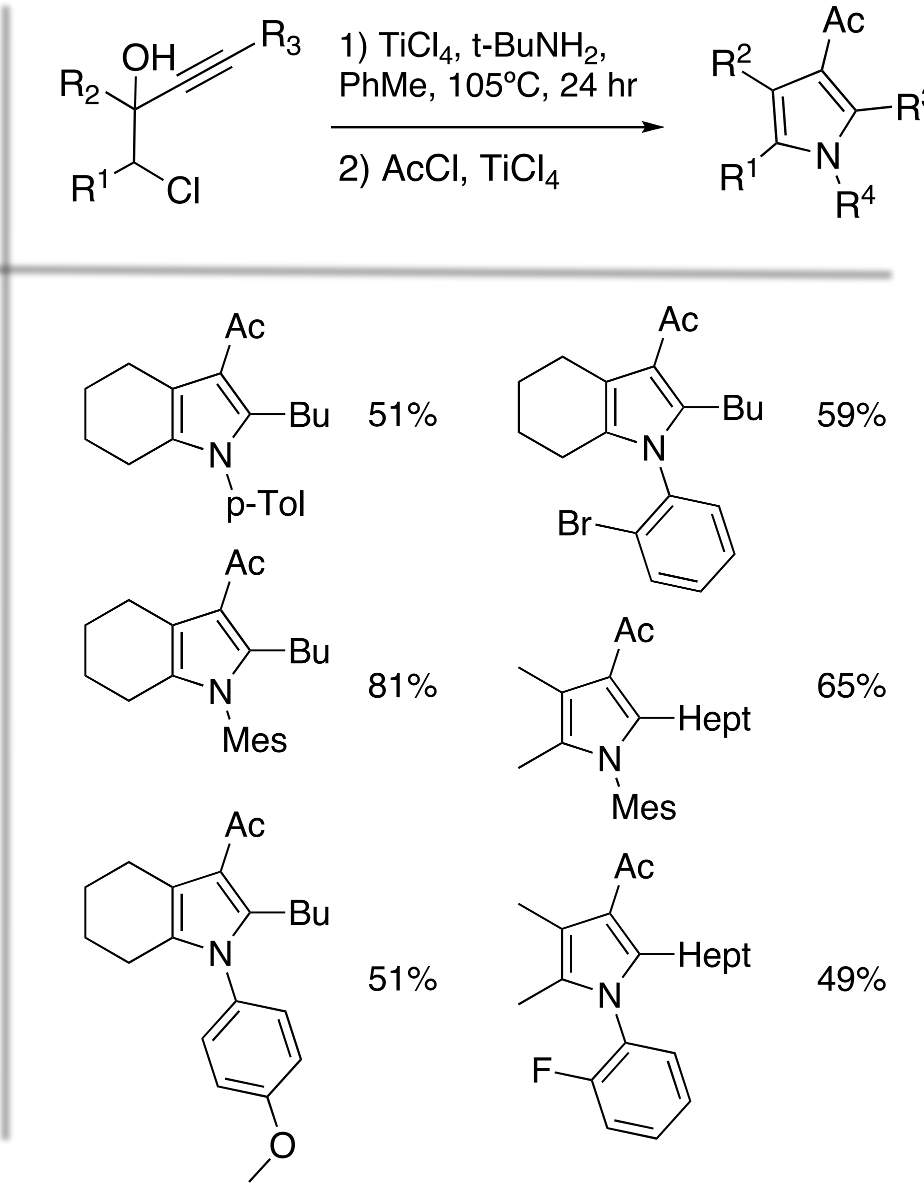
Removes need for diastereomerically pure starting material, expands scope of Nitrogen substitution to include more basic N-nucleophiles allowing for the use of chlorine



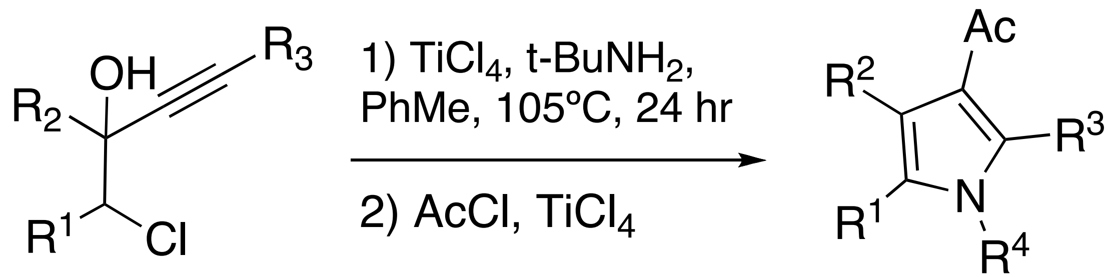
Allows for readily accessible starting material and a one-pot procedure, utilizing $TiCl_4$ as both a dehydrating agent as well as a catalyst in the hydroamination.

Scope


TiCl4 (20 mol %)
t-BuNH2, PhMe
105ºC, 18 hr
86%
63%
71%
76%
39%
87%


1) TiCl4, t-BuNH2,
PhMe, 105ºC, 24 hr
2) AcCl, TiCl4
51%
59%
81%
65%
51%
49%

Conclusions



- Efficient one-pot pyrrole synthesis through a reaction sequence of dehydration, intermolecular hydroamination, [1,5]H sigmatropic shift, and an intramolecular nucleophilic substitution.

- Providing access to di-, tri-, tetra-, and pentasubstituted pyrroles in a highly modular, yet regioselective, fashion

- Improved scope over previous methodology to included more basic *N*-nucleophiles, allowing for the use of chlorides

- Utilizes readily accessible starting materials and an inexpensive catalyst