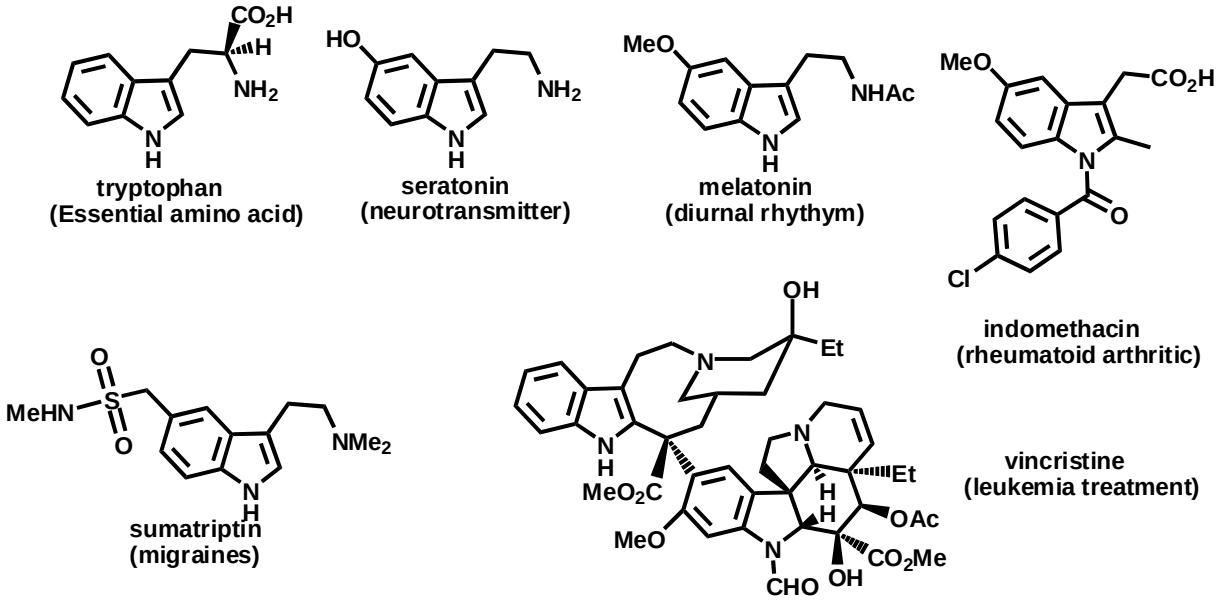
Indoles

Indoles are very commonly encountered in nature and many, many individual examples which have biological implcations. Below is a very small selection of examples.

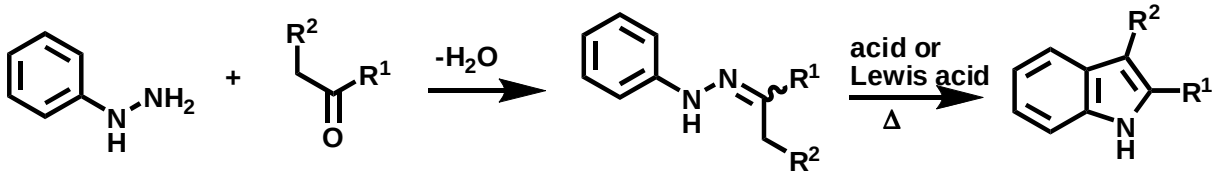


Although these compounds are simply benzo- fused pyrroles, they have their own set of ring synthesis reactions that are disctinct from pyrrole syntheses.

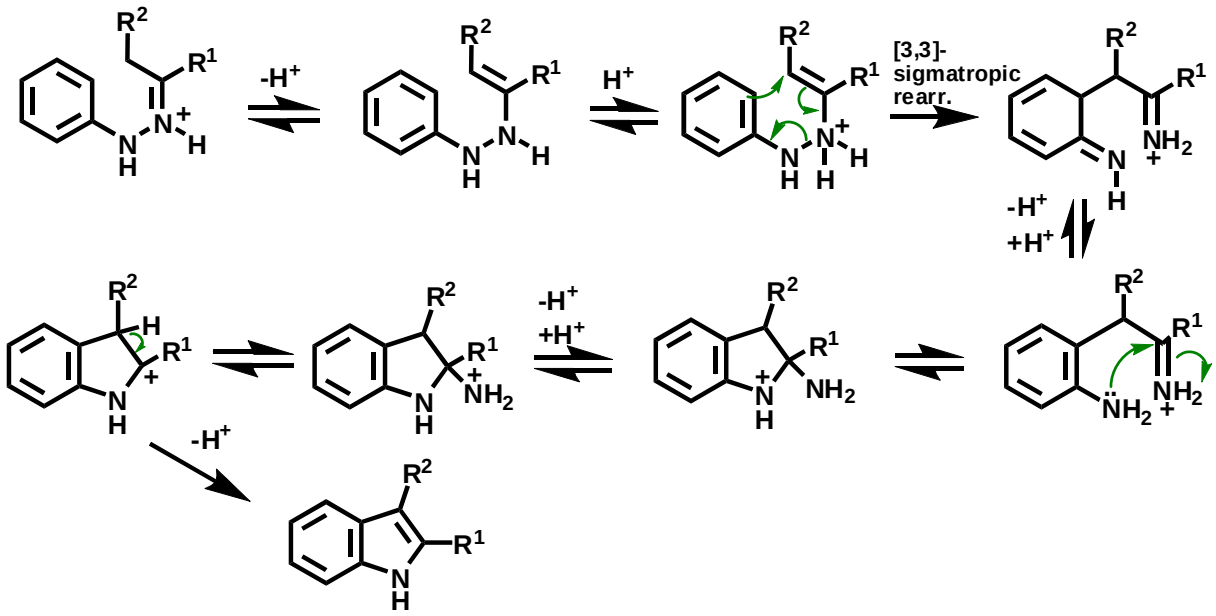
A. Fischer Indole Synthesis

Reviews: Gribble, G. W. *J. Chem. Soc., Perkin trans 1* **2000**, 1045; Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875.

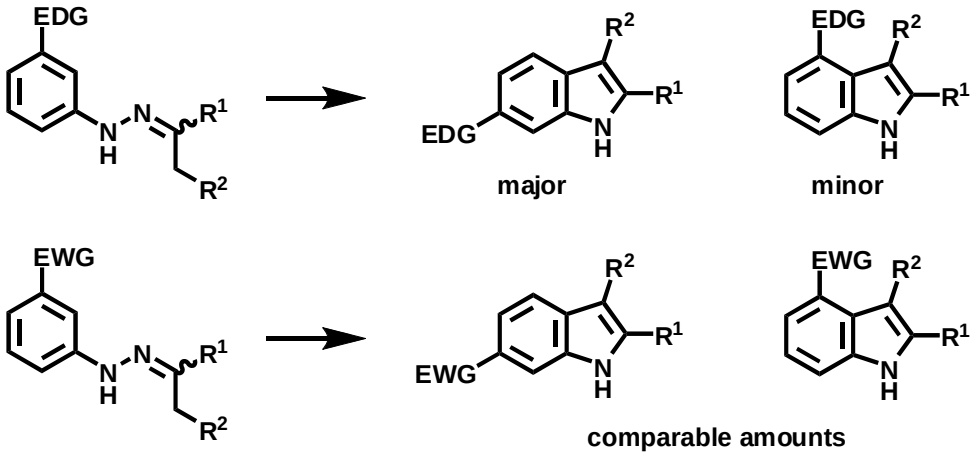
The Fischer Indole Synthesis is the reaction of a hydrazine derivative of a ketone or aldehyde formed from an aryl hydrazine. It is a multistep process involving a sigmatropic rearrangement, much like the Cope or Claisen rearrangement. It can occur purely thermally, but is normally done at much lower temperature in the presence of a protic acid or Lewis acid. Polyphosphoric acid, 100 ^{o}C are often used conditions.



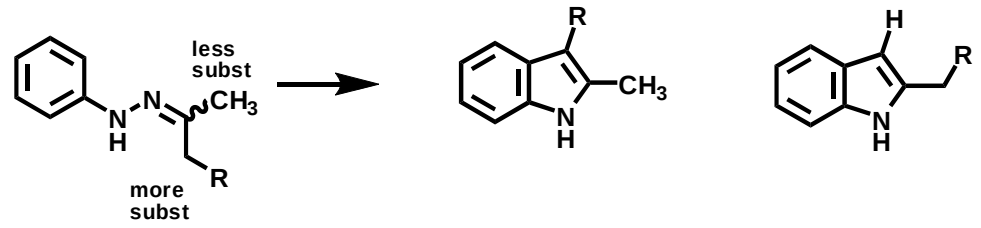
Here is the mechanism:



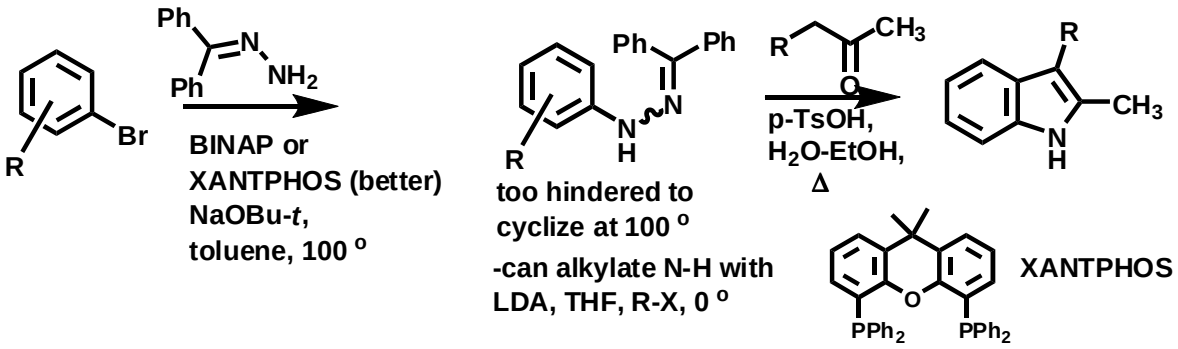
Since the alkene partner is electron poor, the arene partner in the [3,3]- sigmatropic rearrangement is normally the more electron rich partner. This means that electron donating groups on the arene normally speed up the reaction, and that electron withdrawing groups slow it down. Nevertheless, with EWG's *or* EDG's, the reaction *will go.* This does, however, bring up the question of regiochemistry of cyclization. For substitutents on the arene ring meta to the hydrazine/hydrazone, the general rule is…



Of course, not every ketone that is used in the Fischer is symmetric, or capable of having only one side enolize. In general, for unsymmetrical cases, the following is the major regiochemical route.

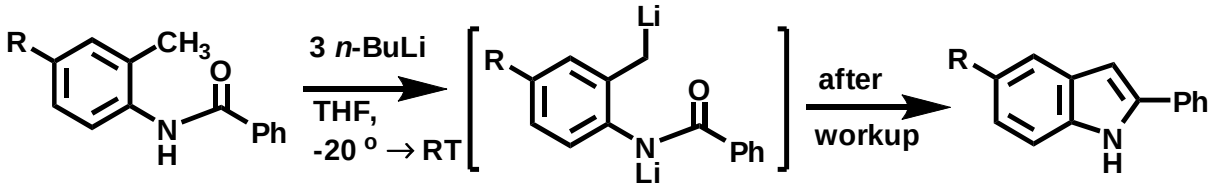


The reaction is apparently limited by the availability of aryl hydrazines, but a recent modification of Buchwald has made this much easier, by making the aryl hydrazone directly by C-N cross coupling. The hydrazone is a 'dummy' hydrazone, in that it's too hindered to do the [3,3]- sigmatropic rearrangement on its own. In the presence of another ketone, though, the hydrazones exchange, and the new hydrazone ca complete the Fischer indole synthesis. Notice that the regiochemical outcome is is very selectively the 'weak acid' outcome.



B. **Madelung Synthesis**

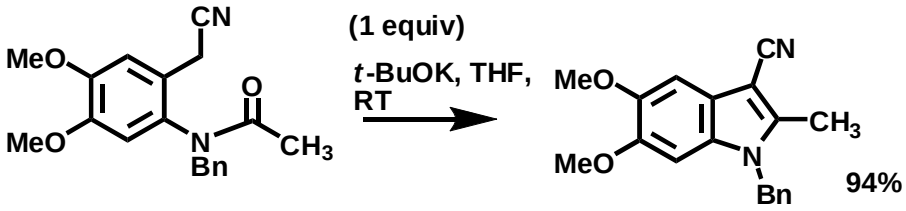
A second reasonable approach to an indole would involve an attack of a benzylic anion on an amide function. This deprotonation is workable in many cases because a N-aryl linked amide is a good directing group, so benzylic lithiation is encouraged. At low temperature, you could introduce an electrophile at this benzylic site, but if it's allowed to come to room T, the amide is attacked.



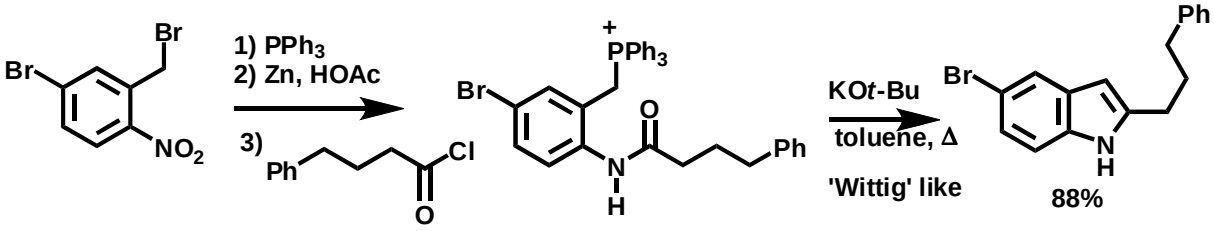
The availability of alkyllithiums for this was quite a development, as the 'traditional' conditions were $NaNH_2$ or KO^tBu, 300 °. The N- doesn't act as a leaving group because…

1) It's intramolecular, and 2) with most cases being 2° amides, it's deprotonated already
However, it *is limited* to amides with no other acidic sites (i.e, NH-C(O)-CH_3 won't work)

There are useful modifications of this process where the benzylic site has an acidifying group. This makes the conditions of reaction milder (i.e., weaker base required) and allows alkyl substitution of the amide. Furthemore, it now isn't *always* a 2 ^{o} amide.

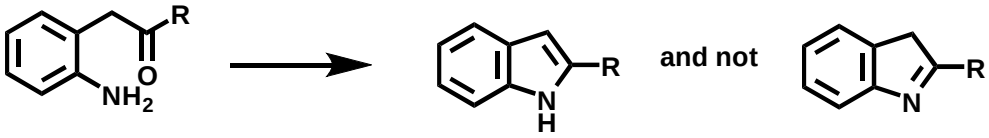


J. Am. Chem. Soc. **1968**, *90*, 7008.

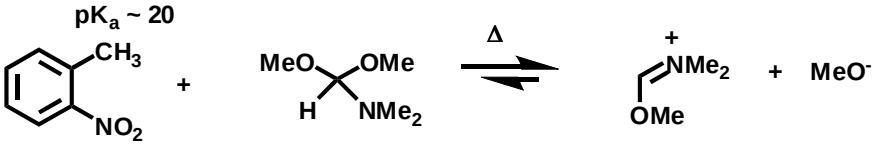


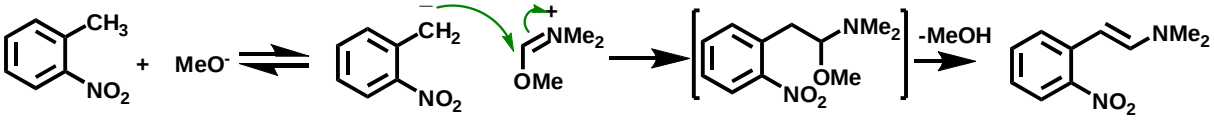
C. Leimgruber-Batcho Synthesis

One of the conceptually simplest ways to make an indole would be to set up an imine formation of a benzylic ketone/aldehyde and an aniline. The elimination step would go in a different direction than in traditional imine synthesis, due to aromatic stabilization driving force.

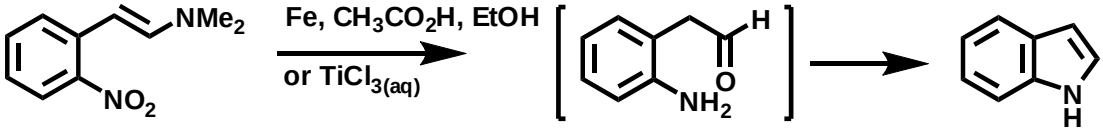


This ↑↑↑ is the problem, as it is an umpolung synthon (α-carbonyl cation) disconnection. The way it is normally done is to take advantage of the fact that a methyl group *ortho*- to an NO_2 is substantially acidified, and to use dimethylformamide dimethyl acetal (DMFDMA) as a partner, because it forms an iminium ion and methoxide ion upon heating.

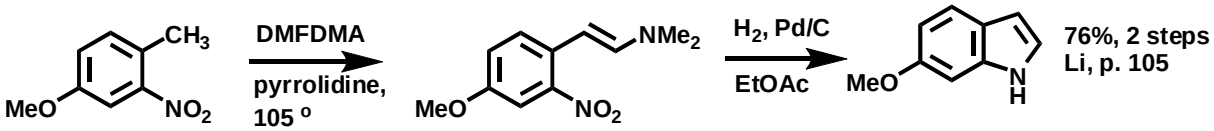




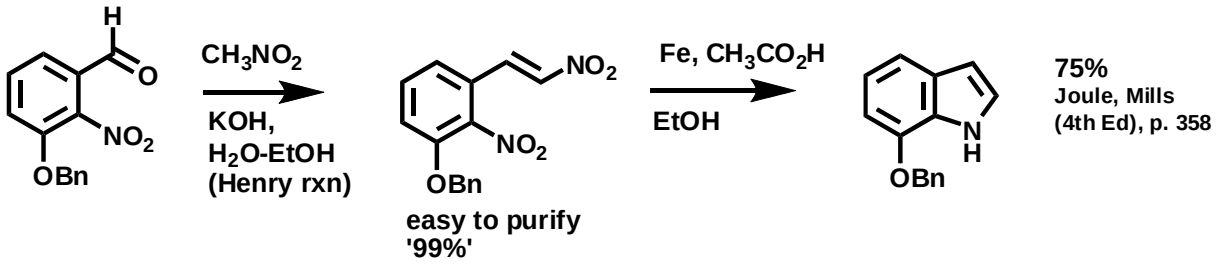
If the nitro group is reduced under even slightly acidic conditions, then the enamine hydrolyzes to the carbonyl and the aniline/benzyic carbon are formed – they then in turn rapidly form the indole.



In many of the literature cases, H_2, Pd/C is used as the reductant; there must be enough residual H^+ around to hydrolyze the enamine.

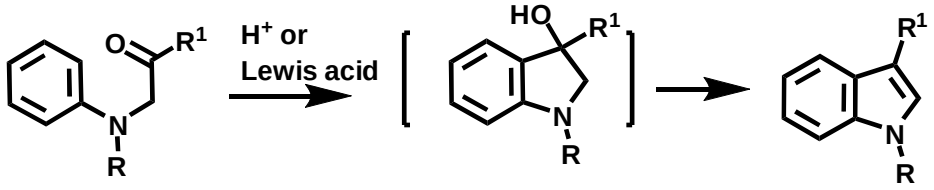


There are other modifications that fall under the same reaction name, without explicitly using the same reagents. The following is an example that follows closely from the Henry reaction chemistry discussed earlier.



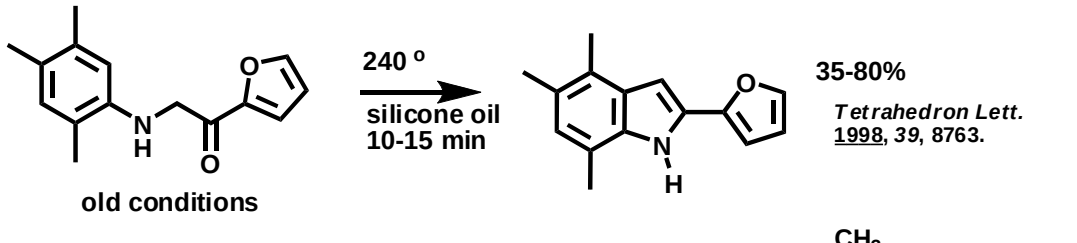
D. Bischler Synthesis (or Bischler-Möhlau Indole Synthesis)

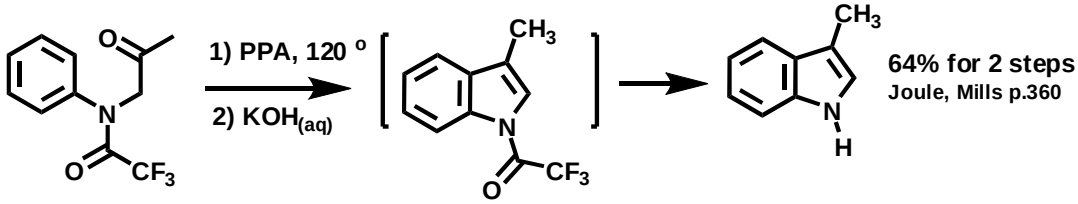
The other conceptually simple way for indole synthesis would be to simply do an electrophilic aromatic substitution ….of the following type.

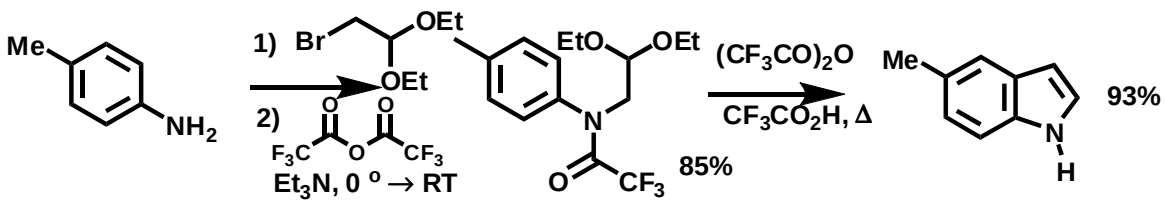


These do exist, and often are done just thermally – often under brutal conditions. The problem is that for an acid or Lewis acid, the 'N' is too basic, and protonates or coordinate first.

A good solution to this is to put an acyl group on N, to render it an amide; it's still an *ortho-/para-*director, but not as basic/Lewis basic to H^+/Lewis acid. This acyl group is commonly the N-C(O)CF_3 group, because it is fairly easily removed by hydrolysis.

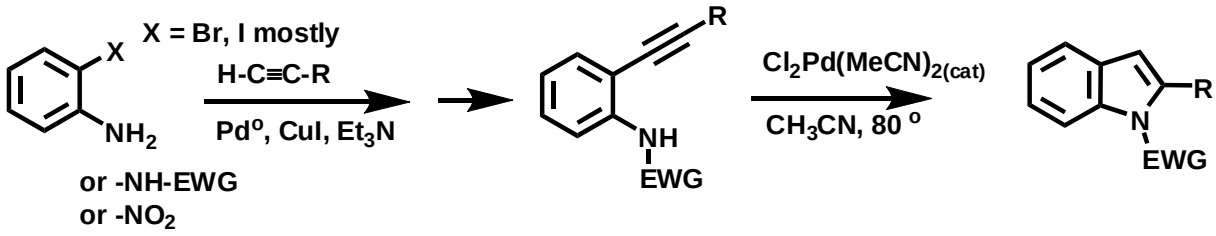






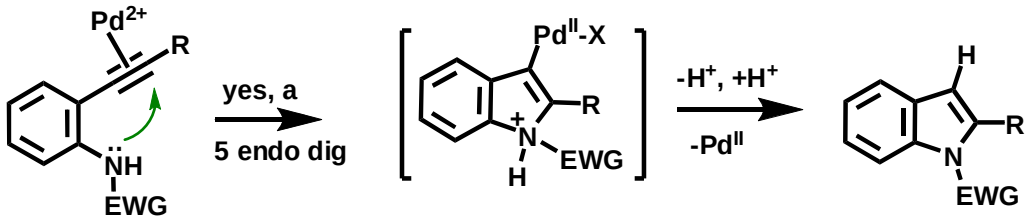
E. Organopalladium Based Routes

Part 1. What has become increasingly popular in indole formation is the use of *o*-alkynyl amide derivatives and a metal catalysts, most often Pd^{2+} (but it can be others). These are especially easily obtained 'starting materials' because they can come readily from Pd catalyzed Sonogashira reactions.

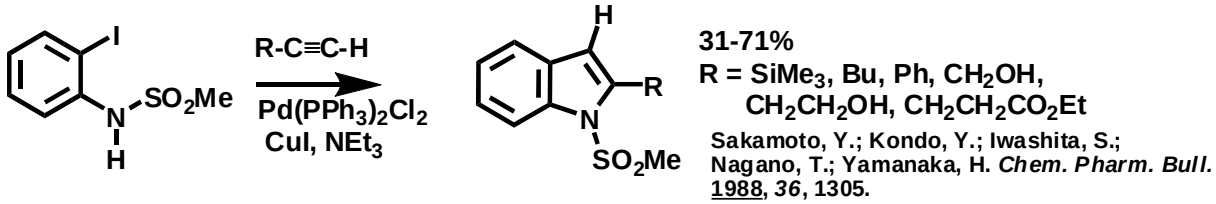


The reaction goes by way of an alkyne complex to the metal (i.e., Pd^{II}); this makes the alkyne electron poor, so that the amine/amide attacks it as a nucleophile. Other metal salts that prefer CΞC over carbonyl complexation (Cu^{I}, Cu^{II}, Ag^{I}, In^{III}) have also been used in this cyclization.

In most cases, the N atom has an electron withdrawing group on it (-SO_2R, -Boc, others) because without it the Ar-NH_2 is too good a ligand for Pd^{2+} and displaces the alkyne.



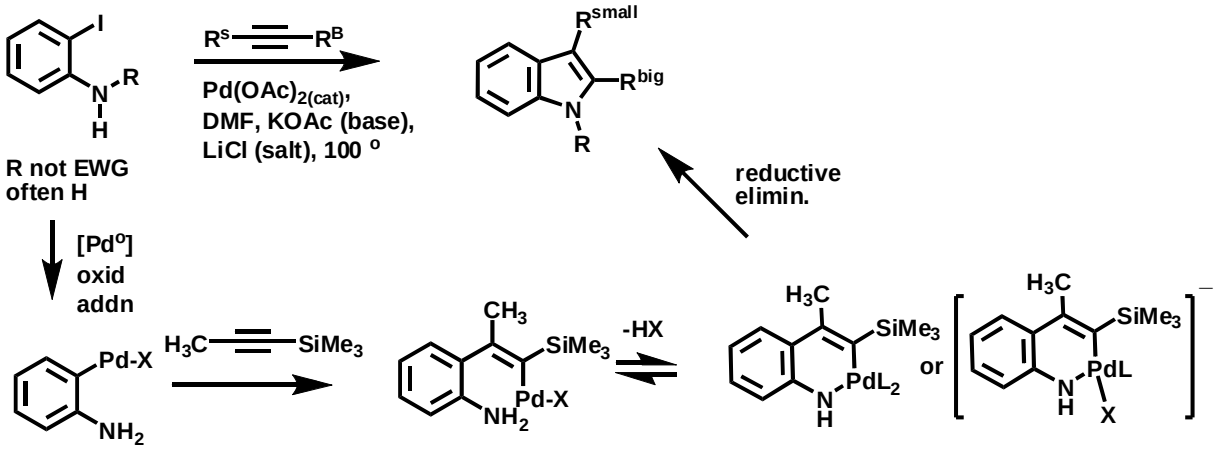
In fact, since the Pd^{II} / Pd^{o} interconversion is quite facile, there occasional are examples of the whole Sonogashira/cyclization being done in one synthetic operation.



Sakamoto, Y.; Kondo, Y.; Iwashita, S.; Nagano, T.; Yamanaka, H. *Chem. Pharm. Bull.* 1988, *36*, 1305.

Part 2. The Larock Indole Synthesis

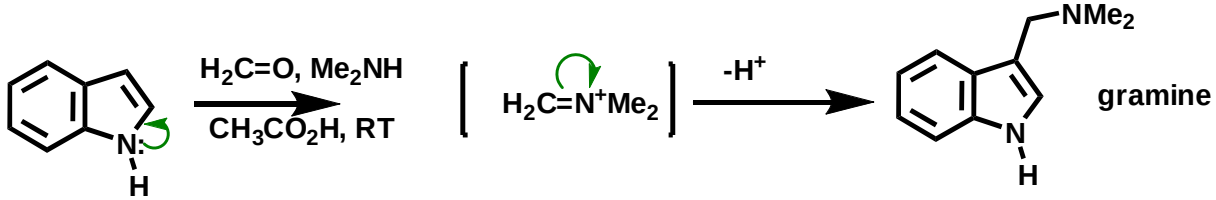
The above case uses only terminal alkynes as starting material, but there is a superficially similar reaction where the alkyne is internal and a Pd^{II} catalyst is employed. In these cases the N atom does not normally have an EWG. The mechanism is different now, similar to a Heck reaction, followed by a N-based cross coupling reaction.



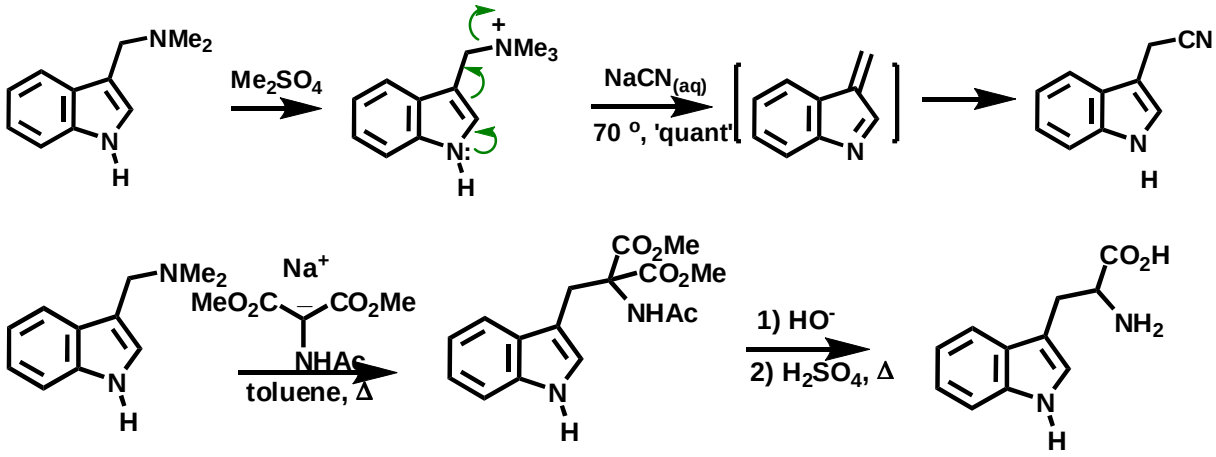
R^{Big} is very often $SiMe_3$, or a hydroxyl containing alkyl.

Reactions of Indoles – Selected Points

You may recall from earlier chemistry that indoles undergo electrophilic substitution at C-3. One of the most common versions this reaction is the Mannich reaction (formaldehyde, dimethylamine) in acetic acid; this gives the 'benzylic' dimethylamino compound, known as **gramine**.



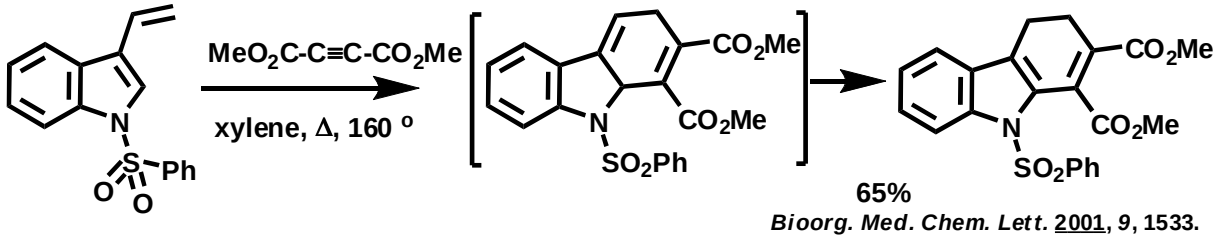
This is a particularly important derivative of indole in further chemistry, as most of the nucleophilic substitutions that take place at the 'benzylic' position use this intermediate (or a version that is quaternized). The benzylic bromides, which would normally be expected to be the source of this reactivity, are generally not stable compounds.



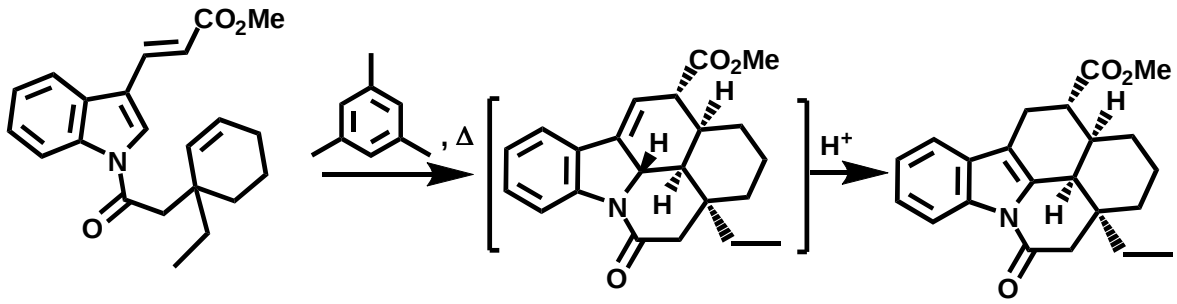
There are many other consequences of this part of the molecule being 'enamine like', which we do not have time to discuss here.

Diels-Alder Reactions

Despite the 'relatively aromatic' nature of the 5- membered ring of indole, it is fairly common to use the formal 2,3- C=C of indole, when it is substituted with an alkene at C-3. In part this is because indole is less aromatic that benzene, but in most cases (not in all) the substrates tend to have electron withdrawing groups on N-, reducing aromaticity further.



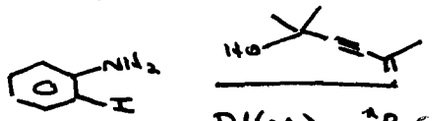
Bioorg. Med. Chem. Lett. 2001, *9*, 1533.

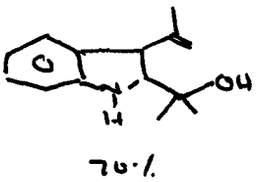


There are examples of the 2,3-C=C acting as dienophiles, as well. These are usually inverse electron demand Diels-Alder reactions (i.e., dienophile as electron rich, diene as electron poor), and are often bonded to the diene via a tether (meaning it's an *intra*molecular reaction).

Larock Indole Synthesis

- Examples





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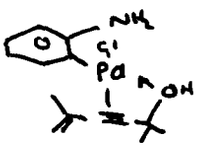

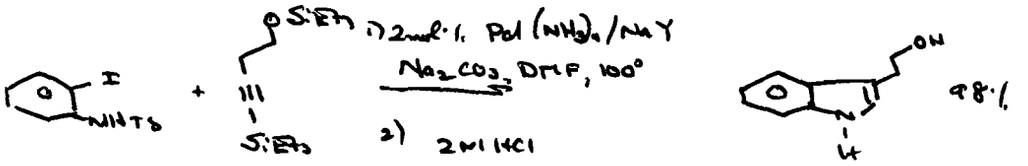

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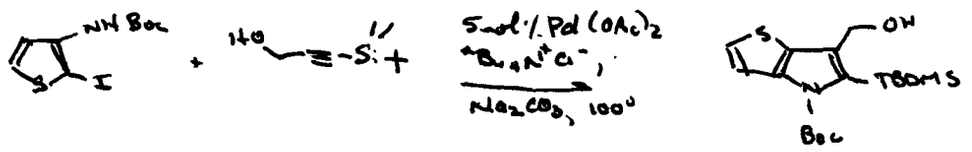

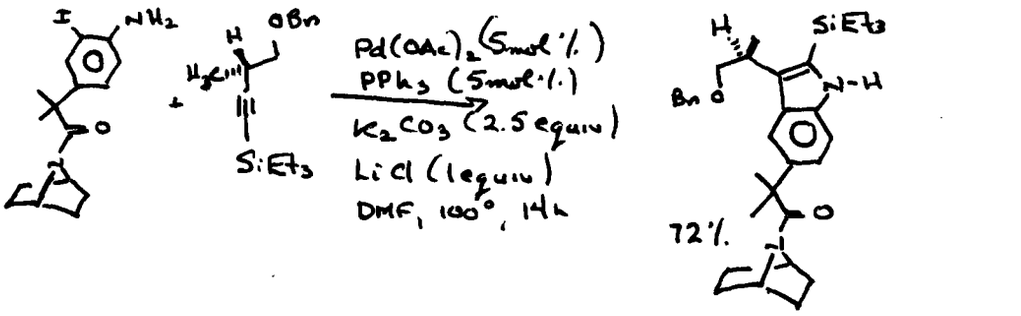

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