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Indoles Synthesized from Amines via Copper Catalysis

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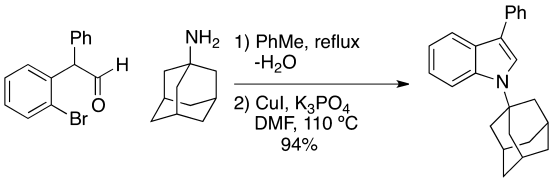
ABSTRACT



***N*-Substituted indoles are synthesized from primary amines through a tandem reaction sequence. Initial condensation of the amine with an α-(*o*-haloaryl)ketone or aldehyde is followed by intramolecular aryl amination catalyzed by CuI. A variety of anilines and alkyl amines, including those with significant steric demands, are converted to indoles in high yields and with varying indole substitution.**

Methods for indole synthesis are important in natural product synthesis[1] and medicinal chemistry.[2] Consequently, a myriad of methods for their synthesis have been reported.[3] A noticeably underexploited synthetic strategy is to build indoles from amines.[3b] Such an approach would allow for indoles with large and/or complex *N*-substituents, which are difficult to introduce to existing indoles, to be built from the appropriate amines.[4] An implementation of this approach could use readily available α-aryl ketones **2**[5] via a tandem[6] imine formation/*N*-arylation sequence (Scheme 1).[7] While a few examples of palladium-catalyzed indole formation similar to this approach have been disclosed,[8,9] few reports use copper-catalyzed arylation of imines to form indoles,[10,11] even though copper catalysis offers advantages over palladium.[12] The few examples of copper catalysis do not use the facile formation of imines from α-aryl ketones and aldehydes to set up C−N bond formation, but require more roundabout syntheses of enamines via condensations or conjugate additions that limit substrate scope.[13] Attempts at initial copper-catalyzed amino-arylation to form aniline **3**, which would be followed by dehydrative cyclization to indole **6**, produced only benzofurans **4**.[14]

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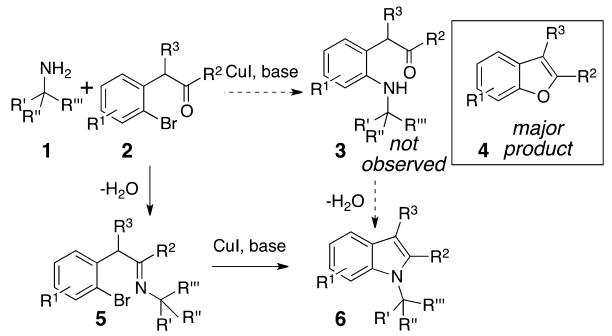
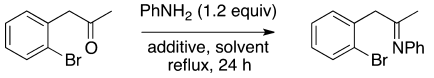
Scheme 1. Indoles from Amines and α-Aryl Ketones



We envisioned that a reversal of these steps, namely dehydrative formation of imine **5**, followed by arylation of the intermediate imine or enamine, would be more successful. We report herein facile, scalable conditions for dehydrative imine formation and copper-catalyzed indole formation from a variety of amines and α-aryl carbonyl compounds.

As the formation of imines from ketones is not a trivial process, we first examined several approaches for the condensation reaction. While magnesium sulfate is sufficient to form an imine from an aldehyde (Table 1, entry 1), it was ineffective for the complete condensation to the imine from the corresponding ketone (entry 2). Stronger in situ dehydrating agents also proved unsatisfactory (entry 3). Fortunately, a catalytic amount of acid and azeotropic removal of water turned out to be simple and effective (entries 4 and 5). Care had to be taken not to expose the ketimines to the atmosphere, as hydrolysis back to the ketone is quite rapid. Concentration of the reaction by distillative removal of the solvent without opening the reaction vessel assured that the imine was obtained without hydrolysis. While toluene was effective for imine formation, the distillation of benzene was more facile and its lower boiling point allows amines with lower molecular weights to be used without loss. Toluene could still be used for more difficult imine formations. The next stage of the reaction was implemented by the addition of the reagents to this same flask under an inert atmosphere.

Table 1. Imine Formation



entry	additive	solvent	SM/imine[a]
1[b]	$MgSO_4$	PhMe	3:97
2	$MgSO_4$	PhMe	70:30
3	3 Å mol sieves	PhMe	20:80
4	*p*-TsOH (0.1 equiv)	PhMe (-H_2O)[c]	4:96
5	*p*-TsOH (0.1 equiv)	PhH (-H_2O)[c]	1:99

[a] Measured by GC. Each entry is a single experiment. [b] 2-(2-Bromophenyl)acetaldehyde used. [c] Dean–Stark apparatus used to remove water.

Initial attempts at intramolecular imino-arylation of the ketimine followed protocols using CuI and K_3PO_4 in DMF.[13,15] However, hydrolysis proved to be competing with indole formation (Table 2, entry 1). Finely ground and anhydrous base proved to be essential for an excellent yield of the indole (entry 2). Other bases were less effective (entries 3 and 4). Unfortunately, many attempts to effect

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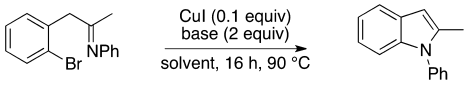
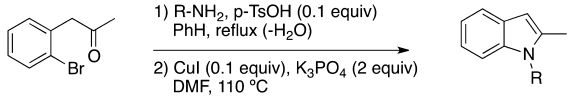
Table 2. Intramolecular Imino-Arylation



entry	base	ligand	solvent	indole/benzofuran/ ketone[a]
1	K_3PO_4	–	DMF	62:37:0 23%:0%:10%[b]
2	**K_3PO_4**[c]	–	**DMF**	**99:1:0** **80%:0%:0%**[b]
3	Cs_2CO_3[d]	–	DMF	68:32:0
4	NaOtBu[d]	–	DMF	81:9:0[e]
5	K_3PO_4[c]	–	PhMe	0:0:100
6	K_3PO_4[c]	$H_2N(CH_2)_2NH_2$	PhMe	0:0:100
7	K_3PO_4[c]	$Me_2N(CH_2)_2NMe_2$	PhMe	10:0:90

[a] Measured by GC. Each entry is a single experiment. [b] Isolated yields. [c] Base flame-dried under vacuum. [d] Anhydrous from a glovebox. [e] Formation of side products observed.

Table 3. Amine-Based Indole Synthesis



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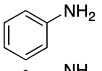
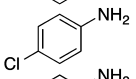
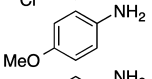
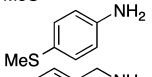
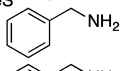
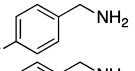
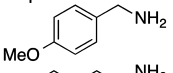
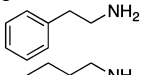
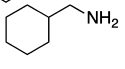
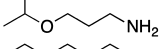
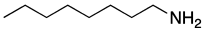
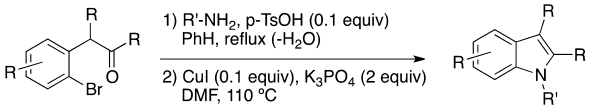
1		84%
2		80%
3		83%
4		86%
5		79%
6		87%
7		74%
8		72%
9		75%
10		72%
11		79%

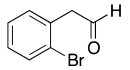
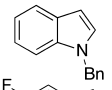
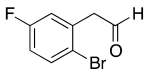
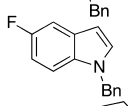
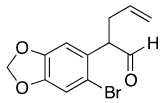
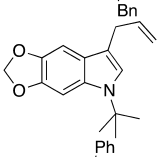
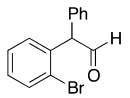
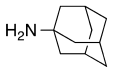
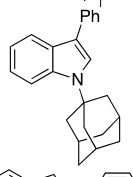
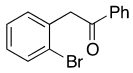
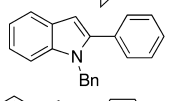
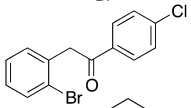
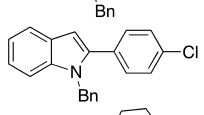
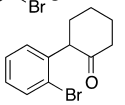
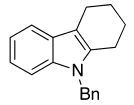
[a] Isolated yield averaged from multiple runs.

the cyclization in toluene or benzene were unsuccessful, even with the use of ligands shown to be active for amino arylation in toluene in other contexts (entries 5–7).[16,17]

(17) Please see the Supporting Information for substrate synthesis, complete experimental procedures, and compound data.

Table 4. Diverse Indole Products



entry	ketone/aldehyde	R'-NH_2	product	yield[a]
1				40%
2				63%
3[b]				59%
4				94%
5[c]				69%
6[c]				61%
7[c]				90%

[a] Isolated yield averaged from multiple runs. [b] 4 Å molecular sieves at rt. [c] Toluene at reflux used as solvent.

This experimental protocol proved to be amenable to the formation of a wide variety of *N*-functionalized indoles (Table 3). Anilines, benzylamines, and aliphatic amines were all incorporated into the product indole with good yields. Substituents on the aniline aryl ring showed little effect on the reaction (entries 1–4). The *N*-benzyl indoles

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are important motifs in their own right[18] but also allow for access to indoles without substitution on N1 through hydrogenolysis.[19] Despite the potential for copper species[20] and/or base[21] to isomerize *N*-alkyl imines, products derived from such an isomerization were not observed and *N*-alkyl indoles were generated in uniformly good yields.

A benefit of α-arylketones as indole precursors is that the simplicity of their synthesis allows for a variety of functional groups to be present to either side of the ketone and/or around the aryl ring.[22] Thus, further diversification of the indole products is possible from this one-pot, two-stage sequence. Notably, aldehydes work very well (entries 1−4, Table 4). Substituents are easily incorporated at the benzylic carbon to give 3-substituted indoles (entries 3 and 4). Importantly, even highly hindered amines may be used to build indoles. Ketones allow for controlled installation of C2 substituents in the products (entries 5−6). Cyclic ketones afford ring-fused indoles, which is a motif common in pharmaceuticals[23] and natural products (entry 7).[24]

In conclusion, a strategy to build indoles around a variety of primary amines has been designed and reduced to practice. Both simple and sterically hindered amines readily produce indoles. The conditions employed are inexpensive and amenable to large-scale implementation.

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Supporting Information Available. Additional optimization data, experimental procedures, and characterization data for all compounds are included. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.