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## Efficient and General Synthesis of 3-Aminoindolines and 3-Aminoindoles via Copper-Catalyzed Three Component Coupling Reaction

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### Abstract

An efficient three component coupling (TCC) reaction toward a variety of 3-aminoindoline and 3-aminoindole derivatives has been developed. This cascade transformation proceeds via the copper-catalyzed coupling reaction between 2-aminobenzaldehyde, secondary amine, and alkyne leading to propargylamine intermediate, which, under the reaction conditions, undergoes cyclization into the indoline core. The latter, upon treatment with a base, smoothly isomerizes into indole. Alternatively, indole can directly be synthesized in a one-pot sequential reaction.

### Keywords

three component coupling; 3-aminoindolines; 3-aminoindoles; copper; synthetic methods

Indole and indoline structural motifs are ubiquitously found in a wide range of natural products and pharmaceuticals.<sup>[1]</sup> In particular, 3-aminoindoles and indolines have found a broad application in medicinal chemistry as effective anticancer agents, compounds with analgesic properties, and agents for prevention of type II diabetes. However, the reported examples on synthesis of 3-aminoindoles<sup>[2]</sup> and 3-aminoindolines<sup>[3]</sup> are limited in scope and require multistep preparation of starting materials. Thus, the development of simple and general synthesis of 3-aminoindoles and 3-aminoindolines from easily available starting materials is warranted. One of the reasonable solutions to this problem would be the assembly of indole and indoline cores via multicomponent coupling reaction (MCR).<sup>[4]</sup>

Herein, we wish to report an efficient Cu-catalyzed three component coupling reaction of *N*-protected 2-aminobenzaldehydes **1** with secondary amines **2** and terminal acetylenes **3** into the 3-aminoindolines **5** and their subsequent isomerization into indoles **6** (Scheme 1). Multicomponent Mannich reaction between benzaldehydes, secondary amines and acetylenes is well-documented.<sup>[5]</sup> Recently, synthesis of benzofurans via three-component coupling reaction of *o*-hydroxybenzaldehydes, acetylenes and secondary amines catalyzed by copper salts has been reported.<sup>[6]</sup> However, analogous multicomponent reactions of 2-aminobenzaldehydes are unknown. We envisioned that a TCC reaction of *N*-protected 2-aminobenzaldehydes **1**, secondary amine **2** and terminal alkyne **3** would lead to the formation of propargyl amine intermediate **4**,<sup>[7]</sup> which, upon activation of triple bond with a  $\pi$ -philic metal, would undergo an intramolecular 5-*exo*-dig cyclization<sup>[8,9,10]</sup> into indoline

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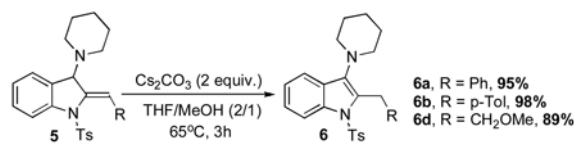
Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/adsc.200#####>.

**5**. It was expected that under reaction conditions, a subsequent isomerization of **5** into 3-aminoindoles **6** would occur (Scheme 1).

To test this hypothesis, the reaction of *N*-(2-formylphenyl)-4-methylbenzenesulfonamide, piperidine and phenylacetylene in the presence of different metal salts has been examined (Table 1). It was found that employment of gold (I) and (III), as well as silver and copper salts, was not effective resulting in formation of propargylamine intermediate **4** only (entries 1–6). The TCC reaction in the presence of CuCl and Cu(OTf)<sub>2</sub> produced trace amounts of **5** (entry 7). Substantial improvement of the yields was achieved in the presence of stoichiometric amounts of Et<sub>3</sub>N and Cs<sub>2</sub>CO<sub>3</sub> (entries 8 and 9). Furthermore, employment of DMAP led to nearly quantitative formation of indoline **5** (entry 10)! Employment of sole copper source in the presence of DMAP (entries 11–12) was less efficient as compared to use of Cu<sup>I</sup>/Cu<sup>II</sup> binary system.<sup>[11]</sup>

Surprisingly, no formation of indole **6** was observed under these reaction conditions. Next, under the optimized conditions, the scope of this new TCC reaction has been examined (Table 2). Gratifyingly, we found that this transformation is very general for a wide range of different acetylenes, aldehydes and secondary amines providing an easy access to densely-substituted indolines **5**. Thus, employment of piperidine, morpholine, and pyrrolidine produced aminoindolines in good to excellent yields. Acyclic dibenzyl, diallyl, diethyl and diisobutyl amines were similarly effective. Different alkynes, bearing alkyl or aryl substituents, displayed high reactivity in this transformation. A variety of different groups at the aromatic moiety of aldehyde, such as chloro (entries 18–19), bromo (entries 20–23), methyl (entry 24), methoxy (entry 25), and fluoro (entry 26), were also perfectly tolerated. Additionally, we have shown that *N*-4-nitrobenzenesulfonyl group can be tolerated under reaction conditions resulting in formation of indoline **5aa** in good yield (entry 27). Reaction of *N*-tosylamino-3-naphthalaldehyde resulted in formation of tricyclic indoline **5ab** although in slightly decreased yield (entry 28). Employment of 1,2,3,4-tetrahydroquinoline resulted in formation of corresponding indoline **5ac** in 68% isolated yield (entry 29). Furthermore, by utilizing trimethylsilylacetylene as acetylene surrogate,<sup>[11]</sup> an exomethylene moiety possessing indoline **5ad** was obtained in 64% yield (entry 30).

Next, conversion of indolines **5** into their more stable aromatic isomers, indoles **6**, was explored. We reasoned that this isomerization reaction should occur in the presence of a base.<sup>[12]</sup> Indeed, it was found that heating indolines **5** with cesium carbonate in THF/MeOH mixture at 65°C resulted in formation of the corresponding indoles **6a–c** in excellent yields (Eq 1).

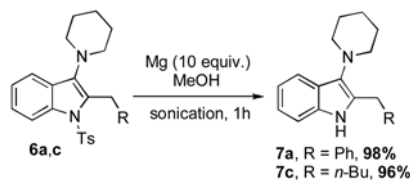


(eq 1)

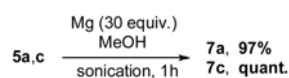
Encouraged by these results, we attempted a three-component one-pot synthesis of 3-aminoindoles **6** (Scheme 2).

Thus, the Cu-catalyzed TCC reaction of *N*-(2-formylphenyl)-4-methylbenzenesulfonamide **1**, piperidine **2**, and acetylenes **3** produced indolines **5**. Subsequent base-assisted one-pot isomerization of the latter produced indoles **6a,b,d** in good to high yields (Scheme 2). It

deserves mentioning that *N*-tosylindoles **6** upon treatment with magnesium powder<sup>[13]</sup> could smoothly be detosylated into the corresponding *N*-H indoles **7a,c** (Eq 2). Interestingly, treatment of *N*-tosylindolines **5a,c** with Mg not only caused *N*-detosylation, but also highly efficient isomerization into indoles **7a,c** (Eq 3).



(eq 2)



(eq 3)

With the new efficient methodology for assembly of the 3-aminoindoline core in hand, we performed initial studies toward enantioselective version of this transformation (Scheme 3). It was found that under modified Knochel's protocol for enantioselective TCC assembly of propargyl amines<sup>[14, 15]</sup> (with Trost's *C*<sub>2</sub>-symmetrical ligand<sup>[16]</sup>), *N*-(2-formylphenyl)-4-methylbenzenesulfonamide **1**, piperidine **2**, and trimethylsilylacetylene **3** underwent smooth coupling reaction to produce **4ad** in high yield and 93% enantioselectivity. Employment of alkyl- and arylacetylenes **3** in the synthesis of propargyl amines (**4c** and **4b**) resulted in good chemical yields, but moderate enantioselectivity (53 and 52% *ee*, respectively). Direct cycloisomerization of **4ad** gave poor yield of desired indoline **5ad**\* (30%). However, desilylation of **4ad** into **4ad'** followed by its cyclization under standard conditions produced enantioenriched indoline **5ad**\* in good yield with virtually complete preservation of enantioselectivity (Scheme 3).

In summary, we have developed a novel highly efficient and general copper-catalyzed three component coupling reaction of *N*-protected 2-aminobenzaldehydes with secondary amines and terminal acetylenes into 3-aminoindolines. It was shown that the 3-aminoindolines, under basic conditions, could highly efficiently be transformed into the isomeric 3-aminoindoles. Alternatively, the latter can be obtained via a one-pot TCC procedure. In addition, we have demonstrated that the optically active indoline could be synthesized via a stepwise enantioselective version of this novel TCC protocol.

## Experimental Section

**General Procedure:** In a dry and argon flushed Wheaton 1mL V-vial, equipped with a magnetic stirring bar and a screw cap, CuCl (0.015 mmol, 5 mol%), Cu(OTf)<sub>2</sub> (0.015 mmol, 5 mol%), DMAP (0.3 mmol, 1 equiv.) and aldehyde (0.3 mmol, 1 equiv.) were suspended in dry acetonitrile (0.3 mL). Secondary amine (0.3 mmol, 1 equiv.) and alkyne (0.45 mmol, 1.5 equiv.) were added and the reaction mixture was stirred at 80°C until TLC analysis showed full conversion of an aldehyde. Reaction mixture then was filtered through Celite and washed with dichloromethane. The crude product was concentrated *in vacuo* and purified by column chromatography on silica gel.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

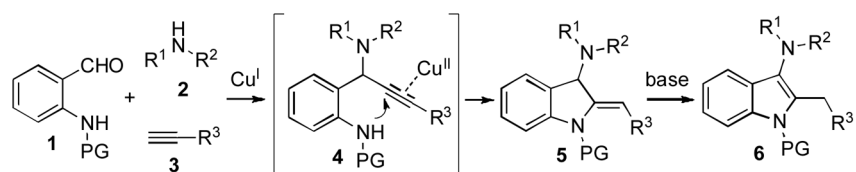
## Acknowledgments

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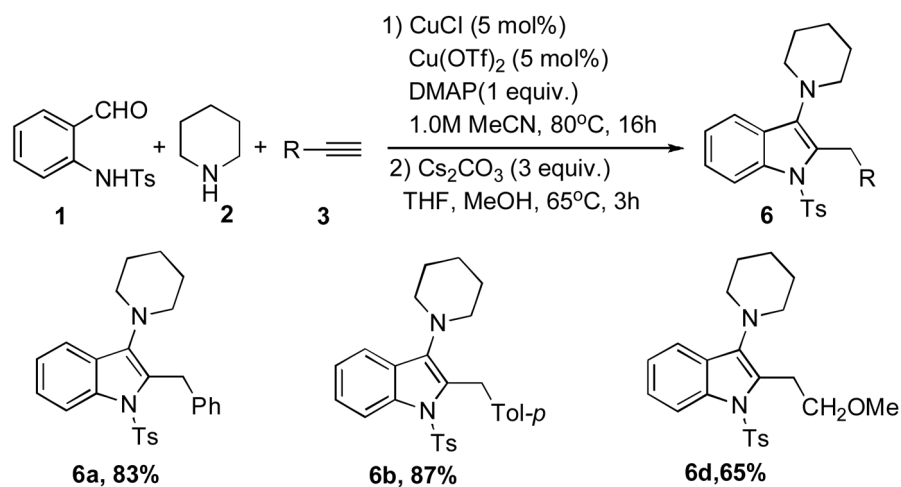
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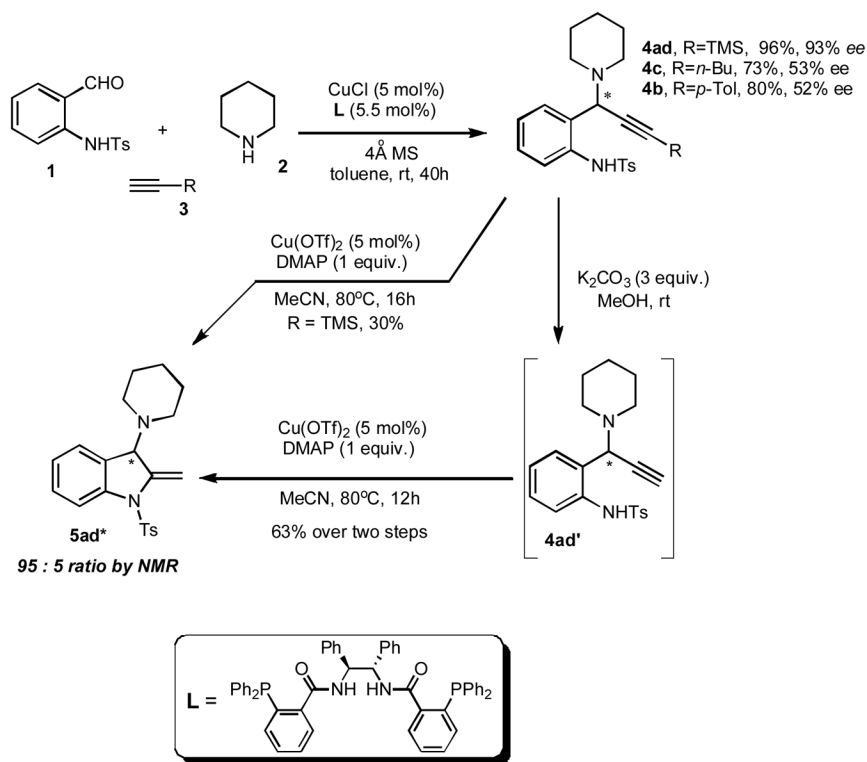
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**Scheme 1.**  
Proposed synthesis of 3-aminoindoles.



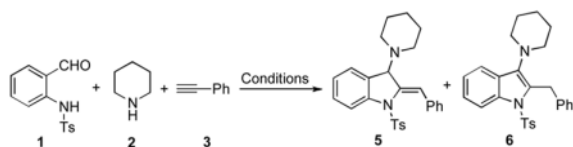
**Scheme 2.**  
One-pot TCC synthesis of indoles **6**.



**Scheme 3.**  
Enantioselective TCC Synthesis of Indoline **5\***



Table 1

Optimization of TCC coupling.<sup>a)</sup>

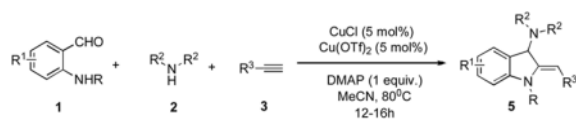
#	Conditions	Catalyst (mol%)	Additive (equiv.)	5, yield % <sup>b)</sup>
1		AuCl (5)	none	–(83) <sup>c)</sup>
2		AuCl <sub>3</sub> (5)	none	–(75) <sup>c)</sup>
3		NaAuCl <sub>4</sub> •2H <sub>2</sub> O (5)	none	traces
4		AgOTf (5)	none	–(70) <sup>c)</sup>
5		CuCl (5)	none	–(60) <sup>c)</sup>
6		Cu(OTf) <sub>2</sub> (5)	none	–(51) <sup>c)</sup>
7		CuCl (5), Cu(OTf) <sub>2</sub> (5)	none	7(80) <sup>c)</sup>
8		CuCl (5), Cu(OTf) <sub>2</sub> (5)	NEt <sub>3</sub> (1.0)	48
9		CuCl (5), Cu(OTf) <sub>2</sub> (5)	Cs <sub>2</sub> CO <sub>3</sub> (1.0)	51
10		<b>CuCl (5), Cu(OTf)<sub>2</sub> (5)</b>	<b>DMAP(1.0)</b>	<b>98</b>
11		CuCl (5)	DMAP(1.0)	70(10)
12		Cu(OTf) <sub>2</sub> (5)	DMAP(1.0)	47(21)

<sup>a)</sup>All reactions were performed with **1** (0.3 mmol), **2** (0.3 mmol) and **3** (0.45 mmol) in MeCN at 80°C.

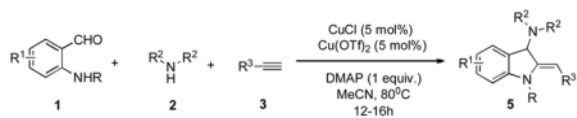
<sup>b)</sup>Yield of the isolated product after flash chromatography on silica gel.

<sup>c)</sup>Yield in parentheses given for formation of the corresponding propargylamine **4**.

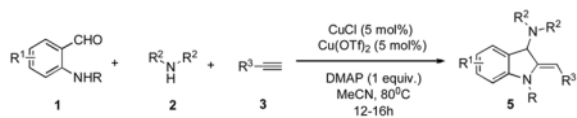
Table 2

TCC Synthesis of 3-Aminoindolines<sup>a)</sup>

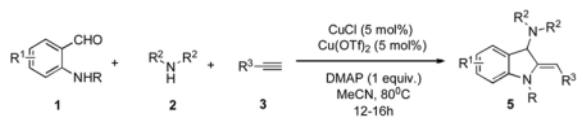
entry	product	yield <sup>b)</sup> %
1	 <b>5a</b>	98
2	 <b>5b</b>	94
3	 <b>5c</b>	78
4	 <b>5d</b>	92
5	 <b>5e</b>	90
6	 <b>5f</b>	61



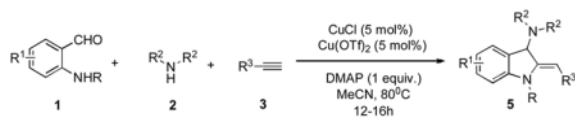
entry	product	yield <sup>b)</sup> %
7		78
8		84
9		95
10		87
11		75
12		77
13		78



entry	product	yield <sup>b)</sup> %
14	 <b>5n</b>	70
15	 <b>5o</b>	74
16	 <b>5p</b>	68
17	 <b>5q</b>	90
18	 <b>5r</b>	68
19	 <b>5s</b>	57
20	 <b>5t</b>	82



entry	product	yield <sup>b)</sup> %
21	 <b>5u</b>	80
22	 <b>5v</b>	89
23	 <b>5w</b>	80
24	 <b>5x</b>	97
25	 <b>5y</b>	34
26	 <b>5z</b>	32
27	 <b>5aa</b>	73



entry	product	yield <sup>b)</sup> %
28	<p><b>5ab</b></p>	45
29	<p><b>5ac</b></p>	68
30	<p><b>5ad</b></p>	64 <sup>c)</sup>

<sup>a)</sup> All reactions were performed with **1** (0.3 mmol), amine **2** (0.3 mmol), acetylene **3** (0.45 mmol) in MeCN (1M) at 80°C for 12–16h.

<sup>b)</sup> Yield of the isolated product after flash chromatography on silica gel.

<sup>c)</sup> Reaction was performed with trimethylsilylacetylene (1.5equiv.).