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Synthesis of Indolines via a Domino Cu-Catalyzed Amidation/Cyclization Reaction

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Abstract

A highly efficient one-pot procedure for the synthesis of indolines and their homologues based on a domino Cu-catalyzed amidation/nucleophilic substitution reaction has been developed. Substituted 2-iodophenethyl mesylates and related compounds afforded the corresponding products in excellent yields. No erosion of optical purity was observed when transforming enantiomerically pure mesylates under the reaction conditions.

The indoline moiety[1] can be found in numerous biologically active alkaloid natural products[2] and pharmaceuticals.[3] Recently, highly efficient indoline-based organic dyes for dye-sensitized solar cells have also been developed.[4]

Since our earlier reports on the Pd-catalyzed intramolecular amination reactions for the formation of indolines,[5] a variety of *intramolecular* transition metal-catalyzed amination and amidation processes have emerged for the synthesis of N-protected indolines (Scheme 1, eq. 1).[6,7,8] More versatile routes toward the synthesis of the indoline core incorporate an *intermolecular* Pd-catalyzed amidation or amination reaction as part of a sequential or domino process (Scheme 1, eq. 2 and 3).[9] Although, this strategy represents a significant improvement in the modular synthesis of indolines, several drawbacks limit the reported methods. Specifically, certain methods only allow access to 3-substituted,[9a] 2-substituted[9c] or non-substituted[9d,e] indolines, and the Pd-catalyzed C–C/C–N coupling of bromoalkylamines with an aryl iodide requires ortho-substituted aryl iodides and a para-nitrophenyl-protected amine.[9f] We felt that a one-pot procedure for the synthesis of indolines that overcomes these limitations would be highly desirable.

Herein, we report the development of a general domino Cu-catalyzed amidation/nucleophilic substitution process for the synthesis of substituted indolines and their homologues (Scheme 1, eq. 4).[10]

We began our investigation with 1-iodo-2-(2-iodoethyl)benzene (**1a**) and *tert*-butylcarbamate (**2a**) as the model substrates to examine the reaction conditions, which we previously reported for the Cu-catalyzed amidation of aryl halides (Table 1) [5 mol % CuI, 20 mol % *N*,*N′*-dimethylethylenediamine (DMEDA), Cs_2CO_3 in THF].[7a,11] Only low conversion of **1a** was observed at room temperature after 16 h. At 80 °C, however, full conversion and up to 37% of the *N*-Boc-protected indoline **3a** were obtained, along with 23% of 2-*N*-Boc-styrene (**4a**). Systematic variation of the solvent, base, and diamine-ligand did not increase the yield of the desired product, although varying amounts of the products **4a** and **5a** were observed (Table 1, entries 1–7).

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Variation of the nucleofuge proved to be crucial. Switching from the phenethyl iodide **1a** to the phenethyl chloride **1b** or the phenethyl mesylate **1c** resulted in exclusive formation of the desired product **3a** in high yields (87% and 89%, respectively).

Under the optimized reaction conditions 2-iodophenethyl mesylate (**1c**) reacted equally efficiently with other commonly used carbamates **2b–c** and amides **2d** and yielded the corresponding N-protected indolines **3b–d** in comparably high yields without formation of any side products (Table 2).

Encouraged by these results, we investigated the substrate scope of this reaction sequence. Various 2-iodophenethyl mesylates were subjected to the domino amidation sequence (Table 3).

A wide variety of functional groups, such as ethers, acetals, halogens, esters, and siloxy or alkyl groups were tolerated on the aryl ring (entries 1–3) and in positions R^2 and R^3 (entries 4–8). In all cases, the reaction proceeded smoothly and the corresponding substituted indolines were obtained in excellent yield. This method was further applied to the synthesis of indoline homologues, which are difficult to access using the previously reported domino processes.[8] The corresponding mesylates gave access to *N*-Boc-tetrahydroquinoline (**3n**), -benzoxazine (**3o**) and -3-methyl-2,3,4,5-tetrahydro-1*H*-1-benzazepine (**3p**) in yields up to 76% (entries 9–11).

Three distinct mechanistic pathways for this domino process can be envisioned for the formation of the indoline structure (Scheme 2): 1) base-promoted formation of 2-iodo-styrene followed by intermolecular Cu-catalyzed C–N coupling and intramolecular hydroamidation of styrene **I** (pathway **A**);[12] 2) intermolecular Cu-catalyzed or uncatalyzed substitution of the alkyl mesylate and subsequent Cu-catalyzed intramolecular C–N coupling with the aryl iodide **II** (pathway **B**); 3) initial intermolecular Cu-catalyzed amidation of the aryl iodide, followed by an intramolecular S_N2 reaction of the carbamate or amide **III** onto the alkyl mesylate (pathway **C**).

To elucidate the reaction mechanism, we synthesized compounds **1q**, **1r**, **4** and **5** (Scheme 3).

Under the reaction conditions racemic *trans* mesylate **1q** yielded the racemic *cis*-fused hexahydrocarbazole **3q** - as confirmed by an NOE experiment - as a single diastereosiomer in 94%, and the enantiomerically pure mesylate **1r** afforded indoline **3r** in excellent yield and with 99% *ee*.[13]

Based upon these results, pathway **A** is unlikely to be the operative mechanism, since hydroamidation of the achiral intermediate **I** would lead to a mixture of *cis*- and *trans*[14]-products in the case of **3q** and to racemization of the stereocenter in position 2 in the case of **3r**. Furthermore, pathway **B** can be ruled out, since no substitution at the alkyl mesylate took place in model systems **4** and **5** under our reaction conditions. Finally, the fact that complete stereochemical inversion was observed in cases **1q** and **1r** strongly suggests a nucleophilic displacement of the mesylate group *via* an S_N2 mechansim (pathway **C** in Scheme 2). Attempts to isolate reaction intermediate **III** were unsuccessful. Only the final product and remaining starting material could be detected by GC or NMR in various ratios over the course of the reaction.

In summary, we have developed a highly efficient domino Cu-catalyzed amidation/ nucleophilic substitution reaction for the synthesis of indolines and their homologues from ortho-iodophenalkyl mesylates. The mild reaction conditions and the broad substrate scope render this method attractive and complementary to existing methods for the synthesis of indolines. Finally, this approach also allows the synthesis of enantiomerically pure indolines, since the second step proceeds with complete stereochemical inversion and therefore no erosion of optical purity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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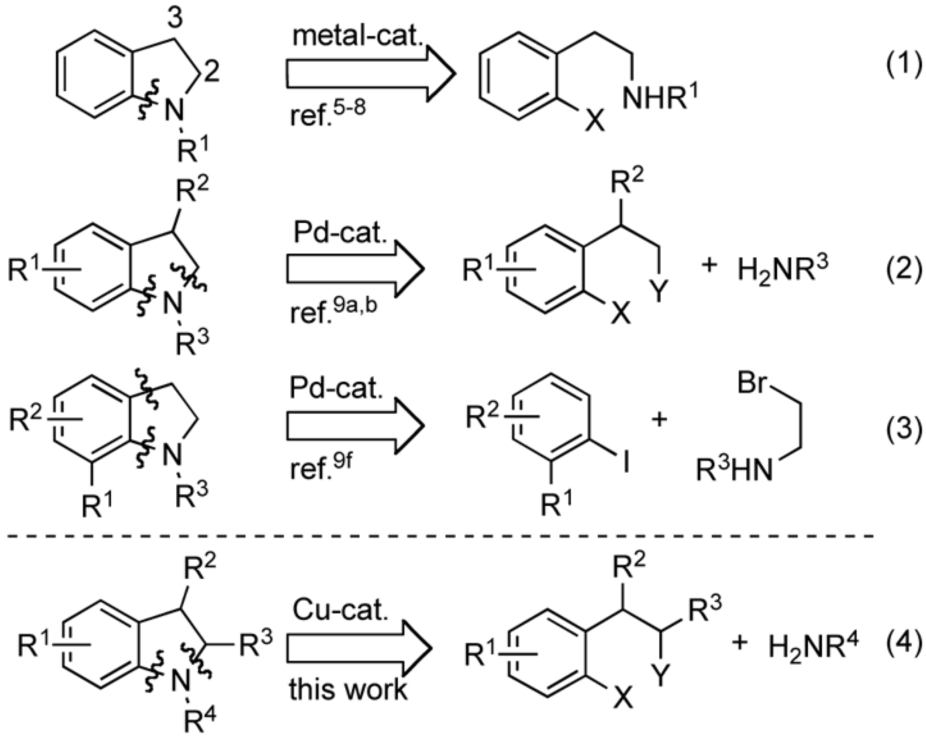
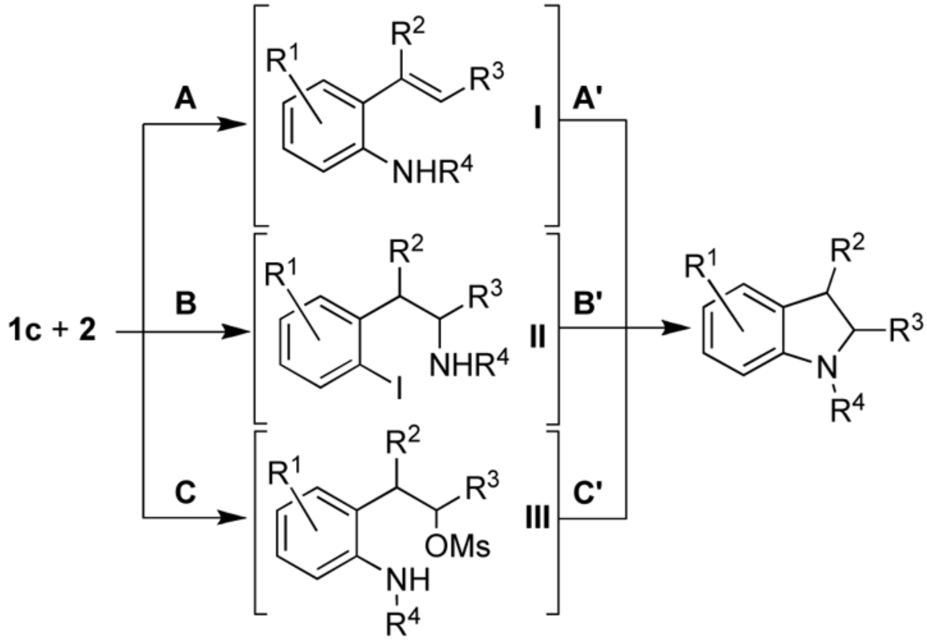


Scheme 1.

Known and Envisioned Strategies for the Synthesis of Indolines

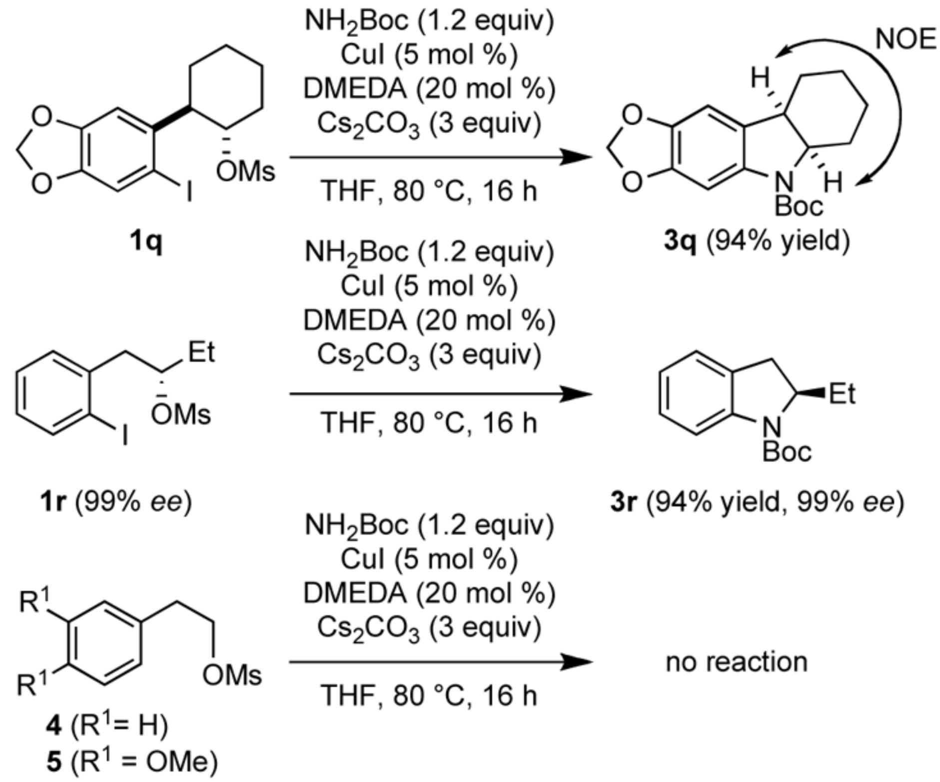


Scheme 2. Possible Mechanistic Pathways

A, A′: intermolecular Cu-cat. amidation and hydroamidation.

B, B′: intermolecular Cu-cat. or uncat. amidation and intramolecular Cu-cat. amidation.

C, C′: intermolecular Cu-cat. amidation and S_N2 reaction.



Scheme 3.
Experiments Conducted to Elucidate the Reaction Mechanism

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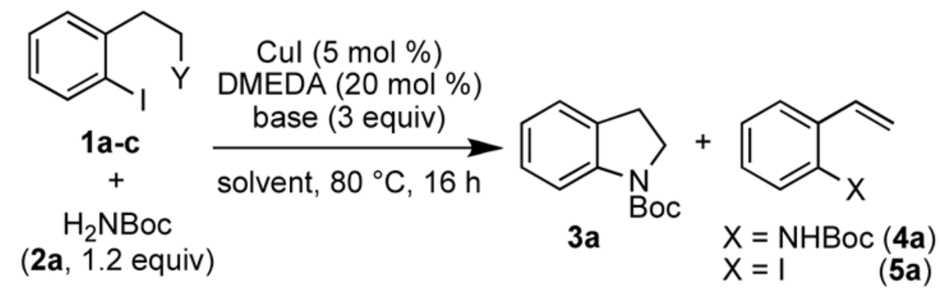
Table 1

Optimization of the Domino Cu-Catalyzed Amidation/Cyclization Reaction



entry	Y	base	solvent	yield 3a[a]	yield 4a	yield 5a
1[b]	I (**1a**)	Cs_2CO_3	THF	6%	-	14%
2	**1a**	Cs_2CO_3	THF	37%	23%	-
3	**1a**	Cs_2CO_3	1,4-dioxane	35%	11%	6%
4	**1a**	Cs_2CO_3	toluene	3%	-	11%
5[c]	**1a**	Cs_2CO_3	THF	40%	31%	-
6	**1a**	K_3PO_4	THF	9%	23%	14%
7	**1a**	K_2CO_3	THF	-	-	33%
8	Cl (**1b**)	Cs_2CO_3	THF	87%		-
9	OMs (**1c**)	Cs_2CO_3	THF	89%[d]	-	-

[a] GC yield with dodecane as an internal standard; 99% conversion of **1**, unless indicated otherwise.

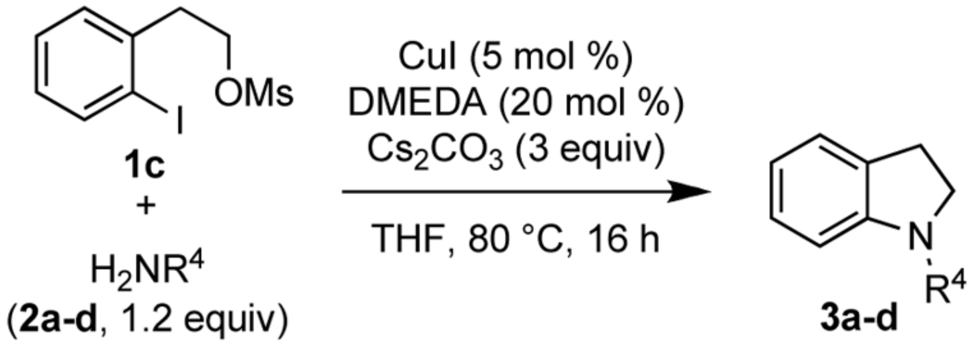
[b] Experiment performed at rt; 41% conversion of **1a.**

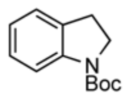
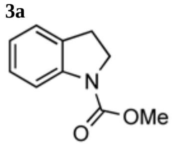
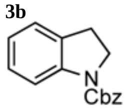
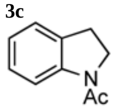
[c] Racemic *trans*-1,2-*N,N′*-dimethylcyclohexanediamine was used as a ligand.

[d] Isolated yield.

Table 2

Synthesis of N-protected Indolines via Domino Cu-Catalyzed Amidation/Cyclization Reaction

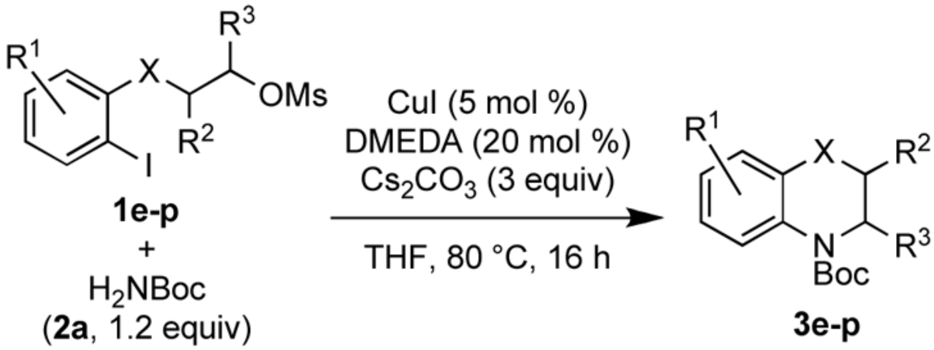


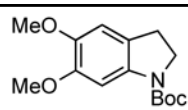
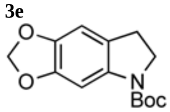
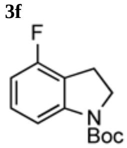
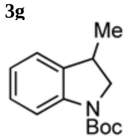
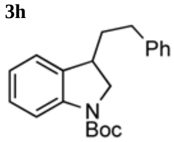
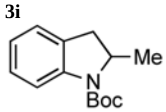
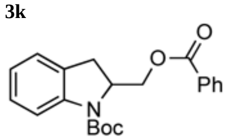
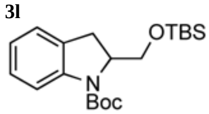
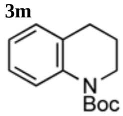
entry	R^4	product	yield[a]
1	Boc (**2a**)	 **3a**	89%
2	C(O)OMe (**2b**)	 **3b**	90%
3	Cbz (**2c**)	 **3c**	90%
4	Ac (**2d**)	 **3d**	87%

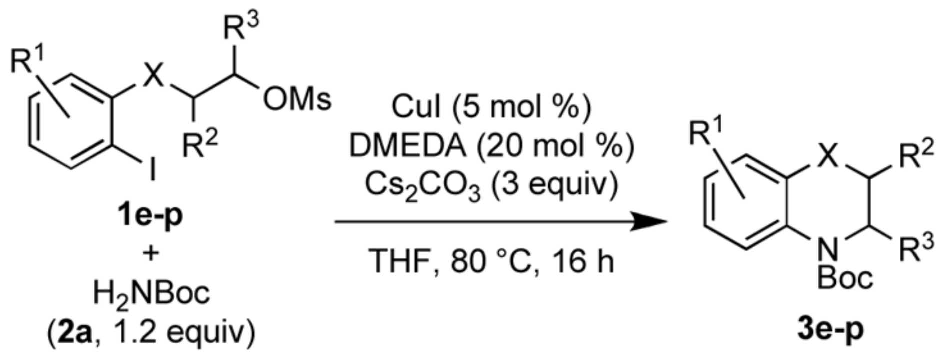
[a] Yields of the isolated products are an average of two runs and the products are estimated to be over 95% pure by ^1H NMR spectroscopic and GC analysis.

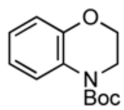
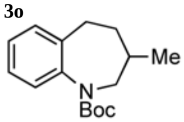
Table 3

Substrate Scope of the Cu-Catalyzed Domino Amidation Reaction



entry	product	yield[a]
1	 **3e**	75%
2	 **3f**	82%
3	 **3g**	95%
4	 **3h**	95%
5	 **3i**	92%
6	 **3k**	96%
7	 **3l**	88%
8	 **3m**	91%
9	 **3n**	74%



entry	product	yield[a]
10	 **3o**	76%
11	 **3p**	57%

[a]Yields of the isolated products are an average of two runs and the products are estimated to be over 95% pure by ^1H NMR spectroscopic and GC analysis.