Synthesis of N-Fused Indolines via Copper (II)-Catalyzed Dearomatizing Cyclization of Indoles

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Abstract: Herein, a copper(II)-catalyzed dearomative cyclization amination of N-(2-aminobenzoyl) indoles is presented. Under mild reaction conditions, the cyclization proceeds to afford tetracyclic indolines by forming a new C–N bond in good yields. The tetracyclic 5a,6-dihydroindolo[2,1-b] quinazolin-12(5H)-ones are obtained in good to excellent yields (up to 99% yield) by using trifluoromethanesulfonic acid (TfOH) mediated N–Ts bond cleavage. The obtained compounds could be easily functionalized by simple synthetic methods.

Keywords: Indoline; cyclization; dearomatization; indoles; copper catalyst

Introduction

Indole and its derivatives continue to inspire developments in organic synthetic chemistry even after so many years since their discovery. The specific scaffold is a privileged structure and is ubiquitous in pharmaceuticals and biologically active compounds.[1] Fused indolines as indole derivatives are of particular interest as they are often found in natural products and bioactives,[2] for example, strychnine and tryptanthrins (**1**, **2**, alkaloids),[3] mitosanes and mitosenes (**3**, antitumor activity),[4] and isatisine (**4**, antiviral activity) (Figure 1).[5]

To date, some initial synthetic approaches for N-fused indoline synthesis have already been developed.[6] In past decades, methodologies for preparation of indolines has been a focus of attention,[2,7] however, establishing an efficient protocol to construct privileged skeletons with therapeutic potential remains highly challenging in synthetic chemistry. The dearomatization of indoles has been recognized as an efficient approach to obtain indolines. Recently, dearomatizing strategies have attracted increased attention, with a myriad of methods to access indolines via intramolecular[8] or intermolecular dearomatization[9] having been developed.

Up to this point, some cases involving *N*-tethered indoles are used to synthesize indolines via dearomatizing cyclization (Scheme 1).[10–13] These reactions usually proceed in the presence of a catalyst, such as palladium or nickel salts, or by visible-light photocatalysis. The dearomative cyclization proceeds with C–C bond formation (Scheme 1, a).[10] On the other hand, just recently, our group and others developed protocols for the synthesis of fused indolines by dearomatizing cyclization of *N*-acylindoles.[11,12,13] These reactions involve C–O bond formation in the presence of a palladium catalyst, BBr_3 or triflic acid, and an $FeCl_3$ catalyst (Scheme 1, b). Only one low yield example involving C–N bond formation was reported in the previous work.[13] However, developing mild and effective reaction conditions to access novel indoline structures is still highly desirable.

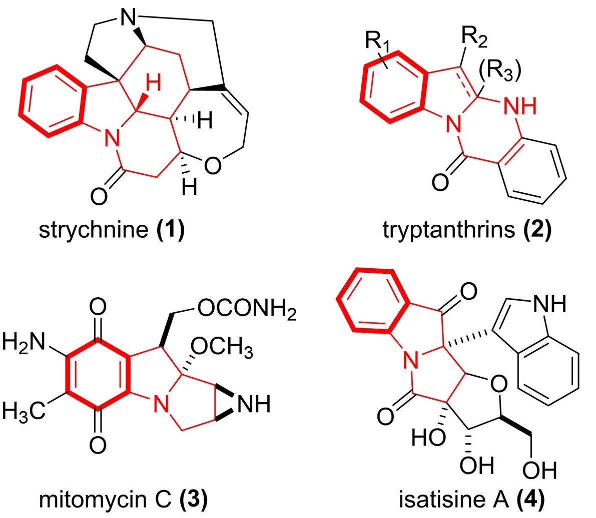
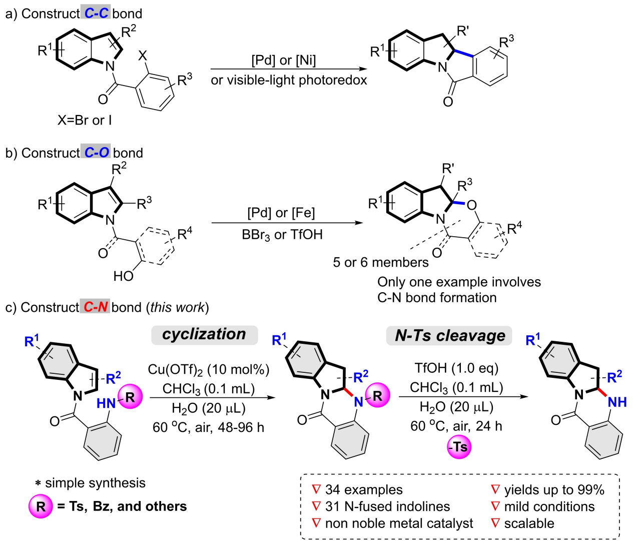


Figure 1. Natural products and bioactives bearing the N-fused indoline core.



Scheme 1. Dearomatization cyclization reactions at indole skeleton.

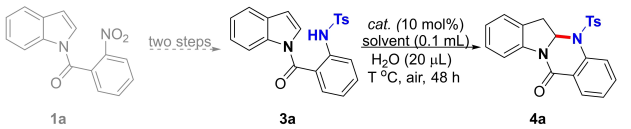
Our recent discovery of an iron catalyzed dearomatization cyclization of phenol-substituted acylindoles opened the door to exploring potential protocols for the preparation of new indoline structures. In a first attempt the cyclization proceeds by tosylamides forming the C–N bonds in modest yield.[13] Encouraged by these results and following our continuous effort of polycyclic framework synthesis, we now report a copper(II) trifluoromethanesulfonate catalyzed dearomatizing cyclization of *N*-acylindoles by forming a new C–N bond, yielding N-fused indolines in moderate to good yields. Selective N–Ts bond cleavage in the presence of TfOH affords tetracyclic 5a,6-dihydroindolo[2,1-*b*]quinazolin-12(5*H*)-ones in good to excellent yields (Scheme 1, c).

Results and Discussion

The *N*-acylindole **3a** (*N*-(2-(1*H*-indole-1-carbonyl)phenyl)-4-methylbenzenesulfonamide) is easily available in three steps from commercially available indole (see experimental section) and was selected as the standard substrate for this study. Initially, we began the investigation employing $Fe_2(SO_4)_3$ (10 mol%) and H_2O (20 μL) in chloroform (0.1 mL) at 60 °C for 48 hours and obtained the cyclization product **4a** in only 5% yield. To our delight, the cyclization product was obtained in 44% yield with $FeCl_3 \cdot 6H_2O$. The yield improved dramatically when $FeCl_2 \cdot 4H_2O$ and $FeCl_3$ were used, giving **4a** in 91% and 92%, respectively. However, $Y(OTf)_3$ and $Ga(acac)_3$ did not yield any of the cyclization product, while $MnCl_2 \cdot 2H_2O$, $YbCl_3 \cdot 6H_2O$, $Cu(OAc)_2$, $CuCl_2$, and the “classical” Lewis acid $TiCl_4$ gave **4a** in low yields. Several additional Lewis acids were also screened. The best yield (99%) of **4a** was obtained by employing $Cu(OTf)_2$ as the catalyst, with $SnCl_4$ or $Ga(OTf)_3$ also yielding the desired product in good to excellent yields. The use of TfOH (10 mol%) affords **4a** in 21% yield as well as 53% of **7aa**. Hence, TfOH derived from $Cu(OTf)_2$ also catalyzes the dearomative cyclization. Nevertheless, the copper salt seems to be essential to obtain excellent yields of the direct cyclization product **4a**.[14] The effects of the reaction solvent and the reaction temperature were also subsequently screened. However, the desired product yield decreased dramatically by using CH_3CN or THF as the solvent. Nevertheless, in toluene the desired **4a** was obtained in 95% yield. When the reaction temperature was decreased to 40 °C or even to room temperature almost no **4a** was formed. The concentration of the substrates as well as the presence of water was also found to influence the reaction (Table 1).

To evaluate the generality of this novel transformation, the reaction was conducted by employing 10 mol% $Cu(OTf)_2$ with H_2O (20 μL) in chloroform (0.1 mL) at 60 °C for 48 hours under an atmosphere of air (standard conditions). The scope of the reaction is shown in Scheme 2. Initially, the substituent effect at the terminal amine was tested, and generally, the dearomative cyclization products can be obtained in moderate yields. Notably, it was found that the electron-donating methyl group at different positions of the benzene ring showed different reactivity. Only 4% of the product **4c** was obtained when the methyl group was located at the *ortho* position. Shifting this group to the *meta*- or *para*-positions, products **4d** or **4a** were obtained in moderate or excellent yields. When no substituent was present at the phenyl ring, a moderate yield of **4b** was found. Inspired by these results, other substituents were investigated at the *para*-position of the phenyl ring. It was found that the substrates with electron-donating groups, halogens,

Table 1. Effects of reaction parameters.[a]



Entry	*Cat.* (0.1 eq.)	Solvent	T (°C)	**4a** (%)[b]
1	$Fe_2(SO_4)_3$	$CHCl_3$	60	5
2	$FeCl_3 \cdot 6H_2O$	$CHCl_3$	60	44
3	$FeCl_2 \cdot 4H_2O$	$CHCl_3$	60	91
4	$FeCl_3$	$CHCl_3$	60	92
5	$Y(OTf)_3$	$CHCl_3$	60	0
6	$YbCl_3 \cdot 6H_2O$	$CHCl_3$	60	trace
7	$TiCl_4$	$CHCl_3$	60	13
8	$SnCl_4$	$CHCl_3$	60	71
9	$MnCl_2 \cdot 2H_2O$	$CHCl_3$	60	trace
10	$Ga(acac)_3$	$CHCl_3$	60	0
11	$Ga(OTf)_3$	$CHCl_3$	60	94
12	$Cu(OAc)_2$	$CHCl_3$	60	trace
13	$CuCl_2$	$CHCl_3$	60	5
14	$Cu(OTf)_2$	$CHCl_3$	60	99 (94)
15	$Cu(OTf)_2$	CH_3CN	60	trace
16	$Cu(OTf)_2$	THF	60	0
17	$Cu(OTf)_2$	Toluene	60	95
18	$Cu(OTf)_2$	$CHCl_3$	40	trace
19	$Cu(OTf)_2$	$CHCl_3$	rt	0
20[c]	$Cu(OTf)_2$	$CHCl_3$	60	51
21[d]	$Cu(OTf)_2$	$CHCl_3$	60	55
22[e]	$Cu(OTf)_2$	$CHCl_3$	60	83

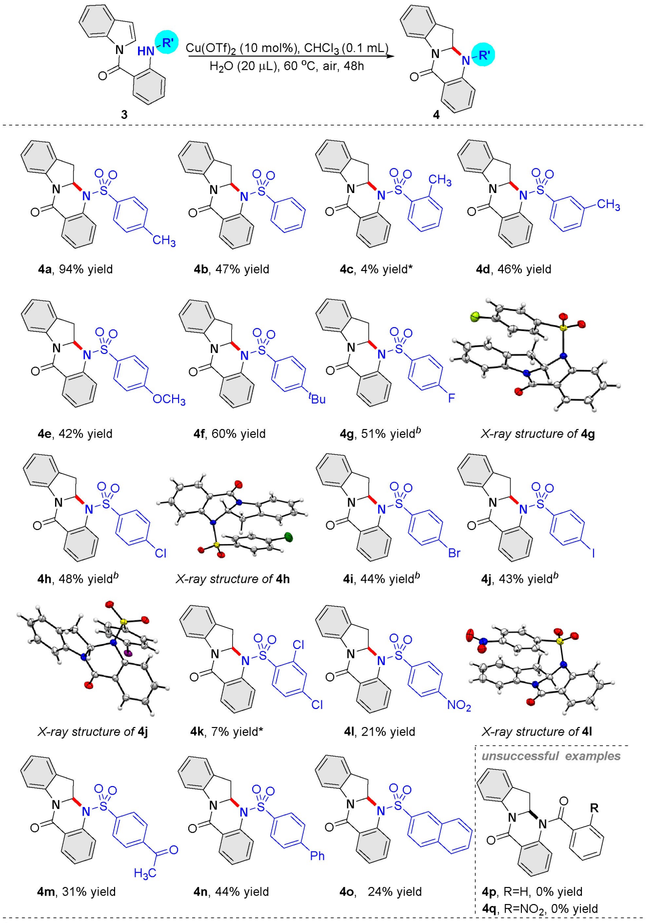
[a] Standard conditions: **1a** (0.2 mmol), $Cu(OTf)_2$ (10 mol%), $CHCl_3$ (0.1 mL), H_2O (20 µL), 60 °C, air, 48 hrs.

[b] Yield are determined by ^1H NMR with 1,3,5-trimethoxybenzene as the internal standard; Isolated yields are shown in brackets.

[c] $CHCl_3$ (0.2 mL).

[d] $CHCl_3$ (0.4 mL).

[e] without H_2O.



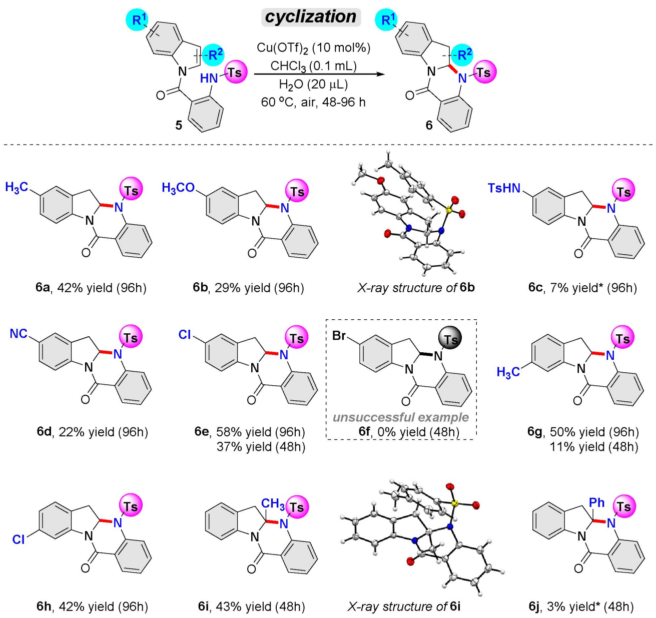
a) Standard conditions: **3** (0.2 mmol), $Cu(OTf)_2$ (10 mol%), $CHCl_3$ (0.1 mL), H_2O (20 µL), 60 ºC, air, 48h. *NMR yield using 1,3,5-trimethoxybenzene as the internal standard; b) $Cu(OTf)_2$ (20 mol%), $CHCl_3$ (0.2 mL), 96h.

Scheme 2. Scope of substrates bearing terminal aryl amine.

and electron-withdrawing groups at the *para*-position of the aromatic ring were compatible with the reaction conditions, with the desired products formed in moderate to good yields (**4e**–**4m**). Notably, only 7% of **4k** was obtained with two chloro substituents. Moreover, phenyl groups and additional rings at the phenyl moiety can also yield the desired products in moderate yields (**4n**–**4o**). Unfortunately, when benzoyl and substituted benzoyl groups were used instead of the aryl sulfonyl groups at the nitrogen atom, no desired products (**4p**–**4q**) were obtained. Compounds **4g**, **4h**, **4j**, **4l** were confirmed by X-ray crystallographic analysis (Scheme 2).

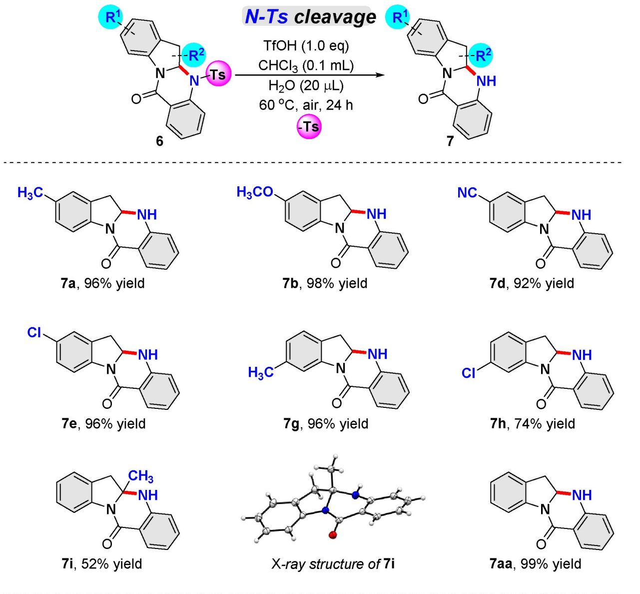
In light of these results, we found that a tosyl group at the terminal amine was the most favoured substituent for the dearomative cyclization reaction. Following this, the influence of the substituents at the indole ring were tested. Both electron-donating and withdrawing groups at the C5- and C6-position of the indole (**6a**–**6b**, **6c**–**6d**, and **6g**) were compatible with the reaction. However, rather moderate yields of the cyclization products were formed when strong electron-donating or withdrawing groups at the C5-position (**6b**–**6d**) were introduced. Chloro substituents at the C5- or C6-position of the indole has a positive effect compared with a bromine atom at the C5-position (**6e**–**6f**, and **6h**). The methyl substituent at the C2-position of indole resulted in a moderate cyclization yield, while the phenyl at the C2-position only afforded a low yield (3%) of the product (**6j**). Notably, there are still large amounts of unreacted starting substrates in the test reactions. The structures of **6b** and **6i** were confirmed by X-ray crystallographic analysis (Scheme 3).

Subsequently, a facile and selective N–Ts bond cleavage approach to access novel tetracyclic indolines was carried out by employing one equivalent trifluoromethanesulfonic acid (TfOH) in the presence of water (Scheme 4). Without water the yield drops significantly. The substrates bearing electron-donating



[a] Standard conditions: **5** (0.2 mmol), $Cu(OTf)_2$ (10 mol%), $CHCl_3$ (0.1 mL), H_2O (20 μL), 60 °C, air, 48h. *NMR yield

Scheme 3. Scope of substrates with substituents on indole.



[a] N-Ts cleavage conditions: **6** (0.1 mmol), TfOH (1.0 eq.), $CHCl_3$ (0.1 mL), H_2O (20 μL), 60 °C, air, 24h.

Scheme 4. Selective cleavage N–Ts bond to access novel tetracyclic indolines.

groups, electron-withdrawing groups, and chloro substituents at the C5 or C6-position were suitable for this reaction to afford the desired tetracyclic indolines in good to excellent yields (**7a**–**7h**). Many kinds of functional groups, such as methoxy (**7b**), cyano (**7d**), and chloro (**7e** and **7h**) were all tolerated well. Moreover, when the steric bulk of the methyl group was introduced at the C2-position, a good yield of the desired product **7i** was observed, and its structure confirmed by X-ray crystallographic analysis. Notably, without a substituent at the indole ring, a near quantitative yield of **7aa** was obtained.

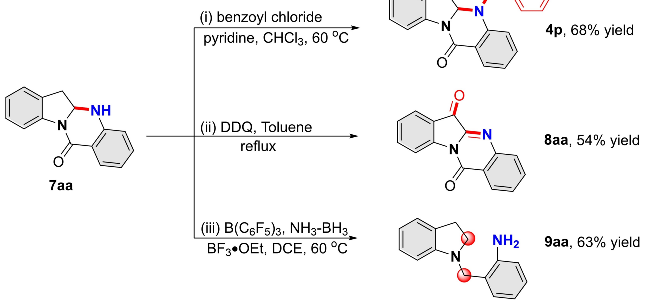
Finally, facile and selective derivatizations at the tetracyclic 5a,6-dihydroindolo[2,1-*b*]quinazolin-12(5*H*)-one (**7aa**) were carried out in Scheme 5. Herein, benzoylation of **7aa** provides an easy approach to access **4p**, which was not possible following the protocol in Scheme 2. Moreover, **7aa** can be oxidized to obtain alkaloid tryptanthrin (**8aa**). Its antiviral activities have been studied recently.[15] The carbonyl group and C–N bond of **7aa** can be selectively reduced by employing $B(C_6F_5)_3$ and NH_3-BH_3 to generate the indoline product **9aa**.

Conclusion

In conclusion, a versatile copper(II)-catalyzed dearomative cyclization of indoles with terminal amine has been developed. Various tetracyclic indolines were obtained by forming a new C–N bond in moderate to good yields. The TfOH mediated selective N–Ts bond cleavage gives access to N-fused indolines in good to excellent yields. In subsequent reaction steps, the tetracyclic 5a,6-dihydroindolo[2,1-*b*]quinazolin-12(5*H*)-one can be easily functionalized by simple procedures.

Experimental Section

General procedure I: The dearomatizing cyclization of N-acylindoles. A solution of **3** or **5** (0.2 mmol), $Cu(OTf)_2$ (7.2 mg, 10 mol%), H_2O (20 μL) in $CHCl_3$ (0.1 mL) were stirred under an atmosphere of air at 60 °C for 48–96 h. The reaction mixture was washed with water and extracted with CH_2Cl_2 for three times. The combined organic layers were dried with Na_2SO_4.



Scheme 5. Derivatization of 5a,6-dihydroindolo[2,1-*b*]quinazolin-12(5*H*)-one (7aa): (i) N-acylation of the product 7aa. (ii) oxidation of 7aa synthesis of tryptanthrin. (iii) reduction of (C=O) and (C–N) bonds by $B(C_6F_5)_3$ and NH_3-BH_3.

The solvent was evaporated under reduced pressure. The residue was purified by flash chromatography over silica gel with n-pentane/ethyl acetate to afford the pure products **4** and **6**.

General procedure II: Cleavage of the N-tosyl group. A solution of 5-tosyl-5a,6-dihydroindolo[2,1-b]quinazolin-12(5H)-one **4** or **6** (0.1 mmol), trifluoromethanesulfonic acid (TfOH) (8.8 μL, 0.1 mmol), H_2O (20 μL) in $CHCl_3$ (0.1 mL) were stirred in a flask under an atmosphere of air at 60 °C for 24 h. The reaction mixture was washed with water and extracted with CH_2Cl_2 for three times. The combined organic layers were dried with Na_2SO_4. The solvent was evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel with n-pentane/ethyl acetate to afford the pure products **7**.

CCDC-2067943 (**4g**), CCDC-2067944 (**4h**), CCDC-2067945 (**4j**), CCDC-2067946 (**4l**), CCDC-2067947 (**6b**), CCDC-2067948 (**6i**), and CCDC-2067949 (**7i**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

The supporting information contains further crystal structure information, compound characterization and copies of ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra.

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UPDATES

Synthesis of N-Fused Indolines via Copper (II)-Catalyzed Dearomatizing Cyclization of Indoles

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