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Synthetic Methods

Brønsted-Acid-Mediated Divergent Reactions of Betti Bases with Indoles: An Approach to Chromeno[2,3-*b*]indoles through Intramolecular Dehydrogenative C2-Alkoxylation of Indole

Mohit L. Deb,*[a] Choitanya Dev Pegu,[a] Bhaskar Deka,[a] Prantu Dutta,[a] Amol S. Kotmale,[b] and Pranjal K. Baruah*[a]

Abstract: Divergent reactions of various 1-(aminoalkyl)naphthols and 2-(aminoalkyl)phenols (commonly known as Betti bases) with indoles under Brønsted acid catalysis is reported. With the reaction strategies, one can efficiently synthesize important indole derivatives such as 3-(α,α-diarylmethyl)indoles and chromeno[2,3-*b*]indoles. Furthermore, we disclose here a new C–C bond-cleavage reaction, in which naphthol and phenol behave as leaving groups to produce diarylmethanes. Inexpensive reagents such as *p*-toluenesulfonic acid monohydrate and molecular iodine are used to catalyze the reactions. No metal catalyst is required. The starting material of the reactions, Betti bases, are easily prepared from a three-component reaction of naphthol/phenol, aldehydes, and secondary amines. The mechanisms for the reactions are established through some control experiments. Quinone methide is the key intermediate for all the reactions reported herein.

Introduction

Betti bases, 1-(aminoalkyl)naphthols and 2-(aminoalkyl)phenols, were discovered at the beginning of the 20th century and were synthesized by a three-component Mannich reaction of 2-naphthol or phenol, aldehydes, and amines by Mario Betti.[1] Betti bases have a broad range of applications; for example, they are very good precursors for the synthesis of many nitrogen-containing pharmaceuticals and are key intermediates in many multistep organic synthesis.[2] A few Betti base derivatives have been reported as biologically active ingredients.[3] Over the last two decades, Betti bases have been extensively used as ligands in organometallic and asymmetric catalysis.[4] Besides that, a few reports describe the synthesis of several worthy heterocycles from Betti bases.[5] The amine functional group of Betti bases is crucial in forming C–C and C–X bonds to the benzylic carbon.[6] Therefore, the massive scope of manipulating the Betti base structure is still buried.

The indole skeleton is an important structural motif in organic and medicinal chemistry. For instance, a derivative of indole acts as a free-radical scavenger and has a broad spectrum of antioxidant activity.[7] Many derivatives of indole are used as antihypertensive, antineoplastic, and antimitotic agents.[8] Moreover, C3-substituted indoles are venerable pharmacophores for medicinal chemists and have a wide range of biological applications; for example, some indole derivatives are potent antifungal and antibacterial agents[9] and HIV-1 integrase inhibitors.[10] Chromeno[2,3-*b*]indole is a ring-fused indole derivative having medicinal importance. To date, there are very few reports to synthesize these indole derivatives. In one instance, 7-methylchromeno[2,3-*b*]indole was synthesized from the decomposition of the diazonium sulfate, which itself was prepared from 3-*o*-aminobenzylidene-7-methyloxindole.[11] Some other reports reveal the synthesis of chromono[2,3-*b*]-indoles from the corresponding 3-(2-hydroxybenzoyl)oxindoles[12] or through an aminoisoflavone–salicyloylindole ring transformation.[13] Recently, in another report, a number of new chromeno[2,3-*b*]indole derivatives were synthesized by the reaction of 2-hydroxyacetophenones with oxindoles under harsh reaction conditions.[14] The researchers claim that this type of fused ring skeleton can serve as a candidate for modulating RNA-binding proteins.[15] Therefore, the synthesis and functionalization of indoles have been the focal point of active research over the years.

Results and Discussion

There are a number of research articles regarding the C2-functionalization of indole derivatives through the formation of C–C,[16] C–N,[17] and C–S[18] bonds, but C–O bond formation is rarely reported.[19] Most of these are intermolecular reactions. A few reports on intramolecular C–O bond formation at the 2-position of indole leading to indolines are available.[20a,20b] To the best of our knowledge, there are only a couple of reports on intramolecular dehydrogenative C–O bond formation at the 2-position of indole.[20b,20c] Therefore, we became interested in

[a] *Department of Applied Sciences, GUIST, Gauhati University, Guwahati 781014, Assam, India*
E-mail: mohitdd.deb@gmail.com
baruah.pranjal@gmail.com
http://www.gauhati.ac.in/profile-faculty.php?id=304
[b] *Central NMR Facility, National Chemical Laboratory, Pune 411008, India*

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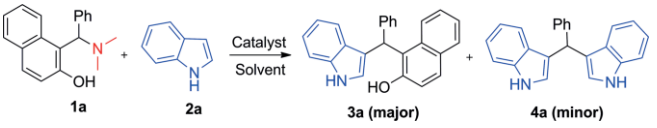
developing a protocol for intramolecular C–O bond formation at the 2-position of indole to obtain chromeno[2,3-*b*]indole derivatives.

Initially, our research plan was to synthesize **3** by three-component reaction of 2-naphthol (or phenol), indole, and aldehyde and then cyclization of **3** to chromeno[2,3-*b*]indole **5**. However, the difficulty we faced in using this strategy was the sole formation of bis(indolyl)methanes **4**[21] instead of **3**. Therefore, we switched our reaction route to a two-component approach, in which Betti bases were treated with indoles under acid-catalyzed conditions (Scheme 1).

Betti bases **1** were efficiently synthesized by the reported three-component one-pot process involving naphthol/phenol, aromatic aldehydes, and *N*,*N*-dimethylamine.[22] We observed during the synthesis of **3** by using the two-component approach the unanticipated formation of a minor quantity of **4** as a side product, which rendered the purification of **3** difficult. To minimize the formation of **4**, we tried a variety of acid catalysts and H-bond catalyst such as thiourea (Table 1). After a careful screening of catalysts and solvents, we found *p*-toluenesulfonic acid monohydrate (*p*TsOH·H_2O, 0.1 equiv.) in toluene at 100 °C to be the optimum conditions for the synthesis of **3a** from the reaction of Betti base **1a** and indole (**2a**), which we considered as our model reaction. The reaction gave **3a** in 75 % yield with no formation of bis(indolyl)methanes (Table 1).

Having identified the optimized conditions, we next investigated the substrate scope for the synthesis of **3** by examining various Betti bases and indole derivatives. To our delight, compounds **3** containing a wide range of substituents were obtained in moderate to good yields, as summarized in Scheme 2. Electron-donating groups on the aryl ring (Ar) of Betti bases **1** decreased the product yield, whereas electron-withdrawing groups increased the yield (see **3j** vs. **3k**, Scheme 2). Betti bases having *ortho*-substituted aryl rings provided lower yields with longer reaction times (see **3r**, Scheme 2). If Ar = H, **3** was not formed; instead, we obtained an intractable mixture of products (Scheme 2). *N*-Alkylindoles produced lower yields of **3** (see **3m**–**y**, Scheme 2).

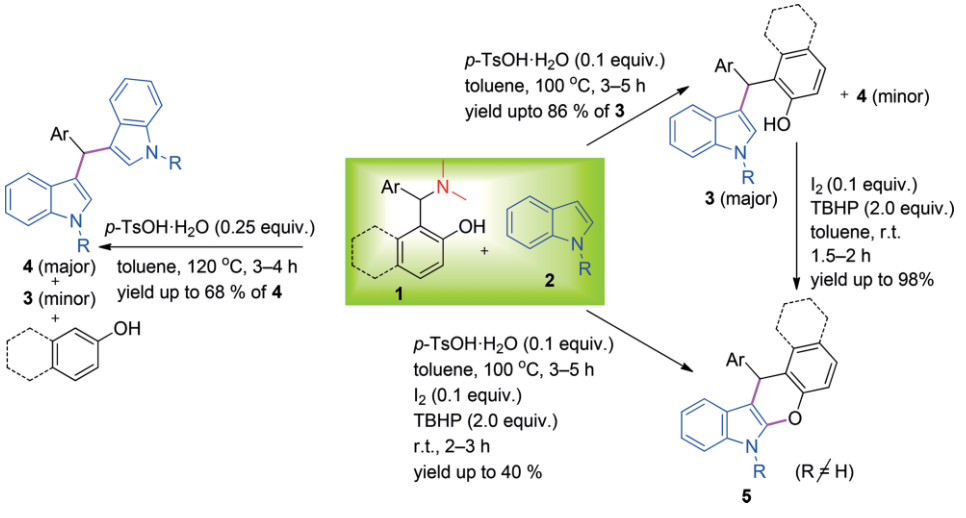
Table 1. Optimization of the synthesis of **3**.[a]



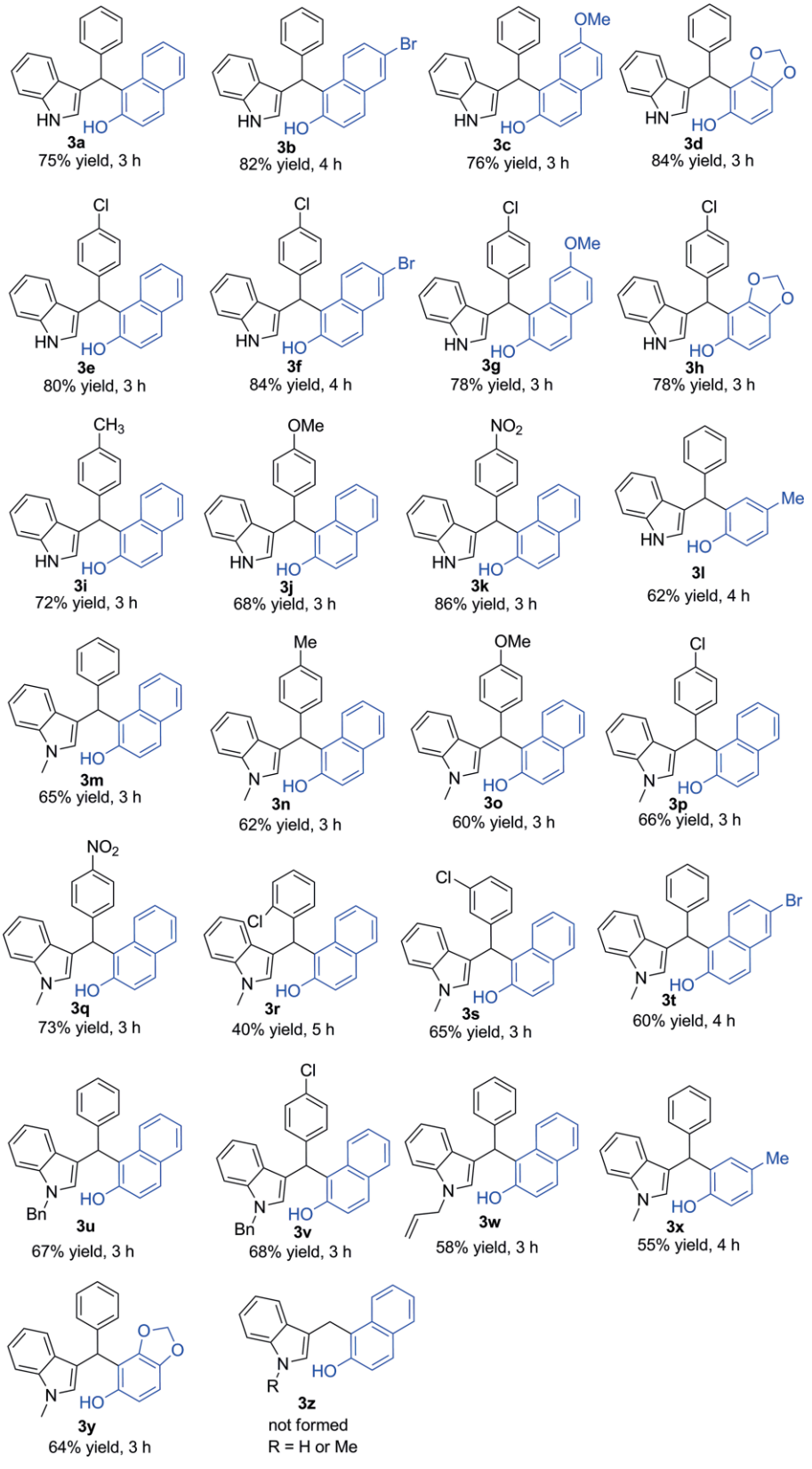
Entry	Catalyst (equiv.)	Solvent	Temp. [°C]	Time [h]	Yield[b] [%] **3a**	**4a**
1	–	–	100	4	–	–
2	*p*TsOH·H_2O (0.1)	–	100	4	35	10
3	*p*TsOH·H_2O (0.1)	EtOH	reflux	4	–	–
4	*p*TsOH·H_2O (0.1)	MeCN	reflux	4	20	trace
5	*p*TsOH·H_2O (0.1)	DMF	100	4	15	–
6	*p*TsOH·H_2O (0.1)	$CHCl_3$	reflux	5	trace	–
7	*p*TsOH·H_2O (0.1)	toluene	110	3	48	15
8	*p*TsOH·H_2O (0.1)	toluene	100	3	75	–
9	*p*TsOH·H_2O (0.1)	toluene	100	4	60	12
10	*p*TsOH·H_2O (0.2)	toluene	100	3	45	20
11	*p*TsOH·H_2O(0.05)	toluene	100	3	40	–
12	*p*TsOH·H_2O (0.1)	toluene	25	24	15	–
13	TFA (0.1)	toluene	100	3	50	15
14[c]	TNBA (0.2)	toluene	100	4	25	–
15[d]	PNBA (0.2)	toluene	100	4	10	–
16	CH_3CO_2H (0.2)	toluene	100	4	–	–
17	thiourea (0.3)	toluene	100	4	–	–

[a] Unless otherwise mentioned, all reactions were performed by using **1a** (0.5 mmol, 138.5 mg) and **2a** (0.5 mmol, 58.5 mg). [b] Products were purified by column chromatography by using silica gel (100–200 mesh) and yields are for the isolated products. [c] TNBA: 2,4,6-trinitrobenzoic acid. [d] PNBA: *p*-nitrobenzoic acid.

We noticed that upon increasing the temperature, time, or catalyst loading in the synthesis of compound **3a**, an increase in the formation of bis(indolyl)methane **4a** was observed, which decreased the yield of **3a** (Table 1, entries 7, 9, and 10). For the generation of **4a**, a molecule of naphthol must be eliminated from substrate **1a**, which we isolated and characterized by NMR spectroscopy and mass spectrometry. To the best of our knowledge, there is no report of such metal-free dearylation (de-naphtholation or dephenolation) in a chemical reaction. There-



Scheme 1. Divergent reactions of Betti bases with indoles.



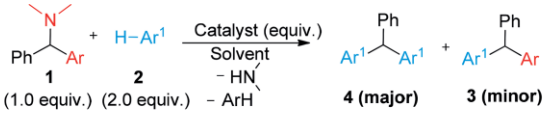
Scheme 2. Substrate scope for the synthesis of **3**. Reaction conditions: **1** (1.0 mmol), **2** (1.0 mmol), *p*TsOH·H_2O (19 mg, 0.1 equiv.), toluene (2.0 mL), 100 °C. Products were purified by column chromatography by using silica gel (100–200 mesh) and yields are for the isolated products.

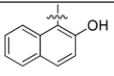
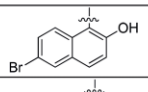
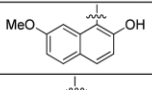
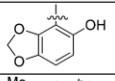
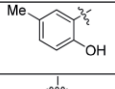
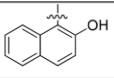
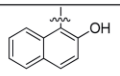
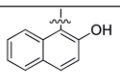
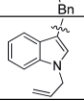
fore, we became interested to set the reaction conditions whereby we could obtain a maximum yield of dearylated product **4** of the Betti base. Hence, we screened the catalyst loading, reaction time, temperature, and solvent for our model reaction

and found that 0.25 equiv. of *p*TsOH·H_2O in toluene at 120 °C for 3 h produced a maximum yield of **4a** (68 %) along with **3a** (12 %) from the reaction of **1a** (1.0 equiv.) with **2a** (2.0 equiv., Table 2). To check the substrate scope for the formation of **4**, we performed the reaction by using various substituted Betti bases and indoles and established that elimination of naphthol from the Betti base was much easier than that of phenol (Table 2). We used stronger acids, including trifluoroacetic acid (TFA) and triflic acid, believing that they might accelerate the formation of **4**. However, in practice we obtained lower yields (Table 2). Moreover, TFA and triflic acid provided a maximum yield of **4** at 1 h, and after that time the yield decreased, which may be due to decomposition of the bis(indolyl)methanes. We also examined polar solvents such as ethanol and acetonitrile, but unfortunately, we obtained a low yield of **4a** in both cases.

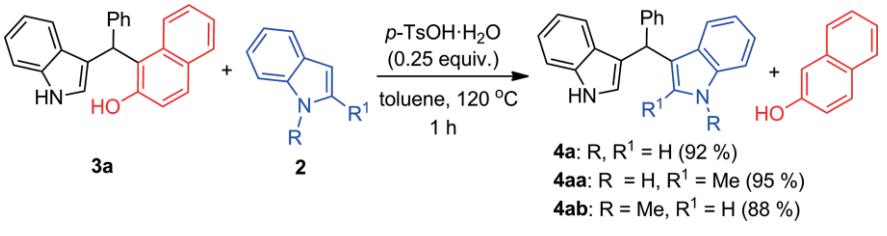
We assumed that bis(indolyl)methane **4** was formed via **3** and, therefore, to ensure the mechanistic pathway, we first isolated **3a** and then treated it with indole in the presence of *p*TsOH·H_2O (0.25 equiv.) in toluene at 120 °C; this resulted in an excellent yield of symmetrical as well as unsymmetrical bis (indolyl)methanes (see **4a**, **4aa**, and **4ab**; Scheme 3). Therefore, we believe that compound **4** is formed from **1** through elimination–addition reactions via **3** under acid-catalyzed conditions (Scheme 5, a).

Table 2. Dearylation of Betti bases.[a]



Entry	Ar	Ar[1]	Catalyst (equiv.)	Solvent	Time (h)	Temp. (°C)	Yield (%), **4** [**3**][b]
1			*p*-TsOH·H_2O (0.20)	toluene	3	120	**4a**, 60 [**3a**, 20]
			***p*-TsOH·H_2O (0.25)**	**toluene**	**3**	**120**	**4a, 68 [3a, 12]**
			p-TsOH·H_2O (0.30)	toluene	3	120	**4a**, 66 [**3a**, 10]
			p-TsOH·H_2O (0.25)	toluene	4	120	**4a**, 68 [**3a**, 12]
			p-TsOH·H_2O (0.25)	toluene	3	115	**4a**, 60 [**3a**, 20]
			p-TsOH·H_2O (0.25)	toluene	3	125	**4a**, 68 [**3a**, 12]
			p-TsOH·H_2O (0.25)	EtOH	3	120	**4a**, 10 [**3a**, 15]
			p-TsOH·H_2O (0.25)	CH_3CN	3	120	**4a**, 20 [**3a**, 10]
			TFA (0.25)	toluene	1	120	**4a**, 60 [**3a**, 15]
			TFA (0.25)	toluene	1.5	120	**4a**, 45 [**3a**, 10]
			triflic acid (0.25)	toluene	1	120	**4a**, 52 [**3a**, trace]
			triflic acid (0.25)	toluene	1.5	120	**4a**, 45 [**3a**, trace]
2			*p*-TsOH·H_2O (0.25)	toluene	3	120	**4a**, 65 [**3b**, 20]
3			*p*-TsOH·H_2O (0.25)	toluene	3	120	**4a**, 60 [**3c**, 15]
4			*p*-TsOH·H_2O (0.25)	toluene	4	120	**4a**, 45 [**3d**, 30]
5			*p*-TsOH·H_2O (0.25)	toluene	4	120	**4a**, 15 [**3l**, 45]
6			*p*-TsOH·H_2O (0.25)	toluene	4	120	**4m**, 55 [**3m**, 15]
7			*p*-TsOH·H_2O (0.25)	toluene	4	120	**4u**, 58 [**3u**, 15]
8			*p*-TsOH·H_2O (0.25)	toluene	4	120	**4w**, 52 [**3w**, 10]

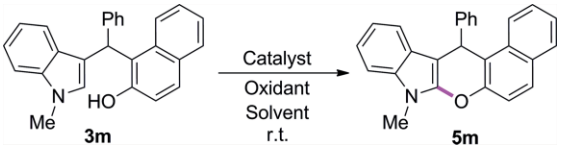
[a] All reactions were performed by using **1** (0.5 mmol) and **2** (1.0 mmol) in toluene at 120 °C. [b] Bis(indolyl)methanes and the corresponding eliminated naphthols/phenols were purified by column chromatography by using silica gel (100–200 mesh).



Scheme 3. Reaction of **3a** with indoles to furnish bis(indolyl)methanes.

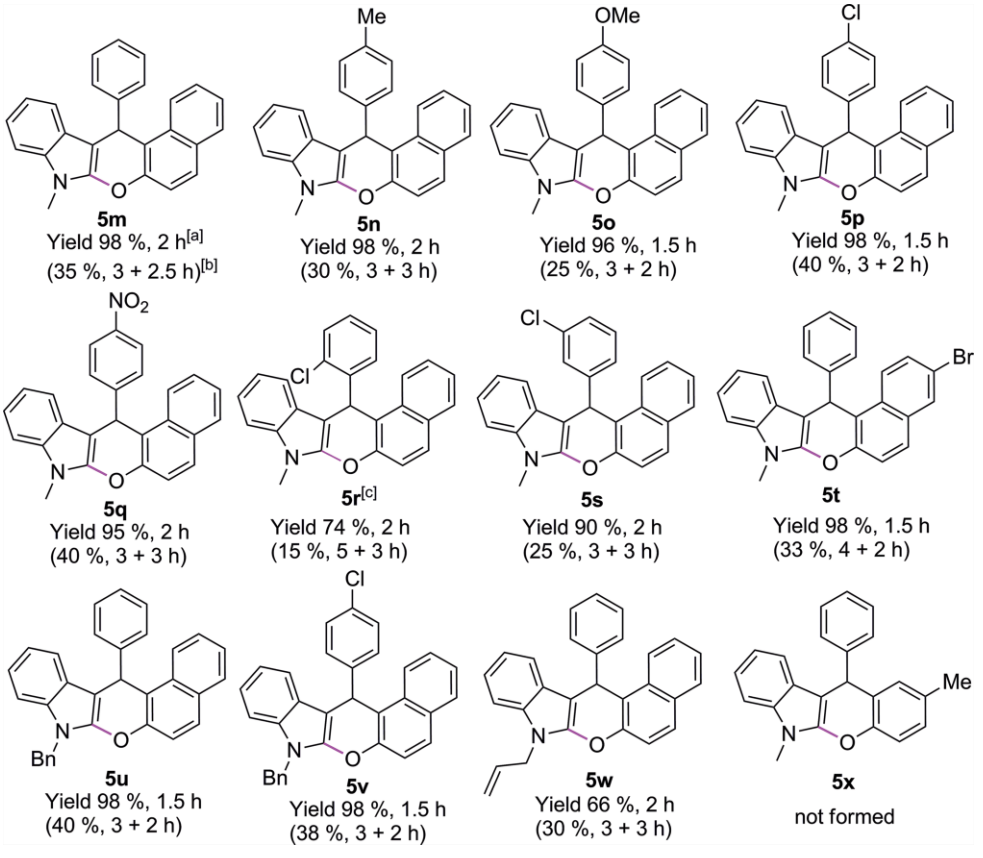
We next made an effort to synthesize **5** through C2 cyclization of the indole ring of **3** (Scheme 1). We chose the conversion of **3a** into **5a** as a model reaction, for which the substrate was an NH-indole derivative. We tried a variety of catalysts and solvents, but unluckily, we did not succeed. Then, we considered the conversion of **3m** into **5m** as a representative example, for which the substrate contains an *N*-methylindole moiety. We found that molecular iodine (0.1 equiv.) with *tert*-butyl hydroperoxide (TBHP, 70 % in H_2O, 2.0 equiv.) in toluene at room temperature were optimal for this cyclization. The reaction took 2 h to complete, and the yield was excellent (98 %; Table 3, entry 5). Next, we investigated the substrate scope for the synthesis of **5** (Scheme 4). Chromeno[2,3-*b*]indoles **5**, which contain a wide variety of substituents, were obtained in good to excellent yields. To our delight, functional groups on the aromatic ring such as –OMe, –Br, –Cl, and $–NO_2$ were also compatible. The compound containing an *N*-allylindole moiety gave a comparatively lower yield (see **5w**, Scheme 4). Compound **3** having a phenolic moiety did not produce the desired product under our optimized condition (e.g., **5x**, Scheme 4). We next attempted to synthesize **5** through the two-component domino approach from the reaction of **1** and *N*-substituted indole without isolating intermediate **3** (Scheme 1). To achieve the goal, compound **1a** was treated with *N*-methylindole in the presence of *p*TsOH·H_2O (0.1 equiv.) under heating at 100 °C in toluene

Table 3. Optimization of the synthesis of chromeno[2,3-*b*]indole **5m**.[a]



Entry	Catalyst (equiv.)	Oxidant/additive (equiv.)	Solvent	Time [h]	Yield[b] [%]
1	I_2 (0.1)	TBHP (2.0)	CH_2Cl_2	5	65
2	I_2 (0.1)	TBHP (2.0)	$CHCl_3$	5	68
3	I_2 (0.1)	TBHP (2.0)	DCE	2	88
4	I_2 (0.1)	TBHP (2.0)	MeOH	5	80
5	I_2 (0.1)	TBHP (2.0)	toluene	2	98
6	I_2 (0.1)	TBHP (1.5)	toluene	2	77
7	I_2 (0.05)	TBHP (2.0)	toluene	2	85
8	I_2 (0.1)	TBHP (2.0)	toluene	1.5	92
9	I_2 (0.1)	H_2O_2 (2.0)	toluene	2	trace
10	KI (0.1)	TBHP (2.0)	toluene	3	80
11	NaI (0.1)	TBHP (2.0)	toluene	3	72
12	TBAI (0.1)	TBHP (2.0)	toluene	3	84
13	NBS (0.1)	TBHP (2.0)	toluene	6	n.r.[c]
14	NCS (0.1)	TBHP (2.0)	toluene	6	n.r.[c]

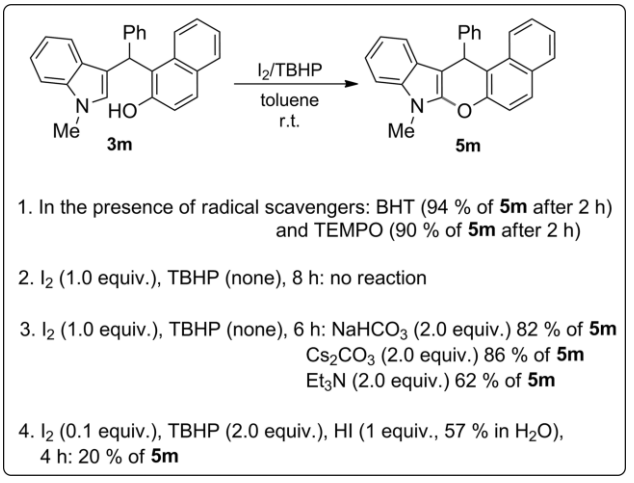
[a] All reactions were performed with **3m** (0.5 mmol, 181.5 mg). TBAI: tetrabutylammonium iodide, NBS: *N*-bromosuccinimide, NCS: *N*-chlorosuccinimide, DCE: 1,2-dichloroethane. [b] Product **5m** was purified by column chromatography by using silica gel (100–200 mesh) and yields are for the isolated products. [c] n.r.: no reaction.



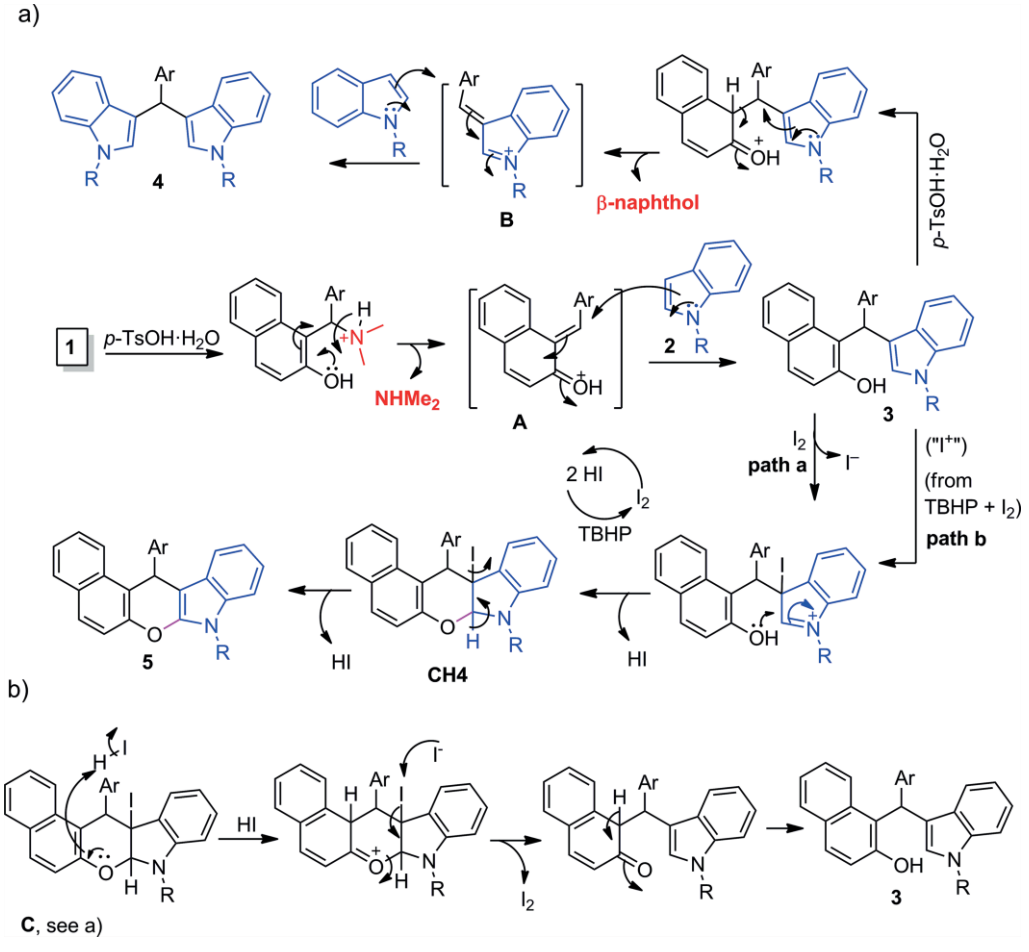
Scheme 4. Substrate scope for the synthesis of chromeno[2,3-*b*]indoles **5**. [a] Reaction conditions for **3**→**5**: **3** (0.5 mmol), I_2 (13 mg, 0.1 equiv.), TBHP (70 % in H_2O, 128.5 mg, 2.0 equiv.), toluene (1.0 mL), r.t. [b] Reaction conditions for **1**→**5**: **1** (0.5 mmol), **2** (0.5 mmol), *p*TsOH·H_2O (0.1 equiv.), toluene (1.0 mL), 100 °C; then, I_2 (0.1 equiv.), TBHP (70 % in H_2O, 2.0 equiv.), r.t. The first fraction of the time is under heating and the last one is at r.t, yields are for the isolated products. [c] Yield of **5r** was determined by analysis of the crude product by ^{1}H NMR spectroscopy, as we could not isolate the pure compound.

for 3 h and then I_2 (0.1 equiv.) and TBHP (2.0 equiv.) were added, and the mixture was stirred for 2.5 h at room temperature. The reaction afforded desired product **5m** but in a low yield (Scheme 4).

A tentative mechanism for the formation of **3**, bis(indolyl)methanes **4**, and chromeno[2,3-*b*]indoles **5** is proposed (Scheme 5, a). *p*TsOH·H_2O helps to eliminate the *tert*-amine of the Betti base by protonation, which generates *o*-quinone methide (**A**).[23] A molecule of indole thereafter attacks **A** to produce 3-(α,α-diarylmethyl)indole **3**. On further heating with an acid catalyst, the naphthol moiety of **3** is protonated and eliminated through the formation of alkylideneindoleninium ion **B**. Subsequently, another molecule of indole attacks **B** to furnish bis(indolyl)methane **4**. The mechanism for the formation of **5** is proposed on the basis of some control experiments (Scheme 6) and relevant reports on the C2-functionalization of indole.[16–19] Given that many reactions involving the use of iodine as a catalyst involve a free-radical pathway,[24] we performed the reaction in the presence of a couple of radical scavengers, such as butylated hydroxytoluene (BHT) and 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO), under the optimized reaction conditions. However, we did not observe any significant reaction inhibition (Scheme 6). Therefore, we conclude that the dehydrogenative coupling reaction of **3** to **5** is not a free-radical-mediated process. To ensure the role of TBHP, we performed the reaction by using an equivalent amount of iodine in the absence of TBHP and found that there was no reaction at all (Scheme 6). This result implies that iodine is probably not the active catalytic species. Therefore, we assume that the purpose of TBHP is not only to reoxidize the resulting HI to I_2 but also to generate the electrophilic iodine species ("I^+") from the reaction of iodine and TBHP.[25]



Scheme 6. Control experiments to explore the mechanism.



Scheme 5. (a) Proposed mechanism for the formation of **3**, **4**, and **5**. (b) Proposed mechanism for the prevention of **5** by HI.

To gain more insight into the mechanism, we next performed the reaction by using a stoichiometric amount of both iodine and the base, including $NaHCO_3$, Cs_2CO_3, and Et_3N, in the absence of TBHP. We obtained a good yield of **5m**, although a longer time was needed relative to that required for the I_2/TBHP method. These results suggest that in situ generation of "I^+" is not indispensable to the reaction. Iodination of **3** may take place by direct attack either to iodine (path a, Scheme 5, a) or to "I^+" (path b, Scheme 5, a). Therefore, we strongly believe that the expulsion of HI from the reaction medium is necessary for a successful reaction either by means of neutralization (using base) or reoxidation to I_2 (using oxidant). To reinforce this thought, whether HI could prevent product formation, we performed a dehydrogenative coupling in the presence of an equivalent amount of HI under the optimized conditions. We observed a remarkable decrease in the yield, and we were able to isolate **5m** in only 20 % yield even after 4 h (Scheme 6). The presence of HI seems to prevent the formation of **5** most likely through the pathway shown in Scheme 5 (b).

Conclusions

In summary, we successfully developed reactions of Betti base with indoles by which we can efficiently synthesize 3-(α,α-diarylmethyl)indoles and chromeno[2,3-*b*]indoles. In addition, we revealed a new reaction strategy for which naphthol/phenol behaves as a leaving group to generate bis(indolyl)methane derivatives. The reactions do not use any expensive metal catalyst or solvent. Neither dry solvents nor precautions for an inert atmosphere are required. This method for the synthesis of 3-(α,α-diarylmethyl)indoles and chromeno[2,3-*b*]indoles should be of great utility in medicinal chemistry. Further studies regarding applications of these reactions and screening of biological activities of the synthesized compounds are underway and will be disclosed in due course.

Experimental Section

General Procedure for the Synthesis of 3: Compound **2** (1.0 mmol) was added to a solution of **1** (1.0 mmol) in toluene (2 mL). Then, *p*TsOH·H_2O (19 mg, 0.1 equiv.) was added, and the mixture was heated at 100 °C for 3–5 h (monitored by TLC) and brought to room temperature. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (silica gel, 100–200 mesh; ethyl acetate/hexane).

General Procedure for the Synthesis of 4: Compound **2** (1.0 mmol) was added to a solution of **1** (0.5 mmol) in toluene (2 mL). Then, *p*TsOH·H_2O (24 mg, 0.25 equiv.) was added, and the mixture was heated at 120 °C for 3–4 h (monitored by TLC) and brought to room temperature. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (silica gel, 100–200 mesh; ethyl acetate/hexane).

General Procedure for the Synthesis of 5 (from 3): I_2 (13 mg, 0.1 equiv.) and TBHP (70 % in H_2O, 128.5 mg, 2.0 equiv.) were added to a solution of **3** (0.5 mmol) in toluene (1 mL). The mixture was stirred at room temperature for 1.5–2 h (monitored by TLC). The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (silica gel, 100–200 mesh; ethyl acetate/hexane).

General Procedure for the Synthesis of 5 (from 1 and 2): Compound **2** (0.5 mmol) was added to a solution of **1** (0.5 mmol) in toluene (1 mL). Then, *p*TsOH·H_2O (9.5 mg, 0.1 equiv.) was added, and the mixture was heated at 100 °C for 3–5 h and brought to room temperature. I_2 (13 mg, 0.1 equiv.) and TBHP (70 % in H_2O, 128.5 mg, 2.0 equiv.) were added, and the mixture was stirred at room temperature for 2–3 h (monitored by TLC). The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (silica gel, 100–200 mesh; ethyl acetate/hexane).

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Keywords: Nitrogen heterocycles · Fused-ring systems · C–O bond formation · Dearylation · Betti bases

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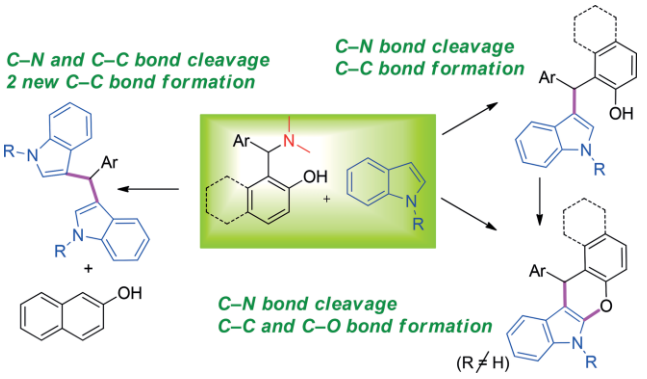
Synthetic Methods



Parents of three siblings: Three different kinds of indole derivatives, namely, 3-(α,α-diarylmethyl)indoles, chromeno[2,3-*b*]indoles, and bis(indolyl)methanes, can be synthesized from the reaction of indole with Betti bases. *o*-Quinone methide is the key intermediate in the reactions. A metal-free dearylation is also reported here for the first time.

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