chemistry

MDPI

Communication

Aluminum-Catalyzed Cross Selective C3–N1′ Coupling Reactions of *N*-Methoxyindoles with Indoles

Keisuke Tokushige, Toshiki Yamashiro, Seiya Hirao and Takumi Abe *

Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, Okayama City 700-8530, Japan

* Correspondence: t-abe@okayama-u.ac.jp

Abstract: C3–N1′ bond formation of bisindoles has been a great challenge due to the intrinsic reactivity of indoles as both C3 and N1-nucleophilic character. Herein, we demonstrate an C3–N1′ cross-coupling reaction of indoles using *N*-methoxyindoles as N-electrophilic indole reagents in the presence of Lewis acid. The bisindoles generated in this transformation are latent C3-nucleophile, allowing them to be used as strategic intermediates in sequential C3–N1′–C3′–N1″ triindole formations. The potential synthetic usefulness of this sequential transformation was highlighted upon application to the construction of C3–N1 looped polyindoles.

Keywords: 1′*H*-1,3′-biindole; N-electrophilic; *N*-methoxyindoles; bisindoles; aluminum; cross-coupling

check for updates

Citation: Tokushige, K.; Yamashiro, T.; Hirao, S.; Abe, T. Aluminum-Catalyzed Cross Selective C3–N1′ Coupling Reactions of *N*-Methoxyindoles with Indoles. *Chemistry* **2023**, *5*, 452–462. https://doi.org/10.3390/chemistry5010033

Academic Editor: Min Kim

Received: 13 February 2023
Revised: 27 February 2023
Accepted: 2 March 2023
Published: 3 March 2023

1. Introduction

C3–N1′ Heterodimeric tryptophan or tryptamine dimers comprising a pyrroloindoline skeleton are ubiquitous in biologically active alkaloids and form a class of privileged components in medicinal chemistry [1–12]. In sharp contrast, construction of C3–N1′ heterodimeric indole skeletons have proven more challenging due to the difficulties associated with introduction of the indole nitrogen (N1′) in the C3-position of indoles, and no approaches have been reported to date (Figure 1) [13,14]. In general, a C3–N1′ cross-coupling reaction between two indole derivatives is one of the most difficult challenges because the most nucleophilic position is the C3-position of the indole nucleus and the most electrophilic site is the C2-position [15–19]. Consequently, cross-coupling reactions take place largely at C2–C3′ due to the intrinsic property. Therefore, in contrast to the well-established C2–C3′ cross-coupling reactions, the C3–N1′ cross-coupling reactions of indoles has received much less attention [20–25].

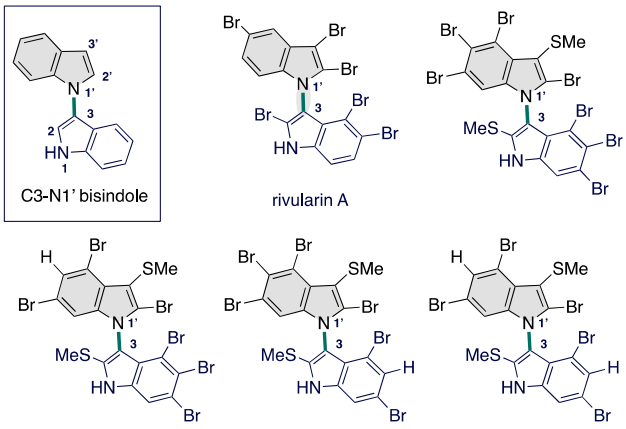
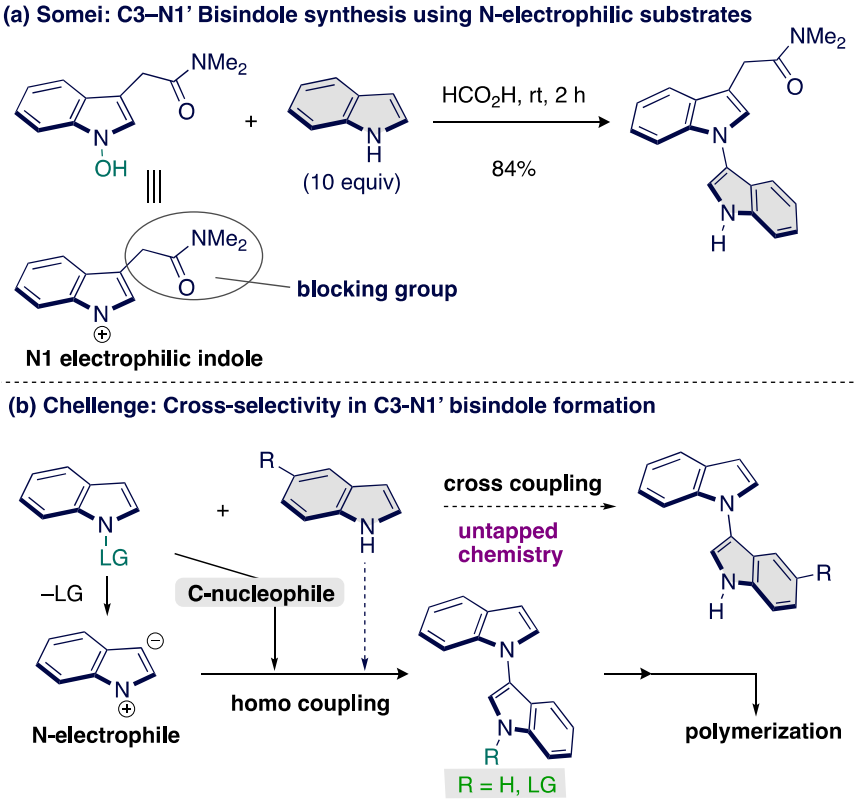


Figure 1. Structures of C3–N1′ bisindole alkaloids.

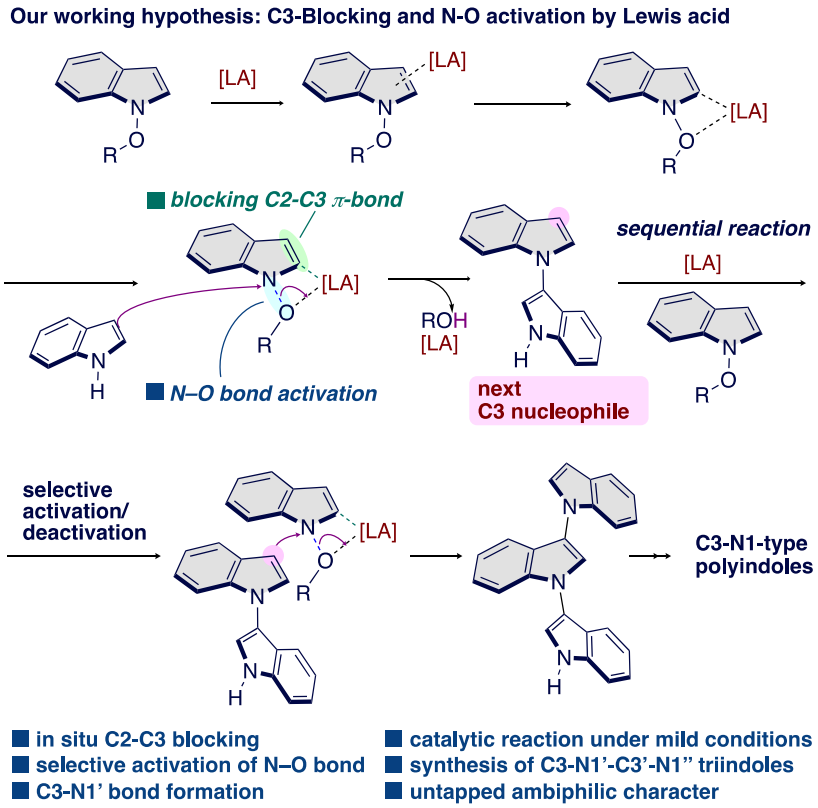
Somei has reported on C3–N1′ bond-forming reactions of N-hydroxy tryptamines in the presence of excess amounts of strong acids to form C3–N1′ heterodimers in 84% yield (Scheme 1a) [26–30]. Although it is necessary to use C3-substituted indoles such as a tryptamine, this strategy contrasts the many indole coupling efforts motivated by the intrinsic C3- and N1-nucleophilicity. However, umpolung of indole nitrogen constitutes a rarely developed latent alternative for direct C3–N1′ bond-forming reactions, whereas electrophilic nitrogen chemistry is well-developed with the leaving group placed at the amine nitrogen atom [31]. Nonetheless, underlying cross-selectivity challenges using C3-unsubstituted indoles remain for development (Scheme 1b). Recently, Buchwald and co-workers described a CuH-catalyzed *N*-alkylation of C3-unsubstituted *N*-benzyloxyindoles via hydroamination, which relies on the polarity reversal strategy triggered by the Cu catalyst [32]. To date, other than their use as electrophilic indole nitrogen surrogates toward site-selective alkylation, no general and useful synthetic methods of construction of C3–N1′ bisindoles have been exploited.



Scheme 1. State-of-the-art N-electrophilic indoles. (**a**) Previous works by Somei; (**b**) Remaining challenge.

Over the past five years, our group has had an intensive focus on the development and application of umpoled indole surrogates [33–44]. These results led us to find that in situ generated 3-methoxyindoles act as a C3-electrophilic reagent that can be harnessed for C–N, C–O, and C–C bond-forming S_NAr reactions under indium catalysts [45,46]. In this context, our group has successfully established indium-mediated C–O bond activation for the S_NAr reaction with a release of MeOH as a leaving group. By analogy to our indium-catalyzed S_NAr reaction, we hypothesized that *N*-alkoxy indoles might be suitable competent substrate as a N1-electrophilic indole precursor by a Lewis acid activation of alkoxy group through an elimination of ROH, thereby producing a C3–N1′ bisindole (Scheme 2). In this hypothesis, *N*-alkoxyindole is first combined with Lewis acids (LA) to form an LA–indole complex, which shows an *N*-electrophilic character by N–O bond activation along with reducing C3-nucleophilicity by coordinating at the C2–C3 π-bond [47–49]. Thus, the use of

LA could potentially enhance the rate of C3–N1′ cross-coupling in the use of indoles as a nucleophile [50,51], thus altering the balance between homo- and cross-coupling process. This bisindole can serve as re-birthed nucleophiles in a sequential protocol to multiple C3–N1′ bond formation that are otherwise incompatible with Lewis acid-mediated methods. We therefore decided to focus on umpolung of *N*-alkoxy indoles [52,53]. Herein, we report the successful execution of this hypothesis to enable the construction of C3–N1′ heterodimeric indole skeletons from simple indoles and *N*-methoxy indoles. The resulting investigations offer most concise catalytic protocol for constructing C3-N1′ heterodimeric indole skeletons developed to date, and shed light on the "old and new" *N*-methoxyindoles. Notably, this is the first example of a catalytic S_NAr reaction at the nitrogen center of C3-unsubstituted *N*-methoxyindoles is performed in the C–N bond formations [26–30,32].



Scheme 2. Our working hypothesis inspired by our previous S_NAr reaction under indium catalyst.

2. Materials and Methods

High-resolution MS spectra were recorded with a Brucker micrOTOF mass spectrometers (ESI-TOF-MS). The NMR experiments were performed with JEOL JNM-ECZ600R (^{1}H NMR: 600 MHz, ^{13}C NMR: 151 MHz) spectrometer, Varian 600-MR ASW (^{1}H NMR: 600 MHz, ^{13}C NMR: 151 MHz) spectrometer and Varian 400-MR ASW (^{1}H NMR: 400 MHz, ^{13}C NMR: 100 MHz) spectrometer, and chemical shifts are expressed in ppm (δ) using residual undeuterated solvent as an internal reference ($CDCl_3$, ^{1}H NMR: δ 7.25, ^{13}C NMR: δ 77.1). The following abbreviations were used to explain NMR peak multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, sep = septet, m = multiplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, br = broad; coupling constants in Hz; integration. Reactions were monitored by thin layer chromatography (TLC) carried out on a silica gel plates (60F-254) and visualized under UV illumination at 254 or 365 nm depending on the compounds. Flash column chromatography was performed on silica gel (WAKO Gel 75–150 mesh, WAKO Co., Ltd., Tokyo, Japan).

2.1. General Procedure for Synthesis of NMeOINs [54,55]

A solution with the indoline (2 mmol) and $Na_2WO_4 \cdot 2H_2O$ (0.1 mmol, 0.05 eq) in MeOH (6 mL) and H_2O (0.6 mL) was cooled to 0 °C. A total of 30% H_2O_2 (2.24 mL, 20 mmol) was added dropwise. The mixture was stirred for 5–10 min at room temperature. Then, $(MeO)_2SO_2$ (6 mmol, 3 eq) and K_2CO_3 (10 mmol, 5 eq) was added to the reaction mixture and stirred until the complete disappearance of *N*-hydroxyindolines indicated by TLC. After H_2O (20 mL) was added to the mixture, the whole was extracted with AcOEt (3 × 20 mL), washed with brine (20 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (AcOEt/hexane = 1/20–1/5) to give 1.

*5-Methyl-1-methoxyindole (**1b**):* 167 mg, 52% yield. colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.43 (d, *J* = 6.0 Hz, 1H), 7.40–7.37 (m, 1H), 7.25 (d, *J* = 3.0 Hz, 1H), 7.14–7.11 (m, 1H), 6.31 (d, *J* = 3.0 Hz, 1H), 4.09 (s, 3H), 2.49 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 130.4, 129.3, 124.7, 124.1, 123.2, 120.9, 108.1, 97.6, 65.8, 21.5; HRMS (ESI) *m/z*: 162.0920 (Calcd for $C_{10}H_{12}NO$ $[M + H]^+$: 162.0919).

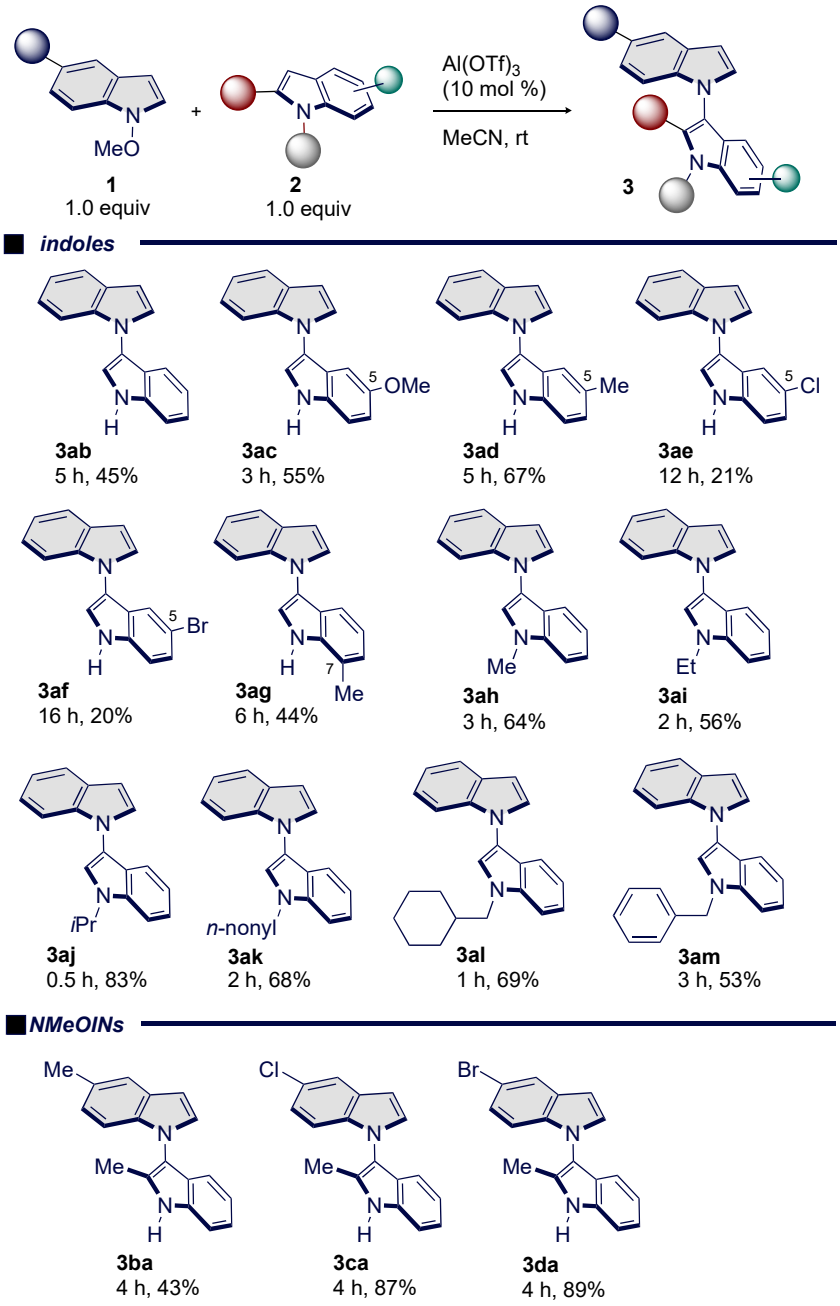
*5-Chloro-1-methoxyindole (**1c**):* 184 mg, 51% yield. colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.56 (d, *J* = 2.0 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.29 (d, *J* = 3.6 Hz, 1H), 7.20 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.31 (d, *J* = 3.6 Hz, 1H), 4.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 130.2, 125.6, 125.1, 124.2, 122.6, 120.5, 109.3, 97.6, 65.9; HRMS (ESI) *m/z*: 182.0373, 184.0344 (Calcd for C_9H_9ClNO $[M + H]^+$: 182.0373, 184.0343).

*5-Bromo-1-methoxyindole (**1d**):* 230 mg, 51% yield. colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.71 (s, 1H), 7.31–7.31 (m, 2H), 7.25–7.25 (m, 1H), 6.29 (d, *J* = 3.6 Hz, 1H), 4.07 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ:130.5, 125.9, 125.3, 124.1, 123.7, 113.2, 109.7, 97.6, 66.2; HRMS (ESI) *m/z*: 225.9867, 227.9847 (Calcd for C_9H_9rNO $[M + H^+$: 225.9868, 227.9847).

2.2. General Procedure for Synthesis of 1′H-1,3′-Biindole Derivatives (Scheme 3)

To a solution of 1a (1 mmol) and 2 (1 mmol, 1 eq) in MeCN (10 mL, 0.1 M) was added $Al(OTf)_3$ (0.1 mmol, 10 mol%) at room temperature. The mixture was stirred until the complete disappearance of starting material indicated by TLC. After H_2O (20 mL) was added to the mixture, the whole was extracted with AcOEt (3 × 20 mL), washed with brine (20 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (AcOEt/hexane = 1/20–1/5) to give 3.

*1,3′-Bisindole (**3ab**):* 105 mg, 45% yield. colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.17 (br s, 1H), 7.73–7.71 (m, 1H), 7.49–7.45 (m, 2H), 7.37–7.28 (m, 4H), 7.21–7.13 (m, 3H), 6.71–6.70 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.5, 134.7, 129.6, 128.6, 123.7, 123.1, 122.0, 120.9, 120.5, 120.0, 119.2, 118.6, 117.6, 111.7, 110.9, 102.5; HRMS (ESI) *m/z*: 233.1079 (Calcd for $C_{16}H_{13}N_2$ $[M + H]^+$: 233.1079).



Scheme 3. Substrate scope.

2.3. General Procedure for Synthesis of Oligoindoles (Scheme 4)

To a solution of **1a** (53.0 mg, 0.36 mmol) and **3ah** (73.9 mg, 0.3 mmol) in MeCN (3 mL, 0.1 M) was added $Al(OTf)_3$ (28.5 mg, 0.06 mmol) under reflux. The mixture was stirred until the complete disappearance of starting material indicated by TLC. After H_2O (10 mL) was added to the mixture, the whole was extracted with AcOEt (3 × 10 mL), washed with brine (10 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (AcOEt/hexane = 1/20–1/5) and PTLC (acetone/hexane = 1/5) to give **3ah** (24.4 mg, 33% yield), 4 (16.3 mg, 15% yield), 5 (7.2 mg, 5% yield) and 6 (1.0 mg, 1% yield).

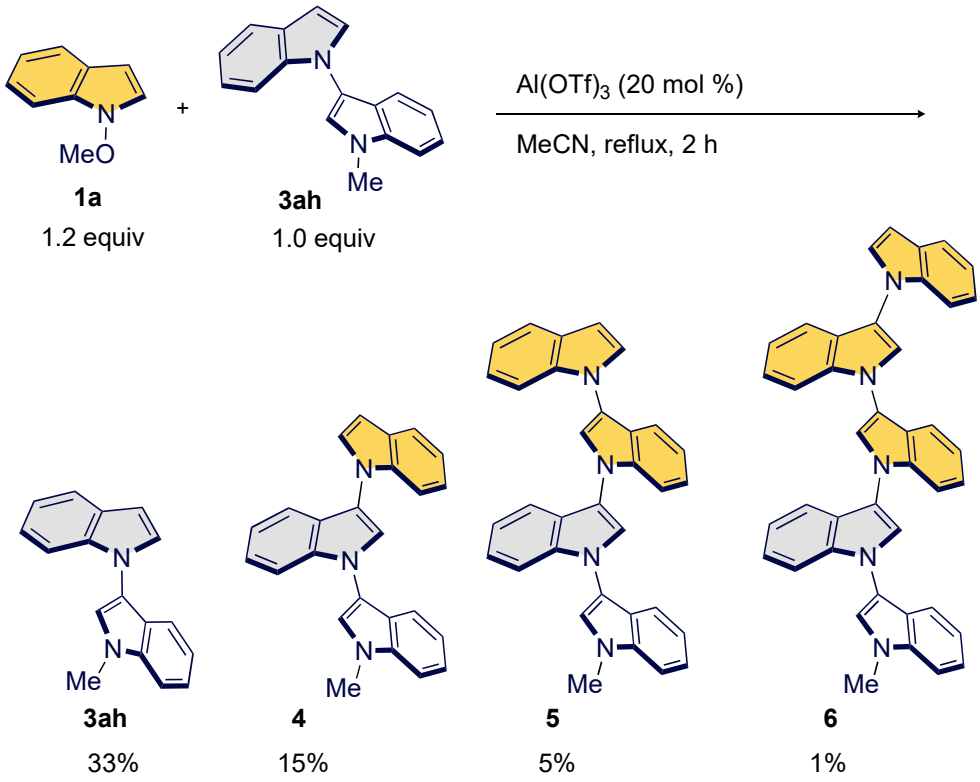
*1″-Methyl-1,3′:1′,3″-terindole (**4**):* 16.3 mg, 15% yield. colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.73 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.57–7.53 (m, 3H), 7.48–7.42 (m, 4H), 7.37–7.34 (m, 2H), 7.26 (ddd, *J* = 7.8, 6.6, 1.2 Hz, 1H), 7.22–7.16 (m, 4H), 6.73 (dd, *J* = 3.0, 1.2 Hz, 1H), 3.92 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ:137.5, 136.6, 135.7, 129.7, 128.7, 124.5, 124.2, 124.1,

124.1, 123.1, 123.0, 122.1, 120.9, 120.6, 120.4, 120.0, 118.8, 118.6, 117.5, 115.3, 111.5, 111.0, 109.9, 102.6, 33.3; HRMS (ESI) *m/z*: 362.1658 (Calcd for $C_{25}H_{20}N_3$ $[M + H]^+$: 362.1657).

*1‴-Methyl-1,3′:1′,3″:1″,3‴-quaterindole (**5**):* 7.2 mg, 5% yield. colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.73 (d, *J* = 7.8 Hz, 1H), 7.66 (s, 1H), 7.63 (s, 1H), 7.62 (d, *J* = 7.8 Hz, 1H), 7.58–7.53 (m, 3H), 7.50–7.44 (m, 4H), 7.37–7.34 (m, 2H), 7.31–7.27 (m, 2H), 7.24–7.16 (m, 5H), 6.73 (dd, *J* = 3.0, 0.6 Hz, 1H), 3.93 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ: 137.5, 136.6, 136.5, 135.7, 129.7, 128.7, 124.7, 124.3, 124.1, 124.1, 123.4, 123.2, 123.1, 122.1, 120.9, 120.7, 120.4, 120.1, 118.8, 118.6, 117.6, 116.7, 115.2, 111.6, 111.5, 111.0, 110.0, 102.6, 33.3; HRMS (ESI) *m/z*: 477.2075 (Calcd for $C_{33}H_{25}N_4$ $[M + H]^+$: 477.2079).

*1⁗-Methyl-1,3′:1′,3″:1″,3‴:1‴,3⁗:1⁗,3⁗′-quinqueindole (**6**):* 1.0 mg, 1% yield. colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.76 (s, 1H), 7.74 (d, *J* = 7.8 Hz, 1H), 7.69 (s, 1H), 7.66–7.64 (m, 3H), 7.60–7.59 (m, 3H), 7.56–7.51 (m, 2H), 7.49–7.46 (m, 3H), 7.39–7.29 (m, 6H), 7.24–7.17 (m, 5H), 6.74 (d, *J* = 3.0 Hz, 1H), 3.95 (s, 3H); HRMS (ESI) *m/z*: 592.2505 (Calcd for $C_{41}H_{30}N_5$ $[M + H]^+$: 592.2501).

Detailed synthetic procedure and corresponding analytic data can be found in the Supplementary Materials.



Scheme 4. Oligomerization.

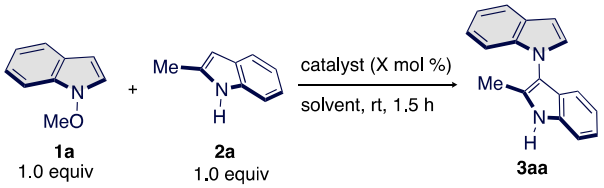
3. Results and Discussion

3.1. Optimization of Reaction Conditions

To investigate the feasibility of the envisaged S_NAr reaction, we select N-methoxyindole (NMeOIN, **1a**) and 2-methylindole (**2a**) as model substrates for optimization. Initially, **1a** and **2a** were reacted in the presence of $In(OTf)_3$ [47] in MeCN at room temperature for 1.5 h (Table 1, run 1). We were gratified to observe that the use of indium catalyst enabled our proposed reactivity, leading to C3-N1′ bisindole **3aa** in 72% yield. From the catalysts tested ($InF{\cdot}3H_2O$, $InBr_3$, $InCl_3{\cdot}4H_2O$, $Ga(OTf)_3$, $La(OTf)_3$, $Bi(OTf)_3$, AgOTf, $Yb(OTf)_3$, $Cu(OTf)_2$, $Zn(OTf)_2$, and $Al(OTf)_3$) (runs 2–12), $In(OTf)_3$, $Ga(OTf)_3$, $Bi(OTf)_3$, $Cu(OTf)_2$, and $Al(OTf)_3$) [50,51] were found to promote the reaction quite well, affording the C3-N1′ bisindole **3aa** in 72%, 79%, 60%, 72%, and 83 % yields, respectively. The highest isolated yield 87% was obtained from the reaction with $Al(OTf)_3$ (run 12). Among the aluminum

catalysts ($Al(OTf)_3$, $AlCl_3$, and $Al(OiPr)_3$), $Al(OTf)_3$ proved to be the best catalyst (runs 12–14). Next, to investigate the effect of the solvent with $Al(OTf)_3$, additional optimization was performed (runs 15–17). To our surprise, different solvents showed a notable effect on the $Al(OTf)_3$-catalyzed reaction. Chlorobenzene (PhCl) showed the same effects as $CHCl_3$ (runs 15 and 17), while 1,4-dioxane led to low conversion (run 16). When performed in the presence of TfOH, the reaction gave **3aa** in 54% yield (run 18). Finally, the reaction failed to proceed in the absence of catalyst or solvent (runs 19 and 20). In our cases, $Al(OTf)_3$ could not be recovered after the reactions [51]. Based on the above results, the optimized reaction conditions were determined (10 mol% of $Al(OTf)_3$, MeCN, and room temperature).

Table 1. Optimization of reaction conditions.



1a 1.0 equiv | **2a** 1.0 equiv | **3aa**

Run [1]	Catalyst	Solvent	Time (h)	Yield (%) of 3aa [2]
1	$In(OTf)_3$	MeCN	1.5	72
2	$InF_3{\cdot}3H_2O$	MeCN	1.5	14
3	$InBr_3$	MeCN	1.5	18
4	$InCl_3{\cdot}4H_2O$	MeCN	1.5	8
5	$Ga(OTf)_3$	MeCN	1.5	79
6	$La(OTf)_3$	MeCN	1.5	31
7	$Bi(OTf)_3$	MeCN	1.5	60
8	AgOTf	MeCN	1.5	15
9	$Yb(OTf)_3$	MeCN	1.5	0
10	$Cu(OTf)_2$	MeCN	1.5	72
11	$Zn(OTf)_2$	MeCN	1.5	7
12	**$Al(OTf)_3$**	**MeCN**	**1.5**	**83 (87) [3]**
13	$AlCl_3$	MeCN	1.5	23
14	$Al(O\text{-}iPr)_3$	MeCN	1.5	9
15	$Al(OTf)_3$	PhCl	1.5	69
16	$Al(OTf)_3$	1,4-dioxane	1.5	43
17	$Al(OTf)_3$	$CHCl_3$	1.5	71
18	TfOH	MeCN	1.5	54
19	—	MeCN	24	nr
20	$Al(OTf)_3$	—	24	0

[1] **1a** (0.1 mmol), **2a** (0.1 mmol), and catalyst (0.001 × X mmol) in solvent (5 mL). [2] NMR yields. [3] Isolated yields.

3.2. Scope and Limitations

With the optimized reaction conditions in hand, we investigated a range of indoles **2** and NMeOIN **1a** to assess the generality of this transformation (Scheme 3). Unsubstituted indole afforded bisindole **3ab** in 45% yield. The presence of electron-withdrawing group was found to have a negative influence on the reaction (**3ac**, **3ad**, **3ag** vs. **3ae**, **3af**), which might be due to the lack of nucleophilicity. Next, we focused on the reactivity of *N*-substituted indoles. *N*-Methylindole reacted well with NMeOIN **1a** yielding product **3ah** in 64% yield. Further investigations revealed that some N-alkylindoles were applicable to deliver the N-alkylated bisindoles bearing the ethyl (**3ai**), isopropyl (**3aj**), *n*-nonyl (**3ak**), and cyclohexylmethylene (**3al**) groups. Additionally, the reaction of benzyl-substituted indole afforded **3am** in 53% yield. However, the reaction of Ts-indole with **1a** resulted in no reaction due to its low nucleophilicity.

The scope of the NMeOIN **1** was also investigated. With the electro-donating group attached to the indole-ring, the reaction proceeded smoothly, leading to **3ba** in 45% yield. Interestingly, in contrast to **3ba**, the presence of electron-withdrawing group attached to the

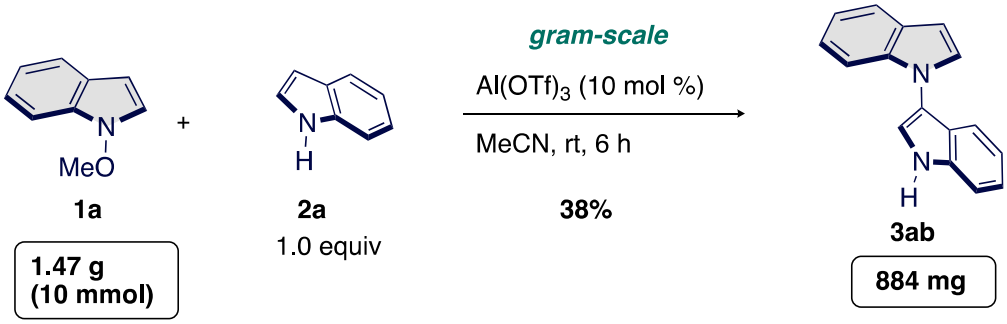
indole-ring was found to have a positive effect, increasing in yields (**3ca**: 87%, **3da**: 89%). From the scope and limitation experiments, we conclude that this transformation is quite sensitive to substituents on the indole-ring. In addition, the preferential C3–N1′ reactivity of NMeOIN in all cases can be rationalized based on the both N-activated and C2–C3 deactivated abilities of $Al(OTf)_3$ toward **1a**. This observed selectivity can prove helpful in synthetic application such as C3–N1′-type bisindole alkaloids and polyindoles [13,14].

3.3. Synthesis of Oligoindoles

To probe the feasibility of a formation of oligoindoles, we tested the reaction of bisindole **3ah** with **1a** (Scheme 4). As construction of oligoindoles through C3–N1′ bond formation is unprecedented [56–59]; we hope this transformation will promote further progress in the material sciences [60–64]. After intensive investigations, we found that a reaction using 20 mol% of $Al(OTf)_3$ under reflux conditions plays a crucial role in delivering previously untapped C3–N1′ homologs such as trimer **4**, tetramer **5**, and pentamer **6** in one-pot protocol.

3.4. Scalability of the Aluminum-Catalyzed Cross Selective C3–N1′Cross-Coupling Reaction

Considering the potential synthetic utility, we next scaled-up synthesis of **3**. The synthesis of bisindole **3** could be scalable; as shown in Scheme 5, we efficiently prepared large quantities of a representative bisindole **3ab** from NMeOIN (10 mmol) with indole. Notably, our transformation could be scaled up to 10 mmol with an acceptable loss of efficiency for **3ab** (38% yield vs. 45% yield).



Scheme 5. Gram-scale synthesis of bisindole **3ab**.

As mentioned above, this is the first example that *N*-methoxyindoles showed unprecedented ambiphilic reactivity of N1-electrophile and C3-nucleophile triggered by σ-activation/π-deactivation [47–49]. Our protocol also expands the umpolung chemistry of indoles [52,53], thereby affording unprecedented construction of C3–N1′ polyindoles.

4. Conclusions

In conclusion, we have successfully developed a novel strategy that addresses the latent N-electrophilicity and intrinsic C3-nucleophilicity of *N*-methoxyindoles toward less well-developed C3–N1′ bond formation of bisindoles in the presence of Lewis acid. Given the C2–C3 deactivation/N–O activation protocol, our transformation was applicable to site-selective synthesis of C3–N1′ bisindoles and C3–N1′–C3′–N1″ triindoles. Importantly, these transformations could be achieved only with the aid of Lewis acid. Additionally, the C3–N1 oligomerization paves the way for further application in material sciences.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/chemistry5010033/s1, The Supplementary Materials contain detailed procedures for synthesis of compounds and analytical data including ^{1}H- and ^{13}C-NMR spectra.

Author Contributions: Conceptualization, T.A.; investigation, T.A.; resources, T.A.; visualization, T.A.; structures, T.A.; experiments, K.T., T.Y. and S.H.; writing—original draft preparation, T.A.; writing—review and editing, T.A. All authors have read and agreed to the published version of the manuscript.

Funding: This work was partly supported by JSPS KAKENHI (22K06503). This work was also supported by JST SPRING, Grant Number JPMJSP2126.

Data Availability Statement: Not applicable.

Acknowledgments: T.Y. thanks Nagai Memorial Research Scholarship from the Pharmaceutical Society of Japan.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Espejo, V.R.; Rainier, J.D. An expeditious synthesis of C(3)-N(1′) heterodimeric indolines. *J. Am. Chem. Soc.* **2008**, *130*, 12894–12895. [CrossRef]
2. Newhouse, T.; Baran, P.S. Total synthesis of (±)-psychotriamine. *J. Am. Chem. Soc.* **2008**, *130*, 10886–10887. [CrossRef]
3. Espejo, V.R.; Rainier, J.D. Total synthesis of kapakahine E and F. *Org. Lett.* **2010**, *12*, 2154–2157. [CrossRef]
4. Pérez-Balado, C.; de Lera, Á.R. Concise total synthesis and structural revision of (+)-pestalazine B. *Org. Biomol. Chem.* **2010**, *8*, 5179–5186. [CrossRef]
5. Foo, K.; Newhouse, T.; Mori, I.; Takayama, H.; Baran, P.S. Total synthesis of guided structure elucidation of (+)-psychotetramine. *Angew. Chem. Int. Ed.* **2011**, *50*, 2716–2719. [CrossRef]
6. Li, Q.; Xia, T.; Yao, L.; Deng, H.; Liao, X. Enantioselective and diastereoselective azo-coupling/iminium-cyclizations: A unified strategy for the total syntheses of (–)-psychotriasine and (+)-pestalazine B. *Chem. Sci.* **2015**, *6*, 3599–3605. [CrossRef]
7. Adhikari, A.A.; Chisholm, J.D. Lewis acid catalyzed displacement of trichloroacetamidates in the synthesis of functionalized pyrroloindolines. *Org. Lett.* **2016**, *18*, 4100–4103. [CrossRef]
8. Liu, C.; Yi, J.-C.; Xheng, Z.-B.; Tang, Y.; Dai, L.-X.; You, S.-L. Enantioselective synthesis of 3a-amino-pyrroloindolines by copper-catalyzed direct asymmetric dearomative amination of tryptamines. *Angew. Chem. Int. Ed.* **2016**, *55*, 751–754. [CrossRef]
9. Dai, J.; Xiong, D.; Yuan, T.; Liu, J.; Chen, T.; Shao, Z. Chiral primary amine catalysis for asymmetric Mannich reactions of aldehydes with ketimines: Stereoselectivity and reactivity. *Angew. Chem. Int. Ed.* **2017**, *56*, 12697–12701. [CrossRef]
10. Nelson, B.M.; Loach, R.P.; Schiesser, S.; Movassaghi, M. Concise total synthesis of (+)-asperazine A and (+)-pestalazine B. *Org. Biomol. Chem.* **2018**, *16*, 202–207. [CrossRef]
11. Gentry, E.C.; Rono, L.J.; Hale, M.E.; Matsuura, R.; Knowles, R.R. Enantioselective synthesis of pyrroloindolines via noncovalent stabilization of indole radical cations to the synthesis of alkaloid natural products. *J. Am. Chem. Soc.* **2018**, *140*, 3394–3402. [CrossRef] [PubMed]
12. Hakamata, H.; Ueda, H.; Tokuyama, H. Construction of indole structure on pyrroloindolines via $AgNTf_2$-mediated amination/cyclization cascade: Application to total synthesis of (+)-pestazine B. *Org. Lett.* **2019**, *21*, 4205–4209. [CrossRef] [PubMed]
13. Norton, R.S.; Wells, R.J. A series of chiral polybrominated biindoles from the marine blue-green alga *Rivularia firma*. Application of carbon-13 NMR spin-lattice relaxation data and carbon-13-proton coupling constants to structure elucidation. *J. Am. Chem. Soc.* **1982**, *104*, 3628–3635. [CrossRef]
14. Kubota, N.K.; Iwamoto, H.; Fukuzawa, Y.; Uchio, Y. Five new sulfur-containing polybrominated bisindoles from the red alga *Laurencia brongniartii*. *Heterocycles* **2005**, *65*, 2675–2682.
15. Liang, Z.; Zhao, J.; Zhang, Y. Palladium-catalyzed regioselective oxidative coupling of indoles and one-pot synthesis of acetoxylated biindolyls. *J. Org. Chem.* **2010**, *75*, 170–177. [CrossRef]
16. Li, Y.-X.; Ji, K.-G.; Wang, H.-X.; Ali, S.; Liang, Y.-M. Iodine-induced regioseletive C–C and C–N bonds formation of *N*-protected indoles. *J. Org. Chem.* **2011**, *76*, 744–747. [CrossRef]
17. Guo, T.; Han, S.-L.; Liu, Y.-C.; Liu, Y.; Liu, H.-M. Convenient synthesis of antiproliferative 2,3-dihydro-2,3′-bisindoles via dimerization of *N*–H indole derivatives. *Tetrahedron Lett.* **2016**, *57*, 1097–1099. [CrossRef]
18. Huang, P.; Peng, X.; Hu, D.; Liao, H.; Tang, S.; Liu, L. Regioselective synthesis of 2,3′-biindoles mediated by an NBS-induced homo-coupling of indoles. *Org. Biomol. Chem.* **2017**, *15*, 9622–9629. [CrossRef]
19. Yin, B.; Huang, P.; Lu, Y.; Liu, L. TEMPO-catalyzed oxidative homocoupling route to 3,2′-biindolin-2-ones via an indolin-3-one intermediate. *RSC Adv.* **2017**, *7*, 606–610. [CrossRef]
20. Benkovics, T.; Guzei, I.A.; Yoon, T.P. Oxaziridine-mediated oxyamination of indoles: An approach to 3-aminoindoles and enantiomerically enriched 3-aminopyrroloindolines. *Angew. Chem. Int. Ed.* **2010**, *49*, 9153–9157. [CrossRef]
21. Lee, D.J.; Yoo, E.J. Efficient synthesis of C–N-couped heterobiaryls by sequential N–H functionalization reactions. *Org. Lett.* **2015**, *17*, 1830–1833. [CrossRef] [PubMed]
22. Li, T.-R.; Cheng, B.-Y.; Wang, Y.-N.; Zhang, M.-M.; Lu, L.-Q.; Xiao, W.-J. A copper-catalyzed decarboxylative amination/hydroamination sequence: Switchable synthesis of functionalized indoles. *Angew. Chem. Int. Ed.* **2016**, *55*, 12422–12426. [CrossRef] [PubMed]

23. Yonekura, K.; Yoshimura, Y.; Akehi, M.; Tsuchimoto, T. A heteroarylamine library: Indium-catalyzed nucleophilic aromatic substitution of alkoxyheteroarenes with amines. *Adv. Synth. Catal.* **2018**, *360*, 1159–1181. [CrossRef]
24. Wang, Y.-H.; Tian, J.-S.; Tan, P.-W.; Cao, Q.; Zhang, X.-X.; Cao, Z.-Y.; Zhou, F.; Wang, X.; Zhou, J. Ragiodivergent intramolecular nucleophilic addition of ketimines for the diverse synthesis of azacycles. *Angew. Chem. Int. Ed.* **2020**, *59*, 1634–1643. [CrossRef] [PubMed]
25. Shan, X.-H.; Zheng, H.-X.; Yang, B.; Tie, L.; Fu, J.-L.; Qu, J.-P.; Kang, Y.-B. Copper-catalyzed oxidative benzylic C–H cyclization via iminyl radical from intermolecular anion-radical redox relay. *Nat. Commun.* **2019**, *10*, 908. [CrossRef] [PubMed]
26. Somei, M. 1-Hydroxyindoles. *Heterocycles* **1999**, *50*, 1157–1211. [CrossRef]
27. Somei, M. A frontier in indole chemistry: 1-Hydroxyindoles, 1-hydroxytryptamines, and 1-hydrxytryptophans. *Top. Heterocycl. Chem.* **2006**, *6*, 77–111.
28. Somei, M.; Yamada, F.; Hayashi, T.; Goto, A.; Saga, Y. Nucleophilic substitution reaction on the nitrogen of indole nucleus: Formation of 1-(indol-3-yl)indoles upon reaction of 1-hydroxyindoles with indole in formic acid. *Heterocycles* **2001**, *55*, 457–460. [CrossRef]
29. Hayashi, T.; Peng, W.; Nakai, Y.; Yamada, K.; Somei, M. Nucleophilic substitution reaction on the nitrogen of indole nucleus: A novel synthesis of 1-aryltryptamines. *Heterocycles* **2002**, *57*, 421–424.
30. Yamada, F.; Goto, A.; Peng, W.; Hayashi, T.; Saga, Y.; Somei, M. Nucleophilic substitution reaction at the 1-position of 1-hydroxytryptamine and -tryptophan derivatives. *Heterocycles* **2003**, *61*, 163–172.
31. O'Neil, L.G.; Bower, J.F. Electrophilic aminating agents in total synthesis. *Angew. Chem. Int. Ed.* **2021**, *60*, 25640–25666. [CrossRef] [PubMed]
32. Ye, Y.; Kim, S.-T.; Jeong, J.; Baik, M.-H.; Buchwald, S.L. CuH-Catalyzed enantioselective alkylation of indole derivatives with ligand-controlled regiodivergence. *J. Am. Chem. Soc.* **2019**, *141*, 3901–3909. [CrossRef] [PubMed]
33. Abe, T.; Suzuki, T.; Anada, M.; Matsunaga, S.; Yamada, K. 2-Hydroxyindoline-3-triethylammonium bromide: A reagent for formal C3-electrophilic reactions of indoles. *Org. Lett.* **2017**, *19*, 4275–4278. [CrossRef] [PubMed]
34. Abe, T.; Yamada, K. Dehydrative Mannich-type reaction for the synthesis of azepinobisindole alkaloid iheyamine A. *Org. Lett.* **2018**, *20*, 1469–1472. [CrossRef] [PubMed]
35. Abe, T.; Shimizu, H.; Takada, S.; Tanaka, T.; Yoshikawa, M.; Yamada, K. Double "open and shut" transformation of g-carbolines triggered by ammonium salts: One-pot synthesis of multiheterocyclic compounds. *Org. Lett.* **2018**, *20*, 1589–1592. [CrossRef]
36. Abe, T.; Satake, S.; Yamada, K. Biomimetic synthesis of iheyamine A from spirocyclic oxindoles. *Heterocycles* **2019**, *99*, 379–388. [CrossRef]
37. Abe, T.; Aoyama, S.; Ohmura, M.; Taniguchi, M.; Yamada, K. Revisiting furodiindolines: One-pot synthesis of furodiindolines using indole 2,3-epoxide surrogates and their synthetic applications. *Org. Lett.* **2019**, *21*, 3367–3371. [CrossRef]
38. Abe, T.; Yamada, K.; Nishi, T. Development and application of indole-2,3-epoxide surrogates. *J. Synth. Org. Chem.* **2020**, *78*, 597–607. [CrossRef]
39. Abe, T.; Yamashiro, T.; Hirao, S. A metal-, oxidant-, and fluorous solvent-free synthesis of a-indolylketones enabled by an umpolung strategy. *Chem. Commun.* **2020**, *56*, 10183–10186. [CrossRef]
40. Abe, T.; Noda, K.; Sawada, D. Synthesis of a-substituted indolylacetamide using acetonitriles as acetamide enolate equivalents through O-transfer reactions. *Chem. Commun.* **2021**, *57*, 7493–7496. [CrossRef]
41. Yamashiro, T.; Abe, T.; Tanioka, M.; Kamino, S.; Sawada, D. *cis*-3-Azido-2-methoxyindolines as safe and stable precursors to overcome he instability of fleeting 3-azidoindoles. *Chem. Commun.* **2021**, *57*, 13381–13384. [CrossRef] [PubMed]
42. Yamashiro, T.; Abe, T.; Sawada, D. Synthesis of 2-monosubstituted indolin-3-ones by *cine*-substitution of 3-azido-2-methoxyindolines. *Org. Chem. Front.* **2022**, *9*, 1897–1903. [CrossRef]
43. Abe, T.; Yamashiro, T.; Shimizu, K.; Sawada, D. Indole editing enabled by HFIP-mediated ring-switch reactions of 3-amino-2-hydroxyindolines. *Chem. Eur. J.* **2022**, *28*, e202201113. [CrossRef] [PubMed]
44. Abe, T.; Nakajima, R.; Yamashiro, T.; Sawada, D. First total synthesis of reassigned echinosulfonic acid D. *J. Nat. Prod.* **2022**, *85*, 2122–2125. [CrossRef] [PubMed]
45. Hirao, S.; Yamashiro, T.; Kohira, K.; Mishima, N.; Abe, T. 2,3-Dimethoxyindolines: A latent electrophile for S_NAr reactions triggered by indium catalysts. *Chem. Commun.* **2020**, *56*, 5139–5142. [CrossRef]
46. Abe, T.; Hirao, S. Rapid access to indole-fused bicyclo[2.2.2]octanones by merging the umpolung strategy and molecular iodine as a green catalyst. *Chem. Commun.* **2020**, *56*, 5139–5142. [CrossRef]
47. Sestelo, J.P.; Sarandeses, L.A.; Martínez, M.M.; Alonso-Marañón, L. Indium(III) as p-acid catalyst for the electrophilic activation of carbon-carbon unsaturated systems. *Org. Biomol. Chem.* **2018**, *16*, 5733–5747. [CrossRef]
48. Shen, Z.-L.; Wang, S.-Y.; Chok, Y.-K.; Xu, Y.-H.; Loh, T.-P. Organoindium reagents: The preparation and application in organic synthesis. *Chem. Rev.* **2013**, *113*, 271–401. [CrossRef]
49. Zhao, K.; Shen, L.; Shen, Z.-L.; Loh, T.-P. Transition metal-catalyzed cross-coupling reactions using organoindium reagents. *Chem. Rev.* **2017**, *46*, 586–602. [CrossRef]
50. Gohain, M.; Marais, C.; Bezuidenhoudt, C.B. An $Al(OTf)_3$-catalyzed environmentally benign process for the propargylation of indoles. *Tetrahedron Lett.* **2012**, *53*, 4704–4707. [CrossRef]
51. Ajvazi, N.; Stavber, S. Alcohols in direct carbon-carbon and carbon-heteroatom bond-forming reactions: Recent advances. *Arkivoc* **2018**, *2018*, 288–329. [CrossRef]

52. Bandini, M. Electrophilicity: The "dark-side" of indole chemistry. *Org. Biomol. Chem.* **2013**, *11*, 5206–5212. [CrossRef] [PubMed]
53. Cerveri, A.; Bandini, M. Recent advances in the catalytic functionalization of "electrophilic" indoles. *Chin. J. Chem.* **2020**, *38*, 287–294. [CrossRef]
54. Kawasaki, T.; Kodama, A.; Nishida, T.; Shimizu, K.; Somei, M. Preparation of 1-hydroxyindole derivatives and a new route to 2-substituted indoles. *Heterocycles* **1991**, *32*, 221–227.
55. Vo, Q.V.; Trenerry, C.; Rochfort, S.; Wadespm, J.; Leyton, C.; Hughes, A.B. Synthesis and anti-inflammatory activity of indole glucosinolates. *Bioorg. Med. Chem.* **2014**, *22*, 856–864. [CrossRef]
56. Pezzella, A.; Panzella, L.; Natangelo, A.; Arzillo, M.; Napolitano, A.; d'Ischia, M. 5,6-Dihydroxyindole tetramers with "anomalous" interunit bonding patterns by oxidative coupling of 5,5′,6,6′-tetrahydroxy-2,7′-biindolyl: Emerging complexities on the way toward an improved model of eumelanin build up. *J. Org. Chem.* **2007**, *72*, 9225–9230. [CrossRef] [PubMed]
57. Arzillo, M.; Pezzella, A.; Crescezi, O.; Napolitano, A.; Land, E.J.; Barone, V.; d'Ischia, M. Cyclic structural motifs in 5,6-dihydroxyindole polymerization uncovered: Biomimetic modular buildup of a unique five-membered macrocycle. *Org. Lett.* **2010**, *12*, 3250–3253. [CrossRef]
58. Chen, C.-T.; Chuang, C.; Cao, J.; Ball, V.; Ruch, D.; Buehler, M.J. Excitonic effects from geometric order and disorder explain broadband optical absorption in eumelanin. *Nat. Commun.* **2014**, *5*, 3859. [CrossRef]
59. Jamison, C.R.; Badillo, J.J.; Lipshultz, J.M.; Comito, R.J.; MacMillan, D.W.C. Catalyst-controlled oligomerization for the collective synthesis of polypyrroloindoline natural products. *Nat. Chem.* **2017**, *9*, 1165–1169. [CrossRef]
60. Chang, K.-J.; Kang, B.-N.; Lee, M.-H.; Jeong, K.-S. Oligoindole-based foldamers with a helical conformation induced by chloride. *J. Am. Chem. Soc.* **2005**, *127*, 12214–12215. [CrossRef]
61. Wu, J.; Zhou, W.; Jiang, F.; Chang, Y.; Zhou, Q.; Li, D.; Ye, G.; Li, C.; Nie, G.; Xu, J.; et al. Three-dimensional porous carbon derived from polyindole hollow nanospheres for high-performance supercapacitor electrode. *ACS Appl. Energy Mater.* **2018**, *1*, 4572–4579. [CrossRef]
62. Bürger, M.; Ehrhardt, N.; Barber, T.; Ball, L.T.; Namyslo, J.C.; Jones, P.G.; Werz, D.B. Phosphine-catalyzed aryne oligomerization: Direct access to a,w-bisfunctionalized oligo(*ortho*-arylenes). *J. Am. Chem. Soc.* **2021**, *143*, 16796–16803. [CrossRef] [PubMed]
63. Boknevitz, K.; Darrigan, C.; Chrostowska, A.; Liu, S.-Y. Cation–p binding ability of BN indole. *Chem. Commun.* **2020**, *56*, 3749–3752. [CrossRef] [PubMed]
64. Chang, G.; Wang, Y.; Wang, C.; Li, Y.; Xu, Y.; Yang, L. A recyclable hydroxyl functionalized polyindole hydrogel for sodium hydroxide extraction via the synergistic effect of cation-p interactions and hydrogen boning. *Chem. Commun.* **2018**, *54*, 9785–9788. [CrossRef] [PubMed]