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Indium-Catalyzed Annulation of 2-Aryl- and 2-Heteroarylindoles with Propargyl Ethers: Concise Synthesis and Photophysical Properties of Diverse Aryl- and Heteroaryl-Annulated[*a*]carbazoles

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Abstract: Treatment of 2-aryl- and 2-heteroarylindoles with propargyl ethers in the presence of a catalytic amount of indium nonafluorobutanesulfonate [$In(ONf)_3$] gave aryl- and heteroaryl-annulated[*a*]carbazoles in good yields. The synthetically attractive feature is reflected by its applicability to a wide range of 2-aryl- and 2-heteroarylindoles. In the annulation reaction, propargyl ethers act as C3 sources ($HC{\equiv}C{-}CH_2OR$). Among these, two carbon atoms are incorporated into the product as members of a newly constructed aromatic ring and the remaining carbon atom forms a methyl group on the aromatic ring, where the methyl group is always located next to the C3 position of the indole nucleus. The methyl group can be easily removed through SeO_2 oxidation followed by decarbonylation with $RhCl(CO)(PPh_3)_2{-}Ph_2P(CH_2)_3PPh_2$ as a catalyst. The new annulation strategy is applicable also to symmetrical dimers such as bithiophene and bifuran derivatives. Mechanistic studies suggest that the first step is addition reaction initiated by regioselective nucleophilic attack of the C3 of 2-aryl- and 2-heteroarylindoles to the internal carbon atom of the C≡C bond in propargyl ethers. The next stage is ring-closing S_N2 process kicking out the alkoxy group and then aromatization via a 1,3-hydrogen shift is the final step. The two carbon−carbon bond-forming reactions achieved in one-pot contribute largely to the reduction in the number of steps for the synthesis of aryl- and heteroaryl-annulated[*a*]carbazoles. Furthermore, utilization of the Fischer indole synthesis for efficient supply of the substrates, 2-aryl- and 2-heteroarylindoles, is another important factor shortening the overall process. The development of the annulation with a wide substrate scope provided a unique opportunity to evaluate photophysical properties of a series of aryl- and heteroaryl-annulated[*a*]-carbazoles. Almost all the compounds evaluated in this study were found to emit purple to green light in the visible region. Some interesting structure−property correlations are also described.

1. Introduction

Aryl- and heteroaryl-annulated carbazoles (AHACs) have received considerable attention in view of their remarkable biological and pharmacological activities.[1] AHACs are classified into [*a*]-, [*b*]- and [*c*]-annulated carbazoles based on the position at which an aryl or a heteroaryl ring is fused to a carbazole nucleus (Chart 1). In the case of heteroaryl derivatives, each positional isomer is further sorted according to the mode of annulation, as exemplified by tetracyclic heteroaryl[2,3-*a*] and -[3,2-*a*]carbazoles. Among these derivatives, indolo[2,3-*a*]-carbazole alkaloids including tjipanazoles and staurosporine (**A**, **B** and **C** in Chart 1) are the most abundant. Actually, indolo[2,3-*a*]carbazoles with diverse biological activities,[1] such as antimicrobial,[2] antifungal[3] and antitumor[4] activities in addition to protein kinase C inhibitory action,[5] have appeared in the literature. Although other analogues are rather rare in nature,[6] a variety of synthetic compounds and some natural products have been targets of research because of their broad spectrum of potential applications. In this context, the first total syntheses of furostifoline,[7] furoclausine A[8] and eustifoline D[9] (**D**, **E** and

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§ Kyoto University.

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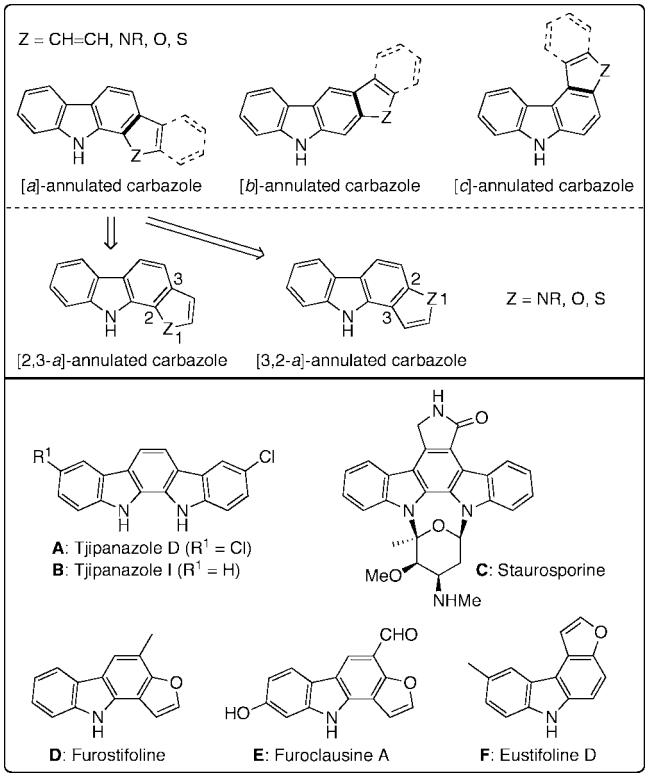
10.1021/ja803954e CCC: $40.75

Chart 1. Classification of AHACs[a] and Structural Examples of Indolo[2,3-*a*]-, Furo[3,2-*a*]- and Furo[2,3-*c*]carbazole Alkaloids

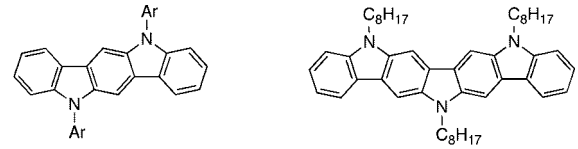


[a] Bold lines indicate the position of [*a*], [*b*] and [*c*] in a carbazole nucleus.

F in Chart 1) consisting of a furocarbazole framework have been accomplished by Knölker and co-workers and also Beccalli and co-workers.

On the other hand, applications of AHACs have recently been increasing in the field of material chemistry. In this regard, benzo[*a*]-, benzo[*c*]- and indolo[3,2-*b*]carbazoles have been utilized as molecular platforms for luminescent, hole-transporting and host materials in organic light-emitting diodes (OLEDs)

Chart 2. Structural Examples of Electroactive Indolocarbazoles



(**G** in Chart 2).[10] Benzofuro[2,3-*c*]oxazolocarbazoles are of interest as donor−acceptor π-conjugated fluorescent dyes.[11] The starburst monodisperse macromolecules with a diindolo[3,2-*a*:3′,2′-*c*]carbazole core have recently been synthesized as promising blue luminescent materials.[12] Moreover, *N,N*′-disubstituted indolo[3,2-*b*]carbazoles exhibit high performance as p-channel semiconductors (**H** in Chart 2).[13] As ladder-type molecules, diindolo[3,2-*b*:2′,3′-*h*]carbazoles with amphiphilic side chains have been shown to have potential for fabricating well-defined thin films (**I** in Chart 2).[14] Incorporation of indolo[3,2-*b*]carbazoles into a polymer chain and its effect on optical, electrochemical, magnetic and conductive properties have also been investigated.[15] Besides their organic electronic applications, indolo[2,3-*a*]carbazoles are important as anion sensors[16] and diindolo[3,2-*a*:3′,2′-*c*]carbazoles as liquid crystals.[17]

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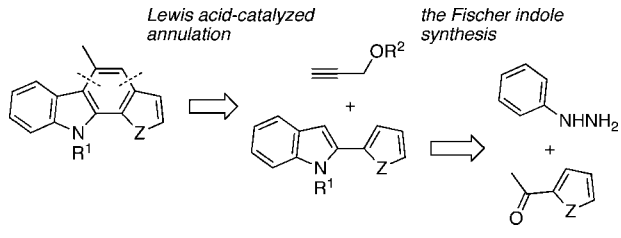
Obviously, AHACs play a vital role in a variety of aspects. However, a major concern as photoactive and electroactive materials has been poured into indolo[3,2-*b*]carbazole frameworks probably due to the structural accessibility. Scarcity of straightforward synthetic methods for other AHACs could potentially restrict their application. Therefore, development of convenient and practical synthetic routes for various aryl- and heteroaryl[*a*]carbazoles (AHA[*a*]Cs) surely opens up a further opportunity to utilize AHA[*a*]Cs as material sources. Although a vast amount of synthetic research on individual AHA[*a*]Cs has been performed so far,[1,18] only two strategies have been reported for synthesis of a variety of AHA[*a*]Cs to the best of our knowledge. Thus, Marchesini and co-workers have synthesized benzo[*a*]-, thieno[*a*]-, furo[3,2-*a*]-, benzofuro[3,2-*a*]-, pyrido[*a*]-, pyrrolo[3,2-*a*]- and indolo[2,3-*a*]carbazoles by photochemical cyclization of 3-(2-styryl)indole derivatives.[19] Photochemical cyclization of 3-indolyl-4-arylmaleimides or the Mizoroki−Heck-type cyclization of 3-indolyl-4-bromoarylmaleimides reported by Sanchez-Martinez and co-workers is another approach for synthesis of benzo[*a*]-, naphtho[*a*]-, tetrahydronaphtho[2,1-*a*]-, thieno[*a*]-, benzothieno[2,3-*a*]-, imidazolo[4,5-*a*]-, pyrido[*a*]- and 7-aza-indolo[2,3-*a*]carbazoles.[20] However, none of these examples that focus on biological research seem to provide suitable structures for material design.

Recently, we demonstrated that metal sulfonates such as indium triflate [$In(OTf)_3$, Tf = SO_2CF_3] are efficient catalysts for addition of arenes and heterocyclic arenes to alkynes,[21] where activation of C≡C bonds with metal sulfonates is crucial.[22,23] We have reported also that metal triflates catalyze alkylation of arenes with alcohols or acetals via activation of C−O bonds.[24] We thus envisaged that the metal sulfonate-catalyzed annulation of 2-aryl- and 2-heteroarylindoles with propargyl ethers through two successive carbon−carbon bond-forming reactions utilizing the activation of both the C≡C and C−O bonds in one-pot would lead to a short-step synthesis of various AHA[*a*]Cs. A variety of starting indoles are readily accessible through an established protocol such as the Fischer indole synthesis. The overview of our strategy is summarized in Scheme 1. Herein we report a new method for synthesis of a wide range of AHA[*a*]Cs utilizing an indium-catalyzed addition−substitution sequence of various 2-aryl- and 2-heteroarylindoles with propargyl ethers.[25] Furthermore, the development of the protocol with substrate versatility gave us an opportunity to understand the effect of frameworks and substituents on the optical properties of AHA[*a*]Cs.

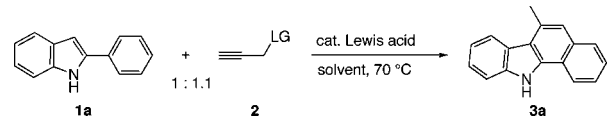
Scheme 1. Retrosynthetic Strategy for the Synthesis of AHA[*a*]Cs (Z = CH=CH, S, O, NH, NMe; R^1 = H, Me, aryl; R^2 = alkyl)



2. Results and Discussion

2.1. Optimization of Reaction Conditions. We first investigated the effect of Lewis acid catalysts (entries 1−9 of Table 1), solvents (entries 10−17) and leaving groups (LGs) at the propargylic position of propargyl alcohol derivatives **2** (entries 18−22) in the reaction of commercially available 2-phenylindole (**1a**). The use of 30 mol % of $In(OTf)_3$, which exhibited high performance for the activation of alkynes in the addition of arenes or heterocyclic arenes,[21] for the reaction of **1a** with methyl propargyl ether (**2a**, LG = OMe) in dibutyl ether (Bu_2O) at 70 °C for 72 h gave 6-methyl-11*H*-benzo[*a*]carbazole (**3a**)[26] in 62% yield (entry 1). This involves two successive inter- and intramolecular carbon−carbon bond-forming reactions. Replacing the catalyst with the corresponding nonaflate salt [$In(ONf)_3$, Nf = $SO_2C_4F_9$] accelerated the reaction and increased the yield up to 69% (entry 2). The higher activity of $In(ONf)_3$ should be due partially to the stronger Lewis acidity[27] based on the higher electron-withdrawing character of the ligand.[28] The other important factor is likely to be the superior solubility of $In(ONf)_3$ in Bu_2O, giving an almost homogeneous solution. A prolonged reaction period reduced the yield slightly, in spite of the complete consumption of **1a** (entry 3). With a lower loading of $In(ONf)_3$ (10 mol %), the annulation also proceeded but sluggishly (entry 4). In contrast to the promising activity of

Table 1. Lewis Acid-Catalyzed Annulation of 2-Phenylindole with Propargyl Alcohol Derivatives: Optimization of Reaction Conditions[a]



entry	Lewis acid	LG in **2**	solvent	time (h)	conv. (%)[b] of **1a**	yield (%)[b] of **3a**
1	$In(OTf)_3$	OMe (**2a**)	Bu_2O	72	78	62
2	**$In(ONf)_3$**	**OMe (2a)**	**Bu_2O**	**24**	**87**	**69**
3	$In(ONf)_3$	OMe (**2a**)	Bu_2O	35	>99	64
4	$In(ONf)_3$[c]	OMe (**2a**)	Bu_2O	120	68	53
5	$Sc(OTf)_3$	OMe (**2a**)	Bu_2O	24	1	<1
6	$Zr(OTf)_4$	OMe (**2a**)	Bu_2O	24	1	<1
7	$InCl_3$	OMe (**2a**)	Bu_2O	24	1	<1
8	BF_3•OEt_2	OMe (**2a**)	Bu_2O	24	1	<1
9	$TiCl_4$	OMe (**2a**)	Bu_2O	24	14	<1
10	$In(ONf)_3$	OMe (**2a**)	DME	24	3	1
11	$In(ONf)_3$	OMe (**2a**)	1,4-dioxane	24	1	<1
12	$In(ONf)_3$	OMe (**2a**)	MeCN	24	2	1
13	$In(ONf)_3$	OMe (**2a**)	$MeNO_2$	24	45	29
14	$In(ONf)_3$	OMe (**2a**)	$ClCH_2CH_2Cl$	24	53	50
15	**$In(ONf)_3$**	**OMe (2a)**	**PhCl**	**24**	**72**	**66**
16	$In(ONf)_3$	OMe (**2a**)	PhH	24	49	48
17	$In(ONf)_3$	OMe (**2a**)	methylcyclohexane	24	49	13
18	$In(ONf)_3$	OH	Bu_2O	24	96	56
19	$In(ONf)_3$	$OSiMe_3$	Bu_2O	24	94	27
20	$In(ONf)_3$	OCO_2Et	Bu_2O	24	84	23
21	$In(ONf)_3$	OCOBu	Bu_2O	24	82	29
22	$In(ONf)_3$	OSO_2Me	Bu_2O	24	67	16

[a] The reaction was carried out in a solvent (1.5 mL) at 70 °C using **1a** (0.10 mmol) and **2** (0.11 mmol) in the presence of a Lewis acid (30 μmol). [b] Determined by GC using *o*-dichlorobenzene as an internal standard. [c] $In(ONf)_3$ (10 μmol) was used.

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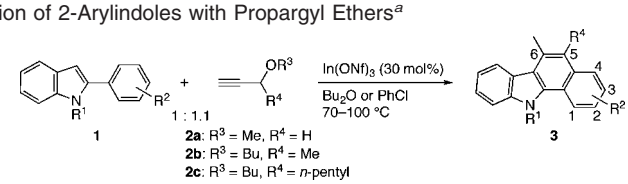
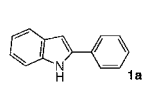
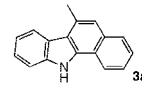
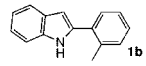
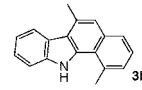
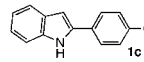
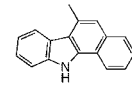
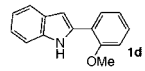
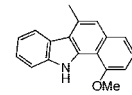
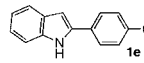
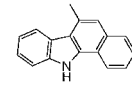
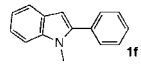
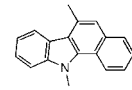
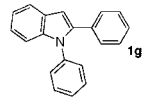
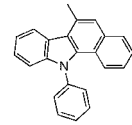
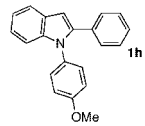
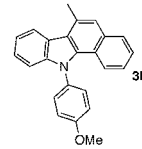
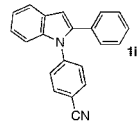
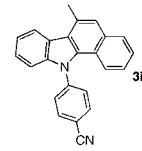
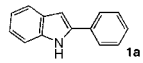
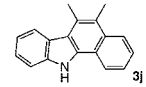
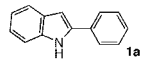
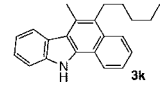
Table 2. In(ONf)$_3$-Catalyzed Annulation of 2-Arylindoles with Propargyl Ethers[a]



entry	2-arylindole **1**	propargyl ether **2**	solvent	time (h)	conv. (%) of **1**	product **3**	yield (%)[b] of **3**
1	 **1a**	**2a**	Bu_2O	24	91	 **3a**	65
2[c]	 **1b**	**2a**	PhCl	22	75	 **3b**	72
3[d]	 **1c**	**2a**	Bu_2O	11	78	 **3c**	67
4[d]	 **1d**	**2a**	Bu_2O	10	88	 **3d**	59
5[d]	 **1e**	**2a**	Bu_2O	45	90	 **3e**	48
6[e]	 **1f**	**2a**	Bu_2O	11	76	 **3f**	52
7	 **1g**	**2a**	PhCl	20	73	 **3g**	57
8[c]	 **1h**	**2a**	PhCl	60	64	 **3h**	60
9	 **1i**	**2a**	PhCl	85	80	 **3i**	48
10	 **1a**	**2b**	Bu_2O	18	77	 **3j**	68
11	 **1a**	**2c**	Bu_2O	20	82	 **3k**	74

[a] The reaction was carried out in Bu_2O or PhCl (3.0 mL) at 70 °C using **1** (0.20 mmol) and **2** (0.22 mmol) in the presence of In(ONf)$_3$ (60 μmol). [b] Isolated yield based on the 2-arylindole (**1**). [c] In PhCl (9.0 mL). [d] In Bu_2O (9.0 mL) at 100 °C. [e] In Bu_2O (9.0 mL).

indium sulfonates, triflates of other metals and halide salts were totally inactive (entries 5−9). The soft character of indium[29] is likely to contribute to the reliable activity of indium sulfonates, which shows strong affinity for soft Lewis bases such as the alkyne moiety in **2a** on the basis of the hard and soft acids and bases (HSAB) principle.[30]

With In(ONf)$_3$ as a catalyst, we next investigated the effect of solvents and found that less coordinating solvents such as Bu_2O and chlorobenzene (PhCl) were superior to strong

Chart 3. Incompatible Alkynes in the In(ONf)$_3$-Catalyzed Annulation Reaction.

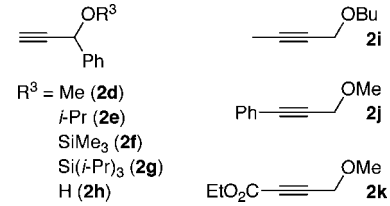
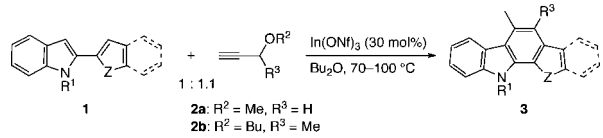
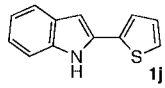
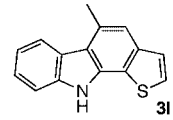
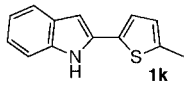
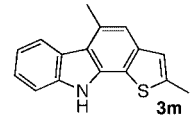
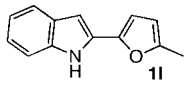
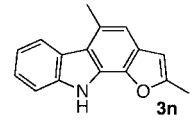
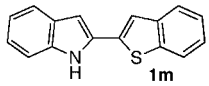
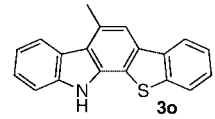
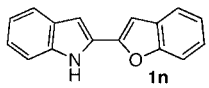
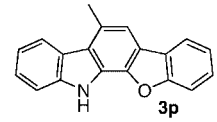
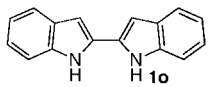
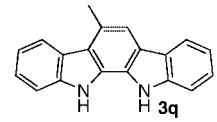
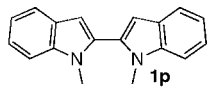
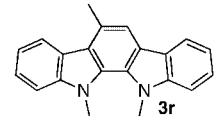
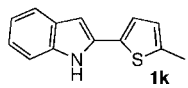
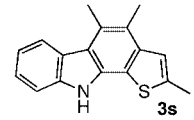


Table 3. In(ONf)$_3$-Catalyzed Annulation of 2-(2-Heteroaryl)indoles with Propargyl Ethers[a]



entry	2-heteroarylindole **1**	propargyl ether **2**	time (h)	conv. (%) of **1**	product **3**	yield (%)[b] of **3**
1	 **1j**	**2a**	25	80	 **3l**	70
2	 **1k**	**2a**	50	83	 **3m**	79
3	 **1l**	**2a**	8	61	 **3n**	57
4	 **1m**	**2a**	8	76	 **3o**	61
5	 **1n**	**2a**	40	87	 **3p**	60
6[c]	 **1o**	**2a**	24	73	 **3q**	54
7	 **1p**	**2a**	25	89	 **3r**	64
8	 **1k**	**2b**	110	84	 **3s**	74

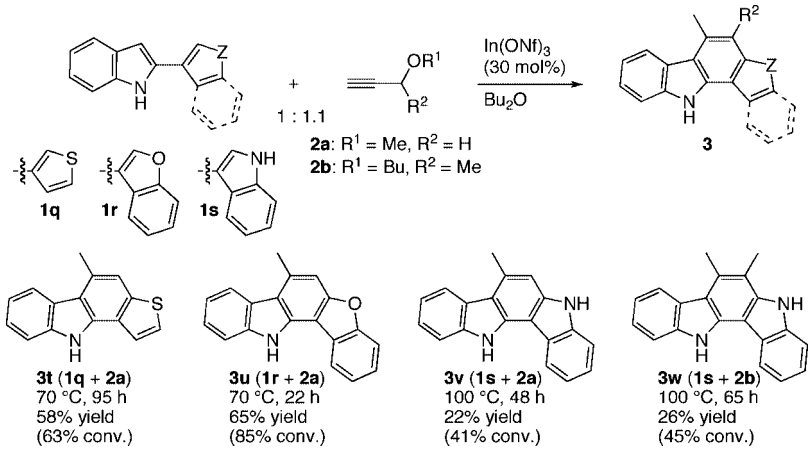
[a] The reaction was carried out in Bu_2O (3.0 mL) at 70 °C using **1** (0.20 mmol) and **2** (0.22 mmol) in the presence of In(ONf)$_3$ (60 μmol). [b] Isolated yield based on the 2-heteroarylindole (**1**). [c] At 100 °C.

coordinating solvents such as 1,2-dimethoxyethane (DME), 1,4-dioxane and acetonitrile (MeCN). Solvents of the latter type plausibly make In(ONf)$_3$ inactive by the coordination (entries 2 and 10−16). Methylcyclohexane, a noncoordinating and nonpolar solvent, was ineffective because of the low solubility of both In(ONf)$_3$ and substrate **1a** in the medium (entry 17).

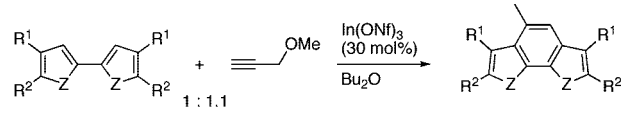
The yield of **3a** depends also on the nature of LGs in **2**. The reaction of **1a** with propargyl alcohol (LG = OH) gave **3a** in a moderate yield (entry 18). However, the use of 3-trimethylsilyloxy-1-propyne (LG = $OSiMe_3$) and propargyl electrophiles **2** having a good leaving functionality such as OCO_2Et, OCOBu or OSO_2Me resulted in a low yield albeit relatively high conversion of **1a**, as was confirmed by the formation of a considerable amount of unidentified oligomeric products including a moiety of **1a** and/or **2** (entries 19−22). These results show that **2a** with an alkoxy leaving group is the substrate of choice for the annulation.

2.2. Synthesis of Aryl-Annulated[*a*]carbazoles (AA[*a*]Cs). The optimized reaction conditions were applied to the synthesis of various AA[*a*]Cs (Table 2). Besides **1a**, 2-arylindoles **1b**−**1e** having a methyl, methoxy or hydroxy group on the phenyl group underwent the indium-catalyzed annulation with methyl propargyl

Scheme 2. In(ONf)$_3$-Catalyzed Synthesis of HA[3,2-*a*]Cs



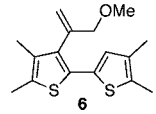
Scheme 3. In(ONf)$_3$-Catalyzed Annulation of Bithiophenes or a Bifuran with Methyl Propargyl Ether



4a: $R^1 = R^2$ = Me, Z = S
4b: R^1 = H, R^2 = Et, Z = S
4c: $R^1 = R^2$ = Me, Z = O

5a: $R^1 = R^2$ = Me, Z = S
5b: R^1 = H, R^2 = Et, Z = S
5c: $R^1 = R^2$ = Me, Z = O

4	time	temp.	conv. of 4	yield of 5
4a	2 h	90 °C	69%	40% (6: 13%)
4b	5 h	70 °C	46%	40%
4c	20 h	70 °C	76%	43%



6

ether (**2a**) to give the corresponding AA[*a*]Cs (**3b**−**3e**) in moderate to good yields (entries 1−5). With respect to the reaction of 2-(*o*-tolyl)indole (**1b**) in Bu_2O instead of PhCl, solvent Bu_2O itself reacted with **1b** to produce undesired 3-butyl-2-(*o*-tolyl)indole in 6% yield, along with 59% yield of **3b**. Therefore, in such cases, PhCl was used as a solvent in subsequent experiments. 2-Phenylindoles **1f**−**1i**[31] bearing an alkyl or aryl group with diverse electronic character on the nitrogen atom also reacted with **2a** to afford desired **3f**, **3g**, **3h** and **3i** (entries 6−9). Among these, 6,11-dimethyl-11*H*-benzo[*a*]carbazole (**3f**) reportedly exhibits a pronounced antitumor activity against leukemia, renal tumor, colon cancer and malignant melanoma tumor cell lines.[32] Remarkably, the indium-catalyzed annulation provides **3f** in only one step from commercially available **1f** and **2a**, in contrast to the five-step synthesis reported by Fürstner and co-workers.[18x] It is worth noting that the methyl group derived from **2a** is always located at the C6 of annulation products **3**. In addition to **2a**, propargyl ethers with an alkyl group at the propargylic position such as 3-butoxy-1-butyne (**2b**, R^3 = Bu, R^4 = Me) and 3-butoxy-1-octyne (**2c**, R^3 = Bu, R^4 = *n*-pentyl) participated in the annulation with **1a** in perfect regioselectivities (entries 10 and 11). On the other hand, the synthesis of **3a** having a phenyl group at the C5 could not be achieved successfully due to dominant oligomerization between **1a** and propargyl ether **2d**, **2e**, **2f**, **2g** or propargyl alcohol **2h** (Chart 3). No annulation proceeded in the reaction of **1a** with internal alkynes **2i**−**2k** (Chart 3).

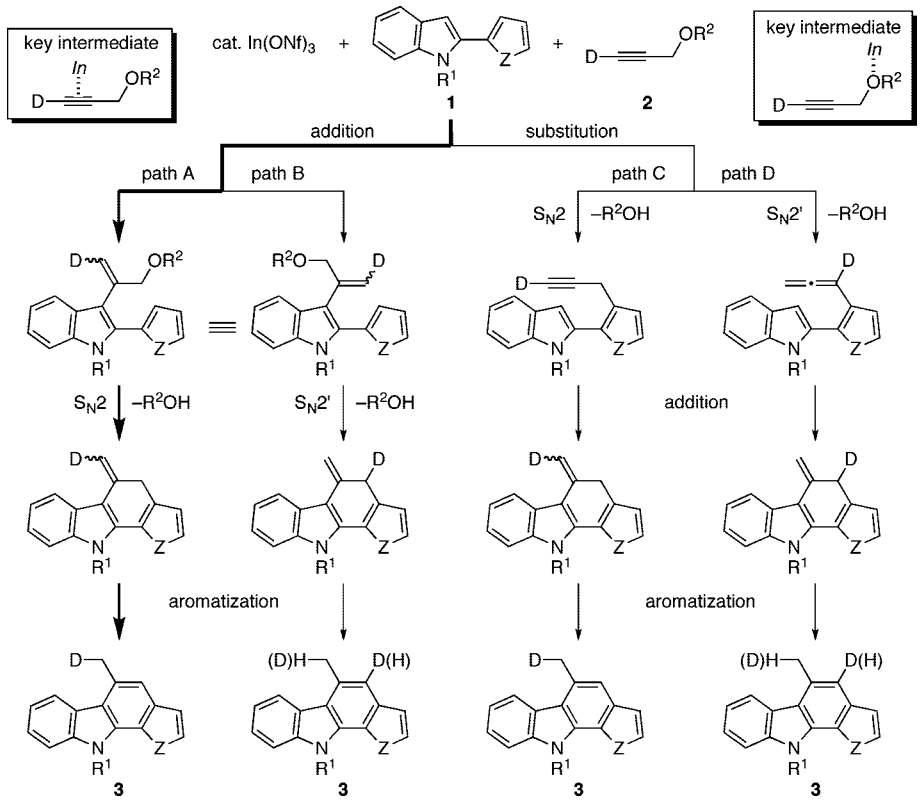
2.3. Synthesis of Heteroaryl-Annulated[2,3-*a*]carbazoles (HA[2,3-*a*]Cs). We next examined the annulation of 2-(2-heteroaryl)indoles **1j**−**1p** with propargyl ether **2a** or **2b** (Table 3). The treatment of 2-(2-thienyl)- and 2-(2-furyl)indoles **1j**−**1l** with methyl propargyl ether (**2a**) in Bu_2O in the presence of In(ONf)$_3$ as a catalyst brought about the formation of tetracyclic HA[2,3-*a*]Cs in 57−79% yields (entries 1−3). In spite of nucleophilic character of α-positions of thiophene,[33] no problematic side reactions were observed in the reaction of **1j**. However, application of our strategy to 2-(2-pyrrolyl)- and 2-(5-methyl-2-pyrrolyl)indole was unsuccessful; only a trace amount of the desired annulation products was produced due to low solubility of the substrates in Bu_2O. In contrast, a series of pentacyclic analogues **3o**−**3r** comprising two heterocyclic rings such as thiophene, furan or pyrrole were prepared successfully (entries 4−7). In these cases, no competing butylation of 2-(2-heteroaryl)indoles occurred even with Bu_2O as a solvent. Note that the perfect regioselectivities of the methyl groups were observed here again in all cases. The use of 3-butoxy-1-butyne (**2b**) instead of **2a** allowed us to introduce another methyl group onto a thieno[2,3-*a*]carbazole framework, giving **3s** in 74% yield (entry 8).

2.4. Synthesis of Heteroaryl-Annulated[3,2-*a*]carbazoles (HA[3,2-*a*]Cs). We found that the annulation protocol is compatible also with 2-(3-heteroaryl)indoles, being transformed into HA[3,2-*a*]Cs (Scheme 2). 2-(3-Thienyl)indole (**1q**) thus reacted with methyl propargyl ether (**2a**) to give 5-methyl-10*H*-thieno[3,2-*a*]carbazole (**3t**) as the sole product. To our delight, no [3,4-*a*]-isomer, which would be produced by the participation of the C4 atom instead of the C2 in the thienyl part, was observed at all. Benzofuro[3,2-*a*]carbazole **3u** was produced in 65% yield by the annulation between 2-(3-benzofuranyl)indole (**1r**) and **2a**. The reaction of 2,3′-biindolyl (**1s**)[34] with **2a** or **2b** also proceeded, albeit in a lower yield probably due to the low solubility of **1s** in Bu_2O.

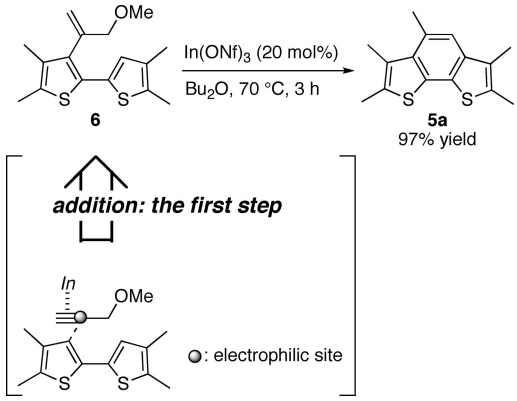
2.5. Application to Synthesis of Benzodiheteroarenes. In order to demonstrate further the potential of our method, we performed the annulation of symmetric dimers of heteroarenes leading to benzodiheteroarenes (Scheme 3), which also are important frameworks as electroactive materials.[35] Both 4,4′,5,5′-tetramethyl-2,2′-bithiophene (**4a**) and the diethyl analogue (**4b**) reacted with methyl propargyl ether (**2a**) under similar conditions to afford benzodithiophenes **5a** and **5b**, respectively.[36] In the reaction of **4a**, the formation of 1:1 adduct **6** was observed, which contributed to our understanding of the reaction mechanism (*vide infra*). Benzodifuran **5c** also was synthesized in 43% yield by the reaction of tetramethylbifuran **4c** with **2a**.[37]

2.6. Reaction Mechanism. In the present annulation, 2-(hetero)arylindoles **1** behave as nucleophiles, and the character of propargyl ethers **2** should be electrophilic through the coordination of the π-electrons of the C≡C bond or the lone pair of the oxygen atom to indium(III).[21,24] The fact that **2** loses one degree of

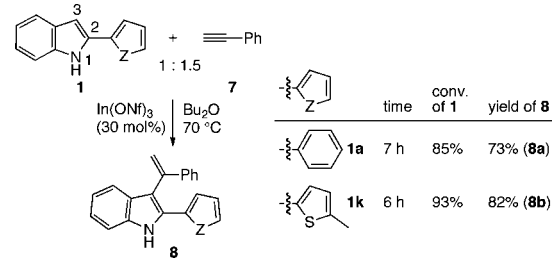
Scheme 4. Possible Reaction Mechanisms



Scheme 5. $In(ONf)_3$-Catalyzed Annulation of 1:1 Adduct **6**



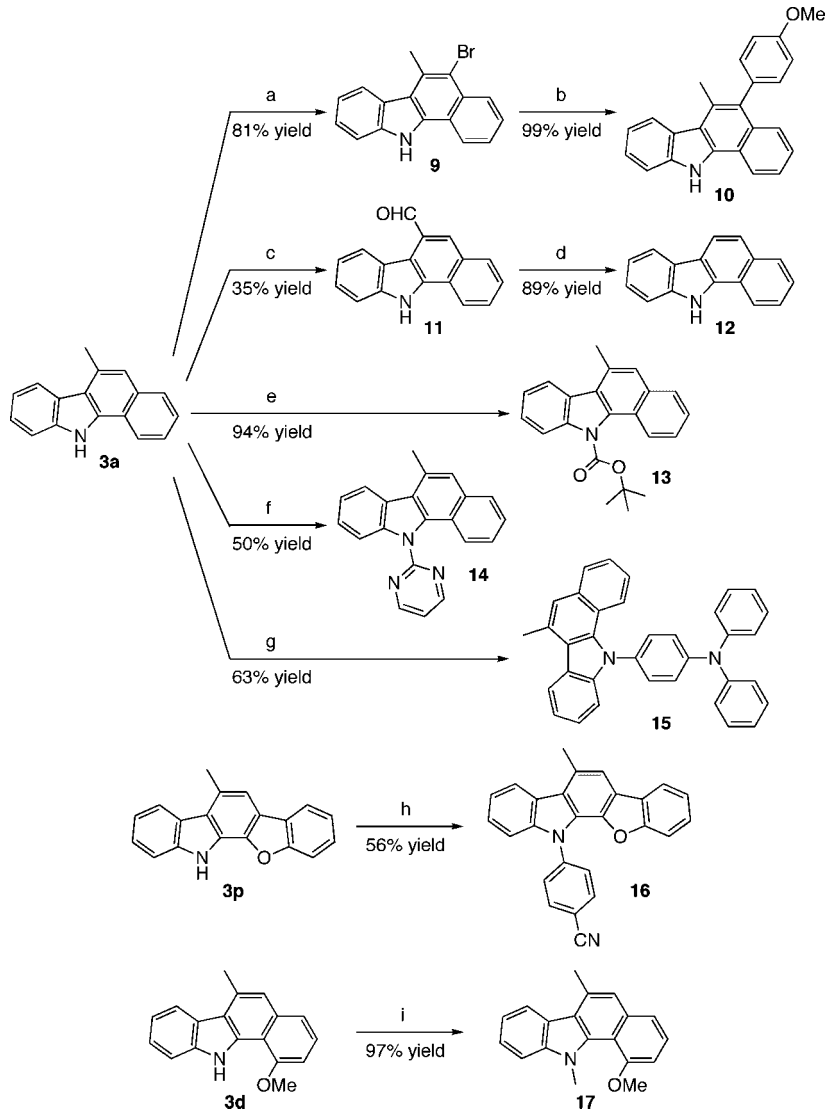
Scheme 6. $In(ONf)_3$-Catalyzed Addition of 2-Phenyl- or 2-(5-Methyl-2-thienyl)indole to Phenylacetylene



unsaturation and the alkoxy group through the annulation reaction strongly suggests that the reaction mechanism includes both addition and substitution as crucial steps. Taking into consideration that terminal alkynes such as **2** accept attack of arenes and heterocyclic arenes exclusively at the internal carbon atom of the C≡C bond[21] and that the S_N2 or S_N2' reaction takes place as the substitution process, we draw all possibilities leading to the same structure as **3** (Scheme 4). This is exemplified by the formation of tetracyclic AHA[*a*]Cs using deuterated propargyl ether **2**. In both paths A and B, the first step is the addition of the indolyl C3−H bond to the C≡C bond in a Markovnikov fashion, and the next stage is intramolecular S_N2 or S_N2' cyclization. In contrast, paths C and D start with the intermolecular S_N2 and S_N2' reactions, respectively, by the nucleophilic attack of the (hetero)aryl part of **1**, followed by the intramolecular addition. In all cases, isomerization of the resulting C=C bond via a 1,3-hydrogen shift, i.e., aromatization, is the final step.[38]

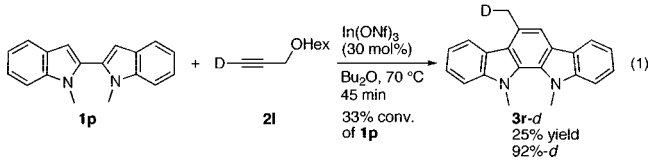
Some pieces of experimental observations are available to specify the most plausible route among paths A−D. We first focused on the result of the reaction of tetramethylbithiophene **4a** with methyl propargyl ether (**2a**) giving 1:1 adduct **6** and desired **5a** (Scheme 3), though no formation of 1:1 adducts was observed in the annulation of 2-(hetero)arylindoles. Thus, the treatment of **6** under milder conditions [20 mol % of $In(ONf)_3$, 70 °C] than those in Scheme 3 gave **5a** in an almost quantitative yield (Scheme 5).[39] This result implies the following: the 1:1 adduct **6** is an intermediate for **5a**, and thus the first step of the annulation is addition, and the internal carbon atom of the C≡C bond of **2** is the most electrophilic among the three possible electrophilic sites. Next, we carried out the indium-catalyzed reaction of **1** with phenylacetylene (**7**) and found that both **1a** and **1k** add to **7** at the C3 of the indole nucleus regioselectively (Scheme 6).[40] These results clearly show that the C3 position of **1** is the most nucleophilic to add to C≡C bonds, which reasonably excludes the possibilities of paths C and D starting with the nucleophilic attack by the (hetero)aryl ring. Therefore, it is reasonable to consider that the present annulation starts with the regioselective addition as in paths A and B. Among two possibilities, S_N2 (path A) or S_N2'(path B), after the addition process, the fact that the indium-catalyzed

Scheme 7. Transformation of AHA[*a*]Cs[a]



[a] Reagents and conditions: (a) NBS (1.0 equiv), $FeCl_3$ (30 mol %), CH_2Cl_2, 0 °C, 30 min; (b) 4-MeO–C_6H_4–$B(OH)_2$ (2.0 equiv), $Pd(PPh_3)_4$ (20 mol %), K_3PO_4 (3.0 equiv), DMF, 100 °C, 24 h; (c) SeO_2 (1.5 equiv), K_2CO_3 (0.5 equiv), pyridine, 115 °C, 19 h; (d) $RhCl(CO)(PPh_3)_2$ (10 mol %), $Ph_2P(CH_2)_3PPh_2$ (25 mol %), xylenes, 140 °C, 24 h; (e) $(Boc)_2O$ (2.0 equiv), DMAP (1.0 equiv), MeCN, rt, 5 h; (f) 2-Cl–pyrimidine (1.8 equiv), NaH (2.2 equiv), DMF, 130 °C, 25 h; (g) 4-Br–C_6H_4–NPh_2 (1.0 equiv), CuI (5.0 mol %), $MeHN(CH_2)_2NHMe$ (20 mol %), K_3PO_4 (2.1 equiv), toluene, 110 °C, 65 h; (h) 4-Br–C_6H_4–CN (1.0 equiv), CuI (20 mol %), $MeHN(CH_2)_2NHMe$ (40 mol %), K_3PO_4 (2.1 equiv), toluene, 110 °C, 60 h; (i) MeI (2.0 equiv), KOH (4.0 equiv), DMSO, rt, 2.5 h.

reaction of 2,2′-bis(*N*-methylindolyl) (**1p**) with 1-deuterio-3-hexyloxy-1-propyne (**2l**) gave **3r**-*d* with the deuterium atom exclusively at the methyl group supports the probability of path A (eq 1). Supposing that path B via S_N2' process works, the deuterium atom should be observed mainly on the aromatic ring, whereas a part of the deuterium atom may migrate onto the methyl group according to deuterium isotope effects through the aromatization.[41] Thus, path A proceeding in the order of addition, S_N2 cyclization and aromatization is concluded to be the most plausible pathway. It is noteworthy that high selectivities for the annulation should be attributed to the first contact of indium with C≡C bonds that triggers regioselective carbon−carbon bond formation.



(1)

2.7. Transformation of AHA[*a*]Cs.[42] The utility of our method can be enhanced by the synthetic application of AHA[*a*]Cs (Scheme 7). Regioselective mono-bromination of **3a** was chosen as the first application. After screening various conditions for bromination, we found that a bromine atom can be introduced exclusively at the C5 of **3a** using an *N*-bromosuccinimide (NBS)–$FeCl_3$ system.[43,44] The palladium-catalyzed cross-coupling reaction is highly useful for extending the π-system of bromide **9**. For example, the Suzuki−Miyaura cross-coupling of **9** with 4-methoxyphenylboronic acid gave **10** quantitatively.[45] SeO_2 oxidation[46] and rhodium-catalyzed decarbonylation[47] sequence enabled us to remove the methyl group of **3a**, giving 11*H*-benzo[*a*]carbazole (**12**).

We have demonstrated that the annulation of 2-(hetero)arylindoles having alkyl or aryl groups on the nitrogen atom proceeds efficiently (entries 6−9 of Table 2 and entry 7 of Table 3). In addition to the installation of these groups prior to the annulation, various organic functional groups were found to be

introduced successfully onto the nitrogen atom of AHA[*a*]Cs after the annulation. Thus, annulation product **3a** reacted with di-*tert*-butyl dicarbonate [$(Boc)_2O$] with the aid of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) to give **13** in a high yield.[48] The **3a**–Na complex prepared *in situ* from **3a** and NaH reacted with 2-chloropyrimidine through S_NAr process to give **14**.[49] The Buchwald *N*-arylation also worked well for the transformation of **3a** or **3p** to **15** or **16**, respectively.[31] Furthermore, the treatment of **3d** with MeI and KOH in DMSO gave *N*-methylated compound **17** in a high yield.[50] Such flexible behavior of AHA[*a*]Cs that accepts a variety of organic transformations is promising, for instance, for structural design in the case of their application to electroactive materials as shown in the next section.

2.8. Photophysical Properties of AHA[*a*]Cs. Because of the broad substrate diversity on the indium-catalyzed annulation, we were intensely interested in the potential of the AHA[*a*]Cs as electroactive materials. We therefore investigated the photophysical properties of the AHA[*a*]Cs; the results are collected in Table 4.

First, we focused on evaluating the effect of substituents on AA[*a*]Cs and HA[*a*]Cs. For example, in the UV−vis spectrum of 6-methyl-11*H*-benzo[*a*]carbazole (**3a**), the absorption bands ascribed to the $\pi-\pi^*$ transitions with the relatively large extinction coefficients were detected, ranging from 260 to 300 nm.[51] It was then found that **3a** ($\Phi_F = 0.165$) exhibits purple emission derived from the emission λ_{max} around 360−400 nm.[52] Although the absorption and emission patterns of **3b**, **3f**, **3j** and **3k** that have another alkyl group at the different position of **3a** resemble those of **3a**, the introduction of the alkyl group was always accompanied by a red-shift of the emission spectra regardless of the position of the alkyl group (**3a** vs **3b**, **3f**, **3j** or **3k**). A similar correlation was observed also between indolo[2,3-*a*]carbazoles **3q** and **3r**. Moreover, FL efficiency was found to be highly dependent on the methoxy group (**3a** vs **3c** or **3d**). Thus, though the Φ_F value of **3c** slightly decreased compared with that of **3a**, the installation of the methoxy group onto the C1 position resulted in higher Φ_F value. Comparisons between **3a** and the *N*-arylated derivatives (**3a** vs **3g**, **3h**, **15** or **3i**) also showed significant differences in photophysical properties. Phenyl and electron-rich aryl groups on **3a** (**3g**: –Ph, **3h**: $-C_6H_4$–*p*-OMe, **15**: $-C_6H_4$–*p*-NPh_2) made their absorption bands around 250−260 nm indefinite, whereas the corresponding band of **3i** having an aryl group with electron-deficient character ($-C_6H_4$–*p*-CN) was intensified. Furthermore, the structural change from **3a** to **3g**, **3h** or **15** resulted in a red-shift of the FL spectra and an increase in the FL quantum yield. Interestingly, the electron-deficient aryl group caused a drastic color change from purple to green light (**3a** vs **3i**, $\Delta\lambda_{max} = 92$ nm). The effect of $-C_6H_4$–*p*-CN holds true also for benzofuro[2,3-*a*]carbazole **3p**, where blue-emitting **16** was derived from purple-fluorescent **3p** (**3p** vs **16**, $\Delta\lambda_{max} = 51$ nm). Compound **14** with a

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Table 4. Photophysical Properties of AHA[*a*]Cs[a]

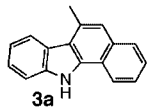
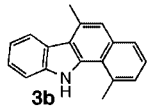
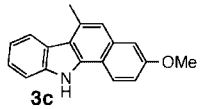
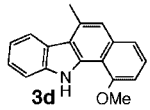
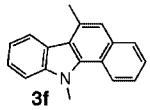
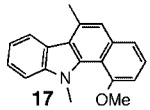
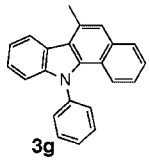
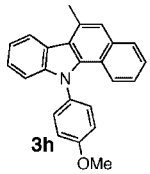
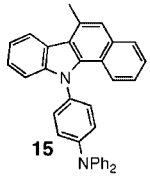
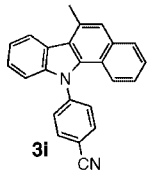
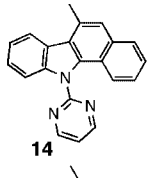
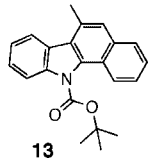
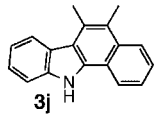
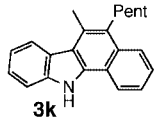
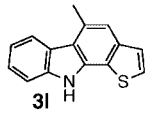
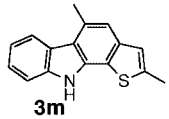
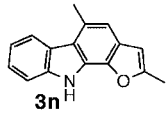
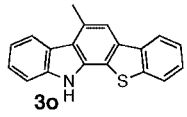
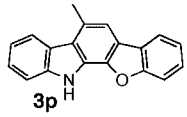
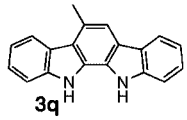
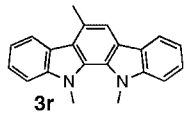
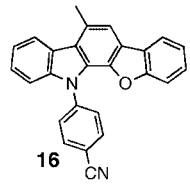
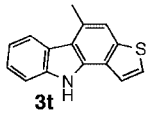
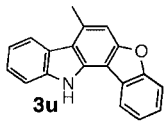
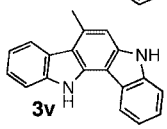
	UV-vis	fluorescence[b]	
AHA[*a*]Cs	λ_{max}/nm (log ε)	λ_{max}/nm[c]	Φ_F[d]
 **3a**	259 (4.64), 278 (4.70), 300 (4.38)	360, 378, 397	0.165
 **3b**	261 (4.53), 276 (4.52), 296 (4.25)	364, 382, 402	0.223
 **3c**	262 (4.60), 284 (4.73), 305 (4.37)	363, 378, 395sh	0.109
 **3d**	262 (4.71), 297 (4.41), 360 (4.13)	365, 384, 404	0.284
 **3f**	264 (4.51), 281 (4.56), 300 (4.31)	371, 389, 408sh	0.184
 **17**	268 (4.66), 304 (4.39), 370 (3.95)	380, 398, 420sh	0.215
 **3g**	279 (4.64), 303 (4.37)	366, 384, 403sh	0.239
 **3h**	280 (4.63), 303 (4.35)	367, 385, 404sh	0.264
 **15**	281 (4.73), 304 (4.61)	404	0.262
 **3i**	256 (4.68), 274 (4.61), 303 (4.31)	470	0.040
 **14**	257 (4.69), 303 (4.31)	nd[e]	nd[e]
 **13**	271 (4.76), 300 (4.33)	355, 373, 391	0.185

Table 4. Continued

AHA[*a*]Cs	UV-vis λ_{max}/nm (log ε)	fluorescence[b] λ_{max}/nm[c]	Φ_F[d]
 **3j**	264 (4.61), 281 (4.64), 302 (4.38)	370, 388, 407sh	0.156
 **3k**	264 (4.60), 282 (4.62), 302 (4.37)	369, 388, 407	0.167
 **3l**	253 (4.70), 310 (4.34)	351, 367, 383sh	0.037
 **3m**	255 (4.74), 312 (4.38)	351, 367, 383sh	0.047
 **3n**	252 (4.79), 302 (4.32)	338, 353, 368sh	0.200
 **3o**	258 (4.62), 295 (4.46), 320 (4.60)	365, 383, 400sh	0.058
 **3p**	254 (4.78), 280 (4.57), 314 (4.58)	353, 369, 385sh	0.444
 **3q**	259 (4.76), 287 (4.45), 323 (4.54)	371, 388, 403sh	0.075
 **3r**	275 (4.76), 329 (4.57)	391, 410, 431sh	0.114
 **16**	254 (4.76), 316 (4.63), 354 (4.26)	420	0.267
 **3t**	245 (4.69), 290 (4.41)	346, 362, 378sh	0.053
 **3u**	271 (4.63), 297 (4.53), 337 (4.05)	342, 357, 375sh	0.485
 **3v**	268 (4.68), 282 (4.61), 305 (4.47)	355, 370	0.223

[a] Dichloromethane was used as a solvent for measurement of UV−vis ($c = 1.5 \times 10^{-5}$ M) and fluorescence ($c = 1.5 \times 10^{-6}$ M) spectra. [b] Excited at 265 nm. [c] sh = shoulder. [d] Determined with reference to the quantum yield of *p*-terphenyl. [e] nd = not detected.

2-pyrimidyl group resulted in quenching of fluorescence. In contrast to the bathochromic effect in the FL maxima wavelengths of alkyl, methoxy and aryl groups, only a Boc group exhibited a hypsochromic effect (**3a** vs **13**).

Next, we focused on evaluating structure−property correlations of HA[*a*]Cs. Among a series of pentacyclic HA[2,3-*a*]Cs **3o**, **3p** and **3q**, benzofuro[2,3-*a*]carbazole **3p** having a furan ring was found to be the most emissive,[53] which is likely to be responsible for the largest extinction coefficients. Although we could not synthesize a pyrrolo[2,3-*a*]carbazole, tetracyclic **3n** (Φ_F = 0.200) with the furan moiety also showed higher FL efficiency in comparison to the corresponding thiophene derivative (**3m**, Φ_F = 0.047). The trend holds true for HA[3,2-*a*]Cs, and thus a larger Φ_F value of benzofuro[3,2-*a*]carbazole **3u** (Φ_F = 0.485) was confirmed compared with that of indolo[3,2-*a*]carbazole **3v** (Φ_F = 0.223). The consistency that HA[3,2-*a*]Cs are always superior to HA[2,3-*a*]Cs in view of the FL efficiency is of particular importance (**3l** vs **3t**, **3p** vs **3u**, and **3q** vs **3v**).

To gain further insight into the photophysical properties of AHA[*a*]Cs, we investigated their spectral dependence on solvent polarity. When benzo[*a*]carbazole **3a** and benzofuro[2,3-*a*]carbazole **3p** were excited at 265 nm in three kinds of solvents, i.e., ethyl acetate (AcOEt), dichloromethane (CH_2Cl_2) and dimethyl sulfoxide (DMSO),[54] their emission spectra were not affected irrespective of the solvent polarity. In contrast, significant positive solvatochromism in the fluorescence spectrum of **15**, which has an *N*,*N*-diphenylaminophenyl group on the nitrogen atom of **3a**, was observed as the solvent polarity increased (Figure 1). Thus, a 42 nm red-shift was confirmed by changing the solvent from AcOEt to DMSO. In addition to **15**, *p*-cyanophenyl-substituted **16** derived from **3p** similarly exhibited solvatochromic behavior as shown in Figure 2 (61 nm red-shift from AcOEt to DMSO). These results clearly show that the solvatochromic properties appear for the *N*-aryl-AHA[*a*]Cs. The considerable red-shift observed in **15** and **16** should be due mainly to the charge transfer character of the fluorescent state leading to the significant change in the dipole moment from the ground state to the excited state in polar solvents.[55]

3. Conclusion

We have developed the first annulation reaction that allows the assembly of two readily accessible building blocks, 2-(hetero)arylindoles and propargyl ethers, into aryl- and heteroaryl-annulated[*a*]carbazoles (AHA[*a*]Cs). The methodology with substrate diversity enables us to synthesize various AA[*a*]Cs, HA[2,3-*a*]Cs and HA[3,2-*a*]Cs. The achievement of the short-step process is attributed to the indium-catalyzed annulation including two carbon−carbon bond-forming reactions in combination with the reliable Fischer indole synthesis. The reaction can be applied also to bithiophene and bifuran derivatives. The annulation most likely proceeds in the following order: intermolecular addition reaction, intramolecular S_N2 reaction and then aromatization, which reasonably explains the regiochemical outcome of AHA[*a*]Cs. In the transformation of AHA[*a*]Cs, some organic functional groups are efficiently introduced. Furthermore, a methyl group on an AHA[*a*]C is successfully removed. Photophysical properties of AHA[*a*]Cs are described on the basis of the novel annulation reaction. The evaluation of FL properties showed that almost all their emission bands appear in the visible region (purple to green) and that FL quantum yields are highly dependent on the core structures, character of substituents and position of substituents attached. Some

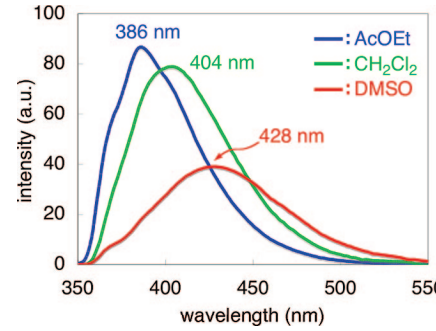


Figure 1. Solvent-dependent fluorescence spectra of **15** ($c = 1.1 \times 10^{-6}$ M in each solvent) excited at 265 nm. a.u. = arbitrary units.

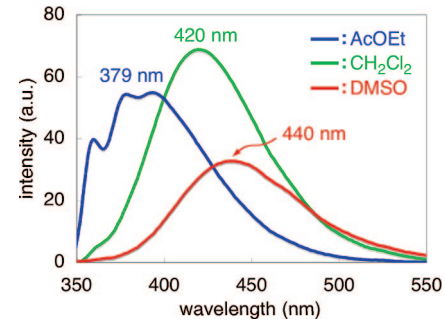


Figure 2. Solvent-dependent fluorescence spectra of **16** ($c = 1.1 \times 10^{-6}$ M in each solvent) excited at 265 nm. a.u. = arbitrary units.

structure−property correlations on AHA[*a*]Cs elucidated in the present study are as follows: (1) Introduction of an electron-rich aryl group onto the nitrogen atom enhances FL efficiency and causes a red-shift of FL spectra. (2) A *p*-cyanophenyl group on the nitrogen atom has a large bathochromic effect. (3) Furan rings are more effective than pyrrole and thiophene rings for achieving higher Φ_F values. (4) HA[3,2-*a*]Cs are more fluorescent compared with the corresponding HA[2,3-*a*]Cs. (5)

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(25) Preliminary communication: Tsuchimoto, T.; Matsubayashi, H.; Kaneko, M.; Shirakawa, E.; Kawakami, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 1336–1340.

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(27) It has been reported that metal nonaflates (metal = Sc, Ga) exhibit higher catalytic activity than the corresponding triflate and chloride salts in the Friedel−Crafts acylation, see: (a) Matsuo, J.; Odashima, K.; Kobayashi, S. *Synlett* **2000**, 403–405. (b) Kawada, A.; Mitamura, S.; Matsuo, J.; Tsuchiya, T.; Kobayashi, S. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 2325–2333.

(28) Koppel, I. A.; Taft, R. W.; Anvia, F.; Zhu, S.-Z.; Hu, L.-Q.; Sung, K.-S.; Desmarteau, D. D.; Yagupolskii, L. M.; Yagupolskii, Y. L.; Ignat'ev, N. V.; Konfratenko, N. V.; Volkonskii, A. Y.; Vlasov, V. M.; Notario, R.; Maair, P.-C. *J. Am. Chem. Soc.* **1994**, *116*, 3047–3057.

(29) Chatani and co-workers have described that softness of gallium contributes to the high catalytic acitivity of $GaCl_3$ in the cycloisomerization of ω-aryl-1-alkynes. As indium is located below gallium in the periodic table, indium metal of $In(ONf)_3$ should also be soft: Inoue, H.; Chatani, N.; Murai, S. *J. Org. Chem.* **2002**, *67*, 1414–1417.

(30) For a review of the HSAB principle, see: Ho, T.-L. *Chem. Rev.* **1975**, *75*, 1–20.

(31) *N*-Aryl-2-phenylindoles **1h** and **1i** other than commercially available **1g** were easily prepared from 2-phenylindole and the corresponding aryl halides according to the procedure reported by Buchwald and co-workers, see: Antilla, J. C.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 11684–11688.

AHA[*a*]Cs having an aryl group on the nitrogen atom exhibit positive solvatochromic behavior as solvent polarity increases.

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Supporting Information Available: Full experimental procedures, and analytical and spectral data for all new compounds prepared in this study. This material is available free of charge via the Internet at http://pubs.acs.org.

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(33) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*; Blackwell Science: Oxford, 2000; pp 273−295.
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(37) For previous reports on synthesis of benzodifurans, see: (a) Royer, R.; Bisagni, E.; Hudry, C.; Cheutin, A.; Desvoye, M.-L. *Bull. Soc. Chim. Fr.* **1963**, 1003–1007. (b) Singh, K.; Banerjee, S. K.; Atal, C. K. *Ind. J. Chem., Sect. B* **1981**, *20B*, 108–110. (c) Chandratre, S. P.; Trivedi, K. N. *Ind. J. Chem., Sect. B* **1987**, *26B*, 1148–1150. (d) Soman, S. S.; Trivedi, K. N. *Ind. J. Chem., Sect. B* **1994**, *33B*, 1075–1079.
(38) For example, see: (a) Martins, J. C.; Rompaey, K. V.; Wottmann, G.; Tömböly, C.; Tóth, G.; Kimpe, N. D.; Tourwé, D. *J. Org. Chem.* **2001**, *66*, 2884–2886. (b) Garçon, S.; Vassiliou, S.; Cavicchioli, M.; Hartmann, B.; Monteiro, N.; Balme, G. *J. Org. Chem.* **2001**, *66*, 4069–4073. (c) Miki, K.; Fujita, M.; Uemura, S.; Ohe, K. *Org. Lett.* **2006**, *8*, 1741–1743.
(39) The facile cyclization of **6** to **5a** with 20 mol % of $In(ONf)_3$ at 70 °C may be due to the reaction conditions in the absence of **2a**. Thus, in the reaction of **4a** in the presence of 1.1 mol equiv of **2a** shown in Scheme 3, coordination of unreacted **2a** to $In(ONf)_3$ may partially retard the formation of **5a** by activation of **6** with $In(ONf)_3$. In this regard, we have demonstrated that alkynes have a strong affinity to $In(OTf)_3$ in the addition of arenes to alkynes. See reference 21a.
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(42) Detailed experimental procedures for the synthesis of **9**−**17** are provided in Supporting Information.
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