Synthetic Methods

Easy Access to Aryl- and Heteroaryl-Annulated[*a*]carbazoles by the Indium-Catalyzed Reaction of 2-Arylindoles with Propargyl Ethers**

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Aryl- and heteroaryl-annulated[*a*]carbazoles constitute an attractive class of compounds in view of their biological and pharmacological activities that result from their special affinity toward DNA.[1] Among them, indolo[*a*]carbazoles, which are found in many natural products,[1,2] seem to be the most intriguing, and thus numerous studies on their activities[3] and synthetic methodologies[4] have been reported. Although other analogues are rather rare in nature,[5] synthetic approaches to such molecules have also been developed owing to their potential as antitumor agents.[1] However, no short synthetic route that is applicable to the various compounds has appeared in the literature despite the vast amount of work performed in this area.[6] Thus, we

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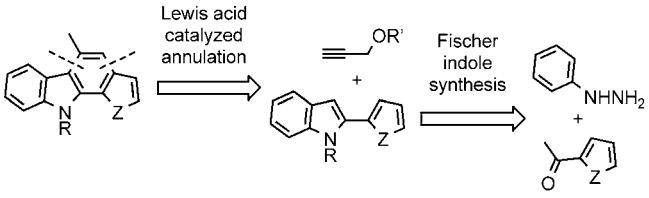
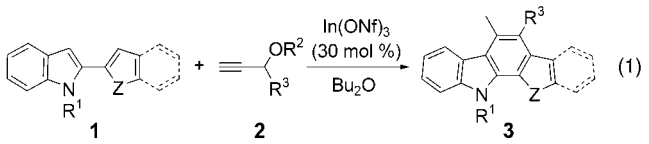
envisaged that Lewis acid catalyzed annulation of 2-arylindoles with propargyl ethers in a route that comprises two successive carbon–carbon bond-forming reactions should make for a short-step synthesis of aryl- and heteroaryl-annulated[*a*]carbazoles. Various 2-arylindoles are readily accessible through the Fischer indole synthesis,[7] and an overview of our strategy is summarized in Scheme 1. Herein



Scheme 1. Retrosynthetic strategy for the synthesis of aryl- and heteroaryl-annulated[*a*]carbazoles. Z = CH=CH, S, O, NH, NMe; R = H, Me; R′ = Alkyl.

we report a new method for the synthesis of a wide range of aryl- and heteroaryl-annulated[*a*]carbazoles that uses an indium-catalyzed addition–substitution sequence[8,9] of various 2-arylindoles with propargyl ethers.

First, we investigated the reaction of 2-phenylindole (**1a**: R^1 = H, Z = CH=CH) with methyl propargyl ether (**2a**: R^2 = Me, R^3 = H; see Equation (1) and Table 1). Treatment of **1a**



(1)

Table 1: Lewis acid catalyzed annulation of 2-phenylindole with methyl propargyl ether.[a]

Entry	Lewis acid	*t* [h]	Conv. [%] of **1a**[b]	Yield [%] of **3aa**[b]
1	$In(OTf)_3$	72	78	62
2	$In(ONf)_3$	24	87	69
3	$In(ONf)_3$	35	>99	64
4	$In(ONf)_3$[c]	120	68	53
5	$Sc(OTf)_3$	24	1	<1
6	$Zr(OTf)_4$	24	1	<1
7	$InCl_3$	24	1	<1
8	$BF_3{\cdot}Et_2O$	24	1	<1
9	$TiCl_4$	24	14	<1

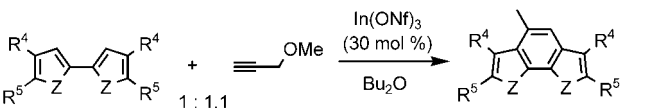
[a] The reaction was carried out in Bu_2O (3.0 mL) at 70 °C using **1a** (0.20 mmol) and **2a** (0.22 mmol) in the presence of a Lewis acid (60 μmol). [b] Determined by GC using 1,2-dichlorobenzene as an internal standard. [c] $In(ONf)_3$ (20 μmol) was used.

and **2a** with 30 mol % of indium triflate (triflate = CF_3SO_3), $In(OTf)_3$,[10] in Bu_2O at 70 °C for 72 h gave 6-methyl-11*H*-benzo[*a*]carbazole (**3aa**) in 62 % yield (Table 1, entry 1) by a route in which two subsequent inter- and intramolecular carbon–carbon bond-forming reactions took place in one step. With the nonaflate analogue $In(ONf)_3$ (nonaflate = $C_4F_9SO_3$),[11] which should be a stronger Lewis acid than $In(OTf)_3$,[12] as a catalyst, the yield of **3aa** was improved and the reaction rate was also increased (entry 2). Prolonging the reaction time to ensure complete consumption of **1a** led to a slight decrease in the yield (entry 3). Use of a lower loading of $In(ONf)_3$ gave **3aa** in an acceptable yield, but the reaction was sluggish (entry 4). Other metal triflate salts as well as metal halides were totally inactive (entries 5–9). The reliable activity of indium nonaflate may be ascribed to the soft nature of indium which renders it compatible with soft Lewis bases such as alkynes.[13]

We next turned to other 2-arylindoles, which were prepared here by the Fischer indole synthesis[7,14] and then subjected to the annulation reaction with **2a** in the presence of $In(ONf)_3$ [Eq. (1) and Table 2]. As well as **1a**, its *N*-methyl derivative **1b** and 2-phenylindoles that have a methoxy or hydroxy group on the phenyl ring reacted with **2a** to give the corresponding benzo[*a*]carbazoles (Table 2, entries 1–5);[15] a functional group such as -OMe should be useful for further carbon–carbon bond formation through nickel-catalyzed cross-coupling reaction with Grignard reagents.[16] The annulation of 2-thienyl- and 2-furylindoles also provided tetracyclic heteroaryl-annulated[*a*]carbazoles in moderate to good yields (entries 6–8). A series of pentacyclic analogues which comprise a heterocyclic ring such as thiophene, furan, or pyrrole were also prepared (entries 9–11). Note that the methyl group on the newly formed aromatic ring was always located next to C3 of the indole nucleus.[17] Besides **2a**, 3-butoxy-1-butyne (**2b**) also underwent the annulation reaction (entry 12).

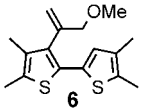
The strategy is also applicable to the annulation of bithiophenes and a bifuran (Scheme 2). Thus, both 4,4′,5,5′-tetramethyl-2,2′-bithiophene (**4a**) and the diethyl analogue **4b** reacted with **2a** under similar conditions to afford the corresponding benzodithiophenes **5aa** and **5ba**, respectively, although in rather low yields. In the reaction of **4a**, formation of the 1:1 adduct of **4a**/**2a** (**6**) was observed which may be informative for a discussion of the reaction mechanism. Benzodifuran **5ca** was also produced in 43 % yield in the reaction of tetramethylbifuran **4c** with **2a** (Scheme 2).

The annulation reaction should involve three distinct steps that comprise addition of an arene to a carbon–carbon triple bond, substitution of an alkoxy group with an arene, and aromatization. Consideration of the observed perfect regioselectivity should give us insight into the order of the



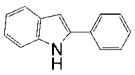
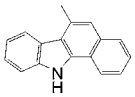
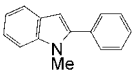
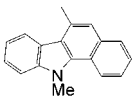
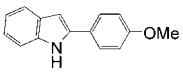
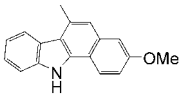
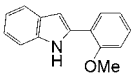
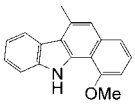
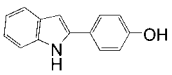
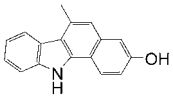
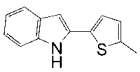
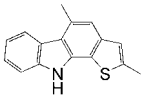
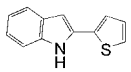
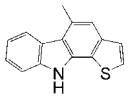
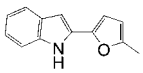
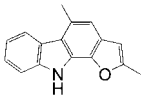
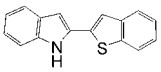
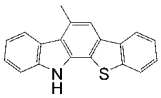
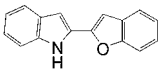
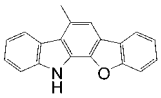
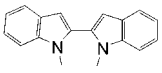
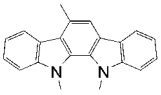
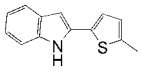
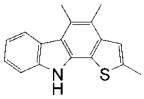
4a: R^4 = R^5 = Me, Z = S **2a** **5aa**: R^4 = R^5 = Me, Z = S
4b: R^4 = H, R^5 = Et, Z = S **5ba**: R^4 = H, R^5 = Et, Z = S
4c: R^4 = R^5 = Me, Z = O **5ca**: R^4 = R^5 = Me, Z = O

4	*t*	*T*	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%



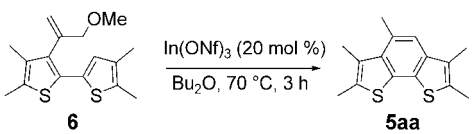
Scheme 2. $In(ONf)_3$-catalyzed annulation of bithiophenes or a bifuran with methyl propargyl ether.

Table 2: In(ONf)$_3$-catalyzed annulation of 2-arylindoles **1** with propargyl ethers **2**.[a]

Entry	2-Arylindole (**1**)		*t* [h]	Conv. [%] of **1**[b]	Product (**3**)		Yield [%] of **3**[c]
1		**1a**	24	91		**3aa**	65
2[d]		**1b**	11	76		**3ba**	52
3[e]		**1c**	11	78		**3ca**	67
4[e]		**1d**	10	88		**3da**	59
5[e]		**1e**	45	90		**3ea**	48
6		**1f**	50	83		**3fa**	79
7		**1g**	25	80		**3ga**	70
8		**1h**	8	61		**3ha**	57
9		**1i**	8	76		**3ia**	61
10		**1j**	40	87		**3ja**	60
11		**1k**	25	89		**3ka**	64
12[f]		**1f**	110	84		**3fb**	74

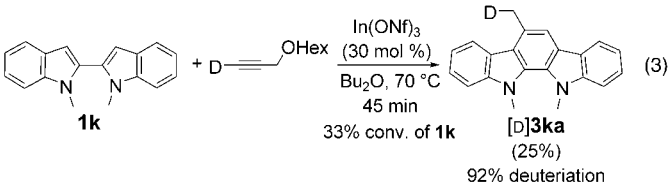
[a] The reaction was carried out in Bu_2O (3.0 mL) at 70 °C using **1** (0.20 mmol) and **2a** (0.22 mmol) in the presence of In(ONf)$_3$ (60 μmol). [b] Determined from recovered **1**. [c] Isolated yield based on the 2-arylindole. [d] In Bu_2O (9.0 mL). [e] In Bu_2O (9.0 mL) at 100 °C. [f] 3-Butoxy-1-butyne (**2b**) was used instead of **2a**.

sequence. We previously demonstrated that 1-octyne, an aliphatic terminal alkyne, undergoes addition of heterocyclic arenes exclusively at the internal carbon atom of the carbon–carbon triple bond.[8b] Therefore, considering that C3 of 2-arylindoles, which should be the most nucleophilic in **1**,[18] added first to **2a** in a similar manner, the position of the resulting methyl group should be rationally understood. Furthermore, formation of **6**, which should be an intermediate in the reaction of **4a** with **2a**, possibly suggests that the first step is not substitution but addition, though the formation of a 1:1 adduct such as **6** was not observed in the annulation of 2-arylindoles. Actually, transformation of **6** into **5aa** in Bu_2O at 70 °C for 3 h using 20 mol % of In(ONf)$_3$ proceeded smoothly [Eq. (2)]. Despite two possible routes for the next cyclization, that is, S_N2 and S_N2' reactions, the fact that the reaction of **1k** with 1-deuterio-3-hexyloxy-1-propyne afforded [D]**3ka** which contains a deuterium atom only in the CH_3 group should

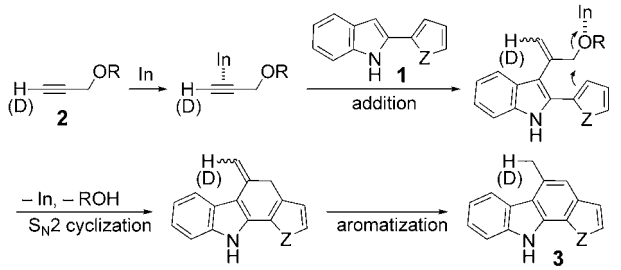


6 → **5aa** (97%) (2)

support the probability of S_N2 cyclization [Eq. (3)].[19] Thus, coordination of the carbon–carbon triple bond of **2a** to an



indium atom should induce regioselective addition of **1** followed by intramolecular S_N2 reaction. Finally, aromatization should give **3** (Scheme 3).



Scheme 3. Proposed mechanism for the $In(ONf)_3$-catalyzed annulation of 2-arylindoles with propargyl ethers.

In conclusion, we have demonstrated a novel annulation reaction that allows the assembly of readily accessible building blocks into diverse aryl- and heteroaryl-annulated-[*a*]carbazoles with the aid of an indium catalyst. The highlight of our approach is the direct use of aromatic C–H bonds and the absence of the need to introduce reactive functional groups into the substrates. Studies on the mechanistic details as well as application of the reaction to other substrates are currently underway.

Experimental Section

General procedure for the synthesis of aryl- and heteroaryl-annulated[*a*]carbazoles (see also Table 2): $In(ONf)_3$ (60.7 mg, 60.0 μmol) was placed in a 20-mL Schlenk tube and heated at 150 °C in vacuo for 2 h. The tube was cooled to room temperature and filled with nitrogen. Dibutyl ether (3.0 or 9.0 mL) was added to the tube, and the contents were stirred for 10 min at room temperature. A 2-arylindole (0.20 mmol) and a propargyl ether (0.22 mmol) were added successively to the catalyst mixture, and the resulting mixture was stirred at 70 or 100 °C. After the time specified in Table 2, the mixture was diluted with ethyl acetate (10 mL), washed with aqueous saturated $NaHCO_3$ solution (1 mL) and brine (1 mL), and then dried over anhydrous sodium sulfate. The mixture was filtered through a pad of Celite and the solvents were evaporated, then the residue was purified by column chromatography on silica gel to give the corresponding aryl- or heteroaryl-annulated[*a*]carbazole.

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[4] For recent examples, see: a) S. P. Gaudêncio, M. M. M. Santos, A. M. Lobo, S. Prabhakar, *Tetrahedron Lett.* **2003**, *44*, 2577–2578; b) X. Cai, V. Snieckus, *Org. Lett.* **2004**, *6*, 2293–2295; c) M. M. Faul, K. A. Sullivan, J. L. Grutsch, L. L. Winneroski, C. Shih, C. Sanchez-Martinez, J. T. Cooper, *Tetrahedron Lett.* **2004**, *45*, 1095–1098; d) M. M. M. Santos, A. M. Lobo, S. Prabhakar, M. M. B. Marques, *Tetrahedron Lett.* **2004**, *45*, 2347–2349; e) J. T. Kuethe, I. W. Davies, *Tetrahedron Lett.* **2004**, *45*, 4009–4012.

[5] For furo[*a*]carbazoles, see: H.-J. Knölker, M. P. Krahl, *Synlett* **2004**, 528–530, and references therein.

[6] To the best of our knowledge, only two precedents for the synthesis of several (hetero)aryl-annulated[*a*]carbazoles have been reported. For the synthesis of benzo-, thieno-, and pyrrolo[*a*]carbazoles using photochemical cyclization of 3-(2-styryl)indoles, see: a) E. M. Beccali, A. Marchesini, T. Pilati, *Synthesis* **1992**, 891–894. For the synthesis of benzo-, naphtho-, thieno-, and benzothieno[*a*]carbazoles using photochemical cyclization of 3-indolyl-4-arylmaleimides or the Mizoroki–Heck-type cyclization of 3-indolyl-4-(2-bromoaryl)maleimides, see: b) C. Sanchez-Martinez, M. M. Faul, C. Shih, K. A. Sullivan, J. L. Grutsch, J. T. Cooper, S. P. Kolis, *J. Org. Chem.* **2003**, *68*, 8008–8014.

[7] For example, see: a) R. L. Shriner, W. C. Ashley, E. Welch, *Org. Synth. Coll. Vol. 3* **1955**, 725–727; b) K. C. Joshi, R. Jain, S. Garg, *J. Indian Chem. Soc.* **1985**, *62*, 388–390; c) J. Slätt, J. Bergman, *Tetrahedron* **2002**, *58*, 9187–9191; For a review, see: d) B. Robinson, *Chem. Rev.* **1969**, *69*, 227–250.

[8] We recently demonstrated that a C–H bond of arenes and heterocyclic arenes adds to alkynes in the presence of a metal triflate catalyst, see: a) T. Tsuchimoto, T. Maeda, E. Shirakawa, Y. Kawakami, *Chem. Commun.* **2000**, 1573–1574; b) T. Tsuchimoto, K. Hatanaka, E. Shirakawa, Y. Kawakami, *Chem. Commun.* **2003**, 2454–2455.

[9] We previously reported that metal triflates catalyze the substitution reaction of the C–O bond of alcohols and acetals with arenes, see: a) T. Tsuchimoto, K. Tobita, T. Hiyama, S. Fukuzawa, *Synlett* **1996**, 557–559; b) T. Tsuchimoto, T. Hiyama, S. Fukuzawa, *Chem. Commun.* **1996**, 2345–2346; c) T. Tsuchimoto, K. Tobita, T. Hiyama, S. Fukuzawa, *J. Org. Chem.* **1997**, *62*, 6997–7005.

[10] $In(OTf)_3$ is commercially available from Aldrich.

[11] $In(ONf)_3$ was prepared for the first time from In_2O_3 and $CF_3CF_2CF_2CF_2SO_3H$ in an easy manner. For details, see Supporting Information.

[12] It has been reported that gallium nonaflate exhibits higher catalytic activity than the corresponding triflate and chloride salts in the Friedel–Crafts acylation reactions, see: J. Matsuo, K. Odashima, S. Kobayashi, *Synlett* **2000**, 403 – 405.
[13] Murai and co-workers have described that softness of gallium contributes to the high catalytic activity of $GaCl_3$ in the cycloisomerization of ω-aryl-1-alkynes. As indium is located below gallium in the periodic table, indium nonaflate should also be soft: H. Inoue, N. Chatani, S. Murai, *J. Org. Chem.* **2002**, *67*, 1414 – 1417. For a review of hard and soft acids and bases (HSAB) principle, see: T.-L. Ho, *Chem. Rev.* **1975**, *75*, 1 – 20.
[14] For the synthesis of a homodimer such as 2,2′-bis(*N*-methylindolyl) (**1k**), oxidative homocoupling of *N*-methylindole is more straightforward, see: U. Pindur, Y.-S. Kim, D. Schollmeyer, *J. Heterocycl. Chem.* **1994**, *31*, 377 – 386.
[15] The benzo[*a*]carbazole **3ba** is known to exhibit pronounced antitumor activity against, for example, leukemia, renal tumor, and colon cancer, see: U. Pindur, T. Lemster, *Recent Res. Dev. Org. Bioorg. Chem.* **1997**, 33 – 53. See also reference [1c].
[16] Alkoxy groups of alkenyl and aryl ethers have been reportedly transformed into alkyl and aryl groups by using Grignard reagents in the presence of a nickel catalyst, see: E. Wenkert, E. L. Michelotti, C. S. Swindell, M. Tingoli, *J. Org. Chem.* **1984**, *49*, 4894 – 4899.
[17] The position of the methyl group was determined by ^{1}H–^{1}H COSY and NOESY NMR techniques.
[18] a) M. F. Gotta, H. Mayr, *J. Org. Chem.* **1998**, *63*, 9769 – 9775; b) J. A. Joule, K. Mills, *Heterocyclic Chemistry*, Blackwell Science, Oxford, **2000**, pp. 324 – 379.
[19] The ^{2}H NMR spectrum showed no incorporation of the deuterium atom at the other carbon atoms.

