Heterocycles

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One-Pot Approach to Installing Eight-Membered Rings onto Indoles**

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Eight-membered rings combined with an aromatic skeleton, a class of fused eight-membered compounds, have attracted considerable attention.[1,2] Such units have been found in various natural products as well as in pharmacologically active substances:[3,4] Iprindole (**1**),[5] the first second-generation antidepressant (TCA), and jolynamine (**2**),[6] which was isolated from a dark brown alga belonging to the family Scytosiphonaceae, contain a cycloocta[*b*]indole skeleton (Figure 1). Very limited methods, especially those involving the unfavorable formation of eight-membered rings, have been developed for the synthesis of these type of products.[2b,c,d,7] Thus, new methodologies for the efficient synthesis of this type of skeleton are highly desired.

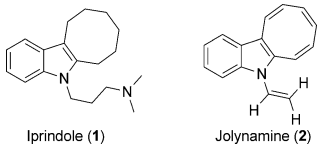
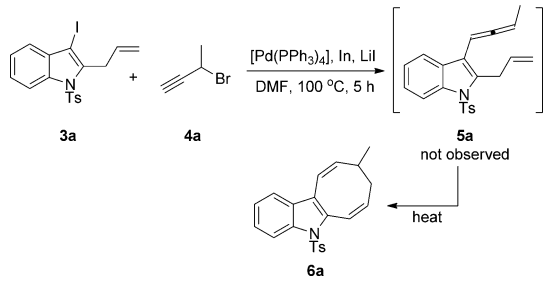


Figure 1. Natural products and pharmaceuticals with the fragment of cycloocta[*b*]indole skeleton.

Coupling reactions involving allenylic/propargylic organometallic reagents have been developed as an efficient approach for the synthesis of allenes.[8] On this basis, we envisioned a new approach for the synthesis of 3-allenylindoles by starting from 3-iodoindoles and propargylic bromides given the fact that propargylic bromide is much more reactive towards metals forming allenylic/propargylic organometallic reagents in situ.[9] On the basis of this concept, the synthesis of 2-allyl-3-(buta-1,2-di-enyl)-1-tosyl-1*H*-indole (**5a**) was attempted by conducting the coupling reaction of 2-allyl-3-iodo-1-tosyl-1*H*-indole (**3a**) with 3-bromobut-1-yne (**4a**) in the presence of In and $[Pd(PPh_3)_4]$ (Scheme 1).

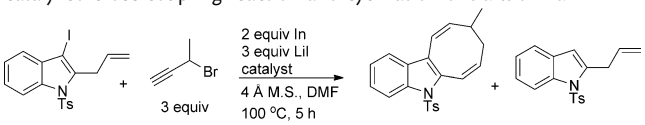


Scheme 1. One-pot reaction to construct dihydrocycloocta[*b*]indole. DMF = *N*,*N*-dimethylformamide, Ts = 4-methylbenzenesulfonyl.

Interestingly, the reaction in *N*,*N*-dimethylformamide (DMF) at 100 °C with 3.0 equivalents of LiI as the additive afforded the dihydrocycloocta[*b*]indole **6a** in 65 % yield, and the formation of its precursor **5a** was not detected.

With the unexpected results in hand, we turned to optimizing the reaction conditions. Along with the dihydrocycloocta[*b*]indole **6a**, the reduced indole **7** was also found in 22 % yield (Table 1, entry 1). We reasoned that a trace amount of water may be critical to the reaction. Thus, 12.5 mg mL^{-1} of 4 Å molecular sieves (M.S.) was added to

Table 1: Optimization of the reaction conditions for the palladium-catalyzed cross-coupling reaction and cyclization of **3a** with **4a**[a]



Entry	Catalyst	**6a** Yield [%][b]	**7** Yield [%][b]
1[c]	$[Pd(PPh_3)_4]$	65	22
2[d]	$[Pd(PPh_3)_4]$	79	12
3	$[Pd(PPh_3)_4]$	83	10
4	$Pd(OAc)_2$	53	31
5	$Pd(OAc)_2/PPh_3$	18	49
6	$Pd(OAc)_2$/L1[e]	82	15
7	$Pd(OAc)_2$/L2[f]	32	58
8	$Pd(OAc)_2/MePPh_2$	55	39
9	$Pd(OAc)_2$/TFP	90	7
10[g]	$Pd(OAc)_2$/TFP	79	9
11[h]	$Pd(OAc)_2$/TFP	84	6
12[i]	$Pd(OAc)_2$/TFP	47	42

[a] The reaction was carried out using **3a** (c = 0.1 M), **4a** (3.0 equiv), In (2.0 equiv), LiI (3.0 equiv), 4 Å M.S. (25.0 mg mL^{-1}), palladium complex (4 mol %) and ligand (8 mol %) at 100 °C in DMF. [b] Determined by ^{1}H NMR analysis with nitromethane as the internal standard. [c] The reaction was carried out without 4 Å M.S. [d] 12.5 mg mL^{-1} 4 Å M.S. was added to the reaction mixture. [e] L1 = tris(4-methoxyphenyl)phosphine. [f] L2 = tris(2,4,6-trimethoxyphenyl)phosphine. [g] NaI (3.0 equiv) was used instead of LiI. [h] LiCl (3.0 equiv) was used instead of LiI. [i] No LiI was added to the reaction mixture.

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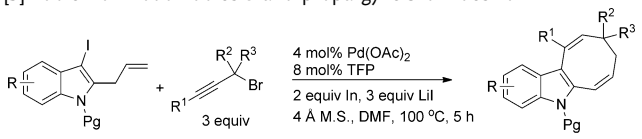
remove moisture and the yield was improved to 79% (Table 1, entry 2); increasing the loading of the 4 Å M.S. to 25.0 mg mL^{-1} improved the yield of **6a** additionally to 83%, while the reduced indole **7** was formed in 10% yield (Table 1, entry 3). $Pd(OAc)_2$ together with different phosphine ligands was screened (Table 1, entries 4–9), and tris(2-furyl)phosphine (TFP) was observed to be the best: The yield of **6a** was improved to 90% with a less than 7% yield of **7** (Table 1, entry 9). Other additives failed to show better performance than LiI (Table 1, entries 10–12). Thus, $Pd(OAc)_2$ (4 mol%), TFP (8 mol%), In (2.0 equiv), LiI (3.0 equiv), and 4 Å M.S. (25.0 mg mL^{-1}) in DMF at 100°C were defined as the optimized reaction conditions for additional study.

The scope of the reaction was then investigated by using the optimal reaction conditions (Table 2). We first studied the cyclization reaction of iodoindole **3a** with different propargyl bromides. Secondary halides gave good yields (Table 2, entries 1 and 2). When R^1 is H, methyl, or allyl, the reaction showed moderate to good results (Table 2, entries 3–5). The reaction worked equally well using a tertiary halide ($R^2 = R^3 = Me$), thus producing **6g** in 75% yield (Table 2, entry 6). Notably, various substituents on the benzene ring turned out to be compatible under the standard reaction conditions. Different R groups, such as fluoro, chloro, trifluoromethyl, bromo, and methyl ester (Table 2, entries 8–12) at the 5-position and chloro (Table 2, entry 13) at 6-position, may be introduced to the indole unit, thus leading to the corresponding dihydrocycloocta[*b*]indole derivatives in good yields. Further studies showed that the substituent on the nitrogen atom also has a great influence on the reaction (Table 2, entries 1, 14, and 15). Finally, it is easy to conduct the reaction of **3a** and **4g** to afford **6g** in 76% yield on a one gram scale (Table 2, entry 7). The structures of the products **6a–n** were determined by the single-crystal X-ray diffraction study of **6g** (see the Supporting Information).[10]

Table 2: Palladium-catalyzed one-pot synthesis of dihydrocycloocta[*b*]indole from iodoindoles **3** and propargylic bromides **4**.[a]

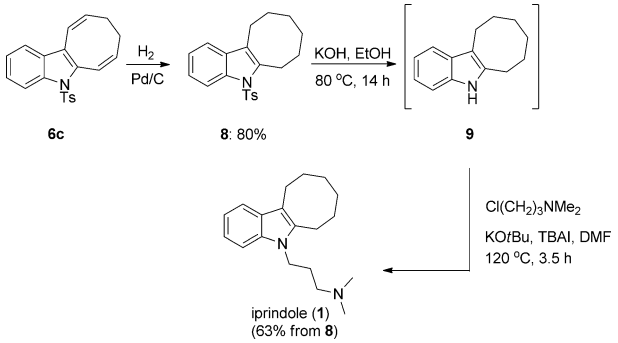


3 **4** **6**

Entry	**3** R/Pg	**4** $R^1/R^2/R^3$	**6** Yield [%][b]
1	H/Ts (**3a**)	H/Me/H (**4a**)	79 (**6a**)
2	H/Ts (**3a**)	H/*n*-Pr/H (**4b**)	75 (**6b**)
3[c]	H/Ts (**3a**)	H/H/H (**4c**)	63 (**6c**)
4	H/Ts (**3a**)	Me/H/H (**4d**)	52 (**6d**)
5[d]	H/Ts (**3a**)	Allyl/H/H (**4e**)	67 (**6e**)
6	H/Ts (**3a**)	H/Me/Me (**4g**)	75 (**6g**)[e]
7[f]	H/Ts (**3a**)	H/Me/Me (**4g**)	76 (**6g**)[e]
8	5-F/Ts (**3b**)	H/Me/H (**4a**)	75 (**6h**)
9	5-Cl/Ts (**3c**)	H/Me/H (**4a**)	79 (**6i**)
10	5-Br/Ts (**3d**)	H/Me/H (**4a**)	74 (**6j**)
11	5-CF_3/Ts (**3e**)	H/Me/H (**4a**)	69 (**6k**)
12	5-CO_2Me/Ts (**3f**)	H/Me/Me (**4g**)	75 (**6l**)
13	6-Cl/Ts (**3g**)	H/Me/H (**4a**)	69 (**6m**)
14	H/Ms (**3h**)	H/Me/H (**4a**)	67 (**6n**)
15	H/*p*-Ns (**3i**)	H/Me/H (**4a**)	trace (**6o**)

[a] The reaction was conducted at 100°C in DMF with **3** ($c = 0.1$ M), **4** (3.0 equiv), 4 Å M.S. (25.0 mg mL^{-1}), In (2.0 equiv), and LiI (3.0 equiv) in the presence of $Pd(OAc)_2$ (4 mol%) and TFP (8 mol%). [b] Yield of isolated product. [c] The reaction was carried out at 110°C for 5 h. [d] The reaction was carried out at 60°C for 30 h and then 110°C for 5 h with 4 mol% $[Pd(PPh_3)_4]$ as the catalyst. [e] Yield of product isolated after chromatography on silica gel and then recrystallized from dichloromethane and petroleum ether. [f] Gram-scale reaction was conducted with **3a** (1.0942 g) and **4g** (1.1025 g) to provide **6g** (0.7134 g). Pg = protecting group, Ms = methanesulfonyl, *p*-Ns = 4-nitrobenzenesulfonyl.

As mentioned previously, iprindole (**1**) is a tricyclic antidepressant (TCA) used in Europe for the treatment of depression. We demonstrated the potential of our method by applying to the synthesis of iprindole:[7] Hydrogenation of our product **6c** produced the hexahydrocycloocta[*b*]indole **8** in 80% yield and subsequent deprotection and N alkylation led to **1** in 63% yield after two steps (Scheme 2). The contamination of palladium and indium in the prepared compound **1** was determined by AES (atomic emission spectrometry) to be less than 0.0001% (1 ppm). The traditional synthetic route of iprindole is based on the reaction of an aromatic substrate with cyclooctanone in a Fischer indole synthesis, for example.[11] It should be noted that different substituted cyclic ketones are not readily available. In contrast, our approach provides diversity in both the eight-membered and benzene rings, because of the ready availability of both substituted iodoindoles and propargylic bromides, for the synthesis of iprindole derivatives, which may display better biological or pharmacological activities.



Scheme 2. Approach for the synthesis of iprindole (**1**).

To investigate the mechanism, the reaction was conducted at a lower temperature, that is, 60°C, for 6 hours, and the coupling product **5c** was produced in 33% yield upon isolation. Heating a solution of **5c** in DMF at 100°C produced dihydrocycloocta[*b*]indole **6c** in 61% yield, thus indicating the intermediacy of the coupling product **5c** for this transformation (Scheme 3).

DFT calculations[12] have been performed to investigate the cyclization of 1,2,4*Z*,7-tetraene **5c** to afford **6c**. Figure 2 presents the energy profile for the favored pathway of the cycloisomerization reaction of **5c**. It is clear that the rate-limiting step is the initial [1,5]-H migration step, which is computed to be exothermic ($\Delta H = -9.7$ kcal mol^{-1}) and requires an activation enthalpy of 26.6 kcal mol^{-1} as the

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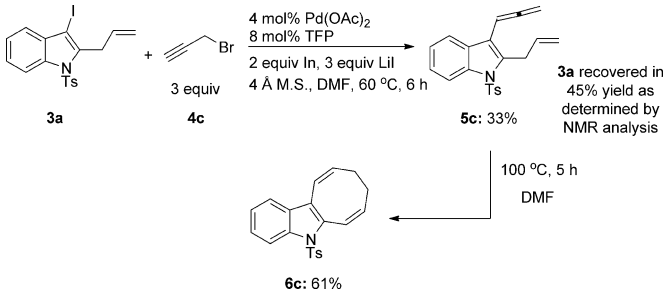

Scheme 3. Mechanistic studies.

aromaticity of the indole ring is lost.[13] This initial [1,5]-H migration step leads to the formation of the intermediate (2*E*,3*Z*)-2,3-diallylidene-1-tosylindoline (**A**) having two *s-trans* allylidenes. Conformer **A** then undergoes two single-bond rotations to afford the 8π-electrocyclization precursor **C**, which has both allylidenes in the *s-cis* conformation. The computed enthalpy difference of 9.8 kcal mol^{-1} between **A** and **C**, with the former species being favored, results from the steric effect between the two terminal methylene groups of conformer **C**. There is an approximately 11 kcal mol^{-1} barrier for interconversion of these two structures. At last, the final product dihydrocycloocta[*b*]indole (**6c**) is formed by the 8π-electrocyclization of **C**, which requires an activation enthalpy of only 1.2 kcal mol^{-1} as a result of the rearomatization. Overall, the cycloisomerization reaction of **5c** is calculated to occur irreversibly, as the final product **6c** is about 27 kcal mol^{-1} below the energy of the starting material, and the [1,5]-H migration is the rate-limiting step.

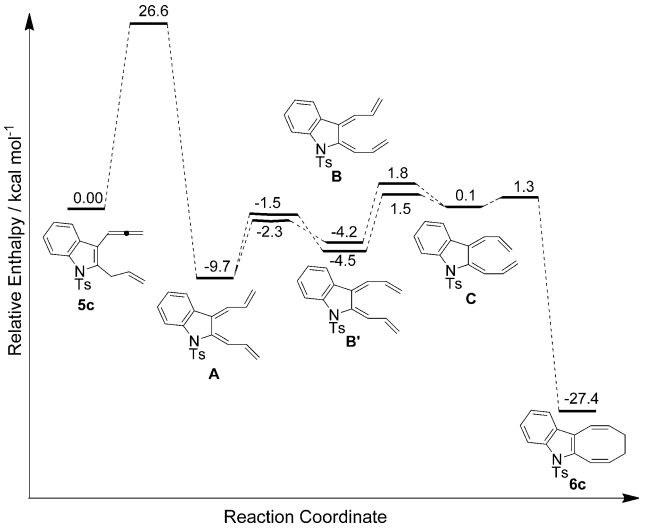

Figure 2. Reaction coordinate for the cycloisomerization reaction of **5c**. Enthalpies are given in kcal mol^{-1} and are relative to **5c**.

In conclusion, we have developed a one-pot reaction for the synthesis of dihydrocycloocta[*b*]indoles from 2-allyl-3-iodoindoles and propargyl bromides. This coupling/cyclization reaction is highly efficient, and proceeds through palladium(0)-catalyzed carbon–carbon coupling, [1,5]-hydrogen migration, and electrocyclization, involving overall a dearomatization and aromatization. Finally, because of the success of our approach in the efficient synthesis of iprindole, this chemistry will be of high interest for organic and medicinal chemists. Further studies in this area are currently under way in our laboratory.

Experimental Section

Procedure for the preparation of (6*Z*,10*Z*)-9,9-Dimethyl-5-tosyl-8,9-dihydro-5*H*-cycloocta[*b*]indole (**6g**, Table 2, entry 7): Indium powder (diameter ≈ 32 μm; 572.9 mg, 5.0 mmol), LiI (1.0017 g, 7.5 mmol) in DMF (6 mL), and 3-bromo-3-methylbut-1-yne (**4g**; 1.1025 g, 7.5 mmol) in DMF (6 mL) were sequentially added to a flame dried three-necked flask under an Ar atmosphere. After the mixture was stirred at room temperature for 15 min, iodoindole **3a** (1.0942 g, 2.5 mmol), $Pd(OAc)_2$ (22.4 mg, 0.10 mmol), TFP (47.3 mg, 0.20 mmol), 4 Å molecular sieves (628.0 mg), and DMF (13 mL) were added to the reaction mixture sequentially. The resulting mixture was stirred at 100 °C and after 5 h the reaction was over as monitored by TLC. 50 mL of HCl (1.0 M) and 200 mL of H_2O were added to the resulting mixture. The water layer was extracted with Et_2O (3 × 150 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, evaporated, and purified by column chromatography on silica gel (eluent: *n*-pentane/ethyl ether = 50:1 then petroleum ether/dichloromethane = 15:1). Recrystallization from dichloromethane and petroleum ether afforded the desired product **6g** (713.4 mg, 76 %): solid; m.p. 206–208 °C (petroleum ether/dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.21$ (d, $J =$ 8.4 Hz, 1H, Ar-H), 7.62 (d, $J = 8.0$ Hz, 2H, Ar-H), 7.44 (d, $J =$ 7.6 Hz, 1H, Ar-H), 7.36–7.30 (m, 1H, Ar-H), 7.28–7.22 (m, 1H, Ar-H), 7.11 (d, $J = 8.0$ Hz, 2H, Ar-H), 7.05 (d, $J = 10.8$ Hz, 1H, CH=), 6.47–6.38 (m, 1H, CH=), 6.15 (d, $J = 13.2$ Hz, 1H, CH=), 5.76 (d, $J =$ 12.8 Hz, 1H, CH=), 2.29 (s, 3H, Ar-CH_3), 2.14 (d, $J = 8.0$ Hz, 2H, CH_2), 1.10 ppm (s, 6H, 2 × CH_3). ^{13}C NMR ($CDCl_3$, 100.5 MHz): $\delta =$ 144.7, 144.6, 136.8, 135.9, 135.4, 131.9, 131.1, 129.5, 126.7, 125.1, 123.7, 123.4, 119.7, 119.1, 115.0, 114.6, 38.9, 38.5, 31.8, 21.5 ppm. MS (EI): *m*/*z* 377 (M^+, 29.90), 222 (100). IR (KBr): $\tilde{\nu}$ =3040, 2956, 2925, 2862, 1597, 1494, 1471, 1455, 1371, 1306, 1292, 1224, 1195, 1186, 1174, 1151, 1121, 1090, 1025 cm^{-1}. Anal. (%) calcd for $C_{23}H_{23}NO_2S$: C 73.18; H 6.14; N 3.71; S 8.49. Found: C 73.36; H 6.15; N 3.46; S 8.63.

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[10] Crystal data for **6g**: $C_{23}H_{23}NO_2S$, MW = 377.50, monoclinic, space group $P2(1)/c$, final R indices $[I > 2\sigma(I)]$, $R_1 = 0.0351$, $wR_2 = 0.0953$, R indices (all data), $R_1 = 0.0375$, $wR_2 = 0.0981$, $a = 9.4240(9)$, $b = 14.7239(14)$, $c = 14.2847(14)$ Å, $\alpha = 90$, $\beta = 101.7000(10)$, $\gamma = 90°$, $V = 1940.9(3)$ Å^3, $T = 133$ (2) K, $Z = 4$, reflections collected/unique: 13726/4222 (R(int) = 0.0189), number of observations $[> 2\sigma(I)]$ 3919; parameter: 247. Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Center. CCDC 875477 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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Communications

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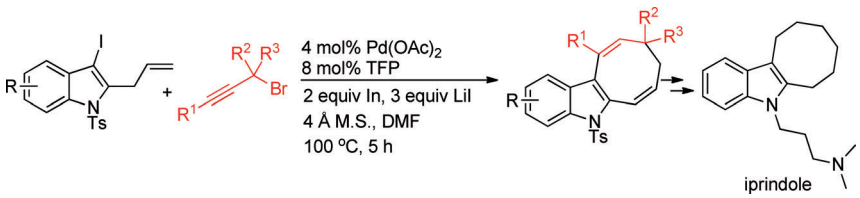

Ring fusion: The Pd^0-catalyzed reaction of 2-allyl-3-iodo-1-tosyl-1*H*-indoles and propargylic bromides affords dihydrocycloocta[*b*]indoles (see scheme; M.S. = molecular sieves, TFP = tris(2-furyl)phosphine, Ts = 4-toluenemethanesulfonyl), and proceeds by carbon–carbon coupling, [1,5]-hydrogen migration, and electrocyclization. The newly established method was used to efficiently access iprindole.

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