Synthesis M. Henkel, T. Bach Paper

Annulation of Indoles with 1,n-Dibromoalkanes by a Pd(II)-Catalyzed and Norbornene-Mediated Reaction Cascade

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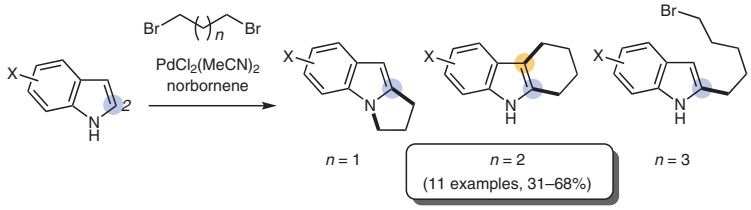
Dedicated to Professor Mark Lautens on the occasion of his 60th birthday

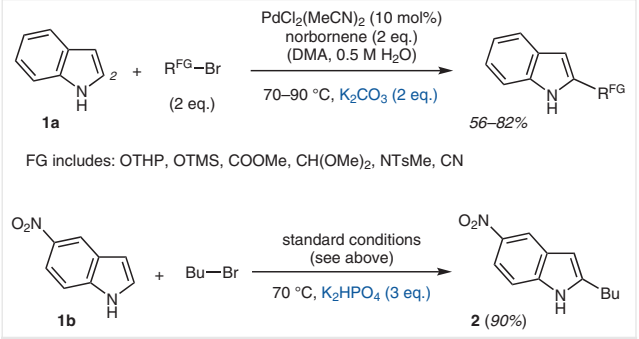


Received: 30.08.2019
Accepted after revision: 16.09.2019
Published online: 02.10.2019
DOI: 10.1055/s-0039-1690693; Art ID: ss-2019-c0495-op

Abstract Employing 1,3-dibromopropane, 1,4-dibromobutane, and 1,5-dibromopentane as biselectrophiles, the annulation of indoles was probed in the presence of $PdCl_2(MeCN)_2$ as a catalyst and norbornene as a transpositional ligand. Ring formation to a five-membered ring was observed at positions C2 and N, while annulation of a six-membered ring occurred at positions C2 and C3. The latter cascade process was successfully applied to the direct synthesis of 1,2,3,4-tetrahydrocarbazoles from indoles (11 examples, 31–68% yield). Seven-membered-ring annulation was feasible by an initial coupling at positon C2 followed by alkylation at C3.

Key words alkylation, C–H activation, domino reaction, indoles, Pd catalysis

The importance of indoles for many applications has stimulated extensive research efforts towards their synthesis and their functionalization.[1] Positions C2 and C3 of the indole core can be addressed by electrophilic reagents and there is a plethora of C–C bond-forming reactions known that allow for the attachment of different substituents.[2] Despite the broad scope of reported methods, limitations remain and several desirable transformations lack a general procedure. Along these lines, we recognized some time ago that a C2 alkylation of *N*-unsubstituted indoles would be a useful synthetic method for which no precedence existed. It was found that Pd(II) serves, in combination with norbornene as a transpositional ligand,[3] as an effective catalyst to allow for C–H activation at position C2 of the indole core. Indole (**1a**) itself and several substituted indoles undergo a clean regioselective alkylation reaction with a large variety of alkyl bromides (Scheme 1).[4] The functional group (FG) tolerance of the reaction is high and typical reaction conditions include the use of K_2CO_3 as a base in *N*,*N*-dimethylacetamide (DMA) as the solvent. Minimal quantities of water (0.5 M) are necessary for the reaction to be successful, possibly because the base needs to be dissolved in the organic solvent.



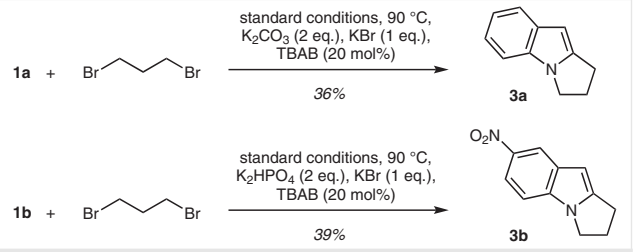
Scheme 1 Pd(II)-catalyzed, C2-selective alkylation[4] of indoles **1a** and **1b** with various alkyl bromides

For electron-deficient indoles such as 5-nitroindole (**1b**) a milder base (K_2HPO_4) was required to direct the alkylation to position C2 and to avoid *N*-alkylation. The yield of butylated product **2** was high under these conditions. The C2-selective indole alkylation method has been vividly embraced by the synthetic community and several applications to the synthesis of substituted indoles have been reported.[5]

Since the alkylation at position C2 leaves both the indole nitrogen atom and the nucleophilic carbon atom C3 available for a second attack of an electrophile we wondered how 1,n-dibromoalkanes would behave in the Pd(II)-catalyzed alkylation reaction. Three dibromides (1,3-dibromopropane, 1,4-dibromobutane, and 1,5-dibromopentane) were chosen to probe the reactivity of indoles towards a twofold substitution. Ideally, a reaction cascade should occur which would lead to an annulation of a ring to the indole core.[6] Indeed, five-membered-ring formation occurred at C2 and the nitrogen atom (C2/N) and six-membered-ring

formation at C2 and C3 (C2/C3) while seven-membered-ring formation was retarded. Detailed results of our experiments are described in this account.

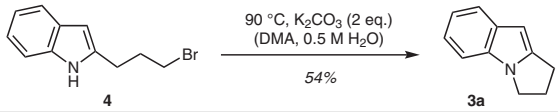
In all reactions studied, we retained the same palladium catalyst, norbornene (2 eq.), concentration (0.2 M), reaction time (24 h), and solvent mixture identical (standard conditions) and varied only the temperature, the base, and potential additives. The reaction of indoles with 1,3-dibromopropane turned out to be sluggish and the reaction of indole **1a** at 70 °C with K_2CO_3 as base delivered only 8% of annulated product, the majority (7%) of which was the C2/N annulation product **3a** (Scheme 2). Monosubstitution at C2 was the predominant reaction pathway (31%) and some substrate was recovered (17%). Optimization of the reaction (for details, see the Supporting Information) revealed a beneficial influence of potassium bromide and tetrabutylammonium bromide (TBAB)[7] on the reaction course, but the reaction remained incomplete and product **3a** was isolated together with 21% of substrate. The yield of product **3a** based on conversion was 46%, which is lower than the yield (60%) reported for the reaction in the presence of Cs_2CO_3 as disclosed in a recent patent procedure.[8] Employing the same additives, the reaction of 5-nitroindole to the respective nitro-substituted 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole (**3b**)[9] could be achieved in 39% yield.



Scheme 2 Annulation of indoles **1a** and **1b** with 1,3-dibromopropane to 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indoles **3a** and **3b**

A possible explanation for the low conversion in the reaction of **1a** and **1b** with 1,3-dibromopropane may be the formation of allylic side products by 1,2-elimination of HBr either in the starting material or in the initial coupling product. In our previous work,[4a] we had noted that terminal olefins are not compatible with the regioselective alkylation reaction presumably due to a competitive binding to the active Pd(II) species. When applying 1,3-dibromopropane as the reagent, the formation of olefins could not be completely suppressed under any of the chosen conditions and their presence may be responsible for the sluggish conversion.

Since we observed in all experiments with 1,3-dibromopropane as biselectrophile a monoalkylation at position C2 we probed whether the ring formation was also possible in the absence of palladium. Indeed, there is precedence for an intramolecular alkylation at nitrogen and compound **3a** has been previously prepared by this process.[10] Likewise, there is also precedence for the formation of 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indoles[11] by an intramolecular C–C bond formation at position C2.[12] In our hands, the expected cyclization was mediated by the same base (K_2CO_3) that was previously used in the Pd(II)-catalyzed process. Starting from 2-(3-bromopropyl)indole (**4**) the desired product was obtained in 54% yield (Scheme 3). Given the precedence for the cyclization to tricyclic product **3a**, further optimization was not attempted. In combination with the low yields obtained for the direct conversion of indole into product **3a** (Scheme 1), the results suggest that palladium is not required for the cyclization, but rather has a detrimental influence.

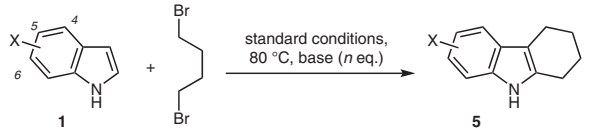


Scheme 3 Preparation of 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole (**3a**) by intramolecular alkylation of bromide **4**

Gratifyingly, the reactions of 1,4-dibromobutane and indoles **1** delivered synthetically more useful results than the reactions of 1,3-dibromopropane. It was found that particularly electron-deficient indoles underwent a smooth cascade reaction that eventually led to 1,2,3,4-tetrahydrocarbazoles in a single reaction step. Although reactions of indoles with a related bond set have been previously reported[13] there is only limited precedence[14] for the annulation of an unsubstituted cyclohexane ring to indoles in a single synthetic step. Table 1 summarizes the best results for a given indole substrate **1** obtained from employing either 2 equivalents of K_2CO_3 or 3 equiv of K_2HPO_4 as the base under standard conditions at 80 °C.

Remarkably, the reactions of indoles **1** did not generate any 2-(4-bromobutyl)indole as side product indicating that the cyclization to the 1,2,3,4-tetrahydrocarbazole is fast once the C2–alkyl bond is formed. The weaker base K_2HPO_4 turned out to be the preferred choice for most substrates, potentially because it avoids any base-induced olefin formation. In a test reaction, it was found that the presence of allyl bromide completely suppresses the reactions of **1b** to **5b** under otherwise identical conditions. The annulation reaction turned out to be compatible with nitro (Table 1, entries 2, 8, 10), cyano (entries 3, 9), chloro (entries 4, 11), bromo (entry 5), and alkoxycarbonyl substituents (entry 7). As opposed to the reaction with 1,3-dibromopropane, the presence of an additive did not have a beneficial effect on the reaction. Rather, it led to the formation of minor quantities of the C2/N annulation product. With acidic indoles like **1b** and stronger bases such as K_2CO_3 the C2/N annulation product could be detected, but the desired C2/C3 product **5b** prevailed (see the Supporting Information). Blind experiments performed with indole **1b** in the absence of either norbornene or palladium catalyst led to no reaction in the

Table 1 Formation of 1,2,3,4-Tetrahydrocarbazoles from Indoles by a Pd(II)-Catalyzed and Norbornene-Mediated Twofold Alkylation Cascade



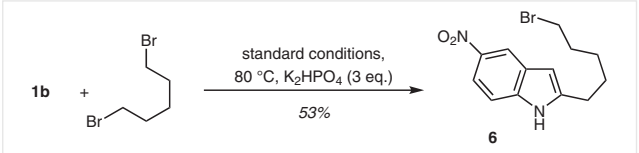
1 5

Entry	X[a]	Indole	Base	Eq.[b]	Product	Yield (%)
1	H	**1a**	K_2CO_3	2	**5a**	31
2	5-NO_2	**1b**	K_2HPO_4	3	**5b**	68
3	5-CN	**1c**	K_2HPO_4	3	**5c**	60
4	5-Cl	**1d**	K_2CO_3	2	**5d**	58
5	5-Br	**1e**	K_2CO_3	2	**5e**	47
6	5-CF_3	**1f**	K_2HPO_4	3	**5f**	38
7	5-CO_2t-Bu	**1g**	K_2CO_3	2	**5g**	56
8	4-NO_2	**1h**	K_2HPO_4	3	**5h**	55
9	4-CN	**1i**	K_2HPO_4	3	**5i**	50
10	6-NO_2	**1j**	K_2HPO_4	3	**5j**	58
11	6-Cl	**1k**	K_2CO_3	2	**5k**	53

[a] Position in starting indole **1**.
[b] Equivalents *n* of base employed in the individual reaction.
[c] Yield of isolated product after column chromatography.

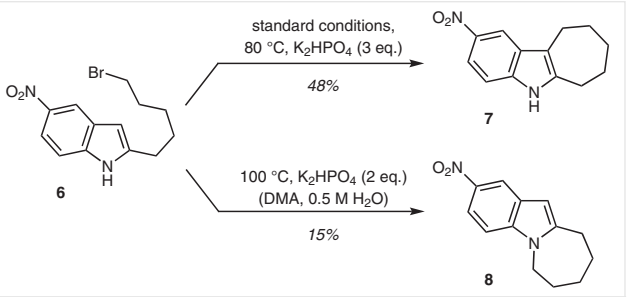
latter case and to a minimal conversion in the former case with the respective *N*-substituted indole being the only product.

Attempts to convert 1,5-dibromopentane with indoles into the respective 5,6,7,8,9,10-hexahydrocyclohepta[*b*]indoles resulted mainly in C2-monosubstitution products (Scheme 4). The reaction of 5-nitroindole (**1b**), for example, provided at 80 °C the 2-(5-bromopentyl)indole **6** in 53% yield together with the desired C2/C3 annulated indole as a byproduct (10% yield).



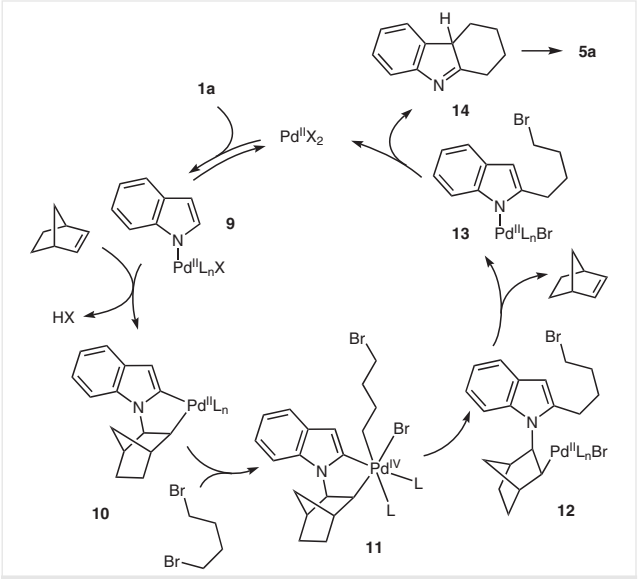
Scheme 4 C2-selective alkylation of 5-nitroindole (**3b**) to 2-(5-bromopentyl)indole **6**

The minor quantities of C2/C3 annulation product obtained in the direct reaction of indole **1b** indicated that it was possible to achieve a cyclization in a subsequent step. Indeed, application of the standard conditions to substrate **6** led to the expected product **7**[15] in 48% yield (Scheme 5). In contrast to 2-(3-bromopropyl)indoles, the cyclization to position C3[16] seems feasible for 2-(5-bromopentyl)indoles and offers access to cyclohepta[*b*]indoles.[17,18] In the absence of palladium and norbornene, base treatment of substrate **6** did not lead to a notable cyclization. However, at a higher temperature (100 °C) an intramolecular alkylation to product **8** was observed. In the absence of palladium, the regioselectivity of the cyclization changed from a C3-alkylation to an *N*-alkylation. The synthesis of 7,8,9,10-tetrahydro-6*H*-azepino[1,2-*a*]indoles by intramolecular *N*-alkylation has been previously reported.[19]



Scheme 5 Regiodivergent cyclization of 2-(5-bromopentyl)-5-nitroindole (**6**) to products **7** and **8**

In combination with the results obtained for the other 1,n-dibromoalkanes it appears as if palladium coordination to the indole nitrogen atom favors alkylation[20] at carbon atom C3 but retards *N*-alkylation. This hypothesis is supported by the exclusive formation of product **7** from **6** upon palladium catalysis and by the fact that there was no formation of 2-(4-bromobutyl)indoles observed in the reaction of indoles with 1,4-dibromobutane (Table 1). Rather, the C3 alkylation succeeded rapidly the initial C–C bond-forming step at carbon atom C2. Mechanistically, the reaction is suggested to follow the established pattern for a norbornene-mediated C2 alkylation (Scheme 6).[4b] Palladation at the



Scheme 6 Mechanistic proposal for the cascade reaction of indoles to 1,2,3,4-tetrahydrocarbazoles with the transformation **1a** → **5a** as a representative example

nitrogen atom generates intermediate **9** (L = ligand, X = Br, Cl) which undergoes intermolecular aminopalladation at norbornene[21,22] followed by C–H activation at position C2. The intermediate palladacycle **10** could be isolated with stabilizing ligands L at the palladium center and its structure was proven by single crystal X-ray crystallography.[4b] Oxidative addition to 1,4-dibromobutane provides access to Pd(IV) intermediate **11** which after reductive elimination delivers the C2-alkylated intermediate **12**. After liberation of norbornene, palladium complex **13** is perfectly suited for an intramolecular nucleophilic substitution of the second bromide. This step is irreversible and closes the catalytic cycle delivering indolenine **14** which tautomerizes to the final product **5a**.

If the cyclization is slow the catalytic cycle can also be closed by hydro-de-palladation which appears to be the preferred reaction course for 1,5-dibromopentane as the biselectrophile. For 1,3-dibromopropane, cyclization at C3 seems not possible for stereoelectronic reasons[23] and a slow cyclization to 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole occurs.

In summary, the reactions of indoles with 1,n-dibromoalkanes in the presence of $PdCl_2(MeCN)_2$ and norbornene provide access to annulated indoles. Substitution reactions at C2 and N prevail with 1,3-dibromopropane as the biselectrophile but the overall transformation suffers from a relatively low yield. The reaction with 1,4-dibromobutane is a synthetically useful method for the preparation of 1,2,3,4-tetrahydrocarbazoles and offers options for further optimization. Indeed, all reactions were performed under standard conditions without a specific adaption to the individual substrate. Finally, the attempted reaction with 1,5-dibromopentane gave mainly monoalkylation at C2, but the primary product could be cyclized to a cyclohepta[*b*]indole.

Thin-layer chromatography (TLC) was performed on silica-coated glass plates (silica gel 60 F254) with detection by UV (λ = 254 nm) and $KMnO_4$ (0.5% in water) upon subsequent heating. Flash column chromatography (FCC) was performed on silica gel 60 (Merck, 230–400 mesh) with the indicated eluent. Common solvents for chromatography (pentane, Et_2O) were distilled prior to use. Solutions refer to saturated aqueous solutions unless otherwise stated. All melting points were determined using a Büchi M 565 melting point apparatus, with a range quoted to the nearest integer. IR spectra were recorded on a JASCO IR-4100 instrument (ATR). HRMS measurements were performed on a Thermo Scientific LTQ-FT Ultra (ESI) or a Thermo Scientific DFS-HRMS spectrometer (EI). ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 K on a Bruker AVHD-400, Bruker AV-500cr or a Bruker AVHD-500 instrument. Chemical shifts are reported relative to TMS (δ = 0.00). Apparent multiplets that occur as a result of the accidental equality of coupling constants to those of magnetically non-equivalent protons are marked as virtual (*virt*). Assignments are based on COSY, HMBC, and HSQC experiments. Signals that could not be assigned unambiguously are marked with an asterisk (*).

General Alkylation Procedure (GP)

A round-bottom flask was charged with the corresponding indole (1.0 eq.), norbornene (2.0 eq.), base [K_2CO_3 (2.0 eq.) or K_2HPO_4 (3.0 eq.); as indicated], $PdCl_2(MeCN)_2$ (10 mol%), and the corresponding bromide (2.0 eq.). A 0.5 M solution of water in DMA (ca. 5 mL per mmol indole) was added. The mixture was then placed in a preheated oil bath at 80 °C. Vigorous stirring was applied and the mixture was kept under a balloon pressure of argon for 24 h. After cooling to r.t., the mixture was diluted with Et_2O (80 mL) and washed with water (80 mL). The aqueous layer was extracted with Et_2O (2 × 80 mL). The combined organic layers were washed with brine (80 mL) and dried (Na_2SO_4). All volatiles were removed in vacuo and the crude material was subjected to FCC (silica gel, pentane/Et_2O) to yield the respective product.

2,3-Dihydro-1*H*-pyrrolo[1,2-*a*]indole (3a)

According to the GP, indole (117.1 mg, 1.00 mmol, 1.00 eq.), norbornene (187.7 mg, 1.99 mmol, 1.99 eq.), K_2CO_3 (276.5 mg, 2.00 mmol, 2.00 eq.), $PdCl_2(MeCN)_2$ (26.0 mg, 0.10 mmol, 0.10 eq.), 1,3-dibromopropane (210 µL, 407.5 mg, 2.02 mmol, 2.02 eq.), KBr (119.1 mg, 1.00 mmol, 1.00 eq.), and TBAB (64.1 mg, 200 µmol, 0.20 eq.) were converted as described above, but at 90 °C. After workup, the crude material was subjected to FCC (pentane/Et_2O 19:1) to afford **3a** (57.2 mg, 364 µmol, 36%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$, 300 K): δ = 2.61 (*virt* p, $^3J_1 \approx {}^3J_2$ = 7.2 Hz, 2 H, H-2), 3.02 (t, ^3J = 7.2 Hz, 2 H, H-1), 4.07 (t, ^3J = 7.2 Hz, 2 H, H-3), 6.16 (s, 1 H, H-9), 7.05 (ddd, ^3J = 7.1 Hz, 8.0 Hz, ^4J = 1.1 Hz, 1 H, H-7)*, 7.11 (ddd, ^3J = 7.1 Hz, 8.0 Hz, ^4J = 1.1 Hz, 1 H, H-6)*, 7.23 (*virt* dt, ^3J = 8.0 Hz, $^4J_1 \approx {}^4J_2$ = 1.1 Hz, 1 H, H-5), 7.54 (dd, ^3J = 8.0 Hz, ^4J = 1.1 Hz, 1 H, H-8).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ = 24.4, 28.0, 43.7, 92.4, 109.5, 119.2, 120.2, 120.4, 132.8, 133.4, 144.7.

The spectroscopic data match the literature values.[10a,12a]

7-Nitro-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole (3b)

According to the GP, 5-nitroindole (162.5 mg, 1.00 mmol, 1.00 eq.), norbornene (189.0 mg, 2.01 mmol, 2.02 eq.), K_2HPO_4 (522.9 mg, 3.00 mmol, 3.03 eq.), $PdCl_2(MeCN)_2$ (26.2 mg, 0.10 mmol, 0.10 eq.), 1,3-dibromopropane (210 µL, 407.5 mg, 2.02 mmol, 2.03 eq.), KBr (119.6 mg, 1.01 mmol, 1.01 eq.), and TBAB (64.4 mg, 200 µmol, 0.20 eq.) were converted as described above. After workup, the crude material was subjected to FCC (pentane/Et_2O 9:1) to afford **3b**[9] (78.0 mg, 386 µmol, 39%) as a yellow solid; mp 150 °C.

IR (ATR): 3080 (w, C_{ar}–H), 2953 (w, C_{alk}–H), 1510 (s), 1312 (s), 1297 (s), 895 (m), 748 cm^{-1} (s).

^{1}H NMR (500 MHz, $CDCl_3$, 300 K): δ = 2.67 (*virt* p, $^3J_1 \approx {}^3J_2$ = 7.2 Hz, 2 H, H-2), 3.06 (t, ^3J = 7.2 Hz, 2 H, H-1), 4.12 (t, ^3J = 7.2 Hz, 2 H, H-3), 6.33 (s, 1 H, H-9), 7.20 (d, ^3J = 9.0 Hz, 1 H, H-5), 8.01 (dd, ^3J = 9.0 Hz, ^4J = 2.2 Hz, 1 H, H-6), 8.47 (d, ^4J = 2.2 Hz, 1 H, H-8).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ = 24.5, 28.0, 44.1, 95.5, 109.1, 116.3, 117.6, 132.5, 135.6, 141.4, 148.2.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{11}N_2O_2$: 203.0815; found: 203.0815.

2-(3-Bromopropyl)-1*H*-indole (4)

According to the GP, indole (117.2 mg, 1.00 mmol, 1.00 eq.), norbornene (191.3 mg, 2.03 mmol, 2.03 eq.), K_2CO_3 (276.7 mg, 2.00 mmol, 2.00 eq.), $PdCl_2(MeCN)_2$ (26.0 mg, 0.10 mmol, 0.10 eq.), and 1,3-dibromopropane (210 µL, 407.5 mg, 2.02 mmol, 2.02 eq.)

were converted as described above, but at 70 °C. After workup, the crude material was subjected to FCC (pentane/Et_2O 9:1) to afford **4** (74.9 mg, 315 µmol, 31%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$, 300 K): δ = 2.26 (*virt* p, $^3J_1 \approx {}^3J_2$ = 6.8 Hz, 2 H, H-2′), 2.95 (t, ^3J = 6.8 Hz, 2 H, H-1′), 3.47 (t, ^3J = 6.8 Hz, 2 H, H-3′), 6.29 (s, 1 H, H-3), 7.09 (*virt* td, $^3J_1 \approx {}^3J_2$ = 7.5 Hz, ^4J = 1.1 Hz, 1 H, H-5), 7.15 (*virt* td, $^3J_1 \approx {}^3J_2$ = 7.5 Hz, ^4J = 1.3 Hz, 1 H, H-6), 7.32 (dd, ^3J = 7.5 Hz, ^4J = 1.1 Hz, 1 H, H-7), 7.55 (dd, ^3J = 7.5 Hz, ^4J = 1.3 Hz, 1 H, H-4), 7.92 (br s, 1 H, *N*-H).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ = 26.5, 32.1, 33.3, 100.2, 110.6, 119.9, 112.0, 121.4, 128.8, 136.0, 137.7.

The spectroscopic data match the literature values.[24]

1,2,3,4-Tetrahydro-9*H*-carbazole (5a)

According to the GP, indole (117.2 mg, 1.00 mmol, 1.00 eq.), norbornene (189.9 mg, 2.02 mmol, 2.02 eq.), K_2CO_3 (276.2 mg, 2.00 mmol, 2.00 eq.), $PdCl_2(MeCN)_2$ (26.3 mg, 0.10 mmol, 0.10 eq.), and 1,4-dibromobutane (240 µL, 439.2 mg, 2.03 mmol, 2.03 eq.) were converted as described above. After workup, the crude material was subjected to FCC (pentane/Et_2O 30:1) to afford **5a** (53.8 mg, 314 µmol, 31%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$, 300 K): δ = 1.86–1.99 (m, 4 H, H-2, H-3), 2.70–2.78 (m, 4 H, H-1, H-4), 7.08–7.17 (m, 2 H, H-6, H-7), 7.28 (dd, ^3J = 7.3 Hz, ^4J = 1.6 Hz, 1 H, H-8), 7.50 (dd, ^3J = 7.0 Hz, ^4J = 1.6 Hz, 1 H, H-5), 7.61 (br s, 1 H, *N*-H).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ = 21.0, 23.3, 23.3, 23.4, 110.2, 110.5, 117.8, 119.2, 121.1, 127.9, 134.2, 135.7.

The spectroscopic data match the literature values.[25]

6-Nitro-1,2,3,4-tetrahydro-9*H*-carbazole (5b)

According to the GP, 5-nitroindole (164.1 mg, 1.00 mmol, 1.00 eq.), norbornene (189.6 mg, 2.01 mmol, 2.01 eq.), K_2HPO_4 (523.3 mg, 3.00 mmol, 3.00 eq.), $PdCl_2(MeCN)_2$ (26.4 mg, 0.10 mmol, 0.10 eq.), and 1,4-dibromobutane (240 µL, 439.2 mg, 2.03 mmol, 2.03 eq.) were converted as described above. After workup, the crude material was subjected to FCC (pentane/Et_2O 4:1) to afford **5b** (148.3 mg, 686 µmol, 68%) as a yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$, 300 K): δ = 1.87–1.98 (m, 4 H, H-2, H-3), 2.71–2.78 (m, 4 H, H-1, H-4), 7.28 (d, ^3J = 8.9 Hz, 1 H, H-8), 8.03 (dd, ^3J = 8.9 Hz, ^4J = 2.2 Hz, 1 H, H-7), 8.08 (br s, 1 H, *N*-H), 8.42 (d, ^4J = 2.2 Hz, 1 H, H-5).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ = 20.8, 23.0, 23.1, 23.3, 110.2, 112.9, 115.1, 117.0, 127.5, 137.8, 138.9, 141.4.

The spectroscopic data match the literature values.[25]

1,2,3,4-Tetrahydro-9*H*-carbazole-6-carbonitrile (5c)

According to the GP, indole-5-carbonitrile (145.1 mg, 1.00 mmol, 1.00 eq.), norbornene (189.0 mg, 2.01 mmol, 2.01 eq.), K_2HPO_4 (522.6 mg, 3.00 mmol, 3.00 eq.), $PdCl_2(MeCN)_2$ (26.6 mg, 0.10 mmol, 0.10 eq.), and 1,4-dibromobutane (240 µL, 439.2 mg, 2.03 mmol, 2.03 eq.) were converted as described above. After workup, the crude material was subjected to FCC (pentane/Et_2O 4:1) to afford **5c** (116.8 mg, 595 µmol, 60%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$, 300 K): δ = 1.85–1.97 (m, 4 H, H-2, H-3), 2.69 (t, ^3J = 6.0 Hz, 2 H, H-4), 2.75 (t, ^3J = 6.0 Hz, 2 H, H-1), 7.30 (d, ^3J = 8.4 Hz, 1 H, H-8), 7.35 (dd, ^3J = 8.4 Hz, ^4J = 1.5 Hz, 1 H, H-7), 7.78 (d, ^4J = 1.5 Hz, 1 H, H-5), 8.02 (br s, 1 H, *N*-H).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ = 20.7, 23.0, 23.1, 23.3, 102.0, 111.1, 111.2, 121.3, 123.3, 124.3, 127.9, 136.7, 137.5.

The spectroscopic data match the literature values.[26]

6-Chloro-1,2,3,4-tetrahydro-9*H*-carbazole (5d)

According to the GP, 5-chloroindole (153.8 mg, 1.00 mmol, 1.00 eq.), norbornene (189.5 mg, 2.01 mmol, 2.01 eq.), K_2CO_3 (276.4 mg, 2.00 mmol, 2.00 eq.), $PdCl_2(MeCN)_2$ (26.9 mg, 0.10 mmol, 0.10 eq.), and 1,4-dibromobutane (240 µL, 439.2 mg, 2.03 mmol, 2.03 eq.) were converted as described above. After workup, the crude material was subjected to FCC (pentane/Et_2O 7:1) to afford **5d** (119.3 mg, 580 µmol, 58%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$, 300 K): δ = 1.82–1.95 (m, 4 H, H-2, H-3), 2.66 (t, ^3J = 6.0 Hz, 2 H, H-4), 2.72 (t, ^3J = 6.1 Hz, 2 H, H-1), 7.05 (dd, ^3J = 8.5 Hz, ^4J = 2.1 Hz, 1 H, H-7), 8.49 (d, ^3J = 8.5 Hz, 1 H, H-8), 7.41 (d, ^4J = 2.1 Hz, 1 H, H-5), 7.69 (br s, 1 H, *N*-H).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ = 20.8, 23.1, 23.1, 23.3, 110.1, 111.2, 117.4, 121.0, 124.7, 129.0, 133.9, 135.7.

The spectroscopic data match the literature values.[25]

6-Bromo-1,2,3,4-tetrahydro-9*H*-carbazole (5e)

According to the GP, 5-bromoindole (198.7 mg, 1.00 mmol, 1.00 eq.), norbornene (190.3 mg, 2.01 mmol, 2.01 eq.), K_2CO_3 (276.4 mg, 2.00 mmol, 1.99 eq.), $PdCl_2(MeCN)_2$ (26.9 mg, 0.10 mmol, 0.10 eq.), and 1,4-dibromobutane (240 µL, 439.2 mg, 2.03 mmol, 2.03 eq.) were converted as described above. After workup, the crude material was subjected to FCC (pentane/Et_2O 7:1) to afford **5e** (118.0 mg, 472 µmol, 47%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$, 300 K): δ = 1.83–1.94 (m, 4 H, H-2, H-3), 2.65 (t, ^3J = 5.9 Hz, 2 H, H-4), 2.72 (t, ^3J = 6.0 Hz, 2 H, H-1), 7.13 (d, ^3J = 8.5 Hz, 1 H, H-8), 7.18 (dd, ^3J = 8.5 Hz, ^4J = 1.8 Hz, 1 H, H-7), 7.57 (d, ^4J = 1.8 Hz, 1 H, H-5), 7.69 (br s, 1 H, *N*-H).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ = 20.9, 23.2, 23.3, 23.3, 110.1, 111.8, 112.4, 120.5, 123.7, 129.8, 134.4, 135.7.

The spectroscopic data match the literature values.[27]

6-(Trifluoromethyl)-1,2,3,4-tetrahydro-9*H*-carbazole (5f)

According to the GP, 5-(trifluoromethyl)indole (114.6 mg, 600 µmol, 1.00 eq.), norbornene (113.9 mg, 1.21 mmol, 2.01 eq.), K_2HPO_4 (313.7 mg, 1.80 mmol, 3.00 eq.), $PdCl_2(MeCN)_2$ (16.3 mg, 61.6 µmol, 0.10 eq.), and 1,4-dibromobutane (145 µL, 265.4 mg, 1.23 mmol, 2.05 eq.) were converted as described above. After workup, the crude material was subjected to FCC (pentane/Et_2O 7:1) to afford **5f** (54.9 mg, 229 µmol, 38%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$, 300 K): δ = 1.86–1.97 (m, 4 H, H-2, H-3), 2.70–2.77 (m, 4 H, H-1, H-4), 7.31 (d, ^3J = 8.5 Hz, 1 H, H-8), 7.36 (dd, ^3J = 8.5 Hz, ^4J = 1.8 Hz, 1 H, H-7), 7.75 (d, ^4J = 1.8 Hz, 1 H, H-5), 7.84 (br s, 1 H, *N*-H).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ = 20.8, 23.2, 23.2, 23.3, 110.5, 111.3, 115.5 (q, $^3J_{CF}$ = 4.3 Hz, C-5), 117.9 (q, $^3J_{CF}$ = 3.6 Hz, C-7), 121.6 (q, $^2J_{CF}$ = 31 Hz, C-6), 125.8 (q, $^1J_{CF}$ = 271 Hz, CF_3), 127.4, 136.1, 137.2.

The spectroscopic data match the literature values.[27]

tert-Butyl 1,2,3,4-Tetrahydro-9*H*-carbazole-6-carboxylate (5g)

According to the GP, *tert*-butyl indole-5-carboxylate[28] (222.2 mg, 1.01 mmol, 1.00 eq.), norbornene (190.7 mg, 2.03 mmol, 2.01 eq.), K_2CO_3 (276.1 mg, 2.00 mmol, 1.98 eq.), $PdCl_2(MeCN)_2$ (27.1 mg, 0.10 mmol, 0.10 eq.), and 1,4-dibromobutane (240 µL, 439.2 mg, 2.03

mmol, 2.03 eq.) were converted as described above. After workup, the crude material was subjected to FCC (pentane/Et_2O 4:1) to afford **5g** (153.4 mg, 565 µmol, 56%) as a white solid; mp 154 °C.

IR (ATR): 3370 (s, NH), 2927 (m, C_{alk}–H), 2841 (w, C_{alk}–H), 1682 (vs), 1477 (m), 1312 (m), 1243 (m), 1171 (s), 1085 (vs), 765 (s), 738 cm^{-1} (m).

^1H NMR (500 MHz, $CDCl_3$, 300 K): δ = 1.62 (s, 9 H, 3 CH_3), 1.84–1.95 (m, 4 H, H-2, H-3), 2.71–2.75 (m, 4 H, H-1, H-4), 7.24 (d, ^3J = 8.5 Hz, 1 H, H-8), 7.78 (dd, ^3J = 8.5 Hz, ^4J = 1.8 Hz, 1 H, H-7), 7.82 (br s, 1 H, *N*-H), 8.16 (d, ^4J = 1.8 Hz, 1 H, H-5).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ = 20.9, 23.2, 23.2, 23.3, 28.5, 80.3, 109.8, 111.7, 120.5, 122.7, 123.1, 127.6, 135.4, 138.2, 167.4.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{22}NO_2$: 272.1645; found: 272.1645.

5-Nitro-1,2,3,4-tetrahydro-9*H*-carbazole (5h)

According to the GP, 4-nitroindole (165.0 mg, 1.00 mmol, 1.00 eq.), norbornene (190.5 mg, 2.02 mmol, 2.02 eq.), K_2HPO_4 (524.3 mg, 3.01 mmol, 3.00 eq.), $PdCl_2(MeCN)_2$ (26.5 mg, 0.10 mmol, 0.10 eq.), and 1,4-dibromobutane (240 µL, 439.2 mg, 2.03 mmol, 2.03 eq.) were converted as described above. After workup, the crude material was subjected to FCC (pentane/Et_2O 3:1) to afford **5h** (118.9 mg, 550 µmol, 55%) as a yellow solid; mp 156 °C.

IR (ATR): 3341 (m, NH), 2931 (m, C_{alk}–H), 2861 (m, C_{alk}–H), 1505 (m), 1310 (s), 1271 (s), 1252 (s), 982 (s), 729 cm^{-1} (vs).

^1H NMR (500 MHz, $CDCl_3$, 300 K): δ = 1.81–1.94 (m, 4 H, H-2, H-3), 2.80 (t, ^3J = 6.2 Hz, 2 H, H-4), 2.91 (t, ^3J = 6.1 Hz, 2 H, H-1), 7.11 (*virt* t, $^3J_1 \approx {}^3J_2$ = 8.0 Hz, 1 H, H-7), 7.51 (dd, ^3J = 8.0 Hz, ^4J = 1.0 Hz, 1 H, H-8), 7.82 (dd, ^3J = 8.0 Hz, ^4J = 1.0 Hz, 1 H, H-6), 8.14 (br s, 1 H, *N*-H).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ = 22.3, 23.7, 23.8, 24.1, 109.8, 116.2, 117.3, 119.7, 120.8, 138.1, 139.4, 142.0.

HRMS-EI (70 eV): *m*/*z* [M]$^+$ calcd for $C_{12}H_{12}N_2O_2$: 216.0893; found: 216.0890; calcd for $C_{11}{}^{13}C_1H_{12}N_2O_2$: 217.0927; found: 217.0925.

1,2,3,4,-Tetrahydro-9*H*-carbazole-5-carbonitrile (5i)

According to the GP, indole-4-carbonitrile (144.7 mg, 1.00 mmol, 1.00 eq.), norbornene (189.1 mg, 2.01 mmol, 2.00 eq.), K_2HPO_4 (522.7 mg, 3.00 mmol, 2.99 eq.), $PdCl_2(MeCN)_2$ (26.8 mg, 0.10 mmol, 0.10 eq.), and 1,4-dibromobutane (240 µL, 439.2 mg, 2.03 mmol, 2.03 eq.) were converted as described above. After workup, the crude material was subjected to FCC (pentane/Et_2O 3:1) to afford **5i** (97.5 mg, 497 µmol, 50%) as a white solid; mp 137 °C.

IR (ATR): 3285 (m, NH), 3061 (w, C_{ar}–H), 2915 (w, C_{alk}–H), 2850 (w, C_{alk}–H), 2220 (m), 1328 (m), 1285 (m), 1141 (m), 778 (s), 733 cm^{-1} (s).

^1H NMR (500 MHz, $CDCl_3$, 300 K): δ = 1.86–1.95 (m, 4 H, H-2, H-3), 2.77 (t, ^3J = 5.7 Hz, 2 H, H-4), 3.03 (t, ^3J = 5.6 Hz, 2 H, H-1), 7.10 (*virt* t, $^3J_1 \approx {}^3J_2$ = 7.8 Hz, 1 H, H-7), 7.38 (d, ^3J = 7.8 Hz, 1 H, H-8), 7.46 (d, ^3J = 7.8 Hz, 1 H, H-6), 7.97 (br s, 1 H, *N*-H).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ = 21.1, 22.7, 23.1, 23.5, 100.9, 110.4, 115.0, 119.9, 120.6, 125.4, 128.1, 135.7, 137.8.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{13}N_2$: 197.1073; found: 197.1073.

7-Nitro-1,2,3,4-tetrahydro-9*H*-carbazole (5j)

According to the GP, 6-nitroindole (164.9 mg, 1.00 mmol, 1.00 eq.), norbornene (188.1 mg, 2.00 mmol, 1.99 eq.), K_2HPO_4 (526.2 mg, 3.02 mmol, 3.02 eq.), $PdCl_2(MeCN)_2$ (26.5 mg, 0.10 mmol, 0.10 eq.), and 1,4-dibromobutane (240 µL, 439.2 mg, 2.03 mmol, 2.03 eq.) were converted as described above. After workup, the crude material was subjected to FCC (pentane/Et_2O 3:1) to afford **5j** (126.4 mg, 585 µmol, 58%) as a yellow solid; mp 171 °C.

IR (ATR): 3359 (m, NH), 2929 (w, C_{alk}–H), 2844 (w, C_{alk}–H), 1556 (m), 1501 (m), 1316 (s), 1292 (vs), 1065 (s), 886 (m), 754 (s), 731 cm^{-1} (s).

^1H NMR (500 MHz, $CDCl_3$, 300 K): δ = 1.85–1.98 (m, 4 H, H-2, H-3), 2.73 (t, ^3J = 6.0 Hz, 2 H, H-4), 2.80 (t, ^3J = 6.1 Hz, 2 H, H-1), 8.71 (d, ^3J = 8.7 Hz, 1 H, H-5), 7.99 (dd, ^3J = 8.7 Hz, ^4J = 2.0 Hz, 1 H, H-6), 8.15 (br s, 1 H, *N*-H), 8.24 (d, ^4J = 2.0 Hz, 1 H, H-8).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ = 20.8, 22.8, 23.0, 23.7, 107.3, 111.9, 115.3, 117.4, 132.8, 134.1, 141.3, 142.4.

HRMS-EI (70 eV): *m*/*z* [M]$^+$ calcd for $C_{12}H_{12}N_2O_2$: 216.0893; found: 216.0888; calcd for $C_{11}{}^{13}C_1H_{12}N_2O_2$: 217.0927; found: 217.0926.

7-Chloro-1,2,3,4-tetrahydro-9*H*-carbazole (5k)

According to the, 6-chloroindole (154.1 mg, 1.00 mmol, 1.00 eq.), norbornene (192.0 mg, 2.04 mmol, 2.04 eq.), K_2CO_3 (277.4 mg, 2.01 mmol, 2.00 eq.), $PdCl_2(MeCN)_2$ (27.3 mg, 0.10 mmol, 0.10 eq.), and 1,4-dibromobutane (240 µL, 439.2 mg, 2.03 mmol, 2.03 eq.) were converted as described above. After workup, the crude material was subjected to FCC (pentane/Et_2O 7:1) to afford **5k** (109.8 mg, 534 µmol, 53%) as a white solid; mp 180 °C.

IR (ATR): 3389 (s, NH), 2941 (m, C_{alk}–H), 2853 (w, C_{alk}–H), 1619 (w), 1424 (m), 1302 (m), 1234 (m), 1060 (m), 800 cm^{-1} (vs).

^1H NMR (500 MHz, $CDCl_3$, 300 K): δ = 1.83–1.94 (m, 4 H, H-2, H-3), 2.67 (t, ^3J = 6.0 Hz, 2 H, H-4), 2.71 (t, ^3J = 6.0 Hz, 2 H, H-1), 7.03 (dd, ^3J = 8.4 Hz, ^4J = 1.8 Hz, 1 H, H-6), 7.25 (d, ^4J = 1.8 Hz, 1 H, H-8), 7.34 (d, ^3J = 8.4 Hz, 1 H, H-5), 7.66 (br s, 1 H, *N*-H).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ = 20.9, 23.2, 23.3, 23.4, 110.4, 111.2, 118.6, 119.8, 126.6, 126.8, 135.0, 136.1.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{13}N^{35}Cl$: 206.0731; found: 206.0731.

2-(5-Bromopentyl)-5-nitro-1*H*-indole (6)

According to the GP, 5-nitroindole (165.7 mg, 1.01 mmol, 1.00 eq.), norbornene (189.1 mg, 2.01 mmol, 1.99 eq.), K_2HPO_4 (523.9 mg, 3.01 mmol, 2.97 eq.), $PdCl_2(MeCN)_2$ (26.4 mg, 0.10 mmol, 0.10 eq.), and 1,5-dibromopentane (280 µL, 466.5 mg, 2.03 mmol, 2.01 eq.) were converted as described above. After workup, the crude material was subjected to FCC (pentane/Et_2O 2:1) to afford **6** (167.8 mg, 539 µmol, 53%) as a yellow solid; mp 67 °C.

IR (ATR): 3324 (m, NH), 2934 (w, C_{alk}–H), 2856 (w, C_{alk}–H), 1473 (s), 1068 (s), 892 (m), 750 cm^{-1} (s).

^1H NMR (500 MHz, $CDCl_3$, 300 K): δ = 1.53–1.59 (m, 2 H, H-3′), 1.74–1.86 (m, 2 H, H-2′), 1.88–1.97 (m, 2 H, H-4′), 2.82 (t, ^3J = 7.6 Hz, 2 H, H-1′), 3.42 (t, ^3J = 6.7 Hz, 2 H, H-5′), 6.41 (s, 1 H, H-3), 7.32 (d, ^3J = 9.0 Hz, 1 H, H-7), 8.04 (dd, ^3J = 9.0 Hz, ^4J = 2.3 Hz, 1 H, H-6), 8.37 (br s, 1 H, *N*-H), 8.48 (d, ^4J = 2.3 Hz, 1 H, H-4).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ = 27.9, 28.1, 28.2, 32.5, 33.7, 102.0, 110.3, 117.0, 117.1, 128.3, 139.2, 142.0, 143.0.

HRMS-EI (70 eV): *m*/*z* [M]$^+$ calcd for $C_{13}H_{15}N_2O_2{}^{79}Br$: 310.0311; found: 310.0304; calcd for $C_{12}{}^{13}C_1H_{15}N_2O_2{}^{79}Br$: 311.0345; found: 311.0341.

2-Nitro-5,6,7,8,9,10-hexahydrocyclohepta[*b*]indole (7)

According to the GP, 2-(5-bromopentyl)-5-nitro-1*H*-indole (**6**; 31.1 mg, 99.9 µmol, 1.00 eq.), norbornene (18.9 mg, 200 µmol, 2.01 eq.), K_2HPO_4 (51.9 mg, 298 µmol, 2.98 eq.), and $PdCl_2(MeCN)_2$

(3.00 mg, 11.3 µmol, 0.11 eq.) were converted as described above. After workup, the crude material was subjected to FCC (pentane/Et_2O 3:1) to afford **7**[15] (11.0 mg, 47.8 µmol, 48%) as a yellow solid; mp 163 °C.

IR (ATR): 3328 (m, NH), 3101 (w, C_{ar}–H), 2921 (m, C_{alk}–H), 2847 (w, C_{alk}–H), 1475 (m), 1316 (s), 1276 cm^{-1} (m).

^1H NMR (500 MHz, $CDCl_3$, 300 K): δ = 1.75–1.84 (m, 4 H, H-7, H-8)*, 1.88–1.95 (m, 2 H, H-9)*, 2.82–2.89 (m, 4 H, H-6, H-10), 7.26 (d, ^3J = 8.9 Hz, 1 H, H-4), 8.01 (dd, ^3J = 8.9 Hz, ^4J = 2.2 Hz, 1 H, H-3), 8.10 (br s, 1 H, *N*-H), 8.44 (d, ^4J = 2.2 Hz, 1 H, H-1).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ = 24.7, 27.3, 28.5, 29.7, 31.6, 110.1, 115.2, 116.4, 116.6, 128.9, 137.5, 140.9, 141.5.

HRMS-EI (70 eV): *m*/*z* $[M]^+$ calcd for $C_{13}H_{14}N_2O_2$: 230.1050; found: 230.1047; calcd for $C_{12}{}^{13}C_1H_{14}N_2O_2$: 231.1083; found: 231.1081.

2-Nitro-7,8,9,10-tetrahydro-6*H*-azepino[1,2-*a*]indole (8)

2-(5-Bromopentyl)-5-nitro-1*H*-indole (**6**; 30.9 mg, 99.3 µmol, 1.00 eq.) and K_2HPO_4 (34.9 mg, 200 µmol, 2.02 eq.) were dissolved in 0.5 M water in DMA solution (5 mL). The mixture was heated at 100 °C for 24 h. After usual workup (see GP), the crude material was subjected to FCC (pentane/Et_2O 9:1) to afford **8** (3.5 mg, 15.2 µmol, 15%) as a yellow solid; mp 115 °C.

IR (ATR): 3089 (w, C_{ar}–H), 2932 (m, C_{alk}–H), 2854 (w, C_{alk}–H), 1510 (s), 1332 (s), 1285 (m), 1070 (m), 753 cm^{-1} (m).

^1H NMR (500 MHz, $CDCl_3$, 300 K): δ = 1.74–1.85 (m, 4 H, H-7, H-8), 1.86–1.93 (m, 2 H, H-9), 2.93 (t, ^3J = 5.5 Hz, 2 H, H-10), 4.20 (t, ^3J = 4.5 Hz, 2 H, H-6), 6.41 (s, 1 H, H-11), 7.25 (d, ^3J = 9.2 Hz, 1 H, H-4), 8.05 (dd, ^3J = 9.2 Hz, ^4J = 2.3 Hz, 1 H, H-3), 8.47 (d, ^4J = 2.3 Hz, 1 H, H-1).

^{13}C NMR (126 MHz, $CDCl_3$, 300 K): δ = 27.9, 28.8, 29.4, 31.0, 45.5, 101.8, 108.5, 116.5, 117.2, 127.2, 139.9, 141.2, 146.9.

HRMS-EI (70 eV): *m*/*z* $[M]^+$ calcd for $C_{13}H_{14}N_2O_2$: 230.1050; found: 230.1048; calcd for $C_{12}{}^{13}C_1H_{14}N_2O_2$: 231.1083; found: 231.1083.

Funding Information

This project was supported by the Deutsche Forschungsgemeinschaft (BA 1372/19-1) and by the Technische Universität München (TUM) Graduate School.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690693.

Primary Data

for this article are available online at https://doi.org/10.1055/s-0039-1690693 and can be cited using the following DOI: 10.4125/pd0108th.

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