JOC The Journal of Organic Chemistry

Article

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Synthesis of 1,2-Disubstituted Indoles from α-Aminonitriles and 2-Halobenzyl Halides

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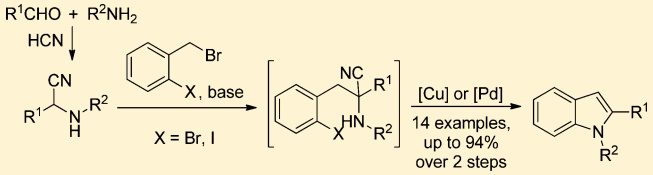
Supporting Information

ABSTRACT: The α-alkylation of deprotonated Strecker products derived from primary amines and aromatic aldehydes with 2-halobenzyl halides furnishes intermediates that can be cyclized to 1,2-disubstituted indoles in moderate to high yields (up to 94% over two steps) by microwave-assisted copper- or palladium-catalyzed intramolecular cross-coupling.



INTRODUCTION

The indole nucleus is one of the most ubiquitous moieties found in bioactive heterocyclic compounds. Various drugs and an overwhelming number of natural products bearing an indole moiety are known, e.g., serotonin, lysergic acid, and the triptans.[1−3] Due to its paramount role in the chemistry of life, numerous synthetic approaches toward indoles have been developed over the last century, including well-established procedures like the Fischer indole synthesis, the Larock indole synthesis, and the Batcho−Leimgruber synthesis.[4−7] In view of the large structural diversity of indole derivatives and their importance for biomedical applications, the development of new and efficient protocols for the assembly and decoration of indoles still represent a rewarding task for academic and industrial research. In the past decades transition-metal-catalyzed cross-coupling reactions and cyclizations have emerged as powerful tools for the synthesis of heterocycles. Today numerous transition-metal-catalyzed syntheses of indoles exist, including catalysis by copper, palladium, ruthenium, and other metals.[8,9] The Hegedus indole synthesis and the Larock indole synthesis are only two out of many examples for transition-metal-catalyzed indole syntheses.[4,10]

One possible retrosynthetic strategy for the synthesis of substituted indoles (**9**) focuses on the transition-metal-catalyzed cyclization of imines **3** or the corresponding enamines. The employed imines or enamines are mostly formed in situ from ketones **1** and amines, as reported by May and co-workers and by Karchava and co-workers.[11,12] A Pd-catalyzed double arylation of preformed imines was used by the Barluenga group to access intermediates **3** in situ, which cyclize to indoles **9** under the same reaction conditions.[13] The Buchwald group obtained indoles **9** by dehydrogenation of indolines **11** prepared by Pd-catalyzed aryl amination reaction from dibromides **12**.[14] Following the same strategy, Monguchi et al. obtained indoles **9** from phenethylamines **10**.[15] The Willis group synthesized benzofurans and benzothiphenes from benzyl ketones.[16] The same authors also employed 2-(2-haloalkenyl) halides **2** and amines as substrates for the synthesis of indoles **9**.[17] Following this retrosynthetic approach, we assumed that it should also be possible to prepare 1,2-substituted indoles **9** by transition-metal-catalyzed cyclization from α-aminonitriles **8**, which in turn can be prepared by C-benzylation of α-aminonitriles **7**. Substrates **7** can be easily obtained commercially available and cheap starting materials using a Strecker reaction. Thus, the C2−N-fragment of the indole ring would be preassembled in a modular fashion prior to attachment of the other ring atoms (Scheme 1).

The outlined route should also permit the synthesis of isoquinolin-1-ones by a carbonylative process. Isoquinolin-1-ones (isocarbostyrils) are also found in nature, although they are not as well-known and widespread as indoles. Nevertheless, their skeleton is represented in a number of alkaloids and drugs with interesting pharmaceutical and biological properties, e.g., narciclasine, palonosetron, and tilisolol. Since isoquinolin-1-ones are found in antidepressant, anti-inflammatory, and anticancer drugs, diverse methods for their preparation exist.[18−21] Two of these strategies also feature the construction of the C1−C8a and C1−N bonds. Lete et al. prepared isoquinolin-1-ones by *ortho*-lithiiation, formylation, and cyclization of phenethylamines, while a transition-metal-catalyzed carbonylation/cyclization from *o*-bromophenethylamines was employed by Beak et al.[22,23]

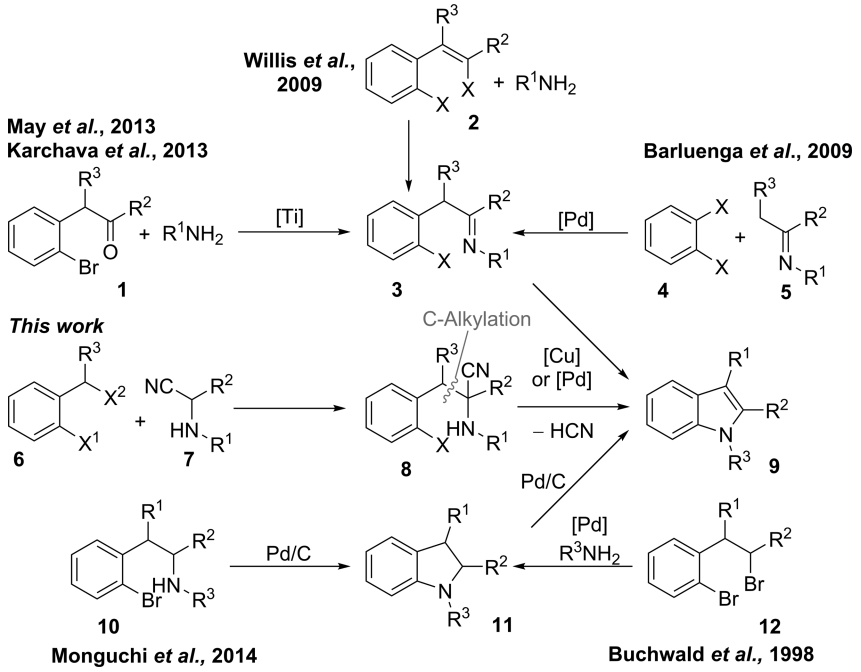
RESULTS AND DISCUSSION

In a first attempt to synthesize 1,2-disubstituted indoles **9**, 1,2-diphenyl-1*H*-indole (**9a**) was chosen as a model compound. 2-Phenyl-2-phenylaminoacetonitrile (**7a**) was C-alkylated with 1-(bromomethyl)-2-iodobenzene (**6a**) to obtain a starting material for transition-metal-catalyzed cyclization reactions. An alkylation procedure developed earlier by us for the synthesis of 4-quinolones was used as the starting point for an optimization of the reaction conditions.[24] It turned out that the deprotonation should be carried out at −78 °C, while the temperature should be gradually raised to −20 °C after addition of the electrophile to ensure a complete conversion and to prevent the undesired retro-Strecker reaction (Scheme 2).

Received: November 20, 2015
Published: February 2, 2016

DOI: 10.1021/acs.joc.5b02659
J. Org. Chem. 2016, 81, 1858−1869

Scheme 1. Exemplary Synthetic Approaches toward Indoles



Scheme 2. Deprotonation and Alkylation of α-Aminonitriles 7 Affording α-Aminonitriles 8

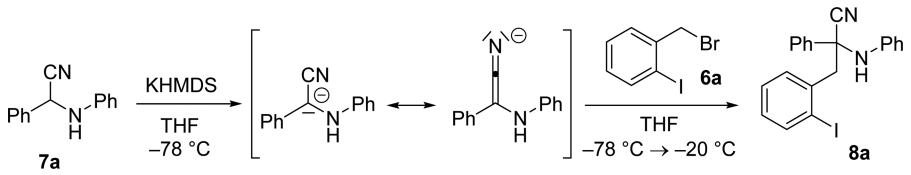
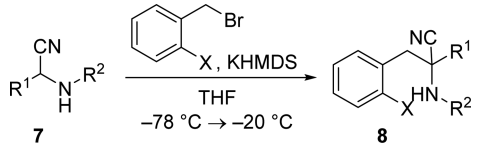


Table 1. Synthesis of Alkylated α-Aminonitriles 8a–o[a]



entry	aminonitrile	R^1	R^2	X	product	yield/%
1	**7a**	Ph	Ph	I	**8a**	43[b]
2	**7a**	Ph	Ph	Br	**8b**	70[b]
3	**7b**	Ph	Cy	I	**8c**	85[c]
4	**7c**	Ph	^{i}Pr	Br	**8d**	77[c]
5	**7d**	4-ClC_6H_4	mesityl	Br	**8e**	39[c]
6	**7e**	4-$MeOC_6H_4$	4-benzoylphenyl	I	**8f**	66[b]
7	**7f**	4-ClC_6H_4	4-$MeOC_6H_4$	I	**8g**	70[c]
8	**7g**	naphthalen-2-yl	4-$MeOC_6H_4$	I	**8h**	32[c]
9	**7h**	naphthalen-2-yl	4-benzoylphenyl	I	**8i**	95[c]
10	**7i**	naphthalen-2-yl	Me	I	**8j**	62[c]
11	**7j**	4-$MeOC_6H_4$	mesityl	I	**8k**	38[c]
12	**7k**	4-ClC_6H_4	4-ClC_6H_4	I	**8l**	96[c]
13	**7l**	4-ClC_6H_4	*p*-tolyl	I	**8m**	71[c]
14	**7m**	4-$MeOC_6H_4$	*p*-tolyl	I	**8n**	31[c]
15	**7n**	4-FC_6H_4	CH_2CH_2Ph	I	**8o**	68[c]

[a]Reaction conditions: **7** (1.0 equiv), KHMDS (1.3 equiv), **6a** or **6b** (1.3 equiv) in THF (12 mL per mmol **7**) at −78 to −20 °C. [b]Isolated yield. [c]Determined using dimethyl sulfone as internal NMR standard.[26]

The anion-stabilizing effect of at least one C=C double bond or an aromatic or heteroaromatic ring in conjugation to the α-center of the α-aminonitrile is required to ensure the correct regiochemistry in the deprotonation step if no N-protecting groups are used.[25] The results of the alkylation of α-aminonitriles **7a–n** with 1-(bromomethyl)-2-iodobenzene (**6a**) or 1-(bromo-

DOI: 10.1021/acs.joc.5b02659
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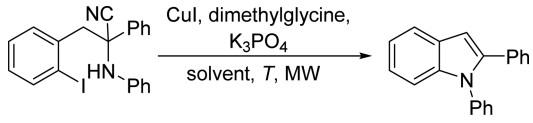
methyl)-2-bromobenzene (**6b**) are summarized above (Table 1). In particular, the alkylation of α-aminonitriles **7** carrying bulky N-substituents R^2 with the sterically more demanding electrophile **6a** afforded lower yields, while higher yields were observed for α-aminonitriles with electron-withdrawing N-substituents (e.g., the 4-benzoylphenyl-substituent in **8f** and **8i**). Since the alkylation products **8** were prone to spontaneous dehydrocyanation, isolation and purification by silica gel column chromatography were impracticable and the crude alkylation products were subjected to the metal-catalyzed ring closure (vide infra). Only compounds **8a**, **8b**, and **8f** could be purified by flash chromatography without significant losses of yield or complete decomposition.

The cyclization of alkylation product **8a** to indole **9a** was attempted in a copper-catalyzed Ullmann-type reaction and with a palladium-catalyzed Buchwald–Hartwig-type reaction.[27−30] Both methods were optimized with respect to catalyst loadings and yields before α-aminonitriles **7b–n** were synthesized and subjected to the reaction sequence to investigate the scope of the reaction. As the bromides proved to be unsuitable for the copper-catalyzed cross-coupling reaction, only the iodides could be employed.

Initial experiments on the Ullmann-type cyclization of **8a** to **9a** were performed according to a modified protocol of Ma and Cai employing CuI (50 mol %), dimethylglycine (50 mol %), and K_3PO_4 (2.0 equiv) in 1,4-dioxane with microwave irradiation at 150 °C.[31] Since **9a** could not be obtained under these conditions, other solvents (DMF, DMSO, NMP) were tested, proving NMP to be the most suitable reaction medium (Table 2).

Table 2. Screening of Different Solvents for the Ullmann-Type Reaction[a]

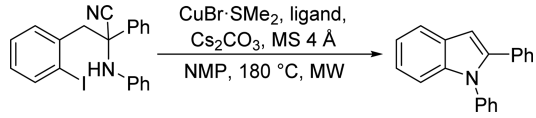


entry	solvent	reaction conditions	yield/%
1	1,4-dioxane	150 °C, 10 min	–
2	DMF	220 °C, 10 min	40[b]
3	DMSO	290 °C, 10 min	–
4	NMP	180 °C, 10 min	62[b]

[a]Reaction conditions: CuI (0.5 equiv), dimethylglycine (0.5 equiv), K_3PO_4 (2.0 equiv) under microwave irradiation. [b]Determined using dimethyl sulfone as internal NMR standard.[26]

Under the above-mentioned conditions with NMP as the solvent, **9a** could be obtained in a yield of 62%. In the course of the optimization process, the catalytic system was changed to CuBr·SMe_2 (50 mol %) and Cs_2CO_3 (2.0 equiv) in NMP with microwave irradiation at 180 °C and afforded **9a** in quantitative yield within 1 h without any ligand added. Attempts to reduce the catalyst loading to 20 mol % resulted in lower yields, but these could be increased by addition of neocuproine hemihydrate as a ligand for copper. Prior to the optimization process, 1,10-phenanthroline, and 1,2-diaminocyclohexane were screened as alternative ligands. While the utilization of 1,2-diaminocyclohexane resulted in slightly lower yields compared to neocuproine, utilization of dimethylglycine was impractible due to low conversion. Application of 1,10-phenanthroline surprisingly did not lead to any conversion of **8a** to **9a**, since the catalyst precipitated under identical conditions. The optimization process also revealed that a longer reaction time resulted in decreased yields (Table 3).

Table 3. Optimization of the Ullmann-Type Reaction[a]



entry	catalyst loading/mol %	ligand	solvent	reaction conditions	yield/%
1	50	–	NMP	180 °C, 60 min	quant[b]
2	20	–	NMP	180 °C, 60 min	43[b]
3	20	neocup[c]	NMP	180 °C, 60 min	64[b]
4	20	1,2-diamino-cyclohexane	NMP	180 °C, 60 min	58[d]
5	20	neocup	NMP	180 °C, 20 min	32[d]
6	20	neocup	NMP	150 °C, 60 min	–[e]
7	20	neocup	NMP	180 °C, 120 min	54[b]
8	10	neocup	NMP	180 °C, 120 min	20[d]

[a]Reaction conditions: CuBr·SMe_2, ligand (ligand–copper ratio 1:1), Cs_2CO_3 (2.0 equiv) in NMP with microwave irradiation. [b]Isolated yield. [c]Neocup = neocuproine. [d]Determined using dimethyl sulfone as internal NMR standard.[26] [e]Due to low purity, the yield could not be determined.

Decreasing the temperature led to a drastically increased amount of byproducts and incomplete conversion. Subsequently, other alkylated α-aminonitriles were subjected without prior purification to the modified reaction conditions to obtain indoles **9a–g** in 28–76% yield over two steps from aminonitriles **7** (Table 4).

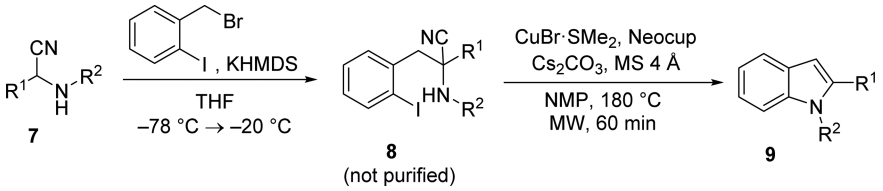
The cyclization of alkylated α-aminonitriles **8** was also performed in a palladium-catalyzed Buchwald–Hartwig-type reaction. The method was optimized for the conversion of **8b** to indole **9a** (for key steps of the optimization process, see Table 5).

Initially, the procedure of Wennemers and co-workers using $Pd(OAc)_2$ (50 mol %), DPEphos (50 mol %), and Cs_2CO_3 (3.0 equiv) in toluene at 110 °C (conventional heating) was applied.[32] Since **9a** was only formed in traces under these conditions, all subsequent reactions were carried out under microwave irradiation. An initial attempt to synthesize **9a** using the above-mentioned catalytic system in toluene under microwave irradiation (150 °C) afforded **9a** with a yield of 32% after a reaction time of 30 min. Screening of other solvents proved EtOH to be more effective, but lowering of the catalyst loading to 10 mol % led to a drastically increased formation of byproducts. Therefore, the catalytic system was switched to $PdCl_2$ (10 mol %), dppf (10 mol %), and NaO^{t}Bu (3.0 equiv) in toluene at 150 °C under microwave irradiation.[33] The reaction time was extended to 90 min to ensure the complete conversion of the starting materials. This method afforded indole **9a** with a yield of 85%. Lowering of the catalyst loading to 5 mol % still provided **9a** in 84% yield.

The reaction was applied to other substrates, but for practical reasons, the cyclization was again performed without purification of the alkylated aminonitriles **8** (Table 6).

DOI: 10.1021/acs.joc.5b02659
J. Org. Chem. 2016, 81, 1858–1869

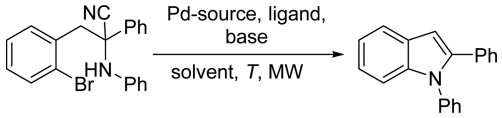
Table 4. Synthesis of Indoles 9 from α-Aminonitriles 7 by Copper-Catalyzed Cyclization



entry	aminonitrile	R^1	R^2	product	yield (from 7)/%[a]
1	**7a**	Ph	Ph	**9a**	28
2	**7b**	Ph	Cy	**9b**	76
3	**7f**	4-ClC_6H_4	4-$MeOC_6H_4$	**9c**	56
4	**7h**	naphthalen-2-yl	4-benzoylphenyl	**9d**	76
5	**7i**	naphthalen-2-yl	Me	**9e**	46
6	**7k**	4-ClC_6H_4	4-ClC_6H_4	**9f**	64
7	**7n**	4-FC_6H_4	CH_2CH_2Ph	**9g**	58

[a]Isolated yield.

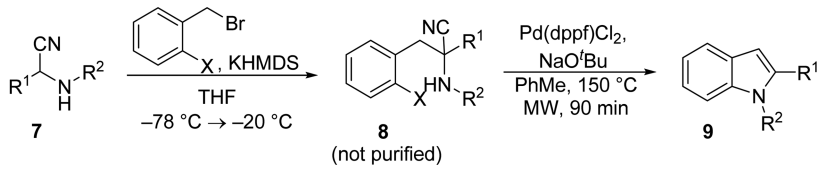
Table 5. Optimization of the Buchwald−Hartwig-Type Reaction



entry	Pd source, mol %	ligand, mol %	base, equiv	solvent	reaction conditions	yield/%
1	$Pd(OAc)_2$, 50	DPEphos, 50	Cs_2CO_3, 3.0; 4 Å MS[d]	toluene	110 °C (conventional heating), 30 min	–[c]
2	$Pd(OAc)_2$, 50	DPEphos, 50	Cs_2CO_3, 3.0; 4 Å MS	toluene	150 °C (MW[e]), 30 min	32[a]
3	$Pd(OAc)_2$, 20	DPEphos, 30	Cs_2CO_3, 3.0; 4 Å MS	DMF	180 °C (MW), 30 min	47[a]
4	$Pd(OAc)_2$, 20	DPEphos, 30	Cs_2CO_3, 3.0; 4 Å MS	EtOH	150 °C (MW), 30 min	76[b]
5	$Pd(OAc)_2$, 10	DPEphos, 15	Cs_2CO_3, 3.0; 4 Å MS	EtOH	150 °C (MW), 30 min	–[c]
6	$PdCl_2$, 10	dppf, 10	NaO^tBu, 3.0	toluene	180 °C (MW), 90 min	85[b]
7	$PdCl_2$, 5	dppf, 5	NaO^tBu, 3.0	toluene	180 °C (MW), 90 min	84[a]

[a]Isolated yield. [b]Determined using dimethyl sulfone as internal NMR standard.[26] [c]Due to low purity, the yield could not be determined. [d]MS = molecular sieve. [e]MW = microwave irradiation.

Table 6. Synthesis of 1,2-Substituted Indoles 9 from Alkylated α-Aminonitriles 8 by Palladium-Catalyzed Cyclization



entry	aminonitrile	R^1	R^2	X	product	yield over two steps/%[a]
1	**7a**	Ph	Ph	Br	**9a**	59
2	**7b**	Ph	Cy	I	**9b**	4
3	**7f**	4-ClC_6H_4	4-$MeOC_6H_4$	I	**9c**	34
4	**7h**	naphthalen-2-yl	4-benzoylphenyl	I	**9d**	94
5	**7i**	naphthalen-2-yl	Me	I	**9e**	26
6	**7k**	4-ClC_6H_4	4-ClC_6H_4	I	**9f**	64
7	**7n**	4-FC_6H_4	CH_2CH_2Ph	I	**9g**	49
8	**7c**	Ph	^{i}Pr	Br	**9h**	34
9	**7d**	4-ClC_6H_4	mesityl	Br	**9i**	32
10	**7e**	4-$MeOC_6H_4$	4-benzoylphenyl	I	**9j**	49
11	**7j**	4-$MeOC_6H_4$	mesityl	I	**9k**	28
12	**7g**	naphthalen-2-yl	4-$MeOC_6H_4$	I	**9l**	31
13	**7l**	4-ClC_6H_4	*p*-tolyl	I	**9m**	55
14	**7m**	4-$MeOC_6H_4$	*p*-tolyl	I	**9n**	21

[a]Isolated yield.

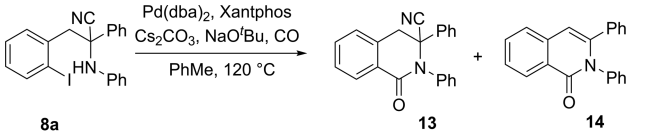
Generally, the cyclization proceeded more efficiently on aryl iodides, but since the yields for the alkylation of α-aminonitriles **7** with **6a** were low in some cases, alkylation with bromide **6b** was applied instead. Both *N*-aryl and *N*-alkyl substituents were

DOI: 10.1021/acs.joc.5b02659
J. Org. Chem. 2016, 81, 1858−1869

tolerated, although the Ullmann procedure was more efficient than palladium catalysis for *N*-alkyl substrates. Electron-withdrawing substituents R^1 and R^2 increased the efficiency of the indole synthesis, while steric hindrance and/or electron-donating substituents led to lower overall yields.

To access isoquinolin-1-ones from intermediates **8** in a palladium-catalyzed carbonylative cross-coupling reaction, **8a** was again chosen as a model substrate, and a modified protocol of Buchwald et al. was used.[34] Different palladium sources or complexes [$Pd(OAc)_2$, $Pd(dba)_2$, $Pd(dppf)Cl_2$], ligands (Xantphos, PCy_3), and bases (NaO^tBu, Cs_2CO_3) were screened in combination with gaseous CO in toluene. The system $Pd(dba)_2$ (5 mol %)/Xantphos (5.5 mol %)/Cs_2CO_3 (3.0 equiv) proved to be most effective. Using $Pd(dppf)Cl_2$ as the catalytic system as well as NaO^tBu as the base afforded large amounts of indole **9a** instead. Since application of Cs_2CO_3 as the base did not yield **9a** as a byproduct but also did not promote complete dehydrocyanation of the previously formed carbonitrile **13**, NaO^tBu was added after complete consumption of the starting material (TLC and HPLC–ESI-MS) to promote the dehydrocyanation of intermediate **13** to isoquinolin-1-one **14** (Scheme 3).

Scheme 3. Synthesis of 2,3-diphenylisoquinolin-1-one (14) from 8a



We also found that the reaction temperature had to be increased to 120 °C compared to the temperature used by Buchwald et al. (80 °C), since only incomplete conversion of the starting materials was otherwise observed. With the optimized protocol, 2,3-diphenylisoquinolin-1-one (**14**) was obtained from **8a** in 53% yield. Although higher conversions were likely achievable in this way, the use of pressurized CO in the cyclocarbonylation was refrained from for safety reasons.

CONCLUSION

In summary, two simple procedures for the synthesis of 1,2-disubstituted indoles from α-aminonitriles based on an Ullmann- and a Buchwald–Hartwig-type ring closure were developed, and yields of up to 94% over two steps could be achieved. A modification of the latter procedure also permits the synthesis of isoquinolin-1-ones. While the N-substituent can either be an alkyl or an aryl group in both cases, the Ullmann procedure proved more suitable for the former. The introduction of aliphatic 2-substituents into indoles (and of 3-substituents into isoquinolin-1-ones) would require an additional protection/deprotection at nitrogen and was not undertaken for the sake of operational simplicity. Advantages of the presented synthetic strategy are the modular assembly of stable precursors, i.e., the α-aminonitriles, in a facile three-component reaction that does not require strongly dehydrating conditions as, for example, necessary for the formation of imines. There is no risk for the formation of regioisomeric products, and the use of substituted 2-halobenzyl halides should allow the selective synthesis of more complex indoles. The employed elements of diversity (aldehyde, amine) are inexpensive and are available with large structural diversity. High yields can be achieved, and the use of a carbonylative coupling permits the synthesis of isoquinolin-1-ones from the same precursors.

EXPERIMENTAL SECTION

Materials and Methods. Unless otherwise noted, all reagents were reagent grade and used without further purification. NMP was purchased in "extra dry" quality (99.5%, over molecular sieves). All reactions involving air or moisture sensitive reagents or intermediates were performed in oven-dried glassware under an inert atmosphere of argon. Compounds **7d** and **7n** were previously synthesized by Jens Emsermann (Johannes Gutenberg-Universität Mainz) (for NMR data, see the Supporting Information).[35] Reaction temperatures are referred to a particular cooling/heating bath. Microwave reactions were carried out in a monomode laboratory microwave reactor with pressure monitoring and IR temperature control. Melting points were determined in open capillary tubes using an electrothermal apparatus with a resolution of 0.1 °C. NMR spectra were recorded on a 300, 400, or 600 MHz spectrometer equipped with a 5 mm BBFO probe with *z*-gradient and ATM capability. Chemical shifts were referenced to deuterated solvent (e.g., for $CDCl_3$, δ = 7.26 and 77.16 ppm; for DMSO-d_6, δ = 2.50 and 39.52 ppm for ^1H and ^{13}C NMR, respectively) and are reported in parts per million (ppm, δ) relative to tetramethylsilane (TMS, δ = 0.00 ppm).[36] Coupling constants (J) are reported in Hertz, and the splitting abbreviations used are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Standard pulse sequences were used for the 2D experiments. To evaluate the yields of compounds that could not be isolated, a defined amount of dimethyl sulfone was added to the NMR samples as internal standard.[26] To calculate the yield, the NMR signals of dimethyl sulfone were integrated and compared to characteristic signals of the sample, respectively. Infrared spectra were recorded as FT-IR spectra using a diamond ATR unit and are reported in terms of frequency of absorption (ν, cm^{-1}). High-resolution masses were recorded on a QToF-instrument with a dual electrospray source and a suitable external calibrant. Thin-layer chromatography (TLC) was carried out on 0.25 mm silica gel plates (60 F_{254}) using UV light as visualizing agent and an ethanolic solution of hydrochloric acid and 4-(*N*,*N*-dimethylamino)benzaldehyde (Ehrlich's reagent), Seebach's reagent [ethanolic solution of ammonium pentamolybdate, diluted aqueous sulfuric acid and cerium(IV) sulfate], and ninhydrin reagent (ethanolic solution of ninhydrin and acetic acid). Flash column chromatography was performed with silica gel of 35–70 μm particle size. Solvent ratios are referred to the volume fractions before mixing.

General Procedure for the Synthesis of α-Aminonitriles 7. (***Caution!*** *KCN and α-aminonitriles may release highly toxic HCN. Caution should be exercised.*) Unless otherwise stated, α-aminonitriles **7** were prepared according to the procedure of Emsermann et al.[35] The crude products were purified by washing with *n*-hexane and/or diethyl ether.

*2-Phenyl-2-(phenylamino)acetonitrile (**7a**).* The title compound was prepared according to the protocol of Opatz et al. using benzaldehyde (59.2 g, 86.5 mmol), aniline (8.05 g, 86.4 mmol), and KCN (6.19 g, 95.2 mmol).[25] Purification of the crude product by recrystallization from diethyl ether/*n*-hexane (3:1) yielded **7a** (12.7 g, 61.0 mmol, 70%, Lit.:[25] 83%) as colorless needles: mp 84.9–86.0 °C (lit.[37] mp 85–86 °C); R_f = 0.41 (silica gel, cyclohexane/ethyl acetate 5:1); IR (ATR) $\tilde{\nu}$ (cm^{-1}) = 3362, 3056, 1603, 1503, 1453, 1314, 1267, 1101, 752, 694; ^1H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 7.63–7.60 (m, 2H, *H*-2′,6′), 7.49–7.44 (m, 3H, *H*-3′,4′,5′), 7.33–7.276 (m, 2H, *H*-3″,4″), 6.94–6.89 (m, 1H, *H*-5″), 6.81–6.78 (m, 2H, *H*-2″,6″), 5.44 (d, ^3J = 8.3 Hz, 1H, *H*-2), 4.06 (d_{br}, ^3J = 8.3 Hz, 1H, N*H*); ^{13}C NMR, HSQC, HMBC (75.5 MHz, $CDCl_3$) δ (ppm) = 144.8 (*C*-1″), 134.0 (*C*-1′), 129.7 (2C, *C*-3″,5″), 129.6 (*C*-4′), 129.4 (2C, *C*-3′,5′), 127.4 (2C, *C*-2′,6′), 120.4 (*C*-4″), 118.3 (*C*-1), 114.2 (2C, *C*-2″,6″), 50.3 (*C*-2). The data are in accordance with the literature.[37]

*2-(Cyclohexylamino)-2-phenylacetonitrile (**7b**).* The title compound was prepared from benzaldehyde (5.30 g, 49.9 mmol), cyclohexylamine (4.99 g, 50.3 mmol), and KCN (6.50 g, 99.8 mmol). Purification of the crude product by washing with *n*-hexane yielded **7b** (4.71 g, 21.0 mmol, 44%) as a light yellow solid: mp 52.7–54.9 °C (lit.[38]

DOI: 10.1021/acs.joc.5b02659
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mp 56−58 °C); R_f = 0.19 (silica gel, cyclohexane/ethyl acetate 20:1); IR (ATR) $\bar{\nu}$ (cm^{-1}) = 3317, 3065, 2928, 1451, 1375, 1192, 1117, 1029, 758, 697; ^{1}H NMR, COSY (300 MHz, $CDCl_3$) δ (ppm) = 7.53−7.49 (m, 2H, *H*-2′,6′), 7.44−7.37 (m, 3H, *H*-3′,4′,5′), 4.83 (s, 1H, *H*-2), 2.90−2.83 (m, 1H, *H*-1″), 2.02−1.99 (m, 1H, CH_2^{Cy}), 1.82−1.72 (m, 3H, CH_2^{Cy}), 1.67−1.62 (m, 1H, CH_2^{Cy}), 1.41−1.10 (m, 5H, CH_2^{Cy}); ^{13}C NMR, HSQC, HMBC (75.5 MHz, $CDCl_3$) δ (ppm) = 135.5 (*C*-1′), 129.3 (*C*-4′), 129.2 (2C, *C*-3′,5′), 127.4 (2C, *C*-2′,6′), 119.4 (*C*-1), 55.1 (*C*-1″), 51.8 (*C*-2), 33.9 (CH_2^{Cy}), 32.0 (CH_2^{Cy}), 26.0 (CH_2^{Cy}), 24.8 (CH_2^{Cy}), 24.4 (CH_2^{Cy}). The data are in accordance with the literature.[38]

*2-(Isopropylamino)-2-phenylacetonitrile (**7c**).* The title compound was prepared from benzaldehyde (5.41 g, 51.0 mmol), isopropylamine (2.95 g, 49.9 mmol), and KCN (6.56 g, 101 mmol). Purification of the crude product by washing with cold *n*-hexane yielded **7c** (3.06 g, 17.6 mmol, 35%) as a light yellow solid: mp 32.7−34.3 °C (lit.[39] colorless oil); R_f = 0.08 (silica gel, cyclohexane/ethyl acetate 15:1); IR (ATR) $\bar{\nu}$ (cm^{-1}) = 3321, 3035, 2934, 1454, 1373, 1176, 1029, 929, 755, 697; ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 7.54−7.50 (m, 2H, *H*-2′,6′), 7.44−7.35 (m, 3H, *H*-3′,4′,5′), 4.78 (s, 1H, *H*-2), 3.23 (sept, ^3J = 6.2 Hz, 1H, *H*-1′), 1.16 (d, ^3J = 6.2 Hz, 6H, CH_3); ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ (ppm) = 135.5 (*C*-1′), 129.1 (2C, *C*-3′,5′), 129.1 (*C*-4′), 127.4 (2C, *C*-2′,6′), 119.3 (*C*-1), 52.4 (*C*-2), 47.3 (*C*-1″), 23.7 (CH_3), 21.6 (CH_3) ppm. The data are in accordance with the literature.[39]

*((4-Benzoylphenyl)amino)-2-(4-methoxyphenyl)acetonitrile (**7e**).* The title compound was prepared from 4-methoxybenzaldehyde (3.42 g, 25.1 mmol), 4-aminobenzophenone (4.57 g, 25.5 mmol), and KCN (3.29 g, 50.5 mmol). Purification of the crude product by washing with *n*-hexane and diethyl ether yielded **7e** (5.12 g, 15.0 mmol, 60%) as a light yellow solid: mp 136.2−137.3 °C; R_f = 0.10 (silica gel, cyclohexane/ethyl acetate/triethylamine 30:10:1); IR (ATR) $\bar{\nu}$ (cm^{-1}) = 3334, 1598, 1513, 1318, 1279, 1178, 1150, 1030, 839, 701; ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 7.83−7.80 (AA′-part of AA′XX′-system, 2H, *H*-3″,5″), 7.76−7.73 (m, 2H, *H*-2‴,6‴), 7.58−7.54 (m, 1H, *H*-4‴), 7.53−7.50 (XX′-part of AA′XX′-system, 2H, *H*-2′,6′), 7.49−7.45 (m, 2H, *H*-3‴,5‴), 7.00−6.96 (AA′-part of AA′XX′-system, 2H, *H*-3′,5′), 6.81−6.77 (XX′-part of AA′XX′-system, 2H, *H*-2″,6″), 5.45 (s, 1H, *H*-2), 4.51 (s_{br}, 1H, N*H*), 3.85 (s, 3H, OCH_3); ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ (ppm) = 195.4 (CO), 160.8 (*C*-4′), 148.5 (*C*-1″), 138.6 (*C*-1‴), 132.9 (2C, *C*-3″,5″), 131.9 (*C*-4‴), 129.8 (2C, *C*-2″,6‴), 129.1 (*C*-4″), 128.8 (2C, *C*-2′,6′), 128.3 (2C, *C*-3‴,5‴), 125.1 (*C*-1′), 117.8 (*C*-1), 115.0 (2C, *C*-3′,5′), 112.9 (*C*-2″), 55.6 (OCH_3), 49.1 (*C*-2); ESI-HRMS (*m*/*z*) calcd for $[C_{22}H_{18}N_2O_2 + Na]^+$ 365.1266, found 365.1262.

*2-(4-Chlorophenyl)-2-((4-methoxyphenyl)amino)acetonitrile (**7f**).* The title compound was prepared from 4-chlorobenzaldehyde (3.51 g, 25.0 mmol), *p*-anisidine (3.13 g, 25.4 mmol), and KCN (3.29 g, 50.5 mmol). Purification of the crude product by washing with *n*-pentane and diethyl ether yielded **7f** (4.42 g, 16.2 mmol, 65%) as a light gray solid: mp 86.1−87.4 °C (lit.[40] mp 78−80 °C); R_f = 0.10 (silica gel, cyclohexane/ethyl acetate 7:1); IR (ATR) $\bar{\nu}$ (cm^{-1}) = 3342, 2935, 1598, 1512, 1465, 1244, 1093, 1034, 820, 699; ^{1}H NMR, COSY (300 MHz, $CDCl_3$) δ (ppm) = 7.55−7.52 (AA′-part of AA′XX′-system, 2H, *H*-2′,6′), 7.44−7.39 (XX′-part of AA′XX′-system, 2H, *H*-3′,5′), 6.87−6.82 (XX′-part of AA′XX′-system, 2H, *H*-3″,5″), 6.77−6.72 (AA′-part of AA′XX′-system, 2H, *H*-2″,6″), 5.33 (s, 1H, *H*-2), 3.77 (s, 3H, OCH_3); ^{13}C NMR, HMBC, HSQC (75.5 MHz, $CDCl_3$) δ (ppm) = 154.4 (*C*-4″), 138.3 (*C*-1″), 135.5 (*C*-4′), 132.7 (*C*-1′), 129.5 (2C, *C*-3′,5′), 128.7 (2C, *C*-2′,6′), 118.2 (*C*-1), 116.7 (2C, *C*-2″,6″), 115.1 (2C, *C*-3″,5″), 55.7 (OCH_3), 51.1 (*C*-2). The data are in accordance with the literature.[41]

*2-((4-Methoxyphenyl)amino)-2-(naphthalen-2-yl)acetonitrile (**7g**).* The title compound was prepared from 2-naphthaldehyde (2.51 g, 16.1 mmol), *p*-anisidine (2.27 g, 18.4 mmol), and KCN (2.16 g, 33.2 mmol). Purification of the crude product by washing with diethyl ether yielded **7g** (3.10 g, 10.8 mmol, 67%) as a light gray solid: mp 105.0−107.5 °C; R_f = 0.13 (silica gel, cyclohexane/diethyl ether 7:1); IR (ATR) $\bar{\nu}$ (cm^{-1}) = 3346, 3057, 1618, 1512, 1465, 1243, 1127, 1034, 819, 751; ^{1}H NMR, COSY (300 MHz, $CDCl_3$) δ (ppm) = 8.13 (s_{br}, 1H, *H*-1′), 7.94−7.86 (m, 3H, *H*-6,3′,7′), 7.64 (dd, ^3J = 8.5 Hz, ^4J = 1.9 Hz, 1H, *H*-8′), 7.59−7.54 (m, 2H, *H*-4′,5′), 6.88−6.84 (XX′-part of AA′XX′-system, 2H, *H*-3″,5″), 6.82−6.78 (AA′-part of AA′XX′-system, 2H, *H*-2″,6″), 5.52 (s, 1H, *H*-2), 3.78 (s, 3H, OCH_3); ^{13}C NMR, HSQC, HMBC (75.7 MHz, $CDCl_3$) δ (ppm) = 154.3 (*C*-4″), 138.7 (*C*-1″), 133.6 (*C*-4a′), 133.2 (*C*-2′), 131.5 (*C*-8a′), 129.5 (*C*-7′), 128.4 (*C*-3′), 127.9 (*C*-1′), 127.2 (*C*-4′), 127.1 (*C*-5′), 126.7 (*C*-1′), 124.6 (*C*-8′), 118.6 (*C*-1), 116.5 (2C, *C*-2″,6″), 115.2 (2C, *C*-3″,5″), 55.8 (OCH_3), 51.9 (*C*-2). The data are in accordance with the literature.[42]

*2-((4-Benzoylphenyl)amino)-2-(naphthalen-2-yl)acetonitrile (**7h**).* The title compound was prepared from 2-naphthaldehyde (2.54 g, 16.2 mmol), 4-aminobenzophenone (3.17 g, 16.1 mmol), and KCN (2.25 g, 34.6 mmol). Purification of the crude product by washing with diethyl ether yielded **7h** (3.39 g, 9.40 mmol, 58%) as a light yellow solid: mp 137.6−138.4 °C; R_f = 0.12 (silica gel, cyclohexane/ethyl acetate 3:1); IR (ATR) $\bar{\nu}$ (cm^{-1}) = 3328, 3058, 1640, 1596, 1522, 1318, 1281, 1150, 740, 700; ^{1}H NMR, COSY (300 MHz, $CDCl_3$) δ (ppm) = 8.11 (s_{br}, 1H, *H*-1′), 7.94−7.87 (m, 3H, *H*-4′,5′,7′), 7.80−7.78 (AA′-part of AA′XX′-system, 2H, *H*-3″,5″), 7.74−7.71 (m, 2H, *H*-2‴,6‴), 7.60−7.53 (m, 4H, *H*-3′,6′,8′,4‴), 7.48−7.43 (m, 2H, *H*-3‴,5‴), 6.82−6.80 (XX′-part of AA′XX′-system, 2H, *H*-2″,6″), 5.67 (d, ^3J = 5.6 Hz, 1H, *H*-2), 4.88 (d_{br}, ^3J = 5.6 Hz, 1H, N*H*); ^{13}C NMR, HMBC, HSQC (75.5 MHz, $CDCl_3$) δ (ppm) = 195.5 (CO), 148.5 (*C*-1″), 138.5 (*C*-1‴), 133.7 (*C*-4a′), 133.2 (*C*-2′), 132.9 (2C, *C*-3″,5″), 131.9 (*C*-8′), 130.4 (*C*-8a′), 129.8 (*C*-4′), 129.7 (2C, *C*-2‴,6‴), 129.1 (*C*-4″), 128.3 (*C*-7′), 128.3 (2C, *C*-3‴,5‴), 127.9 (*C*-5′), 127.5 (*C*-6′), 127.3 (*C*-4‴), 126.9 (*C*-1′), 124.2 (*C*-3′), 117.7 (*C*-1), 113.0 (2C, *C*-2″,6″), 49.6 (*C*-2); ESI-HRMS (*m*/*z*) calcd for $[C_{25}H_{18}N_2O - CN]^+$ 336.1388, found 336.1390.

*2-(Methylamino)-2-(naphthalen-2-yl)acetonitrile (**7i**).* The title compound was prepared from 2-naphthaldehyde (3.46 g, 22.2 mmol), methylamine (33 wt % in EtOH, 2.80 mL, 2.12 g, 22.5 mmol), and KCN (2.89 g, 44.4 mmol). Purification of the crude product by recrystallization from diethyl ether/*n*-hexane yielded **7i** (3.42 g, 17.4 mmol, 79%) as a light yellow solid: mp 69.4−71.7 °C (lit.[25] mp 72.0−73.5 °C); R_f = 0.30 (silica gel, cyclohexane/ethyl acetate 1:1); IR (ATR) $\bar{\nu}$ (cm^{-1}) = 3331, 3057, 2947, 1691, 1509, 1451, 1273, 1143, 819, 750; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.02 (s, 1H, *H*-1′), 7.90−7.83 (m, 3H, *H*-4′,5′,8′), 7.60−7.51 (m, 3H, *H*-3′,6′,7′), 4.94 (s, 1H, *H*-2), 2.61 (s, 3H, NCH_3). The data are in accordance with the literature.[25]

*2-(Mesitylamino)-2-(4-methoxyphenyl)acetonitrile (**7j**).* The title compound was prepared from 4-methoxybenzaldehyde (3.40 g, 25.0 mmol), 2,4,6-trimethylaniline (3.44 g, 25.4 mmol), and KCN (3.29 g, 50.5 mmol). Purification of the crude product by washing with *n*-pentane and diethyl ether yielded **7j** (4.06 g, 14.5 mmol, 58%) as a light brown solid: mp 92.7−95.6 °C (lit.[43] mp 102 °C); R_f = 0.56 (silica gel, cyclohexane/ethyl acetate 7:1); IR (ATR) $\bar{\nu}$ (cm^{-1}) = 3356, 2936, 1612, 1512, 1484, 1306, 1252, 1157, 1032, 854; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.60−7.55 (AA′-part of AA′XX′-system, 2H, *H*-2′,6′), 7.01−6.96 (XX′-part of AA′XX′-system, 2H, *H*-3′,5′), 6.90 (s, 2H, *H*-3″,5″), 5.04 (s, 1H, *H*-2), 3.85 (s, 3H, OCH_3), 2.33 (s, 6H, *o*-CH_3), 2.27 (s, 3H, *p*-CH_3). The data are in accordance with the literature.[43]

*2-(4-Chlorophenyl)-2-((4-chlorophenyl)amino)acetonitrile (**7k**).* The title compound was prepared from 4-chlorobenzaldehyde (3.54 g, 25.2 mmol), 4-chloroaniline (3.26 g, 25.5 mmol), and KCN (3.28 g, 50.4 mmol). Purification of the crude product by washing with *n*-pentane and diethyl ether yielded **7k** (5.25 g, 18.9 mmol, 75%) as a colorless solid: mp 116.3−117.4 °C (lit.[40] mp 121−123 °C); R_f = 0.37 (silica gel, cyclohexane/ethyl acetate/triethylamine 50:10:1); IR (ATR) $\bar{\nu}$ (cm^{-1}) = 3354, 3028, 1617, 1518, 1492, 1262, 1094, 1015, 928, 803; ^{1}H NMR, COSY (300 MHz, $CDCl_3$) δ (ppm) = 7.53−7.50 (AA′-part of AA′BB′-system, 2H, *H*-2′,6′), 7.45−7.40 (BB′-part of AA′BB′-system, 2H, *H*-3′,5′), 7.24−7.19 (XX′-part of AA′XX′-system, 2H, *H*-3″,5″), 6.70−6.65 (AA′-part of AA′XX′-system, 2H, *H*-2″,6″), 5.37 (s, 1H, *H*-2), 4.14 (s_{br}, 1H, N*H*); ^{13}C NMR, HSQC, HMBC (75.5 MHz, $CDCl_3$) δ (ppm) = 143.0 (*C*-1″), 135.8 (*C*-4′), 132.0 (*C*-1′), 129.7 (2C, *C*-3′,5′), 129.6 (2C, *C*-3″,5″), 128.6 (2C, *C*-2′,6′), 125.5 (*C*-4″), 117.7 (*C*-1), 115.6 (2C, *C*-2″,6″), 49.8 (*C*-2). The data are in accordance with the literature.[44]

*2-(4-Chlorophenyl)-2-(p-tolylamino)acetonitrile (**7l**).* The title compound was prepared from 4-chlorobenzaldehyde (3.56 g, 25.3 mmol), *p*-toluidine (2.70 g, 25.2 mmol), and KCN (3.26 g, 50.1 mmol).

DOI: 10.1021/acs.joc.5b02659
J. Org. Chem. 2016, 81, 1858−1869

Purification of the crude product by washing with *n*-pentane and diethyl ether yielded **7l** (4.76 g, 18.6 mmol, 73%) as a light yellow solid: mp 89.0−91.5 °C (lit.[40] mp 92−94 °C); R_f = 0.38 (silica gel, cyclohexane/ethyl acetate/triethyl amine 50:10:1); IR (ATR) $\tilde{\nu}$ (cm^{-1}) = 3305, 1597, 1490, 1237, 1085, 1014, 907, 818, 730, 651; ^{1}H NMR, COSY (300 MHz, $CDCl_3$) δ = 7.55−7.52 (AA′-part of AA′BB′-system, 2H, *H*-2′,6′), 7.44−7.41 (BB′-part of AA′BB′-system, 2H, *H*-3′,5′), 7.10−7.07 (XX′-part of AA′XX′-system, 2H, *H*-3″,5″), 6.70−6.67 (AA′-part of AA′XX′-system, 2H, *H*-2″,6″), 5.38 (s, 1H, *H*-2), 3.97 (s_{br}, 1H, N*H*), 2.29 (s, 3H, CH_3); ^{13}C NMR, HSQC, HMBC (75.5 MHz, $CDCl_3$) δ (ppm) = 142.2 (*C*-1″), 135.5 (*C*-4′), 132.7 (*C*-1′), 130.2 (2C, *C*-3″,5″), 130.1 (*C*-4″), 129.5 (2C, *C*-3′,5′), 128.7 (2C, *C*-2′,6′), 118.1 (*C*-1), 114.7 (2C, *C*-2″,6″), 50.2 (*C*-2), 20.6 (CH_3). The data are in accordance with the literature.[45]

*2-(4-Methoxyphenyl)-2-(p-tolylamino)acetonitrile (**7m**).* The title compound was prepared from 4-methoxybenzaldehyde (3.48 g, 25.6 mmol), *p*-toluidine (2.76 g, 25.8 mmol), and KCN (3.36 g, 51.6 mmol). Purification of the crude product by washing with *n*-pentane and diethyl ether yielded **7m** (3.73 g, 14.8 mmol, 58%) as a colorless solid: mp 102.2−104.5 °C (lit.[45] mp 101−103 °C); R_f = 0.26 (silica gel, cyclohexane/ethyl acetate/triethylamine 50:10:1); IR (ATR) $\tilde{\nu}$ (cm^{-1}) = 3359, 2936, 1613, 1512, 1463, 1250, 1178, 1031, 926, 809; ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 7.53−7.49 (AA′-part of AA′XX′-system, 2H, *H*-2′,6′), 7.10−7.08 (XX′-part of AA′XX′-system, 2H, *H*-3″,5″), 6.98−6.95 (XX′-part of AA′XX′-system, 2H, *H*-3′,5′), 6.72−6.69 (AA′-part of AA′XX′-system, 2H, *H*-2″,6″), 5.33 (d, ^3J = 6.7 Hz, 1H, *H*-2), 3.84 (s, 3H, OCH_3), 2.30 (s, 3H, CH_3); ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ (ppm) = 160.4 (*C*-4′), 142.6 (*C*-1″), 130.1 (2C, *C*-3″,5″), 129.7 (*C*-4″), 128.7 (2C, *C*-2′,6′), 126.2 (*C*-1′), 118.7 (*C*-1), 114.7 (2C, *C*-3′,5′), 114.5 (2C, *C*-2″,6″), 55.5 (OCH_3), 50.2 (*C*-2), 20.6 (CH_3).

General Procedure for the Alkylation of α-Aminonitriles 7. (***Caution!*** *α-Aminonitriles may release highly toxic HCN. Caution should be exercised.*) The alkylation of α-aminonitriles **7** was performed according to a modified procedure from Romek and Opatz.[24] Unless otherwise stated, α-aminonitrile **7** (1.0 equiv) was dissolved in dry THF (4.0 mL per mmol α-aminonitrile) under an argon atmosphere and the solution was cooled to −78 °C. A solution of KHMDS (1.3 equiv) in dry THF (4.0 mL per mmol α-aminonitrile) was quickly added at −78 °C. The mixture was stirred at −78 °C for 5 min before a solution of 1-(bromomethyl)-2-iodobenzene (1.3 equiv) in dry THF (4.0 mL per mmol α-aminonitrile) was added over a period of 60 min. After stirring for a further 60 min at −78 °C, the solution was allowed to warm to −20 °C before a saturated solution of sodium bicarbonate (12.0 mL per mmol α-aminonitrile) and ethyl acetate (5.0 mL per mmol α-aminonitrile) were added. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 5.0 mL per mmol of α-aminonitrile). The combined organic layers were washed with brine (5.0 mL per mmol of α-aminonitrile), dried over $MgSO_4$, and evaporated under reduced pressure. Unless otherwise stated, alkylated aminonitriles **8** were subjected to the next reaction step without further purification due to their instability during chromatography on silica gel.

*3-(2-Iodophenyl)-2-phenyl-2-(phenylamino)propanenitrile (**8a**).* The general procedure was applied using **7a** (705 mg, 3.39 mmol), KHMDS (870 mg, 4.40 mmol), and 1-(bromomethyl)-2-iodobenzene (1.30 g, 4.37 mmol). Purification of the crude product by flash column chromatography (cyclohexane/ethyl acetate, 30:1) on silica gel yielded **8a** (619 mg, 1.46 mmol, 43%) as a colorless solid: mp 170.8−171.8 °C; R_f = 0.18 (silica gel, cyclohexane/ethyl acetate 30:1); IR (ATR) $\tilde{\nu}$ (cm^{-1}) = 3379, 3030, 1602, 1499, 1436, 1315, 1256, 1012, 751, 698; ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 7.94−7.92 (m, 1H, *H*-3‴), 7.64−7.60 (m, 2H, *H*-2′,6′), 7.43−7.38 (m, 3H, *H*-3′,4′,5′), 7.35−7.30 (m, 2H, *H*-5‴,6‴), 7.10−7.01 (m, 2H, *H*-3″,5″), 7.04−7.00 (m, 1H, *H*-4‴), 6.78−6.74 (m, 1H, *H*-4″), 6.50−6.47 (m, 2H, *H*-2″,6″), 4.68 (s_{br}, 1H, N*H*), 3.63−3.54 (m, 2H, CH_2); ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ (ppm) = 143.3 (*C*-1″), 140.4 (*C*-3‴), 138.4 (*C*-1′), 136.6 (*C*-1‴), 132.0 (*C*-5‴), 130.2 (*C*-4‴), 129.3 (*C*-4′), 129.0 (2C, *C*-3′,5′), 128.9 (2C, *C*-3″,5″), 126.1 (2C, *C*-2′,6′), 120i.0 (*C*-4″), 119.7 (*C*-1), 116.0 (2C, *C*-2″,6″), 102.9 (*C*-2‴), 62.3 (*C*-2), 53.4 (CH_2); ESI-HRMS (*m*/*z*) calcd for $[C_{21}H_{17}IN_2 + Na]^+$ 447.0334, found 447.0336.

*3-(2-Bromophenyl)-2-phenyl-2-(phenylamino)propanenitrile (**8b**).* The general procedure was applied using **7a** (250 mg, 1.20 mmol), KHMDS (335 mg, 1.68 mmol), and 1-(bromomethyl)-2-bromobenzene (390 mg, 1.56 mmol). Purification of the crude product by flash column chromatography (cyclohexane/ethyl acetate, 30:1) on silica gel yielded **8b** (315 mg, 0.840 mmol, 70%) as a colorless solid: mp 171.7−172.3 °C; R_f = 0.16 (silica gel, cyclohexane/ethyl acetate 30:1); IR (ATR) $\tilde{\nu}$ (cm^{-1}) = 3384, 3056, 3030, 1601, 1499, 1438, 1318, 1027, 744, 692; ^{1}H NMR, COSY (300 MHz, $CDCl_3$) δ (ppm) = 7.64−7.56 (m, 3H, *H*-2′,6′,3‴), 7.43−7.36 (m, 3H, *H*-3′,4′,5′), 7.30−7.17 (m, 3H, *H*-4‴,5‴,6‴), 7.11−7.04 (m, 2H, *H*-3″,5″), 6.78−6.72 (m, 1H, *H*-4″), 6.50−6.46 (m, 2H, *H*-2″,6″), 4.86 (s_{br}, 1H, N*H*), 3.66−3.51 (m, 2H, CH_2); ^{13}C NMR, HSQC, HMBC (75.5 MHz, $CDCl_3$) δ (ppm) = 143.3 (*C*-1″), 138.3 (*C*-1′), 133.4 (*C*-3‴), 133.1 (*C*-1‴), 133.0 (*C*-6‴), 130.0 (*C*-4‴), 129.2 (2C, *C*-3′,5′), 129.0 (3C, *C*-3″,5″,2‴), 127.9 (*C*-5‴), 126.0 (3C, *C*-2′,4′,6′), 119.9 (*C*-4″), 119.7 (*C*-1), 115.9 (2C, *C*-2″,6″), 62.3 (*C*-2), 49.2 (CH_2); ESI-HRMS (*m*/*z*) calcd for $[C_{21}H_{17}{}^{79}BrN_2 + Na]^+$ 399.0473, found 399.0473.

*2-((4-Benzoylphenyl)amino)-3-(2-iodophenyl)-2-(4-methoxyphenyl)propanenitrile (**8f**).* The general procedure was applied using **7e** (406 mg, 1.19 mmol), KHMDS (315 mg, 1.58 mmol), and 1-(bromomethyl)-2-iodobenzene (451 mg, 1.52 mmol). The crude product [693 mg, 0.863 mmol (internal NMR standard), 73%] was obtained as a yellow solid. Purification of an aliquot (201 mg) by flash column chromatography (cyclohexane/ethyl acetate/triethylamine 40:10:1) on silica gel yielded **8f** (133 mg, 0.237 mmol, 66%) as a colorless solid: mp 189.8−190.7 °C; R_f = 0.13 (silica gel, cyclohexane/ethyl acetate/triethylamine 40:10:1); IR (ATR) $\tilde{\nu}$ (cm^{-1}) = 3351, 1645, 1597, 1510, 1254, 1173, 1151, 1014, 837, 740; ^{1}H NMR, COSY (300 MHz, DMSO-d_6) δ (ppm) = 7.94 (s_{br}, 1H, N*H*), 7.83 (dd, ^3J = 8.0 Hz, ^4J = 1.2 Hz, 1H, *H*-6‴), 7.61−7.46 (m, 7H, *H*-3‴,4‴,5‴,2‴,6‴,3″,5″), 7.33−7.27 (m, 1H, *H*-3‴), 7.18−7.13 (AA′-part of AA′BB′-system, 2H, *H*-2′,6′), 7.07−6.99 (m, 2H, *H*-4‴,5‴), 6.95−6.90 (BB′-part of AA′BB′-system, 2H, *H*-3′,5′), 6.67−6.63 (AA′-part of a AA′XX′-system, 2H, *H*-2″,6″), 3.88 (d, ^2J = 13.7 Hz, 1H, *H*-3_a), 3.74 (s, 3H, OCH_3), 3.48 (d, ^2J = 13.7 Hz, 1H, *H*-3_b); ^{13}C NMR, HSQC, HMBC (75.5 MHz, DMSO-d_6) δ (ppm) = 193.9 (*C*O), 159.5 (*C*-4′), 148.6 (*C*-1″), 139.5 (*C*-6‴), 138.2 (*C*-1‴), 136.2 (*C*-1‴), 131.6 (3C, *C*-3″,5″,4‴), 129.6 (*C*-5‴), 129.0 (2C, *C*-2‴,6‴), 128.3 (2C, *C*-3‴,5‴), 128.3 (*C*-1′), 127.8 (*C*-3‴), 127.4 (2C, *C*-2′,6′), 126.5 (*C*-4″), 118.9 (*C*-1), 114.3 (2C, *C*-3′,5′), 114.2 (2C, *C*-2″,6″), 104.1 (*C*-2‴), 60.5 (*C*-2), 55.2 (OCH_3), 51.3 (*C*-3); ESI-HRMS (*m*/*z*) calcd for $[C_{29}H_{23}IN_2O_2 - CN]^+$ 532.0774, found 532.0787.

*2-((4-Benzoylphenyl)amino)-3-((2-iodophenyl)-2-naphthalen-2-yl)propanenitrile (**8i**).* The general procedure was applied using **7h** (300 mg, 0.828 mmol), KHMDS (215 mg, 1.08 mmol), and 1-(bromomethyl)-2-iodobenzene (320 mg, 1.08 mmol). The crude product [535 mg, 0.782 mmol (internal NMR standard), 95%] was obtained as a yellow solid. Purification of an aliquot (205 mg) of the crude product by flash column chromatography (cyclohexane/ethyl acetate/triethylamine 50:10:1) on silica gel yielded **8i** (65.1 mg, 0.112 mmol, 35%) as a colorless solid: mp 205.0−205.9 °C; R_f = 0.17 (silica gel, cyclohexane/ethyl acetate/triethylamine 50:10:1); IR (ATR) $\tilde{\nu}$ (cm^{-1}) = 3347, 3059, 1644, 1596, 1518, 1282, 1151, 906, 729, 648; ^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ (ppm) = 8.10 (s_{br}, 1H, N*H*), 7.94−7.91 (m, 2H, *H*-6′,7′), 7.87−7.85 (m, 1H, *H*-1′), 7.78−7.77 (m, 2H, *H*-3′,6‴), 7.58−7.51 (m, 7H, *H*-8′,3″,5″,2‴,6‴,3‴,5‴), 7.48−7.41 (m, 3H, *H*-4′,5′,4‴), 7.24−7.20 (m, 1H, *H*-3‴), 7.02−6.97 (m, 2H, *H*-4‴,5‴), 6.71−6.67 (AA′-part of AA′XX′-system, 2H, *H*-2″,6″), 4.00 (d, ^2J = 13.7 Hz, 1H, *H*-3_a), 3.63 (d, ^2J = 13.7 Hz, 1H, *H*-3_b); ^{13}C NMR, HSQC, HMBC (100.6 MHz, DMSO-d_6) δ (ppm) = 193.9 (*C*O), 148.6 (*C*-1″), 139.5 (*C*-6‴), 138.1 (*C*-1‴), 136.1 (*C*-1‴), 134.2 (*C*-4a′), 132.8 (*C*-8a′), 131.6 (3C, *C*-3″,5″,4‴), 131.5 (*C*-4‴), 129.7 (*C*-5‴), 129.0 (4C, *C*-1′,6′,2‴,6‴), 128.3 (2C, *C*-3‴,5‴), 128.2 (2C, *C*-5′,2′), 127.8 (*C*-7′), 127.6 (*C*-3‴), 126.8 (*C*-8′), 126.6 (*C*-4″), 125.8 (*C*-3′), 123.1 (*C*-4′), 118.8 (*C*-1), 114.1 (2C, *C*-2″,6″), 104.0 (*C*-2‴), 61.2 (*C*-2), 51.0 (*C*-3); ESI-HRMS (*m*/*z*) calcd for $[C_{32}H_{23}IN_2O - CN]^+$ 552.0824, found 552.0803.

Synthesis of 1,2-Disubstituted Indoles 9. (***Caution!*** *α-Aminonitriles may release highly toxic HCN. Caution should be exercised.*) Unless

DOI: 10.1021/acs.joc.5b02659
J. Org. Chem. 2016, 81, 1858−1869

otherwise stated, catalyst loadings for the conversion of crude intermediates **8** were calculated on the basis of an assumed quantitative yield of the preceding alkylation reactions.

General Procedure A. A modification of the procedure by Lange et al. was applied.[46] Unless otherwise stated, Cs_2CO_3 (2.0 equiv) and 4 Å molecular sieves (115 mg per mmol of α-aminonitrile) were flame-dried in a 15 mL microwave vessel equipped with a magnetic stirring bar. The vessel was charged with CuBr·SMe_2 (20 mol %), neocuproine hemihydrate (20 mol %), and the alkylated α-aminonitrile **8** (1.0 equiv). The vessel was evacuated and backfilled with argon three times before dry NMP (0.4 mL per 0.1 mmol alkylated α-aminonitrile) was added. The resulting suspension was irradiated in a monomode microwave reactor (200 W, 180 °C) for 1 h. Subsequently, the mixture was diluted with ethyl acetate (1.5 mL per mmol of alkylated α-aminonitrile), filtered over a plug of silica, and eluted with ethyl acetate (7.0 mL per 0.1 mmol of alkylated α-aminonitrile). The filtrate was washed with water (3 × 1.5 mL per 0.1 mmol of α-alkylated aminonitrile), the combined aqueous layers were extracted with ethyl acetate (3 × 1.5 mL per 0.1 mmol of alkylated α-aminonitrile respectively), and the combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The resulting crude products were purified by flash column chromatography on silica gel.

General Procedure B. The palladium-catalyzed synthesis of indoles **9** was performed according to a modified protocol of Wennemers and co-workers[32] A flame-dried 15 mL microwave reaction vessel equipped with a magnetic stirring bar was charged with the alkylated α-aminonitrile **8** (1.0 equiv), Pd(dppf)Cl_2 (5.0 mol %), and NaO^{t}Bu (3.0 equiv). The vessel was evacuated and backfilled with nitrogen three times before dry, degassed toluene was added (0.5 mL per 0.1 mmol of alkylated α-aminonitrile). The resulting suspension was irradiated in a monomode microwave reactor (300 W, 150 °C) for 1.5 h. Subsequently, the reaction mixture was evaporated in vacuo, and the crude products were purified by flash column chromatography on silica gel.

*1,2-Diphenyl-1H-indole (**9a**).* General procedure A was applied using **8a** (30.2 mg, 71.2 μmol), CuBr·SMe_2 (3.87 mg, 18.8 μmol), neocuproine hemihydrate (4.44 mg, 20.5 μmol), Cs_2CO_3 (82.4 mg, 253 μmol), and 4 Å molecular sieves (94.5 mg). Purification of the crude product by flash column chromatography (cyclohexane/ethyl acetate 200:1) on silica gel yielded **9a** (12.3 mg, 45.6 μmol, 64%, 28% over two steps) as A colorless solid. Alternatively, general procedure B was applied using **8b** (99.4 mg, 0.263 mmol), Pd(dppf)Cl_2 (10.2 mg, 0.0139 mmol), and NaO^{t}Bu (75.7 mg, 0.788 mmol). Purification of the crude product by flash column chromatography (cyclohexane/ethyl acetate 100:1) on silica gel yielded **9a** (59.3 mg, 0.220 mmol, 84%, 59% over two steps) as a colorless solid: mp 79.2−85.0 °C (lit.[13] mp 78−80 °C); R_f = 0.34 (silica gel, cyclohexane/ethyl acetate 60:1); IR (ATR) $\tilde{\nu}$ (cm^{-1}) = 3058, 1596, 1500, 1456, 1381, 1323, 1208, 794, 761, 697; ^{1}H NMR, COSY (300 MHz, DMSO-d_6) δ (ppm) = 7.69−7.64 (m, 1H, *H*-5), 7.52−7.46 (m, 2H, *H*-3″,5″), 7.44−7.39 (m, 1H, *H*-4″), 7.29−7.26 (m, 7H, *H*-2′−6′,2″,6″), 7.17−7.12 (m, 3H, *H*-4,6,7), 6.88 (s, 1H, *H*-3); ^{13}C NMR, HSQC, HMBC (75.5 MHz, DMSO-d_6) δ (ppm) = 140.2 (*C*-7a), 138.7 (*C*-2), 137.9 (*C*-1″), 131.9 (*C*-1′), 129.6 (*C*-3″,5″), 128.5 (2C, *C*-3′,5′), 128.3 (2C, *C*-2′,6′), 127.9 (2C, *C*-2″,6″), 127.8 (*C*-3a), 127.6 (*C*-4″), 127.5 (*C*-4′), 122.4, 120.6, 120.5 (3C, *C*-4,5,7), 110.3 (*C*-6), 103.5 (*C*-3). The data are in accordance with the literature.[13]

*1-Cyclohexyl-2-phenyl-1H-indole (**9b**).* The general procedure for alkylation was applied using **7b** (254 mg, 1.19 mmol), KHMDS (323 mg, 1.62 mmol), and 1-(bromomethyl)-2-iodobenzene (451 mg, 1.51 mmol). The crude alkylation product [**8c**, 581 mg, 1.01 mmol (internal NMR standard), 85%] was obtained as a yellow oil and was directly subjected to the next reaction step: R_f = 0.11 (silica gel, cyclohexane/ethyl acetate 30:1); IR (ATR) $\tilde{\nu}$ (cm^{-1}) = 3059, 2929, 1689, 1579, 1448, 1331, 1218, 1013, 752, 699; ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 7.86 (dd, ^3J = 7.9 Hz, ^4J = 1.3 Hz, 1H, *H*-3‴), 7.67−7.64 (m, 2H, *H*-1′,6′), 7.39−7.35 (m, 3H, *H*-3′,4′,5′), 7.24 (dd, ^3J = 7.9 Hz, ^4J = 1.3 Hz, 1H, *H*-5‴), 7.15 (dd, ^3J = 7.9 Hz, ^4J = 1.5 Hz, 1H, *H*-6‴), 6.97−6.93 (dt, ^3J = 7.9 Hz, ^4J = 1.5 Hz, 1H, *H*-4‴), 3.47 (d, 1H, ^2J = 13.7 Hz, *H*-3$_a$), 3.28 (d, 1H, ^2J = 13.7 Hz, *H*-3$_b$), 2.62−2.55 (m, 1H, *H*-1″), 1.98−1.96 (m, 1H, CH_2^{Cy}), 1.65−1.60 (m, 2H, CH_2^{Cy}), 1.53−1.46 (m, 2H, CH_2^{Cy}), 1.23−1.07 (m, 4H, CH_2^{Cy}) 0.99−0.90 (m, 1H, CH_2^{Cy}); ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ (ppm) = 140.2 (*C*-3‴), 139.7 (*C*-1′), 137.4 (*C*-1‴), 131.4 (*C*-6‴), 129.5 (*C*-4‴), 128.8 (*C*-4′), 128.6 (2C, *C*-3′,5′), 128.3 (*C*-5‴), 127.0 (2C, *C*-2′,6′), 121.3 (*C*-1), 103.4 (*C*-2‴), 64.9 (*C*-2), 54.1 (*C*-1″), 53.3 (*C*-3), 35.1 (CH_2^{Cy}), 34.5 (CH_2^{Cy}), 25.8 (CH_2^{Cy}), 25.2 (CH_2^{Cy}), 25.1 (CH_2^{Cy}); ESI-HRMS (*m/z*) calcd for $[C_{21}H_{23}IN_2 - CN]^+$ 404.0875, found 404.0878. The indole synthesis was performed according to general procedure A using **8c** (crude, 36.6 mg), CuBr·SMe_2 (4.64 mg, 22.5 μmol), neocuproine hemihydrate (4.70 mg, 21.6 μmol), Cs_2CO_3 (69.1 mg, 212 μmol), and 4 Å molecular sieves (81.7 mg). Purification of the crude product by flash column chromatography (cyclohexane/ethyl acetate 200:1) on silica gel yielded **9b** (15.7 mg, 57.0 μmol, 76% over two steps) as a colorless solid. Alternatively, general procedure B was applied using **8c** (crude, 210 mg), Pd(dppf)Cl_2 (18.6 mg, 0.0254 mmol), and NaO^{t}Bu (137 mg, 1.42 mmol). Purification of the crude product by flash column chromatography (cyclohexane/ethyl acetate 500:1) on silica gel yielded **9b** (4.70 mg, 17.1 μmol, 4% over two steps) as a colorless solid: mp 102.6−104.3 °C (lit.[13] mp 103.7−104.5 °C); R_f = 0.34 (silica gel, cyclohexane/ethyl acetate 60:1); IR (ATR) $\tilde{\nu}$ (cm^{-1}) = 3059, 1602, 1489, 1455, 1345, 1315, 1011, 750, 734, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.70−7.63 (m, 2H), 7.52−7.40 (m, 5H), 7.22−7.17 (m, 1H), 7.15−7.09 (m, 1H), 6.49 (s$_{br}$, 1H), 4.29−4.18 (m, 1H), 2.47−2.33 (m, 2H, CH_2^{Cy}), 1.96−1.88 (m, 4H, CH_2^{Cy}), 1.77−1.72 (m, 1H, CH_2^{Cy}), 1.35−1.26 (m, 3H, CH_2^{Cy}). The data are in accordance with the literature.[13]

*2-(4-Chlorophenyl)-1-(4-methoxyphenyl)-1H-indole (**9c**).* The general procedure for alkylation was applied using **7f** (254 mg, 0.931 mmol), KHMDS (241 mg, 1.21 mmol), and 1-(bromomethyl)-2-iodobenzene (376 mg, 1.27 mmol). The crude alkylation product [**8g**, 501 mg, 0.651 mmol (internal NMR standard), 70%] was obtained as a green solid that was directly subjected to the next reaction step: mp 135.2−136.4 °C; R_f = 0.15 (silica gel, cyclohexane/ethyl acetate 10:1); IR (ATR) $\tilde{\nu}$ (cm^{-1}) = 3017, 1511, 1291, 1242, 1134, 1093, 1013, 936, 761, 821; ^{1}H NMR, COSY (300 MHz, $CDCl_3$) δ (ppm) = 7.92−7.90 (m, 1H, *H*-3‴), 7.57−7.52 (AA′-part of AA′BB′-system, 2H, *H*-2′,6′), 7.39−7.35 (BB′-part of AA′BB′-system, 2H, *H*-3′,5′), 7.34−7.32 (m, 2H, *H*-4‴,6‴), 7.06−7.00 (m, 1H, *H*-5‴), 6.69−6.64 (BB′-part of AA′BB′-system, 2H, *H*-3″,5″), 6.47−6.42 (AA′-part of AA′BB′-system, 2H, *H*-2″,6″), 4.36 (s$_{br}$, 1H, N*H*), 3.68 (s, 3H, OCH_3), 3.60−3.49 (m, 2H, CH_2); ^{13}C NMR, HSQC, HMBC (75.5 MHz, $CDCl_3$) δ (ppm) = 154.1 (*C*-4″), 140.4 (*C*-3‴), 137.0 (*C*-1′), 136.7 (*C*-1″), 136.3 (*C*-1‴), 135.0 (*C*-4′), 131.8 (*C*-6‴), 130.2 (*C*-5‴), 129.4 (2C, *C*-3′,5′), 128.9 (*C*-4‴), 127.8 (2C, *C*-2′,6′), 119.7 (*C*-1), 118.1 (2C, *C*-2″,6″), 114.6 (2C, *C*-3″,5″), 103.0 (*C*-2‴), 62.7 (*C*-2), 55.6 (OCH_3), 53.1 (*C*-3); ESI-HRMS (*m/z*) calcd for $[C_{22}H_{18}{}^{35}ClIN_2O - CN]^+$ 462.0122, found 462.0117. For indole synthesis, general procedure A was applied using **8g** (crude, 151 mg), CuBr·SMe_2 (12.3 mg, 0.0598 mmol), neocuproine hemihydrate (13.7 mg, 0.0631 mmol), Cs_2CO_3 (209 mg, 0.641 mmol), and 4 Å molecular sieves (241 mg). Purification of the crude product by flash column chromatography (cyclohexane/ethyl acetate 60:1) on silica gel yielded **9c** (52.2 mg, 0.156 mmol, 56% over two steps) as a colorless solid. Alternatively, general procedure B was applied using **8g** (crude, 150 mg), Pd(dppf)Cl_2 (12.2 mg, 16.7 μmol), and NaO^{t}Bu (87.8 mg, 913 μmol). Purification of the crude product by flash column chromatography (cyclohexane/ethyl acetate 100:1) on silica gel yielded **9c** (32.0 mg, 95.9 μmol, 34% over two steps) as a light yellow solid: mp 154.3−156.0 °C; R_f = 0.34 (silica gel, cyclohexane/ethyl acetate 30:1); IR (ATR) $\tilde{\nu}$ (cm^{-1}) = 2921, 1511, 1453, 1247, 1093, 1033, 1014, 833, 790, 736; ^{1}H NMR, COSY (300 MHz, $CDCl_3$) δ (ppm) = 7.72−7.66 (m, 1H, *H*-4), 7.25−7.21 (m, 5H, *H*-7,2′,3′,5′,6′), 7.20−7.14 (m, 4H, *H*-5,6,2″,6″), 6.98−6.93 (BB′-part of AA′BB′-system, 2H, *H*-3″,5″), 6.79 (d, ^4J = 0.8 Hz, 1H, *H*-3), 3.87 (s, 3H, OCH_3); ^{13}C NMR, HSQC, HMBC (75.5 MHz, $CDCl_3$) δ = 158.8 (*C*-4″), 139.7 (*C*-2), 139.6 (*C*-7a), 133.4 (*C*-4′), 131.2 (*C*-1′), 131.1 (*C*-1″), 130.1 (2C, *C*-3′,5′), 129.3 (2C, *C*-2″,6″), 128.5 (2C, *C*-2′,6′), 128.1 (*C*-3a), 122.6 (*C*-5), 120.8 (*C*-6), 120.7 (*C*-4), 114.7 (2C, *C*-3″,5″), 110.8 (*C*-7), 103.5 (*C*-3), 55.6 (OCH_3). The data are in accordance with the literature.[47]

*4-(2-(Naphthalen-2-yl)-1H-indol-1-yl)phenyl)(phenyl)methanone (**9d**).* General procedure A was applied using **8i** (crude, 101 mg), CuBr·SMe_2 (6.99 mg, 34.0 μmol), neocuproine hemihydrate (7.50 mg, 34.5

DOI: 10.1021/acs.joc.5b02659
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μmol), Cs_2CO_3 (113 mg, 347 μmol), and 4 Å molecular sieves (215 mg). Purification of the crude product by flash column chromatography (cyclohexane/ethyl acetate 20:1) on silica gel yielded **9d** (50.2 mg, 119 μmol, 76% over two steps) as a colorless oil. General procedure B was applied using **8i** (crude, 53.5 mg), $Pd(dppf)Cl_2$ (3.85 mg, 5.26 μmol), and NaO^tBu (32.3 mg, 336 μmol). Purification of the crude product by flash column chromatography (cyclohexane/ethyl acetate 30:1) on silica gel yielded **9d** (33.0 mg, 77.9 μmol, 94% over two steps) as a colorless oil: R_f = 0.18 (silica gel, cyclohexane/ethyl acetate 20:1); IR (ATR) $\tilde{\nu}$ (cm^{-1}) = 3056, 1657, 1579, 1508, 1450, 1274, 908, 795, 730, 700; ^1H NMR, COSY (300 MHz, $CDCl_3$) δ (ppm) = 7.89−7.85 (XX′-part of AA′XX′-system, 2H, *H*-3″,5″), 7.82−7.71 (m, 7H, *H*-4,1′,4′,5′,8′,2‴,6‴), 7.63−7.57 (m, 1H, *H*-4‴), 7.51−7.45 (m, 5H, *H*-7,6′,7′,3‴,5‴), 7.44−7.40 (AA′-part of AA′XX′-system, 2H, *H*-2″,6″), 7.33 (dd, ^3J = 8.6 Hz, ^4J = 1.8 Hz, 1H, *H*-3′), 7.29−7.22 (m, 2 H, *H*-5,6), 6.97 (d, ^4J = 0.8 Hz, 1H, *H*-3); ^{13}C NMR, HSQC, HMBC (75.5 MHz, $CDCl_3$) δ (ppm) = 195.8 (CO), 142.4 (*C*-1″), 140.6 (*C*-2), 138.8 (*C*-7a), 137.5 (*C*-1‴), 135.9 (*C*-4″), 133.3 (*C*-2′), 132.7 (*C*-4‴), 132.6 (*C*-4a′), 131.4 (2C, *C*-3″,5″), 130.1 (2C, *C*-2‴,6‴), 129.8 (*C*-8a′), 128.8 (*C*-3a), 128.5 (2C, *C*-3‴,5‴), 128.2, 127.8, 126.6, 126.5 (4C, *C*-5′−8′), 128.1 (*C*-4′), 128.0 (*C*-1′), 127.6 (2C, *C*-2″,6″), 126.8 (*C*-3′), 123.0 (*C*-6), 121.4 (*C*-5), 121.0 (*C*-4), 110.6 (*C*-7), 105.6 (*C*-3); ESI-HRMS (*m*/*z*) calcd for $[C_{31}H_{21}NO + Na]^+$ 446.1521, found 446.1508.

*1-Methyl-2-(naphthalen-2-yl)-1H-indole (**9e**).* The general procedure for alkylation was applied using **7i** (216 mg, 1.10 mmol), KHMDS (264 mg, 1.32 mmol), and 1-(bromomethyl)-2-iodobenzene (393 mg, 1.32 mmol). The crude alkylation product [**8j**, 522 mg, 0.686 mmol (internal NMR standard), 62%] was obtained as an orange oil that was directly subjected to the next reaction step: R_f = 0.09 (silica gel, cyclohexane/ethyl acetate 30:1); IR (ATR) $\tilde{\nu}$ (cm^{-1}) = 3057, 1681, 1467, 1436, 1275, 1185, 1125, 1014, 819, 748; ^1H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 8.07 (d, ^4J = 1.8 Hz, 1H, *H*-1′), 7.89−7.86 (m, 4H, *H*-4′,7′,8′,3‴), 7.74 (dd, ^3J = 8.6 Hz, ^4J = 1.8 Hz, 1H, *H*-3′), 7.56−7.51 (m, 3H, *H*-5′,6′,5‴), 7.25−7.24 (m, 1H, *H*-6‴), 7.01−6.94 (m, 1H, *H*-4‴), 3.59 (d, ^2J = 13.7 Hz, 1H, *H*-3_a), 3.44 (d, ^2J = 13.7 Hz, 1H, *H*-3_b), 2.34 (s, 3H, N−CH_3); ^{13}C NMR, HSQC, HMBC (75.5 MHz, $CDCl_3$) δ (ppm) = 140.3 (*C*-3‴), 137.3 (*C*-1‴), 135.3 (*C*-2′), 133.5 (*C*-4a′), 133.1 (*C*-8a′), 131.4 (*C*-6‴), 129.6 (*C*-4‴), 129.0 (*C*-4′), 128.5 (2C, *C*-7′,8′), 127.8 (*C*-5‴), 126.8 (*C*-1′), 126.7 (2C, *C*-5′,6′), 123.7 (*C*-3′), 120.1 (*C*-1), 103.4 (*C*-2‴), 67.0 (*C*-2), 52.2 (*C*-3), 31.6 (N-CH_3); ESI-HRMS (*m*/*z*) calcd for $[C_{20}H_{17}IN_2 - CN]^+$ 386.0406, found 386.0394. For indole synthesis, general procedure A was applied using **8j** (crude, 141 mg), $CuBr{\cdot}SMe_2$ (14.9 mg, 0.0724 mmol), neocuproine hemihydrate (16.3 mg, 0.0750 mmol), Cs_2CO_3 (264 mg, 0.810 mmol), and 4 Å molecular sieves (242 mg). Purification of the crude product by flash column chromatography (cyclohexane/ethyl acetate 300:1) on silica gel yielded **9e** (33.5 mg, 0.130 mmol, 46% over two steps) as a colorless solid. Alternatively, general procedure B was applied using **8j** (crude, 154 mg), $Pd(dppf)Cl_2$ (14.5 mg, 0.0198 mmol), and NaO^tBu (108 mg, 1.12 mmol). Purification of the crude product by flash column chromatography (cyclohexane/ethyl acetate 300:1) on silica gel yielded **9e** (20.4 mg, 0.0793 mmol, 26% over two steps) as a colorless solid: mp 156.1−158.4 °C (lit.[48] mp 151.0−152.4 °C); R_f = 0.28 (silica gel, cyclohexane/ethyl acetate 100:1); IR (ATR) $\tilde{\nu}$ (cm^{-1}) = 3053, 1601, 1464, 1341, 1311, 900, 862, 787, 750, 733; ^1H NMR, COSY (300 MHz, $CDCl_3$) δ (ppm) = 7.99 (d, ^4J = 1.4 Hz, 1H, *H*-1′), 7.96−7.88 (m, 3H, *H*-4′,5′,8′), 7.70−7.64 (m, 2H, *H*-4,3′), 7.59−7.51 (m, 2H, *H*-6′,7′), 7.41 (d, ^3J = 8.0 Hz, 1H, *H*-7), 7.32−7.26 (m, 1H, *H*-6), 7.21−7.15 (m, 1H, *H*-5), 6.69 (s, 1H, *H*-3), 3.83 (s, 3H, NCH_3); ^{13}C NMR, HSQC, HMBC (75.5 MHz, $CDCl_3$) δ (ppm) = 141.7 (*C*-2), 138.7 (*C*-7a), 133.4 (*C*-8a′), 132.9 (*C*-4a′), 130.4 (*C*-2′), 128.4 (*C*-1′), 128.3 (*C*-4′), 128.2, 127.9 (3C, *C*-3a′,5′,8′), 127.3 (*C*-3′), 126.7, 126.5 (2C, *C*-6′,7′), 121.9 (*C*-6), 120.7 (*C*-4), 120.1 (*C*-5), 109.8 (*C*-7), 102.3 (*C*-3), 31.5 (NCH_3). The data are in accordance with the literature.[48]

*1,2-Bis(4-chlorophenyl)-1H-indole (**9f**).* The general procedure for alkylation was applied using **7k** (261 mg, 0.942 mmol), KHMDS (239 mg, 1.20 mmol), and 1-(bromomethyl)-2-iodobenzene (360 mg, 1.21 mmol). The crude alkylation product [**8l**, 550 mg, 0.901 mmol (internal NMR standard), 96%] was obtained as a yellow solid that was directly subjected to the next reaction step: mp 164.2−165.3 °C; R_f = 0.16 (silica gel, cyclohexane/ethyl acetate 30:1); IR (ATR) $\tilde{\nu}$ (cm^{-1}) = 3384, 1596, 1493, 1401, 1309, 1252, 1094, 1013, 818, 734; ^1H NMR, COSY (300 MHz, $CDCl_3$) δ (ppm) = 7.94−7.91 (m, 1H, *H*-3‴), 7.52−7.48 (AA′-part of AA′BB′-system, 2H, *H*-2′,6′), 7.40−7.36 (BB′-part of AA′BB′-system, 2H, *H*-3′,5′), 7.35−7.31 (m, 2H, *H*-4‴,6‴), 7.08−7.00 (m, 3H, *H*-3″,5″,5‴), 6.43−6.38 (AA′-part of AA′XX′-system, 2H, *H*-2″,6″), 4.71 (s_{br}, 1H, N*H*), 3.55 (s, 2H, CH_2); ^{13}C NMR, HSQC, HMBC (75.5 MHz, $CDCl_3$) δ (ppm) = 141.5 (*C*-1″), 140.5 (*C*-3‴), 136.3 (*C*-1′), 135.9 (*C*-1‴), 135.2 (*C*-4′), 132.0 (*C*-6‴), 130.4 (*C*-5‴), 129.6 (2C, *C*-3′,5′), 129.1 (2C, *C*-3″,5″), 129.0 (*C*-4‴), 127.5 (2C, *C*-2′,6′), 125.3 (*C*-4″), 119.2 (*C*-1), 117.2 (2C, *C*-2″,6″), 102.9 (*C*-2‴), 61.9 (*C*-2), 53.0 (*C*-3); ESI-HRMS (*m*/*z*) calcd for $[C_{21}H_{15}{}^{35}Cl_2IN_2 - CN]^+$ 465.9626, found 465.9613. For indole synthesis, general procedure A was applied using **8l** (crude, 101 mg), $CuBr{\cdot}SMe_2$ (3.30 mg, 0.0404 mmol), neocuproine hemihydrate (8.72 mg, 0.0401 mmol), Cs_2CO_3 (132 mg, 0.405 mmol), and 4 Å molecular sieves (214 mg). Purification of the crude product by flash column chromatography (cyclohexane/ethyl acetate) on silica gel yielded **9f** (37.3 mg, 0.111 mmol, 64% over two steps) as a colorless solid. Alternatively, general procedure B was applied using **8l** (crude, 101 mg), $Pd(dppf)Cl_2$ (7.52 mg, 0.0103 mmol), and NaO^tBu (58.4 mg, 0.608 mmol). Purification of the crude product by flash column chromatography (cyclohexane/ethyl acetate 300:1) on silica gel yielded **9f** (37.2 mg, 0.110 mmol, 64% over two steps) as a colorless solid: mp 149.6−152.2 °C; R_f = 0.31 (silica gel, cyclohexane/ethyl acetate 200:1); IR (ATR) $\tilde{\nu}$ (cm^{-1}) = 3031, 1494, 1453, 1319, 1092, 1015, 833, 792, 749, 722; ^1H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 7.71−7.66 (m, 1H, *H*-4), 7.43−7.39 (XX′-part of AA′BB′-system, 2H, *H*-3″,5″), 7.28−7.23 (m, 3H, *H*-7,2′,6′), 7.22−7.16 (m, 6H, *H*-5,6,3′,5′,2″,6″), 6.80 (d, ^4J = 0.8 Hz, 1H, *H*-3); ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ (ppm) = 139.4 (*C*-1′), 139.0 (*C*-7a), 136.9 (*C*-1″), 133.7 (*C*-4′), 133.3 (*C*-4″), 130.8 (*C*-2), 130.2 (2C, *C*-2″,6″), 129.8 (2C, *C*-3″,5″), 129.3 (2C, *C*-3′,5′), 128.7 (2C, *C*-2′,6′), 128.3 (*C*-3a), 123.0 (*C*-6), 121.3 (*C*-5), 120.9 (*C*-4), 110.6 (*C*-7), 104.6 (*C*-3); ESI-HRMS (*m*/*z*) calcd for $[C_{20}H_{13}{}^{35}Cl_2N + H]^+$ 338.0503, found 338.0504.

*2-(4-Fluorophenyl)-1-(2-phenethyl)-1H-indole (**9g**).* The general procedure for alkylation was applied using **7n** (257 mg, 1.07 mmol), KHMDS (301 mg, 1.51 mmol), and 1-(bromomethyl)-2-iodobenzene (411 mg, 1.38 mmol). The crude alkylation product [**8o**, 573 mg; 0.730 mmol (internal NMR standard), 68%] was obtained as a light yellow oil and was directly subjected to the next reaction step: R_f = 0.12 (silica gel, cyclohexane/ethyl acetate 30:1); IR (ATR) $\tilde{\nu}$ (cm^{-1}) = 3027, 1603, 1507, 1292, 1225, 1137, 1013, 935, 761, 700; ^1H NMR, COSY (300 MHz, $CDCl_3$) δ (ppm) = 7.83 (dd, ^3J = 8.0 Hz, ^4J = 1.2 Hz, 1H, *H*-3‴″), 7.50−7.43 (m, 2H, *H*-2′,6′), 7.27−7.14 (m, 7H, *H*-2‴−6‴,5‴″,6‴″), 7.05−7.00 (m, 2H, *H*-3′,5′), 6.97−6.91 (m, 1H, *H*-4‴″), 3.40−3.27 (m, 2H, CH_2-3), 2.97−2.92 (m, 1H, *H*-1_a″), 2.85−2.70 (m, 2H, CH_2-2″), 2.61−2.53 (m, 1H, *H*-1_b″), 1.72 (s_{br}, 1H, N*H*); ^{13}C NMR, HSQC, HMBC (75.5 MHz, $CDCl_3$) δ (ppm) = 162.9 (d, $^1J_{CF}$ = 248.2 Hz, *C*-4′), 140.2 (*C*-3‴″), 139.2 (*C*-1‴), 136.9 (*C*-1‴″), 134.0 (d, $^4J_{CF}$ = 3.1 Hz, *C*-1′), 131.3 (*C*-6‴″), 129.6 (*C*-4‴″), 129.0 (2C, *C*-2″,6‴), 128.6 (2C, *C*-3‴,5‴″), 128.5 (d, $^3J_{CF}$ = 8.2 Hz, *C*-2′,6′), 128.4 (*C*-5‴″), 126.4 (*C*-4‴), 120.0 (*C*-1), 115.7 (d, $^2J_{CF}$ = 21.6 Hz, 2C, *C*-3′,5′), 103.3 (*C*-2‴″), 65.1 (*C*-2), 52.5 (CH_2-3), 45.8 (CH_2-1″), 36.1 (CH_2-2″); ESI-HRMS (*m*/*z*) calcd for $[C_{23}H_{20}FIN_2 + H]^+$ 471.0733, found 471.0734. For indole synthesis, general procedure A was applied using **8o** (crude, 103 mg), $CuBr{\cdot}SMe_2$ (8.17 mg, 0.0397 mmol), neocuproine hemihydrate (8.40 mg, 0.0386 mmol), Cs_2CO_3 (255 mg, 0.782 mmol), and 4 Å molecular sieves (213 mg). Purification of the crude product by flash column chromatography (cyclohexane/ethyl acetate 300:1) on silica gel yielded **9g** (35.4 mg, 0.112 mmol, 58% over two steps) as a colorless oil. Alternatively, general procedure B was applied using **8o** (crude, 157 mg), $Pd(dppf)Cl_2$ (12.8 mg, 0.0175 mmol), and NaO^tBu (101 mg, 1.05 mmol). Purification of the crude product by flash column chromatography (cyclohexane/ethyl acetate 400:1) on silica gel yielded **9g** (45.0 mg, 0.143 mmol, 49% over two steps) as a colorless oil: R_f = 0.25 (silica gel, cyclohexane/ethyl acetate 300:1); IR (ATR) $\tilde{\nu}$ (cm^{-1}) = 3061, 1496, 1460, 1350, 1224, 1157, 842, 789, 736, 698; ^1H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 7.66−7.64 (m, 1H, *H*-4), 7.46−7.44 (m, 1H, *H*-7), 7.29−7.22 (m, 3H, *H*-6,2′,6′), 7.21−7.15 (m, 4H, *H*-5,3‴,5‴,4‴), 7.12−

DOI: 10.1021/acs.joc.5b02659
J. Org. Chem. 2016, 81, 1858−1869

7.06 (m, 2H, *H*-3′,5′), 6.91−6.86 (m, 2H, *H*-2‴,6‴), 6.46 (d, ^4J = 0.8 Hz, 1H, *H*-3), 4.33 (t, ^3J = 7.6 Hz, 2H, CH_2-1″), 2.94 (t, ^3J = 7.6 Hz, 2H, CH_2-2″); ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ (ppm) = 162.7 (d, $^1J_{CF}$ = 248.2 Hz, *C*-4′), 140.1 (*C*-2), 138.3 (*C*-1‴), 137.1 (*C*-7a), 131.3 (d, $^3J_{CF}$ = 8.2 Hz, 2C, *C*-2′,6′), 129.2 (d, $^4J_{CF}$ = 3.1 Hz, *C*-1′), 128.8 (2C, *C*-2‴,6‴), 128.7 (2C, *C*-3‴,5‴), 128.4 (*C*-3a), 126.7 (*C*-4‴), 121.9 (*C*-6), 120.8 (*C*-4), 120.1 (*C*-5), 115.5 (d, $^2J_{CF}$ = 21.6 Hz, 2C, *C*-3′,5′), 110.1 (*C*-7), 102.5 (*C*-3), 54.7 (CH_2-1″), 36.4 (CH_2-2″); ESI-HRMS (*m*/*z*) calcd for $[C_{22}H_{18}FN + H]^+$ 316.1502, found 316.1506.

*1-Isopropyl-2-phenyl-1H-indole (**9h**).* The general procedure for alkylation was applied using **7c** (260 mg, 1.49 mmol), KHMDS (402 mg, 2.02 mmol), and 1-(bromomethyl)-2-bromobenzene (466 mg, 1.87 mmol). The crude alkylation product [**8d**, 605 mg, 1.14 mmol (internal NMR standard), 77%] was obtained as a yellow oil that was directly subjected to the next reaction step: R_f = 0.10 (silica gel, cyclohexane/ethyl acetate 60:1); IR (ATR): $\overline{\nu}$ (cm^{-1}) = 3398, 3059, 1689, 1448, 1333, 1207, 1027, 751, 692; ^{1}H NMR, COSY (300 MHz, $CDCl_3$) δ (ppm) = 7.64−7.61 (m, 2H, *H*-2′,6′), 7.57−7.54 (m, 1H, *H*-3‴), 7.48−7.43 (m, 1H, *H*-4′), 7.37−7.35 (m, 2H, *H*-3′,5′), 7.22−7.17 (m, 1H, *H*-6‴), 7.15−7.08 (m, 2H, *H*-4‴,5‴), 3.51 (d, ^2J = 13.7 Hz, 1H, H-3$_a$), 3.28 (d, ^2J = 13.7 Hz, 1H, H-3$_b$), 2.96 (sept, ^3J = 6.3 Hz, 1H, *H*-1″), 1.16 (d, ^3J = 6.3 Hz, 3H, CH_3), 0.85 (d, ^3J = 6.3 Hz, 3H, CH_3); ^{13}C NMR, HSQC, HMBC (75.5 MHz, $CDCl_3$) δ (ppm) = 139.4 (*C*-1′), 133.9 (*C*-1‴), 133.3 (*C*-3‴), 132.4 (*C*-4‴), 129.3 (*C*-5‴), 128.8 (*C*-4′), 128.5 (2C, *C*-3′,5′), 127.3 (*C*-6‴), 126.9 (2C, *C*-2′,6′), 126.5 (*C*-2‴), 121.1 (*C*-1), 64.8 (*C*-2), 48.9 (*C*-3), 46.8 (*C*-1″), 24.8 (CH_3), 24.2 (CH_3); ESI-HRMS (*m*/*z*) calcd for $[C_{18}H_{19}{}^{79}BrN_2 - CN]^+$: 316.0701, found 316.0712. For indole synthesis, general procedure B was applied using **8d** (crude, 155 mg), Pd(dppf)Cl_2 (17.4 mg, 0.0238 mmol), and NaO^{t}Bu (149 mg, 1.54 mmol). Purification of the crude product by flash column chromatography (cyclohexane/ethyl acetate 500:1) on silica gel yielded **9h** (30.8 mg, 0.131 mmol, 34% over two steps) as a colorless oil: R_f = 0.22 (silica gel, cyclohexane/ethyl acetate 200:1); IR (ATR) $\overline{\nu}$ (cm^{-1}) = 3057, 1603, 1456, 1443, 1347, 1303, 1173, 786, 750, 701; ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 7.66−7.62 (m, 2H, *H*-4,7), 7.48−7.40 (m, 5H, *H*-2′,3′,4′,5′,6′), 7.22−7.18 (m, 1H, *H*-6), 7.14−7.10 (m, 1H, *H*-5), 6.47 (s$_{br}$, 1H, *H*-3), 4.69 (sept, ^3J = 6.9 Hz, 1H, *H*-1″), 1.62 (d, ^3J = 6.9 Hz, 6H, CH_3); ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ (ppm) = 141.5 (*C*-2), 135.5 (*C*-7a), 133.9 (*C*-1′), 129.8, 128.5, 128.0 (5C, *C*-2′−6′), 129.2 (*C*-3a), 121.1 (*C*-6), 121.0 (*C*-4), 119.6 (*C*-5), 112.5 (*C*-7), 102.3 (*C*-3), 48.0 (*C*-1″), 21.7 (CH_3). The data are in accordance with the literature.[49]

*2-(4-Chlorophenyl)-1-mesityl-1H-indole (**9i**).* The general procedure for alkylation was applied using **7d** (254 mg, 0.892 mmol), KHMDS (229 mg, 1.15 mmol), and 1-(bromomethyl)-2-bromobenzene (302 mg, 1.21 mmol). The crude alkylation product [**8e**, 475 mg, 0.350 mmol (internal NMR standard), 39%] was obtained as an orange oil that was directly subjected to the next reaction step: R_f = 0.19 (silica gel, cyclohexane/ethyl acetate 30:1), IR (ATR): $\overline{\nu}$ (cm^{-1}) = 3358, 1697, 1591, 1488, 1441, 1094, 1028, 1014, 854, 755; ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 7.64−7.59 (AA′-part of AA′XX′-system, 2H, *H*-2′,6′), 7.59−7.56 (m, 1H, *H*-3‴), 7.39−7.34 (XX′-part of AA′XX′-system, 2H, *H*-3′,5′), 7.32−7.23 (m, 2H, *H*-5‴,6‴), 7.20−7.16 (m, 1H, *H*-4‴), 6.78 (s$_{br}$, 2H, *H*-3″,5″), 3.91 (d, ^2J = 13.7 Hz, 1H, H-3$_a$), 3.42 (d, ^2J = 13.7 Hz, 1H, H-3$_b$), 2.20 (s, 3H, 4″-CH_3), 1.85 (s, 6H, 2″-CH_3, 6″-CH_3); ^{13}C NMR, HSQC, HMBC (75.5 MHz, $CDCl_3$) δ (ppm) = 138.6 (*C*-1′), 138.1 (*C*-1″), 135.2 (3C, *C*-2″,4″,6″), 134.9 (*C*-4′), 133.7 (*C*-1‴), 133.4 (*C*-3‴), 132.8 (*C*-6‴), 130.0 (2C, *C*-3″,5″), 129.8 (*C*-4‴), 128.8 (2C, *C*-3′,5′), 128.7 (2C, *C*-2′,6′), 127.8 (*C*-5‴), 126.8 (*C*-2‴), 118.8 (*C*-1), 66.6 (*C*-2), 47.5 (*C*-3), 20.8 (2C, 2″-CH_3, 6″-CH_3), 19.6 (4″-CH_3); ESI-HRMS (*m*/*z*) calcd for $[C_{24}H_{22}{}^{79}Br^{35}ClN_2 - CN]^+$ 426.0624, found 426.0618. For indole synthesis, general procedure B was applied using **8e** (crude, 116 mg), Pd(dppf)Cl_2 (9.85 mg, 0.0135 mmol), and NaO^{t}Bu (73.0 mg, 0.76 mmol). Purification of the crude product by flash column chromatography (cyclohexane/ethyl acetate 200:1) on silica gel yielded **9i** (24.4 mg, 0.0705 mmol, 32% over two steps) as a colorless oil: R_f = 0.45 (silica gel, cyclohexane/ethyl acetate 100:1); IR (ATR) $\overline{\nu}$ (cm^{-1}) = 3056, 1487, 1454, 1356, 1320, 1095, 1013, 831, 787, 750; ^{1}H NMR, COSY (300 MHz, $CDCl_3$) δ (ppm) = 7.72−7.67 (m, 1H, *H*-6), 7.20 (s, 4H, *H*-2′,3′,5′,6′), 7.19−7.11 (m, 2H, *H*-4,7), 6.96 (s$_{br}$, 2H, *H*-3″,5″), 6.86 (d, ^4J = 0.8 Hz, 1H, *H*-3), 6.85−6.80 (m, 1H, *H*-5), 2.36 (s, 1H, 4″-CH_3), 1.82 (2″-CH_3, 6″-CH_3); ^{13}C NMR, HSQC, HMBC (75.5 MHz, $CDCl_3$) δ (ppm) = 139.4 (*C*-2), 138.5 (*C*-4″), 138.1 (*C*-7a), 137.0 (2C, *C*-2″,6″), 133.7 (*C*-1″), 133.4 (*C*-4′), 131.4 (*C*-1′), 129.5 (2C, *C*-3″,5″), 128.8, 128.7 (4C, *C*-2′,3′,5′,6′), 128.2 (*C*-3a), 122.5 (*C*-4), 120.6 (*C*-7), 120.5 (*C*-6), 110.7 (*C*-5), 102.4 (*C*-3), 21.3 (4″-CH_3), 17.8 (2″-CH_3, 6″-CH_3); ESI-HRMS (*m*/*z*) calcd for $[C_{23}H_{20}{}^{35}ClN + H]^+$ 346.1363, found 346.1375.

*4-(2-(4-Methoxyphenyl)-1H-indol-1-yl)phenyl)(phenyl)-methanone (**9j**).* General procedure B was applied using **8f** (45.1 mg, 80.8 μmol), Pd(dppf)Cl_2 (2.73 mg, 3.73 μmol), and NaO^{t}Bu (21.5 mg, 224 μmol). Purification of the crude product by flash column chromatography (cyclohexane/ethyl acetate 30:1) on silica gel yielded **9j** (23.2 mg, 57.8 μmol, 72%, 49% over two steps) as a colorless oil: R_f = 0.47 (silica gel, cyclohexane/ethyl acetate 10:1); IR (ATR) $\overline{\nu}$ (cm^{-1}) = 3055, 1658, 1598, 1502, 1453, 1250, 1176, 1031, 835, 702; ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 7.90−7.87 (XX′-part of AA′XX′-system, 2H, *H*-3″,5″), 7.85−7.82 (m, 2H, *H*-2‴,6‴), 7.71−7.67 (m, 1H, *H*-4), 7.64−7.59 (m, 1H, *H*-4‴), 7.53−7.49 (m, 2H, *H*-3‴,5‴), 7.42−7.38 (m, 1H, *H*-7), 7.38−7.35 (AA′-part of AA′XX′-system, 2H, *H*-2″,6″), 7.23−7.18 (m, 4H, *H*-5,6,2′,6′), 6.84−6.81 (XX′-part of AA′XX′-system, 2H, *H*-3′,5′), 6.77 (d, ^4J = 0.8 Hz, 1H, *H*-3), 3.80 (s, 3H, OCH_3); ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ (ppm) = 195.7 (CO), 159.1 (*C*-4′), 142.3 (*C*-1″), 140.4 (*C*-7a), 138.2 (*C*-3a), 137.3 (*C*-1‴), 135.6 (*C*-4″), 132.5 (*C*-4‴), 131.2 (2C, *C*-3″,5″), 130.2 (2C, *C*-2′,6′), 129.9 (2C, *C*-2‴,6‴), 128.6 (*C*-2), 128.3 (2C, *C*-3‴,5‴), 127.5 (2C, *C*-2″,6″), 124.6 (*C*-1′), 122.4 (*C*-6), 121.1 (*C*-5), 120.5 (*C*-4), 113.8 (2C, *C*-3′,5′), 110.3 (*C*-7), 104.0 (*C*-3), 55.2 (OCH_3); ESI-HRMS (*m*/*z*) calcd for $[C_{28}H_{21}NO_2 + H]^+$ 404.1651, found 404.1659.

*1-Mesityl-2-(4-methoxyphenyl)-1H-indole (**9k**).* The general procedure for alkylation was applied using **7j** (206 mg, 0.735 mmol), KHMDS (213 mg, 1.07 mmol), and 1-(bromomethyl)-2-iodobenzene (292 mg, 0.983 mmol). The crude alkylation product [**8k**, 454 mg, 0.282 mmol (internal NMR standard), 38%] was obtained as a yellow oil that was directly subjected to the next reaction step: due to the low purity, no NMR data could be assigned; R_f = 0.22 (silica gel, cyclohexane/ethyl acetate 30:1); ESI-HRMS (*m*/*z*) calcd for $[C_{25}H_{25}IN_2O - CN]^+$ 470.0981, found 470.0988. For indole synthesis, general procedure B was applied using **8k** (crude, 175 mg), Pd(dppf)Cl_2 (15.8 mg, 0.0216 μmol), and NaO^{t}Bu (122 mg, 1.27 mmol). Purification of the crude product by flash column chromatography (cyclohexane/ethyl acetate 300:1) on silica gel yielded **9k** (27.4 mg, 80.3 μmol, 28% over two steps) as a colorless oil: R_f = 0.23 (silica gel, cyclohexane/ethyl acetate 200:1); IR (ATR) $\overline{\nu}$ (cm^{-1}) = 2919, 1612, 1499, 1285, 1250, 1178, 1032, 833, 784, 751; ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 7.69−7.67 (m, 1H, *H*-4), 7.23−7.19 (AA′-part of AA′XX′-system, 2H, *H*-2′,6′), 7.16−7.09 (m, 2H, *H*-5,6), 6.95 (m, 2H, *H*-3″,5″), 6.82−6.80 (m, 1H, *H*-7), 6.79−6.75 (m, 3H, *H*-3,3′,5′), 3.77 (s, 3H, OCH_3), 2.36 (s, 3H, 4″-CH_3), 1.83 (s, 6H, 2″-CH_3, 6″-CH_3); ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ (ppm) = 159.0 (*C*-4′), 140.6 (*C*-2), 138.2 (*C*-4″), 137.9 (*C*-7a), 137.2 (2C, *C*-2″,6″), 134.1 (*C*-1″), 129.3 (2C, *C*-3″,5″), 128.9 (2C, *C*-2′,6′), 128.5 (*C*-3a), 125.6 (*C*-1′), 121.8 (*C*-6), 120.2 (2C, *C*-4,5), 113.9 (2C, *C*-3′,5′), 110.5 (*C*-7), 101.2 (*C*-3), 55.3 (OCH_3), 21.3 (4″-CH_3). ESI-HRMS (*m*/*z*) calcd for $[C_{24}H_{23}NO + H]^+$ 342.1858, found 342.1857.

*1-(4-Methoxyphenyl)-2-(naphthalen-2-yl)-1H-indole (**9l**).* The general procedure for alkylation was applied using **7g** (250 mg, 0.867 mmol), KHMDS (262 mg, 1.31 mmol), and 1-(bromomethyl)-2-iodobenzene (343 mg, 1.16 mmol). The crude alkylation product [**8h**, 568 mg, 0.275 mmol (internal NMR standard), 32%] was obtained as a green oil and was directly subjected to the next reaction step: due to the low purity, no NMR signals could be assigned; R_f = 0.15 (silica gel, cyclohexane/ethyl acetate 10:1); ESI-HRMS (*m*/*z*) calcd for $[C_{26}H_{21}IN_2O - CN]^+$ 478.0668, found 478.0669. For indole synthesis, general procedure B was applied using **8h** (crude, 160 mg), Pd(dppf)Cl_2 (11.9 mg, 16.3 μmol), and NaO^{t}Bu (85.9 mg, 894 μmol). Purification of the crude product by flash column chromatography (cyclohexane/ethyl acetate 100:1) on silica gel yielded **9l** (26.2 mg, 75.0 μmol, 31% over two steps) as a light yellow oil: R_f = 0.27 (silica gel, cyclohexane/ethyl acetate 100:1); IR (ATR) $\overline{\nu}$ (cm^{-1}) = 3055, 1512, 1454, 1247, 1033, 909, 834,

DOI: 10.1021/acs.joc.5b02659
J. Org. Chem. 2016, 81, 1858−1869

788, 728, 750; ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 7.82 (d, ^4J = 1.6 Hz, 1H, *H*-1′), 7.80−7.76 (m, 1H, *H*-7′), 7.74−7.69 (m, 3H, *H*-4,4′,6′), 7.48−7.43 (m, 2H, *H*-5′,8′), 7.37 (dd, ^3J = 8.6 Hz, ^4J = 1.8 Hz, 1H, *H*-3′), 7.30−7.28 (m, 1H, *H*-7), 7.25−7.22 (AA′-part of AA′XX′-system, 2H, *H*-2″,6″), 7.21−7.18 (m, 2H, *H*-5,6), 6.95−6.91 (m, 3H, *H*-3,3″,5″), 3.84 (s, 3H, OCH_3); ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ (ppm) = 158.4 (*C*-4″), 140.6 (*C*-2), 139.3 (*C*-7a), 133.0 (*C*-2′), 132.2 (*C*-4a′), 131.2 (*C*-1″), 129.9 (*C*-7a′), 129.0 (2C, *C*-2″,6″), 128.0 (2C, *C*-3a,6′), 127.7 (*C*-4′), 127.4 (2C, *C*-1′,7′), 126.6 (*C*-3′), 126.0, 125.9 (2C, *C*-5′,8′), 122.1 (*C*-6), 120.4 (*C*-5), 120.3 (*C*-4), 114.3 (2C, *C*-3″,5″), 110.5 (*C*-7), 103.5 (*C*-3), 55.3 (OCH_3); ESI-HRMS (*m*/*z*) calcd for $[C_{25}H_{19}NO + H]^+$ 350.1545, found 350.1541.

*2-(4-Chlorophenyl)-1-(p-tolyl)-1H-indole (**9m**).* The general procedure for alkylation was applied using **7l** (251 mg, 0.978 mmol), KHMDS (264 mg, 1.32 mmol), and 1-(bromomethyl)-2-iodobenzene (378 mg, 1.27 mmol). The crude alkylation product [**8m**, 578 mg, 0.698 mmol (internal NMR standard), 71%] was obtained as a yellow solid and was directly subjected to the next reaction step: mp 127.1−129.3 °C; R_f = 0.14 (silica gel, cyclohexane/ethyl acetate 30:1); IR (ATR) $\tilde{\nu}$ (cm^{-1}) = 3391, 1615, 1517, 1437, 1300, 1253, 1094, 1013, 809, 755; ^{1}H NMR, COSY (300 MHz, $CDCl_3$) δ (ppm) = 7.92−7.90 (m, 1H, *H*-3‴), 7.55−7.51 (AA′-part of AA′BB′-system, 2H, *H*-2′,6′), 7.38−7.33 (m, 4H, *H*-3′,5′,4‴,6‴), 7.06−7.00 (m, 1H, *H*-5‴), 6.91−6.88 (XX′-part of AA′XX′-system, 2H, *H*-3″,5″), 6.42−6.37 (AA′-part of AA′XX′-system, 2H, *H*-2″,6″), 4.54 (s_{br}, 1H, N*H*), 3.55 (s, 2H, CH_2), 2.18 (s, 3H, CH_3); ^{13}C NMR, HSQC, HMBC (75.5 MHz, $CDCl_3$) δ (ppm) = 140.5 (*C*-1″), 140.4 (*C*-4″), 140.2 (*C*-3‴), 136.9 (*C*-1′), 136.2 (*C*-1‴), 134.9 (*C*-4′), 131.9 (*C*-6‴), 130.2 (*C*-5‴), 129.6 (2C, *C*-3″,5″), 129.4 (2C, *C*-3′,5′), 128.9 (*C*-4‴), 127.7 (2C, *C*-2′,6′), 119.5 (*C*-1), 116.2 (2C, *C*-2″,6″), 103.0 (*C*-2‴), 62.0 (*C*-2), 53.1 (*C*-3), 20.6 (CH_3); ESI-HRMS (*m*/*z*) calcd for $[C_{22}H_{18}{}^{35}ClIN_2 - CN]^+$ 446.0173, found 446.0181. For indole synthesis, general procedure B was applied using **8m** (crude, 153 mg), $Pd(dppf)Cl_2$ (13.0 mg, 0.0178 mmol), and NaO^{t}Bu (93.9 mg, 0.977 mmol). Purification of the crude product by flash column chromatography (cyclohexane/ethyl acetate 300:1) on silica gel yielded **9m** (45.5 mg, 0.143 mmol, 55%) as a light yellow oil: R_f = 0.36 (silica gel, cyclohexane/ethyl acetate 200:1); IR (ATR) $\tilde{\nu}$ (cm^{-1}) = 3019, 1513, 1453, 1406, 1317, 1090, 1015, 830, 785, 737; ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 7.72−7.68 (m, 1H, *H*-4), 7.31−7.27 (m, 1H, *H*-7), 7.25−7.22 (m, 6H, *H*-2′,3′,5′,6′,3″,5″), 7.21−7.19 (m, 2H, *H*-5,6), 7.15−7.12 (AA′-part of AA′BB′-system, 2H, *H*-2″,6″), 6.80 (d, ^4J = 0.8 Hz, 1H, *H*-3), 2.43 (s, 3H, 4″-CH_3); ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ (ppm) = 139.6 (*C*-2), 139.3 (*C*-7a), 137.4 (*C*-4″), 135.7 (*C*-1″), 133.4 (*C*-4′), 131.3 (*C*-1′), 130.2 (2C, *C*-3″,5″), 130.1, 128.5 (4C, *C*-2′,3′,5′,6′), 128.2 (*C*-3a), 127.9 (2C, *C*-2″,6″), 122.6 (*C*-6), 120.9 (*C*-5), 120.7 (*C*-4), 110.9 (*C*-7), 103.8 (*C*-3), 21.3 (4″-CH_3). ESI-HRMS (*m*/*z*) calcd for $[C_{21}H_{16}{}^{35}ClN + H]^+$ 318.1050, found 318.1058.

*2-(4-Methoxyphenyl)-1-(p-tolyl)-1H-indole (**9n**).* The general procedure for alkylation was applied using **7m** (266 mg, 1.05 mmol), KHMDS (257 mg, 1.29 mmol), and 1-bromomethyl)-2-iodobenzene (375 mg, 1.26 mmol). The crude alkylation product [**8n**, 553 mg; 0.320 mmol (internal NMR standard), 31%] was obtained as a yellow oil and was directly subjected to the next reaction step: due to the low purity, no NMR signals could be assigned; R_f = 0.12 (silica gel, cyclohexane/ethyl acetate 30:1); ESI-HRMS (*m*/*z*) calcd for $[C_{23}H_{21}IN_2O - CN]^+$ 442.0668, found 442.0681. For indole synthesis, general procedure B was applied using **8n** (crude, 160 mg), $Pd(dppf)Cl_2$ (12.3 mg, 0.0168 mmol), and NaO^{t}Bu (106 mg, 1.10 mmol). Purification of the crude product by flash column chromatography (cyclohexane/ethyl acetate 200:1) on silica gel yielded **9n** (19.6 mg, 0.0625 mmol, 21% over two steps) as a colorless oil. R_f = 0.19 (silica gel, cyclohexane/ethyl acetate 100:1); IR (ATR) $\tilde{\nu}$ (cm^{-1}) = 3015, 1610, 1514, 1454, 1248, 1178, 1033, 834, 812, 749; ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 7.70−7.65 (m, 1H, *H*-4), 7.29−7.25 (m, 1H, *H*-7), 7.24−7.20 (m, 4H, *H*-2′,6′,3″,5″), 7.18−7.13 (m, 4H, *H*-5,6,2″,6″), 6.82−6.78 (XX′-part of AA′XX′-system, 2H, *H*-3′,5′), 6.73 (d, ^4J = 0.8 Hz, 1H, *H*-3), 3.79 (s, 3H, OCH_3), 2.42 (s, 3H, 4″-CH_3); ^{13}C NMR, HSQC, HMBC (100.6 Hz, $CDCl_3$) δ (ppm) = 159.0 (*C*-4′), 140.8 (*C*-2), 139.1 (*C*-7a), 137.1 (*C*-4″), 136.1 (*C*-1″), 130.3 (2C, *C*-2′,6′), 130.0 (2C, *C*-3″,5″), 128.4 (*C*-3a), 128.0 (2C, *C*-2″,6″), 125.3 (*C*-1′), 122.0 (*C*-6), 120.6 (*C*-5), 120.3 (*C*-4), 113.8 (2C, *C*-3′,5′), 110.7 (*C*-7), 102.6 (*C*-3), 55.3 (OCH_3), 21.3 (4″-CH_3); ESI-HRMS (*m*/*z*) calcd for $[C_{22}H_{19}NO + H]^+$ 314.1545, found 314.1540.

*2,3-Diphenylisoquinolin-1-one (**14**).* In an oven-dried 10 mL Schlenk tube equipped with a magnetic stirring bar, the alkylated α-aminonitrile **8a** (55.5 mg, 131 μmol), $Pd(dba)_2$ (3.61 mg, 6.28 μmol, 5.0 mol %), Xantphos (4.12 mg, 7.12 μmol, 5.0 mol %), and Cs_2CO_3 (123 mg, 378 μmol, 2.9 equiv) were placed, and the vessel was evacuated and backfilled with argon three times. Dry, degassed toluene (1.3 mL) was added and the resulting suspension was purged with CO for 2−3 min. Subsequently, the tube was sealed and heated to 120 °C in a preheated oil bath for 24−48 h. After complete consumption of the starting material (reaction monitoring by TLC and HPLC−ESI-MS), NaO^{t}Bu (27,1 mg, 282 μmol, 2.2 equiv) was added and the mixture was heated to 120 °C for 2 h. Subsequently, the reaction mixture was evaporated in vacuo. Purification of the crude product by flash column chromatography (cyclohexane/ethyl acetate 7:1) on silica gel yielded isoquinolone **14** (19.4 mg, 69.5 μmol, 53%) as a colorless solid: mp 175.2−178.1 °C (lit.[50] mp 177−179 °C); R_f = 0.16 (silica gel, cyclohexane/ethyl acetate 5:1); IR (ATR) $\tilde{\nu}$ (cm^{-1}) = 3060, 2923, 1660, 1623, 1593, 1491, 1379, 1279, 766, 694; ^{1}H NMR, COSY (300 MHz, $CDCl_3$) δ (ppm) = 8.47 (d, ^3J = 8.0 Hz, 1H, *H*-8), 7.72−7.62 (m, 1H, *H*-6), 7.57 (d, ^3J = 7.8 Hz, 1H, *H*-5), 7.55−7.49 (m, 1H, *H*-7), 7.30−7.20 (m, 3H, *H*-4′,3″,4″,5″), 7.18−7.17 (m, 5H, *H*-2′−6′), 7.14−7.11 (m, 2H, *H*-2″,6″), 6.61 (s_{br}, 1H, *H*-4); ^{13}C NMR, HSQC, HMBC (75.7 MHz, $CDCl_3$) δ (ppm) = 163.2 (*C*O), 143.7 (*C*-3), 139.2 (*C*-1″), 136.9 (*C*-4a), 136.3 (*C*-1′), 132.9 (*C*-6), 129.5 (2C, *C*-2″,6″), 129.4 (2C, *C*-2′,6′), 128.8 (2C, *C*-3″,5″), 128.5 (*C*-8), 128.1 (*C*-4′), 127.9 (2C, *C*-3′,5′), 127.8 (*C*-4″), 127.1 (*C*-7), 126.2 (*C*-5), 125.6 (*C*-8a), 108.2 (*C*-4). The data are in accordance with the literature.[50]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02659.

^{1}H and ^{13}C NMR spectra for α-aminonitriles **7a−n**; intermediates **8a,b,f,i** (pure) and **8b−g,j,l,m,o** (crude); and products **9a−n** and **14** (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Dr. J. C. Liermann (Johannes Gutenberg-Universität Mainz) for NMR spectroscopy and Dr. N. Hanold (Johannes Gutenberg-Universität Mainz) for ESI-HRMS measurements. Compounds **7d** and **7n** were kindly provided by Jens Emsermann (Johannes Gutenberg-Universität Mainz).[35] Financial support by the Rhineland-Palatinate Center for Natural Products Research is gratefully acknowledged.

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DOI: 10.1021/acs.joc.5b02659
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