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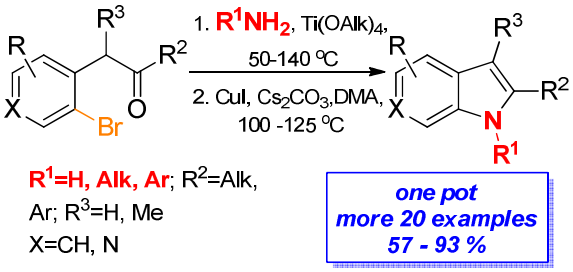
Ferdinand S. Melkonyan,*‡ Daniil E. Kuznetsov, Marina A. Yurovskaya and Alexander V. Karchava*



A new efficient protocol for the synthesis of substituted indoles from *o*-bromobezyl ketones and primary amines or ammonia was developed.

ARTICLE TYPE

One-Pot Synthesis of Substituted Indoles via Titanium (IV) Alkoxide Mediated Imine Formation – Copper-Catalyzed *N*-Arylation†

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Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

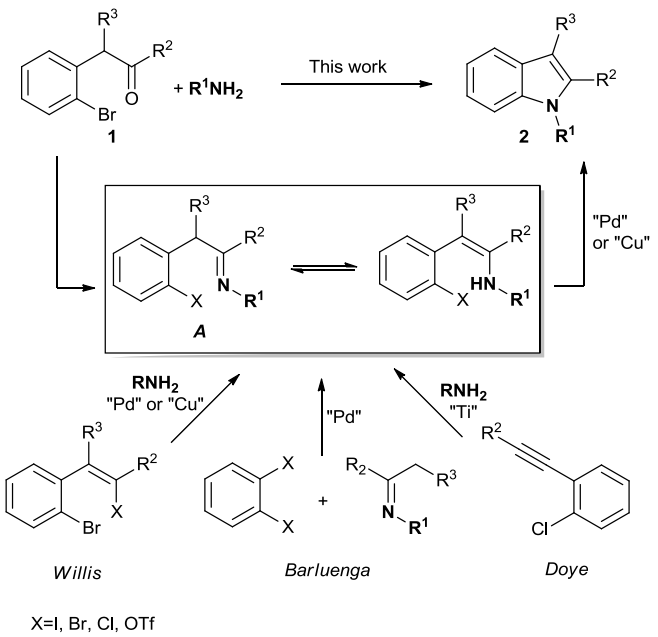
Readily accessible *o*-bromobenzylketones and primary alkyl amines and anilines were used for the construction of substituted indoles in good to excellent yields. The sequence involves a titanium-mediated reaction of ketones with amines to afford imines and subsequent intramolecular cyclization into indoles employing copper catalysis. The two-step protocol allows for the preparation of indoles bearing both N-alkyl and N-aryl groups as well as N-unsubstituted indoles without isolation of the intermediates and is tolerant of a wide range of functionality.

Introduction

Benzo-fused five-membered heterocycles, particularly indoles, benzothiophenes and benzofurans, are the key structural elements found in a great number of natural products and developed and marketed drugs.[1] Compounds containing these heterocyclic cores are privileged structures and their exploitation in drug discovery programs allows to rapidly identify new high-binding ligands to variety of biological targets.[2] Due to the importance of these heterocyclic structures in medicinal chemistry, numerous of diverse approaches have been developed for preparing them,[2-5] including a great number of recent routes based on the use of transition metal-catalyzed reactions or oxidative cyclizations.[6]

In 2004 Willis and co-workers demonstrated that *o*-bromobenzylketones **1** and thioketones derived from ketones **1** could be easily converted to benzofurans and benzothiophenes respectively via a $Pd_2(dba)_3$/DPEphos-catalyzed base-promoted cyclization.[7] The same direct conversion of ketones **1** (and related aldehydes) to substituted benzofurans can be achieved by the use of a Pd-NHC-catalyst[8] or by employing a low-cost copper[9] or an iron catalyst.[10] The ready availability of compounds of the type **1** by various methods[6a,7-10] makes this metal-catalyzed cyclization a practically useful synthetic route to deliver both functionalized benzofuran and benzothiophene from a single precursor.

Following the same retrosynthetic strategy, it could be assumed that reactions of ketones **1** with primary amines should directly provide imines ***A*** (in equilibrium with the corresponding enamines) which could in turn undergo a base-promoted metal-catalyzed cyclization to supply substituted indoles **2** in a regiodefined fashion (Scheme 1). However, compounds of the general type **1** have rarely been used as starting materials for the preparation of substituted indoles. Published examples are restricted to Pd[11] and Cu-catalyzed[12,13] cyclizations of preformed imines[12] and hydrazones[11,13] of *o*-haloarylacetaldehydes (**1**, R^2=H) to deliver 2-unsubstituted indoles, but there is no report on the preparation of 2-substituted indoles starting from ketones **1**.



Scheme 1 Complementary strategies for the synthesis of indoles through the cyclization of *in situ* generated imines ***A***

On the other hand, a few recently developed strategies for indole synthesis are based on an intramolecular cyclization of imines ***A*** generated in situ without using ketones **1** (Scheme 1). In a two-step, one-pot sequence to 2-alkylindoles presented by Doye and co-workers imines ***A*** were generated employing a titanium-catalyzed hydroamination process.[14] The Willis research group developed a cascade strategy where the same intermediates ***A*** were provided through an initial intermolecular metal-catalyzed amination of 2-(2-haloalkenyl)arylhalides.[15] In the approach disclosed by Barluenga and co-workers the indole precursors were formed by palladium catalyzed α-arylation of imines of enolizable ketones with 1,2-dihaloarenes under basic

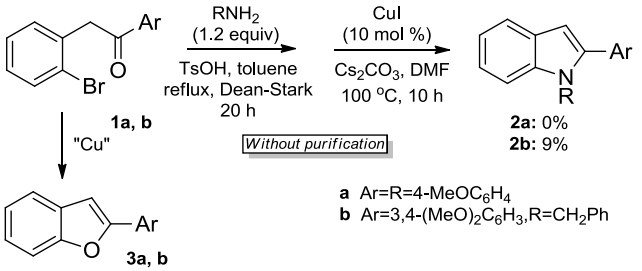
conditions.[16] Normally, for the intramolecular *N*-arylation/cyclization step these protocols use an expensive catalyst based on palladium associated with either phosphines[15,16] or N-heterocyclic carbenes[14] as ligands. The Willis' approach was also briefly exemplified with using a copper–diamine catalyst only for the synthesis of 2-unsubstituted 1-alkyl and 1-arylindoles.[15e]

Despite the success of the above strategies, it would be desirable to develop an alternative method for the generation of ketimines ***A*** and, thus, for the synthesis of substituted indoles employing easily accessible *o*-bromobenzylketones **1** and primary amines as the starting material pool. This approach would complement the existing syntheses of both *N*-alkyl and *N*-aryl indoles, and in particular, a range of diversely 1,2-disubstituted indoles,[17] which are usually achieved through a functionalization at the nitrogen atom of preformed *NH*-indoles. Furthermore, an opportunity for three classes of five-membered benzo-fused heterocycles to be prepared in an expeditious fashion using the same preassembled precursors with slight modifications of the reaction conditions would be of significant value for medicinal chemistry.

With this in mind we sought to extend the synthetic utility of *o*-bromobenzylketones **1** to access substituted indoles **2** (Scheme 1). We aimed to develop a practical synthesis of indoles via a one-pot, two-step process comprising the generation of imines from ketones **1** and various primary amines and their subsequent cyclization into indoles through an intramolecular *N*-arylation reaction (Scheme 1). Given that imines ***A***, though assembled using other approaches, were explored in palladium-catalyzed cyclizations before,[14–16] we chose copper-catalyzed C–N coupling conditions[18] for the second step of our process. In recent years, the field of copper-catalyzed reactions has seen a great number of contributions and the intramolecular version of the Ullmann coupling reaction has emerged as a powerful method for the construction of various heterocycles[6a,d;19] including indoles[12,13,15e,20] through the formation of a carbon–heteroatom bond.

Results and discussion

We began our study by examining *p*-anisidine and benzylamine in the reactions with *o*-bromobenzylketones **1a** and **1b** respectively in the presence of catalytic amount of *p*-toluenesulfonic acid monohydrate in toluene at reflux in a Dean–Stark apparatus containing 4Å molecular sieves for 20 h.[21] The crude mixtures obtained after removal of the solvent were used without further purification in the cyclization step. In our initial examination the Cu-catalyzed cyclization was carried out under standard conditions (10 mol % of CuI, 2 equiv Cs_2CO_3, DMF, 100 °C, 10 h) previously reported by us for the synthesis of *N*-substituted indole-3-carboxylates.[12a,b] To our surprise, no desired indole **2a** was formed when less nucleophilic *p*-anisidine was utilized, while N-benzylindole **2b** was obtained in only 9% yield (based on ^{1}H NMR) when benzylamine was employed in the reaction with ketone **1b** (Scheme 2). The major product in both cases was identified as benzofurans **3a and 3b** respectively formed from *o*-bromobenzylketone **1a,b** through a copper-catalyzed intramolecular C–O-bond formation.[9] Thus, our initial experiments showed that ketones **1** undergo nucleophilic attack

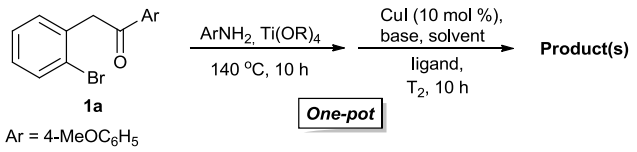


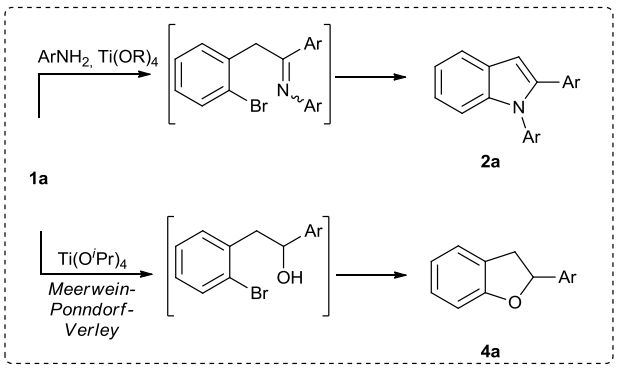
Scheme 2 Initial experiments

by primary amines extremely slowly (which is probably attributed to the steric congestion at the carbonyl group and/or easy enolization of ketones **1**) and a simple Brønsted acid (*p*-TsOH) was not a suitable catalyst for the preparation of the corresponding ketimines. Because our challenge lay in developing a one-pot procedure to access substituted indoles, the first step of our sequence must give the intermediate imines ***A*** (Scheme 1) in reasonably high yields and proceed cleanly enough for the next step to continue without isolation and purification of intermediates. Therefore, we next focused our attention on the use of titanium (IV) alkoxides[22] as promoters for the reaction of ketones **1** with primary amines. Titanium-based reagents are both Lewis acids, which have a high affinity to oxygenated organic molecules, and dehydrating reagents. The mild nature of titanium (IV) alkoxides makes this type of reagents best suitable for our needs and should provide a high degree of functional group tolerance. The optimization of the indole synthesis was performed on 0.5 mmol scale using a one-pot procedure (Table 1). A mixture of ketone **1a** and *p*-anisidine as test substrates and 5 equiv of titanium (IV) alkoxides were initially heated to generate the imine, then the reagents and solvent needed for the Ullmann reaction were introduced and the cyclization step was carried out under the same conditions as above. Using less than 5 equiv of titanium (IV) alkoxides resulted in incomplete homogenization of the reaction mixture even at an elevated temperature. At a temperature below 140 °C, the reaction of ketone **1a** with *p*-anisidine in $Ti(O^iPr)_4$ did not take place and after subsequent cyclization benzofuran **3a** was obtained exclusively. Conducting the first step at 140 °C led to the expected indole **2a** (45%) along with 2,3-dihydrobenzofuran **4a** (15%) (entry 1). The formation of the latter is probably due to the partial reduction of the starting ketone **1a** to the corresponding alcohol (Meerwein-Ponndorf-Verley reaction)[23] followed by a copper-catalyzed intramolecular cyclization.[24] Heating of ketone **1a** with 10 equiv of $Ti(O^iPr)_4$ without adding *p*-anisidine after the following cyclization gave dihydrobenzofuran **4a** in 70% yield (entry 2). The use of titanium (IV) tert-butoxide[25] in place of $Ti(O^iPr)_4$ at 140 °C lead to the desired indole **2a** in 77% isolated yield with no trace of benzofuran **3a** (entry 3). However, reducing of the reaction temperature and/or shortening of the reaction time in the first step of the process resulted in a lower yield of indole **2a** and the formation of the undesired benzofuran **3a**. Replacing DMF with DMA in the cyclization step afforded a better yield of indole **2a** (85%, isolated, entry 4). Notably, when the scale was increased from 0.5 to 2 mmol, the best yield of indole **2a** (93%, entry 5) was observed with using of 2 equiv of $Ti(O^tBu)_4$. Omitting DMA under otherwise identical condition did not give the cyclization product (entry 6). Attempts to reduce the requisite amount of

$Ti(O^tBu)_4$ from 5 to 2 equiv by partially replacing with *o*-xylene or DMA were unsuccessful, as no desired product was obtained in both cases (entries 7 & 8). Titanium (IV) ethoxide as a promoter for the in situ imine formation and other inorganic bases (K_2CO_3, K_3PO_4) for the following cyclization step were also examined, but in all cases the desired product **2a** was obtained in lower yield (entries 9–11).

Table 1 Optimization of the one pot indole synthesis [a]



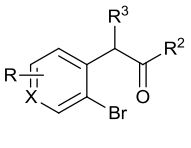


Entry	$Ti(OR)_4$, equiv	Base	Solvent	T[2], °C	Ligand	Product(s): yield, %[b]
1	$Ti(O^iPr)_4$; 5	Cs_2CO_3	DMF	125		**2a**: 45; **4a**: 15
2	$Ti(O^iPr)_4$; 10	Cs_2CO_3	DMF	125		**4a**: (70)[c]
3	$Ti(O^tBu)_4$; 5	Cs_2CO_3	DMF	125		**2a**: 77
4	$Ti(O^tBu)_4$; 5	Cs_2CO_3	DMA	125		**2a: (**85)
5[d]	$Ti(O^tBu)_4$; 2	Cs_2CO_3	DMA	125		**2a: (**93)
6	$Ti(O^tBu)_4$; 5	Cs_2CO_3	none	125		
7	$Ti(O^tBu)_4$; 2	Cs_2CO_3	*o*-xylene[e]	125		
8	$Ti(O^tBu)_4$; 2	Cs_2CO_3	DMA[e]	125		**2a**: 50
9	$Ti(OEt)_4$; 5	Cs_2CO_3	DMA	125		**2a**:70
10	$Ti(O^tBu)_4$; 5	K_2CO_3	DMA	125		**2a**: 67
11	$Ti(O^tBu)_4$; 5	K_3PO_4	DMA	125		**2a**: 73
12	$Ti(O^tBu)_4$; 5	Cs_2CO_3	DMA	90		**2a**: 11
13	$Ti(O^tBu)_4$; 5	Cs_2CO_3	DMA	90	***L*[1]**	**2a:** (75)
14	$Ti(O^tBu)_4$; 5	Cs_2CO_3	DMA	90	***L*[2]**	**2a**: 20
15	$Ti(O^tBu)_4$; 5	Cs_2CO_3	DMA	90	***L*[3]**	**2a**: 26
16	$Ti(O^tBu)_4$; 5	Cs_2CO_3	DMA	90	***L*[4]**	**2a**: 43

[a] Reaction scale: **1a** (0.5 mmol, 0.25 M); *p*-anisidine (0.65 mmol), base (1 mmol, 2 equiv), under argon. [b]NMR yields determined using CH_2Br_2 as an internal standard. Isolated yields are in parentheses. [c]Without $ArNH_2$. [d]Reaction scale: **1a** (2 mmol, 0.25 M); *p*-anisidine (2.6 mmol) base (4 mmol, 2 equiv). [e]Added at the beginning of the two step reaction. ***L*[1]**= *L*-proline. ***L*[2]**=ethylene glycol. ***L*[3]**=*N*,*N*′-dimethylethylenediamine. ***L*[4]**=1,10-phenantroline.

We also screened the effect of several commonly employed ligands on the copper-catalyzed cyclization reaction. We anticipated that the using of a suitable ligand would permit the cyclization to successfully proceed at lower temperature allowing good functional group tolerance. Among all ligands tested, *L*-proline gave a comparable yield of indole **2a** (75%) at 90 °C (entry 13), whereas ethylene glycol, DMEDA and 1,10-phenantroline were much less effective (entries 14–16).

Based on the above studies, $Ti(O^tBu)_4$ as the promoter and conducting the reaction at 140 °C for 10 h were selected as the optimal conditions for the formation of imines from ketone **1a** and *p*-anisidine. We also found that the combination of DMA as the solvent and Cs_2CO_3 as the base provided the highest yield of indole **2a** through the copper-catalyzed intramolecular cyclization under ligandless conditions at 125 °C (Table 1, entry 4).

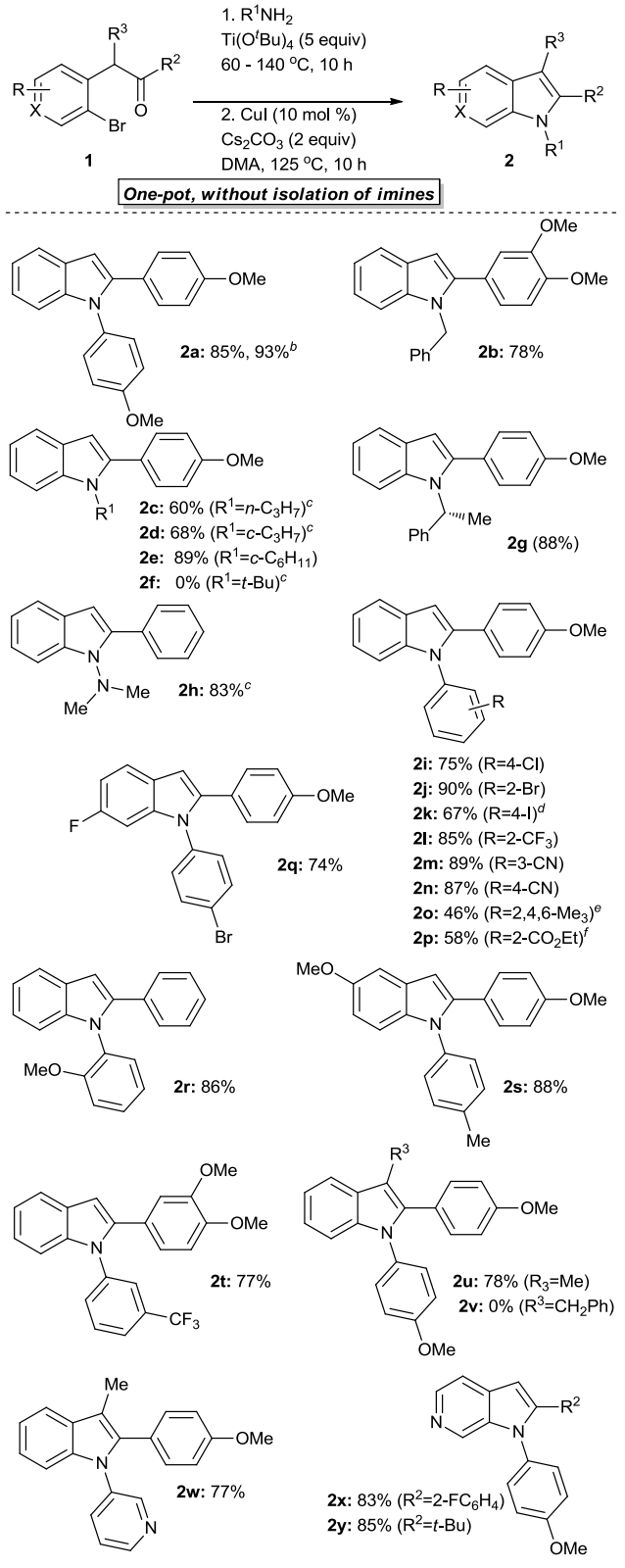


1a R=R[3]=H, R[2]=4-MeOC_6H_4, X=CH
1b R=R[3]=H, R[2]=3,4-$(MeO)_2C_6H_3$, X=CH
1c R=5-MeO, R[2]=4-MeOC_6H_4, R[3]=H, X=CH
1d R=4-F, R[2]=4-MeOC_6H_4, R[3]=H, X=CH
1e R=R[3]=H, R[2]=Ph, X=CH
1f R=H, R[2]=4-MeOC_6H_4, R[3]=Me, X=CH
1g R=H, R[2]=4-MeOC_6H_4, R[3]=CH_2Ph, X=CH
1h R=R[3]=H, R[2]=2-FC_6H_4, X=N
1i R=R[3]=H, R[2]=*t*-Bu, X=N

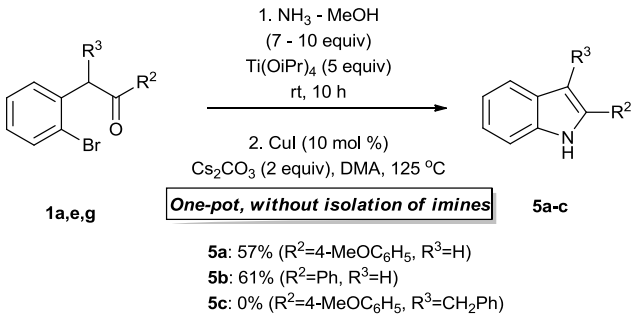
Fig. 1 *o*-Bromobenzyl ketones **1** used in the one-pot indole synthesis

The scope and limitations of this one-pot two-step method for the preparation of substituted indoles (Table 2) was explored with a variety of aliphatic amines and anilines and 2-bromobenzylketones **1a–i** bearing different substituents (Fig. 1), which were readily prepared using known methods. When the more nucleophilic aliphatic amines were employed, the first step of the process was performed at 60 °C. A series of primary aliphatic amines with both primary and secondary alkyl groups reacted smoothly to give the corresponding *N*-alkylated indoles **2b**–**2e,** and **2g** in good to high yields. A high yield of the desired product **2h** was also obtained when *N*,*N*-dimethylhydrazine was used. However, steric effects of amines appeared to play a significant role in the reaction efficiency, as exposing *tert*-butylamine to the optimal reaction conditions lead only to the formation of benzofuran **3a**. Alternative reaction conditions, namely, a prolonged heating of ketone **1a** and $Ti(O^tBu)_4$ with a large excess (~10 equiv) of *tert*-butylamine at 100 °C in a sealed tube did not afford the desired indole **2f**. Several substituted anilines and 3-aminopyridine were found to react with ketones **1** to form *N*-arylated indoles in high yields. The process is tolerant a range of aryl substituents such as methyl, methoxy, halogens, trifluoromethyl, cyano, esters. Notably, we found that, besides fluoro-, chloro-, bromo-substituted indoles, even iodo-compound **2k** could be prepared in 67% yield if the cyclization step was performed at lower temperature (90 °C) in the presence of 20 mol % *L*-proline. *Ortho*-substituted anilines also reacted smoothly affording the desired indoles **2j**, **2l**, **2p** and **2r** cleanly and usually in high yields. In contrast, 2,4,6-trimethylaniline proved to be more problematic substrate and gave under the optimal conditions an inseparable mixture (~1:1) of indole **2o** and benzofuran **3a**. To further examine the scope of the method *o*-bromobenzylketones **1f**,**g** bearing a substituent at the benzylic position were employed for the synthesis of 3-substituted indoles. While 3-methylindoles **2u** and **2w** were prepared in ~77% yield, 3-benzylindole **2v** could not be synthesized using this method; only the corresponding 2-(4-methoxyphenyl)-3-benzylbenzofuran (**3b**) was isolated in the latter case, presumably because the considerable steric hindrance caused by the benzyl group disfavours the reaction of ketone **1g** with amines. On the contrary, ketone **1i** bearing *tert*-butyl group afforded the expected 2-*tert*-butylindole **2y** without attenuation of the yield.

Table 2 One pot synthesis of N-substituted indoles [a]



[a] Reaction scale: **1a** (0.5 mmol, 0.25 M); amine (0.65 mmol), base (1 mmol, 2 equiv), under argon. Isolated yields. [b]Reaction scale: **1a** (2 mmol, 0.25 M); *p*-anisidine (2.6 mmol) base (4 mmol, 2 equiv).[c] The 1st step performed at 60 °C. [d] For the conditions, see: Tab.1, entry 13. [e]Isolated as an inseparable mixture (~1:1) with **3a**. [f]$Ti(OEt)_4$ was used to avoid transesterification.



Scheme 3 Synthesis of N-unsubstituted indoles

The electronic nature of the substituent in the phenyl rings does not affect the efficiency of the method (**2a** and **2x**).

Finally, we were interested whether our procedure for the preparation of *N*-substituted indoles could be extended to the synthesis of *N*-unsubstituted indoles by employing ammonia in the first step of the process. We used a commercially available solution of ammonia in MeOH (7 M) (7–10 equiv) and $Ti(O^iPr)_4$ for the preparation of the cyclization precursors. Unfortunately, under standard reaction conditions for the copper-catalyzed cyclization indoles **5a** and **5b** were obtained only in moderate yields, whereas ketone **1f** bearing benzyl group gave only trace amounts of the target product **5c**.

Conclusions

In summary, we have developed an effective one-pot procedure for the synthesis of substituted indoles through a Ti-mediated imine formation/Cu-catalyzed *N*-arylation sequence. The protocol allows the preparation of 2-substituted indoles from *o*-bromobenzylketones and ammonia, alkyl amines with 1° and 2° groups, and anilines, excluding 2,6-disubstituted, in good to high overall yields without using expensive reagents and catalysts. Due to the simplicity and versatility of the proposed method, we believe it could be an attractive and highly practical alternative to other protocols for the synthesis of indoles, especially those bearing substituents at both the 1 and 2 positions.

Experimental

General Information. All commercially available chemicals were used without purification. Solvents were purified using standard procedures. Column chromatography was performed in flash conditions using silica gel (0.040–0.063 mm). Analytical thin-layer chromatography (TLC) was carried out on silica gel 60 F_{254} plates that were visualized by exposure to UV light. ^1H and ^{13}C NMR were recorded at 400MHz/100MHz for solutions in $CDCl_3$ or DMSO-d_6. Chemical shifts are quoted in δ (ppm) and J values are reported in Hz and referenced against residual proton signals of the deuterated solvents. Mass-spectra were recorded by EI mode at 70 eV. All reactions were run in inert atmosphere. Yields refer to chromatographically and spectroscopically pure

compounds and represent an average of at least two independent runs. Melting points were determined in open capillaries and are uncorrected.

General Procedure for the Synthesis of Indoles 2. Indoles **2** (except for compound **2k**) were synthesized according to the following general procedure. An oven-dried screw-cap test tube equipped with a Teflon-coated magnetic stir bar was charged with a ketone **1** (0.5 mmol), an appropriate amine (0.65 mmol, 1.3 equiv) and Ti(O^tBu)4 (965 µL, 2.5 mmol, 5 equiv). The tube was evacuated and backfilled with argon (sequence was repeated three times) and was placed into a preheated reaction block. After stirring at 60 °C (for indoles **2c**, **2d** and **2h**) or at 140 °C (for all other indoles) for 10 h the reaction mixture was allowed to cool to room temperature and Cs_2CO_3 (326 mg, 1 mmol, 2 equiv), CuI (9.5 mg, 0.05 mmol, 10 mol %) and DMA (2 mL) were added. The tube was then evacuated and backfilled with argon (sequence was repeated three times) and was placed into a preheated reaction block. After stirring at 125 °C for 10 h the mixture was allowed to cool down and directly poured on top of a short silica gel chromatography column. The crude product was eluted with a mixture EtOAc/hexanes, 1:1. The residue after evaporation of the solvent was purified by column chromatography on silica gel (EtOAc/hexanes, 1:10).

1,2-bis(4-Methoxyphenyl)-1*H*-indole (2a): synthesized from ketone **1a** (153 mg) and *p*-anisidine (80 mg); yellow solid; yield 85 % (140 mg); mp 139–141 °C. (lit.[26] mp 136–137 °C). ^{1}H NMR ($CDCl_3$): δ 3.81(s, 3H), 3.88 (s, 3H),6.73 (s, 1H), 6.81 (d, 2H, *J*=8.8 Hz), 6.96 (d, 2H, *J*=8.9 Hz), 7.14–7.25 (m, 7H), 7.20–7.65 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 55.2, 55.5, 102.2, 110.5, 113.7, 114.5, 120.2, 120.5, 121.9, 125.2, 128.2, 129.2, 130.2, 131.4, 139.2, 140.8, 158.5, 158.9. MS, *m/z* (I, %): 329 (M^+, 56), 254(40), 242(56), 165 (48), 127 (72), 121 (80), 77 (48), 63 (96). Anal. Calcd for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25. Found: % C, 80.17; H, 5.87; N, 4.29. Indole **2a** was also synthesized from ketone **1a** (610 mg, 2 mmol) and *p*-anisidine (321 mg,2.6 mmol) following the general procedure and using Ti(O^tBu)$_4$ (1,54 mL, 2equiv) and DMA (8 mL) in 93 % (613 mg) yield.

1-Benzyl-2-(3,4-dimethoxyphenyl)-1*H*-indole (2b): synthesized from ketone **1b** (168 mg) and benzylamine (70 mg); white solid; yield 78 % (135 mg); mp 132–134 °C. ^{1}H NMR ($CDCl_3$): δ 3.60 (s, 3H), 3.93 (s, 3H), 5.39 (s, 2H), 6.66 (s, 1H), 6.84–6.94 (m, 2H), 7.03–7.34 (m, 9H), 7.66–7.77 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 47.7, 55.5, 55.9, 101.7, 110.3, 111.2, 112.3, 120.3, 120.4, 121.7, 121.8, 125.3, 125.9, 127.2, 128.3, 128.8, 138.0, 138.6, 141.8, 148.7, 149.0. MS, *m/z* (I, %): 343 (M^+,100), 252 (92), 237 (40), 192 (40), 166 (47), 139 (48), 91 (88), 65 (84). Anal. Calcd for $C_{23}H_{21}NO_2$: C, 80.44; H, 6.16; N, 4.08. Found: C, 80.39; H, 6.24; N, 4.00.

2-(4-Methoxyphenyl)l-1-propyl-1*H*-indole (2c): synthesized from ketone **1a** (153 mg) and propylamine (40 mg); white solid; yield 60 % (80 mg); mp 80–81 °C. ^{1}H NMR ($CDCl_3$): δ 0.88 (t, *J*=7.6 Hz, 3H), 1.82 (sextet, *J*=7.6 Hz, 2H), 3.95 (s, 3H), 4.15–4.20 (m, 2H), 6.58 (s, 1H), 7.09 (d, *J*=8.8 Hz, 2H), 7.20–7.26 (m, 1H), 7.28–7.36 (m, 1H), 7.45–7.49 (m, 1H), 7.51 (d, *J*=8.8 Hz, 2H), 7.73 (d, *J*=7.8 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 11.0, 23.0, 45.2, 55.0, 101.2, 109.7, 113.6, 119.3, 120.0, 120.9, 125.4, 127.9, 130.3, 136.9, 140.9, 159.1. MS, *m/z* (I, %): 265 (M^+, 100), 236 (90), 205 (25), 41 (35). Anal. Calcd for $C_{18}H_{19}NO$: C, 81.48; H, 7.22; N, 5.28. Found: C, 81.52; H, 7.28; N, 5.24.

1-Cyclopropyl-2-(4-methoxyphenyl)-1*H*-indole (2d): synthesized from ketone **1a** (153 mg) and cyclopropylamine (40 mg); white solid; yield 68 % (90 mg); mp 114–116 °C. ^{1}H NMR ($CDCl_3$): δ 0.77–0.83 (m, 2H), 1.04–1.10 (m, 2H), 3.46–3.54 (m, 1H), 3.96 (c, 3H), 6.61 (s, 1H), 7.09 (d, *J*=8.8 Hz, 2H), 7.23–7.31 (m, 1H), 7.36–7.39 (m, 1H), 7.67 (d, *J*=8.8 Hz, 2H), 7.71–7.76 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 8.8, 25.7, 55.0, 100.8, 110.6, 113.4, 119.6, 120.0, 121.0, 125.7, 127.5, 129.7, 138.4, 141.4, 158.8. MS, *m/z* (I, %): 263 (M^+, 100), 248 (24). Anal. Calcd for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32. Found: C, 82.16; H, 6.55; N, 5.27.

1-Cyclohexyl-2-(4-methoxyphenyl)-1*H*-indole (2e): synthesized from ketone **1a** (153 mg) and cyclohexylamine (64 mg); white solid; yield 89 % (136 mg); mp 146–148 °C. ^{1}H NMR ($CDCl_3$): δ 1.32–1.44 (m, 3H), 1.75–1.85 (m, 1H), 1.93–2.04 (m, 4H), 2.40–2.54 (m, 2H), 3.96 (s, 3H), 4.24–4.35 (m, 1H), 6.52 (s, 1H), 7.08 (d, *J*=8.7 Hz, 2H), 7.16–7.23 (m, 1H), 7.24–7.29 (m, 1H), 7.46 (d, *J*=8.7 Hz, 2H), 7.69–7.79 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 25.7, 26.4, 31.6, 55.4, 56.4, 102.0, 112.7, 114.0, 119.4, 120.7, 120.8, 126.3, 129.1, 130.9, 135.8, 141.4, 159.0. MS, m/z (I, %): 305 (M+, 100), 223 (92), 208 (56), 55 (40). Anal. Calcd for $C_{21}H_{23}NO$: C, 82.58; H, 7.59; N, 4.59. Found: C, 82.50; H, 7.52; N, 4.64.

(*R*)-2-Phenyl-1-(1-phenylethyl)-1*H*-indole (2g): synthesized from ketone **1a** (153 mg) and R-(+)-1-phenylethylamine (79 mg); light-yellow solid; yield 88 % (144 mg); $[\alpha]^{25}_D$ = 44.5 °; mp 89–92 °C. ^{1}H NMR ($CDCl_3$): δ 1.99 (d, *J*=7.0 Hz, 3H), 5.91 (q, *J*=6.9 Hz, 1H), 6.72 (s, 1H), 7.06–7.15 (m, 2H), 7.16–7.23 (m, 1H), 7.33–7.39 (m, 3H), 7.39–7.46 (m, 2H), 7.47–7.57 (m, 3H), 7.59–7.66 (m, 2H), 7.73–7.80 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 18.3, 53.1, 102.4, 112.7, 119.5, 120.4, 120.9, 125.9, 126.7, 127.8, 128.3, 128.8, 129.1, 133.0, 135.5, 141.4, 141.7. MS, m/z (I, %): 297 (M+, 32), 193 (98), 105 (84). Anal. Calcd for $C_{22}H_{19}N$: C, 88.85; H, 6.44; N, 4.71. Found: C, 88.89; H, 6.39; N, 4.66.

***N*,*N*-Dimethyl-2-phenyl-1*H*-indol-1-amine (2h):** synthesized from ketone **1e** (137 mg) and *N*,*N*-dimethylhydrazine (40 mg); white solid; yield 83 % (100 mg); mp 115–116 °C. ^{1}H NMR ($CDCl_3$): δ 3.24 (s, 6H), 6.65 (s, 1H), 7.25–7.31 (m, 1H), 7.32–7.37 (m, 1H), 7.46–7.52 (m, 1H), 7.54–7.60 (m, 2H), 7.72–7.80 (m, 2H), 7.81–7.86 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 44.5, 99.3, 111.2, 119.7, 121.0, 126.9, 127.2, 127.7, 128.7, 132.4, 134.5, 140.2. MS, *m/z* (I, %): 236 (M^+, 24), 165 (44), 132 (98). Anal. Calcd for $C_{16}H_{16}N_2$: C, 81.32; H, 6.82; N, 11.85.Found C, 81.28; H, 6.77; N, 11.94.

1-(4-Chlorophenyl)-2-(4-methoxyphenyl)-1*H*-indole (2i): synthesized from ketone **1a** (153 mg) and 4-chloroaniline (83 mg); yellow solid; yield 75 % (125 mg); mp 134–1 36 °C. ^{1}H NMR ($CDCl_3$): δ 3.82 (s, 3H), 6.75 (s, 1H), 6.83 (d, 2H, *J*=8.8 Hz), 7.18–7.27 (m, 7H), 7.41 (d, 2H, *J*=8.8 Hz), 7.67–7.70 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 55.3, 103.3, 110.3, 113.8, 120.5, 120.9, 122.3, 124.7, 128.5, 129.3, 129.5, 130.2, 132.8, 137.2, 138.6, 140.6, 159.1. MS, *m/z* (I, %): 333(M^+, 100), 254 (56). Anal. Calcd for $C_{21}H_{16}ClNO$: C, 75.56; H, 4.83; N, 4.20. Found: C, 75.61; H, 4.78; N, 4.23.

1-(2-Bromophenyl)-2-(4-methoxyphenyl)-1*H*-indole (2j): synthesized from ketone **1a** (153 mg) and 2-bromoaniline (112 mg); light-brown solid; yield 90 % (170 mg); mp 150–153 °C. ^{1}H

NMR ($CDCl_3$): δ 3.86 (s, 3H), 6.87–6.92 (m, 3H), 7.06–7.11 (m, 1H), 7.28–7.48 (m, 7H), 7.79–7.85 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 54.9, 102.2, 110.5, 113.4, 114.0, 120.1, 120.4, 121.8, 123.8, 124.6, 128.1, 129.4, 129.5, 131.1, 133.4, 137.9, 138.3, 140.8, 158.8. MS, m/z (I, %): 379, 377 (M+, 100, 100), 298 (24), 283 (40), 254 (100), 127 (56). Anal. Calcd for $C_{21}H_{16}BrNO$: C, 66.68; H, 4.26; N, 3.70.Found: C, 66.63; H, 4.32; N, 3.74.

2-(4-Methoxyphenyl)-1-[2-(trifluoromethyl)phenyl]-1*H*-indole (2l): synthesized from ketone **1a** (153 mg) and 2-(trifluoromethyl)aniline (81 mg); yellow oil; yield 85 % (156 mg). ^1H NMR ($CDCl_3$): δ 3.77 (s, 3H), 6.78 (d, *J*=8.9 Hz, 2H), 6.80 (c, 1H), 6.87–6.91 (m, 1H), 7.13–7.20 (m, 2H), 7.23 (d, *J*=8.8 Hz, 2H), 7.36 (m, 1H), 7.57–7.61 (m, 1H), 7.63–7.67 (m, 1H), 7.67–7.70 (m, 1H), 7.83–7.85 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 54.7, 102.5, 110.4, 113.3, 119.8, 120.2, 121.6, 122.4 ($J_{C\text{-}F}$=274 Hz), 124.5, 127.3 ($J_{C\text{-}F}$=5 Hz), 127.8, 128.5, 129.3, 130.5 ($J_{C\text{-}F}$=33 Hz), 132.2, 132.5, 136.6, 140.0, 141.4, 158.6. MS, m/z (I, %): 367 (M^+, 100), 352 (96), 283 (30), 254 (99), 184 (99), 142 (80), 127 (97), 75 (30), 63 (30). Anal. Cacld for $C_{22}H_{16}F_3NO$: C, 71.93; H, 4.39; N, 3.81.Found: C, 71.99; H, 4.35; N, 3.86.

3-[2-(4-Methoxyphenyl)-1*H*-indol-1-yl]benzonitrile (2m): synthesized from ketone **1a** (153 mg) and 3-aminobenzonitrile (77 mg); white solid; yield 89 % (144 mg); mp 200–203 °C. ^1H NMR ($CDCl_3$): δ 3.84 (s, 3H), 6.79 (s, 1H), 6.85 (d, *J*=8.8 Hz, 2H), 7.17 (d, *J*=8.8 Hz, 2H), 7.21–7.31 (m, 3H), 7.47–7.51 (m, 1H), 7.53–7.58 (m, 1H), 7.64–7.68 (m, 1H), 7.69–7.74 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 54.9, 103.8, 109.5, 113.1, 113.6, 117.6, 120.3, 121.0, 122.3, 123.7, 128.2, 129.9, 130.2, 130.7, 132.1, 137.9, 139.3, 140.0, 159.0. MS, *m/z* (I, %): 324 (M^+, 100), 309 (30), 279 (30). Anal. Calcd for $C_{22}H_{16}N_2O$: C, 81.47; H, 4.97; N, 8.64. Found: C, 81.42; H, 4.98; N, 8.61.

4-[2-(4-Methoxyphenyl)-1*H*-indol-1-yl]benzonitrile (2n): synthesized from ketone **1a** (153 mg) and 3-aminobenzonitrile (77 mg); white solid; yield 87 % (141 mg), mp 176–178 °C. ^1H NMR ($CDCl_3$): δ 3.86 (s, 3H), 6.82 (s, 1H), 6.88 (d, *J*=8.5 Hz, 2H), 7.20 (d, *J*=8.6 Hz, 2H), 7.22–7.31 (m, 2H), 7.32–7.41 (m, 3H), 7.67–7.78 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 55.3, 104.7, 110.1, 110.4, 114.1, 118.4, 120.8, 121.6, 122.8, 124.3, 128.4, 128.9, 130.3, 133.3, 138.1, 140.3, 142.7, 159.4. MS, *m/z* (I, %): 324 (M^+, 100), 309 (30), 279 (30). Anal. Calcd for $C_{22}H_{16}N_2O$: C, 81.46; H, 4.97; N, 8.64. Found: C, 81.49; H, 4.92; N, 8.60.

Ethyl 2-[2-(4-methoxyphenyl)-1*H*-indol-1-yl]benzoate (2p): synthesised following the general procedure from ketone **1a** (153 mg) and ethyl 2-aminobenzoate (83 mg) using $Ti(OEt)_4$ (525 µL, 2.5 mmol, 5 equiv) instead of $Ti(O^tBu)_4$; light-yellow solid; yield 58 % (108 mg); mp 139–141°C. ^1H NMR ($CDCl_3$): δ 0.79 (m, 3H), 3.81 (s, 3H), 3.88–4.00 (m, 2H), 6.78 (s, 1H), 6.81 (d, *J*=8.9 Hz, 2H), 7.04–7.09 (m, 1H), 7.13–7.20 (m, 2H), 7.25 (d, *J*=8.9 Hz, 2H), 7.31–7.34 (m, 1H), 7.47–7.54 (m, 1H), 7.56–7.62 (m, 1H), 7.68–7.72 (m, 1H), 7.98–8.04 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 13.0, 54.7, 60.8, 102.0, 109.6, 113.3, 119.8, 120.0, 121.6, 124.5, 127.5, 128.0, 129.6, 130.2, 130.5, 130.8, 132.2, 137.5, 138.7, 140.6, 158.6, 165.7. MS, m/z (I, %): 371 (M^+, 100), 298 (30), 254 (32). Anal. Calcd for $C_{24}H_{21}NO_3$: C, 77.61; H, 5.70; N, 3.77. Found: C, 77.65; H, 5.65; N, 3.75.

1-(4-Bromophenyl)-6-fluoro-2-(4-methoxyphenyl)-1*H*-indole (2q): synthesized from ketone **1d** (162 mg) and 3-bromoaniline (112 mg); light-yellow amorphous solid; yield 74 % (147 mg). ^1H NMR ($CDCl_3$): δ 3.84 (s, 3H), 6.74 (s, 1H), 6.86 (d, *J*=8.8 Hz, 2H), 6.96–7.04 (m, 2H), 7.15 (d, *J*=8.7 Hz, 2H), 7.21 (d, *J*=8.9 Hz, 2H), 7.57–7.64 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 54.8, 96.6 ($J_{C\text{-}F}$=26.8 Hz), 102.7, 109.1 ($J_{C\text{-}F}$=24.5 Hz), 113.5, 120.7, 120.8 ($J_{C\text{-}F}$=10.0 Hz), 124.0, 124.5, 129.0, 129.7 (2S), 132.2, 137.0, 138.3 ($J_{C\text{-}F}$=12.7 Hz), 140.6 ($J_{C\text{-}F}$=3.8 Hz), 158.8, 159.5 ($J_{C\text{-}F}$=239 Hz). MS, *m/z* (I, %): 397, 395 (M^+, 71, 75), 272 (98), 136 (32), 84 (36). Anal. Calcd for $C_{21}H_{15}BrFNO$: C, 63.65; H, 3.82; N, 4.79. Found: C, 63.69; H, 3.74; N, 4.76.

1-(2-Methoxyphenyl)-2-phenyl-1*H*-indole (2r): synthesized from ketone **1e** (137 mg) and *o*-anisidine (80 mg); colourless oil; yield 86 % (129 mg). 1H NMR ($CDCl_3$): δ 3.54 (s, 3H), 6.82 (s, 1H), 6.97–7.07 (m, 2H), 7.09–7.13 (m, 1H), 7.15–7.20 (m, 2H), 7.23–7.34 (m, 6H), 7.36–7.41 (m, 1H), 7.67–7.72 (m, 1H). 13C NMR ($CDCl_3$): δ 55.1, 102.3, 110.5, 112.2, 120.1, 120.2, 120.6, 121.8, 126.9, 127.7, 127.8, 127.9, 128.1, 129.0, 129.8, 132.9, 138.8, 141.3, 155.3. MS, m/z (I, %): 299 (M+, 100), 127 (32), 77 (24), 51 (24). Anal. Calcd for $C_{21}H_{17}NO$: C, 84.25; H, 5.72; N, 4.68. Found: C, 84.21; H, 5.78; N, 4.65.

5-Methoxy-2-(4-methoxyphenyl)-1-(4-methylphenyl)-1*H*-indole (2s): synthesized from ketone **1c** (168 mg) and *p*-anisidine (80 mg); light-yellow oil; yield 88 % (158 mg). ^1H NMR ($CDCl_3$): δ 2.44 (s, 3H), 3.82 (s, 3H), 3.93 (s, 3H), 6.70 (s, 1H), 6.79–7.89 (m, 3H), 7.14–7.29 (m, 8H). ^{13}C NMR ($CDCl_3$): δ 21.2, 55.2, 56.0, 102.0, 102.3, 111.4, 112.0, 113.7, 125.3, 127.8, 128.7, 129.9, 130.1, 134.4, 136.2, 136.9, 141.2, 154.8, 158.9. MS, *m/z* (I, %): 343 (M^+, 100), 328 (23), 300 (30), 91 (28). Anal. Calcd for $C_{23}H_{21}NO_2$: C, 80.44; H, 6.16; N, 4.08. Found: C, 80.38; H, 6.26; N, 4.10.

2-(3,4-Dimethoxyphenyl)-1-[3-(trifluoromethyl)phenyl]-1*H*-indole (2t): synthesized from ketone **1b** (168 mg) and 3-(trifluoromethyl)aniline (81 mg); light-yellow solid; yield 77% (153 mg); mp 144–146 °C. ^1H NMR ($CDCl_3$): δ 3.69 (s, 3H), 3.91 (s, 3H), 6.73 (d, 2H, *J*=1.9 Hz), 6.81–6.88 (m, 2H), 6.93 (m, 1H), 7.24–7.29 (m, 2H), 7.30–7.35 (m, 1H), 7.39–7.44 (m, 1H), 7.56 (t, *J*=7.8 Hz, 1H), 7.66–7.77 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 55.2, 55.4, 103.3, 109.7, 110.8, 111.8, 120.2, 120.8, 121.3, 122.2, 123.1 ($J_{C\text{-}F}$= 272.6 Hz), 123.4 ($J_{C\text{-}F}$=3.5 Hz), 124.2, 124.4 ($J_{C\text{-}F}$=3.8 Hz), 128.2, 129.6, 131.2, 131.4 ($J_{C\text{-}F}$= 33.0 Hz), 138.2, 139.1, 140.2, 148.2, 148.4. MS, *m/z* (I, %): 397 (M^+,100) 322 (15), 241 (15). Anal. Calcd for $C_{23}H_{18}F_3NO_2$: C, 69.52; H, 4.57; N, 3.52 Found: C, 69.56; H, 4.52; N, 3.56.

1,2-bis(4-Methoxyphenyl)-3-methyl-1*H*-indole (2u): synthesized from ketone **1f** (160 mg) and *p*-anisidine (80 mg); yellow solid; yield 78 % (134 mg); mp 158–160 °C. ^1H NMR ($CDCl_3$): δ 2.41 (s, 3H), 3.82 (s, 3H), 3.84 (s, 3H), 6.85 (d, *J*=8.8 Hz, 2H), 6.89 (d, *J*=9.0 Hz, 2H), 7.12 (d, *J*=9.0 Hz, 2H), 7.16 (d, *J*=8.8 Hz, 2H), 7.18–7.28 (m, 3H), 7.63–7.70 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 9.7, 55.2, 55.4, 109.6, 110.3, 113.5, 114.3, 118.7, 119.9, 122.1, 124.5, 128.9, 129.1, 131.6, 131.8, 137.1, 137.9, 158.1, 158.7. MS, m/z (I, %): 343 (M^+, 100), 107 (18). Anal. Calcd for $C_{23}H_{21}NO_2$: C, 80.44; H, 6.16; N, 4.08. Found: C, 80.40; H, 6.22; N, 4.11.

2-(4-Methoxyphenyl)-3-methyl-1-pyridin-3-yl-1*H*-indole (2w): synthesized from ketone **1f** (160 mg) and 3-aminopyridine (61 mg); yellow solid; yield 77 % (121 mg); mp 168–170°C. ^1H NMR ($CDCl_3$): δ 2.43 (s, 3H), 3.82 (s, 3H), 6.87 (d, *J*=8.8 Hz, 2H), 7.15 (d, *J*=9.0 Hz, 2H), 7.23–7.36 (m, 4H), 7.46–7.52 (m,

1H), 7.18–7.28 (m, 1H), 8.51–8.59 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 9.5, 55.2, 109.8, 111.3, 113.9, 119.0, 120.7, 122.8, 123.7, 129.5, 131.9, 134.9, 136.6, 137.4, 147.5, 148.9, 150.0. MS, m/z (I, %): 314 (M^+, 100), 269 (19), 255 (15), 207 (28). Found, %: C, 80.27; H, 5.82; N, 8.95. $C_{21}H_{18}N_2O$. Calculated, %: C, 80.23; H, 5.77; N, 8.91.

2-(2-Fluorophenyl)-1-(4-methylphenyl)-1*H*-pyrrolo[2,3-c]pyridine (2x): synthesized from ketone **1h** (147 mg) and *p*-anisidine (80 mg); yellow oil, yield 83 % (132 mg). ^{1}H NMR ($CDCl_3$): δ 2.39 (s, 3H), 6.81 (s, 1H), 7.03 (m, 1H), 7.09 (m, 1H), 7.14 (d, *J*=8.3 Hz, 2H), 7.20 (d, *J*=8.3 Hz, 2H), 7.25–7.29 (m, 1H), 7.29–7.34 (m, 1H), 7.59 (m, 1H), 8.29–8.38 (br. s, 1H), 8.65–8.78 (br. s, 1H). ^{13}C NMR ($CDCl_3$): δ 24.1, 107.2, 117.8, 118.9 ($J_{C\text{-}F}$=21.9 Hz), 122.7 ($J_{C\text{-}F}$=14.9 Hz), 126.9 ($J_{C\text{-}F}$=3.0 Hz) 129.9, 132.9, 133.5 ($J_{C\text{-}F}$=8.2 Hz), 134.9, 135.6, 136.9, 137.4, 140.7, 141.0, 142.4, 162.7 ($J_{C\text{-}F}$=250.3 Hz). MS, m/z (I, %): 302 (M^+, 100), 180 (20), 157 (25), 143 (30). Anal. Calcd for $C_{20}H_{15}FN_2$: C, 79.45; H, 5.00; N, 9.27. Found: C, 79.51; H, 5.07; N, 9.35.

2-*tert*-Butyl-1-(4-methoxyphenyl)-1*H*-pyrrolo[2,3-c]pyridine (2y): synthesized from ketone **1i** (128 mg) and *p*-anisidine (80 mg); yellow solid; yield 85 % (119 mg); mp 149–151 °C. ^{1}H NMR ($CDCl_3$): δ 1.29 (s, 9H), 3.92 (s, 3H), 6.46 (s, 1H), 7.03 (d, *J*=8.9 Hz, 2H), 7.30 (d, *J*=8.8 Hz, 2H), 7.45 (d, *J*=5.5 Hz, 1H), 8.00–8.12 (br. s, 1H), 8.18–8.28 (br. s, 1H). ^{13}C NMR ($CDCl_3$): δ 33.7, 36.4, 58.5, 101.5, 116.9, 117.2, 134.1, 134.2, 134.5, 136.2, 142.0, 157.5, 162.8. MS, m/z (I, %): 280 (M^+, 72), 265 (100), 250 (20), 219 (30). Anal. Calcd for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found: C, 77.15; H, 7.30; N, 9.95.

1-(4-Iodophenyl)-2-(4-methoxyphenyl)-1*H*-indole (2k). An oven-dried screw-cap test tube equipped with a Teflon-coated magnetic stir bar was charged with ketone **1a** (153 mg, 0.5 mmol), 4-iodoaniline (142 mg, 0.65 mmol) and Ti(O^{t}Bu)$_4$ (965 µL, 2.5 mmol, 5 equiv). The tube was evacuated and backfilled with argon (sequence was repeated three times) and was placed into a preheated reaction block. After stirring at 140 °C for 10 h the reaction mixture was allowed to cool to room temperature and Cs_2CO_3 (326 mg, 1 mmol, 2 equiv), CuI (9.5 mg, 0.05 mmol, 10 mol %), *L*-proline (11.5 mg, 0.1 mmol, 20 mol %), and DMA (2 mL) were added. The tube was evacuated and backfilled with argon (sequence was repeated three times) and was placed into a preheated reaction block (90 °C). After stirring at this temperature for 10 h, the reaction mixture was allowed to cool to room temperature. DMA was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexanes, 1:10). Yield 67 % (142 mg); light-brown solid; mp 110–115 °C. ^{1}H NMR ($CDCl_3$): δ 3.83 (s, 3H), 6.74 (s, 1H), 6.84 (d, *J*=8.7 Hz, 2H), 7.02 (d, *J*=8.5 Hz, 2H), 7.15–7.24 (m, 4H), 7.26–7.32 (m, 1H), 7.64–7.32 (m, 1H), 7.75 (d, *J*=8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 54.9, 91.7, 103.0, 109.9, 113.4, 120.1, 120.5, 121.9, 124.3, 128.1, 129.4, 129.8, 138.0, 140.1, 158.7. MS, *m/z* (I, %): 425 (M^+, 70), 298 (22), 254 (95), 127 (40). Anal. Calcd for $C_{21}H_{16}INO$: C, 59.31; H, 3.79; N, 3.29. Found: C, 59.37; H, 3.72; N, 3.23.

2-(4-Methoxyphenyl)-2,3-dihydro-1-benzofuran (4a).[27] An oven-dried screw-cap test tube equipped with a Teflon-coated magnetic stir bar was charged with ketone **1a (**152 mg, 0.5 mmol) and Ti(O^{i}Pr)$_4$ (1450 µL, 5 mmol, 10 equiv). The tube was evacuated and backfilled with argon; sequence was repeated three times. The mixture was stirred at 140 °C for 10 h. Then the reaction mixture was cooled to room temperature and Cs_2CO_3 (326 mg, 1 mmol, 2 equiv) and CuI (9.5 mg, 0,05 mmol, 10 mol %), and DMA (4 ml) were added. The tube was evacuated and backfilled with argon; sequence was repeated three times. The resulting mixture was stirred at 125 C° for 10 h. The mixture was allowed to cool to room temperature, DMA was removed under reduced pressure and the residue was purified by column chromatography (EtOAc/hexanes, 1:5) to afford 80 mg (70 %) of **4a** as white solid; mp 65–66 °C. (lit.[29] mp 51–52 °C) ^{1}H NMR ($CDCl_3$): δ 3.21 (dd, *J*=15.3, 8,2 Hz, 1H), 3.57 (dd, *J*=15.5, 9.4 Hz, 1H), 3.80 (c, 3H), 5.70 (t, *J*=9.2 Hz, H), 6.82–6.93 (m, 4H), 7.11–7.21 (m, 2H), 7.33 (d, *J*=8.6 Hz, 2H). MS, *m/z* (I, %): 226 (M^+, 100), 211(25), 165 (38).

Synthesis of N*H*-Indoles 5. An oven-dried screw-cap test tube equipped with a Teflon-coated magnetic stir bar was charged with ketone **1 (**0.5 mmol) and Ti(O^{i}Pr)$_4$ (740 µL, 2.5 mmol, 5 equiv). To the ice-cooled resulting suspension NH_3–MeOH (714 µL, 5 mmol, 10 equiv, 7N) was added slowly via syringe. The resulting mixture was stirred at 50 °C for 10 h, after which time reaction mixture was allowed to cool to room temperature and MeOH was distilled off under reduced pressure. DMA (2mL), Cs_2CO_3 (326 mg, 1 mmol, 2 equiv), CuI (9.5 mg, 10 mol %) were added to the residue. The tube was evacuated and backfilled with argon (sequence was repeated three times) and was placed into a preheated reaction block. After stirring at 100 °C for 10 h the mixture was allowed to cool to room temperature, DMA was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexanes, 1:5).

2-(4-Methoxyphenyl)-1*H*-indole (5a):[28] synthesized from ketone **1a** (153 mg); yellow solid; yield 61% (68 mg); mp 225–227 °C. (lit.[29] mp 227–231 °C). NMR ^{1}H (DMSO-d_6): δ 3.81 (s, 3H), 6.76 (d, *J*=1.4 Hz, 1H), 6.96–7.12 (m, 4H), 7.41 (d, *J*=8.2 Hz, 1H), 7.81 (d, *J*=8.9 Hz, 2H),11.40–11.46 (br. s, 1H). ^{13}C NMR (DMSO-d_6): δ 60.0, 102.1, 115.9, 119.1, 124.0, 124.5, 125.8, 129.7, 131.2, 133.7, 141.7, 142.6, 163.6.

2-Phenyl-1*H*-indole (5b):[28] synthesized from ketone **1b** (137 mg); yellow solid; yield 57% (55 mg); mp 186–188 °C. (lit.[29] mp 186–189 °C). ^{1}H NMR (DMSO-d_6): δ 6.88 (d, *J*=1.6 Hz, 1H), 7.00 (t, *J*=7.0 Hz, 1H), 7.11 (t, *J*=7.0 Hz, 1H), 7.30 (t, *J*=7.4 Hz, 1H), 7.41–7.46 (m, 3H), 7.54 (d, *J*=7.8 Hz, 1H), 7.87 (d, *J*=8.4 Hz, 2H). 11.51–11.54 (br. s, 1H). ^{13}C NMR (DMSO-d_6): δ 102.0, 114.7, 122.7, 123.4, 124.9, 128.3, 130.7, 131.6, 132.2, 135.6, 140.5, 141.0.

Notes and references

Department of Chemistry, Moscow State University, Moscow 119992, Russia. Fax: +7 495 932 8846; Tel: +7 495 932 5376; E-mail: karchava@org.chem.msu.ru

† Electronic Supplementary Information (ESI) available: Experimental procedures, analitical and spectral characterization data for starting materials; additional optimization data and copies of ^{1}H and ^{13}C NMR spectra for all new compounds.

‡ Present address: Department of Chemistry, University of Illinois at Chicago, 845 W. Taylor St., Chicago, IL, 60607 USA. E-mail: fmelkon@uic.edu

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