ChemPubSoc Europe

DOI: 10.1002/ejoc.201801607

EurJOC European Journal of Organic Chemistry

Full Paper

Ring Closure

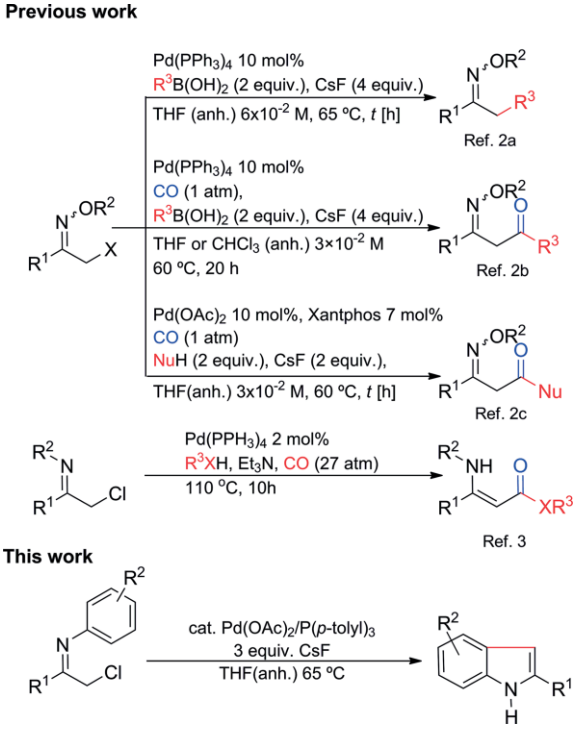
Palladium-Catalyzed C–C Ring Closure in α-Chloromethylimines: Synthesis of 1*H*-Indoles

Delia Bellezza,[a] Bárbara Noverges,[a] Francesco Fasano,[a] Jeymy T. Sarmiento,[a] Mercedes Medio-Simón,*[a] and Gregorio Asensio[a]

Abstract: The C-C ring closure of α-chloromethyl alkyl or aryl N-aryl imines catalyzed with 1 to 10 % $Pd(OAc)_2/P(p\text{-tolyl})_3$ afford efficiently 2-aryl- and 2-alkyl-1*H*-indoles. The heterocyclization reaction involves the initial formation of [2-(arylimino)-ethyl]palladium(II) chloride complexes with subsequent C-H activation of the aromatic amine ring. Readily or commercially available α-chloromethyl-aryl or -alkyl ketones are used as the precursors. Functionalized indoles at the benzene ring are obtained when the imines are derived from substituted anilines.

Introduction

α-Chloromethyl ketones are unsuitable substrates to participate in Pd(0)-catalyzed cross-coupling reactions leading preferentially to dehalogenation processes and oxidative homocoupling of the organometallic counterpart.[1] However, they are easily available compounds and valuable reagents in many synthetic procedures. We have shown how its use can be extended by transforming them into α-chloromethyl oxime ethers, which are suitable substrates for easy Pd(0) catalyzed cross-coupling and carbonylative cross-coupling reactions with boronic acids, alcohols and amine.[2] More recently α-chloromethylimines and 2-chloromethylaza-heterocycles have also been used successfully in this type of Pd(0) catalyzed transformations.[3] With this background (Scheme 1) we wonder if the phenyl amino group present in the ((arylimino)methyl)palladium(II) chloride complex resulting from the oxidative addition of a Pd(0) complex to an α-chloromethylimine would undergo *ortho* palladation and subsequent coupling to provide a new and direct route to the indole ring. Indoles are recurrent objectives in organic synthesis due to their utility and ubiquity. Numerous methodologies have been developed for the preparation of these heterocycles in keeping with their importance.[4] Among the different methods described, transition metal catalyzed approaches based on imines/enamines have awakened great interest (Scheme 2). In this regard two alternative general synthetic strategies have been applied requiring the use of an *ortho* disubstituted aromatic ring[5] (Type A) or an *N*-aryl imine (Type B) as starting materials.[6] The second alternative is more practical using less elaborate reagents but requires an oxidant in stoichiometric amount to accomplish the final dehydrogenative coupling. The crucial oxidative cyclization step of the second strategy has been widely explored in order to find the optimal oxidant.[6c–6f] Apparently, this strategy uses starting materials more readily available than the *ortho*-disubstituted aromatic derivatives used in the first route, but the enamine tautomer is necessary to accomplish the transformation into the corresponding indole and this tautomer only predominates in β-substituted imines containing an electron-withdrawing group.[6b–6g] More recently, Yoshikai et al.[6h] extended this approach to the synthesis of 3-unsubstituted indoles by reacting simple arylamines with acetophenone in DMSO as the solvent in the presence of

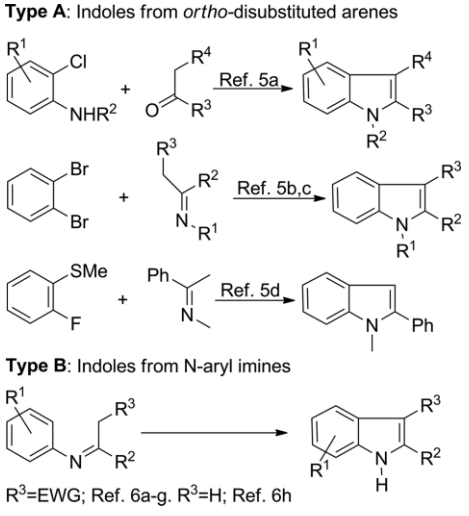


Scheme 1. Palladium-catalyzed reactions of α-halomethyl carbonyl derivatives.

[a] *Department of Organic Chemistry, University of Valencia, Ave Vicent Andrés Estellés s/n, Spain*
E-mail: Mercedes.Medio@uv.es

Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under https://doi.org/10.1002/ejoc.201801607.

Bu_4NBr (2 equiv.). This additive is critical for the efficiency of the transformation. The scope of this method is limited since alkyl ketones do not afford efficiently the corresponding *N*-unsubstituted 2-alkylindoles. Despite the considerable advances in this area several limitations regarding the scope, reaction conditions and type of oxidant yet persist. In spite of the broad application of transition metal catalysis in the preparation of varied heterocycles,[7] metal-catalyzed reactions of α-chloromethyl imines have not yet been explored in this context.



Scheme 2. Metal-catalyzed routes to indoles.

Results and Discussion

We wish to report now the efficient synthesis of 2-substituted-1*H*-indoles in the palladium-catalyzed reaction of α-chloromethyl *N*-aryl imines (Figure 1), generated from the corresponding α-chloromethyl ketones or 1-chloro acetylenes and *o*-unsubstituted anilines..

In this heterocyclization reaction neither the intermediacy of an enamine nor the use of an oxidant is required.

α-Chloromethyl aryl ketones **1** are versatile reagents largely used in organic synthesis for which numerous synthetic procedures have been described.[8] Regular α-chloromethyl aryl ketones **1** were commercially available. Branched α-chloromethyl alkyl ketones **1e–f** containing one quaternary α′ carbon were readily prepared by reacting the corresponding ketone with a chlorine source[9] (Scheme 3, Equation (1)).

By contrast, the regioselective chlorination of unbranched methyl alkyl ketones could not be achieved following the usual chlorination procedure which leads, in these cases, to a mixture of monochlorinated and dichlorinated regioisomers. Alternatively, α-chloromethyl alkyl ketones **1g–i** were readily available by Au(I) catalyzed hydration of the corresponding 1-chloroalkyne (Scheme 3, Equation (2)).[10] α-Chloromethyl aryl imines **3** were easily available following Taguchi's protocol upon condensation of the corresponding α-chloromethyl aryl ketone and aromatic amine **2** using molecular sieves as dehydrating agent[11] (Method A, see Exp. Sect.). Alternatively, P_2O_5 (Method B, see Exp. Sect.) can also be used as the water trapping reagent. While the diastereoisomer *syn*-**3** largely predominated in chloroimines derived from α-chloromethyl aryl **1a-d** or bulky α-chloromethyl alkyl ketones **1e–f**, a nearly equimolecular *syn*/*anti* mixture was obtained in the condensation of aliphatic α-chloromethyl ketones **1g–i** with aromatic amines (see Scheme 3 and Experimental Section). With compounds **3** in our hands we essayed the additive oxidation of a series of Pd(0) complexes under different reaction conditions.

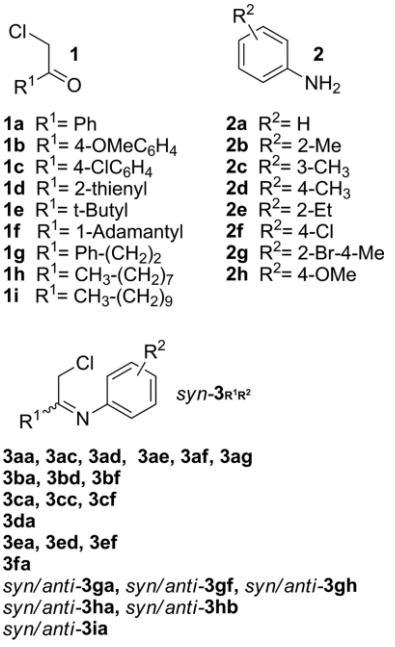
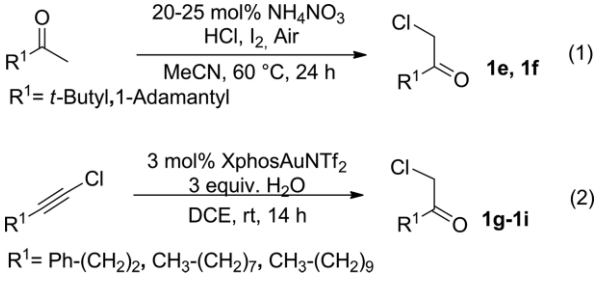


Figure 1. α-Chloromethyl ketones **1**, amines **2**, and α-chloromethyl *N*-aryl imines **3**.



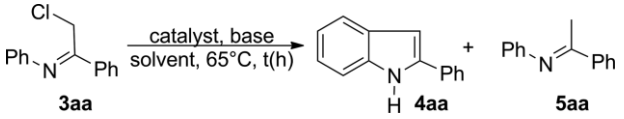
Scheme 3. Synthesis of α-chloromethyl ketones.

Synthesis of 2-Aryl-1*H*-Indoles

Chloroimine **3aa**, obtained by condensation of **1a** and **2a**, was selected as benchmarking substrate to optimize the reaction condition aimed to achieve a palladium catalyzed intramolecular carbocyclization leading to the synthesis of indole **4aa**. Effectively, when $Pd(PPh_3)_4$ was used as the catalyst in THF solution and CsF as an additive, the undesired dehalogenation reaction did not take place and **4aa** was obtained with a 95 % yield (Table 1, entry 1). This also reveals that the expected cyclopalladation reaction occurs efficiently.

Conversely, in absence of catalyst **3aa** was recovered unchanged (Table 1, entry 2). It should be noted that the cycliza-

Table 1. Pd-catalyzed heterocarbocyclization of α-chloromethylphenyl *N*-phenyl imine **3aa** to give indole **4aa**.



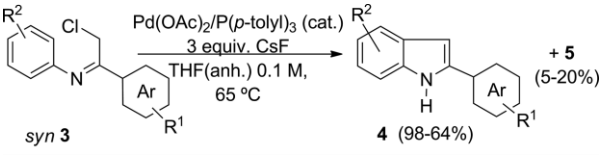
3aa **4aa** **5aa**

Run	Catalyst (mol%)	Base (equiv.)	Solvent	t (h)	**4aa** (%)[a]	**5aa** (%)[a]
1	$Pd(PPh_3)_4$ (10)	CsF (3)	THF	2	95	5
2	none	CsF (3)	THF	15	0	5
3	$Pd(PPh_3)_4$ (10)	none	THF	15	3	22
4	$Pd(PPh_3)_4$ (10)	CsF (1)	THF	15	60	37
5	$Pd(PPh_3)_4$ (10)	CsF (1)	toluene	36	54	30
6	$Pd(PPh_3)_4$ (10)	CsF (3)	toluene	14	80	20
7	$Pd(PPh_3)_4$ (10)	Cs_2CO_3 (1)	toluene	15	72	18
8	$Pd(PPh_3)_4$ (10)	NBu_4F (1)	toluene	14	44	56
9	$Pd(PPh_3)_4$ (5)	CsF (3)	THF	17	98	2
10	$Pd(PPh_3)_4$ (1)	CsF (3)	THF	21	97	3
11	$Pd(OAc)_2$ /PPh_3 (1:3)	CsF (3)	THF	37	46	6
12	$Pd_2(dba)_3$ / P(*p*-tolyl)$_3$ (1:3)	CsF (3)	THF	27	93	3
13	$Pd(OAc)_2$ / P(*p*-toyl)$_3$ (1:3)	CsF (3)	THF	26	92	5
14	$Pd_2(dba)_3$ / P(*p*-C_6H_4F)$_3$ (1:3)	CsF (3)	THF	36	95	5
15	$Pd(OAc)_2$ / P(*p*-C_6H_4F)$_3$ (1:3)	CsF (3)	toluene	36	69	1
16	$Pd(OAc)_2$ / P(*p*-C_6H_4F)$_3$ (1:3)	CsF (3)	THF	17	79	9
17	$Pd(OAc)_2$ / P(*p*-C_6H_4F)$_3$ (1:3)	CsF (3)	THF	7	92	8
18	$Pd_2(dba)_3$ / dppe (1:3)	CsF (3)	THF	72	28	8
19	$Pd_2(dba)_3$ / P(OPh)$_3$ (1:3)	CsF (3)	THF	96	2	96

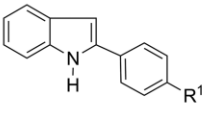
[a] Yield determined by GC analysis.

tion did not take place in the absence of CsF and the starting material was recovered (Table 1, entry 3). Moreover, **4aa** was obtained with only 60 % yield when the amount of CsF (1 equiv.) was decreased (Table 1, entry 4) but instead the amount of dehalogenated product **5aa** increased suggesting some influence of the salt in the carbon–carbon bond formation steps.[12,13] Several essays were carried out using toluene as the solvent in different conditions but indol **4aa** was always obtained with a lower yield (Table 1, entries 5 and 6). Other salts such as Cs_2CO_3 or NBu_4F (Table 1, entry 7, 8) were less effective as additives in this transformation. Palladium catalyst loadings of 1 to 5 % (Table 1 entries 9 and 10) allowed to reach high yields but prolonged reaction times, 17–21 h, were required instead with catalyst loadings of 10 % the reaction time was reduced to 2h (Table 1 entry 1). The increase in the reaction time observed with low catalyst loadings suggest the occurrence of unproductive catalyst resting states, probably because the coordination ability of the indole product to the metal. Several palladium catalysts were tested by changing both the metal source and the ligands. In general for chloroimine **3aa**, the reaction runs well with monophosphine ligands regardless their electronic character donor or acceptor (Table 1, entries 1–17) while biphosphines as dppe (Table 1, entry18) or phosphites (Table 1, entry19) were poor ligands. Regarding the palladium source both $Pd(OAc)_2$ or $Pd_2(dba)_3$ were appropriate. Then we explored the scope of the method focused to the synthesis of 2-aryl indoles. The efficiency of the catalytic systems $Pd(PPh_3)_4$ and (1:3) $Pd(OAc)_2$/PAr_3 was quite similar in the heterocyclization of **3aa** and we selected the system $Pd(OAc)_2$/P(*p*-tolyl)$_3$ due to its better performance with substituted imines **3**. With the optimized conditions in our hands, the scope of this procedure was examined (Table 2). Indoles **4aa-4da**, derived from chloromethyl aryl **1a**–**1c** or heteroaryl ketones **1d** and aniline (**2a**), were prepared with excellent yields. The effect of substituents on the amine to obtain substituted indoles in the benzene ring was also explored. Anilines **2c–f** bearing electron donor or ac-

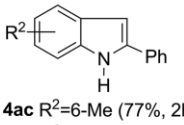
Table 2. Indole synthesis[a] from α-chloromethylaryl N-aryl imines.



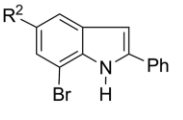
syn **3** **4** (98-64%)



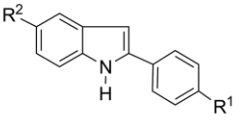
4aa R^1=H (93%, 26h)[b]
4ba R^1=OMe (96%, 4h)[d]
4ca R^1=Cl (95%, 5h)[d]



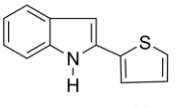
4ac R^2=6-Me (77%, 2h)[d]
4ad R^2=5-Me (98%, 4h)[c]
4ae R^2=7-Et (74%, 20h)[e]
4af R^2=5-Cl (96%, 22h)[c]



4ag R^2=Me (64%, 9h)[d], [f]



4bd R^1=OMe, R^2=Me (81%,38h)[c]
4bf R^1=OMe, R^2=Cl (94%, 17h)[c]
4cd R^1=Cl, R^2=Me (98%, 22h)[c]
4cf R^1=Cl, R^2=Cl (98%, 21h)[c]



4da (91%, 4h)[c]

[a] Isolated yield. [b] 1 % $Pd(OAc)_2$, 3 % P(*p*-tolyl)$_3$. [c] 3 % $Pd(OAc)_2$, 9 % P(*p*-tolyl)$_3$. [d] 5 % $Pd(OAc)_2$, 15 % P(*p*-tolyl)$_3$. [e] 10 % $Pd(OAc)_2$, 30 % P(*p*-tolyl)$_3$. [f] The catalytic system was added in two portions.

ceptor groups were tested. The efficiency of the transformation was retained when *p*-substituted anilines were used independently of the electronic character of the substituent and indoles **4ad**, **4af**, **4bd**, **4bf**, and **4cf** were obtained with excellent yields and reaction times ranging between 4 and 22 hours. The cyclization of **3ac** derived from *m*-toluidine (**2c)** took place with complete regioselectivity at the less hindered position of the ring to afford the corresponding indole **4ac** with good yield. *o*-Substituted amines **2e** and **2g** also were suitable substrates in this reaction regardless of the different electronic character of both substituents although the reaction with the *o,p*-disubstituted amine **2g** was slower than in the case of *p*-toluidine (**2d**). It is to be noted the compatibility of the method with the presence of halogens as substituents in the amine precursor, which potentially would enable the functionalization of these indoles through further cross-coupling reactions.[14]

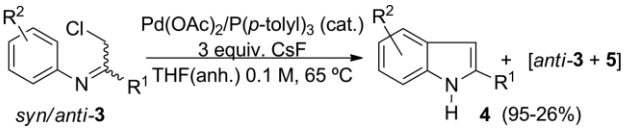
Synthesis of 2-Alkyl-1*H*-Indoles

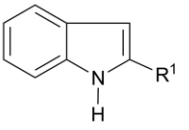
Next, we focused our attention towards the preparation of 2-alkyl NH-indoles. This class of indoles is hardly available due to the failure or complexity of other methods described in the bibliography.[15]

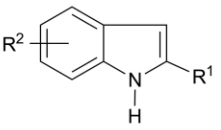
We explored whether the above described methodology for the synthesis of 2-aryl NH-indoles could be used for the synthesis of their 2-alkyl homologous. First, we essayed the palladium catalyzed heterocyclization in the reaction conditions above described for the synthesis of their aryl-substituted counterparts (for details on reaction conditions see Exp. Sect.). The presence of bulky alkyl substituents in imines derived from ketones **1e** and **1f** or substituents on the amine aromatic ring were well tolerated and the corresponding indoles **4** were obtained efficiently. On the other hand, chloroimines **3** derived respectively from linear α-chloromethyl alkyl ketones **1g, 1h** and **1i** and aniline (**2a**) or substituted anilines also afforded the corresponding indoles **4** but in moderate yield. The results are summarized in Table 3. The lower yields obtained from these linear alkyl imines was attributed to the imine geometry. Only the imine isomer *syn*-**3** undergoes the heterocyclization reaction. Unfortunately, the isomers *syn/anti* **3** are not interconverted under our reaction conditions. The isomer *anti*-**3**, accounts for the formation of variable amounts of the undesired dehalogenated product **5** in these cases. The reaction conditions were not further optimized.

The fact that only the imine isomer *syn*-**3** is converted into the corresponding indole **4** strongly suggest that the first step in the heterocyclization process consists of the oxidative addition of Pd^0L_n to the C_{sp3}–Cl bond[16] to afford the corresponding ((arylimino)methyl)palladium(II) chloride complexes **I** without participation of the enamine tautomer in the heterocyclization process since it would result in the loss of the imine stereochemistry. Due to geometrical reasons, only the oxidative addition complex *syn*-**I** can undergo a subsequent fast intramolecular aromatic C-H palladation[17] to afford a six-membered palladacycle **II** from which the reductive elimination of Pd^0L_n and aromatization accounts for the formation of indoles **4**. On the other hand, protodemetallation of the palladium C-bound[18] imino-enolate *anti*-**3** to give the dehalogenated imine **5** by must be faster than the *syn/anti* isomerization of the complexes *syn/anti* **3** and it prevents the formation of **4** from the stereoisomer *anti*-**3** (Scheme 4).

Table 3. Synthesis of 2-alky-1*H*-indoles[a] from α-chloromethyl alkyl N-aryl imines.



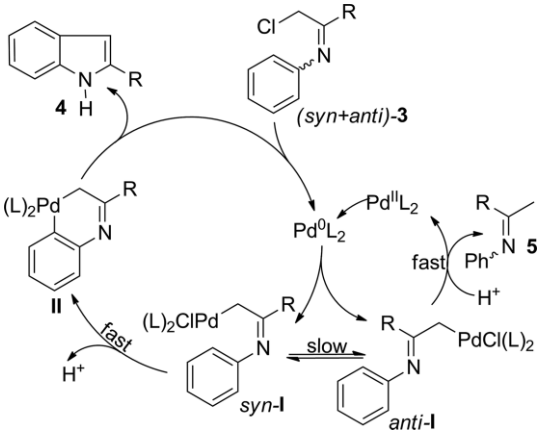




4ea R^1=*t*-Bu, (95%, 4h)[c]
4fa R^1=1-adamantyl (60%, 2h)[b]
4ga R^1=$Ph(CH_2)_2$ (42%, 5h)[c]
4ha R^1= $CH_3(CH_2)_7$ (39%, 24h)[b]
4ia R^1=$CH_3(CH_2)_9$ (52%, 20h)[b]

4ed R^1=*t*-Bu, R^2=5-Me (91%, 6h)[c]
4ef R^1=t-Bu, R^2=5-Cl (95%, 4h)[c]
4gf R^1= $Ph(CH_2)_2$, R^2=5-Cl (47%, 27h)[b]
4gh R^1= $Ph(CH_2)_2$, R^2=5-OMe (29%, 14h)[b]
4hb R1= $CH_3(CH_2)_7$, R^2=7-Me (26%, 21h)[b]

[a] Isolated yield. [b] 5 % $Pd(OAc)_2$, 15 % P(*p*-tolyl)$_3$. [c] 10 % $Pd(OAc)_2$, 30 % P(*p*-tolyl)$_3$.



Scheme 4. Proposed mechanism for $Pd^0(L)_2$-catalyzed heterocyclization of *syn*-3.

Conclusions

α-Chloromethylimines *syn*-**3**, unlike α-chloromethyl ketones **1**, are suitable substrates to participate in Pd(0) catalyzed reactions. The conversion of **3** into 2-alky- and 2-aryl-1*H*-indoles with 26 to 98 % yield is achieved using $Pd(OAc)_2$/P(p-tolyl)$_3$ as the catalyst. α-Chloromethyl alkyl or aryl *N*-aryl imines **3** are readily obtained by condensation of α-chloromethyl ketones **1** with aromatic amines **2** or, alternatively, by Au(I) catalyzed hydroamination of 1-chloro-acetylenes. Unsymmetrical α-

chloromethyl ketones are either commercially available reagents or are regioselectively obtained in the Au(I) catalyzed hydration of 1-chloroalkynes. The palladium catalyzed heterocyclization of α-chloromethylimines (**3**) for the formation of the indole ring requires a 1 to 10 % catalyst load depending on the nature of the precursor ketone and amine. The facile construction of 2-alkyl-1*H*-indoles by our method entails particular interest due to the limited number of synthetic routes described for the synthesis indoles with this substitution pattern. Indoles containing substituents, including halogens, at the benzene ring are also easily accessible simply by choosing the appropriate substituted aromatic amine for the preparation of the intermediate α-chloromethylimine **3**. It is to be noted that the use of (*syn*)-α-chloromethylimines as precursors avoids the need of using *ortho*-disubstituted aromatic compounds, enamines or oxidants in this route to indoles.

Experimental Section

General: All reactions were carried out in oven-dried resealable test tubes under an atmosphere of argon. Tetrahydrofuran (THF) and dichloromethane (DCM) were purchased and distilled from sodium/benzophenone and CaH_2, respectively. All reactions were monitored by gas chromatography. GC analyses were performed on an Agilent 6950 GC system equipped with a column HP5-MSI (length 30 m, internal diameter 0.25 mm, film thickness 0.25 μm) and flame ionization detection under a constant flow 1 mL/min helium carrier gas. GC–MS analyses were performed on an Agilent 6890N GC system equipped with a (5 %-phenyl)-methylpolysiloxane capillary column (length 30 m, internal diameter 0.25 mm, film thickness 0.25 μm) coupled to Agilent 5973N MS low resolution quadrupole. Commercial aluminium sheets precoated (0.2 mm layer thickness) with silica gel 60 F254 were used for analytical thin layer chromatography. Visualization was carried out with UV light. Product purification by flash chromatography was performed using Silica gel (230–400 mesh). ^{1}H (300, 400 and 500 MHz) and ^{13}C NMR (75, 100 and 126 MHz) spectra were recorded with a Bruker instrument. Chemical shifts are reported in δ ppm relative to TMS (δ = ^{1}H = 0.0 ppm) and $CDCl_3$ (δ = ^{13}C = 77.16 ppm) and coupling constants (*J*) are given in Hertz (Hz). Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), septet (sept), multiplet (m), and broad (br). High Resolution Mass Spectra were determined on a TripleTOF™ 5600 (ABSciex, USA) spectrometer by using electrospray in positive mode (ESI^+). Melting points were recorded on a Cambridge Instruments apparatus and are uncorrected.

General Procedures for the Synthesis of α-Chloromethylalkyl and α-Chloromethylaryl-*N*-Arylimines 3: These compounds were prepared using either P_2O_5 or molecular sieves[11] as dehydrating agent.

Method A: An oven dried resealable test tube with a Teflon stirring bar was charged with α-chloromethylketone **1** (0.5 mmol, 1 equiv.), arylamine **2** (0.5 mmol, 1 equiv.) and molecular sieves (3.5 g) and anhydrous Et_2O (10 mL). The mixture was allowed to react at room temperature for 12 to 24 h. until disappearance of the starting ketone **1** determined by GC analysis giving imines **3**.

Method B

(a) Alternative Procedure for the Synthesis of α-Chloromethylaryl-**3aa-3da** and α-Chloromethylalkyl-*N*-Aryl Imines (*syn*)-**3ea**-(*syn*)-**3fa**: An oven dried resealable test tube containing a Teflon stirring bar was charged with **1** (0.5 mmol, 1 equiv.), arylamine **2** (2.5 mmol, 5 equiv.) and P_2O_5 (0.75 mmol, 1.5 equiv.) in anhydrous THF (5 mL). The tube was sealed with a Teflon screw-cap and heated in an oil bath at 110 °C for 12–24 hours until disappearance of the starting ketone 1 determined by GC analysis giving the corresponding imines 3.

(b) Alternative Procedure for the Synthesis of α-Chloromethylalkyl-*N*-Aryl Imines 3ga, 3gf, 3gh, 3ha, 3hb, 3ia: An oven dried resealable test tube containing a Teflon stirring bar was charged with **1** (0.5 mmol, 1 equiv.), arylamine **2** (2.5 mmol, 5 equiv.), P_2O_5 (0.75 mmol, 1.5 equiv.) and $CeCl_3$ (0.5 mmol, 1 equiv.) in anhydrous toluene (5 mL). The tube was sealed with a Teflon screw-cap and heated in an oil bath at 80 °C for 2–5 hours until disappearance of the starting ketone **1** determined by GC analysis giving imines **3**.

General Procedure for the Synthesis of Indoles 4: The crude reaction mixture containing imine **3** (0.5 mmol) was transferred under argon atmosphere to a Schlenk tube by cannulation, the solid residue, consisting of molecular sieves or P_2O_5, was filtered out over Celite and washed several times with CH_2Cl_2. The combined solvents were removed in vacuo and anhydrous THF (5 mL), CsF (3 equiv.) and the catalytic system $Pd(OAc)_2$/P(*p*-tolyl)$_3$ were added in the appropriate amount (1 to 10 %, see Table 2 and Table 3). The resulting mixture was heated at 65 °C and stirred until complete conversion determined by GC. Next, the mixture was cooled to room temperature, diluted with THF (2–3 mL), and filtered through Celite. The solvent was removed under reduced pressure to afford indoles **4** which were isolated and purified by silica gel column chromatography (hexane/ethyl acetate).

2-phenyl-1*H*-indole (4aa): white solid (90 mg, 93 % yield); m.p. 188–190 °C (lit.[19] 188–189 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.25 (br, 1 H), 7.57 (m, 3 H), 7.41–7.28 (m, 3 H), 7.27–7.21 (m, 1 H), 7.15–7.09 (m, 1 H), 7.07–7.01 (m, 1 H), 6.75 (dd, *J* = 2.1, 0.8 Hz, 1 H). ^{13}C NMR (75 MHz, CDCl3): δ = 138.03, 136.97, 132.53, 129.41, 129.16, 127.85, 125.30, 122.49, 120.81, 120.41, 111.04, 100.13. HRMS (ESI) *m/z* calculated for $C_{14}H_{12}N$ $[M + H]^+$ 194.0964, found 194.0961.

2-(4-methoxyphenyl)-1*H*-indole (4ba): white solid (107 mg, 96 % yield); m.p. 226–228 °C (lit.[20] 226–227 °C). ^{1}H NMR (300 MHz, $CDCl_3$/DMSO-[d_6]): δ = 11.64 (br, 1 H), 8.06–8.00 (m, 2 H), 7.73 (d, *J* = 7.8 Hz, 1 H), 7.62 (dd, *J* = 7.9, 0.8 Hz, 1 H), 7.34–7.18 (m, 4 H), 6.99 (dd, *J* = 2.1, 0.7 Hz, 1 H), 4.04 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.40, 143.38, 142.54, 134.45, 131.97, 130.52, 126.65, 125.28, 124.84, 119.96, 116.68, 102.95, 60.80. HRMS (ESI) *m/z* calculated for $C_{15}H_{14}NO$ $[M + H]^+$ 224.1070, found 224.1074.

2-(4-chlorophenyl)-1*H*-indole (4ca): yellowish solid (108 mg, 95 % yield); m.p. 197–198 °C (lit.[21] 197–199 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.17 (br, 1 H), 7.55 (d, *J* = 7.7, 1 H), 7.52–7.45 (m, 2 H), 7.36–7.28 (m, 3 H), 7.09 (m, 2 H), 6.72 (dd, *J* = 2.2, 0.8 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.06, 136.83, 133.59, 131.04, 129.37, 129.31 126.46, 122.83, 120.90, 120.62, 111.09, 100.62. HRMS (ESI) *m/z* calculated for $C_{14}H_{11}ClN$ $[M + H]^+$ 228.0575, found 228.0565.

2-(thyophen-2-yl)-1*H*-indole (4da): yellowish solid (91 g, 91 % yield); m.p. 160–161 °C (lit.[22] 160–161 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = (ppm) 8.11 (br, 1 H), 7.51 (d, *J* = 7.2 Hz, 1 H), 7.25 (dd, *J* = 8.1, 0.8 Hz, 1 H), 7.18 (dd, *J* = 5.1, 1.1 Hz, 2 H), 7.10 (m, 1 H), 7.03 (m, 1 H), 6.98 (dd, *J* = 5.0, 3.6 Hz, 1 H), 6.64 (dd, *J* = 2.0, 0.8 Hz, 1 H): ^{13}C NMR (126 MHz, $CDCl_3$): δ = 136.65, 135.76, 132.47, 129.22, 128.02, 124.71, 123.05, 122.66, 120.67, 120.56, 110.91, 100.54. HRMS (ESI) *m/z* calculated for $C_{12}H_{10}NS$ $[M + H]^+$ 200.0528, found 200.0523.

6-methyl-2-phenyl-1*H*-indole (4ac): white solid (80 mg, 77 % yield); m.p. 187–189 °C. (lit.[23] 190–192 °C). ^{1}H NMR (300 MHz,

[D_6]acetone): δ = 10.35 (br, 1 H), 7.69 (d, J = 7.2 Hz, 2 H), 7.33–7.25 (m, 3 H), 7.14 (t, J = 7.4 Hz, 1 H), 7.08 (dt, J = 2.3, 0.8 Hz, 1 H), 6.73 (m, 1 H), 6.69 (dd, J = 2.2, 0.9 Hz, 1 H), 2.27 (s, 3 H). ^{13}C NMR (75 MHz, Acetone): δ = 138.39, 137.71, 133.31, 131.63, 129.22, 127.62, 127.47, 125.23, 121.77, 120.33, 111.43, 99.31, 21.35. HRMS (ESI) *m/z* calculated for $C_{15}H_{14}N$ $[M + H]^+$ 208. 1121, found 208. 1115.

5-methyl-2-phenyl-1*H*-indole (4ad): white solid (101 mg, 98 % yield); m.p. 210–212 °C (lit.[20] 211–213 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.23 (br, 1 H), 7.69–7.63 (m, 2 H), 7.49–7.41 (m, 3 H), 7.36–7.28 (m, 2 H), 7.04 (dd, J = 8.3, 1.3 Hz, 1 H), 6.77 (dd, J = 2.1, 0.8 Hz, 1 H), 2.47 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.08, 135.30, 132.66, 129.69, 129.62, 129.12, 127.71, 125.20, 124.12, 120.44, 110.68, 99.70, 21.60. HRMS (ESI) *m/z* calculated for $C_{15}H_{14}N$ $[M + H]^+$ 208.1048, found 208.1050.

7-ethyl-2-phenyl-1*H*-indole (4ae): white solid (82 mg, 74 % yield); m.p. 52–54 °C (lit.[19] 53–54 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.13 (br, 1 H), 7.63–7.58 (m, 2 H), 7.40–7.33 (m, 3 H), 7.28–7.21 (m, 1 H), 7.04–6.93 (m, 2 H), 6.76 (d, J = 2.2 Hz, 1 H), 2.84 (q, J = 7.6 Hz, 2 H), 1.33 (t, J = 7.6 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.68, 135.82, 132.73, 129.15, 127.79, 126.41, 125.36, 121.04, 120.70, 118.57, 100.73, 24.19, 13.96. HRMS (ESI) *m/z* calculated for $C_{16}H_{16}N$ $[M + H]^+$ 222.1277, found 222.1275.

5-chloro-2-phenyl-1*H*-indole (4af): white solid (109 mg, 96 % yield); m.p. 198–200 °C (lit.[21] 199–200 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.27 (br, 1 H), 7.61–7.49 (m, 3 H), 7.40–7.32 (m, 2 H), 7.29–7.20 (m, 2 H), 7.06 (dd, J = 8.6, 2.0 Hz, 1 H), 6.67 (dd, J = 2.0, 0.6 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.44, 135.27, 132.01, 130.47, 129.24, 128.26, 125.99, 125.38, 122.71, 120.12, 111.99, 99.70. HRMS (ESI) *m/z* calculated for $C_{14}H_{11}ClN$ $[M + H]^+$ 228.0575, found 228.0562.

7-bromo-5-methyl-2-phenyl-1*H*-indole (4ag):[24] yellowish solid, (91 mg, 64 % yield); m.p. 83–85 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.24 (br, 1 H), 7.61–7.56 (m, 2 H), 7.40–7.33 (m, 2 H), 7.29–7.22 (m, 2 H), 7.10 (dd, J = 1.3, 0.5 Hz, 1 H), 6.71 (d, J = 2.3 Hz, 1 H), 2.34 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.78, 133.98, 132.05, 131.24, 130.56, 129.20, 128.19, 126.09, 125.41, 119.70, 104.04, 100.62, 21.34. HRSM (ESI) *m/z* calculated for $C_{15}H_{13}NBr$ $[M + H]^+$ 286.0226, found 286.0229.

5-methyl-2-(4-methoxyphenyl)-1*H*-indole (4bd): white solid (96 mg, 81 % yield); m.p. 220 °C (lit.[25] 220–221 °C). ^{1}H NMR (300 MHz, DMSO): δ = 11.30 (br, 1 H), 7.81–7.74 (m, 2 H), 7.29–7.23 (m, 2 H), 7.05–6.99 (m, 2 H), 6.89 (dd, J = 8.3, 1.3 Hz, 1 H), 6.65 (d, J = 1.4 Hz, 1 H), 3.80 (s, 3 H), 2.36 (s, 3 H). ^{13}C NMR (75 MHz, DMSO): δ = 159.03, 138.12, 135.66, 129.46, 127.93, 126.60, 125.41, 122.97, 119.66, 114.66, 111.14, 97.22, 55.53, 21.59. HRMS (ESI) *m/z* calculated for $C_{16}H_{16}NO$ $[M + H]^+$ 238.1226, found 238.1227.

5-chloro-2-(4-methoxyphenyl)-1*H*-indole (4bf):[26] yellowish solid (121 mg, 94 % yield); m.p. 236–238 °C. ^{1}H NMR (300 MHz, DMSO): δ = 8.33 (br, 1 H), 7.86–7.80 (m, 2 H), 7.51 (d, J = 2.0 Hz, 1 H), 7.39 (d, J = 8.6 Hz, 1 H), 7.05–6.99 (m, 3 H), 6.74 (d, J = 0.7 Hz, 1 H), 3.80 (s, 3 H). ^{13}C NMR (75 MHz, DMSO): δ = 159.03, 139.65, 135.54, 130.00, 126.62, 124.48, 123.61, 120.70, 118.59, 114.35, 112.59, 96.87, 55.19. HRMS (ESI) *m/z* calculated for $C_{15}H_{13}ClNO$ $[M + H]^+$ 258.0680, found 258.0666.

2-(4-chlorophenyl)-5-methyl-1*H*-indole (4cd): white solid (118 mg, 98 %); m.p. 251–253 °C (lit.[27] 252–253 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.11 (br, 1 H), 7.52–7.47 (m, 2 H), 7.35–7.30 (m, 3 H), 7.21 (d, J = 8.3 Hz, 1 H), 6.96 (dd, J = 8.3, 1.2 Hz, 1 H), 6.65 (d, J = 1.3 Hz, 1 H), 2.37 (s, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 136.89, 135.41, 133.43, 131.20, 129.86, 129.61, 129.32, 126.37, 124.47, 120.51, 110.73, 100.19, 21.60. HRMS (ESI) *m/z* calculated for $C_{15}H_{13}ClN$ $[M + H]^+$ 242.0731, found 242.0721.

5-chloro-2-(4-chlorophenyl)-1*H*-indole (4cf): yellowish solid (128 mg, 98 % yield); m.p. 190–192 °C (lit.[28] 190–192 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.23 (br, 1 H), 7.51–7.47 (m, 3 H), 7.36–7.32 (m, 2 H), 7.23 (d, J = 8.6 Hz, 1 H), 7.08 (dd, J = 8.6, 2.0 Hz, 1 H), 6.66 (d, J = 1.5 Hz, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 138.22, 135.34, 134.06, 130.52, 130.36, 129.46, 126.55, 126.20, 123.06, 120.22, 112.05, 100.16. HRMS (ESI) *m/z* calculated for $C_{14}H_{10}Cl_2N$ $[M + H]^+$ 262.0185, found 262.0180.

2-(*tert*-butyl)-1*H*-indole (4ea): white solid (84 mg, 97 % yield); m.p. 72–73 °C (lit.[29] 74–76 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85 (br, 1 H), 7.48–7.44 (m, 1 H), 7.26–7.20 (m, 1 H), 7.08–6.94 (m, 2 H), 6.18 (dd, J = 2.3, 0.9 Hz, 1 H), 1.31 (s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.90, 135.89, 128.65, 121.20, 120.11, 119.73, 110.48, 97.09, 31.96, 30.45. HRMS (ESI) *m/z* calculated for $C_{12}H_{16}N$ $[M + H]^+$ 174.1277, found 174.1271.

2-(1-adamantyl)-1*H*-indole (4fa): yellowish solid (75 mg, 60 % yield); m.p. 147–149 °C (lit.[30] 146–147 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.91 (br, 1 H), 7.47 (d, J = 7.5 Hz, 1 H), 7.22 (d, J = 7.8 Hz, 1 H), 7.01 (tt, J = 7.0, 6.2 Hz, 2 H), 6.14 (d, J = 1.5 Hz, 1 H), 2.02 (s, 3 H), 1.89 (d, J = 2.2 Hz, 6 H), 1.78–1.65 (m, 7 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.37, 135.53, 128.55, 121.03, 120.10, 119.59, 110.53, 96.40, 42.67, 36.86, 33.80, 28.57. HRMS (ESI) *m/z* calculated for $C_{18}H_{22}N$ $[M + H]^+$ 252.1747, found 252.1743.

2-phenethyl-1*H*-indole (4ga): white solid (46 mg, 42 % yield); m.p. 118–120 °C (lit.[31] 118–120 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.65 (br, 1 H), 7.45 (dd, J = 7.9, 0.9 Hz, 1 H), 7.27–7.13 (m, 6 H), 7.01 (m, 2 H), 6.20 (d, J = 1.2 Hz, 1 H), 3.05–2.92 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.34, 139.14, 135.96, 128.82, 128.70, 128.56, 126.43, 121.25, 120.00, 119.78, 110.47, 99.98, 35.77, 30.28. HRMS (ESI) *m/z* calculated for $C_{16}H_{16}N$ $[M + H]^+$ 222.1277, found 222.1275.

2-octyl-1*H*-indole (4ha): white solid (45 mg, 39 % yield); m.p. 50–51 °C (lit.[32] 50 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.75 (br, 1 H), 7.45 (d, J = 7.7 Hz, 1 H), 7.20 (d, J = 7.7 Hz, 1 H), 7.01 (m, 2 H), 6.15 (d, J = 0.9 Hz, 1 H), 2.66 (t, J = 7.6 Hz, 2 H), 1.67–1.60 (m, 2 H), 1.34–1.17 (m, 10 H), 0.81 (t, J = 6.9 Hz, 3 H) ^{13}C NMR (126 MHz, $CDCl_3$): δ = 140.17, 135.96, 129.02, 121.03, 119.87, 119.70, 110.39, 99.59, 32.01, 29.55, 29.49, 29.37, 29.35, 28.43, 22.81, 14.24. HRMS (ESI) *m/z* calculated for $C_{16}H_{24}N$ $[M + H]^+$ 230.1903, found 230.1903.

2-decyl-1*H*-indole (4ia):[33] white solid (67 mg, 52 % yield); m.p. 48–50 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75 (br, 1 H), 7.47–7.43 (m, 1 H), 7.23–7.19 (m, 1 H), 7.01 (m, 2 H), 6.16 (dd, J = 2.0, 0.9 Hz, 1 H), 2.67 (t, J = 7.6 Hz, 2 H), 1.64 (dt, J = 15.1, 7.7 Hz, 2 H), 1.33–1.16 (m, 14 H), 0.81 (t, J = 6.7 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.16, 135.95, 129.01, 121.04, 119.87, 119.70, 110.38, 99.60, 32.04, 29.75, 29.71, 29.59, 29.48, 29.35, 28.43, 22.83, 14.26. HRMS (ESI) *m/z* calculated for $C_{18}H_{28}N$ $[M + H]^+$ 258.2216, found 258.2218.

2-(*tert*-butyl)-5-methyl-1*H*-indole (4ed): white solid (85 mg, 91 % yield); m.p. 102–104 °C (lit.[29] 101–103 °C);.^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.72 (br, 1 H), 7.24 (td, J = 1.5, 0.7 Hz, 1 H), 7.10 (d, J = 8.2 Hz, 1 H), 6.88–6.83 (m, 1 H), 6.08 (dd, J = 2.2, 0.9 Hz, 1 H), 2.34 (s, 3 H), 1.29 (s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.03, 134.18, 128.94, 128.85, 122.66, 119.83, 110.12, 96.60, 31.94, 30.43, 21.57. HRMS (ESI) *m/z* calculated for $C_{13}H_{18}N$ $[M + H]^+$ 188.1434, found 188.1426.

2-(*tert*-butyl)-5-chloro-1*H*-indole (4ef): white solid (98 mg, 95 % yield); a m.p. 64–66 °C (lit.[28] 62–66 °C);.^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85 (br, H), 7.40 (d, J = 2.0, Hz, 1 H), 7.16–7.08 (m, 1 H), 6.97 (dd, J = 8.6, 2.0 Hz, 1 H), 6.11 (dd, J = 2.2, 0.7 Hz, 1 H), 1.29 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.47, 134.23, 129.81, 125.27, 121.36, 119.49, 111.42, 96.96, 32.03, 30.34. HRMS (ESI) *m/z* calculated for $C_{12}H_{15}ClN$ $[M + H]^+$ 208.0888, found 208.0882.

5-chloro-2-phenethyl-1*H*-indole (4gf): yellowish solid (60 mg, 47 % yield); m.p. 102–104 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.67 (br, 1 H), 7.41 (d, *J* = 2.0 Hz, 1 H), 7.27–7.05 (m, 6 H), 6.98 (dd, *J* = 8.6, 2.0 Hz, 1 H), 6.14 (dd, *J* = 2.0, 0.7 Hz, 1 H), 3.04–2.91 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.09, 140.67, 134.28, 129.93, 128.74, 128.53, 126.53, 125.40, 121.46, 119.43, 111.38, 99.83, 35.63, 30.24. HRMS (ESI) *m/z* calculated for $C_{16}H_{15}ClN$ $[M + H]^+$ 256.0888,found 256.0887.

5-methoxy-2-phenethyl-1*H*-indole (4gh): yellowish solid (36 mg, 29 % yield); m.p. 95–97 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.56 (br, 1 H), 7.27–7.11 (m, 5 H), 7.06 (d, *J* = 8.7 Hz, 1 H), 6.94 (d, *J* = 2.4 Hz, 1 H), 6.69 (dd, *J* = 8.7, 2.5 Hz, 1 H), 6.13 (d, *J* = 1.4 Hz, 1 H), 3.76 (s, 3 H), 3.00–2.92 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.27, 141.35, 140.00, 131.07, 129.29, 128.69, 128.55, 126.41, 111.10, 102.20, 99.88, 56.03, 35.80, 30.35. HRMS (ESI) *m/z* calculated for $C_{17}H_{18}NO$ $[M + H]^+$ 252.1383, found 252.1384.

7-methyl-2-octyl-1*H*-indole (4hb): yellowish solid (32 mg, 26 % yield); m.p. 64–66 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.67 (br, 1 H), 7.30 (d, *J* = 7.7 Hz, 1 H), 6.91 (t, *J* = 7.4 Hz, 1 H), 6.84 (dd, *J* = 6.2, 0.8 Hz, 1 H), 6.16 (d, *J* = 2.1 Hz, 1 H), 2.69 (t, *J* = 7.5 Hz, 2 H), 2.40 (s, 3 H), 1.65 (dt, *J* = 15.2, 7.7 Hz, 2 H), 1.35–1.14 (m, 10 H), 0.81 (t, *J* = 6.7 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.82, 135.46, 128.51, 121.71, 119.89, 119.50, 117.64, 100.09, 32.02, 29.56, 29.51, 29.44, 29.38, 28.51, 22.81, 16.83, 14.24. HRMS (ESI) *m/z* calculated for $C_{17}H_{26}N$ $[M + H]^+$ 244.2060, found 244.2064.

Acknowledgments

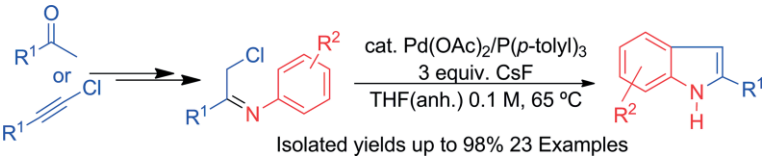
This work was supported by the Spanish Ministerio de Ciencia e Innovación, European Community Funds (FEDER), CTQ2014-52769-C3-2 grant. D. B. thanks the Generalitat Valenciana for a Santiago Grisolia fellowship. B. N. and J. T. S. thank the Spanish Ministerio de Economía y Competitividad for an FPU and an FPI contract respectively. We thank the SCSIE (Universidad de Valencia) for access to instrumental facilities.

Keywords: Palladium · C-H activation · Indoles · Ketones · Amines

[1] Dehalogenation product and oxidative homocoupling of the organometallic counterpart have been reported, see: A. Lei, X. Zhang, *Tetrahedron Lett.* **2002**, *43*, 2525.
[2] a) B. Noverges, C. Mollar, M. Medio-Simon, G. Asensio, *Adv. Synth. Catal.* **2013**, *355*, 2327; b) B. Noverges, M. Medio-Simon, G. Asensio, *Adv. Synth. Catal.* **2014**, *356*, 3649; c) B. Noverges, M. Medio-Simon, G. Asensio, *Adv. Synth. Catal.* **2015**, *357*, 430.
[3] S. Perrone, M. Capua, G. Cannazza, A. Salomone, L. Troisi, *Tetrahedron Lett.* **2016**, *57*, 1421.
[4] For some representative reviews: a) S. Agasti, A. Dey, D. Maiti, *Chem. Commun.* **2017**, *53*, 6544; b) T. Guo, F. Huang, L. Yu, Z. Yu, *Tetrahedron Lett.* **2015**, *56*, 296; c) M. Inman, C. J. Moody, *Chem. Sci.* **2013**, *4*, 29.
[5] a) M. Nazaré, C. Schneider, A. Lindenschmidt, D. W. Will, *Angew. Chem. Int. Ed.* **2004**, *43*, 4526; *Angew. Chem.* **2004**, *116*, 4626; b) J. Barluenga, A. Jiménez-Aquino, C. Valdés, F. Aznar, *Angew. Chem. Int. Ed.* **2007**, *46*, 1529; *Angew. Chem.* **2007**, *119*, 1551; c) J. Barluenga, A. Jiménez-Aquino, F. Aznar, C. Valdés, *J. Am. Chem. Soc.* **2009**, *131*, 4031; d) K. Gao, H. Yorimitsu, A. Osuka, *Angew. Chem. Int. Ed.* **2016**, *55*, 4573; *Angew. Chem.* **2016**, *128*, 4649.
[6] a) S. Würtz, S. Rakshit, J. J. Neumann, T. Dröge, F. Glorius, *Angew. Chem. Int. Ed.* **2008**, *47*, 7230; *Angew. Chem.* **2008**, *120*, 7340; b) R. Bernini, G. Fabrizi, A. Sferrazza, S. Cacchi, *Angew. Chem. Int. Ed.* **2009**, *48*, 8078; *Angew. Chem.* **2009**, *121*, 8222; c) W. Yu, Y. Du, K. Zhao, *Org. Lett.* **2009**, *11*, 2417; d) Z.-H. Guan, Z.-Y. Yan, Z.-H. Ren, X.-Y. Liu, Y.-M. Liang, *Chem. Commun.* **2010**, *46*, 2823; e) Z. He, W. Liu, Z. Li, *Chem. Asian J.* **2011**, *6*, 1340; f) J. J. Neumann, S. Rakshit, T. Dröge, S. Würtz, F. Glorius, *Chem. Eur. J.* **2011**, *17*, 7298; g) Z. Shi, F. Glorius, *Angew. Chem. Int. Ed.* **2012**, *51*, 9220; *Angew. Chem.* **2012**, *124*, 9354; h) Y. Wei, I. Deb, N. Yoshikai, *J. Am. Chem. Soc.* **2012**, *134*, 9098; i) X.-L. Lian, Z.-H. Ren, Y.-Y. Wang, Z. H. Guan, *Org. Lett.* **2014**, *16*, 3360; j) J. Zoller, D. C. Fabry, M. A. Ronge, M. Rueping, *Angew. Chem. Int. Ed.* **2014**, *53*, 13264; *Angew. Chem.* **2014**, *126*, 13480; k) A. Mishra, I. Deb, *Adv. Synth. Catal.* **2016**, *358*, 2267.
[7] Y. Yamamoto, *Chem. Soc. Rev.* **2014**, *43*, 1575.
[8] a) A. Erian, S. Sherif, H. Gaber, *Molecules* **2003**, *8*, 793; b) N. De Kimpe, R. Verhé, in *The Chemistry of α-Haloketones, α-Haloaldehydes and α-Haloimines* Chapter 1 and Appendix p. 121–223 (Eds.: S. Patai, Z. Rappoport.), Wiley, Chichester, **1988**; c) R. Ocampo, W. R. Dolbier Jr., *Tetrahedron* **2004**, *60*, 9325.
[9] R. Prebil, S. Stauber, *Adv. Synth. Catal.* **2014**, *356*, 1266.
[10] L. Xie, Y. Wu, W. Yi, L. Zhu, J. Xiang, W. He, *J. Org. Chem.* **2013**, *78*, 9190.
[11] K. Taguchi, F. H. Westheimer, *J. Org. Chem.* **1971**, *36*, 1570.
[12] T. M. Figg, M. Wasa, J.-Q. Yu, D. G. Musaev, *J. Am. Chem. Soc.* **2013**, *135*, 14206.
[13] Although CsF may play other roles in the reaction, its eventual coordination to palladium and chloro in the oxidative addition complex should favor the subsequent C-H activation step.
[14] Palladium catalyst must be added in two portions in the case of chloroimine **3ag** most probably to avoid the extensive oxidative addition to the C–Br bond.
[15] For direct C2 alkylation of N-protected indoles and other methods for 2-alkyl indoles see L. Jiao, T. Bach, *J. Am. Chem. Soc.* **2011**, *133*, 12990 and references cited therein.
[16] C. Mollar, M. Besora, F. Maseras, G. Asensio, M. Medio-Simón, *Chem. Eur. J.* **2010**, *16*, 13390.
[17] D. R. Stuart, K. Fagnou, *Science* **2007**, *316*, 1172.
[18] A. C. Albéniz, N. M. Catalina, P. Espinet, R. Redón, *Organometallics* **1999**, *18*, 5571.
[19] N. R. Deprez, D. Kalyani, A. Krause, M. S. Sanford, *J. Am. Chem. Soc.* **2006**, *128*, 4972.
[20] L. Ackermann, A. V. Lygin, *Org. Lett.* **2011**, *13*, 3332.
[21] M. Shen, B. E. Leslie, T. G. Driver, *Angew. Chem. Int. Ed.* **2008**, *47*, 5056; *Angew. Chem.* **2008**, *120*, 5134.
[22] H. Sakai, K. Tsutsumi, T. Morimoto, K. Kakiuchi, *Adv. Synth. Catal.* **2008**, *350*, 2498.
[23] X.-D. Xia, J. Xuan, Q. Wang, L.-Q. Lu, J.-R. Chen, W.-J. Xiao, *Adv. Synth. Catal.* **2014**, *356*, 2807.
[24] S. Cacchi, G. Fabrizi, A. Goggiamani, A. Iazetti, R. Vendiglione, *Tetrahedron* **2015**, *71*, 9346.
[25] S. Mahboobi, E. Eichhorn, M. Winkler, A. Sellmer, U. Möllmann, *Eur. J. Med. Chem.* **2008**, *43*, 633.
[26] J. E. Perea-Buceta, T. Wirtanen, O.-V. Laukkanen, M. K. Mkel, M. Nieger, M. Melchionna, N. Huittinen, J. A. Lopez-Sanchez, J. Helaja, *Angew. Chem. Int. Ed.* **2013**, *52*, 11835; *Angew. Chem.* **2013**, *125*, 12051.
[27] V. Sridharan, S. Perumal, C. Avendaño, J. C. Menéndez, *Synlett* **2006**, *1*, 91.
[28] B. Chelli, L. Rossi, E. Da Pozzo, B. Costa, F. Spinetti, M. Rechichi, A. Salvetti, A. Lena, F. Simorini, R. Vanacore, F. Scatena, F. Da Settimo, V. Gremigni, C. Martini, *ChemBioChem* **2005**, *6*, 1082.
[29] Y. Ito, K. Kobayashi, T. Saegusa, *J. Org. Chem.* **1979**, *44*, 2030.
[30] W. J. Houlihan, V. A. Parrino, Y. Uike, *J. Org. Chem.* **1981**, *46*, 4511.
[31] A. García-Rubia, R. Gómez Arrayás, J. C. Carretero, *Angew. Chem. Int. Ed.* **2009**, *48*, 6511; *Angew. Chem.* **2009**, *121*, 6633.
[32] M. Zille, A. Stolle, A. Wildbc, U. S. Schubert, *RSC Adv.* **2014**, *4*, 13126.
[33] P. Rubio-Marqués, M. A. Rivero-Crespo, A. Leyva-Pérez, A. Corma, *J. Am. Chem. Soc.* **2015**, *137*, 11832.

Received: October 30, 2018

Ring Closure



Palladium-catalyzed heterocyclization of α-chloromethyl alkyl or aryl N-aryl imines gives efficiently 2-aryl- and 2-alkyl-1*H*-indoles. Readily or commercially available α-chloromethyl-aryl or -alkyl ketones are used as the precursors. Indoles containing substituents, including halogens, at the benzene ring are also easily accessible simply by use of the appropriate substituted aromatic amine.

DOI: 10.1002/ejoc.201801607