EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201301699

Copper- and Palladium-Cocatalyzed Intramolecular C–H Functionalization/C–N Bond Formation: A Route to the Synthesis of Indoloisoquinoline Derivatives

Somjit Hazra,[a] Biplab Mondal,[a] Habibur Rahaman,[b] and Brindaban Roy*[a]

Keywords: Homogeneous catalysis / C–H activation / C–N bond formation / Nitrogen heterocycles / Copper / Palladium

A Cu and Pd bi-catalytic system is found to be very effective for the indole C2–H functionalization/C–N bond formation process.This is a unique reaction in which isoquinoline systems were synthesized from aldoximes rather than from ketoximes. During the reaction $Cu(OTf)_2$ converts the aldoximes into the corresponding cyanides and indoloisoquinolines, but introduction of $Pd(OAc)_2$ changes the outcome of the reaction significantly, by suppressing the formation of cyano products, thus giving exclusively indoloisoquinolines. A range of substituted indoloisoquinolines and aza-indoloisoquinolines are prepared in good to very good yields under air.

Introduction

Indoloisoquinoline derivatives are important polyheterocyclic compounds and have been successfully studied as drug candidates (Figure 1). Compound **A** showed 51.8% inhibition of Lewis lung cancer cells implanted in mice (at 50 mg kg^{-1}).[1] Compounds **B** and **C** exhibit potent antitumor activity.[2] Other substituted indoloisoquinolines act as anticancer agents and as neoplasm inhibitors and show bactericidal and fungicidal activity.[3] In addition to their use in medicinal chemistry, substituted indoloisoquinolines are recognized as electroluminescent host hole transport devices and as electroluminescent materials or electric materials for organic optoelectronic devices.[4]

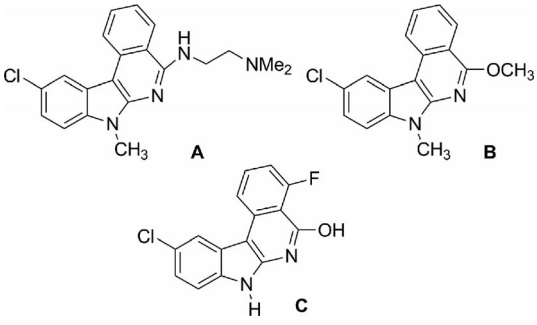


Figure 1. Bioactive indoloisoquinoline.

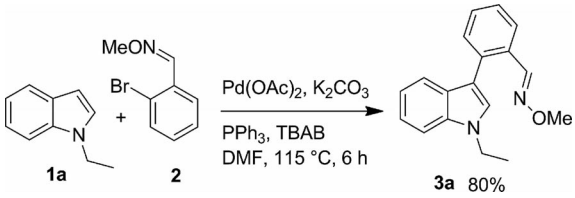
[a] Department of Chemistry, University of Kalyani, Kalyani, Nadia, W.B. 741235, India
E-mail: broybsku@gmail.com
broybsku@rediffmail.com
http://www.klyuniv.ac.in/
[b] Department of Chemistry,Ranaghat College, Ranaghat, Nadia, W.B. 741201, India

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201301699.

Development of efficient methods to construct functionalized indoloisoquinoline systems is thus essential for drug discovery, as well as for organic optoelectronic devices. Methods for the preparation of the patent indoloisoquinoline compounds include heating of 5-chloro-3-(2-fluorophenyl)-2-isocyanatoindole at 240–260 °C or sequential heating of 5-chloro-1-methyl-3-phenylindole-2-carboxazide in DMF.[2a,2b] Another approach involves thermal cyclization of 2,3-disubstituted indoles with PhNCO.[3c] Although these approaches provide access to indoloisoquinolines, none of them involves metal-catalyzed environmentally benign reaction conditions. Over the past years transition-metal-catalyzed direct C–H functionalization/C–C or C-heteroatom bond formation has become attractive due to its versatility and low toxicity.[5] Recent studies have revealed that copper-catalyzed C–H functionalization/C–N or C–O bond formation is useful for the construction of the heterocyclic architectures, with the synthesis of dibenzofurans,[6] 2-arylbenzoxazoles,[7] benzimidazoles,[8] benzoxazoles,[9] 4-aryl-2-quinolones,[10] carbazoles,[11] and quinazoline[12] and indolo[1,2-*c*]quinazoline derivatives[13] being particularly important among them. Many of these reactions were aided by directing groups, and therefore we reasoned that the oxime ether system might well serve as the directing group with an appropriate catalytic system. There are a few methods for obtaining isoquinoline derivatives from oxime ether groups in the literature, but all of them involve ketoximes, because aldoximes always tend to produce cyano byproducts and thereby reduce the efficiency of the reaction.[14] We disclose here a new $Cu(OTf)_2$/$Pd(OAc)_2$-catalyzed synthesis of indoloisoquinolines from suitably substituted indole derivatives directed by the aldoxime ether group through a C–H functionalization/C–N bond-forming process.

Results and Discussion

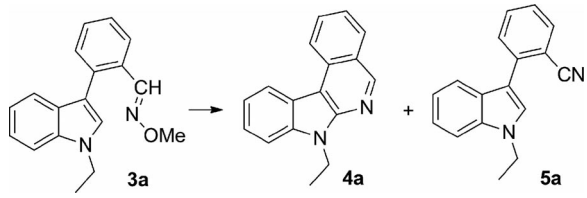
We started our investigation by pursuing a synthetic route for the conversion of indole **1a** into C3-arylated indole **3a**. Our initial plan was to couple 2-bromobenzaldehyde with **1a** at its 3-position and then to convert this C3-arylated aldehyde into an aldoxime by a known procedure. Various palladium-catalyzed C2/C3 arylations of indole are well known in the literature,[15] but we failed to obtain our desired product by those procedures, instead noticing the formation of different product mixtures. We therefore changed our plan and decided to explore C3-arylation with aldoxime **2** instead of the 2-bromobenzaldehyde. We were fortunate enough to isolate the C3-arylated indole derivative **3a** in 80% yield under Pd-catalyzed cross-coupling reaction conditions in the presence of Ph_3P and K_2CO_3 at 115 °C in DMF (Scheme 1).



Scheme 1. Synthesis of C3-arylated indoles.

To develop our idea of C–H functionalization of **3a**, we started a study of conversion of **3a** into indoloisoquinoline **4a**. Preliminary screening with 10 mol-% $Cu(OTf)_2$ failed to provide any product when DMF, dioxane, and THF were used as solvents (Table 1, Entries 1–3). We then turned our attention to nonpolar solvents. To our delight, with toluene as solvent we obtained our desired product in 20% yield along with the cyano derivative **5a** (Table 1, Entry 4). *o*-Xylene proved to be even more fruitful than toluene for the reaction (Table 1, Entry 5). Increasing the catalyst amount to 20 mol-% resulted in further improvement in the yield of the reaction (Table 1, Entry 6). Addition of base (K_2CO_3, K_3PO_4), on the contrary, failed to show any encouraging sign over the initial results. In fact, with K_3PO_4 decomposition of the starting precursor was observed (Entries 7 and 8). We subsequently tested other copper(II) salts but no catalytic activity was noticed (Table 1, Entries 9–11). A Cu^I salt was also found to be ineffective and the starting substrate remained intact (Table 1, Entry 12). The reaction proceeded very slowly and the conversion was very poor when $Pd(OAc)_2$ was employed as a catalyst (Table 1, Entries 13 and 14). External oxidants such as $K_2S_2O_8$ and AgOAc (Entries 15 and 16) also did not improve the situation. The first real breakthrough came along when we decided to use $Pd(OAc)_2$ simultaneously with $Cu(OTf)_2$. This combined catalytic system not only improved the yield but also suppressed the formation of cyano derivative **5a**. We also tried this bi-catalytic system [$Pd(OAc)_2$ and $Cu(OTf)_2$] in other solvents, but *o*-xylene proved to be the best for optimum conversion (Table 1, Entry 17). A slight increase in the yield was observed when the amount of $Pd(OAc)_2$ was raised to 10 mol-% (Table 1, Entry 18). To observe the effect of the Lewis acidic behavior of $Cu(OTf)_2$, we used other triflate salts, namely AgOTf and $Bi(OTf)_3$ (Table 1, Entries 19 and 20), but the starting substrate decomposed on both occasions. The reaction was also found to be equally efficient in air and under inert atmosphere.

Table 1. Optimization of the catalytic cyclization of 3-substituted indole derivative **3a**.

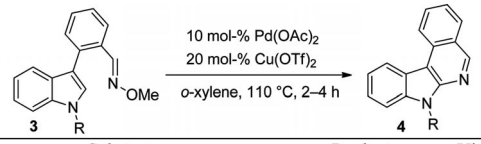


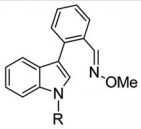
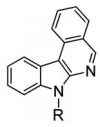
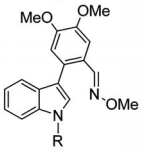
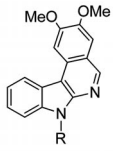
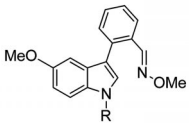
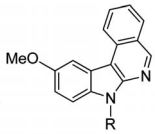
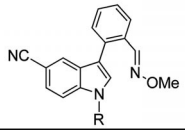
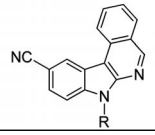
Entry	Cat. [mol-%]	Additive [equiv.]	Solvent	Yield [%][a,b] 4a	5a
1	$Cu(OTf)_2$ [10]	–	DMF[c]	n.r.	
2	$Cu(OTf)_2$ [10]		dioxane[c]	n.r.	
3	$Cu(OTf)_2$ [10]		THF[c]	n.r.	
4	$Cu(OTf)_2$ [10]		toluene[d]	20	15
5	$Cu(OTf)_2$ [10]		*o*-xylene[d]	30	20
6	$Cu(OTf)_2$ [20]		*o*-xylene	45	25
7	$Cu(OTf)_2$ [20]	K_2CO_3 [2]	*o*-xylene	25	18
8	$Cu(OTf)_2$ [20]	K_3PO_4 [2]	*o*-xylene	n.r.	
9	$CuBr_2$ [20]		*o*-xylene	dec.	
10	$CuCl_2 \cdot H_2O$ [20]		*o*-xylene	n.r.	
11	$Cu(OAc)_2 \cdot H_2O$ [20]		*o*-xylene	n.r	
12	CuBr [20]		*o*-xylene	n.r.	
13	$Pd(OAc)_2$ [5]		*o*-xylene	5	0
14	$Pd(OAc)_2$ [10]		*o*-xylene	5	0
15	$Pd(OAc)_2$ [10]	$K_2S_2O_8$ [1]	*o*-xylene	12	0
16	$Pd(OAc)_2$ [10]	AgOAc [1]	*o*-xylene	10	0
17	$Pd(OAc)_2$, $Cu(OTf)_2$[g]		*o*-xylene	66[e]	0
18	$Pd(OAc)_2$, $Cu(OTf)_2$[g]		*o*-xylene	74[f]	0
19	$Pd(OAc)_2$, AgOTf[g]		*o*-xylene	dec.	
20	$Pd(OAc)_2$, $Bi(OTf)_3$[g]		*o*-xylene	dec.	

[a] Yields of the isolated compounds; n.r.: no reaction, dec: decomposition. [b] All the reactions were monitored for 10 h unless the substrate was consumed within the time period. [c] Reaction was conducted at 110 °C, 100 °C, and 67 °C for DMF, dioxane, and THF, respectively. [d] Reaction was performed at 110 °C. [e] Reaction also conducted in DMSO, DMF, and THF. [f] Reaction time = 2 h. [g] 10 mol-% of $Pd(OAc)_2$ and 20 mol-% of the other triflate salt were used and the reaction was performed both in air and under inert atmosphere.

Using the optimized reaction conditions, we next explored the scope and limitations of the substrates and achieved substituent diversity of the reaction (Table 2). A number of substituted indole derivatives were tested under the optimized reaction conditions and very good yields were observed (Table 2, Entries 1–10).The reaction went smoothly with various *N*-alkylindole derivatives. The presence of electron-donating groups (OMe) in the benzene ring of the aldoxime resulted in a very good yield of the products (Table 2, Entries 4–6). The presence of an OMe group in the 5-position of the indole ring produced better yields (Table 2, Entries 7 and 8) than were obtained with 5-cyanoindole derivatives (Table 2, Entries 9 and 10), in which the reactions took longer times for completion and also the yields were slightly diminished.

Table 2. Synthesis of substituted indoloisoquinolines.

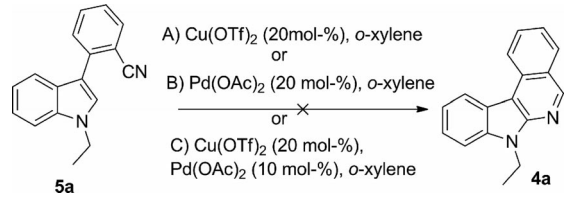


Entry	Substrate		Product		Yield [%][a]
1		**3a**, R = Et		**4a**	74
2		**3b**, R = Me		**4b**	70
3		**3c**, R = *i*Pr		**4c**	68[b]
4		**3d**, R = Me		**4d**	78
5		**3e**, R = Et		**4e**	72
6		**3f**, R = *i*Pr		**4f**	75
7		**3g**, R = Et		**4g**	71
8		**3h**, R = *i*Pr		**4h**	73
9		**3i**, R = Et		**4i**	62[c]
10		**3j**, R = *i*Pr		**4j**	65[d]

[a] Yields of isolated products. [b] Reaction time: 4 h. [c] Reaction time: 5 h with 10% substrate recovery. [d] Reaction time: 6 h.

We extended this method to the preparation of aza-indoloisoquinoline derivatives **7** (Table 3, Entries 1 and 2). Here the presence of an additional nitrogen atom in the aza-indole ring system did not seem to hinder the reaction flow at all and after 4 h reaction time high yields of the products were obtained.

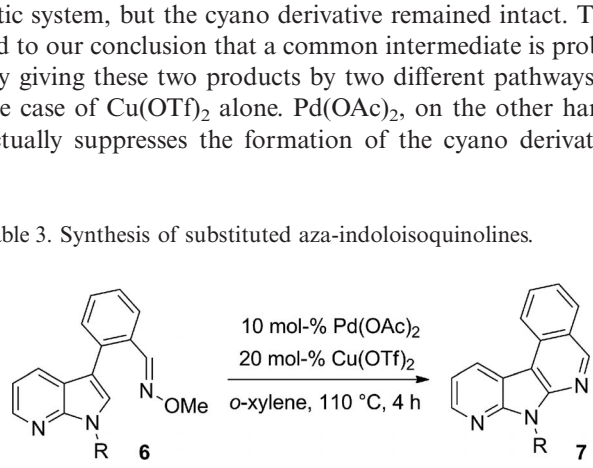
Initially we hypothesized that the cyano derivative **5a** was involved in the reaction pathway. To probe its validity we treated **5a** with $Cu(OTf)_2$ in *o*-xylene but we failed to obtain any product (Scheme 2). We tried this reaction with $Pd(OAc)_2$, and also with the $Pd(OAc)_2/Cu(OTf)_2$ bi-catalytic system, but the cyano derivative remained intact. This led to our conclusion that a common intermediate is probably giving these two products by two different pathways in the case of $Cu(OTf)_2$ alone. $Pd(OAc)_2$, on the other hand, actually suppresses the formation of the cyano derivative altogether rather than merely converting the cyano derivative into compound **4a** (Scheme 2).



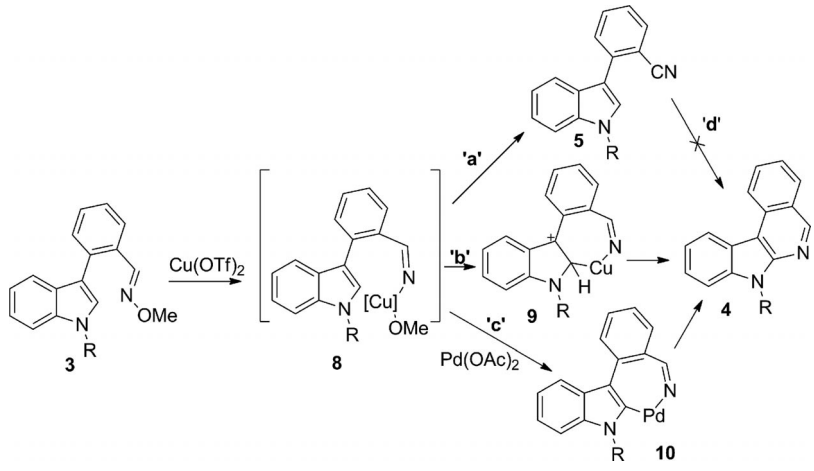
Scheme 2. Reactions with cyanide adduct.

Based on the literature precedent, related reactions, and our probe reactions with the cyano derivative **5a**, the possible pathways for the formation of indoloisoquinoline **4** are outlined in Scheme 3. The initial N–O bond scission of **3** in the presence of $Cu(OTf)_2$ presumably leads to the iminyl-Cu species **8**[8a,16] with the copper either in oxidation state II or III.[16c,17] Now the formation of both the product **4** and **5** in the presence only of $Cu(OTf)_2$ indicates that most probably species **8** affords these products by two simultaneously operative different pathways (pathways "a" and "b"), because the isolated cyano derivative **5** cannot be converted into compound **4** (step "d") in a separate reaction. We think that in pathway "a" demetallation of the iminyl-Cu species gave the cyano derivative **5**, whereas in a different pathway, compound **4** was obtained from **8** through the intermediacy of metallacycle **9**. Earlier reports revealed that an adduct of type **8** can be cyclized similarly, variously through electrophilic aromatic substitution, via a metallacycle, or by electrocyclic ring closure.[18] However, in the presence only of $Cu(OTf)_2$, the slower reaction rate and lower yield of the product **4**, and the formation of significant amounts of cyano derivative **5**, indicate that electrophilic metallation pathway (path "b") is the most reasonable one. We assumed that the instability and difficulty of formation of the seven-membered copper metallacycle intermediate **9** is responsible for the low yield of **4** in the presence only of $Cu(OTf)_2$ as catalyst. We are not entirely sure about the role of $Pd(OAc)_2$, but we found that it suppresses the formation of cyanide adduct in the reaction. We hypothesize that it most probably undergoes a transmetallation reaction[16c] with iminyl-Cu species **8**, followed by C–H activation (path "c"), to give the seven-membered palladacycle **10**. Subsequent C–N bond formation and reductive elimination provide **4** in good to very good yields. The failure to obtain **4** from **5** in the presence of any catalytic combination of $Pd(OAc)_2$ and $Cu(OTf)_2$ under the same reaction condition excludes the possibilities of formation of **4** via the cyano intermediate. Because other metal triflates and Cu^{I} and Cu^{II} salts were found to be ill-suited for the reaction, we concluded that $Cu(OTf)_2$ is most probably not acting here as a Lewis acid. Also, the sluggishness of the reaction in the absence of $Cu(OTf)_2$ led us to believe that the iminyl-Cu species must be involved in the reaction. The equal efficiency of the reaction both in air and under inert atmosphere also suggests that $Cu(OTf)_2$ most probably helps to maintain the catalytic cycle here.

Table 3. Synthesis of substituted aza-indoloisoquinolines.



Entry	Substrate	R	Product	Yield (%)
1	**6a**	ethyl	**7a**	75
2	**6b**	isopropyl	**7b**	72



Scheme 3. Proposed mechanism for the indoloisoquinoline formation.

Conclusions

We have developed a new Pd/Cu-catalyzed intramolecular C–N bond-formation reaction which involves activation of the indole C2–H bond for the synthesis of indoloisoquinoline and aza-indoloisoquinoline derivatives. This reaction features mild reaction conditions and extreme operational simplicity. Our approach provides easy access to organoelectric and medicinally important heterocyclic compounds. Further studies on the development of this methodology in constructing new heterocycles, especially regarding indole C3–H bond activation, are ongoing.

Experimental Section

General: Melting points were determined in open capillaries and are uncorrected. IR spectra ($\tilde{\nu}_{max}$ in cm^{-1}) were recorded with a Perkin–Elmer L 120–000A spectrometer on KBr disks. ^1H NMR and ^{13}C NMR spectra were recorded with a Bruker DPX 400 spectrometer in $CDCl_3$ with TMS as internal standard (chemical shift in δ). Chemical shifts of common trace PMR impurities ($CDCl_3$, ppm) in some samples: H_2O 1.56; solvent impurities 1.26, 0.86; $CHCl_3$ 7.26. In some low-polar samples a ^{13}C peak corresponding to solvent greasy impurities was observed at 29.7 (δ_C). CHN was recorded with a Perkin–Elmer 2400 series II CHN analyzer. MS were recorded with a Q-TOF micro^{Tm} instrument at the Indian Institute of Chemical Biology, Kolkata. In addition, some MS were measured at the Indian Association of Cultivation of Science, Kolkata, and the Indian Institute of Technology, Kharagpur. Silica gel (60–120, 230–400 mesh, Rankem, India) was used for chromatographic separation. Silica gel G (CDH, India) was used for TLC. Petroleum ether (Pet. ether) refers to the fraction boiling between 60 °C and 80 °C.

General Procedure for the Preparation of C3-Arylated Indoles: The *N*-alkylated indole (1 mmol), $Pd(OAc)_2$ (10 mol-%, 0.1 mmol), K_2CO_3 (3 mmol), TBAB (0.2 mmol), and triphenylphosphine (0.1 mmol) were placed in an oven-dried reaction vessel. The reaction vessel was fitted with a silicon septum, evacuated, and backfilled with argon. DMF (10 mL) and the 2-brominated aryl oxime (1.2 mmol) were then added successively under argon at room temperature. The resulting mixture was heated under argon for 6 h to 12 h at 115 °C. The progress of the reaction and the composition of the reaction mixture were monitored by TLC analysis. After completion (monitored by TLC), the reaction mixture was cooled and water (10 mL) was added. The mixture was then extracted with EtOAc (10 mL × 3). The EtOAc extract was washed with water (10 mL × 4) followed by brine (10 mL). The organic layer was dried (Na_2SO_4). Evaporation of EtOAc under reduced pressure furnished a crude mass, which was purified by column chromatography over silica gel. Elution of the column with pet. ether afforded the 3-arylated indole.

(*E*)-2-(1-Ethyl-1*H*-indol-3-yl)benzaldehyde *O*-Methyl Oxime (3a): Yield 80%; yellow solid, m.p. 71–72 °C. ^1H NMR (400 MHz, $CDCl_3$): δ_H = 1.50 (t, *J* = 7.2 Hz, 3 H), 3.93 (s, 3 H, NC*H*$_3$), 4.21 (q, *J* = 7.2 Hz, 2 H), 7.07 (s, 1 H, indole C2-H), 7.14 (t, *J* = 7.6 Hz, 1 H), 7.22–7.28 (m, 1 H), 7.33 (t, *J* = 7.6 Hz, 1 H), 7.38–7.44 (m, 2 H), 7.51 (d, *J* = 7.6 Hz, 1 H), 7.57 (d, *J* = 8.0 Hz, 1 H), 7.99 (d, *J* = 8.0 Hz, 1 H), 8.19 (s, 1 H, oxime C–H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 15.5, 41.1, 61.9, 109.5, 113.8, 120.0, 120.0, 122.1, 126.3, 126.7, 127.0, 127.7, 129.6, 130.4, 131.0, 135.2, 135.9, 148.8 ppm. IR (KBr): $\tilde{\nu}$ = 1457, 1540, 1608, 2813, 2889, 2931 cm^{-1}. HRMS (TOF, ES$^+$): calcd. for $C_{18}H_{18}N_2O$ + H [M + H]$^+$ 279.1497; found 279.1483.

(*E*)-2-(1-Methyl-1*H*-indol-3-yl)benzaldehyde *O*-Methyl Oxime (3b): Yield 78%; yellow solid, m.p. 61–62 °C. ^1H NMR (400 MHz, $CDCl_3$): δ_H = 3.86 (s, 3 H), 3.94 (s, 3 H), 7.02 (s, 1 H, indole C2-H), 7.15 (t, *J* = 7.6 Hz, 1 H), 7.30 (t, *J* = 7.2 Hz, 1 H), 7.34–7.38 (m, 2 H), 7.43 (t, *J* = 7.6 Hz, 1 H), 7.51 (d, *J* = 7.6 Hz, 1 H), 7.56 (d, *J* = 7.6 Hz, 1 H), 7.99 (d, *J* = 8.0 Hz, 1 H), 8.20 (s, 1 H, oxime C–H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 33.0, 61.9, 109.5, 113.7, 119.9, 120.1, 122.3, 126.4, 126.8, 127.6, 128.7, 129.7, 130.4, 131.1, 135.1, 136.9, 148.8 ppm. IR (KBr): $\tilde{\nu}$ = 1481, 1545, 1613, 2816, 2934 cm^{-1}. $C_{17}H_{16}N_2O$ (264.33): calcd. C 77.25, H 6.10, N 10.60; found C 77.08, H 6.25, N 10.69.

(*E*)-2-(1-Isopropyl-1*H*-indol-3-yl)benzaldehyde *O*-Methyl Oxime (3c): Yield 72%; yellow gum. ^1H NMR (400 MHz, $CDCl_3$): δ_H = 1.58 (d, *J* = 6.8 Hz, 6 H), 3.93 (s, 3 H, OCH_3), 4.71–4.75 (m, 1 H), 7.14 (t, *J* = 7.6 Hz, 1 H), 7.18 (s, 1 H, indole C2-H), 7.24–7.28 (m, 1 H), 7.34 (t, *J* = 7.6 Hz, 1 H), 7.40–7.45 (m, 2 H), 7.51 (d, *J* = 7.6 Hz, 1 H), 7.56 (d, *J* = 8.0 Hz, 1 H), 7.99 (d, *J* = 8.0 Hz, 1 H), 8.17 (s, 1 H, oxime C–H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 22.9, 47.3, 61.9, 109.8, 113.9, 120.0, 120.1, 122.0, 123.7, 126.3, 126.8, 127.7, 129.7, 130.4, 131.1, 135.4, 135.8, 148.9 ppm. IR (neat): $\tilde{\nu}$ = 1462, 1543, 1610, 2816, 2932 cm^{-1}. $C_{19}H_{20}N_2O$ (292.38): calcd. C 78.05, H 6.89, N 9.58; found C 78.29, H 6.78, N 9.71.

(*E*)-4,5-Dimethoxy-2-(1-methyl-1*H*-indol-3-yl)benzaldehyde *O*-Methyl Oxime (3d): Yield 72%; yellow solid, m.p. 105–106 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 3.85 (s, 3 H, CH_3), 3.90 (s, 3 H, CH_3), 3.92 (s, 3 H, CH_3), 4.0 (s, 3 H, CH_3), 6.97 (s, 1 H), 7.0 (s, 1 H), 7.16 (t, *J* = 7.6 Hz, 1 H), 7.28 (t, *J* = 7.6 Hz, 1 H), 7.37 (d, *J* = 8.4 Hz, 1 H), 7.50 (s, 1 H), 7.55 (d, *J* = 8.0 Hz, 1 H), 8.14 (s, 1 H, oxime C–H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 32.9, 55.9, 56.0, 61.8, 107.8, 109.5, 113.3, 113.4, 119.7, 120.0, 122.2, 122.9, 127.7, 128.5, 128.7, 136.8, 148.0, 148.5, 150.3 ppm. IR (KBr): $\tilde{\nu}$ = 1508, 1549, 1594, 1612, 2934 cm^{-1}. $C_{19}H_{20}N_2O_3$ (324.38): calcd. C 70.35, H 6.21, N 8.64; found C 70.21, H 6.37, N 8.42.

(*E*)-2-(1-Ethyl-1*H*-indol-3-yl)-4,5-dimethoxybenzaldehyde *O*-Methyl Oxime (3e): Yield 68%; yellow solid, m.p. 115–116 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 1.52 (t, *J* = 7.2 Hz, 3 H), 3.90 (s, 3 H), 3.92 (s, 3 H), 4.0 (s, 3 H), 4.24 (q, *J* = 7.2 Hz, 2 H), 6.98 (s, 1 H), 7.06 (s, 1 H), 7.15 (t, *J* = 7.6 Hz, 1 H), 7.25–7.29 (m, 1 H), 7.40 (d, *J* = 8.0 Hz, 1 H), 7.51 (s, 1 H), 7.55 (d, *J* = 7.6 Hz, 1 H), 8.13 (s, 1 H, oxime C–H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 15.5, 41.1, 56.0, 56.0, 61.8, 107.8, 109.5, 113.3, 113.5, 119.8, 120.0, 122.0, 122.9, 126.8, 127.9, 128.9, 135.8, 148.0, 148.5, 150.3 ppm. IR (KBr): $\tilde{\nu}$ = 1505, 1549, 1594, 1611, 2931 cm^{-1}. $C_{20}H_{22}N_2O_3$ (338.41): calcd. C 70.99, H 6.55, N 8.28; found C 71.16, H 6.69, N 8.12.

(*E*)-2-(1-Isopropyl-1*H*-indol-3-yl)-4,5-dimethoxybenzaldehyde *O*-Methyl Oxime (3f): Yield 66%; pale yellow solid, m.p. 130–131 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 1.58 (d, *J* = 6.8 Hz, 6 H), 3.90 (s, 3 H), 3.91 (s, 3 H), 4.0 (s, 3 H), 4.71–4.76 (m,1 H), 6.97 (s, 1 H), 7.14 (t, *J* = 7.6 Hz, 1 H), 7.15 (s, 1 H), 7.23–7.27 (m, 1 H), 7.42 (d, *J* = 8.4 Hz, 1 H), 7.51 (s, 1 H), 7.54 (d, *J* = 8.0 Hz, 1 H), 8.11 (s, 1 H, oxime C–H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 22.9, 47.3, 56.0, 56.0, 61.7, 107.8, 109.7, 113.3, 113.7, 119.8, 120.0, 121.9, 123.0, 123.4, 127.9, 129.1, 135.6, 148.0, 148.5, 150.3 ppm. IR (KBr): $\tilde{\nu}$ = 1506, 1548, 1593, 1610, 2932 cm^{-1}. $C_{21}H_{24}N_2O_3$ (352.43): calcd. C 71.57, H 6.86, N 7.95; found C 71.35, H 6.98, N 7.84.

(*E*)-2-(1-Ethyl-5-methoxy-1*H*-indol-3-yl)benzaldehyde *O*-Methyl Oxime (3g): Yield 76%; yellow solid, m.p. 97–98 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 1.47 (t, *J* = 7.6 Hz, 3 H), 3.78 (s, 3 H, OCH_3), 3.93 (s, 3 H, NCH_3), 4.15 (q, *J* = 7.6 Hz, 2 H), 6.91 (dd, *J* = 8.8, 2.0 Hz, 1 H), 6.98 (d, *J* = 2.0 Hz, 1 H), 7.04 (s, 1 H, indole C2-H), 7.26 (d, *J* = 8.8 Hz, 1 H), 7.32 (t, *J* = 7.6 Hz, 1 H), 7.42 (t, *J* = 7.6 Hz, 1 H), 7.49 (d, *J* = 7.6 Hz, 1 H), 7.99 (d, *J* = 8.0 Hz, 1 H), 8.19 (s, 1 H, oxime C–H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 15.6, 41.3, 55.9, 61.9, 101.2, 110.4, 112.7, 113.4, 126.4, 126.7, 127.3, 128.0, 129.8, 130.3, 130.9, 131.2, 135.4, 149.0, 154.7 ppm. IR (KBr): $\tilde{\nu}$ = 1488, 1541, 1608, 2932, 2956 cm^{-1}. $C_{19}H_{20}N_2O_2$ (308.38): calcd. C 74.00, H 6.54, N 9.08; found C 74.14, H 6.71, N 8.95.

(*E*)-2-(1-Isopropyl-5-methoxy-1*H*-indol-3-yl)benzaldehyde *O*-Methyl Oxime (3h): Yield 73%; yellow solid, m.p. 80–81 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 1.55 (d, *J* = 6.8 Hz, 6 H), 3.79 (s, 3 H, OCH_3), 3.93 (s, 3 H, NCH_3), 4.64–4.67 (m, 1 H), 6.91 (dd, *J* = 8.8, 2.4 Hz, 1 H), 6.97 (d, *J* = 2.0 Hz, 1 H), 7.15 (s, 1 H, indole C2-H), 7.29–7.35 (m, 2 H), 7.43 (t, *J* = 7.6 Hz, 1 H), 7.49 (d, *J* = 7.6 Hz, 1 H), 7.98 (d, *J* = 7.6 Hz, 1 H), 8.17 (s, 1 H, oxime C–H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 22.9, 47.5, 55.9, 61.8, 101.2, 110.5, 112.5, 113.6, 124.0, 126.3, 126.6, 127.9, 129.7, 130.4, 130.9, 131.0, 135.6, 149.0, 154.6 ppm. IR (KBr): $\tilde{\nu}$ = 1489, 1543, 1610, 2934, 2958 cm^{-1}. $C_{20}H_{22}N_2O_2$ (322.41): calcd. C 74.51, H 6.88, N 8.69; found C 74.68, H 6.73, N 8.78.

(*E*)-1-Ethyl-3-{2-[(methoxyimino)methyl]phenyl}-1*H*-indole-5-carbonitrile (3i): Yield 64%; brown solid, m.p. 110–111 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 1.53 (t, *J* = 7.2 Hz, 3 H), 3.95 (s, 3 H, OCH_3), 4.25 (q, *J* = 7.2 Hz, 2 H), 7.21 (s, 1 H, indole C2-H), 7.38–7.48 (m, 5 H), 7.87 (s, 1 H), 8.00 (d, *J* = 8.0 Hz, 1 H), 8.07 (s, 1 H, oxime C–H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 15.5, 41.5, 62.0, 103.1, 110.5, 115.0, 120.6, 125.0, 125.7, 126.5, 127.6, 127.6, 128.8, 129.8, 130.6, 131.0, 133.4, 137.4, 147.9 ppm. IR (KBr): $\tilde{\nu}$ = 1465, 1542, 1611, 2217, 2932 cm^{-1}. $C_{19}H_{17}N_3O$ (303.36): calcd. C 75.23, H 5.65, N 13.85; found C 75.07, H 5.53, N 13.93.

(*E*)-1-Isopropyl-3-{2-[(methoxyimino)methyl]phenyl}-1*H*-indole-5-carbonitrile (3j): Yield 61%; brown solid, m.p. 146–147 °C ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 1.58 (d, *J* = 6.8 Hz, 6 H), 3.95 (s, 3 H, OCH_3), 4.71–4.78 (m,1 H), 7.32 (s, 1 H, indole C2-H), 7.35–7.49 (m, 5 H), 7.86 (s, 1 H), 8.01 (d, *J* = 8.0 Hz, 1 H), 8.06 (s, 1 H, oxime C–H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 22.8, 47.9, 62.0, 103.1, 110.7, 115.1, 120.7, 124.8, 125.6, 125.7, 126.5, 127.6, 129.8, 130.7, 131.0, 133.6, 137.2, 148.0 (one signal not resolved) ppm. IR (KBr): $\tilde{\nu}$ = 1458, 1545, 1613, 2218, 2929, 2975 cm^{-1}. $C_{20}H_{19}N_3O$ (317.39): calcd. C 75.69, H 6.03, N 13.24; found C 75.61, H 6.17, N 13.35.

(*E*)-2-(1-Ethyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzaldehyde *O*-Methyl Oxime (6a): Yield 65%; yellow gum; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 1.54 (t, *J* = 7.2 Hz, 3 H), 3.95 (s, 3 H, OCH_3), 4.42 (q, *J* = 7.2 Hz,2 H), 7.10 (dd, *J* = 7.6, 4.4 Hz, 1 H), 7.23 (s, 1 H, indole C2-H), 7.36 (t, *J* = 7.2 Hz, 1 H), 7.44–7.46 (m, 2 H), 7.84 (d, *J* = 8.0 Hz, 1 H), 7.99 (d, *J* = 8.0 Hz, 1 H), 8.16 (s, 1 H, oxime C–H), 8.38 (d, *J* = 4.4 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 15.8, 39.5, 61.9, 112.2, 116.3, 120.1, 126.5, 126.8, 127.1, 128.0, 129.8, 130.3, 130.8, 134.4, 143.4, 147.2, 148.3 ppm. IR (neat): $\tilde{\nu}$ = 1429, 1537, 1595, 1609, 2935, 2974 cm^{-1}. MS (EI): *m*/*z* = 280.2 $[M + H]^+$, 248.1. $C_{17}H_{17}N_3O$ (279.34): calcd. C 73.10, H 6.13, N 15.04; found C 73.29, H 6.02, N 14.94.

(*E*)-2-(1-Isopropyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)benzaldehyde *O*-Methyl Oxime (6b): Yield 62%; yellow gum. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 1.58 (d, *J* = 6.8 Hz, 6 H), 3.94 (s, 3 H, OCH_3), 5.25–5.29 (m,1 H), 7.09 (dd, *J* = 7.6, 4.8 Hz, 1 H), 7.30 (s, 1 H, indole C2-H), 7.33–7.37 (m, 1 H), 7.42–7.47 (m, 2 H), 7.83 (dd, *J* = 8.0, 1.6 Hz, 1 H), 8.0 (d, *J* = 7.6 Hz, 1 H), 8.14 (s, 1 H, oxime C–H), 8.37 (dd, *J* = 4.4, 1.6 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 23.0, 45.6, 61.9, 112.4, 116.4, 120.2, 123.7, 126.4, 127.0, 128.0, 129.7, 130.4, 130.8, 134.6, 143.2, 147.0, 148.4 ppm. IR (neat): $\tilde{\nu}$ = 1428, 1537, 1594, 1609, 2933, 2975 cm^{-1}. $C_{18}H_{19}N_3O$ (293.37): calcd. C 73.69, H 6.53, N 14.32; found C 73.82, H 6.67, N 14.08.

General Procedure for the Synthesis of Indoloisoquinolines: A 3-arylated indole oxime (0.5 mmol), $Pd(OAc)_2$ (10 mol-%, 0.05 mmol), and $Cu(OTf)_2$ (20 mol-%, 0.1 mmol) were placed in an oven-dried reaction vessel. *o*-Xylene (5 mL) was subsequently added, and the mixture was then heated (110 °C) while open to the atmosphere. After the completion of the reaction (monitored by TLC), water (5 mL) was added, and the mixture was extracted with EtOAc (10 mL × 3). The organic layer was washed with water (10 mL) and brine (10 mL) and dried (Na_2SO_4). The solvent was evaporated under reduced pressure to furnish a crude mass, which was purified by column chromatography over silica gel (60–120 mesh) with pet. ether as eluent to afford an indoloisoquinoline product.

7-Ethyl-7*H*-indolo[2,3-*c*]isoquinoline (4a): Yield 74%; yellow solid, m.p. 70–71 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 1.52 (t, *J* = 7.2 Hz, 3 H), 4.71 (q, *J* = 7.2 Hz, 2 H), 7.41 (t, *J* = 7.6 Hz, 1 H), 7.49–7.56 (m, 2 H), 7.63 (d, *J* = 8.0 Hz, 1 H),7.84 (t, *J* = 8.0 Hz, 1 H), 8.12 (d, *J* = 8.0 Hz, 1 H), 8.50 (d, *J* = 8.0 Hz, 1 H), 8.63 (d, *J* = 8.4 Hz, 1 H), 9.14 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$):

δ_C = 14.6, 36.6, 106.2, 109.6, 120.1, 121.4, 122.5, 122.5, 123.4, 124.6, 124.8, 129.3, 130.9, 132.8, 137.5, 147.1, 150.2 ppm. IR (KBr): $\tilde{\nu}$ = 1566, 1623, 2854, 2926, 2968, 3039 cm^{-1}. HRMS (TOF, ES^+): calcd. for $C_{17}H_{14}N_2$ + H $[M + H]^+$ 247.124; found 247.1233.

7-Methyl-7*H*-indolo[2,3-*c*]isoquinoline (4b): Yield 70%; yellow solid, m.p. 96–97 °C. ^1H NMR (400 MHz, $CDCl_3$): δ_H = 4.14 (s, 3 H), 7.42 (t, *J* = 7.6 Hz, 1 H), 7.51–7.58 (m, 2 H), 7.62 (d, *J* = 8.0 Hz, 1 H), 7.84–7.88 (m, 1 H), 8.14 (d, *J* = 8.0 Hz, 1 H), 8.50 (d, *J* = 7.6 Hz, 1 H), 8.65 (d, *J* = 8.4 Hz, 1 H), 9.15 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 28.0, 106.2, 109.5, 120.2, 121.2, 122.3, 122.5, 123.4, 124.6, 124.9, 129.3, 130.9, 132.7, 138.6, 147.8, 150.2 ppm. IR (KBr): $\tilde{\nu}$ = 1566, 1622, 2854, 2924, 3045 cm^{-1}. MS (EI): *m*/*z* = 233.1 $[M + H]^+$, 234.1. $C_{16}H_{12}N_2$ (232.28): calcd. C 82.73, H 5.21, N 12.06; found C 82.84, H 5.05, N 12.15.

7-Isopropyl-7*H*-indolo[2,3-*c*]isoquinoline (4c): Yield 68%; yellow gum. ^1H NMR (400 MHz, $CDCl_3$): δ_H = 1.81 (d, *J* = 6.8 Hz, 6 H), 5.67–5.72 (m,1 H), 7.39 (t, *J* = 7.2 Hz, 1 H), 7.49–7.53 (m, 2 H), 7.77 (d, *J* = 8.0 Hz, 1 H), 7.82–7.86 (m, 1 H), 8.12 (d, *J* = 8.0 Hz, 1 H), 8.53 (d, *J* = 7.6 Hz, 1 H), 8.66 (d, *J* = 8.4 Hz, 1 H), 9.12 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 21.2, 45.7, 106.1, 111.4, 119.7, 121.8, 122.5, 122.5, 123.4, 124.4, 129.3, 130.8, 132.7, 136.9, 147.3, 149.7. (one signal not resolved) ppm. IR (neat): $\tilde{\nu}$ = 1566, 1624, 2929, 2971, 3052 cm^{-1}. HRMS (TOF, ES^+): calcd. for $C_{18}H_{16}N_2$+ H $[M + H]^+$ 261.139; found 261.1386.

2,3-Dimethoxy-7-methyl-7*H*-indolo[2,3-*c*]isoquinoline (4d): Yield 78%; pale yellow solid, m.p. 180–181 °C. ^1H NMR (400 MHz, $CDCl_3$): δ_H = 4.06 (s, 3 H, CH_3), 4.08 (s, 3 H, CH_3), 4.19 (s, 3 H, CH_3), 7.37–7.41 (m, 2 H), 7.52–7.59 (m, 2 H), 7.81 (s, 1 H), 8.34 (d, *J* = 7.6 Hz, 1 H), 8.93 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 27.9, 56.0, 56.1, 101.4, 106.1, 107.4, 109.4, 119.8, 120.0, 121.0, 121.8, 124.7, 129.3, 138.7, 147.4, 147.5, 153.6 (one signal not resolved) ppm. IR (KBr): $\tilde{\nu}$ = 1579, 1629, 2847, 2931, 3011 cm^{-1}. HRMS (TOF, ES^+): calcd. for $C_{18}H_{16}N_2O_2$ + H $[M + H]^+$ 293.129; found 293.1285.

7-Ethyl-2,3-dimethoxy-7*H*-indolo[2,3-*c*]isoquinoline (4e): Yield 72%; yellow solid, m.p. 154–155 °C. ^1H NMR (400 MHz, $CDCl_3$): δ_H = 1.52 (t, *J* = 7.2 Hz, 3 H), 4.06 (s, 3 H, CH_3), 4.20 (s, 3 H, CH_3), 4.68 (q, *J* = 7.2 Hz, 2 H), 7.37–7.40 (m, 2 H), 7.53 (t, *J* = 8.0 Hz,1 H),7.61 (d, *J* = 8.0 Hz, 1 H), 7.85 (s, 1 H), 8.37 (d, *J* = 8.0 Hz, 1 H), 8.94 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 14.5, 36.5, 56.0, 56.1, 101.4, 106.1, 107.4, 109.5, 119.6, 120.0, 121.2, 121.9, 124.6, 129.3, 137.6, 146.9, 147.4, 147.5, 153.6 ppm. IR (KBr): $\tilde{\nu}$ = 1583, 1603, 2852, 2919, 3052 cm^{-1}. $C_{19}H_{18}N_2O_2$ (306.36): calcd. C 74.49, H 5.92, N 9.14; found C 74.32, H 5.78, N 9.21.

7-Isopropyl-2,3-dimethoxy-7*H*-indolo[2,3-*c*]isoquinoline (4f): Yield 75%; pale yellow solid, m.p. 147–148 °C. ^1H NMR (400 MHz, $CDCl_3$): δ_H = 1.79 (d, *J* = 6.8 Hz, 6 H), 4.07 (s, 3 H, CH_3), 4.21 (s, 3 H, CH_3), 5.64–5.70 (m,1 H), 7.36–7.40 (m, 2 H), 7.50 (t, *J* = 7.6 Hz, 1 H), 7.76 (d, *J* = 8.0 Hz, 1 H), 7.89 (s, 1 H), 8.31 (d, *J* = 7.6 Hz, 1 H), 8.94 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 21.1, 45.5, 56.0, 56.1, 101.5, 106.0, 107.4, 111.3, 119.3, 119.9, 121.6, 122.0, 124.2, 129.2, 137.0, 147.2, 147.4, 153.6 (one signal not resolved) ppm. IR (KBr): $\tilde{\nu}$ = 1592, 1628, 2853, 2924 cm^{-1}. $C_{20}H_{20}N_2O_2$ (320.39): calcd. C 74.98, H 6.29, N 8.74; found C 75.13, H 6.47, N 8.57.

7-Ethyl-10-methoxy-7*H*-indolo[2,3-*c*]isoquinoline (4g): Yield 71%; yellow solid, m.p. 118–119 °C. ^1H NMR (400 MHz, $CDCl_3$): δ_H = 1.53 (t, *J* = 6.8 Hz, 3 H), 4.03 (s, 3 H, OCH_3), 4.70 (q, *J* = 6.8 Hz, 2 H), 7.21 (dd, *J* = 8.8, 2.4 Hz, 1 H), 7.50–7.59 (m, 2 H), 7.86 (t, *J* = 8.0 Hz, 1 H), 7.97 (s, 1 H), 8.13 (d, *J* = 8.4 Hz, 1 H), 8.58 (d, *J* = 8.4 Hz, 1 H), 9.12 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 14.7, 36.6, 56.3, 105.4, 106.0, 110.3, 114.0, 121.6, 122.2, 123.2, 124.4, 129.4, 130.9, 132.6, 132.8, 147.4, 150.2, 154.3 ppm. IR (KBr): $\tilde{\nu}$ = 1568, 1623, 2831, 2933, 2973 cm^{-1}. $C_{18}H_{16}N_2O$ (276.34): calcd. C 78.24, H 5.84, N 10.14; found C 78.12, H 5.70, N 10.21.

7-Isopropyl-10-methoxy-7*H*-indolo[2,3-*c*]isoquinoline (4h): Yield 73%; brown solid, m.p. 107–108 °C. ^1H NMR (400 MHz, $CDCl_3$): δ_H = 1.78 (d, *J* = 7.2 Hz, 6 H), 4.02 (s, 3 H, OCH_3), 5.66–5.68 (m, 1 H), 7.18 (dd, *J* = 9.2, 2.4 Hz, 1 H), 7.49–7.52 (m, 1 H), 7.68 (d, *J* = 8.8 Hz, 1 H), 7.83–7.87 (m, 1 H), 7.98 (d, *J* = 2.0 Hz, 1 H), 8.11 (d, *J* = 8.0 Hz, 1 H), 8.59 (d, *J* = 8.4 Hz, 1 H), 9.10 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 22.9, 47.7, 56.0, 101.4, 110.6, 110.8, 112.0, 112.3, 119.7, 124.8, 125.7, 126.7, 129.5, 131.3, 132.7, 134.1, 139.5, 154.9 ppm. IR (KBr): $\tilde{\nu}$ = 1571, 1625, 2832, 2935, 2974 cm^{-1}. $C_{19}H_{18}N_2O$ (290.36): calcd. C 78.59, H 6.25, N 9.65; found C 78.75, H 6.39, N 9.41.

7-Ethyl-7*H*-indolo[2,3-*c*]isoquinoline-10-carbonitrile (4i): Yield 62%; brown solid, m.p. 164–165 °C. ^1H NMR (400 MHz, $CDCl_3$): δ_H = 1.52 (t, *J* = 7.2 Hz, 3 H), 4.70 (q, *J* = 7.2 Hz, 2 H), 7.57–7.64 (m, 2 H), 7.75 (d, *J* = 8.4 Hz, 1 H), 7.90 (t, *J* = 7.6 Hz, 1 H), 8.14 (d, *J* = 8.0 Hz, 1 H), 8.51 (d, *J* = 8.4 Hz, 1 H), 8.73 (s, 1 H), 9.17 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 14.6, 37.0, 102.9, 105.9, 110.3, 120.6, 121.4, 122.2, 124.4, 125.0, 127.3, 127.7, 129.6, 131.8, 132.4, 139.1, 147.9, 151.8 ppm. IR (KBr): $\tilde{\nu}$ = 1561, 1624, 2217, 2853, 2924, 2955 cm^{-1}. $C_{18}H_{13}N_3$ (271.32): calcd. C 79.68, H 4.83, N 15.49; found C 79.84, H 4.72, N 15.64.

7-Isopropyl-7*H*-indolo[2,3-*c*]isoquinoline-10-carbonitrile (4j): Yield 65%; brown solid, m.p. 151–152 °C. ^1H NMR (400 MHz, $CDCl_3$): δ_H = 1.81 (d, *J* = 6.8 Hz, 6 H), 5.65–5.69 (m,1 H), 7.60 (t, *J* = 8.0 Hz, 1 H), 7.74 (d, *J* = 8.4 Hz, 1 H), 7.80 (d, *J* = 8.8 Hz, 1 H), 7.93 (t, *J* = 8.0 Hz, 1 H), 8.16 (d, *J* = 8.4 Hz, 1 H), 8.58 (d, *J* = 8.4 Hz, 1 H), 8.83 (s, 1 H), 9.19 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 21.1, 46.3, 102.5, 105.9, 111.8, 120.6, 121.8, 122.2, 124.4, 124.9, 127.2, 127.3, 129.5, 131.7, 132.4, 138.6, 148.1, 151.4 ppm. IR (KBr): $\tilde{\nu}$ = 1562, 1626, 2217, 2852, 2927, 2954 cm^{-1}. HRMS (TOF, ES^+): $[M + H]^+$ calcd. for $C_{17}H_{16}N_2O$ + H 286.135,; found 286.1337.

Compound 7a: Yield 75%; yellow solid, m.p. 55–56 °C. ^1H NMR (400 MHz, $CDCl_3$): δ_H = 1.55 (t, *J* = 6.8 Hz, 3 H), 4.78 (q, *J* = 6.8 Hz, 2 H), 7.27 (dd, *J* = 8.0, 4.8 Hz, 1 H), 7.49 (t, *J* = 7.6 Hz, 1 H), 7.79 (t, *J* = 7.6 Hz, 1 H), 8.06 (d, *J* = 8.0 Hz, 1 H), 8.39 (d, *J* = 8.4 Hz, 1 H), 8.57–8.59 (m, 2 H), 9.12 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 14.9, 35.7, 104.5, 114.6, 116.0, 122.2, 123.8, 124.8, 129.5, 129.8, 131.2, 132.7, 145.2, 146.8, 148.8, 151.0 ppm. IR (KBr): $\tilde{\nu}$ = 1564, 1600, 1624, 2850, 2923, 2967, 3038 cm^{-1}. HRMS (TOF, ES^+): calcd. for $C_{16}H_{13}N_3$ + H $[M + H]^+$ 248.119; found 248.1182.

Compound 7b: Yield 72%; brown solid, m.p. 62–63 °C. ^1H NMR (400 MHz, $CDCl_3$): δ_H = 1.88 (d, *J* = 6.8 Hz, 6 H), 5.78–5.81 (m,1 H), 7.32 (dd, *J* = 8.0, 4.8 Hz, 1 H), 7.54 (t, *J* = 8.0 Hz, 1 H), 7.83–7.87 (m, 1 H), 8.14 (d, *J* = 8.0 Hz, 1 H), 8.53 (d, *J* = 8.4 Hz, 1 H), 8.58–8.60 (m, 1 H), 8.69–8.71 (m, 1 H), 9.18 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 21.0, 45.6, 104.6, 114.7, 115.8, 122.3, 123.8, 124.6, 129.5, 129.8, 131.1, 132.8, 144.9, 147.2, 149.0, 150.6 ppm. IR (KBr): $\tilde{\nu}$ = 1564, 1600, 1624, 2872, 2926, 2968, 3038 cm^{-1}. $C_{17}H_{15}N_3$ (261.33): calcd. C 78.13, H 5.79, N 16.08; found C 78.24, H 5.66, N 16.31.

2-(1-Ethyl-1*H*-indol-3-yl)benzonitrile (5a): Yield 30%; reddish white solid, m.p. 75–76 °C. ^1H NMR (400 MHz, $CDCl_3$): δ_H = 1.52 (t, *J* = 7.2 Hz, 3 H), 4.25 (q, *J* = 7.2 Hz, 2 H), 7.18–7.23 (m, 1 H), 7.27–7.33 (m, 2 H), 7.42 (d, *J* = 8.0 Hz, 1 H), 7.61 (d, *J* = 8.4 Hz, 1 H),

7.64 (s, 1 H), 7.74 (d, J = 8.0 Hz, 1 H), 7.76–7.79 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 15.5, 41.3, 109.9, 110.6, 112.4, 119.5, 119.7, 120.5, 122.3, 125.9, 126.5, 127.4, 129.8, 132.7, 134.1, 136.2, 139.2 ppm. IR (KBr): $\tilde{\nu}$ = 1598, 1609, 2217, 2854, 2924, 2984, 3078, 3111 cm^{-1}. $C_{17}H_{14}N_2$ (246.31): calcd. C 82.90, H 5.73, N 11.37; found C 83.01, H 5.84, N 11.18.

Supporting Information (see footnote on the first page of this article): Experimental details, spectroscopic data, copies of the ^{1}H NMR and ^{13}C NMR spectra of all final products.

Acknowledgments

The authors thank the Department of Science and Technology (DST), New Delhi for financial assistance through the DST PURSE program and DST fast track scheme. S. H. and B. M. are thankful to the Council of Scientific and Industrial Research (CSIR), New Delhi and the University of Kalyani, respectively, for research fellowships. DST is also thanked for providing FT-IR and NMR spectrometers and a CHN analyzer.

[1] Sumitomo Chemical Co., Ltd., Japan, *Jpn. Kokai Tokkyo Koho. Patent*, **1983**, 7 p. (CODEN: JKXXAF, JP 58069882, A).

[2] a) K. Ishizumi, J. Katsube, *U.S. Patent*, **1981**, 6 p. (CODEN: USXXAM, US 4263304, A); b) K. Ishizumi, J. Katsube, *Brit. UK Pat. Appl.* **1980**, 6 p. (CODEN: BAXXDU, GB 2025932, A); c) K. Ishizumi, J. Katsube, *Ger. Offen.* **1979**, 15 p. (CODEN: GWXXBX, DE 2826269, A1).

[3] a) K. Ishizumi, J. Katsube, *Jpn. Kokai Tokkyo Koho.* **1979**, 5 p. (CODEN: JKXXAF, JP 54092999, A); b) G. Winters, N. Di Mola, M. Berti, V. Arioli, *Farmaco, Edizione Scientifica* **1979**, *6*, 507; c) G. Winters, N. Di Mola, *U. S. Patent*, **1978**, 7 p. (CODEN: USXXAM, US 4113731, A).

[4] a) C. S. Kim, S. Y. Lee, Y. G. Kim, H.-J. Lee, S. H. Lee, H. Kim, Y. J. Cho, H. J. Kwon, K. J. Lee, B.-O. Kim, S.-M. Kim, *PCT Int. Appl.* **2012**, 61 p. (CODEN: PIXXD2, WO 2012015274, A2); b) J. H. Park, D. S. Kim, G. W. Kim, Y. U. Park, H. S. Jung, J. H. Byun, J. G. Park, D. H. Choi, D. H. Kim, *Repub. Korean Kongkae Taeho Kongbo* **2011**, 32 (CODEN: KRXXA7, KR 2011105272, A).

[5] For recent reviews and selected examples, see: a) L. Ackermann, A. Althammer, *Angew. Chem. Int. Ed.* **2007**, *46*, 1627; *Angew. Chem.* **2007**, *119*, 1652; b) L. Ackermann, A. Althammer, R. Born, *Angew. Chem. Int. Ed.* **2006**, *45*, 2619; *Angew. Chem.* **2006**, *118*, 2681; c) H.-Q. Do, O. Daugulis, *J. Am. Chem. Soc.* **2008**, *130*, 1128; d) Y. Matsuura, M. Tamura, T. Kochi, M. Sato, N. Chatani, F. Kakiuchi, *J. Am. Chem. Soc.* **2007**, *129*, 9858; e) J. M. Murphy, J. D. Lawrence, K. Kawamura, C. Incarvito, J. F. Hartwig, *J. Am. Chem. Soc.* **2006**, *128*, 13684; f) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174; g) K. Godula, D. Sames, *Science* **2006**, *312*, 67; h) F. Kakiuchi, N. Chatani, *Adv. Synth. Catal.* **2003**, *345*, 1077; i) V. Ritleng, C. Sirlin, M. Pfeffer, *Chem. Rev.* **2002**, *102*, 1731; j) T. Watanabe, S. Ueda, S. Inuki, S. Oishi, N. Fujii, H. Ohno, *Chem. Commun.* **2007**, 4516; k) J. Barluenga, M. Trincado, E. Rubio, J. M. Gonzalez, *Angew. Chem. Int. Ed.* **2006**, *45*, 3140; *Angew. Chem.* **2006**, *118*, 3212; l) K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc.* **2007**, *129*, 11904; m) X. Chen, X.-S. Hao, C. E. Goodhue, J.-Q. Yu, *J. Am. Chem. Soc.* **2006**, *128*, 6790; n) K. Inamoto, T. Saito, M. Katsuno, T. Sakamoto, K. Hiroya, *Org. Lett.* **2007**, *9*, 2931.

[6] J. Zhao, Y. Wang, Y. He, L. Liu, Q. Zhu, *Org. Lett.* **2012**, *14*, 1078.

[7] S. Ueda, H. Nagasawa, *Angew. Chem. Int. Ed.* **2008**, *47*, 6411; *Angew. Chem.* **2008**, *120*, 6511.

[8] a) G. Brasche, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2008**, *47*, 1932; *Angew. Chem.* **2008**, *120*, 1958; b) C. T. Brain, J. T. Steer, *J. Org. Chem.* **2003**, *68*, 6814; c) C. T. Brain, S. A. Brunton, *Tetrahedron Lett.* **2002**, *43*, 1893.

[9] a) R. D. Viirre, G. Evindar, R. A. Batey, *J. Org. Chem.* **2008**, *73*, 3452; b) G. Evindar, R. A. Batey, *J. Org. Chem.* **2006**, *71*, 1802; c) N. Barbero, M. Carril, R. San Martin, E. Dominguez, *Tetrahedron* **2007**, *63*, 10425; d) S. Ueda, H. Nagasawa, *J. Org. Chem.* **2009**, *74*, 4272.

[10] R. Berrino, S. Cacchi, G. Fabrizi, A. Goggiamani, *J. Org. Chem.* **2012**, *77*, 2537.

[11] S. H. Cho, J. Yoon, S. Chang, *J. Am. Chem. Soc.* **2011**, *133*, 5996.

[12] R. Rohini, P. M. Reddy, K. Shanker, A. Hu, V. Ravinder, *Eur. J. Med. Chem.* **2010**, *45*, 1200.

[13] P. Sang, Y. Xie, J. Zou, Y. Zhang, *Org. Lett.* **2012**, *14*, 3894.

[14] a) R. Alonso, P. J. Campos, B. Garcia, M. A. Rodriguez, *Org. Lett.* **2006**, *8*, 3521; b) R. Alonso, P. J. Campos, B. Garcia, M. A. Rodriguez, *Tetrahedron* **2010**, *66*, 8828; c) F. Portela-Cubillo, E. M. Scanlan, J. S. Scott, J. C. Walton, *Chem. Commun.* **2008**, 4189; d) F. Portela-Cubillo, E. M. Scanlan, J. S. Scott, J. C. Walton, *Tetrahedron* **2008**, *64*, 11908; e) R. T. McBurney, A. M. Z. Slawin, L. A. Smart, Y. P. Yu, J. C. Walton, *Chem. Commun.* **2011**, *47*, 7974; f) I. Deb, N. Yoshikai, *Org. Lett.* **2013**, *15*, 4254.

[15] S. Cacchi, G. Fabrizi, *Chem. Rev.* **2011**, *111*, PR215.

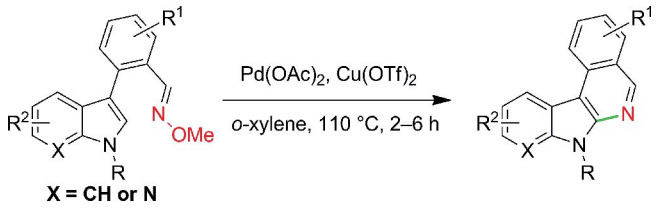
[16] a) S. Chiba, L. Zhang, G. Y. Ang, B. W. Hui, *Org. Lett.* **2010**, *12*, 2052; b) L. Zhang, G. Y. Ang, S. Chiba, *Org. Lett.* **2010**, *12*, 3682; c) P. C. Too, S. H. Chua, S. H. Wong, S. Chiba, *J. Org. Chem.* **2011**, *76*, 6159–6168.

[17] For a discussion of mechanisms involving Cu^{III} intermediates, see: S. V. Ley, A. W. Thomas, *Angew. Chem. Int. Ed.* **2003**, *42*, 5400; *Angew. Chem.* **2003**, *115*, 5558.

[18] For a discussion of mechanisms, see: a) A. E. Wendlandt, A. M. Suess, S. S. Stahl, *Angew. Chem. Int. Ed.* **2011**, *50*, 11062; *Angew. Chem.* **2011**, *123*, 11256.

Received: November 12, 2013
Published Online: ■

C–H Functionalization/Cyclization



X = CH or N

A new approach to the synthesis of indoloisoquinoline derivatives is described. The activation of the indole C2–H bond is accomplished here by using a $Pd(OAc)_2$ and $Cu(OTf)_2$ bi-catalytic system. In this reaction aldoximes are converted into the corresponding isoquinolines in open atmosphere under mild reaction condition.

Keywords: Homogeneous catalysis / C–H activation / C–N bond formation / Nitrogen heterocycles / Copper / Palladium

