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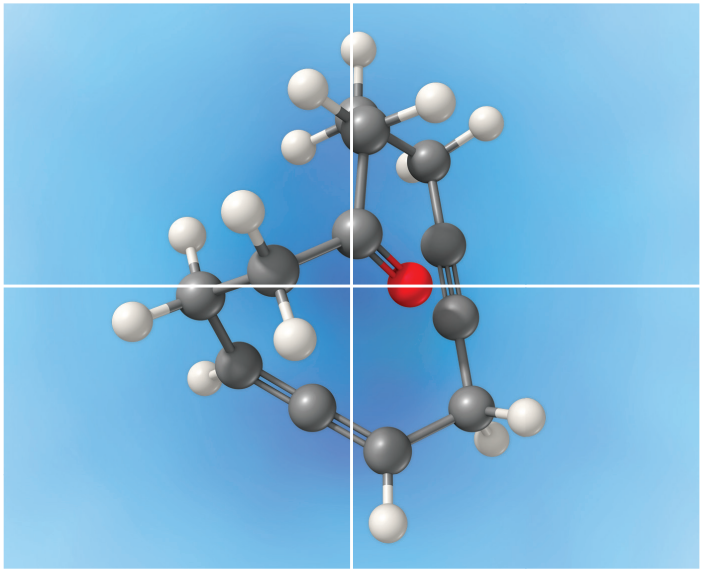

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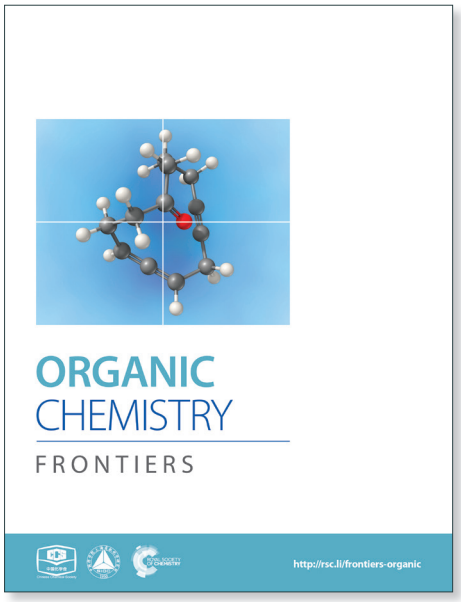

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ARTICLE

Polycyclic imidazo[1,2-*a*]pyridine analogs – synthesis *via* oxidative, intramolecular C-H amination and optical properties

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A novel and straightforward approach towards 5*H*-pyrido[2',1':2,3]imidazo[4,5-*b*]indoles has been developed. The key step is C-H amination of easily available 2-(2'-aminophenyl)imidazo[1,2-*a*]pyridines by the use of copper(II) triflate, trifluoroacetic acid and (diacetoxyiodo)benzene. The whole strategy consists of just four steps starting from 2-aminopyridines and acetophenones, giving target compounds in overall yield 20-35%. The optical properties of the library of π-expanded imidazo[1,2-*a*]pyridines were for the first time fully characterized, showing that these ladder-type compounds strongly absorb UV radiation and exhibit fluorescence in the 415–461 nm region.

Introduction

Imidazo[1,2-*a*]pyridines are a group of very important heterocycles possessing strong and diverse biological activity. Their structural motif can be found in several marketed drugs, such as anxiolytic alpidem,[1] necopidem and saripidem and in drugs used for the treatment of insomnia and brain disorders (zolpidem).[2] Their antiviral,[3-5] antiparasitic,[6] antibacterial,[7] anti-inflammatory,[8] analgesic and antipyretic[9,10] properties are also well documented, as well as the ability to inhibit β-amyloid formation.[11] Not surprisingly, methodology of their synthesis has attracted significant attention in the last decade.[12-21] Besides the pharmacological importance, imidazo[1,2-*a*]pyridines exhibit interesting optical properties. In particular they typically possess high fluorescence quantum yields.[22-28]

In the advent of interest in ladder-type aromatic heterocycles,[29,30] we reasoned that π-expanded imidazo[1,2-*a*]pyridines being analogues of recently explored systems such as indolo[3,2-*b*]indoles,[31,32] can offer new opportunities once the efficient synthetic methodology is developed. Indolo[3,2-*b*]indoles (**1**), benzofuroindoles (**2**) and benzothioindoles (**3**) were recently reported as highly active sex steroid hormone receptor modulators[33] and anticancer agents (Fig 1).[34] Indolo[3,2-*b*]indoles and their analogues were also investigated in optoelectronics.[35,36] Only three inefficient synthetic methodologies leading to our targeted 5*H*-pyrido[2',1':2,3]imidazo[4,5-*b*]indoles were reported: Cadogan cyclization,[37-39] multicomponent Bienaymé reaction followed by *N*-arylation[40,41] and ionic liquid promoted cyclization of *N*-methylisatin and 2-aminopyridine.[42] The synthesis of the library of pyridoimidazoindoles and the analysis of the relationship between their structure and spectroscopic properties might open a door for their future optoelectronic applications. In this paper we propose novel strategy towards this class of nitrogen containing heterocycles, with key step involving oxidative C-H bond amination.

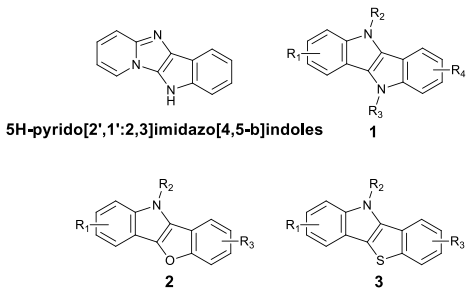


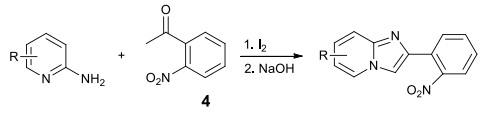
Fig. 1 Comparison of chemical structures of 5*H*-pyrido[2',1':2,3]imidazo[4,5-*b*]indoles, indoloindoles (**1**), benzofuroindoles (**2**) and benzothioindoles (**3**).

Results and discussion

An analysis of possible synthetic routes towards 5*H*-pyrido[2',1':2,3]imidazo[4,5-*b*]indoles led us to conclusion, that oxidative C-H amination of easily available 2-(2'-aminophenyl) substituted imidazo[1,2-*a*]pyridines should be the straightforward strategy towards these compounds. This atom-economical process attracted significant attention in recent years, because it avoids arene preactivation in the synthesis of industrially important heterocycles e.g. carbazoles. The proposed mechanisms for oxidative C-H amination requires the attacked carbon atom to possess certain electron density. For this reason our strategy should benefit from the fact that the most electron-rich position in imidazo[1,2-*a*]pyridines is C-3, which remains unsubstituted if classical Chichibabin method is employed. Thus, we synthesized a series of 2-(2'-nitrophenyl)imidazo[1,2-*a*]pyridines, using one-pot, tandem Ortoleva-King-Chichibabin process[25] (Table 1). Both 2-

aminopyridines and their expanded analogs gave expected imidazopyridines **9**-**12** in good yield (24-69%).

Table 1 Synthesis of 2-(2-nitrophenyl)imidazo[1,2-*a*]pyridines.[a]



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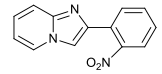
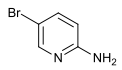
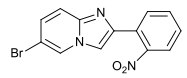
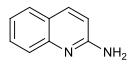
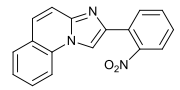
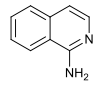
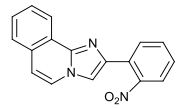
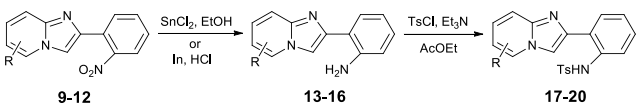
Entry	Amine	Product	Yield (%)
1	 5	 9	69
2	 6	 10	64
3	 7	 11	24
4	 8	 12	49

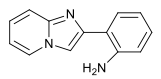
[a] Reaction conditions: 1) amine (20 mmol), 2-nitroacetophenone (10 mmol), I_2 (10 mmol), 110°C, 12h, 2) NaOH aq.

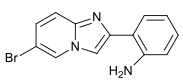
Previously reported reduction of nitroarenes using H_2 and Pd on charcoal did not work in our hands (we observed hydrogenation of pyridine ring).[43] The reaction with iron powder in concentrated hydrochloric acid solution failed too, however the procedure developed by Kundu and co-workers, involving tin(II) chloride, gave the desired 2-(2'-aminophenyl) substituted imidazo[1,2-*a*]pyridines **13**-**16** in good yields.[44] Even better results could be obtained using indium powder in hydrochloric acid which seems to be the best, however a bit expensive reductant (Table 2).

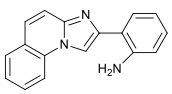
Table 2 Synthesis of *N*-tosyl-2-(2'-aminophenyl)imidazo[1,2-*a*]pyridines.

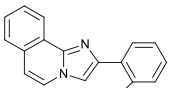


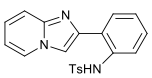
9-12 **13-16** **17-20**

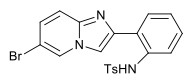

13 (69%)[a]

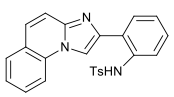

14 (49%),[a] (85%)[b]

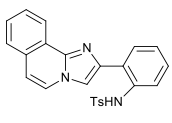

15 (61%)[a]


16 (48%)[a] (88%)[b]


17 (80%)[c]


18 (32%)[c]


19 (88%)[c]


20 (47%)[c]

Reaction conditions: [a] nitroimidazopyridine (10 mmol), $SnCl_2$ (40 mmol), EtOH, 100°C, 1.5h. [b] nitroimidazopyridine (1 mmol), indium powder (4 mmol), THF, 3h, rt. [c] amine (1 mmol), TsCl (2 mmol), Et_3N (2 mmol), AcOEt, 50°C, 16h.

Having 2-(2'-aminophenyl)imidazo[1,2-*a*]pyridine (**13**) as a key substrate, we started to search for suitable conditions for oxidative C-H amination. Literature data revealed that *N*-substituted 2-aryl-1-aminobenzenes possessing various electron-withdrawing group on nitrogen atom, have been transformed into corresponding carbazoles.[45-48] In the preliminary phase of our studies it was found that amination reactions of acetyl- and trifluomethanesulfonyl-protected amine **13** were sluggish regardless the conditions, occasionally giving the expected product in very low yields. Given that subsequently we discovered that tosyl protecting group is the most effective in the C-H bond amination we transformed all amines into tosylamides **17**-**20**.

We decided to test four procedures published for carbazoles[45-48] in oxidative coupling of amide **17** as a model compound. Buchwald's methodology using palladium(II) acetate as catalyst and copper(II) acetate/oxygen as reoxidant did not lead to expected product (Table 3, Entry 1).[45] Thus, we adopted Youn procedure which require Oxone or (diacetoxyiodo)benzene (PIDA) as a reoxidant of palladium(II) acetate (Entry 2-5).[46] The latter reoxidant allowed us to isolate desired tetracyclic compound **21**, however, the yield was still not satisfactory (Entry 4). Finally, we decided to apply Chang's method, which uses copper(II) triflate in combination with PIDA in ethylene chloride.[47] This allowed us to isolate **21** in excellent yield and purity (Entry 7). There are some reports on an analogous transformation that could be achieved without use of any metal catalyst source (intramolecular organocatalytic C-H bond amination). Antonchick and co-workers found that *N*-substituted carbazoles can be obtained by treatment of *N*-protected diphenylamines with PIDA.[48] They also observed the positive effect of fluorinated co-solvent. As this approach offers number of advantages over a transition-metal-catalyzed aminations, we tried to apply these conditions for oxidation of tosylamide **17** which afforded fused compound **21** in fairly good yield (62%, Entry 6). Finally, it was found that second procedure published by Chang and co-workers[47] i.e. (bis-(trifluoroacetoxy)iodo)benzene (PIFA) in presence of trifluoroacetic acid (TFA), could also be applied, albeit the yield of compound **21** was slightly lower (77%, Entry 8).

Table 3 Optimization of oxidative C-H amination of *N*-tosyl-2-(2-aminophenyl) imidazo[1,2-*a*]pyridines.

17 **21**

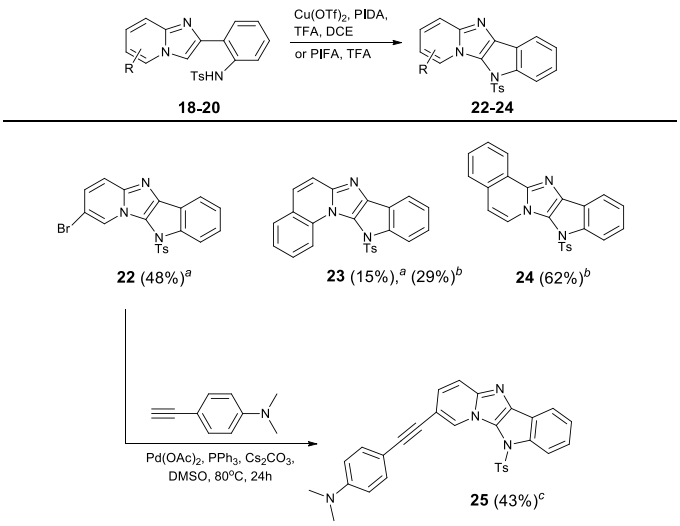
Ent.	Catalyst	Reoxidant	Additives	Solvent	Time (h)	Yield (%)[a]
1	$Pd(OAc)_2$	$Cu(OAc)_2/O_2$	mol. sieves	toluene	12[b]	0
2	$Pd(OAc)_2$	Oxone		PivOH/ DMF	12[c]	0
3	$Pd(OAc)_2$	Oxone	TsOH	PivOH/ DMF	12[c]	0
4	$Pd(OAc)_2$	PIDA		AcOH/ DMF	12[c]	40
5	$Pd(OAc)_2$	PIDA	TsOH	AcOH/ DMF	12[c]	32
6		PIDA		HFIP/ DCM	16[c]	62
7	**$Cu(OTf)_2$**	**PIDA**	**TFA**	**DCE**	**0.5[d]**	**93**
8	-	PIFA	TFA	DCE	0.5[d]	77

[a] isolated yields. [b] 120°C. [c] room temperature. [d] 50°C.

Following well-supported Chang's proposition[47] we think that the copper species works as a Lewis acid to activate PIFA, which is the main oxidant inducing the formation of radical

intermediates. Having optimized the C-H bond amination, we tried to transform the other sulfonamides. Although bromoderivative **22** smoothly undergoes this reaction, in the case of benzo-fused analogues **19** and **20** we observed the formation of many by-products (Table 4). Therefore we changed the catalytic system to copper-free PIFA/TFA mixture which gave much cleaner conversion and higher yields of compounds **23** and **24**. The presence of bromine atom in compound **22** gives an opportunity for further extension of π-system using palladium catalyzed Sonogashira coupling. This reaction proceeded smoothly, resulting in the formation of compound **25**.

Table 4 Synthesis of 5*H*-pyrido[2',1':2,3]imidazo[4,5-*b*]indoles.



Reaction conditions: [a] tosylamide (0.2 mmol), PIDA (0.3 mmol), $Cu(OTf)_2$ (0.01 mmol), TFA (0.6 mmol), DCE, 50°C, 0.5h. [b] tosylamide (0.2 mmol), PIFA (0.3 mmol), TFA (0.6 mmol), DCE, 50°C, 0.5h. [c] **22** (0.27 mmol), 4-ethynyl-*N*,*N*-dimetylaniline (0.69 mmol), Cs_2CO_3 (0.76 mmol), $Pd(OAc)_2$ (0.035 mmol), PPh_3 (0.14 mmol), DMSO, 80°C, 24h.

The successful synthesis of small library of 5*H*-pyrido[2',1':2,3]imidazo[4,5-*b*]indoles and their π-expanded analogs gave us an excellent opportunity for measuring their photophysical properties for the first time. In the case of ladder-type fused heterocycles it is well-known that extending the π-system alters some of the photophysical properties but usually does not lead to bathochromic shift of absorption.[29,30] The spectroscopic data collected for compounds **21**-**25** is presented in Table 5. The electronic spectra of indole-fused imidazopyridines typically consists of two strong bands in 254-355 region, whereas single band was observed in their fluorescence spectra (Fig. 2). Comparison of properties of compound **21** and **22** with unsubstituted imidazo[1,2-*a*]pyridine **IP** leads to conclusion, that fusion with indole scaffold result in 10-30 nm and 58-68 nm bathochromic shift of absorption and emission maxima, respectively. Due to the angular type of fusion of an additional benzene ring in derivatives **23** and **24**, their optical properties strongly resemble that of compound **21**. On the other hand, *N*,*N*-dimethylphenylethynyl substituted imidazopyridine **25** exhibit well pronounced red-shifted absorption and emission maxima, at 355 and 461 nm, respectively. As expected, this compound display the most intense absorption bands (with ε reaching 130000 $M^{-1}\cdot cm^{-1}$), as a result of high π-conjugation and strong dipolar character. The largest Stokes shift was observed for compound **21**, which was almost twice higher than calculated for unsubstituted imidazopyridine. In contrast to imidazo[1,2-*a*]pyridines compounds **21**-**25** display very weak fluorescence. Interestingly, the highest fluorescence quantum yield was measured for compound **21**. Substitution with heavy atom (bromo-derivative **22**), according to expectations, led to further decrease in fluorescence intensity. Extension of π-system probably opens the non-radiative deactivation pathways, which resulted in lower fluorescence quantum yield observed for compounds **21**-**25**.

Table 5 Spectroscopic properties of 5*H*-pyrido[2',1':2,3]imidazo[4,5-*b*]indoles.[a]

Compd.	Abs_{max} (nm)	ε ($\times 10^{-3}$ $M^{-1}\cdot cm^{-1}$)	$Emission_{max}$ (nm)	Stokes shift (cm^{-1})	Φ_{fl}[c]
IP[b]	318		376	4800	
21	254	31.1	444	8000	0.034[d]
	303	9.28			
	328	9.51			
22	265	78.9	434	5700	0.025[d]
	348	9.76			
23	260	27.2	432	6100	0.006[e]
	342	15.8			
24	275	39.7	415	7000	0.008[e]
	322	15.1			
25	274	134	461	6500	0.009[d]
	355	33.2			

[a] measured in DCM. [b] **IP** = unsubstituted imidazo[1,2-*a*]pyridine (data taken from ref. 49). [c] measured with quinine sulphate as a standard. [d] excited at 360 nm. [e] excited at 310 nm.

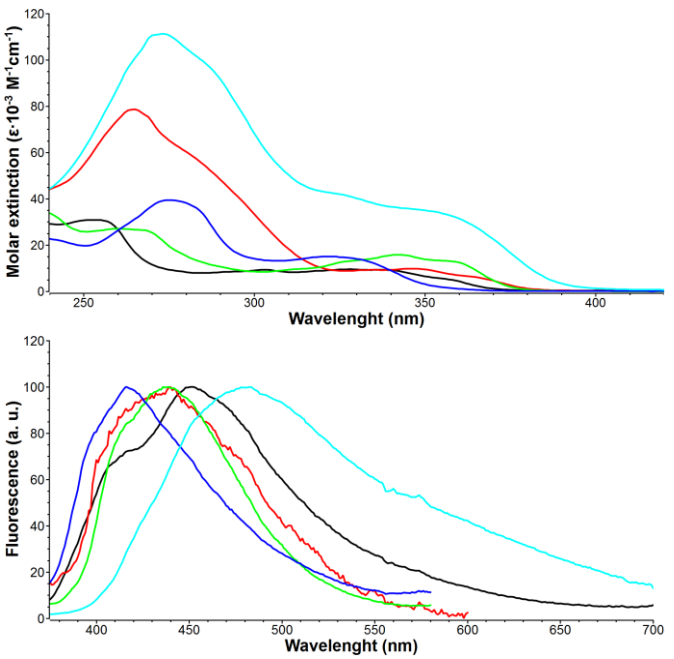


Fig. 2 Absorption (top) and normalized fluorescence (bottom) spectra of **21** (black), **22**(red), **23** (green), **24** (blue) and **25** (cyan) measured in DCM.

Conclusions

It has been was proven that intramolecular oxidative C-H amination can also occur with heterocycles bearing basic nitrogen atom. New, straightforward, four-step synthesis of 5*H*-pyrido[2',1':2,3]imidazo[4,5-*b*]indoles was developed. Two sets of reaction conditions were found for the key step i.e. intramolecular C-H bond amination: $Cu(OTf)_2$/PIDA/TFA and organocatalytic PIFA/TFA combination. In contrast to many analogous structures, the fluorescence quantum yields of

prepared blue-emitting π-expanded imidazo[1,2-*a*]pyridine analogs turned out to be low.

Experimental section

General information.

All reported NMR spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Varian 500 spectrometer. Chemical shifts (δ ppm) were determined with TMS as the internal reference, *J* values are given in Hz. High resolution mass spectra (HRMS) were obtained via electron ions (EI). IR spectra were recorded on JASCO FT/IR-6200 Spectrometer. UV-Vis absorption spectra were recorded on PerkinElmer Lambda 25 Spectrometer. Fluorescence spectra were recorded on Fluorescence Spectrophotometer F-7000 HITACHI. Chromatography was performed on silica gel 60 (230-400 mesh) and thin layer chromatography was performed on TLC plates (Merck, silica gel 60 F_{254}). Compound **13** was prepared according to previously reported procedure.[44]

General procedure for the synthesis of 2-(2-nitrophenyl)imidazo[1,2-*a*]pyridines.

A mixture of 1-(2'-nitrophenyl)ethanone (10 mmol), 2-aminopyridine (20 mmol) and iodine (10 mmol) was heated at 110°C. After 4h the temperature of the oil bath was reduced to 70°C and stirring was continued for additional 12h. The resulting waxy solid was dissolved in distilled water and an excess of conc. aqueous sodium hydroxide (45%) was added. Then reaction mixture was stirred at 100°C for 1h, cooled and diluted with CH_2Cl_2. pH of the resulting mixture was adjusted to neutral using aqueous HCl (10%) and layers were separated. Aqueous layer was extracted with CH_2Cl_2, the combined organic layers were washed with water and brine, dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatography (silica, CH_2Cl_2/AcOEt 95:5, gradually increasing the amount of AcOEt), followed by crystallization from AcOEt-hexanes afforded product of analytical purity.

2-(2'-Nitrophenyl)*H*-imidazo[1,2-*a*]pyridine (9). Yellow solid, 2.02g, 69% yield. The spectroscopic properties were in good agreement with published data.[44]

6-Bromo-2-(2'-nitrophenyl)*H*-imidazo[1,2-*a*]pyridine (10). Yellow solid, 1.865g, 64% yield. M.p. 151°C. ^{1}H NMR (DMSO, 500 MHz): δ 8.99-8.87 (m, 1H), 8.30 (s, 1H), 7.96 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.90 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.77 (td, *J* = 7.7, 1.2 Hz, 1H), 7.60 - 7.65 (m, 2H), 7.44 (dd, *J* = 9.5, 1.9 Hz, 1H). ^{13}C NMR (DMSO, 125 MHz): δ 106.4, 111.4, 117.9, 123.7, 126.3, 127.2, 128.5, 129.2, 130.6, 132.1, 140.5, 143.0, 148.8. IR (KBr, cm^{-1}): 729, 811, 1059, 1342, 1366, 1511, 3026, 3166. HRMS (EI): m/z calculated for $C_{13}H_8BrN_3O_2$ [M^{+}] = 316.9800; found: 316. 9809. Elemental analysis (%): calculated for $C_{13}H_8BrN_3O_2$: C, 49.08; H, 2.53; N, 13.21; found: C, 48.97; H, 2.35; N, 13.16.

2-(2'-Nitrophenyl)*H*-imidazo[1,2-*a*]quinoline (11). Yellow solid, 0,761g, 24% yield. M.p. 190°C. ^{1}H NMR (DMSO, 500 MHz): δ 9.08 (s, 1H), 8.39 (d, *J* = 8.4 Hz, 1H), 8.01 (d, *J* = 7.9 Hz, 1H), 7.96 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.88 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.74-7.80 (m, 3H), 7.55-7.62 (m, 3H). ^{13}C NMR (DMSO, 125 MHz): δ 111.4, 116.4, 117.0, 123.3, 124.3, 125.8, 127.4, 127.4, 129.3, 129.7, 129.8, 130.9, 132.5, 132.6, 140.0, 143.6, 149.1. IR (KBr, cm^{-1}): 741, 760, 810, 1355, 1523, 1611, 3154. HRMS (EI): m/z calculated for $C_{17}H_{11}N_3O_2$ [M^{+}] = 289.0851; found: 289. 0851. Elemental analysis (%):calculated for $C_{17}H_{11}N_3O_2$: C, 70.58; H, 3.83; N, 14.53; found: C, 70.50; H, 3.96; N, 14.40.

2-(2'-Nitrophenyl)*H*-imidazo[2,1-*a*]isoquinoline (12). Yellow solid, 1.30g, 49% yield. M.p. 138-140°C. ^{1}H NMR (DMSO, 500 MHz): δ 8.40 (d, *J* = 7.3 Hz, 2H), 8.30 (s, 1H), 8.01 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.86-7.91 (m, 2H), 7.75 (td, *J* = 7.6, 1.1 Hz, 1H), 7.59 (td, *J* = 7.6, 1.3 Hz, 1H), 7.64-7.71 (m, 2H), 7.31 (d, *J* = 7.3 Hz, 1H). ^{13}C NMR (DMSO, 125 MHz): δ 113.5, 113.7, 123.0, 123.2, 124.0, 124.7, 127.2, 127.8, 128.7 129.1, 129.1, 129.8, 130.7, 132.5, 138.3, 142.5, 149.2. IR (KBr, cm^{-1}): 698, 733, 792, 1360, 1508, 1606, 3169. HRMS (EI): m/z calculated for $C_{17}H_{11}N_3O_2$ [M^{+}] = 289.0851; found: 289.0853.

General procedure for the reduction of nitro-imidazo[1,2-*a*]pyridines.

Method A: A solution of nitroimidazopyridine (10 mmol) and $SnCl_2$ (40 mmol) in ethanol was stirred at 100°C for 1,5h under argon. Then the reaction mixture was cooled to rt and 5% aqueous $NaHCO_3$ was added until pH was made slightly basic (pH 8). The resulting slurry was then filtered through a pad of Celite, washed with small amount of ethanol and concentrated. Aqueous solution was extracted with AcOEt and the combined organic layers were washed with water and brine, dried over Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography (silica, CH_2Cl_2/AcOEt 3:1) and crystallization from AcOEt-hexanes gave expected product of analytical purity.

Method B: To a solution of nitroimidazopyridine (0.56 mmol) in aq THF (3 mL) indium powder (260 mg, 2.26 mmol) was added, followed by concentrated HCl (300μL). After stirring for 3h at r.t., 5% aqueous $NaHCO_3$ was added until pH was neutral. After evaporation the crude product was used in next step without any further purification.

2-(6-Bromo-*H*-imidazo[1,2-*a*]pyridine-2-yl)benzenamine (14). Yellow-cream solid, 0.823g, 49% yield. M.p. 158-159°C. ^{1}H NMR (DMSO, 500 MHz): δ 8.89-8.87 (m, 1H), 8.26 (s, 1H), 7.59 (d, *J* = 9.5 Hz, 1H), 7.55 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.37 (dd, *J* = 9.4, 2.0 Hz, 1H), 7.03 (td, *J* = 6.9, 1.4 Hz, 1H), 6.75 (dd, *J* = 8.3, 0.9 Hz, 1H), 6.59 (td, *J* = 6.8, 1.2 Hz, 1H), 6.54 (s, 2H). ^{13}C NMR (DMSO, 125 MHz): δ 106.0, 109.2, 114.6, 115.6, 116.1, 117.1, 126.2, 127.2, 127.7, 128.7, 142.1, 146.5, 146.7. IR (KBr, cm^{-1}): 745, 789, 1056, 1232, 1610, 3384. HRMS (EI): m/z calculated for $C_{13}H_{10}BrN_3$ [M^{+}] = 287.0058; found: 287.0054. Elemental analysis (%): calculated for $C_{13}H_{10}BrN_3$: C, 54.19; H, 3.50; N, 14.58; found: C 54.42; H 3.63; N 14.79.

2-(*H*-Imidazo[2,1-*a*]quinolin-2-yl)benzenamine (15). Yellow-cream solid, 0.408, 61% yield. M.p. 168-169°C. ^{1}H NMR (DMSO, 500 MHz): δ 9.06 (s, 1H), 8.42 (d, *J* = 8.2 Hz, 1H), 8.00 (d, *J* = 7.9 Hz, 1H), 7.71-7.79 (m, 3H), 7.62 (d, *J* = 9.3 Hz, 1H), 7.56 (t, *J* = 7.1 Hz, 1H), 7.04 (td, *J* = 7.6, 1.3 Hz, 1H), 6.77 (dd, *J* = 8.1, 1.1 Hz, 1H), 6.63 (t, *J* = 8.0 Hz, 1H), 6.57 (s, 2H). ^{13}C NMR (DMSO, 125 MHz): δ 108.9, 115.7, 116.0, 116.5, 116.6, 116.7, 123.3, 125.4, 126.3, 128.1, 128.7, 129.6, 132.3, 142.3, 145.5, 146.9. IR (KBr, cm^{-1}): 740, 815, 1443, 1610, 3331, 3450. HRMS (EI): m/z calculated for $C_{17}H_{13}N_3$ [M^{+}] = 259.1109; found: 259.1113. Elemental analysis (%): calculated for $C_{17}H_{13}N_3$: C, 78.74; H, 5.05; N, 16.20; found: C, 78.52; H, 4.93; N, 16.21.

2-(*H*-Imidazo[2,1-*a*]isoquinolin-2-yl)benzenamine (16). Off-white solid, 0.511g, 48% yield. M.p. 184-185°C. ^{1}H NMR (DMSO, 500 MHz): δ 8.51 (d, *J* = 7.9 Hz, 1H), 8.37 (d, *J* = 7.3 Hz, 1H), 8.32 (s, 1H), 7.90 (d, *J* = 7.9 Hz, 1H), 7.69 (td, *J* =

7.0, 0.9 Hz, 1H), 7.64 (td, *J* = 7.3, 1.0 Hz, 1H), 7.60 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.30 (d, *J* = 7.3 Hz, 1H), 7.03 (td, *J* = 6.9, 1.4 Hz, 1H), 6.78 (d, *J* = 7.9 Hz, 1H), 6.61 (t, *J* = 7.5 Hz, 1H), 6.58 (s, 2H). ^{13}C NMR (DMSO, 125 MHz): δ 111.3, 113.1, 115.9, 116.2, 116.6, 122.9, 123.0, 124.4, 127.8, 127.9, 128.5, 128.6, 128.6, 129.5, 141.2, 144.3, 146.8. IR (KBr, cm^{-1}): 746, 795, 1320, 1511, 1610, 3310, 3453. HRMS (EI): m/z calculated for $C_{17}H_{13}N_3$ [M^{+}] = 259.1109; found: 259.1096. Elemental analysis (%): calculated for $C_{17}H_{13}N_3$: C, 78.74; H, 5.05; N, 16.20; found: C, 78.66; H, 5.01; N, 16.09.

Typical procedure for the preparation of sulfonamides.

A solution of toluenesulphonyl chloride (2 mmol) in AcOEt (15 mL) was slowly added to the mixture of aminoimidazo[1,2-*a*]pyridines (1 mmol) and dry Et_3N (2 mmol) in AcOEt (15 mL). The reaction mixture was stirred at 50°C for 12h under argon. The resulting suspension was diluted with AcOEt and extracted with H_2O. The organic layer was subsequently washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Crystallization from MeOH afforded pure product.

***N*-Tosyl-2-(*H*-imidazo[1,2-*a*]pyridine-2-yl)-benzenamine (17).** White solid, 0.704g, 80% yield. M.p. 181-182°C. ^{1}H NMR (DMSO, 500 MHz): δ 12.69 (s, 1H), 8.58 (d, *J* = 6.7 Hz, 1H), 8.38 (s, 1H), 7.75 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.73 (d, *J* = 9.1 Hz, 1H), 7.54 (d, *J* = 8.5 Hz, 1H), 7.51, 7.14 (AA'BB', *J* = 8.3 Hz, 4H), 7.43-7.38 (m, 1H), 7.27 (td, *J* = 8.5, 1.3 Hz, 1H), 7.12-7.10 (m, 1H), 7.04 (td, *J* = 6.7, 0.8 Hz, 1H), 2.24 (s, 3H). ^{13}C NMR (DMSO, 125 MHz): δ 21.3, 110.9, 113.9, 116.7, 120.6, 121.6, 124.6, 126.8, 127.0, 127.3, 128.0, 129.1, 129.9, 136.0, 136.6, 143.3, 143.8. IR (KBr, cm^{-1}): 544, 568, 676, 736, 748, 916, 1092, 1157, 1289, 1417, 1495, 1585, 3055, 3145. HRMS (EI): m/z calculated for $C_{20}H_{17}N_3O_2S$ [M^{+}] = 363.1041; found: 363.1048. Elemental analysis (%): calculated for $C_{20}H_{17}N_3O_2S$: C, 66.10; H, 4.71; N, 11.56; found: C, 66.02; H, 4.70; N, 11.53.

***N*-Tosyl-2-(6-bromo-*H*-imidazo[1,2-*a*]pyridine-2-yl)-benzenamine (18).** Cream solid, 0.401g, 32% yield. M.p. 203-204°C. ^{1}H NMR (DMSO, 500 MHz): δ 12.32 (s, 1H), 8.95-8.93 (m, 1H), 8.30 (s, 1H), 7.76-7.71 (m, 2H), 7.53-7.48 (m, 4H), 7.29 (td, *J* = 8.3, 1.1 Hz, 1H), 7.12-7.16 (m, 3H), 2.24 (s, 3H). ^{13}C NMR (DMSO, 125 MHz): δ 21.3, 107.5, 111.3, 117.8, 121.0, 121.5, 124.8, 127.0, 127.3, 128.2, 129.4, 129.5, 129.9, 135.9, 136.5, 142.4, 143.8, 144.0. IR (KBr, cm^{-1}): 568, 743, 918, 1092, 1155, 1279, 1495, 1584, 3099, 3136. HRMS (EI): m/z calculated for $C_{20}H_{16}N_3BrO_2S$ [M^{+}] = 441.0147; found: 441.0157. Elemental analysis (%): calculated for $C_{20}H_{16}N_3BrO_2S$: C, 54.31; H, 3.65; N, 9.50; found: C, 54.45; H, 3.67; N, 9.40.

***N*-Tosyl-2-(*H*-imidazo[1,2-*a*]quinolin-2-yl)benzenamine (19).** Cream solid, 0.545g, 88% yield. M.p. 264-265°C. ^{1}H NMR (DMSO, 500 MHz): δ 11.47 (br s, 1H), 9.18 (s, 1H), 8.44 (d, *J* = 8.4 Hz, 1H), 8.19 (d, *J* = 7.8 Hz, 1H), 8.14 (d, *J* = 8.8 Hz, 1H), 7.95 (t, *J* = 7.7 Hz, 1H), 7.80, 7.00 (AA'BB', *J* = 8.5 Hz, 4H), 7.74 (t, *J* = 7.5 Hz, 1H), 7.39-7.49 (m, 4H), 7.33 (t, *J* = 7.2 Hz, 1H), 2.06 (s, 3H). ^{13}C NMR (DMSO, 125 MHz): δ 21.2, 111.9, 113.7, 116.7, 123.0, 123.6, 126.2, 126.8, 127.0, 129.3, 129.7, 130.2, 131.1, 131.7, 135.3, 137.1, 140.8, 143.5. IR (KBr, cm^{-1}): 549, 661, 760, 817, 913, 1158, 1338, 1427, 1492, 2654, 2687, 2730, 3057, 3087. HRMS (EI): m/z calculated for $C_{24}H_{19}N_3O_2S$ [M^{+}] = 413.1198; found: 413.1200.

***N*-Tosyl-2-(*H*-imidazo[2,1-*a*]isoquinolin-2-yl)benzenamine (20).** Cream solid, 0.483g, 47% yield. M.p. 202-203°C. ^{1}H NMR (DMSO, 500 MHz): δ 12.94 (s, 1H), 8.50 (d, *J* = 7.9 Hz, 1H), 8.45 (s, 1H), 8.40 (d, *J* = 7.2 Hz, 1H), 7.99 (d, *J* = 7.9 Hz, 1H), 7.84 (t, *J* = 8.1 Hz, 1H), 7.79 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.75 (td, *J* = 8.1, 1.1 Hz, 1H), 7.55-7.59 (m, 3H), 7.43 (d, *J* = 7.2 Hz, 1H), 7.28 (td, *J* = 8.5, 1.3 Hz, 1H), 7.12-7.16 (m, 3H), 2.23 (s, 3H). ^{13}C NMR (DMSO, 125 MHz): δ 21.2, 114.3, 115.9, 123.5, 124.5, 125.9, 126.9, 128.4, 128.5, 129.7, 130.7, 135.3, 137.2, 143.5. IR (KBr, cm^{-1}): 549, 553, 663, 811, 920, 1092, 1155, 1328, 2774, 3012. HRMS (EI): m/z calculated for $C_{24}H_{19}N_3O_2S$ [M^{+}] = 413.1198; found: 413.1208. Elemental analysis (%): calculated for $C_{24}H_{19}N_3O_2S$: C, 69.71; H, 4.63; N, 10.16; found: C, 69.52; H, 4.62; N, 10.01.

Typical procedure for the oxidative coupling of tosylamides.

Method A: CF_3COOH (46μL, 0,6 mmol) was slowly added to the mixture of tosylamide **17** or **18** (0.2 mmol), $Cu(OTf)_2$ (0.01 mmol) and $PhI(OAc)_2$ (0.3 mmol) in 1,2-dichloroethane (2mL) and the whole reaction mixture was stirred at 50°C for 30 minutes under argon. The resulting solution was cooled, filtered through a pad of Celite and washed with AcOEt. Purification by column chromatography (silica, AcOEt/hexanes 6:4) followed by crystallization from AcOEt-hexanes afforded pure product.

Method B: CF_3COOH (46μL, 0,6 mmol) was slowly added to the mixture of tosylamide **19** or **20** (0.2 mmol) and $PhI(CF_3COO)_2$ (0.3 mmol) in 1,2-dichloroethane (2mL) and the whole reaction mixture was stirred at 50°C for 30 minutes under argon. The product was purified according to the procedure described in method A.

***N*-Tosyl-5*H*-pyrido[2',1':2,3]imidazo[4,5-*b*]indole (21).** Off-white solid, 0.067g, 93% yield. M.p. 177-178°C. ^{1}H NMR (DMSO, 500 MHz): δ 9.14 (d, *J* = 6.8 Hz, 1H), 8.21 (d, *J* = 8.4 Hz, 1H), 7.80-7.76 (m, 2H), 7.54-7.42 (m, 3H), 7.38, 718 (AA'BB', *J* = 8.3 Hz, 4H), 7.24 (t, *J* = 6.9 Hz, 1H), 2.20 (s, 3H, CH_3). ^{13}C NMR (DMSO, 125 MHz): δ 21.4, 113.8, 117.6, 118.2, 119.9, 123.3, 125.7, 126.2, 126.4, 126.9, 127.2, 130.5, 131.0, 138.2, 141.6, 146.4. IR (KBr, cm^{-1}): 539, 677, 740, 971, 1173, 1364, 1529, 1592, 1706, 3057, 3141. HRMS (EI): m/z calculated for $C_{20}H_{15}N_3O_2S$ [M^{+}] = 361.0885; found: 361.0881.

***N*-Tosyl-(5-bromo-5*H*-pyrido[2',1':2,3]imidazo[4,5-*b*])indole (22).** Off-white solid, 0.170g, 48% yield. M.p. 182-183°C. ^{1}H NMR (DMSO, 500 MHz): δ 9.23-9.21 (m, 1H), 8.17 (d, *J* = 8.5 Hz, 1H), 7.79 (d, *J* = 7.3 Hz, 1H), 7.75 (d, *J* = 9.8 Hz, 1H), 7.56 (dd, *J* = 9.8, 1.9 Hz, 1H), 7.52 (t, *J* = 7.8 Hz, 1H), 7.40-7.45 (m, 3H), 7.18 (d, *J* = 8.2 Hz, 2H), 2.20 (s, 3H). ^{13}C NMR (DMSO, 125 MHz): δ 21.4, 107.3, 117.5, 119.8, 120.1, 123.5, 125.5, 126.5, 127.2, 127.4, 128.3, 130.5, 130.9, 141.6, 146.5. IR (KBr, cm^{-1}): 537, 573, 664, 756, 787, 1169, 1365, 1502, 1594, 3137. HRMS (EI): m/z calculated for $C_{20}H_{14}N_3O_2SBr$ [M^{+}] = 438.9990; found: 438.9991.

***N*-Tosyl-5*H*-quinolino[1',2':2,3]imidazo[4,5-*b*]indole (23).** Off-white solid, 0.097g, 29% yield. M.p. 191-193°C. ^{1}H NMR (DMSO, 500 MHz): δ 8.77 (d, *J* = 8.5 Hz, 1H), 8.10 (d, *J* = 8.1 Hz, 1H), 8.06 (d, *J* = 7.8 Hz, 1H), 7.88 (d, *J* = 9.5 Hz, 1H), 7.81 (td, *J* = 8.5, 1.2 Hz, 1H), 7.67 (d, *J* = 9.5 Hz, 1H), 7.63 (t, *J* = 7.5 Hz, 1H), 7.58 (d, *J* = 7.5 Hz, 1H), 7.46 (td, *J* = 8.4, 1.2 Hz, 1H), 7.39 (td, *J* = 7.5, 1.0 Hz, 1H), 7.00, 6.84 (AA'BB', *J* = 8.3 Hz, 4H), 2.17 (s, 3H). ^{13}C NMR (DMSO, 125 MHz): δ 21.4, 117.9, 119.30, 119.34, 120.5, 123.9, 126.0, 126.1, 126.3, 127.6,

127.7, 127.9, 128.1, 128.7, 128.9, 129.4, 131.0, 132.2, 140.6, 144.4, 146.0, 147.4. IR (KBr, cm^{-1}): 535, 573, 665, 750, 808, 1173, 1360, 3052. HRMS (EI): m/z calculated for $C_{24}H_{17}N_3O_2S$ [$M^{\cdot+}$] = 411.1041; found: 411.1038. Elemental analysis (%): calculated for $C_{24}H_{17}N_3O_2S$: C, 70.05; H, 4.16; N, 10.21; found: C, 69.99; H, 4.28; N, 10.10.

***N*-Tosyl-5*H*-isoquinolino[1',2':2,3]imidazo[4,5-*b*]indole (23).** Off-white solid, 0.101 g, 62% yield. M.p. 188-191°C. ^{1}H NMR (DMSO, 500 MHz): δ 8.96 (d, *J* = 7.5 Hz, 1H), 8.62-8.58 (m, 1H), 8.21 (d, *J* = 8.1 Hz, 1H), 8.01-7.97 (m, 1H), 7.83 (dd, *J* = 7.5, 0.8 Hz, 1H), 7.77-7.72 (m, 2H), 7.54 (d, *J* = 7.5 Hz, 1H), 7.49 (td, *J* = 7.4, 1.2 Hz, 1H), 7.47-7.41 (m, 3H), 7.17 (d, *J* = 8.1 Hz, 2H), 2.19, (s, 3H). ^{13}C NMR (DMSO, 125 MHz): δ 21.4, 113.8, 117.6, 119.5, 123.0, 123.5, 123.6, 123.9, 126.2, 126.4, 127.2, 127.8, 128.2, 129.0, 129.3, 129.4, 130.5, 131.2, 136.5, 141.2, 145.6, 146.4. IR (KBr, cm^{-1}): 541, 574, 672, 738, 795, 1176, 1378, 1442, 1740, 3061, 3146. HRMS (EI): m/z calculated for $C_{24}H_{17}N_3O_2S$ [$M^{\cdot+}$] = 411.1041; found: 411.1044.

***N*-Tosyl-(5-(4-*N*,*N*-dimethylaminophenylethynyl)-5*H*-pyrido[2',1':2,3]imidazo[4,5-*b*])indole (25).** The mixture of compound **22** (120 mg, 0.27 mmol), 4-ethynyl-*N*,*N*-dimetylaniline (100 mg, 0.69 mmol), Cs_2CO_3 (247 mg, 0.76 mmol), $Pd(OAc)_2$ (7.8 mg, 0.035 mmol), PPh_3 (36 mg 0.14 mmol) in 10 ml of DMSO was stirred at 80°C for 24h under argon. The resulting solution was diluted with AcOEt and extracted with H_2O. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography (silica, hexanes/AcOEt 7:3), followed by crystallization from AcOEt-hexanes afforded **25** as yellow crystals (0.059g, 43% yield). M.p. 229-232°C. ^{1}H NMR (DMSO, 500 MHz): δ 9.21-9.19 (m, 1H), 8.19 (d, *J* = 8.2 Hz, 1H), 7.79 (d, *J* = 7.7 Hz, 1H), 7.76 (dd, *J* = 9.5, 0.8 Hz, 1H) 7.54-7.48 (m, 2H), 7.46-7.41 (m, 5H), 7.19 (d, *J* = 8.2 Hz, 2H), 6.75 (d, *J* = 9.0 Hz, 2H), 2.89 (s, 6H), 2.21 (s, 3H). ^{13}C NMR (DMSO, 125 MHz): δ 21.4, 84.2, 92.8, 108.2, 109.9, 112.3, 117.6, 118.5, 120.0, 123.4, 126.3, 126.5, 127.1, 127.3, 127.4, 128.0, 130.5, 130.8, 133.0, 139.5, 141.6, 146.5, 147.0, 150.8. IR (KBr, cm^{-1}): 539, 574, 673, 815, 931, 1172, 1371, 1536, 1604, 2211, 3037, 3131. HRMS (EI): m/z calculated for $C_{30}H_{24}N_4O_2S$ [$M^{\cdot+}$] = 504.1620; found: 504.1622.

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