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Electrochemical rhodium catalysed alkyne annulation with pyrazoles through anodic oxidation – a metal oxidant/additive free methodology†

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Pyrazole and its derivatives are important azole heteroarenes prevalent in pharmaceutical compounds and have been used as ligands for protein binding, making them valuable targets for synthetic applications. Herein we disclose an electrochemical intermolecular C–H/N–H oxidative annulation of 2-phenylpyrazoles with alkynes using a rhodium(III) redox regime without any external metal oxidants in a water compatible solvent system. Both symmetrical and unsymmetrical alkynes were shown to be compatible with the optimized conditions.

Introduction

Transition metal catalysed regioselective transformations of inert C–H bonds to C–C/C–X bonds is of significant utility in the synthesis of pharmaceuticals and new materials due to their high atom economy, reduction in the number of synthetic steps and generally mild reaction conditions.[1] A variety of metals have been explored for the elaboration of C–H bonds with saturated or unsaturated substituents.[2] The development of efficient protocols using rhodium catalysts has been performed by the groups of Miura,[3] Fagnou,[4] Chang,[5] Ellman,[6] Rovis,[7] Li[8] and Glorius,[9] among others.[10] Rhodium catalysts exhibit high reactivities towards alkenes and alkynes, thus avoiding the need for prefunctionalized substrates in cross-coupling reactions. Alkyne annulations facilitated by Rh^{III}/Rh^{I} catalytic regimes traditionally employ exogenous metal oxidants to recycle the active catalyst.[11] From the pioneering work of Miura, it can be seen that stoichiometric amounts of metal oxidants are needed in C–H activation reactions, in particular in alkyne annulation for the synthesis of heterocycles.[3] Among these metal oxidants, copper and silver are frequently used in the reoxidation step, despite their environmental and cost issues associated with by-product removal and waste disposal.

The recent renascence arising from the marriage of transition metal catalysis with electrochemistry for electroorganic synthesis has provided environmentally benign redox processes that avoid the use of external toxic and expensive metal oxidants.[12] This electrical control over the oxidation states of metals often provides alternative selectivities and can reduce the high-energy barrier associated with the reductive elimination step,[13,14] as has been demonstrated by Ackermann,[15] Xu,[16] Lei,[17] and Mei,[18] among others,[19] who have developed elegant metalla-electrocatalyzed C–H activation reactions. For example, Ackermann *et al.* have described the synthesis of polycyclic aromatic hydrocarbons by using double electrocatalysis-driven rhodaelectrocatalysis by annulative C–H activation (Scheme 1a).[20] Furthermore, a scalable Rh(III) catalysed aryl C–H phosphorylation enabled by anodic oxidation-induced reductive elimination was reported by the Hu group.[21] Very recently, Mei and co-workers have presented a divergent rhodium-catalysed electrochemical vinylic C–H annulation with alkynes.[22] While significant development has been made using electricity in various Rh(III) catalysed C–H transformations, its use in annulation reactions using heterocycles prone to generate nitrogen-centred radicals though anodic oxidation is very scarce and alkyne annulation remains elusive.[23] Herein we disclose a sustainable rhodaelectro-catalysed intermolecular C–H/N–H oxidative annulation of pyrazole with alkynes using a water-based solvent system (Scheme 1b).

Nitrogen containing azole heterocycles can be found in natural products and in biologically active compounds[24] and are important building blocks in modern medicinal chemistry.[25] Pyrazole-based six-membered azaheterocycles, while not naturally available, do contribute to a wide range of biological activities when used as motifs in drugs (Scheme 1c).[26]

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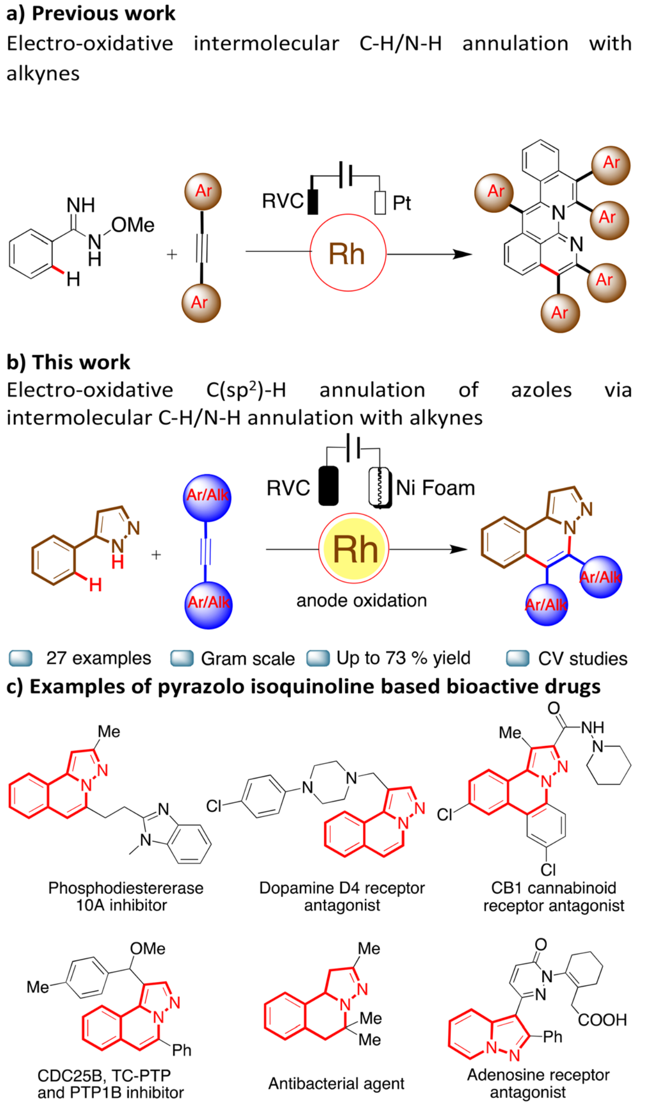
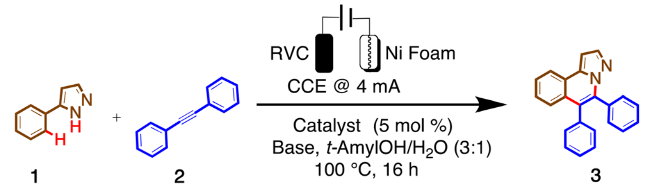
† Electronic supplementary information (ESI) available: Experimental setup, spectra details, NMR & HRMS spectra. See DOI: **https://doi.org/10.1039/d2ob02306g**



Scheme 1 a) Previous work, (b) this work, (c) selected examples of bioactive compounds containing pyrazolo isoquinoline.

Previous exploration of pyrazoles in C–H activation reactions has included alkyne annulations using conventional methods,[27–29] though not with alternative sustainable electrochemical approaches.

Table 1 Optimization of the rhodium-catalysed electrochemical C–H activation[a]



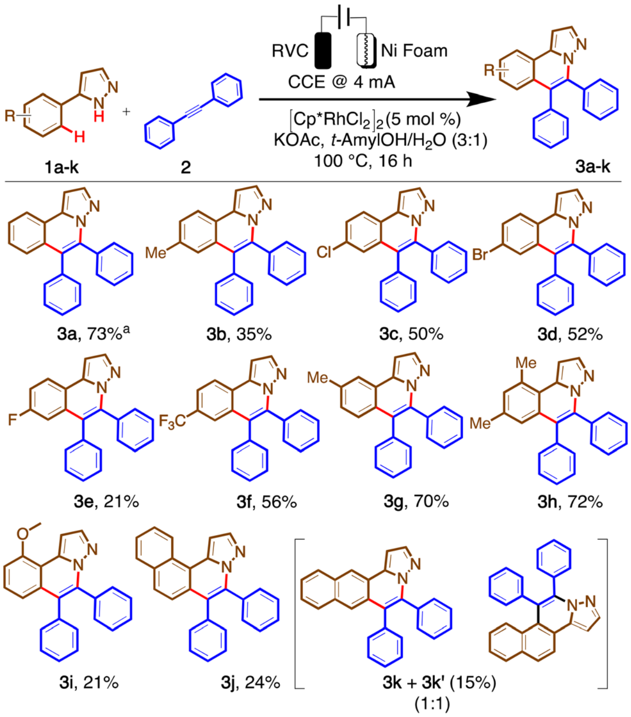
		Yield^b (%)
Effect of metal complexes		
1	$[Cp^*RhCl_2]_2$	73^c
2	$[Cp^*IrCl_2]_2$	35
3	$[(p\text{-Cymene})RuCl_2]_2$	Trace
4	$Pd(OAc)_2$	NR
Effect of additives		
5	NaOPiv	64
6	KOPiv	65
7	KOAc	73
8	LiOAc	40
Effect of electrolytes		
9	KPF_6	34
10	$^nBu_4NBr$	Trace
11	$^nBu_4NOAc$	NR
12	$^nBu_4NClO_4$	NR
Effect of solvents		
13	TFE	Trace
14	TFE + *t*-AmylOH	10
15	TFE + *t*-AmylOH + H_2O	18
Effect of electrodes		
16	RVC/Pt	NR
17	Pt/Pt	NR
Effect of mediators		
18	Ferrocene	NR
19	2,5-Dimethylbenzoquinone	33
20	2-Chlorobenzoquinone	16
21	Benzoquinone	30
22	2,6-Dichlorobenzoquinone	NR
Control experiments		
23	No electricity	13
24	No Rh catalyst	NR
25	Under air	Trace
Effect of current		
26	2 mA	15
27	8 mA	16
Effect of temperature		
28	23 °C	NR
29	60 °C	NR
30	80 °C	NR

[a] Reaction conditions: **1a** (50 mg, 0.34 mmol), **2a** (74 mg, 0.41 mmol), $[Cp^*RhCl_2]_2$ (5 mol%), KOAc (2 equiv.), solvent (12 mL), 100 °C, 16 h, under N_2. [b] Isolated yields. [c] KOAc was the base. NR = no reaction.

Results & discussion

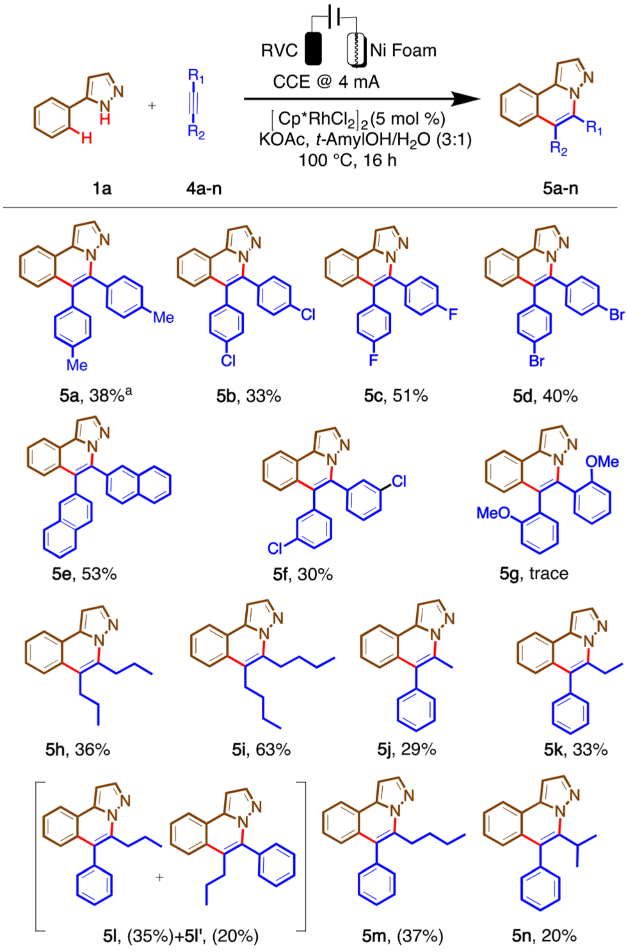
For the initial exploratory and control studies of the envisaged rhodium catalysed C–H activation, 2-phenylpyrazole (**1a**) and diphenylacetylene (**2a**) were used under reaction conditions previously developed by us for a copper catalysed C–H amination (Table 1).[30] Upon comparison of rhodium, iridium, ruthenium and palladium catalysts, rhodium was found to be superior (Table 1, entries 1–4). A series of base additives were then examined, and KOAc was found to give better results than NaOPiv, KOPiv and LiOAc (Table 1, entries 5–8). In a screening of possible electrolytes, using KPF_6 led to the product being formed in 34% yield (Table 1, entry 9); however, the use of tetrabutylammonium bromide, tetrabutylammonium acetate and tetrabutylammonium perchlorate as electrolytes provided little or no support for the reaction (Table 1, entries 10–12). Among the tested solvents, a protic solvent mixture containing *tert*-amyl alcohol mixed with water in a 3 : 1 ratio (v/v) gave the best result. When trifluoroethanol was used, either alone or combined with *tert*-amyl alcohol and water, the product could not be isolated in a good yield (Table 1, entries 13–15). Alternative electrode materials were examined, with the best yield being obtained when using an RVC anode and nickel foam cathode rather than the more expensive platinum electrode containing configurations (Table 1, entries 16 and 17). To determine whether this reaction involves direct or indirect electrocatalysis, we performed the reaction in the presence of known electrochemical mediators.[31] The use of ferrocene was found to be ineffective with no product formation (Table 1, entry 18). The quinone-based electrolytes 2,5-dimethylbenzoquinone, 2-chlorobenzoquinone, and benzoquinone provided the product with a very low yield (Table 1, entries 19–21). The use of 2,6-dichlorobenzoquinone resulted in no product formation (Table 1, entry 22), supporting direct electrocatalysis as the basis for the reaction. Further control experiments revealed that in the absence of electricity or the rhodium catalyst, no reaction was observed, and only traces of the product were obtained when the reaction was performed under air (Table 1, entries 23–25). We studied the effect of electricity on the annulation and determined that 4 mA is the optimal current by using various current values (Table 1, entries 26 and 27). Finally, reactions performed at 23, 60 and 80 °C resulted in the recovery of the starting material with no observed product formation (Table 1, entries 28–30).

With conditions for the electrochemical C–H/N–H alkyne annulation in hand, we proceeded to study the scope and versatility of the reaction using various pyrazole derivatives. The substrate scope screening revealed that both electron donating and electron withdrawing substituents at the *para*-position were well tolerated and delivered the products (**3a–3f**) in good yields (21–73%) (Scheme 2). It is noteworthy that *meta*-methyl substituted pyrazole gave one positional selective product (**3g**). The *ortho*, *meta*-dimethyl substituted pyrazole (**1h**) afforded product **3h** in 72% yield, while the *ortho*-substituted pyrazole (**1i**) furnished product **3i** in 21% yield. Interestingly, the 1-naphthyl pyrazole (**1j**) gave a single product, as the hypothetical **3j′** regioisomer would form an energetically less favored 7-membered ring, while the 2-naphthyl pyrazole (**1k**) gave two regioisomers in a 1 : 1 ratio (**3j** and **3k**).



Scheme 2 Scope of pyrazoles with diphenylacetylene. Reaction conditions: **1a–k** (0.34 mmol), **2a** (0.41 mmol), $[Cp^*RhCl_2]_2$ (5 mol%), KOAc (2 equiv.), solvent (12 mL), 100 °C, 16 h, under N_2; [a] isolated yield.

Subsequently, a variety of internal alkynes were tested for their suitability in the electro-redox C–H activation reaction (Scheme 3). Electronically biased substituted internal alkynes (**4a–4d**) delivered cyclized products (**5a–5d**) with moderate to good yields (33–51%). The tolerance of chloro, bromo, and fluoro at different positions on alkynes is highly appreciable as they can be useful for further cross-coupling reactions. A sterically bulky 2-naphthyl substituted internal alkyne (**4e**) also provided the product (**5e**) in 53% yield. A chlorinated alkyne at the *meta*-position gave the product (**5f**) in 30% yield. The use of 4-octyne (**4h**) and 5-decyne (**4i**) also successfully furnished the annulated products in good yields (**5h** and **5i**). The unsym-



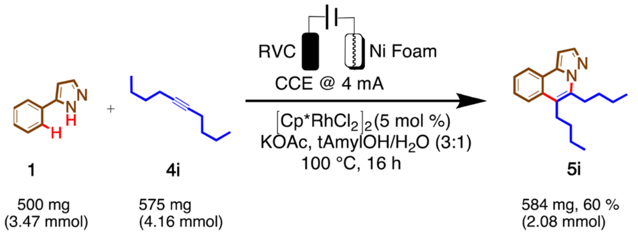
Scheme 3 Scope of alkynes with 2-phenylpyrazole. Reaction conditions: **1a** (2 equiv.), **4a–n** (50 mg, 0.24 mmol, 1 equiv.), $[Cp^*RhCl_2]_2$ (5 mol%), KOAc (2 equiv.), solvent (12 mL), 100 °C, 16 h, under N_2; [a] isolated yield.

metrical alkynes **4j**–**4n** were then tested in this reaction and they successfully gave the expected products in moderate to excellent yields with high regioselectivity (Scheme 3). 1-Phenylpropyne (**4j**) gave one major regioisomer **5j** in 29% yield. 1-Phenylbutyne (**4k**) also reacted with 2-phenylpyrazole (**1**) and provided the regioselective product (**5k**) in 33% yield. When we used 1-phenylpentyne (**4l**) as the coupling partner, we successfully isolated two possible regioisomers (**5l** + **5l′**) in this reaction. 1-Phenylhexyne (**4m**) and 1-phenyl-2,2-dimethyl propyn-1-ol (**4n**) furnished regioselective products **5m** (37%) and **5n** (20%).

This electrochemical C–H activation could be readily scaled up to the 1 mmol scale in an undivided cell setup and provided the product (**5i**) in 60% yield (Scheme 4). To evaluate the efficacy of this green methodology for alkyne annulation with pyrazole, we calculated the *E*-factor associated with this reaction and found a total amount of 18.97, which is quite good in comparison with the conventional methods[27] (see the ESI†).

Next, to elucidate the basis for the efficiency of this rhodo-electrocatalysis, we designed cyclic voltammetry studies under a nitrogen atmosphere with Ag/AgO-, nickel foam-, and RVC electrodes (Fig. 1). The slow conversion without electricity and the very good conversion after electrolysis support the hypothesis that this reaction follows an oxidation-induced reductive elimination pathway. Moreover, the peaks corresponding to the rhodium catalyst and **1a** with a base and an electrolyte are indicative of the formation of a higher oxidation state for the rhodium catalyst and these two species are susceptible to electrochemical redox processes.[32]

Based on the observed experimental details and previously reported methods,[15] we propose a plausible working mechanism for the electrochemical C–H activation reaction (Scheme 5). Initially, the $[RhCp^*Cl_2]_2$ complex upon ligand exchange with KOAc gives $RhCp^*(OAc)_2$. The catalyst in its active form coordinates to the 2-phenylpyrazole and the subsequent C–H bond insertion gives cyclometallated rhodium complex **A**. The acetic acid formed in this step undergoes facile cathodic reduction and produces sustainable hydrogen as the only by-product. Complex **A** upon alkyne coordination results in the formation of **B**, which upon carbo-rhodation generates the cationic complex **C**. This cationic complex undergoes reductive elimination to deliver the annulated product along with reduced $RhCp^*L_2$(L = OAc). Anodic oxidation regenerates the active catalyst, which continues the cycle.



Scheme 4 Reaction at the 1 mmol scale.

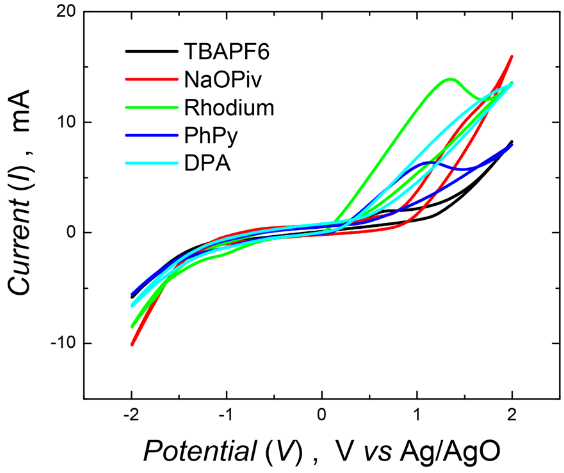
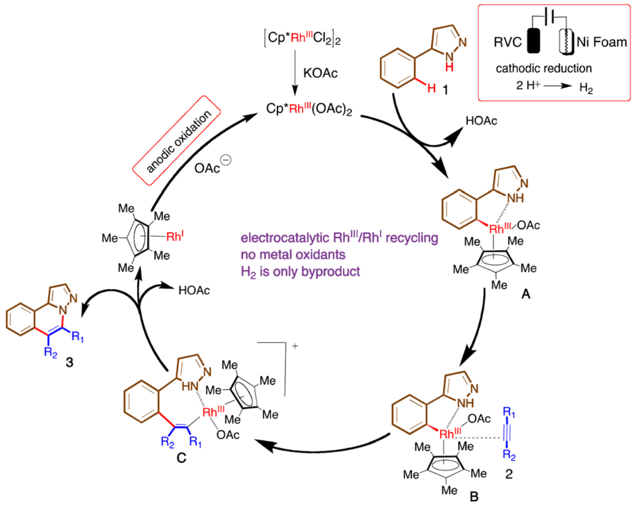


Fig. 1 Cyclic voltammetry studies.



Scheme 5 Plausible rhoda-electrocatalytic C–H/N–H annulation.

Conclusions

In summary, an unprecedented electrochemical intermolecular C–H/N–H oxidative annulation of alkynes with 2-phenylpyrazoles has been successfully achieved using electricity as the sustainable green oxidant with the implicit liberation of hydrogen as the environmentally friendly by-product, which indicates the significance of this protocol. The simple undivided cell setup in common reaction tubes, use of cheaper electrodes and a water-based solvent system, wide substrate scope and high regioselectivity showcase the novel features of this strategy. The overall waste generation with a low *E*-factor and a reaction at the 1 mmol scale were also explored. Further application of rhoda-electrocatalysis for the synthesis of heterocycles is ongoing in our lab and the results will be communicated in due course.

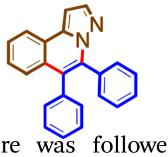
Experimental details

General experimental procedure for the rhodium catalyzed electro-alkyne annulation

An undivided cell was used to carry out electrocatalysis, with an RVC anode (15 mm × 10 mm) and a nickel foam cathode (15 mm × 10 mm). 2-Phenylpyrazole (0.34 mmol), alkyne (0.41 mmol), KOAc (65 mg, 0.66 mmol), and $[Cp^*RhCl_2]_2$ (10 mg, 5 mol%) were placed in a 50 mL cell and the cell was connected to a Schlenk line to add *t*-AmylOH + H_2O (12 mL, 3 : 1). Electrocatalysis was performed at 100 °C with a constant current of 4 mA maintained for 16 h. Then the CC-power supply was stopped and the electrodes were washed with acetone and the combined liquids were evaporated under reduced pressure. The resulting residue was coated on preparative TLC plates (25 cm × 25 cm) and eluted with a petroleum ether and acetone mixture (100 : 5 mL/mL) to afford the corresponding products.

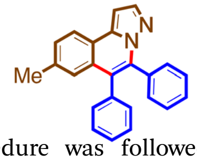
Experimental data

3,4-Diphenylpyrazolo[5,1-*a*]isoquinoline (3a)



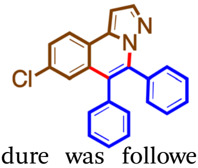
. The general procedure was followed using **1a** (50 mg, 0.34 mmol) and **2a** (74 mg, 0.41 mmol) at 100 °C for 16 h. Purification using preparative TLC plates (petroleum ether/acetone = 100/5 mL/mL) afforded **3a** (74 mg, 68%) as a brown solid. M. pt. 218 °C; **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.24 (d, *J* = 7.9 Hz, 1H), 8.02 (d, *J* = 2.2 Hz, 1H), 7.62 (ddd, *J* = 8.2, 6.4, 2.0 Hz, 1H), 7.51–7.43 (m, 2H), 7.37 (dtd, *J* = 5.7, 4.0, 3.4, 1.7 Hz, 2H), 7.31 (dddd, *J* = 11.3, 8.1, 4.4, 1.6 Hz, 6H), 7.24 (dd, *J* = 7.8, 1.9 Hz, 2H), 7.16 (d, *J* = 2.2 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 141.1, 138.6, 136.4, 136.2, 133.2, 131.6, 130.9, 130.0, 128.4, 128.0, 128.0, 127.8, 127.4, 127.2, 126.8, 124.1, 124.0, 123.6, 97.6. **HRMS** $C_{23}H_{16}N_2$ $[M + H]^+$: calculated 321.1392, found: 321.1389.

4-Methyl-3,4-diphenylpyrazolo[5,1-*a*]isoquinoline (3b)



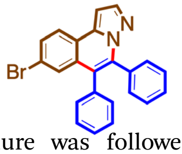
. The general procedure was followed using **1b** (55 mg, 0.34 mmol) and **2a** (72 mg, 0.41 mmol) at 100 °C for 16 h. Purification using preparative TLC plates (petroleum ether/acetone = 100/5 mL/mL) afforded **3b** (19 mg, 17%) as a brown solid. M. pt. 141 °C; ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.03 (s, 1H), 7.99 (d, *J* = 2.2 Hz, 1H), 7.39–7.35 (m, 2H), 7.33 (d, *J* = 4.5 Hz, 3H), 7.30 (dd, *J* = 7.2, 2.1 Hz, 5H), 7.27 (s, 1H), 7.25–7.17 (m, 3H), 7.13 (d, *J* = 2.2 Hz, 1H), 2.59 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 140.9, 138.4, 137.4, 136.3, 135.5, 133.2, 131.6, 130.9, 129.3, 128.3, 127.9, 127.9, 127.7, 127.1, 126.6, 124.1, 123.9, 123.3, 97.4, 21.6. **HRMS** $C_{24}H_{18}N_2$ $[M + H]^+$: calculated 335.1548, found: 335.1543.

4-Chloro-3,4-diphenylpyrazolo[5,1-*a*]isoquinoline (3c)



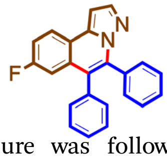
. The general procedure was followed using **1c** (68 mg, 0.34 mmol) and **2a** (74 mg, 0.41 mmol) at 100 °C for 16 h. Purification using preparative TLC plates (petroleum ether/acetone = 100/5 mL/mL) afforded **3c** (60 mg, 50%) as a brown solid. M. pt. 124 °C; **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.16 (d, *J* = 8.5 Hz, 1H), 8.01 (d, *J* = 2.2 Hz, 1H), 7.56 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.41 (d, *J* = 2.1 Hz, 1H), 7.37–7.29 (m, 8H), 7.24–7.18 (m, 2H), 7.13 (d, *J* = 2.1 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 141.3, 138.0, 137.4, 135.4, 133.7, 132.8, 131.5, 131.3, 130.7 128.6, 128.2, 128.0, 127.8, 127.5, 126.0, 125.1, 123.1, 122.4, 97.8. **HRMS** $C_{23}H_{15}ClN_2$ $[M + H]^+$: calculated: 355.1002, found: 355.1001.

4-Bromo-3,4-diphenylpyrazolo[5,1-*a*]isoquinoline (3d)



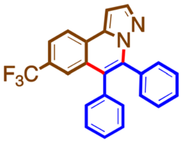
. The general procedure was followed using **1d** (50 mg, 0.45 mmol) and **2a** (60 mg, 0.33 mmol) at 100 °C for 16 h. Purification using preparative TLC plates (petroleum ether/acetone = 87/13 mL/mL) afforded **3d** (93 mg, 52%) as a brown solid. M. pt. 172 °C; **^{1}H NMR (400 MHz, chloroform-*d*)** δ 7.99 (d, *J* = 8.5 Hz, 1H), 7.91 (d, *J* = 2.2 Hz, 1H), 7.60 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.47 (d, *J* = 2.0 Hz, 1H), 7.26–7.17 (m, 8H), 7.12–7.08 (m, 2H), 7.03 (d, *J* = 2.2 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 141.3, 138.0, 137.4, 135.3, 132.7, 131.6, 131.5, 130.7, 130.5, 129.1, 128.6, 128.2, 128.0, 127.5, 125.2, 123.0, 122.7, 121.9, 97.9. **HRMS** $C_{23}H_{15}BrN_2$ $[M + H]^+$: calculated: 401.0476, found: 401.0477.

4-Fluoro-3,4-diphenylpyrazolo[5,1-*a*]isoquinoline (3e)



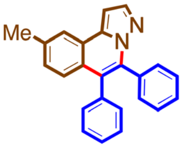
. The general procedure was followed using **1e** (56 mg, 0.34 mmol) and **2a** (72 mg, 0.41 mmol) at 100 °C for 16 h. Purification using preparative TLC plates (petroleum ether/acetone = 100/5 mL/mL) afforded **3e** (25 mg, 21%) as a brown solid. M. pt. 121–123 °C; **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.11 (dd, *J* = 8.8, 5.5 Hz, 1H), 7.90 (d, *J* = 2.2 Hz, 1H), 7.25 (td, *J* = 4.9, 1.8 Hz, 4H), 7.22 (ddd, *J* = 6.5, 3.1, 1.4 Hz, 5H), 7.11 (dd, *J* = 7.6, 1.9 Hz, 2H), 6.99 (td, *J* = 5.5, 2.6 Hz, 2H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.2, 160.8, 141.3, 138.2, 137.4, 135.6, 132.8, 132.0, 131.9, 131.4, 130.7, 128.5, 128.5, 128.2, 128.0, 127.4, 125.8, 125.8, 123.4, 123.3, 120.7, 120.7, 116.1, 115.9, 112.0, 111.8, 97.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ −111.4, −111.4, −111.4, −111.4, −111.4, −111.4, −111.4, −111.4. **HRMS** $C_{23}H_{15}FN_2$ $[M + H]^+$: calculated: 339.1298, found: 339.1294.

4-Trifluoromethyl-3,4-diphenylpyrazolo[5,1-*a*]isoquinoline (3f)



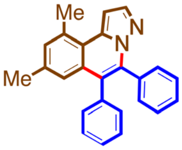
. The general procedure was followed using **1f** (50 mg, 0.23 mmol) and **2a** (63 mg, 0.35 mmol) at 100 °C for 16 h. Purification using preparative TLC plates (petroleum ether/acetone = 100/5 mL/mL) afforded **3f** (50 mg, 56%) as a brown solid. (R_f = 0.53). M. pt. 86 °C; **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.34 (d, J = 8.4 Hz, 1H), 8.06 (d, J = 2.2 Hz, 1H), 7.82 (dd, J = 8.4, 1.8 Hz, 1H), 7.73 (d, J = 1.8 Hz, 1H), 7.34 (tt, J = 7.4, 2.1 Hz, 8H), 7.26–7.19 (m, 3H). **^{13}C NMR (101 MHz, CDCl$_3$)** δ 141.5, 137.8, 137.7, 135.1, 132.6, 131.6, 131.5, 130.7, 129.8, 129.6 (q, J = 32.3 Hz), 128.7, 128.3, 128.1, 127.7, 124.4, 124.0 (q, J = 272.5 Hz), 124.0 (q, J = 4.2 Hz), 123.8, 123.5 (q, J = 3.5 Hz), 98.9. **^{19}F NMR (376 MHz, CDCl$_3$)** δ −62.30. **HRMS** $C_{24}H_{15}F_3N_2$ [M + H]$^+$: calculated: 389.1266, found: 389.1264.

3-Methyl-3,4-diphenylpyrazolo[5,1-*a*]isoquinoline (3g)



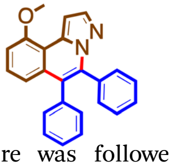
. The general procedure was followed using **1g** (50 mg, 0.32 mmol) and **2a** (74 mg, 0.41 mmol) at 100 °C for 16 h. Purification using preparative TLC plates (petroleum ether/acetone = 100/5 mL/mL) afforded **3g** (80 mg, 70%) as a brown solid. (R_f = 0.8). M. pt. 143–145 °C; **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.14 (d, J = 8.1 Hz, 1H), 7.99 (d, J = 2.2 Hz, 1H), 7.46 (d, J = 1.7 Hz, 1H), 7.40–7.26 (m, 9H), 7.26–7.17 (m, 3H), 2.43 (s, 3H). **^{13}C NMR (101 MHz, CDCl$_3$)** δ 141.0, 138.6, 137.8, 136.4, 136.3, 133.3, 131.6, 130.8, 130.0, 128.9, 128.3, 128.0, 127.9, 127.1, 126.3, 123.8, 123.5, 121.9, 97.0, 21.9. **HRMS** $C_{24}H_{18}N_2$ [M + H]$^+$: calculated: 335.1548, found: 335.1544.

2,4-Dimethyl-3,4-diphenylpyrazolo[5,1-*a*]isoquinoline (3h)



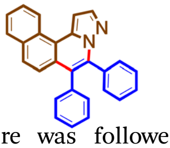
. The general procedure was followed using **1h** (60 mg, 0.34 mmol) and **2a** (72 mg, 0.41 mmol) at 100 °C for 16 h. Purification using preparative TLC plates (petroleum ether/acetone = 100/5 (mL/mL)) afforded **3h** (85 mg, 72%) as a brown solid. M. pt. 158 °C; **^{1}H NMR (400 MHz, chloroform-*d*)** δ 7.91 (d, J = 2.3 Hz, 1H), 7.24–7.14 (m, 9H), 7.10 (dd, J = 7.8, 1.8 Hz, 2H), 7.07 (d, J = 2.3 Hz, 1H), 6.99 (s, 1H), 2.80 (s, 3H), 2.26 (s, 3H). **^{13}C NMR (101 MHz, CDCl$_3$)** δ 140.7, 137.7, 136.9, 136.8, 136.4, 134.4, 133.7, 131.6, 131.3, 130.8, 128.2, 128.0, 127.9, 127.0, 124.6, 124.2, 121.6, 101.7, 23.8, 21.5. **HRMS** $C_{25}H_{20}N_2$ [M + H]$^+$: calculated: 349.1705, found: 349.1700.

2-Methoxy-3,4-diphenylpyrazolo[5,1-*a*]isoquinoline (3i)



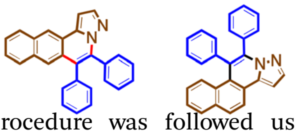
. The general procedure was followed using **1i** (60 mg, 0.34 mmol) and **2a** (74 mg, 0.41 mmol) at 100 °C for 16 h. Purification using preparative TLC plates (petroleum ether/acetone = 100/5 mL/mL) afforded **3i** (25 mg, 21%) as a brown solid. M. pt. 137 °C; **^{1}H NMR (400 MHz, chloroform-*d*)** δ 7.93 (d, J = 2.1 Hz, 1H), 7.39 (d, J = 2.1 Hz, 1H), 7.32 (t, J = 8.1 Hz, 1H), 7.27–7.21 (m, 4H), 7.21–7.15 (m, 8H), 7.00 (d, J = 7.7 Hz, 1H), 6.93 (d, J = 8.2 Hz, 1H), 4.07 (s, 3H). **^{13}C NMR (101 MHz, CDCl$_3$)** δ 155.8, 141.0, 136.9, 136.6, 135.4, 133.4, 131.9, 131.6, 130.7, 128.2, 127.9, 127.9, 127.7, 127.0, 123.6, 118.7, 115.0, 107.7, 102.8, 55.8. **HRMS** $C_{24}H_{18}N_2O$ [M + H]$^+$: calculated: 351.1497, found: 351.1493.

3,4-Diphenylbenzo[*h*]pyrazolo[5,1-*a*]isoquinoline (3j)



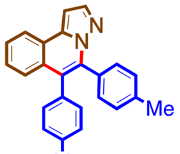
. The general procedure was followed using **1j** (66 mg, 0.34 mmol) and **2a** (72 mg, 0.41 mmol) at 100 °C for 16 h. Purification using preparative TLC plates (petroleum ether/acetone = 100/5 mL/mL) afforded **3j** (30 mg, 24%) as a brown solid. M. pt. 191–192 °C; **^{1}H NMR (400 MHz, chloroform-*d*)** δ 9.14 (d, J = 8.6 Hz, 1H), 8.21 (d, J = 2.3 Hz, 1H), 8.02 (dd, J = 8.0, 1.4 Hz, 1H), 7.88–7.82 (m, 2H), 7.75–7.69 (m, 2H), 7.53 (d, J = 8.9 Hz, 1H), 7.42 (d, J = 2.0 Hz, 1H), 7.41–7.38 (m, 1H), 7.38 (s, 1H), 7.36 (d, J = 0.8 Hz, 1H), 7.35–7.34 (m, 2H), 7.33 (q, J = 1.6 Hz, 2H), 7.28 (d, J = 1.7 Hz, 2H). **^{13}C NMR (101 MHz, CDCl$_3$)** δ 141.8, 137.3, 137.3, 136.6, 133.6, 132.6, 131.7, 130.7, 129.3, 129.0, 129.0, 128.5, 128.4, 128.1, 128.0, 127.5, 127.2, 126.5, 125.3, 124.7, 124.5, 120.6, 101.1. **HRMS** $C_{27}H_{18}N_2$ [M + H]$^+$: calculated: 371.1548, found: 371.1545.

3,4-Diphenylbenzo[*g*]pyrazolo[5,1-*a*]isoquinoline (3k + 3k′)



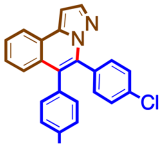
. The general procedure was followed using **1k** (66 mg, 0.34 mmol) and **2a** (93 mg, 0.52 mmol) at 100 °C for 16 h. Purification using preparative TLC plates (petroleum ether/acetone = 100/5 mL/mL) afforded **3k** and **3k′** (18 mg, 15%) as a brown solid. M. pt. 164–166 °C; **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.72 (s, 1H), 8.26 (d, J = 8.7 Hz, 1H), 8.10–7.99 (m, 4H), 7.95–7.87 (m, 2H), 7.83 (d, J = 8.3 Hz, 1H), 7.57 (tt, J = 6.5, 1.3 Hz, 2H), 7.53–7.42 (m, 3H), 7.41 (d, J = 1.9 Hz, 1H), 7.39 (p, J = 1.8 Hz, 2H), 7.37 (d, J = 1.8 Hz, 1H), 7.35 (d, J = 2.8 Hz, 2H), 7.34–7.33 (m, 2H), 7.32 (d, J = 2.6 Hz, 4H), 7.30 (d, J = 2.1 Hz, 3H), 7.28 (d, J = 3.2 Hz, 3H), 7.27 (t, J = 1.9 Hz, 1H), 7.21 (td, J = 3.8, 1.9 Hz, 3H), 7.10 (ddd, J = 8.6, 6.9, 1.6 Hz, 1H). **^{13}C NMR (101 MHz, CDCl$_3$)** δ 141.7, 140.8, 139.9, 139.0, 138.3, 137.9, 136.3, 136.1, 134.1, 133.6, 133.2, 132.6, 132.1, 131.7, 131.6, 131.4, 130.9, 130.8, 130.3, 129.6, 128.9, 128.5, 128.5, 128.5, 128.3, 128.2, 128.1, 128.1, 128.0, 127.9, 127.7, 127.5, 127.3, 127.1, 126.6, 126.2, 126.0, 125.6, 125.4, 124.0, 123.8, 123.3, 122.5, 122.2, 121.9, 99.2, 97.3. **HRMS** $C_{27}H_{18}N_2$ $[M + H]^+$: calculated: 371.1548, found: 371.1546.

3,4-Bis(4-methylphenyl)-pyrazolo[5,1-*a*]isoquinoline (5a)



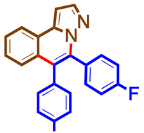
. The general procedure was followed using **1b** (70 mg, 0.34 mmol) and **4a** (50 mg, 0.41 mmol) at 100 °C for 16 h. Purification using preparative TLC plates (petroleum ether/acetone = 85/15 mL/mL) afforded **5a** (31 mg, 38%) as a brown solid. M. pt. 180–182 °C; **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.33–8.15 (m, 1H), 8.01 (s, 1H), 7.60 (s, 1H), 7.46 (s, 2H), 7.39–7.23 (m, 3H), 7.15 (s, 6H), 2.37 (d, J = 11.5 Hz, 6H). **^{13}C NMR (101 MHz, CDCl$_3$)** δ 140.9, 138.5, 138.0, 136.6, 136.5, 133.2, 131.4, 130.6, 130.3, 130.2, 128.7, 127.6, 127.2, 126.8, 124.0, 123.8, 123.5, 97.4, 21.4, 21.3. **HRMS** $C_{25}H_{20}N_2$ $[M + H]^+$: calculated: 349.1705, found: 349.1701.

3,4-Bis(4-chlorophenyl)-pyrazolo[5,1-*a*]isoquinoline (5b)



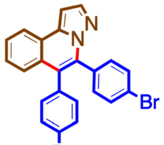
. The general procedure was followed using **1b** (50 mg, 0.34 mmol) and **4b** (50 mg, 0.23 mmol) at 100 °C for 16 h. Purification using preparative TLC plates (petroleum ether/acetone = 100/5 mL/mL) afforded **5b** (26 mg, 33%) as a brown solid. M. pt. 160–162 °C; **^{1}H NMR (400 MHz, chloroform-*d*)** δ 7.91–7.86 (m, 1H), 7.50–7.45 (m, 4H), 7.35 (d, J = 8.5 Hz, 4H), 7.21 (d, J = 8.5 Hz, 1H), 7.10–7.03 (m, 2H), 7.01 (d, J = 8.5 Hz, 1H), 6.77 (d, J = 8.4 Hz, 1H). **^{13}C NMR (101 MHz, CDCl$_3$)** δ 136.6, 134.5, 132.8, 132.4, 132.2, 131.1, 129.6, 128.9, 128.7, 128.3, 128.1, 127.7, 127.5, 125.4, 121.4, 89.1. **HRMS** $C_{23}H_{14}N_2Cl_2$ $[M + H]^+$: calculated: 389.0612, found: 389.0610.

3,4-Bis(4-fluorophenyl)-pyrazolo[5,1-*a*]isoquinoline (5c)



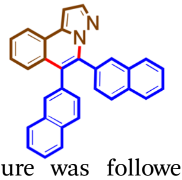
. The general procedure was followed using **1b** (67 mg, 0.34 mmol) and **4c** (50 mg, 0.23 mmol) at 100 °C for 16 h. Purification using preparative TLC plates (petroleum ether/acetone = 100/5 mL/mL) afforded **5c** (41 mg, 51%) as a brown solid. M. pt. 152–154 °C; **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.14 (dd, J = 7.7, 1.1 Hz, 1H), 7.90 (d, J = 2.2 Hz, 1H), 7.55–7.50 (m, 1H), 7.42–7.37 (m, 1H), 7.33–7.28 (m, 1H), 7.26–7.20 (m, 2H), 7.11–7.04 (m, 3H), 6.97–6.90 (m, 4H). **^{13}C NMR (101 MHz, CDCl$_3$)** δ 162.6, 162.1, 160.2, 159.7, 140.1, 137.5, 134.6, 132.1, 132.0, 131.7, 131.6, 130.8, 130.8, 128.7, 127.9, 127.9, 126.9, 126.6, 125.4, 123.0, 122.6, 122.2, 114.4, 114.3, 114.2, 114.1, 96.8. **^{19}F NMR (376 MHz, CDCl$_3$)** δ −112.2, −112.3, −112.3, −112.3, −112.3, −112.3, −112.3, −112.3, −114.2, −114.3, −114.3, −114.3, −114.3, −114.3. **HRMS** $C_{23}H_{14}N_2F_2$ $[M + H]^+$: calculated: 357.1203, found: 357.1200.

3,4-Bis(4-bromophenyl)-pyrazolo[5,1-*a*]isoquinoline (5d)



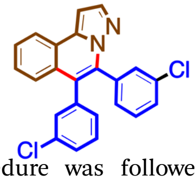
. The general procedure was followed using **1a** (43 mg, 0.29 mmol) and **4d** (50 mg, 0.15 mmol) at 100 °C for 16 h. Purification using preparative TLC plates (petroleum ether/acetone = 100/5 mL/mL) afforded **5d** (28 mg, 40%) as a brown solid. M. pt. 227–230 °C; **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.26–8.20 (m, 1H), 8.00 (d, J = 2.2 Hz, 1H), 7.63 (ddd, J = 8.1, 7.1, 1.2 Hz, 1H), 7.49 (ddt, J = 7.2, 3.0, 1.7 Hz, 5H), 7.39 (dt, J = 8.3, 1.0 Hz, 1H), 7.26–7.21 (m, 2H), 7.15 (d, J = 2.2 Hz, 1H), 7.13–7.07 (m, 2H). **^{13}C NMR (101 MHz, CDCl$_3$)** δ 141.2, 138.5, 135.2, 134.8, 133.1, 132.4, 131.7, 131.5, 131.5, 129.4, 128.0, 127.8, 126.4, 124.1, 123.7, 123.1, 122.9, 121.7, 97.9. **HRMS** $C_{23}H_{14}N_2Br_2$ $[M + H]^+$: calculated: 478.9582, found: 478.9581.

3,4-Bis(2-naphthyl)-pyrazolo[5,1-*a*]isoquinoline (5e)



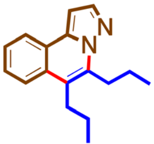
. The general procedure was followed using **1b** (48 mg, 0.33 mmol) and **4e** (50 mg, 0.17 mmol) at 100 °C for 16 h. Purification using preparative TLC plates (petroleum ether/acetone = 85/15 mL/mL) afforded **5e** (40 mg, 53%) as a brown solid. M. pt. 198–200 °C; **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.17 (d, J = 7.9 Hz, 1H), 7.91 (d, J = 2.1 Hz, 1H), 7.77 (s, 1H), 7.65 (dd, J = 13.6, 8.1 Hz, 6H), 7.57 (d, J = 8.0 Hz, 1H), 7.52 (ddd, J = 8.2, 6.4, 2.0 Hz, 1H), 7.46 (dd, J = 8.5, 1.7 Hz, 1H), 7.37–7.23 (m, 6H), 7.08 (d, J = 2.2 Hz, 1H). **^{13}C NMR (101 MHz, CDCl$_3$)** δ 141.1, 138.6, 136.5, 133.6, 133.0, 132.9, 132.3, 130.6, 130.6, 130.5, 130.2, 129.3, 128.3, 128.0, 127.9, 127.8, 127.7, 127.6, 127.6, 127.4, 126.9, 126.4, 126.1, 126.1, 125.8, 124.2, 124.1, 123.6, 97.7. **HRMS** $C_{31}H_{22}N_2$ $[M + H]^+$: calculated: 421.1705, found: 421.1701.

3,4-Bis(3-chlorophenyl)-pyrazolo[5,1-*a*]isoquinoline (5f)



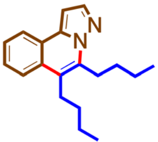
. The general procedure was followed using **1b** (50 mg, 0.34 mmol) and **4f** (50 mg, 0.20 mmol) at 100 °C for 16 h. Purification using preparative TLC plates (petroleum ether/acetone = 100/5 mL/mL) afforded **5f** (70 mg, 99%) as a brown solid. M. pt. 172–174 °C; **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.24 (dt, J = 8.0, 0.9 Hz, 1H), 8.01 (d, J = 2.1 Hz, 1H), 7.64 (ddd, *J* = 8.1, 7.1, 1.2 Hz, 1H), 7.51 (ddd, *J* = 8.4, 7.1, 1.3 Hz, 1H), 7.43–7.36 (m, 2H), 7.34–7.22 (m, 6H), 7.16 (d, *J* = 2.2 Hz, 1H), 7.12 (dt, *J* = 6.9, 1.7 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)** *δ* 141.4, 138.6, 137.6, 135.1, 134.3, 134.1, 134.0, 131.4, 130.9, 129.7, 129.5, 129.4, 129.3, 129.0, 128.9, 128.0, 127.9, 127.8, 126.5, 124.1, 123.7, 123.0, 97.9. **HRMS** $C_{23}H_{14}N_2Cl_2$ $[M + H]^+$: calculated: 389.0612, found: 389.0606.

3,4-Di-*n*-butylpyrazolo[5,1-*a*]isoquinoline (5h)



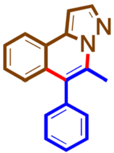
. The general procedure was followed using **1b** (129 mg, 0.89 mmol) and **4h** (50 mg, 0.41 mmol) at 100 °C for 16 h. Purification using preparative TLC plates (petroleum ether/acetone = 85/15 mL/mL) afforded **5h** (31 mg, 36%) as a yellow sticky solid. **^{1}H NMR (400 MHz, chloroform-*d*)** *δ* 7.57 (ddt, *J* = 9.1, 5.5, 1.7 Hz, 3H), 7.37–7.29 (m, 1H), 6.54 (d, *J* = 2.0 Hz, 1H), 6.08 (dd, *J* = 8.0, 6.9 Hz, 1H), 5.47 (t, *J* = 6.8 Hz, 1H), 2.42 (dq, *J* = 15.2, 7.6 Hz, 1H), 2.28 (dq, *J* = 14.9, 7.4 Hz, 1H), 1.81–1.70 (m, 1H), 1.66–1.55 (m, 1H), 1.37–1.23 (m, 3H), 1.15 (t, *J* = 7.5 Hz, 3H), 0.86 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** *δ* 139.1, 132.8, 132.5, 131.8, 128.3, 127.9, 125.0, 124.9, 123.6, 100.2, 58.1, 38.7, 21.5, 18.7, 14.0, 13.8. **HRMS** $C_{17}H_{20}N_2$ $[M + NH_3]^+$: calculated 269.1892, found: 269.1647.

3,4-Di-*n*-butylpyrazolo[5,1-*a*]isoquinoline (5i)



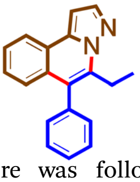
. The general procedure was followed using **1b** (50 mg, 0.34 mmol) and **4i** (153 µL, 0.68 mmol) at 100 °C for 16 h. Purification using preparative TLC plates (petroleum ether/acetone = 100/5 mL/mL) afforded **5i** (60 mg, 63%) as a yellow sticky solid. **^{1}H NMR (400 MHz, chloroform-*d*)** *δ* 8.13 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.99 (d, *J* = 2.2 Hz, 1H), 7.94–7.85 (m, 1H), 7.56 (dddd, *J* = 21.3, 8.3, 7.1, 1.3 Hz, 3H), 7.02 (d, *J* = 2.2 Hz, 1H), 3.38–3.30 (m, 2H), 3.03–2.95 (m, 2H), 1.87–1.76 (m, 2H), 1.73–1.65 (m, 2H), 1.62–1.54 (m, 4H), 1.06 (d, *J* = 7.4 Hz, 3H), 1.02 (d, *J* = 7.5 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** *δ* 139.8, 138.8, 137.7, 136.8, 129.0, 127.9, 127.6, 126.2, 126.2, 123.9, 123.8, 123.8, 123.6, 123.5, 119.0, 97.1, 32.7, 30.1, 27.9, 27.3, 23.1, 23., 14.0, 14.0, 13.9. **HRMS** $C_{19}H_{24}N_2$ $[M + NH_4Cl]^+$: calculated: 333.1972, found: 333.2325.

3-Methyl-4-phenylpyrazolo[5,1-*a*]isoquinoline (5j)



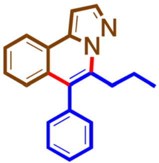
. The general procedure was followed using **1** (50 mg, 0.34 mmol) and **4j** (86 µL, 0.68 mmol) at 100 °C for 16 h. Purification using preparative TLC plates (petroleum ether/acetone = 90/10 mL/mL) afforded **5j** (25 mg, 29%) as a brown solid. M. pt. 80–82 °C; **^{1}H NMR (400 MHz, chloroform-*d*)** *δ* 8.12–8.08 (m, 1H), 7.86–7.82 (m, 1H), 7.81 (d, *J* = 2.1 Hz, 1H), 7.57–7.51 (m, 3H), 7.51–7.47 (m, 2H), 7.47–7.43 (m, 1H), 7.40 (dd, *J* = 8.1, 1.6 Hz, 2H), 6.96 (d, *J* = 2.2 Hz, 1H), 2.28 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** *δ* 140.4, 138.0, 135.9, 133.8, 130.4, 129.8, 128.9, 128.7, 127.8, 127.2, 124.4, 124.1, 123.8, 116.2, 97.3, 15.0. **HRMS** $C_{18}H_{14}N_2$ $[M + Na]^+$: calculated: 281.1055, found: 281.2008.

3-Ethyl-4-phenylpyrazolo[5,1-*a*]isoquinoline (5k)



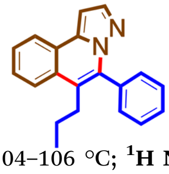
. The general procedure was followed using **1** (50 mg, 0.34 mmol) and **4k** (50 mg, 0.38 mmol) at 100 °C for 16 h. Purification using preparative TLC plates (petroleum ether/acetone = 100/5 mL/mL) afforded **5k** (34 mg, 33%) as a brown solid. M. pt. 88–90 °C; **^{1}H NMR (400 MHz, chloroform-*d*)** *δ* 8.13–8.08 (m, 1H), 7.90–7.84 (m, 1H), 7.81 (d, *J* = 2.2 Hz, 1H), 7.56–7.42 (m, 5H), 7.42–7.36 (m, 2H), 6.96 (d, *J* = 2.2 Hz, 1H), 2.70 (q, *J* = 7.5 Hz, 2H), 1.14 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** *δ* 139.5, 136.9, 134.7, 132.8, 128.8, 127.8, 127.8, 127.5, 126.7, 126.0, 123.6, 123.4, 123.1, 121.3, 96.1, 76.3, 75.9, 75.6, 20.5, 14.1. **HRMS** Calc'd for $C_{19}H_{16}N_2$ $[M + H]^+$: calculated 273.1386 found: 273.1388.

3-Butyl-4-phenylpyrazolo[5,1-*a*]isoquinoline (5l)



. The general procedure was followed using **1** (50 mg, 0.34 mmol) and **4l** (67 µL, 0.41 mmol) at 100 °C for 16 h. Purification using preparative TLC plates (petroleum ether/acetone = 100/5 mL/mL) afforded **5l** (34 mg, 35%) and **5l′** (21 mg, 20%) as a brown solid. M. pt. 48–50 °C; **^{1}H NMR (400 MHz, chloroform-*d*)** *δ* 8.20–8.15 (m, 1H), 8.08 (d, *J* = 2.2 Hz, 1H), 7.58–7.49 (m, 4H), 7.45–7.38 (m, 1H), 7.38–7.35 (m, 2H), 7.21 (d, *J* = 8.1 Hz, 1H), 7.11 (d, *J* = 2.3 Hz, 1H), 3.04–2.97 (m, 2H), 1.83–1.77 (m, 2H), 0.92 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** *δ* 140.2, 138.3, 137.2, 136.7, 130.9, 128.6, 127.7, 127.6, 126.6, 126.3, 123.4, 123.2, 97.5, 31.2, 21.2, 14.2. **HRMS** $C_{20}H_{18}N_2$ $[M + H]^+$: calculated: 287.1548, found: 287.1544.

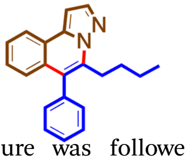
3-Phenyl-4-propylpyrazolo[5,1-*a*]isoquinoline (5l′)



. Brown solid, M. pt. 104–106 °C; **^{1}H NMR (400 MHz, chloroform-*d*)** *δ* 8.24–8.17 (m, 1H), 7.99–7.87 (m, 2H), 7.68–7.52 (m, 5H), 7.52–7.45 (m, 2H), 7.06 (d, *J* = 2.2 Hz, 1H), 2.77–2.70 (m, 2H), 1.73–1.62 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR**

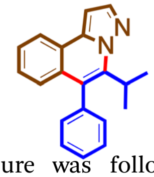
(101 MHz, $CDCl_3$) δ 140.6, 138.0, 136.0, 133.9, 130.0, 128.9, 128.9, 128.7, 128.6, 127.7, 127.1, 124.6, 124.5, 124.1, 121.1, 97.2, 30.5, 24.0, 14.4. **HRMS** $C_{20}H_{18}N_2$ $[M + H]^+$: calculated: 287.1548, found: 287.1542.

3-Butyl-4-phenylpyrazolo[5,1-*a*]isoquinoline (5m)



. The general procedure was followed using **1** (50 mg, 0.34 mmol) and **4m** (122 µL, 0.68 mmol) at 100 °C for 16 h. Purification using preparative TLC plates (petroleum ether/acetone = 100/5 mL/mL) afforded **5m** (38 mg, 37%) as a brown solid. M. pt. 48–50 °C; **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.13–8.07 (m, 1H), 7.85 (dd, *J* = 7.6, 2.0 Hz, 1H), 7.81 (d, *J* = 2.2 Hz, 1H), 7.55–7.42 (m, 5H), 7.41–7.36 (m, 2H), 6.95 (d, *J* = 2.1 Hz, 1H), 2.68–2.60 (m, 2H), 1.57–1.47 (m, 2H), 1.22 (dt, *J* = 14.8, 7.4 Hz, 2H), 0.75 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 140.6, 139.5, 137.9, 135.9, 133.8, 130.1, 130.0, 129.1, 128.3, 128.9, 128.8, 128.7, 128.6, 128.1, 127.7, 127.6, 127.1, 127.1, 124.6, 124.5, 124.4, 124.1, 123.7, 121.2, 97.2, 32.8, 28.0, 22.9, 13.7. **HRMS** $C_{21}H_{20}N_2$ $[M + H]^+$: calculated: 301.1705, found: 301.1707.

3-(2,2-Dimethyl-1-ol)-4-phenylpyrazolo[5,1-*a*]isoquinoline (5n)



. The general procedure was followed using **1** (67 mg, 0.46 mmol) and **4n** (57 mg, 0.31 mmol) at 100 °C for 16 h. Purification using preparative TLC plates (petroleum ether/acetone = 100/5 mL/mL) afforded **5n** (19 mg, 20%) as a brown solid. M. pt. 125–126 °C; **^{1}H NMR (400 MHz, chloroform-*d*)** δ 8.18–8.13 (m, 1H), 8.05 (d, *J* = 2.2 Hz, 1H), 7.58–7.48 (m, 4H), 7.41–7.32 (m, 3H), 7.14–7.07 (m, 2H), 1.66 (s, 1H), 1.53 (d, *J* = 7.1 Hz, 6H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 141.1, 139.9, 138.9, 137.5, 130.6, 130.3, 128.6, 127.6, 127.4, 126.6, 126.5, 123.3, 123.1, 121.8, 96.8, 31.4, 30.2, 19.1. **HRMS** $C_{20}H_{18}N_2O$ $[M + H]^+$: calculated: 303.1497, found: 303.1499.

Author contributions

SK conceived and designed the project and performed the bulk of the experimental studies. PA synthesized the 2-phenylpyrazoles and symmetrical alkynes. Both authors have contributed to the writing of the manuscript.

Conflicts of interest

There are no conflicts to declare.

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