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A Room-Temperature Protocol to Access Isoquinolines through Ag(I) Catalysed Annulation of *o*-(1-Alkynyl) arylaldehydes and Ketones with NH_4OAc: Elaboration to Berberine and Palmatine†

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An efficient and mild protocol for the direct construction of aryl- and alkyl-substituted isoquinolines has been realized through silver nitrate catalyzed aromatic annulation of *o*-(1-alkynyl)arylaldehydes and ketones with ammonium acetate. The salient feature of this methodology is that this annulation could be effected at room temperature leading to a wide range of isoquinoline derivatives in good to excellent yields. Additionally, this approach has been employed to the synthesis of biologically important isoquinoline alkaloids such as berberine and palmatine.

Introduction

The isoquinoline core has been recognized as an important synthetic target due to its existence as a central core in many natural products.[1] Some of the isoquinoline alkaloids exhibit antimalarial, antifungal, antitumor and antihypertensive activities (Fig 1).[2] Classical approaches for the construction of the isoquinoline core such as Pomeranz–Fritch,[3] Pictet–Spengler[4] and Bischler–Napieralski[5] reactions involve either the use of highly corrosive reagents or harsh reaction conditions. In order to overcome these hitches, many alternative methods have been developed, and out of those methods, metal catalysed approaches were found to be dominating as they involve relatively milder conditions.

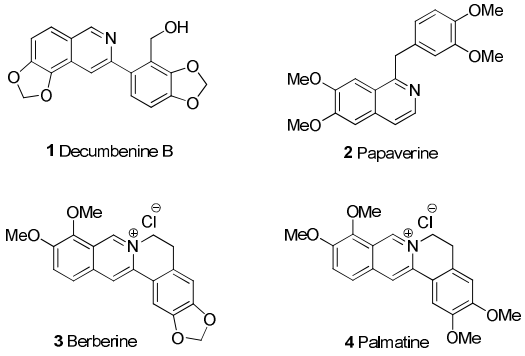

Figure 1: Biologically active natural isoquinolines (**1** – **4**)

Scheme 1 comprehends all the major metal catalysed approaches to the synthesis of the isoquinoline core. Larock's isoquinoline synthesis comprises intramolecular cyclization of *o*-(1-alkynyl)benzaldimines under Pd-catalysed conditions at elevated temperature (path **A**).[6] After this seminal contribution, many modified or alternative protocols have been developed using *o*-(1-alkynyl)benzaldimines,[7] *o*-(1-alkynyl)benzaldoximes[8] and other derivatives[9] under metal (Ag or Pd or Cu) catalysed conditions (path **A**). Yamomoto's group has developed iodine mediated electrophilic cyclisation of *o*-(1-alkynyl)benzyl azides to highly substituted iodo isoquinoline derivatives (path **B**).[10] Later, the same group has developed Gold catalysed cyclization of *o*-(1-alkynyl)benzyl azides to isoquinolines at elevated temperatures.[11] Another interesting approach to isoquinoline comprises of intermolecular annulation of imine or hydroxylamine derivatives with internal alkynes using Rhodium catalysts (path **C**).[12] Apart from these methods, a few direct approaches have been reported, where the synthesis of isoquinolines was effected by treatment of *o*-(1-alkynyl)arylaldehydes with amine source such as ammonia, NH_4Cl etc. under TfOH mediated condition[13] or microwave irradiation[14] or at high temperatures (path **D**).[15] A few other reports have also been reported involving microwave assisted one-pot, three component synthesis of isoquinolines from 2-bromo benzaldehydes through Sonagashira coupling with terminal alkynes followed by cyclisation with ammonium salts.[16] In addition to the above mentioned reports, a few other different strategies have been reported for the synthesis of isoquinoline derivatives.[17]

Surprisingly, the metal catalysed direct synthesis of isoquinoline derivatives from *o*-(1-alkynyl)arylaldehydes or ketones and an amine source at *room temperature* has not been reported so far. While

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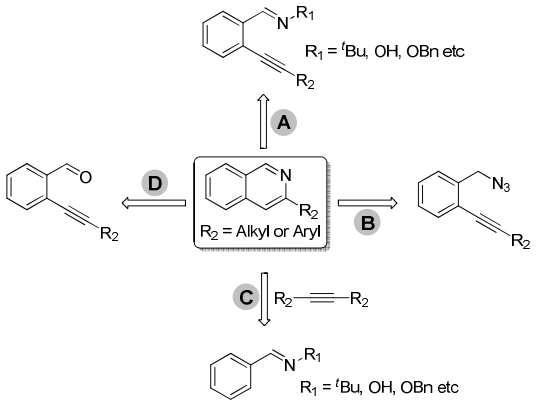
working on the synthesis of isoquinoline alkaloids, we envisioned to develop an efficient protocol for the direct synthesis isoquinolines from readily available precursors under mild conditions. We hereby report silver nitrate catalysed synthesis of isoquinoline derivatives from *o*-(1-alkynyl)arylaldehydes and ketones using ammonium acetate as an amine source at room temperature.

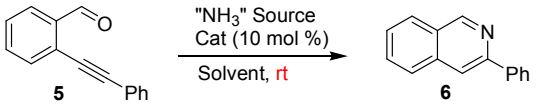


Scheme 1: Major approaches toward isoquinoline core

Results and Discussion

The optimisation studies were carried out using *o*-(phenylethynyl)benzaldehyde (**5**)[18] under various conditions. Our initial studies focused on the selection of a suitable catalyst for this transformation. The preliminary screening of the catalysts gave disappointing results as $Bi(OTf)_3$ and $Yb(OTf)_3$, which are known to activate alkynes,[19] failed to give the desired product **6** even after 12 h at room temperature (Entries 1 & 2, Table 1). Astoundingly, when the reaction was performed using Ag_2O as a catalyst and ammonium acetate as an amine source in ^{t}BuOH, the desired product **6** was obtained in 80% yield (Entry 3). Encouraged by this result, further screening was carried out using a variety of silver catalysts (Entries 4–9). Out of several catalysts tried, AgOTf and $AgNO_3$ (Entries 6 & 7) were found to give better results. Since $AgNO_3$ is much cheaper compared to AgOTf, further optimisation studies were performed using $AgNO_3$ as a catalyst. A few experiments were also performed using other solvents (Entries 10–13) and other ammonia sources (Entries 14–16); but in all those cases, yield of the product was inferior when compared to Entry 7. When the reaction was carried out in the absence of silver catalyst, the isoquinoline **6** was obtained only in <5% yield even after 24 h (Entry 17).

Table 1. Optimisation studies[a]



Entry	Catalyst	"NH_3" Source[b]	Solvent	Time [h]	Yield [%][c]
1	$Bi(OTf)_3$	NH_4OAc	^{t}BuOH	12	--
2	$Yb(OTf)_3$	NH_4OAc	^{t}BuOH	12	--
3	Ag_2O	NH_4OAc	^{t}BuOH	8	80
4	$AgClO_4$	NH_4OAc	^{t}BuOH	8	80
5	$Ag(OCOCF_3)$	NH_4OAc	^{t}BuOH	8	84
6	**AgOTf**	**NH_4OAc**	**^{t}BuOH**	**6**	**95**
7	**$AgNO_3$**	**NH_4OAc**	**^{t}BuOH**	**6**	**95**
8	Ag_2CO_3	NH_4OAc	^{t}BuOH	8	92
9	$AgSbF_6$	NH_4OAc	^{t}BuOH	8	92
10	$AgNO_3$	NH_4OAc	CH_2Cl_2	15	57
11	$AgNO_3$	NH_4OAc	CH_3CN	15	45
12	$AgNO_3$	NH_4OAc	THF	15	33
13	$AgNO_3$	NH_4OAc	EtOH	15	65
14	$AgNO_3$	NH_4HCO_3	^{t}BuOH	9	70
15	$AgNO_3$	NH_4OH	^{t}BuOH	24	70
16	$AgNO_3$	NH_4Cl	^{t}BuOH	24	--
17	--	NH_4OAc	^{t}BuOH	24	<5

[a] *Reaction conditions*: 0.12 M solution of **5** in solvent [b] 1.5 equiv. of NH_3 source was used in all the reactions [c] Isolated yields. rt = 27–30 °C

Having optimised condition in hand, we investigated the substrate scope of this transformation. For this purpose, a wide range of *o*-(1-alkynyl)arylaldehydes[18] and ketones[20] were prepared and subjected to 6-*endo-dig* cyclisation reaction under optimised conditions (Entry 7, Table 1), and the results are summarised in Table 2. It is evident from Table 2 that most of the *o*-(1-alkynyl)arylaldehydes could be converted to their corresponding isoquinoline derivatives in good to excellent yields. The reaction worked very well in the case of *o*-(1-alkynyl)arylaldehydes derived from alkynes bearing electron rich aryl substituents. For example, in the cases of alkyl or alkyloxy phenyl substituted alkynyl aldehydes, the respective isoquinolines (**6a**–**6g**) were obtained in very good yields. In bromo substituted case, the product **6h** was obtained only in 50% yield. For isoquinoline precursors (**5i**–**5n**), derived from other substituted 2-bromo benzaldehydes, the annulation reaction took place capably leading to the products **6i** to **6n** in good yields. The reaction also worked competently in the cases of isoquinoline precursors **5o** and **5p**, which were derived from alkynes with aliphatic substituents, and the products **6o** and **6p** were obtained in 70 and 84% yields respectively. Unfortunately, this methodology was found to be less effective in the cases of *o*-(1-alkynyl)arylaldehydes with electron poor aryl substituents attached to alkyne (**5q**–**5s**). For example, the aldehydes such as **5q** and **5r**, gave the corresponding isoquinolines **6q** and **6r** in only 15–20% yields. No product (**6s**) was observed in the case of *o*-(4-nitrophenylethynyl)benzaldehyde (**5s**). But, gratifyingly, the extension of this methodology to *o*-(1-alkynyl)arylketones,[15,20] gave fruitful results. As seen in Table 2, some of the *o*-(1-alkynyl)acetophenone derivatives such as **5t** and **5u** underwent 6-*endo-dig* cyclisation to the respective methyl substituted isoquinoline derivatives **6t** and **6u** in excellent yields.

At this stage, we were interested in elucidating a reasonable mechanism of this transformation. It is well documented in the literature that the uncatalysed reaction between **5** and an ammonia source at higher temperature proceeds through imine intermediate, which on cyclisation leads to isoquinoline derivative **6**.[15] On the other hand; Swager's group found that TfOH promotes the formation of pyrylium intermediate, which on exposure with ammonia gives the isoquinoline derivative.[13] To understand whether our methodology proceeds through imine or pyrylium intermediate, a few experiments were performed. In one of the experiments, *o*-(1-alkynyl)benzaldehyde **5** was treated with ammonium acetate in the absence of silver catalyst at room temperature and the progress of the reaction was monitored by ^{1}H NMR spectroscopy (in CD_3CN). In this case, the characteristic peak that corresponds to C*H*=N proton was not observed even after 12 h, and most the aldehyde **5** remained

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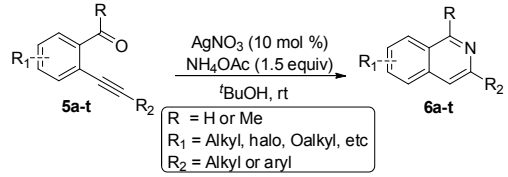
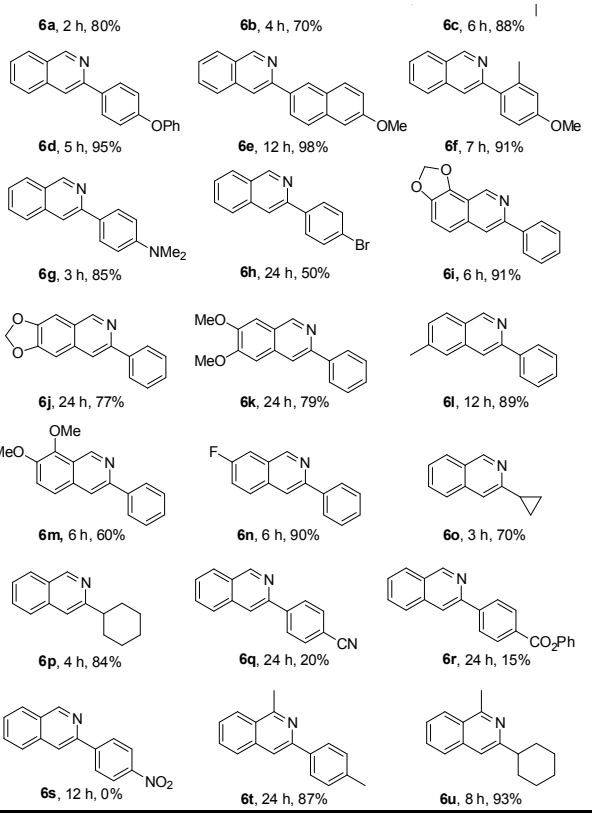
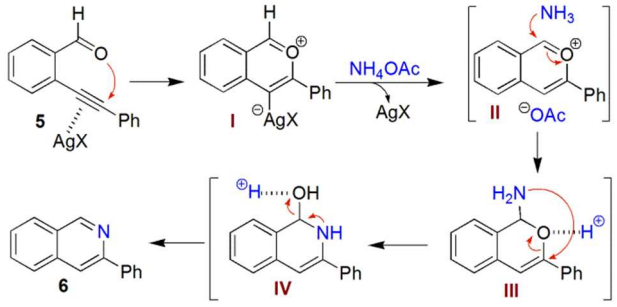
Table 2: Substrate scope:





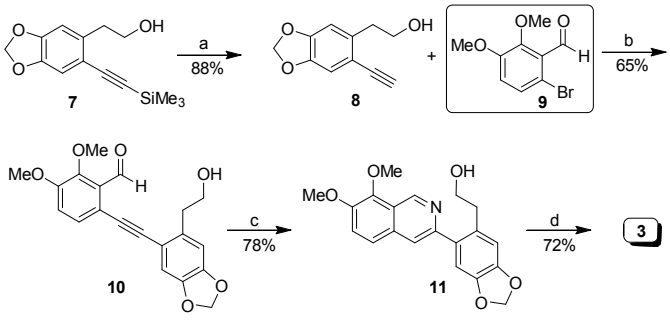
[a] *Reaction conditions*: 0.12 M solution of **5** in ^{t}BuOH. Yields reported are isolated yields. rt = 27–30 °C.

unreacted. In another experiment, **5** was treated with stoichiometric amounts of $AgNO_3$ in CD_3CN at room temperature and the ^{1}H NMR was recorded after 12 h. In this case, along with the aldehyde signal, a new singlet appeared at 10.01 ppm. We presume that the signal at 10.01 ppm corresponds to the C*H*=O proton of the pyrylium salt because this δ value approximately matches with the δ value (10.14 ppm) of the pyrylium C*H*=O proton reported by the Swager's group though the reaction conditions are different (please see SI for spectra).[13] When ammonium acetate was added to this reaction mixture, the signal at 10.01 disappeared and a new signal at 9.35 ppm, which corresponds to the C*H*=N proton of isoquinoline, appeared after 5 h. The signal that corresponds to aldimine C*H*=N proton was not observed in ^{1}H NMR during the reaction. The above experiments indicate that our methodology proceeds through pyrylium intermediate and not through imine. Based on the above observations, a possible mechanism has been proposed (Scheme 2). In the initial step, $AgNO_3$ coordinates with the alkyne and the oxygen of aldehyde group attacks the alkyne in an 6-*endo-dig* fashion to give the pyrylium intermediate **I**, which undergoes protonation with acetic acid (which was produced during the decomposition of ammonium acetate) gives intermediate **II**. Nucleophilic attack of ammonia to the pyrylium C=O leads to the formation of intermediate **III**, which presumably rearranges to hemiaminal **IV** under acidic condition. Finally, hemiaminal **IV** decomposes to isoquinoline **6** (Scheme 2).



Scheme 2: Plausible mechanism for isoquinoline formation

To portray its synthetic application, this protocol was elaborated to the total synthesis of berberine (**3**) and palmatine (**4**). Berberine (**3**), isolated from a plant *Coptis chinensis*, is a member of protoberberine class of isoquinoline alkaloids.[21] Berberine has been used as a drug for the treatment of diarrhea in China for many decades. Berberine possesses a wide range of biological activities such as antimalarial,[22] antifungal,[23] antibacterial,[24] antiviral,[25] anticancer,[26] antileishmanial[27] etc. Recent studies showed that **3** also exhibits cholesterol lowering activity in animals and patients with hypercholesterolemia without any sign of side effects.[28] It was found that the cholesterol lowering activity increased further if **3** was used in combination with statins.[29] Palmatine (**4**), a structural analog of berberine (**3**), also exhibits interesting biological properties. Palmatine has been used for the treatment of dysentery, jaundice, hypertension etc.,[30] and its derivatives are known to possess antimalarial and antimicrobial activities.[31] Only two reports are available in the literature for the total synthesis of berberine (3). In 1969, Kametani's group reported the first synthesis of berberine iodide.[32] While working on this manuscript, a research article has been appeared, from Donohoe's group, for the synthesis of berberine and palmatine through palladium catalysed enolate arylation reaction.[33] A few other reports are available for the synthesis of berberine (3) and palmatine (4) analogues.[21,34]



Reaction conditions: (a) TBAF, THF, rt, 1 h (b) $PdCl_2(PPh_3)_2$, CuI, Et_3N, 70 °C, 3 h (c) NH_4OAc, $AgNO_3$, ^{t}BuOH, rt, 15 h (d) PPh_3, CH_2Cl_2:CCl_4 (1:2), rt, 12 h.

Scheme 3. Total synthesis of berberine (**3**)

Scheme 3 represents our strategy for the synthesis of berberine (**3**). This unprecedented synthetic approach involves four direct steps to

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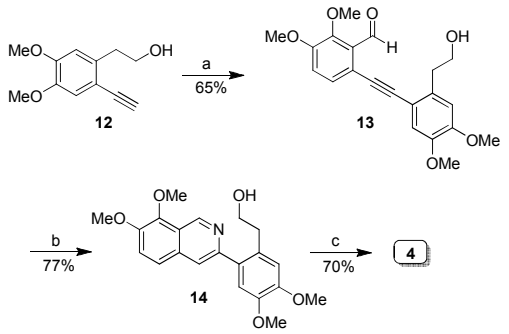
access **3** from readily available silylated alkynyl aryl ethanol derivative **7**.[35] Deprotection of **7** with TBAF gave the 2-alkynyl aryl ethanol derivative **8** in 88% yield. The Sonagashira coupling between **8** and 2,3-dimethoxy-5-bromo benzaldehyde (**9**)[36] gave the isoquinoline precursor **10** in 65% yield. The annulation reaction of **10** was carried out under our optimised reaction condition (Table 2) and the isoquinoline derivative **11** was obtained in 78% yield. Finally, the isoquinoline **11** was subjected to cyclisation under Appel condition[37] to provide berberine (**3**) in 72% yield (32% overall yield from **7**).

In a similar mode, palmatine (**4**) was synthesised from the 2-alkynyl aryl ethanol derivative **12**[38] in three linear steps as shown in Scheme 4. The starting material **12** was subjected to Sonagashira coupling with **9** to give the arylated alkyne **13** in 65% yield. On exposure to ammonium acetate under our optimised condition, **13** underwent 6-*endo-dig* cyclisation to give the isoquinoline derivative **14**, which was then converted to palmatine (**4**) under Appel condition (35% overall yield from **12**).



Reaction conditions: (a) **9**, $PdCl_2(PPh_3)_2$, CuI, Et_3N, 70 °C, 4 h (b) NH_4OAc, $AgNO_3$, ^tBuOH, rt, 14 h (c) PPh_3, CH_2Cl_2:CCl_4 (1:2), rt, 24 h.

Scheme 4. Total synthesis of palmatine (**4**)

Experimental

I. General methods

All reactions were carried out under argon atmosphere in an oven dried round bottom flask. Triethylamine was dried over calcium hydride, distilled and stored with molecular sieves. Melting points were recorded on SMP20 melting point apparatus and are uncorrected. Most of the reagents and starting materials were purchased from commercial sources and used as such. ^1H and ^{13}C spectra were recorded in $CDCl_3$ or DMSO-d_6 (400, 100 MHz respectively) on Bruker FT-NMR spectrometer. Chemical shifts (δ) values are reported in parts per million relative to TMS and the coupling constants (J) are reported in Hz. High resolution mass spectra were recorded on Waters Q-TOF Premier-HAB213 spectrometer. Thin layer chromatography was performed on Merck silica gel 60 F_{254} TLC plates. Column chromatography was carried out through silica gel (100-200 mesh) using EtOAc/hexane as an eluent.

II. Synthesis of 2-(arylethynyl)arylaldehydes and ketones

All the known compounds **5**[39], **5a**[14a], **5d**[40], **5e**[41], **5f**[14a], **5h**[42], **5j**[39], **5k**[39], **5l**[39], **5n**[39], **5o**[39], **5p**[6c], **5s**[42], **5t**[14b] were synthesised according to the literature procedure. Other precursors were prepared by adapting the following procedure.

General procedure:

Aryl acetylene (1.2 equiv) was added to a stirred solution of $PdCl_2(PPh_3)_2$ (0.02 equiv), CuI (0.01 equiv), and 2-bromo-arylaldehyde (1 equiv) or 2′-bromo acetophenone (1 equiv) in triethylamine (0.27 M) at room temperature and the reaction mixture was heated to 70 °C under inert atmosphere. After completion (by TLC), triethylamine was removed under reduced pressure. The residue was then diluted with dichloromethane and water. Organic layer was separated and aqueous layer was extracted two times with DCM. Combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The residue was purified through silica gel column chromatography using hexane/EtOAc to get pure (2-arylethynyl)arylaldehyde or ketone derivatives.

***2-[(4-Pentylphenyl)ethynyl]benzaldehyde (5b)*:** Yield: 70%; brown liquid; ^1H NMR (400 MHz, $CDCl_3$) δ 10.66 (s, 1H), 7.95–7.94 (m, 1H), 7.64–7.62 (m, 1H), 7.59–7.55 (m, 1H), 7.48 (d, J = 8.0 Hz, 2H), 7.46–7.41 (m, 1H), 7.20 (d, J = 7.9 Hz, 2H), 2.63 (t, J = 7.5 Hz, 2H), 1.66–1.59 (m, 2H), 1.37–1.28 (m, 4H), 0.90 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.0, 144.6, 135.9, 133.9, 133.3, 131.7, 128.8, 128.5, 127.33, 127.30, 119.6, 96.8, 84.4, 36.1, 31.6. 31.0, 22.6, 14.2; HRMS (ESI): *m/z* calcd for $C_{20}H_{21}O$ $[M+H]^+$: 277.1592; found: 277.1576.

***2-[(2,4,5-Trimethylphenyl)ethynyl]benzaldehyde (5c)*:** Yield: 86%; yellow solid; mp = 87–89 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 10.68 (d, J = 0.9 Hz, 1H), 7.95 (ddd, J = 7.8, 1.4, 0.6 Hz, 1H), 7.63 (ddd, J = 7.8, 1.4, 0.7 Hz, 1H), 7.60–7.56 (m, 1H), 7.46–7.41 (m, 1H), 7.32 (s, 1H), 7.03 (s, 1H), 2.46 (s, 3H), 2.26 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.1, 138.3, 137.9, 135.8, 134.2, 133.9, 133.3, 133.2, 131.2, 128.4, 127.7, 127.3, 119.4, 96.1, 88.0, 20.4, 19.9, 19.2; HRMS (ESI): *m/z* calcd for $C_{18}H_{17}O$ $[M+H]^+$: 249.1279; found: 249.1295.

***2-[(6-Methoxynaphthalen-2-yl)ethynyl]benzaldehyde (5e)*:** Yield: 90%; colourless solid; mp = 117–119 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 10.72 (d, J = 0.8 Hz, 1H), 8.03 (d, J = 0.9 Hz, 1H), 7.97 (ddd, J = 7.8, 1.4, 0.5 Hz, 1H), 7.75 (d, J = 2.9 Hz, 1H), 7.73 (d, J = 2.8 Hz, 1H), 7.69–7.67 (m, 1H), 7.62–7.58 (m, 1H), 7.57 (dd, J = 8.5, 1.6 Hz, 1H), 7.48–7.44 (m, 1H), 7.20 (dd, J = 8.9, 2.6 Hz, 1H), 7.14 (d, J = 2.5 Hz, 1H), 3.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.0, 158.8, 135.9, 134.7, 134.0, 133.3, 132.9, 131.9, 129.6, 128.9, 128.6, 127.5, 127.3, 127.2, 127.1, 119.8, 117.3, 106.0, 84.8, 55.5; HRMS (ESI): *m/z* calcd for $C_{20}H_{15}O_2$ $[M+H]^+$: 287.1072; found: 287.1081.

***2-[(4-(Dimethylamino)phenyl)ethynyl]benzaldehyde (5g)*:** Yield: 60%; crystalline yellow solid; mp = 100–102 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 10.67 (d, J = 0.8 Hz, 1H), 7.93–7.91 (m, 1H), 7.61–7.58 (m, 1H), 7.56–7.52 (m, 1H), 7.45–7.42 (m, 2H), 7.40–7.36 (m, 1H), 6.69–6.65 (m, 2H), 3.01 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.4, 150.7, 135.5, 133.9, 133.1, 132.9, 128.3, 127.8, 127.2, 111.9, 108.9, 98.4, 83.4, 40.3; HRMS (ESI): *m/z* calcd for $C_{17}H_{16}NO$ $[M+H]^+$: 250.1232; found: 250.1237.

***5-(Phenylethynyl)benzo[d][1,3]dioxole-4-carbaldehyde (5i)*:** Yield: 96%; yellow solid; mp = 138–140 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 10.56 (s, 1H), 7.54–7.51 (m, 2H), 7.38–7.35 (m, 3H), 7.16 (d, J = 8.0 Hz, 1H), 6.97 (d, J = 8.0 Hz, 1H), 6.19 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.2, 149.2, 148.0, 131.6, 128.9, 128.6, 127.6, 122.6, 119.2, 118.8, 113.0, 103.4, 94.3, 85.2; HRMS (ESI): *m/z* calcd for $C_{16}H_{11}O_3$ $[M+H]^+$: 251.0708; found: 251.0696.

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***2,3-Dimethoxy-6-(phenylethynyl)benzaldehyde (5m)*:** Yield: 87%; brown solid; mp = 95–97 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.61 (s, 1H), 7.58-7.55 (m, 2H), 7.35–7.33 (m, 3H), 7.07 (d, J = 8.6 Hz, 1H), 3.94 (s, 3H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.5, 153.4, 151.3, 131.8, 130.3, 130.0, 128.6, 128.5, 123.2, 116.8, 116.6, 93.4, 86.8, 62.2, 56.2; HRMS (ESI): *m/z* calcd for $C_{17}H_{15}O_3$ $[M+H]^+$: 267.1021; found: 267.1032.

***4-[(2-Formylphenyl)ethynyl]benzonitrile (5q)*:** Yield: 85%; off white solid; mp = 110–112 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.59 (d, J = 0.7 Hz, 1H), 7.99–7.96 (m, 1H), 7.70–7.61 (m, 6H), 7.54–7.50 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.2, 136.2, 134.0, 133.6, 132.4, 132.3, 129.6, 128.0, 127.3, 125.5, 118.4, 112.5, 94.2, 89.3; HRMS (ESI): *m/z* calcd for $C_{16}H_{10}NO$ $[M+H]^+$: 232.0762; found:.332.0771.

***Phenyl 4-((2-formylphenyl)ethynyl)benzoate (5r)*:** Yield: 66%; off wihite solid; mp = 122–124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.65 (s, 1H), 8.22 (d, J = 8.1 Hz, 2H), 7.98 (d, J = 7.8 Hz, 1H), 7.71–7.68 (m, 3H), 7.63 (t, J = 7.4 Hz, 1H), 7.51 (t, J = 7.5 Hz, 1H), 7.45 (t, J = 7.8 Hz, 2H), 7.31–7.22 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.5, 164.7, 150.9, 136.1, 134.0, 133.6, 131.9, 130.4, 129.8, 129.7, 129.4, 127.8, 127.7, 126.2, 121.8, 116.5, 100.6, 88.5; HRMS (ESI): *m/z* calcd for $C_{22}H_{15}O_3$ $[M+H]^+$: 327.1021; found: 327.1031.

***1-[2-(Cyclohexylethynyl)phenyl]ethanone (5u)*:** Yield: 50%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (ddd, J = 7.8, 1.4, 0.4 Hz, 1H), 7.48–7.46 (m, 1H), 7.38 (td, J = 7.4, 1.5 Hz, 1H), 7.31 (td, J = 7.7, 1.4 Hz, 1H), 2.73 (s, 3H), 2.66–2.60 (m, 1H), 1.91–1.88 (m, 2H), 1.78–1.71 (m, 2H), 1.58–1.49 (m, 3H), 1.37–1.31 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.3, 141.2, 134.0, 131.2, 128.4, 127.6, 122.6, 100.9, 79.8, 32.5, 30.4, 30.1, 26.0, 25.0; HRMS (ESI): *m/z* calcd for $C_{16}H_{19}O$ $[M+H]^+$: 227.1436; found: 227.1439.

III. General procedure for the synthesis of isoquinolines:

^{t}BuOH (1 ml) was added to a mixture of $AgNO_3$ (0.01 mmol, 0.1 equiv.), ammonium acetate (0.18 mmol, 1.5 equiv.) and 2-ethynyl arylaldehyde or ketone (0.12 mmol, 1 equiv.) under inert atmosphere. The resultant mixture was stirred at room temperature and the reaction was monitored by TLC. After completion, the reaction was quenched by the addition of $NaHCO_3$ (0.48 mmol, 4 equiv.) at room temperature and stirring was continued for additional 4 h. The mixture was then filtered through a cotton plug, washed with EtOAc (5–10 mL) and dried over anhydrous Na_2SO_4. The filtrate was evaporated under reduced pressure and the residue was purified through silica gel column chromatography (EtOAc in hexane) to get the pure isoquinoline derivative.

***3-Phenyisoquinoline (6)*:**[9b] Yield: 95%; brown solid; mp = 101–103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.35 (s, 1H), 8.15–8.12 (m, 2H), 8.07 (s, 1H), 7.99 (dd, J = 8.2, 0.9 Hz, 1H), 7.87 (d, J = 8.3 Hz, 1H), 7.70 (ddd, J = 8.2, 6.9, 1.3 Hz, 1H), 7.59 (ddd, J = 8.1, 6.9, 1.1 Hz, 1H), 7.55–7.50 (m, 2H), 7.45–7.40 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6, 151.4, 139.7, 136.8, 130.7, 128.9, 128.6, 127.9, 127.7, 127.2, 127.1, 127.0, 116.7; HRMS (ESI): *m/z* calcd for $C_{15}H_{12}N$ $[M+H]^+$: 206.0970; found: 206.968.

***3-(p-Tolyl)isoquinoline (6a)*:**[13] Yield: 80%; yellow solid; mp = 72–74 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.33 (s, 1H), 8.04–8.02 (m, 3H), 7.98 (d, J = 8.1 Hz, 1H), 7.85 (d, J = 8.2 Hz, 1H), 7.70–7.66 (m, 1H), 7.59–7.55 (m, 1H), 7.32 (d, J = 8.0 Hz, 2H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5, 151.4, 138.6, 136.9, 136.8, 130.6, 129.7(3C), 127.8, 127.7, 127.0, 116.4, 21.4; HRMS (ESI): *m/z* calcd for $C_{16}H_{13}N$ $[M+H]^+$: 220.1126; found: 220.1122.

***3-(4-Pentylphenyl)isoquinoline (6b)*:** Yield: 70%; brown solid; mp = 62–64 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.33 (t, J = 0.8 Hz,1H), 8.06-8.03 (m, 3H), 7.98 (dd, J = 8.2, 0.8 Hz, 1H), 7.86 (dd, J = 8.2, 0.6 Hz, 1H), 7.69 (ddd, J = 8.2, 6.9, 1.2 Hz, 1H), 7.57 (ddd, J = 8.1, 6.9 1.2 Hz, 1H), 7.33 (d, J = 8.4 Hz, 2H), 2.68 (t, J = 7.6 Hz, 2H), 1.72–1.64 (m, 2H), 1.38–1.33 (m, 4H), 0.93–0.89 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.3, 151.3, 143.8, 136.9, 136.8, 130.8, 129.1, 127.8, 127.7, 127.1, 127.1, 127.0, 116.3, 35.8, 31.6, 31.3, 22.7, 14.2; HRMS (ESI): *m/z* calcd for $C_{20}H_{22}N$ $[M+H]^+$: 276.1752; found: 276.1740.

***3-(2,4,5-Trimethylphenyl)isoquinoline (6c)*:** Yield: 88%; off white solid; mp = 82–84 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (s, 1H), 8.01 (dd, J = 8.2, 0.88 Hz, 1H), 7.84 (d, J = 8.3 Hz, 1H), 7.73–7.68 (m, 2H), 7.61 (ddd, J = 8.1, 6.8, 1.1 Hz, 1H), 7.31 (s, 1H), 7.10 (s, 1H), 2.37 (s, 3H), 2.30 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 151.8, 137.9, 136.6, 136.4, 134.1, 133.3, 132.3, 131.5, 130.6, 127.7, 127.2, 127.1, 126.8, 120.2, 20.0, 19.6, 19.4; HRMS (ESI): *m/z* calcd for $C_{18}H_{18}N$ $[M+H]^+$: 248.1439; found: 248.1441.

***3-(4-Phenoxyphenyl)isoquinoline (6d)*:** Yield: 95%; brown solid; mp = 106–108 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.32 (t, J = 0.8 Hz, 1H), 8.12–8.10 (m, 2H), 8.03 (s,1H), 8.0 (dd, J = 8.2, 0.9 Hz, 1H), 7.86 (dd, J = 8.3, 0.7 Hz, 1H), 7.70 (ddd, J = 8.2, 6.9, 1.3 Hz, 1H), 7.58 (ddd, J = 8.1, 6.9, 1.2 Hz, 1H), 7.39–7.35 (m, 2H), 7.16–7.12 (m, 3H), 7.11–7.07 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 157.1, 152. 2, 137.0, 131.1, 130.0, 128.7, 127.9, 127.6, 127.3, 127.0, 123.7, 122.0, 119.3, 119.1, 118.9, 116.4; HRMS (ESI): *m/z* calcd for $C_{21}H_{16}NO$ $[M+H]^+$: 298.1232; found: 298.1231.

***3-(6-Methoxynaphthalen-2-yl)isoquinoline (6e)*:**[14c] Yield: 98%; off white solid; 166–168 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.39 (s, 1H), 8.59 (d, J = 1.6 Hz, 1H), 8.21 (dd, J = 8.6, 1.8 Hz, 1H), 8.18 (s, 1H), 8.01 (dd, J = 8.2, 0.7 Hz, 1H), 7.91–7.86 (m, 3H), 7.72 (ddd, J = 8.1, 6.9, 1.2 Hz, 1H), 7.60 (ddd, J = 8.1, 6.9, 1.1 Hz, 1H), 7.21–7.18 (m, 2H), 3.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 152.5, 151.2, 137.0, 134.9, 134.6, 130.9, 130.4, 129.3, 127.8, 127.7, 127.5, 127.2, 127.1, 126.4, 125.3, 119.3, 116.6, 105.8, 55.5; HRMS (ESI): *m/z* calcd for $C_{20}H_{16}NO$ $[M+H]^+$: 286.1232; found: 286.1223.

***3-(4-Methoxy-2-methylphenyl)isoquinoline (6f)*:**[14a] Yield: 91%; pale yellow gummy solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (s, 1H), 8.03–8.00 (m, 1H), 7.86–7.84 (m, 1H), 7.74–7.70 (m, 2H), 7.61 (ddd, J = 8.1, 6.9, 1.2 Hz, 1H), 7.47–7.45 (m, 1H), 6.87–6.84 (m, 2H), 3.86 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 153.8, 151.7, 137.6, 136.5, 133.2, 131.5, 130.8, 127.8, 127.2, 126.8, 120.3, 116.3, 112.4, 111.4, 55.5, 21.0; HRMS (ESI): *m/z* calcd for $C_{17}H_{16}NO$ $[M+H]^+$: 250.1232; found: 250.1236.

***4-(Isoquinolin-3-yl)-N,N-dimethylaniline (6g)*:**[9b] Yield: 85%; pale yellow solid; mp = 140–142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.31 (s, 1H), 8.05 (d, J = 9.0 Hz, 2H), 7.97–7.94 (m, 2H), 7.84–7.82 (m, 1H), 7.66 (ddd, J = 8.1, 6.8, 1.2 Hz, 1H), 7.52 (ddd, J = 8.0, 6.8, 1.2 Hz, 1H), 6.85 (d, J = 9.0 Hz, 2H), 3.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.3, 151.7, 150.9, 137.1, 130.4, 127.9, 127.7, 127.6, 127.3, 126.8, 126.3, 114.4, 112.6, 40.6; HRMS (ESI): *m/z* calcd for $C_{17}H_{17}N_2$ $[M+H]^+$: 249.1392; found: 249.1404.

***3-(4-Bromophenyl)isoquinoline (6h)*:** Yield: 50%; brown solid; mp = 158–160 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (s, 1H), 8.06 (s, 1H), 8.04–7.99 (m, 3H), 7.88 (dd, J = 8.1, 0.6 Hz, 1H), 7.72 (ddd, J

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= 8.2, 6.8, 1.2 Hz, 1H), 7.66–7.60 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.7, 150.2, 138.6, 136.7, 132.0, 130.9, 128.7, 128.0, 127.8, 127.5, 127.1, 123.0, 116.6; HRMS (ESI): *m/z* calcd for $C_{15}H_{11}BrN$ $[M+H]^+$: 284.0075; found: 284.0067.

***7-Phenyl-[1,3]dioxolo[4,5-h]isoquinoline (6i)*:** Yield: 91%; off white solid; mp = 122–124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.37 (s, 1H), 8.10–8.07 (m, 2H), 7.98 (s, 1H), 7.52–7.48 (m, 2H), 7.43–6.36 (m, 3H), 6.24 (s, 2H); 13C NMR(100 MHz, $CDCl_3$) δ 149.3, 145.7, 144.7, 141.9, 139.7, 132.5, 128.5, 128.4, 126.9, 120.8, 116.9, 115.2, 114.4, 102.6; HRMS (ESI): *m/z* calcd for $C_{16}H_{12}NO_2$ $[M+H]^+$: 250.0868; found: 250.0867.

***7-Phenyl-[1,3]dioxolo[4,5-g]isoquinoline (6j)*:**[9b] Yield: 77%; white solid; mp = 135–137 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.08 (s, 1H), 8.08–8.06 (m, 2H), 7,91 (s, 1H), 7.52–7.47 (m, 2H), 7.42–7.38 (m, 1H), 7.22 (s, 1H), 7.13 (s, 1H), 6.11 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.4, 150.6, 150.2, 148.6, 139.6, 135.3, 128.9, 128.5, 126.9, 125.2, 116.6, 103.3, 103.0, 101.8; HRMS (ESI): *m/z* calcd for $C_{16}H_{12}NO_2$ $[M+H]^+$: 250.0868; found: 250.0868.

***6,7-Dimethoxy-3-phenylisoquinoline (6k)*:**[43] Yield: 79%; brown solid; mp = 129–131 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (s,1H), 8.09–8.06 (m, 2H), 7.94 (s, 1H), 7.52–7.47 (m, 2H), 7.42–7.37 (m,1H), 7.23 (s, 1H), 7.13 (s, 1H), 4.05 (s, 3H), 4.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 150.5, 150.4, 150.0, 140.0, 133.5, 128.9, 128.3, 126.9, 123.9, 115.7, 105.4, 105.1, 56.3, 56.2; HRMS (ESI): *m/z* calcd for $C_{17}H_{16}NO_2$ $[M+H]^+$: 266.1181; found: 266.1184.

***6-Methyl-3-phenylisoquinoline (6l)*:**[44] Yield: 89%; brown solid; mp = 176–178 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.28 (s, 1H), 8.13–8.10 (m, 2H), 8.00 (s, 1H), 7.89 (d, J = 8.3 Hz, 1H), 7.64 (d, J = 0.4 Hz, 1H), 7.53–7.49 (m, 2H), 7.44–7.39 (m, 2H). 2.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 151.4, 141.1, 139.8, 137.1, 129.6, 128.9, 128.6, 127.5, 127.1, 126.4, 126.0, 116.3, 22.3; HRMS (ESI): *m/z* calcd for $C_{16}H_{14}N$ $[M+H]^+$: 220.1126; found: 220.1121.

***7,8-Dimethoxy-3-phenylisoquinoline (6m)*:** Yield: 60%; brown solid; mp = 102–104 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.62 (t, J = 0.8 Hz, 1H), 8.12–8.10 (m, 2H), 8.0 (d, J = 0.9 Hz, 1H), 7.63 (d, J = 8.9 Hz, 1H), 7.52–7.48 (m, 3H), 7.42–7.38 (m, 1H), 4.09 (s,3H), 4.02 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.8, 148.9, 147.5, 144.1, 139.8, 132.6, 128.9, 128.4, 126.9, 123.3, 123.3, 120.4, 116.1, 61.9, 57.2; HRMS (ESI): *m/z* calcd for $C_{17}H_{16}NO_2$ $[M+H]^+$: 266.1181; found: 266.1178.

***7-Fluoro-3-phenylisoquinoline (6n)*:**[45] Yield: 90%; brown solid; mp = 136–138 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.30 (s, 1H), 8.12–8.09 (m, 2H), 8.06, (s, 1H), 7.88 (dd, J = 9.0, 5.2 Hz, 1H), 7.60 (dd, J = 8.7, 2.6 Hz, 1H), 7.54–7.48 (m, 3H), 7.46–7.40 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9 (d, J_{CF} = 247.9 Hz), 151.7 (d, J_{CF} = 5.9 Hz), 151.1 (d, J_{CF} = 2.9 Hz), 139.3, 133.9, 129.7 (d, J_{CF} = 7.9 Hz), 129.0, 128.7, 128.4 (d, J_{CF} = 7.9 Hz), 121.3, (d, J_{CF} = 25.3 Hz), 116.4 (d, J_{CF} = 2.0 Hz), 110.8, 110.6; HRMS (ESI): *m/z* calcd for $C_{15}H_{11}FN$ $[M+H]^+$: 224.0876; found: 224.0865.

***3-Cyclopropylisoquinoline (6o)*:**[46] Yield: 70%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.11 (s, 1H), 7.88 (d, J = 8.2 Hz, 1H), 7.70 (d, J = 8.3 Hz, 1H), 7.61 (t, J = 8.1 Hz, 1H), 7.48–7.45 (m, 2H), 2.20–2.16 (m, 1H), 1.11–1.08 (m, 2H), 1.06–1.00 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 156.2, 152.2, 136.5, 130.4, 127.7, 127.2, 126.0, 125.9, 116.5, 17.2, 9.4; HRMS (ESI): *m/z* calcd for $C_{12}H_{12}N$ $[M+H]^+$: 170.0970; found: 170.0973.

***3-Cyclohexylisoquinoline (6p)*:**[6c] Yield: 84%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (s, 1H), 7.92 (dd, J = 8.2, 0.9 Hz, 1H), 7.75 (dd, J = 8.2, 0.7 Hz, 1H), 7.64 (ddd, J = 8.1, 6.8, 1.2 Hz, 1H), 7.51 (ddd, J = 8.1, 6.8, 1.2 Hz, 1H), 7.46 (s, 1H), 2.85 (tt, J = 11.7, 3.3 Hz, 1H), 2.08–2.04 (m, 2H), 1.92–1.87 (m, 2H), 1.81–1.75 (m, 1H), 1.66–1.56 (m, 2H), 1.52–1.41 (m, 2H), 1.37–1.30 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 152.0, 136.8, 130.3, 127.6, 127.4, 126.5, 126.4, 116.3, 46.3, 33.3, 26.9, 26.3; HRMS (ESI): *m/z* calcd for $C_{15}H_{18}N$ $[M+H]^+$: 212.1439; found: 212.1442.

***4-(Isoquinolin-3-yl)benzonitrile (6q)*:** Yield: 20%; brown solid; mp = 122–124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.35 (s, 1H), 8.26 (d, J = 7.9 Hz, 2H), 8.13 (s, 1H), 8.02 (d, J = 8.2 Hz, 1H), 7.91 (d, J = 8.2 Hz, 1H), 7.79 (d, J = 8.0 Hz, 2H), 7. 75 (t, J = 7.1 Hz, 1H), 7.66 (t, J = 7.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.9, 149.1, 143.9, 136.5, 132.7, 131.1, 128.4, 128.2, 127.8, 127.6, 127.3, 119.1, 117.8, 112.0; HRMS (ESI): *m/z* calcd for $C_{16}H_{11}N_2$ $[M+H]^+$: 231.0922; found: 231.0915.

***Phenyl 4-(isoquinolin-3-yl)benzoate (6r)*:** Yield: 15%; off white solid; mp = 163–165 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.38 (s, 1H), 8.36–8.33 (m, 2H), 8.31–8.28 (m, 2H), 8.19 (s, 1H), 8.05–8.02 (m, 1H), 7.94–7.92 (m, 1H), 7.75 (ddd, J = 8.2, 6.9, 1.3 Hz, 1H), 7.65 (ddd, J = 8.2, 7.0, 1.2 Hz, 1H), 7.48–7.44 (m, 2H), 7.32–7.29 (m, 1H), 7.28–7.27 (m,1H), 7.26–7.25 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 152.9, 151.1, 150.0, 144.6, 136.6, 131.0, 130.9, 130.4, 129.7, 129.6, 127.9, 127.8, 127.1, 126.1, 121.9, 121.8, 117.8; HRMS (ESI): *m/z* calcd for $C_{22}H_{16}NO_2$ $[M+H]^+$: 326.1181; found: 326.1189.

***1-Methyl-3-(p-tolyl)isoquinoline (6t)*:**[14b] Yield: 87%; brown liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (dq, J = 8.3, 0.9 Hz, 1H), 8.04 (d, J = 8.2 Hz, 1H), 7.89 (s, 1H), 7.85–7.83 (m, 1H), 7.66 (ddd, J = 8.1, 6.9, 1.2 Hz, 1H), 7.55 (ddd, J = 8.3, 6.9, 1.3 Hz), 7.32–7.30 (m, 2H), 3.04 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 150.2, 138.3, 137.1, 136.9, 130.1, 129.1, 127.7, 127.0, 126.7, 126.6, 125.8, 114.9, 22.8, 21.4; HRMS (ESI): *m/z* calcd for $C_{17}H_{16}N$ $[M+H]^+$: 234.1283; found: 234.1282.

***3-Cyclohexyl-1-methylisoquinoline (6u)*:**[47] Yield: 93%; yellow oil; ^{1}NMR (400 MHz, $CDCl_3$) δ 8.08–8.05 (m, 1H), 7.74 (d, J = 8.2 Hz, 1H), 7.61 (ddd, J = 8.0, 6.8, 1.2 Hz, 1H), 7.50 (ddd, J = 8.3, 6.9, 1.3 Hz, 1H), 7.31, (s, 1H), 2.95 (d, J = 0.4 Hz, 3H), 2.84–2.77 (m, 1H), 2.10–2.08 (m, 2H), 1.89–1.86 (m, 4H), 1.59–1.42 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 136.9, 134.2, 129.8, 127.2, 126.2, 126.1, 125.7, 114.5, 46.2, 33.4, 26.9, 26.4, 22.5; HRMS (ESI): *m/z* calcd for $C_{16}H_{20}N$ $[M+H]^+$: 226.1596; found: 226.1598.

IV. Synthesis of Berberine

2-(6-Iodobenzo[d][1,3]dioxol-5-yl)ethanol[48] and 6-bromo-2,3-dimethoxybenzaldehyde (**9**)[36] were synthesized according to the literature procedure.

***2-(6-{(Trimethylsilyl)ethynyl}benzo[d][1,3]dioxol-5-yl)ethanol (7)*:**[35]An oven dried round bottom flask was charged with $PdCl_2(PPh)_3$ (15 mg, 0.014 mmol), CuI (2 mg, 0.010 mmol) and 2-(6-Iodobenzo[d][1,3]dioxol-5-yl)ethanol (250 mg, 0.87 mmol) in Et_3N (2 ml) under inert atmosphere. After stirring for 2-3 minutes, trimethylsilylacetylene (128 mg, 1.30 mmol) was added at room temperature under inert atmosphere and reaction mixture was heated to 50 °C. After completion of reaction (monitored by TLC) solvent was concentrated under reduced pressure and the residue was diluted with EtOAc (30 mL) and water (15 mL). Organic layer was separated and the aqueous layer was washed two times with EtOAc (20 mL). The combined organic layer was dried over Na_2SO_4 and

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concentrated under reduced pressure. Yield: 90%; brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (s, 1H), 6,71 (s, 1H), 5.94 (s, 2H), 3.86 (t, J = 6.4 Hz, 2H), 2.98 (t, J = 6.4 Hz, 2H), 0.02 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.3, 146.0, 136.3, 115.7, 112.0, 110.1, 103.9, 101.5, 96.9, 63.0, 38.0, 0.1; HRMS (ESI): m/z calcd for $C_{14}H_{19}O_3Si$: 263.1103 [M+H]+; found: 263.1116.

***2-(6-Ethynylbenzo[d][1,3]dioxol-5-yl)ethanol (8)*:** TBAF solution (1.0 M in THF, 1.26 mL, 1.26 mmol) was added in a drop-wise manner to a stirred solution of **7** (166 mg, 0.63 mmol) in THF (1.3 mL) at rt. Thr reaction mixture immediately turned to dark brown in colour. After completion of the reaction (monitored by TLC), 1M aqueous HCl (15 mL) was added to the reaction mixture and extracted with diethyl ether (20 mL). Aqueous layer was washed two times with diethyl ether (20 mL) and combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified through a short pad of silica gel column using EtOAc/hexane as an eluent to get pure compound. Yield: 88%; brown liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (s, 1H), 6.73 (s, 1H), 5.95 (s, 2H), 3.85 (t, J = 6.6 Hz, 2H), 3.17 (s, 1H), 2.99 (t, J = 6.6 Hz, 2H); ^{13}C NMR δ (100 MHz, $CDCl_3$) 146.0, 136.4, 112.4, 110.0, 109.5, 101.5, 82.4, 79.7, 63.1, 39.0, 37.7; HRMS (ESI): *m/z* calcd for $C_{11}H_{11}O_3$ $[M+H]^+$: 191.0708; found: 191.0704.

***6-{[6-(2-Hydroxyethyl)benzo[d][1,3]dioxol-5-yl]ethynyl}-2,3-dimethoxybenzaldehyde (10)*:** Triethylamine (1.2 mL) was added to a mixture of $PdCl_2(PPh)_3$ (18 mg, 0.0125 mmol), CuI (1.1 mg, 0.006 mmol), **9** (122 mg, 0.5 mmol) and **8** (124 mg, 0.65 mmol) under inert atmosphere. The reaction mixture was heated to reflux for 3 h. After completion of the reaction (monitored by TLC), Et_3N was removed under reduced pressure. The residue was then diluted with EtOAc (10 mL) and water (5 mL). Organic layer was separated and aqueous layer was washed two times with EtOAc (10 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc/hexane to get pure **10**. Yield: 65%; pale yellow solid; mp = 104–106 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.51 (s, 1H), 7.35 (d, J = 8.5 Hz, 1H), 7.11 (d, J = 8.5 Hz, 1H), 6.99 (s, 1H), 6.75 (s, 1H), 5.96 (s, 2H), 3.97 (s, 3H), 3.93 (s, 3H), 3.87 (t, J = 7.2 Hz, 2H), 3.17 (t, J = 7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.6, 152.8, 152.7, 148.4, 146.1, 136.7, 130.5, 129.7, 117.3, 116.1, 115.4, 112.0, 110.0, 101.5, 92.0, 89.7, 64.1, 62.5, 56.3, 38.5; HRMS (ESI): *m/z* calcd for $C_{20}H_{19}O_6$ $[M+H]^+$: 355.1182; found: 355.1185.

***2-{6-[(7,8-Dimethoxyisoquinolin-3-yl]methyl)benzo[d][1,3]dioxol-5-yl}ethanol (11)*:** ^{t}BuOH (5 mL) was added to a mixture of $AgNO_3$ (9.0 mg, 0.054 mmol), ammonium acetate (62 mg, 0.81 mmol) and **10** (190, 0.54 mmol) under inert atmosphere. The resultant mixture was stirred at room temperature and the reaction was monitored by TLC. After completion, the reaction was quenched by the addition of $NaHCO_3$ (180 mg, 2.12 mmol) at room temperature and stirring was continued for additional 4 h. The mixture was then filtered through a cotton plug, washed with EtOAc (10 mL) and dried over anhydrous Na_2SO_4. The filtrate was evaporated under reduced pressure and the residue was purified through silica gel column chromatography (EtOAc/hexane) to get the pure isoquinoline (**11**). Yield: 78%; brown solid; mp = 137–139 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.52 (t, J = 0.8 Hz, 1H), 7.72 (d, J = 0.8 Hz, 1H), 7.61 (d, J = 9.0, Hz,1H), 7.54 (d, J = 9.0 Hz, 1H), 6.92 (s, 1H), 6.88 (s, 1H), 6.0 (s, 2H), 4.09 (s, 3H), 4.03 (s, 3H), 3.99 (t, J = 5.8 Hz, 2H), 2.82 (t, J = 5.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5, 149.1, 148.2, 146.2, 145.6, 144.1, 133.6, 132.9, 132.7, 122.9, 122.8, 121.0, 120.2, 110.2, 110.1, 101.4, 64.0, 61.9, 57.2, 35.4; HRMS (ESI): *m/z* calcd for $C_{20}H_{20}NO_5$ $[M+H]^+$: 354.1341; found: 354.1350.

***Synthesis of berberine (3)*:**[33] A mixture of Isoquinoline derivative **11** (10 mg, 0.028 mmol), PPh_3 (16 mg, 0.056 mmol) in CH_2Cl_2-CCl_4 mixture (1:2) (0.5 mL) was stirred at room temperature until the starting material got completely consumed (12 h, by TLC). The reaction mixture was carefully filtered and the solid was washed with EtOAc (5 mL x 4) to get berberine (**3**). Yield: 72%; yellow solid; mp = 204–206 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1H), 8.94 (s, 1H), 8,21 (d, J = 9.2 Hz, 1H), 7.99 (d, J = 9.0 Hz, 1H), 7.80 (s, 1H), 7.09 (s, 1H), 6.18 (s, 2H), 4.93 (t, J = 6.2 Hz, 2H), 3.20 (t, J = 6.5 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 150.4, 149.9, 147.7, 145.5, 143.7, 137.5, 133.0, 130.7, 126.8, 123.6, 121.4, 120.5, 120.2, 108.5, 105.5, 102.1, 62.0, 57.1, 55.2, 26.3; HRMS (ESI): *m/z* calcd for $C_{20}H_{19}NO_4$ $[M+H]^+$: 337.1314; found: 337.1323.

V. Synthesis of Palmatine

The starting material, *2-(2-Ethynyl-4,5-dimethoxyphenyl)ethanol (12)*, was prepared according to the literature procedure.[38]

***2-{[2-(2-Hydroxyethyl)-4,5-dimethoxyphenyl]ethynyl}-4,5-dimethoxybenzaldehyde (13)*:** Triethylamine (2 mL) was added to a mixture of $PdCl_2(PPh)_3$ (9.6 mg, 0.014 mmol), CuI (1.3 mg, 0.007 mmol), **12** (144 mg, 0.71 mmol) and **9** (135 mg, 0.55 mmol) under inert atmosphere. The reaction mixture was heated to reflux for 3 h. After completion of the reaction (monitored by TLC), solvent was removed under reduced pressure. The residue was then diluted with EtOAc (20 mL) and water (10 mL). Organic layer was separated and aqueous layer was washed with EtOAc (10 mL x 2). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified through silica gel column using EtOAc/hexane to get pure **13.** Yield: 65%; yellow gummy solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.53 (d, J = 0.6 Hz, 1H), 7.38 (dd, J = 8.5, 0.7 Hz, 1H), 7.11 (d, J = 8.7 Hz, 1H), 7.03, (s, 1H), 6.76 (s, 1H), 3.97 (s, 3H), 3.94 (s, 3H), 3.92–3.91 (m, 2H), 3.90 (s, 3H), 3.89 (s, 3H), 3.18 (t, J = 7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.6, 152.8, 149.8, 147.3, 135.1, 132.2, 130.4, 129.7, 117.3, 115.6, 115.1, 114.9, 112.5, 92.1, 89.7, 64.1, 62.5, 56.2, 56.1, 56.0, 38.4; HRMS (ESI): *m/z* calcd for $C_{21}H_{23}O_6$ $[M+H]^+$: 371.1495; found: 371.1491.

***2-[2-(6,7-Dimethoxyisoquinolin-3-yl)-4,5-dimethoxyphenyl]ethanol (14)*:** ^{t}BuOH (2 mL) was added to a mixture of $AgNO_3$ (3.4 mg, 0.02 mmol), ammonium acetate (23 mg, 0.3 mmol) and **13** (76 mg 0.20 mmol) under inert atmosphere. The resultant mixture was stirred at room temperature and the reaction was monitored by TLC. After completion, the reaction was quenched by the addition of $NaHCO_3$ (83 mg, 1.0 mmol, 4) at room temperature and stirring was continued for additional 4 h. The mixture was then filtered through a cotton plug, washed with EtOAc (10 mL) and dried over anhydrous Na_2SO_4. The filtrate was evaporated under reduced pressure and the residue was purified through silica gel column chromatography (EtOAc/hexane) to get the pure isoquinoline (**14**). Yield: 70%; brown solid; mp = 164–166 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.53 (t, J = 0.9 Hz, 1H), 7.76 (d, J = 0.9 Hz, 1H), 7.62 (d, J = 8.9 Hz, 1H), 7.54 (d, J = 9.0 Hz, 1H), 6.95 (s, 1H), 6.89 (s, 1H), 4.08 (s, 3H), 4.02 (s, 3H), 4.01 (t, J = 5.8 Hz, 2H), 3.94 (s, 3H), 3.91 (s, 3H), 2.86 (t, J = 5.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.7, 149.6, 149.0, 147.4, 145.6, 144.1, 132.8, 132.6, 131.4, 122.9, 122.7, 121.0, 120.0, 113.4, 113.1, 64.1, 61.9, 57.2, 56.3, 56.1, 35.3; HRMS (ESI): *m/z* calcd for $C_{21}H_{24}NO_5$ $[M+H]^+$: 370.1654; found: 370.1658.

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***Synthesis of Palmatine (4)*:**[33] A mixture of Isoquinoline derivative **14** (10 mg, 0.027 mmol), PPh_3 (15 mg, 0.054 mmol) in CH_2Cl_2-CCl_4 mixture (1:2) (0.5 mL) was stirred at room temperature until the starting material got completely consumed (24 h, by TLC). The reaction mixture was carefully filtered and the solid was washed with EtOAc (5 mL x 4) to get palmatine (**4**). Yield: 70%; yellow solid; mp = 195-197°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (s, 1H), 9.06 (s, 1H), 8.22 (d, J = 9.2 Hz, 1H), 8.03, (d, J = 9.1 Hz, 1H), 7.72 (s, 1H), 7.10 (s, 1H), 4.95 (t, J = 6.0 Hz, 2H), 4.10 (s, 3H), 4.07 (s, 3H), 3.94 (s, 3H), 3.87 (s, 3H), 3.23 (t, J = 6.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 151.5, 150.3, 148.8, 145.5, 143.7, 137.8, 133.1, 128.7, 126.8, 123.5, 121.4, 119.9, 117.3, 111.3, 108.7, 62.0, 57.1, 56.2, 55.9, 55.4, 26.01; HRMS (ESI): *m/z* calcd for $C_{21}H_{23}NO_4$ $[M+H]^+$: 353.1627; found: 353.1644.

Conclusions

In conclusion, a silver catalysed room temperature protocol for the synthesis of a wide range of isoquinoline derivatives from *o*-(1-alkynyl)arylaldehydes and ketones has been developed. This mild protocol has been successfully utilized in the total synthesis of biologically active isoquinoline alkaloids such as berberine and palmatine. Since only a few steps are involved, the total synthesis of these alkaloids **3** and **4** were accomplished in a very high overall yield.

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Notes and references

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A Room Temperature Protocol to Access Isoquinolines through Silver (I) Catalysed Annulation of *o*-(1-Alkynyl)arylaldehydes and Ketones with NH_4OAc: Elaboration to Berberine and Palmatine

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A silver catalysed protocol for the synthesis of a wide range of isoquinoline derivatives from *o*-(1-alkynyl)arylaldehydes and ketones has been developed under mild conditions. This protocol has been elaborated to the synthesis of two important isoquinoline alkaloids, berberine and palmatine, which were obtained in 32 and 35% overall yield respectively.