Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: P. Yadav, R. Shaw, A. Elagamy, A. Kumar and R. Pratap, *Org. Biomol. Chem.*, 2018, DOI: 10.1039/C8OB01270A.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/obc

View Article Online
DOI: 10.1039/C8OB01270A

Journal Name

ARTICLE

Base controlled diverse reactivity of allyl cyanide for synthesis of multi-substituted benzenes

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Pratik Yadav,[a] Ranjay Shaw,[a] Amr Elagamy,[a] Abhinav Kumar[b] and Ramendra Pratap*[a]

A base controlled regioselective 1,6-cyanoallylation of suitably functionalized 2*H*-pyran-2-ones has been demonstrated for the synthesis of various functionalized multi-substituted benzenes through a tandem process. We observed that lithium hydroxide provides major product from α-attack and minor product from γ-attack of allyl cyanide. While use of sodium hydride as a base exclusively provides the product by γ-attack of allyl cyanide. We have also performed NMR experiments to understand the mechanistic pathway. Structure of compound was confirmed by single crystal X-ray.

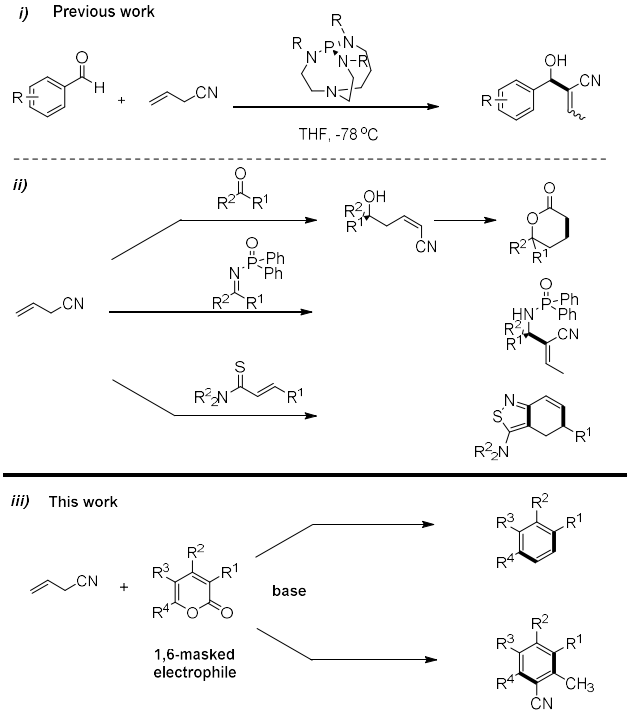
Introduction

Cyanoalkylation is synthetically useful and important reaction because cyano group is present in several natural products and important drugs.[1,2] Therefore during the last decade, continuous efforts have been made for catalytic generation and enantioselective addition of alkylnitrile nucleophiles to different types of electrophiles.[3] Among different cyanoalkylating reagents, allyl cyanide act as a viable pronucleophile bearing an α-proton with reasonable acidity. Therefore, allyl cyanide is unique class of carbon pronucleophile, which generates carbanion at α-position and further it can also isomerize to generate γ-carbanion under basic condition.

In this regard, Kisanga et *al.* used a special base to achieve selective α-addition of allyl cyanide on aldehydes[4] (Scheme 1, entry i). Moreover, in recent years, this cyanoallylating reagent has been successfully applied by Shibasaki and coworkers for various reactions, such as 1,2-addition on ketones,[5a,b,c] aldehydes,[5d] ketoimine,[6a] tosyl imines[6b] and 1,4-addition to unsaturated thioamides[7] for the synthesis of isothiazoles using cooperative catalyst systems (Scheme 1, entry ii).

To the best of our knowledge, none have demonstrated synthetic utility of allyl cyanide for preparing multisubstituted benzenes, which are not only the central building motifs of a various natural products[8,9] and pharmaceuticals[9] but are also serves as versatile auxiliaries for asymmetric syntheses,[10] as chiral phases for chromatography,[11] ligands for various cross coupling/metal catalyzed reactions[12] and as important substrates for advanced materials.[13]

Scheme 1. Allyl cyanide as pronucleophile for various transformations



These results inspired us to study chemoselectivity of carbocyclization between 6-*exo-trig* and 6-*exo-dig* cyclization modes under basic conditions using allyl cyanide and α, β-γ, δ-diunsaturated pyranones for the synthesis of functionalized biaryls.[14] In this reaction mixture of two products 3-methyl-5-*sec.*amino-[1,1'-biaryl]-2,4-dicarbonitriles and 3-*sec.*amino-[1,1'-biaryl]-4-carbonitrile was obtained.

In search of selectivity for the addition of allyl cyanide to α, β-γ, δ-diunsaturated pyranones, we hypothesized that with the

[a]*Department of Chemistry, University of Delhi, North campus, Delhi, India-110007.*
[b]*Department of Chemistry, University of Lucknow, Lucknow, Uttar Pradesh, India-226009.*

† Footnotes relating to the title and/or authors should appear here.

Electronic Supplementary Information (ESI) available: [SI including NMR experiments and NMR spectra of reported compounds are given]. See DOI: 10.1039/x0xx00000x

View Article Online
DOI: 10.1039/C8OB01270A

fine tuning of reaction conditions, carbanion can be selectively generated either at α or γ position of allyl cyanide, which could further undergo 1,6-conjugate addition on electron-deficient α, β-γ, δ-diunsaturated pyranones to afford different intermediates (Michael adduct). The resulting intermediates would provide a potential opportunity for the synthesis of new benzene ring installed with various functional groups (Scheme 1, entry iii). Herein, we wish to report an additive and transition-metal free selective approach to construct functionalized benzenes under base dependent reaction conditions.

To avoid the issue of chemoselectivity between the β- and δ-carbons of pyranone, we initially started our optimization with starting material blocked with secondary amine at β-carbon to reduce the electrophilicity of this position.[15] Subsequently, we found that relatively labile group could also be tolerated under developed conditions.

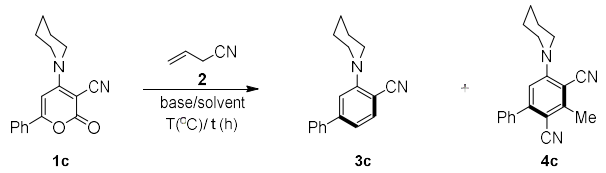
Results and discussion

To optimize the reaction condition 6-phenyl-4-piperidin-1-yl-2*H*-pyran-2-one-3-carbonitrile **1c** and allyl cyanide **2** were selected as model substrates. Initially **1c** and allyl cyanide **2** were treated in the presence of KOH in DMF at room temperature, but no reaction was observed. We next examined several other reaction conditions at room temperature, but we could not achieve desired transformation (SI, Table 1). The reaction was further performed at 60 °C using KOH/DMF, and we found mixture of products **3c** (15%) and **4c** (68%). To achieve higher selectivity and yields, other hydroxide bases such as LiOH and NaOH were also used and LiOH/DMF was found to be the best combination among other bases for this transformation, which yielded **3c** 15% as a minor product while **4c** 75% as major product. LiOH in DMSO was found inferior combination and lower yield was obtained. On the basis of optimized reaction conditions, it was found that hydroxides bases were inefficient to achieve selectivity. These results inspired us to investigate different base and solvent combination to check their effects on selectivity. Bases like Cs_2CO_3, KO^{t}Bu and K_3PO_4 in DMF were also not found suitable for selectivity. Remarkably, when NaH/DMF was used, selective formation of **3c** (82%) was observed. Similarly, $NaNH_2$/DMF provided selectivity and 62% of **3c** was isolated. Organobases like DBU and n-BuLi were inefficient for this transformation and no reaction was observed with DBU, while n-BuLi gave complex mixture probably due to many side reactions with starting material.

To check the influence of solvent, we screened various other solvents such as DMF, DMSO, DMAc, NMP, MeCN and THF in combination with NaH and DMF was found to be best (SI, Table 1). Further elevation in reaction temperature did not provide better result and slightly lower yield was obtained at 100 °C (Table 1, entry 10).

On the basis of optimization, we found that reaction can proceed in two directions under simple reaction conditions, depending on base/solvent employed. To gauge the efficacy of

Table 1 Optimization of reaction conditions[a]



Entry	Base	Solvent	T (°C)	Yield (%)[b]	
				3c	**4c**
1	KOH	DMF	60	15	68
2	NaOH	DMF	60	16	56
3	LiOH	DMF	60	15	75
4	KO^{t}Bu	DMF	60	20	34
5	K_3PO_4	DMF	60	15	35
6	Cs_2CO_3	DMF	60	12	45
7	LiOH	DMSO	60	10	40
8	NaH	THF	60	50	-
9	NaH	DMF	60	82	-
10	NaH	DMF	100	65	-
11	NaH	DMSO	60	40	-
12	$NaNH_2$	DMF	60	62	-
13	DBU	DMF	60	-	-
14[c]	n-BuLi	THF	-78	-	-

[a]The reaction was conducted with 6-phenyl-4-piperidin-1-yl-2*H*-pyran-2-one-3-carbonitrile **1c** (0.5 mmol), allyl cyanide **2** (0.6 mmol), base (0.75 mmol) using solvent (5.0 mL) for 6 hours; [b]Yield of isolated product; [c]reaction was performed for 2 hours.

developed protocol, we first examined the scope of reaction under NaH/DMF condition for the selective synthesis of benzene **3** (Scheme 2).

In each case reaction proceeded very well with various functional groups including cyano, esters, and SMe. All these base sensitive and labile groups were tolerated under this reaction condition and reaction proceeded with complete selectivity. Wide varieties of functionalized benzenes **3a-o** were synthesized by using current protocol in good yields and complete selectivity. Structure of compound **3o** was confirmed by single crystal X-ray.[16]

This protocol was also investigated for other important class of fused benzenes **3p** and **3q** and heteroaryl containing benzenes **3r-t** and all the products were obtained in good yields and selectivity.

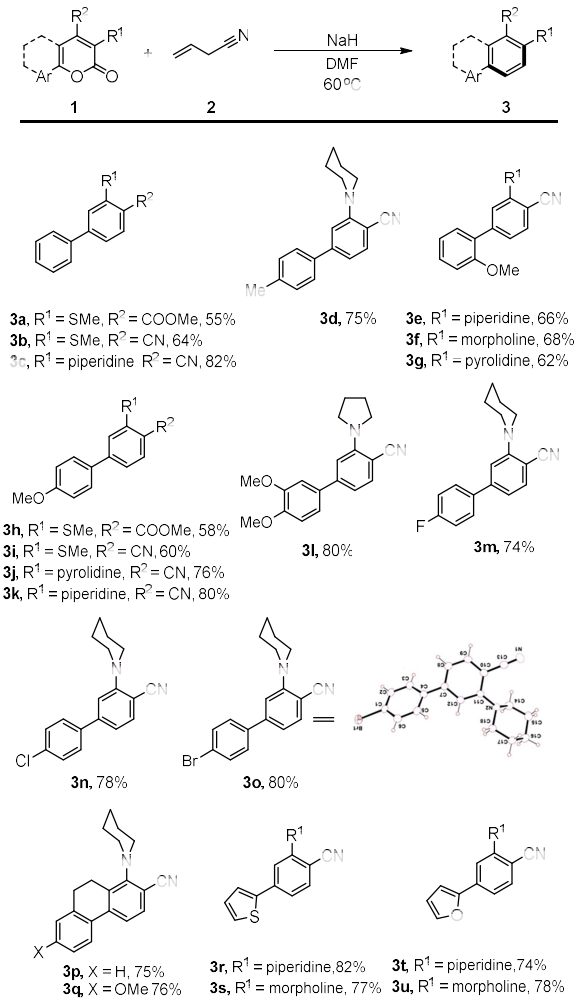
We, therefore used LiOH/DMF combinations and synthesis of various multi-substituted benzenes **4**,[17] but in all the cases benzene **3** obtained as a minor product (Scheme 3). In this case reaction was cleaner and yield was superior to our previous protocol with KOH/DMF.[14]

To get mechanistic insight into the reaction few control experiments were performed (Scheme 4). In first experiment reaction was performed using allyl cyanide and *E*- and *Z*-but-2-

View Article Online
DOI: 10.1039/C8OB01270A

enenitrile without base. In both the reactions no reaction was observed. These results show that reaction does not occur through 4+2 electrocyclization (Scheme 4, entry i).

Scheme 2 Regioselective cyanoallylation of 2-pyranones for the synthesis of multi-substituted benzenes **3**[a]

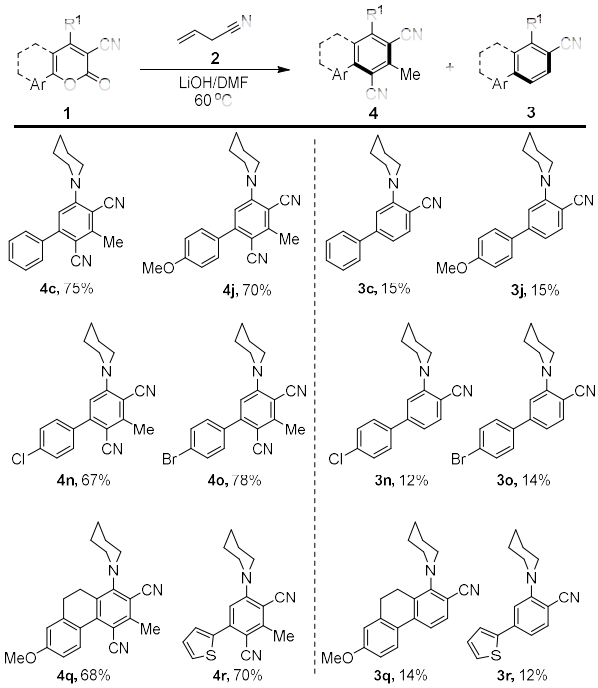


[a] Reactions were performed at 60 °C for 6 h by stirring 1 (0.5 mmol), 2 (0.6 mmol) and NaH (0.75 mmol) in DMF (5.0 mL).

For the second experiment, we tried to capture either α or γ carbanion generated under basic condition from allyl cyanide with iodoethane. No substitution was observed in this case and in the presence of bases like NaH/LiOH/Et_3N and only allyl cyanide was isomerized to give more stable *E/Z*-but-2-enenitrile mixture. This result was supported by ^1H NMR (SI, experiment 1). The reason to perform this experiment was to find out the ratio of α or γ carbanion through trapping, but this experiment shows that reaction of any base with allyl cyanide provides exclusively its isomer *E/Z*-but-2-enenitrile **2'/2''** mixture.

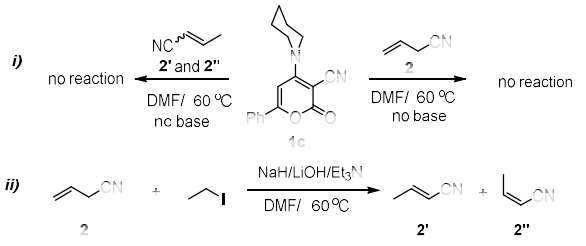
The molecular make up of precursor **1** reveals that it possesses three electrophilic centers C-2, C-4, and C-6. Among them C-6 is highly susceptible to nucleophilic attack because of extended conjugation due to the presence of an electron withdrawing CN/ester substituent at C-3 in the pyranone ring. Presence of electron donating groups like thioether or secondary amine at C-4 avoids chemoselectivity issue between C-4 and C-6 position.

Scheme 3 Regioselective cyanoallylation for the synthesis of multi-substituted benzenes **4**[a]



[a] Reactions were performed at 60 °C for 6h by stirring **1** (0.5 mmol), **2** (0.6 mmol) and LiOH (0.75 mmol) in DMF (5.0 mL).

Scheme 4 Control experiments to probe the mechanism

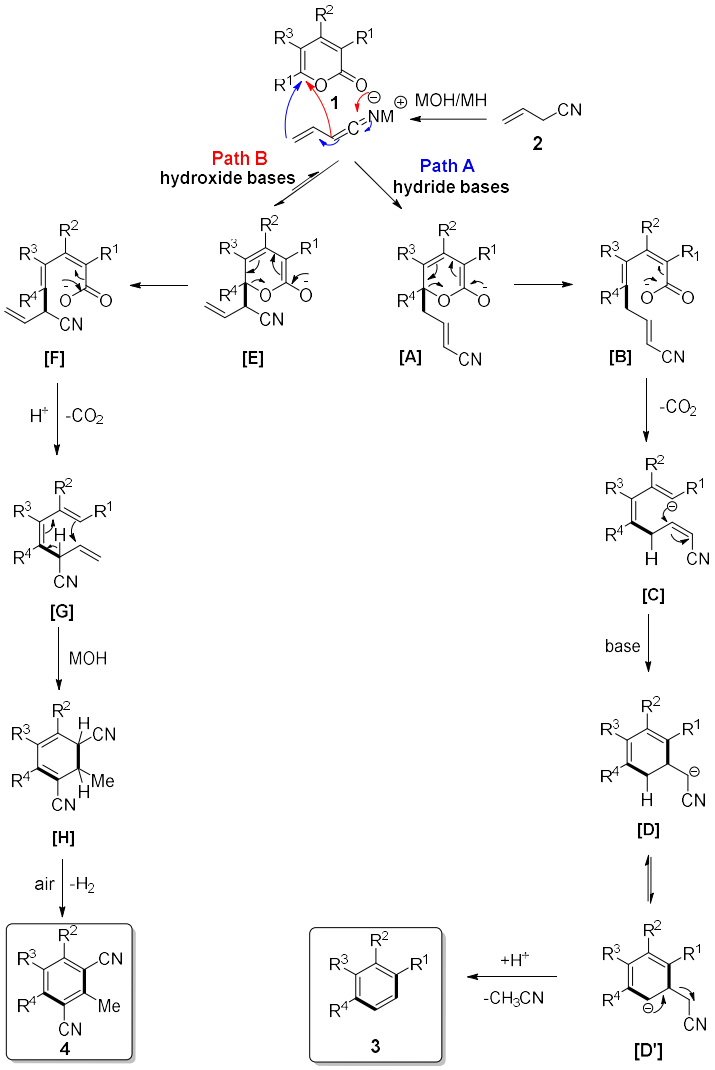


Keeping these facts in mind, we hypothesized the mechanism of the reaction as shown in Scheme 5. In presence of sodium hydride reaction follows path A and lithium hydroxide it follows both path A and B. We proposed that in presence of sodium hydride possibly generated metal-ketenimine intermediate attacks through γ-position exclusively at C-6 position of 2*H*-pyran-2-ones selectively and afford Michael adduct [A]. In the next step intermediate [A] undergoes ring opening to provide intermediate [B] followed by decarboxylation to yield intermediate [C]. Then the carbanion

View Article Online
DOI: 10.1039/C8OB01270A

formed at C-3 of pyranone attack at β-carbon of allyl cyanide through Michael addition and provides the intermediate [D]. Intermediate [D] can isomerize to [D'] through proton migration, which undergo aromatization through loss of acetonitrile to afford the desired product **3**. We proposed that under the influence of strong bases like NaH/$NaNH_2$, reaction exclusively takes place though kinetically stable γ-carbanion **[path A]**. While in presence of hydroxide bases LiOH/KOH there is competitive reaction between α and γ-position of metal-ketenimine intermediate. If reaction proceeds through α-position of metal-ketenimine, it attacks at C-6 position of 2-pyranone through Michael addition to afford intermediate [E] **[path B]**. Intermediate [E] converts into [F] and in next step intermediate [F] undergoes loss of carbon dioxide to yield other probable intermediate [G]. Intermediate [G] can cyclize through intramolecular attack of carbanion at either carbon of C=C or CN group to afford the two possible biaryl but exclusively C=C was involved for the cyclization to afford the intermediate [H]. Intermediate [H] in presence of air undergoes aromatization to achieve the desired multi-substituted benzene **4**. We proposed that in presence of lithium hydroxide reaction is reversible and apart from α-position of metal-ketenimine some of the minor product was obtained by path A.

Scheme 5 Plausible mechanism for the synthesis of differently functionalized benzenes



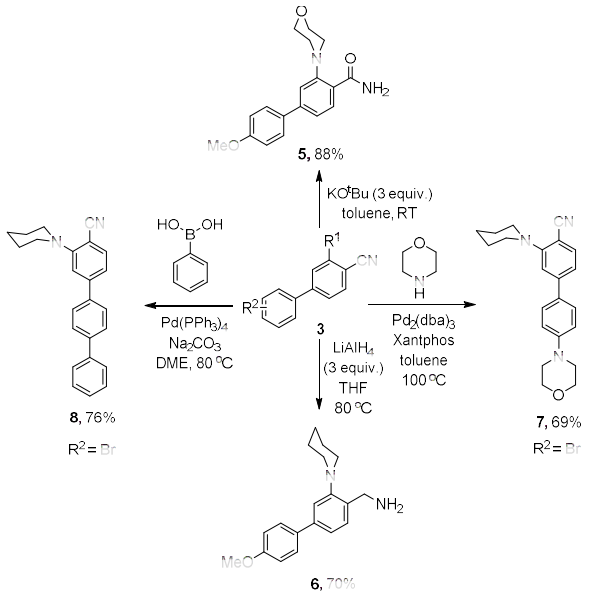
In order to further insight into the reaction, we performed the reaction of 6-phenyl-4-piperidin-1-yl-2*H*-pyran-2-one-3-carbonitrile and allyl cyanide in DMF-d_7 using lithium hydroxide and sodium hydride separately and recorded the ^1H NMR at various interval (SI, experiment 2).

The NMR spectrum of the experiment shows the presence of major E/Z-but-2-enenitrile 2/2' with some unidentified

View Article Online
DOI: 10.1039/C8OB01270A

intermediate and minor existence of allyl cyanide after 30 minutes. After 1h allyl cyanide completely isomerized to E/Z-but-2-enenitrile **2'/2''.** From this experiment we proposed that as soon as base interact with allyl cyanide, it provides more stable isomer *E/Z*-but-2-enenitrile **2'/2''**, which isomerize to metal-ketenimine intermediate and then depending on the strength of base, carbanion attacks via α- and γ-allyl position.
Both the synthesized benzenes contain various synthetically important functional groups like nitrile, aromatic halides, thiomethyl, carbomethoxy groups. Many of these groups can be further modified to achieve further important molecules. Moreover these groups can be removed if necessary. To show the importance of synthesized molecule nitrile group was modified by literature procedure to achieved amide **5** and amines **6**. The p-bromobiaryl was also used for

Scheme 6 Synthetic utility of multi-substituted benzene **3**



the synthesis of *p*-teraryl via Suzuki coupling **8** and amination was also performed through Buchwald Hartwig reaction to achieve **7** in good yield (Scheme 6).

Conclusions

In summary, a selective 1,6-cyanoallylation of 2*H*-pyran-2-ones has been developed under basic conditions to achieve the differently functionalized benzenes. Synthesized benzenes could be used as important scaffolds for various synthetic transformation and potential organic light emitting materials. We have also performed some mechanistic investigation to understand the mechanism of reaction. We also observed that allyl cyanide provides γ-attack from keteniminated salt in presence of strong base while use of relatively weaker base gives reaction through both α and γ-positions. From our study, we conclude that bases can control the reactivity depending on their nature to result different multi-substituted benzenes. Presence of electron withdrawing and donating groups limit the scope of reactions, but these groups can be used for further modification. Further development of this strategy is under investigation.

Experimental

General remarks: We have used commercially available reagents without purification. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz NMR and 100 MHz NMR spectrometer and $CDCl_3$ was used as solvent. Chemical shifts are reported in parts per million shift (*δ*-value) from ($CDCl_3$) (*δ* 7.24 ppm for ^{1}H) or based on the middle peak of the solvent ($CDCl_3$) (*δ* 77.00 ppm for ^{13}C NMR) as an internal standard. Signal patterns are indicated as s, singlet; d, doublet; dd, double doublet; t, triplet; m, multiplet; bs, broad singlet and bm, broad multiplet. Coupling constants (*J*) are given in hertz (Hz). Room temperature was ranging from 25-30 °C during the reactions. Starting materials **1** were prepared in a two-step from known literature process.[14,15]

General procedure for the synthesis of biaryls 3

In an oven dried round bottom flask **1** (0.5 mmol), NaH (0.75 mmol) and DMF (5.0 mL) were taken. The reaction mixture was heated at 60 °C and allyl cyanide **2** (0.6 mmol) was added drop wise for the duration of 1 hour. Completion of reaction was monitored by TLC. After the completion, reaction mixture was poured onto crushed ice and acidified by drop wise addition of dil. HCl. Precipitate obtained, was filtered, dried and purified by column chromatography using 10% ethyl acetate in hexane.

Product characterization data

Methyl 3-(methylthio)-[1,1'-biphenyl]-4-carboxylate (3a): Colorless liquid; yield: 55%; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 2.51 (s, 3H), 3.92 (s, 3H), 7.33 (dd, *J* = 8.0 Hz, *J* = 1.4 Hz, 1H), 7.39-7.48 (m, 4H), 7.59 (d, *J* = 7.2 Hz, 2H), 8.07 (d, *J* = 8.0Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 15.6, 52.0, 122.4, 123.0, 125.3, 127.3, 128.3, 128.9, 131.8, 140.0, 143.9, 145.3, 166.7; HRMS (*m/z*): $[M+H]^+$calcd for $C_{15}H_{15}O_2S$: 259.0787; found: 259.0779.

3-(Methylthio)-[1,1'-biphenyl]-4-carbonitrile (3b): Colorlessliquid; yield: 64%; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 2.55 (s, 3H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.36-7.38 (m, 3H), 7.54-7.60 (m, 3H);^{13}C NMR (100 MHz, $CDCl_3$): *δ* 15.9, 116.9, 118.6, 123.3, 123.9, 124.7, 128.8, 132.3, 134.0, 138.1, 144.2, 144.8;HRMS (*m/z*): $[M+H]^+$calcd for $C_{14}H_{12}NS$: 226.0685; found: 226.0677.

3-(Piperidin-1-yl)-[1,1'-biphenyl]-4-carbonitrile (3c): Colorless liquid; yield: 82%; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.68-1.71 (m, 2H), 1.87 (dd, *J* = 10.8 Hz, *J* = 6.0 Hz, 4H), 3.30 (t, *J* = 6.0 Hz, 4H), 7.23 (dd, *J* = 6.4 Hz, *J* = 1.6 Hz, 2H), 7.48-7.56 (m, 2H), 7.63-7.68 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 23.9, 25.8, 52.4, 104.0, 116.6, 117.1, 117.1, 128.5, 128.7, 129.3, 138.0, 149.4, 150.1, 158.4;HRMS (*m/z*): $[M+H]^+$calcd for $C_{18}H_{19}N_2$: 263.1543; found: 263.1541.

4'-Methyl-3-(piperidin-1-yl)-[1,1'-biphenyl]-4-carbonitrile (3d): Colorless liquid; yield: 75%; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.59-1.64 (m, 2H), 1.76-1-82 (m, 4H), 2.40 (s, 3H), 3.21 (t, *J* = 5.6 Hz, 4H), 7.12-7.14 (m, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.45 (d,

View Article Online
DOI: 10.1039/C8OB01270A

J = 8.0 Hz, 2H); 7.56-7.58 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 20.5, 23.9, 25.8, 52.4, 98.8, 103.6, 112.5, 112.9, 116.6, 117.6, 136.8, 144.0, 149.0, 149.4, 158.7; HRMS (*m/z*): $[M+H]^+$calcd for $C_{19}H_{21}N_2$: 277.1699; found: 277.1692.

2'-Methoxy-3-(piperidin-1-yl)-[1,1'-biphenyl]-4-carbonitrile (3e): Colorless liquid; yield: 66%; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.57-1.61 (m, 2H), 1.74-1.80 (m, 4H), 3.18 (t, *J* = 4.8 Hz, 4H), 3.81 (s, 3H), 6.97-7.04 (m, 2H), 7.18 (d, *J* = 7.6 Hz, 2H), 7.24-7.28 (m, 1H), 7.33-7.37 (m, 1H), 7.18 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 24.1, 26.1, 53.1, 55.6, 104.0, 111.3, 118.9, 119.9, 120.9, 122.4, 129.3, 129.6, 130.5, 133.6, 144.1, 156.3, 156.5; HRMS (*m/z*): $[M+H]^+$calcd for $C_{19}H_{21}N_2O$: 293.1648; found: 293.1640.

2'-Methoxy-3-morpholino-[1,1'-biphenyl]-4-carbonitrile (3f): Colorless liquid; yield: 68%; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 3.24 (t, *J* = 4.6 Hz, 4H), 3.83 (s, 3H), 3.91 (t, *J* = 4.6 Hz, 4H), 7.00-7.07 (m, 2H), 7.22-7.28 (m, 3H), 7.30-7.38 (m, 1H), 7.60 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 51.9, 55.6, 67.0, 104.2, 111.3, 118.6, 119.8, 121.0, 123.5, 129.0, 129.8, 130.5, 133.8, 144.5, 155.1, 156.3; HRMS (*m/z*): $[M+H]^+$calcd for $C_{18}H_{19}N_2O_2$: 295.1441; found: 295.1433.

2'-Methoxy-3-(pyrrolidin-1-yl)-[1,1'-biphenyl]-4-carbonitrile (3g): Colorless liquid; yield: 62%; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.99 (t, *J* = 3.0 Hz, 4H), 3.66 (t, *J* = 3.0 Hz, 4H), 3.81 (s, 3H), 6.77 (s, 1H), 6.81 (d, *J* = 8.2 Hz, 1H), 6.98-7.03 (m, 2H), 7.25-7.35 (m, 2H), 7.45 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 25.7, 49.8, 55.5, 92.8, 111.2, 115.3, 117.7, 120.8, 121.7, 129.4, 129.8, 130.4, 135.1, 143.8, 149.9, 156.4; HRMS (*m/z*): $[M+H]^+$calcd for $C_{18}H_{19}N_2O$: 279.1492; found: 279.1484.

Methyl 4'-methoxy-3-(methylthio)-[1,1'-biphenyl]-4-carboxylate (3h): Colorless liquid; yield: 58%; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 2.50 (s, 3H), 3.84 (s, 3H), 3.91 (s, 3H), 6.90 (d, *J* = 8.8 Hz, 2H), 7.29 (dd, *J* = 8.4 Hz, *J* = 1.6 Hz, 1H), 7.37 (d, *J* = 1.6 Hz, 1H); 7.53 (d, *J* = 8.8 Hz, 2H), 8.02 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 15.6, 52.0, 55.4, 114.4, 121.9, 122.4, 124.6, 128.4, 131.8, 132.4, 143.8, 144.9, 159.9, 166.7; HRMS (*m/z*): $[M+H]^+$calcd for $C_{16}H_{17}O_3S$: 289.0893; found: 289.0886.

4'-Methoxy-3-(methylthio)-[1,1'-biphenyl]-4-carbonitrile (3i): Colorless liquid; yield: 60%; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 2.60 (s, 3H), 3.85 (s, 3H), 6.99 (d, *J* = 8.8 Hz, 2H), 7.35 (dd, *J* = 8.0 Hz, *J* = 1.4 Hz, 1H), 7.43 (d, *J* = 1.4 Hz, 1H), 7.50 (d, *J* = 8.8 Hz, 2H), 7.60 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 15.9, 55.4, 109.6, 114.5, 117.2, 123.6, 124.5, 128.4, 131.5, 133.8, 143.8, 145.6, 160.3; HRMS (*m/z*): $[M+H]^+$calcd for $C_{15}H_{14}NOS$: 256.0791; found: 256.0785.

4'-Methoxy-3-(pyrrolidin-1-yl)-[1,1'-biphenyl]-4-carbonitrile (3j): Colorless liquid; yield: 76%; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.94 (t, *J* = 6.2 Hz, 4H), 3.58 (t, *J* = 6.2 Hz, 4H), 3.77 (s, 3H), 6.70 (s, 1H), 6.76 (d, *J* = 8.0Hz, 1H), 6.89 (d, *J* = 8.8 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.43 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 25.7, 49.9, 55.3, 92.7, 112.1, 114.2, 114.9, 121.6, 128.2, 132.7, 136.0, 145.8, 150.2, 159.8; HRMS (*m/z*): $[M+H]^+$calcd for $C_{18}H_{19}N_2O$: 279.1492; found: 279.1484.

4'-Methoxy-3-(piperidin-1-yl)-[1,1'-biphenyl]-4-carbonitrile (3k): Colorless liquid; yield: 80%; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.54 (t, *J* = 6.0 Hz, 2H), 1.72 (dd, *J* = 11 Hz, *J* = 6.0 Hz, 4H), 3.15 (t, *J* = 6.0 Hz, 4H), 3.79 (s, 3H), 6.91 (dd, *J* = 6.6 Hz, *J* = 2.2 Hz, 2H), 7.04-7.06 (m, 2H), 7.43 (dd, *J* = 6.6 Hz, *J* = 2.2 Hz, 2H), 7.49 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ*24.1, 26.1, 53.1, 55.4, 103.7, 114.3, 116.8, 118.9, 119.4, 128.3, 132.3, 134.5, 146.2, 157.2, 160; HRMS (*m/z*): $[M+H]^+$calcd for $C_{19}H_{21}N_2O$: 293.1648; found: 293.1642.

3',4'-Dimethoxy-3-(pyrrolidin-1-yl)-[1,1'-biphenyl]-4-carbonitrile (3l): Colorless liquid; yield: 80%; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 2.00 (t, *J* = 6.6 Hz, 4H), 3.64 (t, *J* = 6.6 Hz, 4H), 3.90 (s, 3H), 3.92 (s, 3H), 6.73 (d, *J* = 2.0 Hz, 1H), 6.81 (d, *J* = 10.0 Hz, 1H),6.91 (d, *J* = 7.6 Hz, 1H), 7.04 (d, *J* = 2.0Hz, 1H), 7.09 (d, *J* = 2.0Hz, 1H), 7.45 (d, *J* = 7.6 Hz,1H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 25.7, 49.9, 56.0, 92.9, 110.5, 111.4, 112.3, 115.0, 119.7, 122.1, 133.3, 136.0, 146.1, 149.2, 149.5, 150.3; HRMS (*m/z*): $[M+H]^+$calcd for $C_{19}H_{21}N_2O_2$: 309.1598; found: 309.1598.

4'-Fluoro-3-(piperidin-1-yl)-[1,1'-biphenyl]-4-carbonitrile (3m): Colorless liquid; yield: 74%; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.57-1.63 (m, 2H), 1.75-1.81 (m, 4H), 3.21 (t, *J* = 5.2 Hz, 4H), 7.07-7.14 (m, 4H), 7.50-7.57 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 23.9, 26.0, 53.1, 104.3, 115.9, 117.3, 118.6, 119.8, 128.9, 134.7, 136.0, 145.6, 156.9, 163.0; HRMS (*m/z*): $[M+H]^+$calcd for $C_{18}H_{18}FN_2$: 281.1449; found: 281.1442.

4'-Chloro-3-(piperidin-1-yl)-[1,1'-biphenyl]-4-carbonitrile (3n): Colorless liquid; yield: 78%; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.51-1.58 (m, 2H), 1.70-1.76 (m, 4H), 3.15 (t, *J* = 5.2 Hz, 4H), 7.03-7.05 (m, 2H), 7.34-7.37 (m, 2H), 7.41 (d, *J* = 8.8 Hz, 2H), 7.52 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 23.7, 25.8, 53.3, 104.3, 118.4, 120.4, 127.2, 128.5, 128.6, 129.0, 129.2, 134.8, 145.5, 154.7; HRMS (*m/z*): $[M+H]^+$calcd for $C_{18}H_{18}ClN_2$: 297.1153; found: 297.1150.

4'-Bromo-3-(piperidin-1-yl)-[1,1'-biphenyl]-4-carbonitrile (3o): Off white solid; yield: 80%;Melting Point: 120-122 °C; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.51-1.55 (m, 2H), 1.72-1.75 (m, 4H), 3.16 (t, *J* = 5.4 Hz, 4H), 7.03-7.05 (m, 2H), 7.35 (d, *J* = 8.0 Hz,2H), 7.51-7.54 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 24.0, 26.1, 53.1, 104.6, 117.1, 118.6, 119.5, 122.8, 128.8, 132.1, 134.7, 138.9, 145.4, 157.2; HRMS (*m/z*): $[M+H]^+$calcd for $C_{18}H_{18}BrN_2$: 341.0648; found: 341.0644.

1-(Piperidin-1-yl)-9,10-dihydrophenanthrene-2-carbonitrile (3p): Colorless liquid; yield: 75%; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.71-1.72 (m, 6H), 2.80-2.82 (m, 2H), 2.87-2.89 (m, 2H), 3.21 (brs, 4H), 7.25-7.32 (m, 3H), 7.47 (d, *J* = 2.4 Hz, 2H), 7.66-7.68 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 23.3, 24.1, 26.7, 28.5, 52.2, 106.6, 119.7, 119.9, 124.6, 127.1, 127.9, 128.6, 132.6, 133.9, 135.6, 137.8, 140.3, 153.6; HRMS (*m/z*): $[M+H]^+$calcd for $C_{20}H_{21}N_2$: 289.1699; found: 289.1697.

7-Methoxy-1-(piperidin-1-yl)-9,10-dihydrophenanthrene-2-carbonitrile (3q): Colorless liquid; yield: 76%; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.70 (brm, 2H), 2.77 (t, *J* = 4.0 Hz, 2H), 2.86 (t, *J* = 4.0 Hz, 2H), 3.20 (brs, 4H), 3.83 (s, 3H), 6.78 (d, *J* = 2.0 Hz, 1H), 6.83 (dd, *J* = 8.4 Hz, *J* = 2.0 Hz, 1H), 7.39-7.44 (m, 2H), 7.59 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 23.3, 24.1, 26.8, 28.9, 52.2, 55.3, 105.7, 112.5, 113.2, 119.3, 119.8, 126.0, 126.7, 132.6, 134.6, 139.6, 140.3, 153.6, 160.0; HRMS (*m/z*): $[M+H]^+$calcd for $C_{21}H_{23}N_2O$: 319.1805; found: 319.1802.

2-(Piperidin-1-yl)-4-(thiophen-2-yl)benzonitrile (3r): Colorless liquid; yield: 82%; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.61-1.63 (m,

View Article Online
DOI: 10.1039/C8OB01270A

2H), 1.75-1.81 (m, 4H), 3.20 (t, *J* = 5.2 Hz, 4H), 7.09 (d, *J* = 3.6 Hz,1H), 7.16-7.27 (m, 2H), 7.34-7.36 (m, 2H), 7.50 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 24.0, 26.1, 53.0, 104.2, 115.7, 118.4, 118.7, 124.8, 126.5, 128.3, 134.7, 139.4, 142.9, 157.2; HRMS (*m/z*): $[M+H]^+$calcd for $C_{16}H_{17}N_2S$: 269.1107; found: 269.1104.

2-Morpholino-4-(thiophen-2-yl)benzonitrile (3s): Colorless liquid; yield: 77%; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 3.25 (t, *J* = 4.6 Hz, 4H), 3.90 (t, *J* = 4.6 Hz, 4H), 7.10 (dd, *J* = 5.0Hz, *J*= 3.8 Hz, 1H), 7.17-7.26 (m, 2H), 7.37-7.38 (m, 2H), 7.55 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 51.7, 66.9, 104.3, 1165.5, 118.3, 119.4, 125.0, 126.8, 128.4, 134.9, 139.8, 142.5, 155.9; HRMS (*m/z*): $[M+H]^+$calcd for $C_{15}H_{15}N_2OS$: 271.0900; found: 271.0894.

4-(Furan-2-yl)-2-(piperidin-1-yl)benzonitrile (3t): Colorlessliquid; yield: 74%; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.59-1.61 (m, 2H), 1.78 (dd, *J* = 10.4 Hz, *J* = 5.0 Hz, 4H), 3.20 (t, *J* = 5.0 Hz, 4H), 6.48 (dd, *J* = 3.6 Hz, *J* = 1.6 Hz, 1H), 6.73 (d, *J* = 3.6 Hz, 1H), 7.19-7.26 (m, 2H), 7.49-7.52 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 24.0, 26.1, 53.1, 105.2, 107.7, 112.1, 113.4, 116.3, 118.8, 134.6, 135.3, 143.3, 157.2; HRMS (*m/z*): $[M+H]^+$calcd for $C_{16}H_{17}N_2O$: 253.1335; found: 253.1335.

4-(Furan-2-yl)-2-morpholinobenzonitrile (3u): Colorlessliquid; yield: 78%; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 2.02 (t, *J* = 6.4 Hz, 4H), 3.66 (t, *J* = 6.4 Hz, 4H), 6.49 (dd, *J* = 3.6 Hz, *J* = 1.6 Hz, 1H), 6.72 (d, *J* = 3.6 Hz, 1H), 6.91-6.95 (m, 2H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.49 (d, *J* = 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 25.7, 49.8, 92.8, 107.4, 108.6, 111.7, 111.9, 121.5, 134.9, 136.0, 143.0, 150.8, 152.8; HRMS (*m/z*): $[M+H]^+$calcd for $C_{15}H_{15}N_2O_2$: 255.1128; found: 255.1122.

General procedure for the synthesis of biaryls 4: In an oven dried round bottom flask **1** (0.5 mmol), LiOH (0.75 mmol) and DMF (5.0 mL) were taken. The reaction mixture was heated at 60 °C and allyl cyanide **2** (0.6 mmol) was added drop wise for the duration of 1 hour. Completion of reaction was monitored by TLC. After the completion, reaction mixture was poured onto crushed ice and acidified by drop wise addition of dil. HCl. Precipitate obtained, was filtered, dried and purified by column chromatography using 10% ethyl acetate in hexane isolate compound **4** as a major product and .

Product characterization data

3-Methyl-5-(piperidin-1-yl)-[1,1'-biphenyl]-2,4-dicarbonitrile (4c): Off white solid; yield: 75%; Melting Point: 180-182 °C; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.65-1.66 (m, 2H), 1.76 (dd, *J* = 10.8Hz, *J* = 5.6 Hz, 4H), 2.75 (s, 3H) 3.34 (t, *J* = 5.6 Hz, 4H), 6.80 (s, 1H), 7.45-7.49 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 20.5, 23.9, 25.8, 52.4, 103.6, 104.0, 116.6, 117.0, 117.1, 128.5, 128.7, 129.3, 138.0, 149.4, 150.1, 158.4; HRMS (*m/z*): $[M+H]^+$calcd for $C_{20}H_{20}N_3$: 302.1652; found: 302.1643.

4'-Methoxy-3-methyl-5-(piperidin-1-yl)-[1,1'-biphenyl]-2,4-dicarbonitrile (4j): Off white solid; yield: 70%; Melting Point: 204-206 °C; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.62-1.66 (m, 2H), 1.74-1.79 (m, 4H), 2.73(s, 3H), 3.32 (t, *J* = 5.4 Hz, 4H), 3.84 (s, 3H), 6.76 (s, 1H), 6.98 (dd, *J* = 6.6 Hz, *J* = 2.2 Hz, 2H),7.44 (dd, *J* = 6.6 Hz, *J* = 2.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 20.6, 23.9, 25.8, 52.4, 55.4, 103.5, 103.7, 114.2, 116.7, 116.8, 117.4, 129.9, 130.2, 149.4, 149.8, 158.5, 160.6; HRMS (*m/z*): $[M+H]^+$calcd for $C_{21}H_{22}N_3O$: 332.1757; found: 332.1756.

4'-Chloro-3-methyl-5-(piperidin-1-yl)-[1,1'-biphenyl]-2,4-dicarbonitrile (4n): Off white solid; yield: 67%; Melting Point: 190-192 °C; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.61-1.66 (m, 2H), 1.74-1.77 (m, 4H), 2.74 (s, 3H), 3.34 (t, *J* = 5.0 Hz, 4H), 6.74 (s, 1H), 7.43-7.44 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 20.6, 23.8, 25.8, 52.4,103.9, 104.2, 116.5, 116.8, 117.0, 129.0, 129.8, 135.7, 136.3, 148.8, 149.6, 158.4; HRMS (*m/z*): $[M+H]^+$calcd for $C_{20}H_{19}ClN_3$: 336.1262; found: 336.1261.

4'-Bromo-3-methyl-5-(piperidin-1-yl)-[1,1'-biphenyl]-2,4-dicarbonitrile (4o): Off white solid; yield: 78%; Melting Point: 210-212 °C; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.60-1.61 (m, 2H), 1.70-1.72 (m, 4H), 2.70 (s, 3H), 3.30 (t, *J* = 5.6 Hz, 4H), 6.69 (s, 1H), 7.31 (d, *J* = 7.4 Hz, 2H), 7.55 (d, *J* = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 20.6, 23.8, 25.8, 52.4, 104.0, 104.2, 116.5, 116.8, 117.0, 123.9, 130.1, 132.0, 136.8, 148.8, 149.6, 158.4; HRMS (*m/z*): $[M+H]^+$calcd for $C_{20}H_{19}BrN_3$: 380.0757; found: 380.0755.

7-Methoxy-3-methyl-1-(piperidin-1-yl)-9,10-dihydrophenanthrene-2,4-dicarbonitrile (4q): Off white solid; yield: 68%; Melting Point: 180-182 °C; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.65-1.72 (m, 6H), 2.69-2.73 (m, 7H), 3.26 (t, *J* = 4.8 Hz, 4H), 3.84 (s, 3H), 6.80 (d, *J* = 3.0 Hz, 1H) 6.87 (dd, *J* = 8.8 Hz, *J* = 3.0 Hz, 1H), 8.07 (d, *J* = 8.8 Hz,1H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 20.3, 24.0, 24.5, 26.5, 29.3, 52.6, 55.3, 104.0, 106.8, 111.6, 113.4, 117.3, 118.5, 124.6, 128.9, 133.3, 141.2, 143.3, 147.4, 156.4, 160.7; HRMS (*m/z*): $[M+H]^+$calcd for $C_{23}H_{24}N_3O$: 358.1914; found: 358.1912.

2-Methyl-4-(piperidin-1-yl)-6-(thiophen-2-yl)isophthalonitrile (4r): Off white solid; yield: 70%; Melting Point: 168-170 °C; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.63-1.68 (m, 2H), 1.74-1.80 (m, 4H), 2.73 (s, 3H), 3.34 (t, *J* = 5.4 Hz, 4H), 6.90 (s, 1H), 7.14 (dd, *J* = 4.8 Hz, *J* = 4.0 Hz ,1H), 7.45 (d, *J* = 4.8 Hz, 1H), 7.64 (d, *J* = 4.0 Hz , 1H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 20.7, 23.8, 25.8, 52.4, 102.5, 104.0, 116.5, 117.3, 128.1, 128.4, 128.7, 139.0, 141.9, 150.0, 158.4; HRMS (*m/z*): $[M+H]^+$calcd for $C_{18}H_{18}N_3S$: 308.1221; found: 308.1215.

Procedure for the synthesis of 4'-methoxy-3-morpholino-[1,1'-biphenyl]-4-carboxamide (5): A dried flask fitted with a magnetic stir bar was charged with aromatic nitrile (0.2 mmol) and KO^{t}Bu (0.6 mmol), and dry toluene (2.0 mL) was added. The reaction mixture was stirred at room temperature for 10 h under nitrogen atmosphere, and progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was treated with cold water (10.0 mL). The product was extracted with ethylacetate for three times and purified by column chromatography using 2:3 solution of ethyl acetate in hexane. Pure compound was dried under vacuum to provide the corresponding amide in 88% yield. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 3.00 (t, *J* = 4.6 Hz, 4H), 3.75 (d, *J* = 4.6 Hz, 3H), 3.81 (t, *J* = 4.6 Hz, 4H), 6.10-6.38 (1H), 6.87-7.05 (m, 2H), 7.14-7.40 (m, 4H), 8.12 (d, *J* = 8.4 Hz, 1H), 9.20-9.62 (1H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 53.6, 55.6, 67.4, 111.3, 120.9, 121.6, 125.6, 125.9, 129.3, 129.4, 130.6, 131.5, 143.0, 150.7, 156.3, 168.6; HRMS (*m/z*): $[M+H]^+$calcd for $C_{18}H_{21}N_2O_3$: 313.1547; found: 313.1542.

View Article Online
DOI: 10.1039/C8OB01270A

Procedure for the synthesis of (4'-methoxy-3-(piperidin-1-yl)-[1,1'-biphenyl]-4-yl)methanamine (6): A dried flask fitted with a magnetic stir bar was charged with $LiAlH_4$ (0.6 mmol), and dry THF (2.0 mL) was added at 0-5 ^{o}C. The aromatic nitrile (0.2 mmol) was dissolved in dry THF (1.0 mL) and slowly added to the $LiAlH_4$ solution. The reaction mixture was stirred at 0-5 ^{o}C for 30 minutes and then heated to80 ^{o}C for 7 h under nitrogen atmosphere. Progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was treated with cold water (10.0 mL). The product was neutralized by 10% dil. HCl and extracted with ethylacetate for three times and dried in Na_2SO_4. Then the compound was purified by column chromatography using 2:3 solution of ethyl acetate in hexane. Pure compound was dried under vacuum to provide the corresponding amine in 70 % yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.56 (s, 2H), 1.78 (q, *J* = 5.8 Hz, 4H), 2.91 (s, 4H), 3.77 (s, 3H), 4.28 (s, 2H), 6.34 (s, 2H), 7.07-6.89 (m, 2H), 7.26 (m,2H), 7.41-7.28 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.9, 26.5, 42.3, 54.2, 55.5, 111.2, 120.8, 122.7, 126.5, 128.9, 129.9, 130.6, 140.2, 151.6, 156.3; HRMS (*m/z*): $[M+H]^+$calcd for $C_{19}H_{22}N_2O$: 297.1961; found: 297.1955.

Procedure for the synthesis of 4'-morpholino-3-(piperidin-1-yl)-[1,1'-biphenyl]-4-carbonitrile (7): Into an oven-dried screw-cap vial equipped with a stirring bar were placed $Pd_2(dba)_3$ (0.010g, 0.01 mmol) and Xantphos (0.009 g, 0.015 mmol). Toluene (1.0 mL) was added, the vial was flushed with N_2 gas, and the mixture was stirred at room temperature for 10 minutes. To the resulting mixture were added the morpholine (0.02 ml, 0.24 mmol) and bromobiaryl (0.069 g, 0.2 mmol) followed by K_3PO_4 (0.064 g, 0.3 mmol). The reaction mixture was again flushed with N_2 gas, sealed with a Teflon-lined cap, and heated in an oil bath that was maintained at 90 ºC. The reaction was monitored by TLC and judged to be complete within 48 h at which time the mixture was cooled, diluted with EtOAc, and extracted twice with water. The aqueous layer was back extracted with EtOAc and the combined organic layer dried in anhydrous Na_2SO_4 and concentrated on a rotary evaporator. The crude product was purified by silica gel column chromatography, eluting first with hexane and then with 10% EtOAc in hexane to yield 69% of desired compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ1.61 (q, *J* = 5.8 Hz, 2H), 1.88-1.73 (m, 4H), 3.27-3.13 (m, 8H), 3.89 (t, *J* = 5.0 Hz, 4H), 6.98 (d, *J* = 8.8 Hz, 2H), 7.12-7.14 (m, 2H), 7.51 (d, *J* = 8.8 Hz, 2H), 7.55 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.1, 26.1, 48.7, 53.1, 66.8, 103.5, 116.5, 119.2, 125.3, 127.3, 128.0, 128.1, 129.0, 130.1, 134.5, 142.1, 151.3, 157.2; HRMS (*m/z*): $[M+H]^+$calcd for $C_{22}H_{26}N_3O$: 348.2070; found: 348.2062.

Procedure for the synthesis of 3-(piperidin-1-yl)-[1,1':4',1''-terphenyl]-4-carbonitrile (8): To a nitrogen flushed sealed tube the aryl boronic acid (0.3 mmol) was charged and dissolved in ethanol followed by addition of $Pd(PPh_3)_4$(5 mol %) and bromo substituted biaryl (0.2 mmol) and DME (2.0 mL) under nitrogen gas. A solution of Na_2CO_3 (0.8 mmol) in degassed water (0.5 mL) was added to the reaction mixture and the mixture was heated at reflux for 24 h. The reaction mixture was then cooled to room temperature, diluted with ethylacetate (5.0 mL) and transferred to separatory funnel. The layers were separated and the aqueous layer was extracted with ethylacetate (10.0 mL). The layers were separated and aqueous layer was discarded. The combined organic layers were then washed with 1M aqueous NaOH (10 mL) and aqueous layer was discarded. The combined organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material thus obtained was purified by column chromatography on silica gel using 1:19 ethylacetate-hexanes to yield 76% of desired compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.71-1.54 (m, 2H), 1.73-1.89 (m, 4H), 3.25 (t, *J* = 5.3 Hz, 4H), 7.15-7.31 (m, 2H), 7.43 (m, 3H), 7.55-7.76 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.1, 26.1, 53.2, 104.4, 117.2, 118.8, 119.7, 127.1, 127.6, 127.6, 128.9, 134.6, 138.8, 140.3, 141.3, 146.1, 157.2; HRMS (*m/z*): $[M+H]^+$calcd for $C_{24}H_{23}N_2$: 339.1856; found: 339.1850.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank the Department of Science and Technology (DST, New Delhi) and Delhi University for providing DST-DU purse grant and CSIR, New Delhi and ICMR, New Delhi for research funding. RP thanks JSPS, Japan for providing invitation fellowship and Delhi University for providing leave for this fellowship. Author thanks Prof. Hideki Yorimitsu for scientific discussion related to the mechanism of the reaction. PY thanks University Grants Commission (UGC, New Delhi) for providing research fellowship. RS thanks CSIR, New Delhi for research fellowship. AE thanks Biocare DBT for TWAS fellowship for pursuing research. The authors thank University of Delhi for providing research funding and instrumentation facility.

Notes and references

1. F. F. Fleming, *Nat. Prod. Rep.,* 1999, **16**, 597.
2. (*a*) F. F. Fleming, L. Yao, P. C. Ravikumar, L. Funk, B. C.Shook, *J. Med. Chem.,* 2010, **53**, 7902; (*b*) Chemistry of the Cyano Group (Eds.: Z. Pappoport, S. Patai), Wiley, London, 1970.
3. R. Lýpez, C. Palomo, *Angew. Chem. Int. Ed.,* 2015, **54,** 13170.
4. P. B. Kisanga, J. G.Verkade, *J. Org. Chem.,* 2002**, 67**, 426.
5. (*a*) R. Yazaki, N. Kumagai, M.Shibasaki, *J. Am. Chem. Soc.,*2009, **131**, 3195; (*b*) R. Yazaki, N. Kumagai, M.Shibasaki,*J. Am. Chem. Soc.,*2010, **132**, 5522; (*c*) A. Saito, N.Kumagai, M.Shibasaki,*Tetrahedron Lett.,*2014,**55**, 3167; (*d*) Y. Otsuka,H.Takada, S. Yasuda, N. Kumagai, M.Shibasak, *Chem. Asian J.,*2013, **8**, 354.
6. (*a*) R. Yazaki, T.Nitabaru, N. Kumagai, M.Shibasaki,*J. Am. Chem. Soc.,*2008, **130**, 14477; (*b*)J.Aydin, K. J. Szabó, *Org.Lett.,*2008, **10**, 2881.
7. Y. Yanagida, R. Yazaki, N. Kumagai, M. Shibasaki,*Angew. Chem. Int. Ed.*2011, **50**, 7910.
8. M. C.Kozlowski,B. J.Morgan, E. C. Linton, *Chem. Soc. Rev.,* 2009, **38**, 3193.
9. J. Yamaguchi, A. D. Yamaguchi, K.Itami, *Angew. Chem. Int. Ed.,*2012, **51**, 8960.

View Article Online
DOI: 10.1039/C8OB01270A

10. (*a*) R. Noyori, *Chem. Soc. Rev.*,1989, **18**, 187; (*b*) N. G.Andersen, S. P.Maddaford, B. A.; Keay, *J. Org. Chem.,*1996, **61**, 9556.
11. F. Mikes, G. Boshart,*J. Chromatogr.,*1978, **149**, 455.
12. (*a*) R. Martin; S. L. Buchwald, *Acc. Chem. Res.*2008,**41**, 1461; (*b*) D. S.Surry, S. L. Buchwald, *Angew. Chem. Int. Ed.,*2008, **47**, 6338; (*c*) D. S.Surry, S. L. Buchwald,*Chem. Sci.*2011, **2**, 27.
13. (*a*) J. Wencel-Delord, F.Glorius, *Nat. Chem.*2013, **5**, 369; (*b*) S. J.Pickent, W. F. V.Gunsterens, P. T. V.Duijnens, W. H. D.Jew, *Liquid Crystals*1989, **6**, 357; (*c*) S.-W.Joo, T. D.Chung, W. C.Jang, M.-S.Gong, N.Geum, K.Kim, *Langmuir,*2002, **18**, 8813.
14. P.Yadav, R. Shaw, R. Panwar, S. N. Sahu, A. Kumar, R. Pratap,*Asian J. Org. Chem.*2017,**6**, 1394.
15. S. N.Sahu, M. K.Gupta, S. Singh, P. Yadav, R. Panwar, A. Kumar, V. J. Ram, B. Kumar, R. Pratap, *RSC Adv.*2015, **5**, 36979.
16. Crystallographic data information for biaryl**3o** has been deposited with the Cambridge Crystallographic Data Centre with CCDC No. 1520565. Further details are given in SI.
17. P. Yadav, S. Singh, S. N. Sahu, F. Hussain, R. Pratap, Org. Biomol. Chem.2014, 12, 2228.