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Organocatalyst in Direct $C(_{sp}^2)$–H Arylation of Unactivated Arenes: [1-(2-Hydroxyethyl)-piperazine]-catalyzed *Inter-* /*Intra*-molecular C–H bond activation

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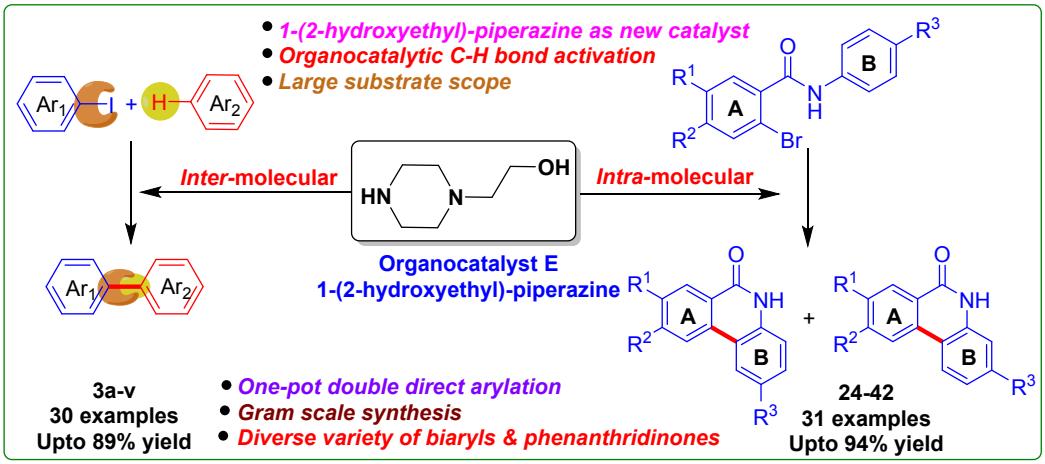


ABSTRACT: This article describes the identification of 1-(2-hydroxyethyl)-piperazine as a new, cost-effective, highly efficient organocatalyst which promotes both *inter*- as well as *intra*-molecular direct $C(_{sp}^2)$–H arylation of unactivated arenes in the presence of potassium *tert*-butoxide. While the *inter*-molecular C–H arylation of unactivated benzenes with aryl halides (Ar–X; X = I, Br, Cl) towards biaryl syntheses underwent smoothly in the presence of only 10 mol% organocatalyst; the *intra*-molecular C-H arylation catalytic system comprises of 40 mol% each of the catalyst and the additive (DMAP). The novel catalyst is also able to perform both *inter*- as well as *intra*-molecular direct arylation simultaneously in a single pot. The mechanistic studies confirmed the involvement of aryl radical anion and proceeded via single electron transfer (SET) mechanism. The large substrate scope, high functional group tolerance, competition experiments, gram-scale synthesis and kinetic studies further highlights the importance and versatile nature of the methodology as well as the compatibility of the new catalyst. To the best of our knowledge, this is the first report by any organocatalyst reported in the literature which gives detailed extensive investigations of both *inter*- as well as *intra*-molecular direct $C(_{sp}^2)$–H arylation of unactivated arenes in a single representation.

Introduction

During the last two decades, organocatalyzed $C_{(sp}^2)$–H bond activation of arenes/heteroarenes has been recognized advantageous over transition-metal catalysis and has been found as a promising area of

research in the field of C–H bond activation.[1] This is due to their inherent non-metal properties, environmentally benign, broad functional group tolerance, mild reaction conditions with high degree of selectivity and productivity.[1] Biaryls are important pharmaceutically previleged structural moieties which are present in several natural products, pharmaceuticals, agrochemicals and functional materials.[2] Recently, organocatalyzed synthesis of biaryls has been reported by the reaction of aryl halides with arenes using small organic molecule as an organocatalyst **I-XI** in the presence of strong base which generally involves radical chain mechanism (Figure 1).[3-5] Several *inter*-molecular organocatalytic approach has been reported by Itami,[3a] Kwong,[3b] Lei,[3b] Shirakawa/ Hayashi,[3c] and Shi[3d] to synthesize biaryl moiety *via* single electron transfer (SET) mechanism (Figure 1).[3,4]

Similarly, many *intra*-molecular C(sp^2)-H direct arylation have also been reported *via* organocatalyzed base-promoted homolytic aromatic substitution (BHAS) reaction to construct various biaryl-based heterocyclic compounds.[5] However, all these *inter*- as well as *intra*-molecular C(sp^2)–H direct arylation are being facilitated by costly organocatalyst such as 1,10-phenanthridinone, 1,2-diamines, 1,2-diols, amino acids, hydrazine derivative, N-heterocyclic carbenes and a pyridone-fused cavity complex, P5a etc (Figure 1).[3-5] Therefore, the identification of a new cost-effective organocatalyst, which can perform both *inter*- as well as *intra*-molecular C(sp^2)–H direct arylation of unactivated arenes, is highly desirable in higher yields under ambient reaction conditions.

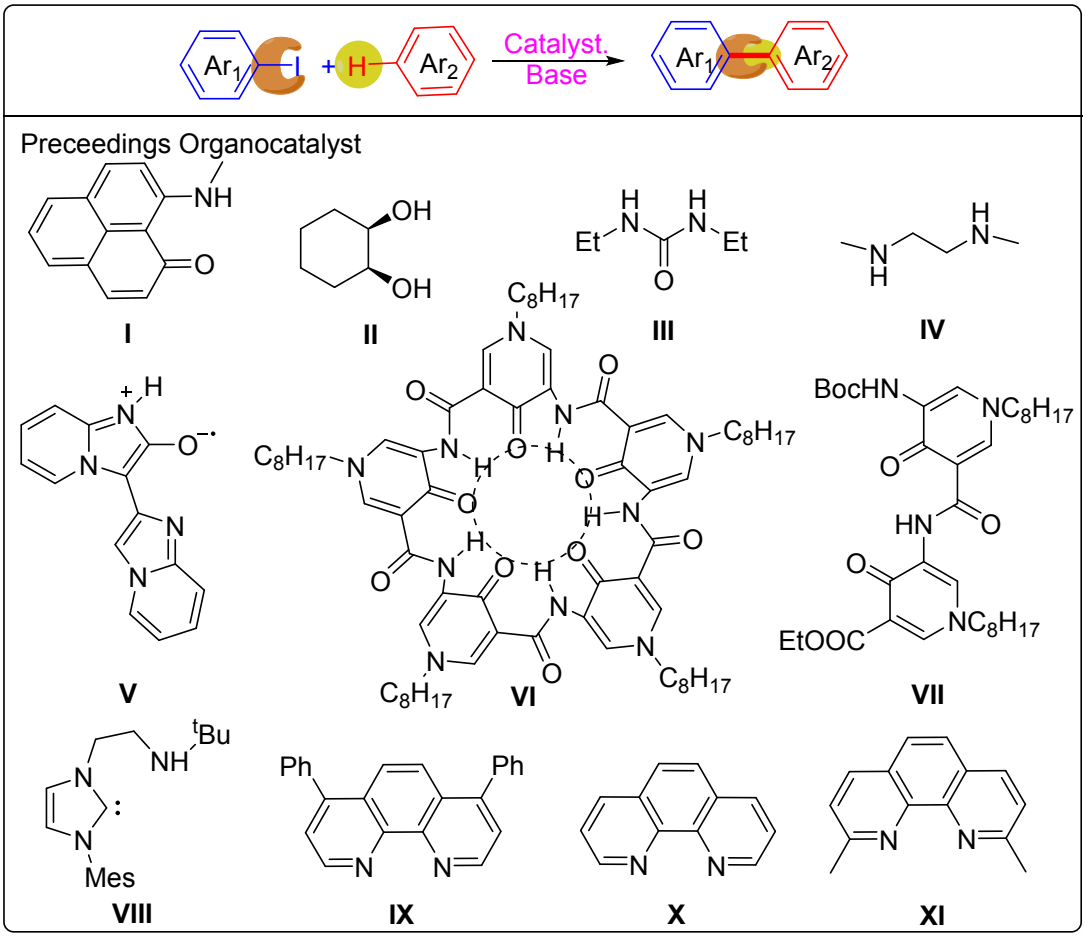


Figure 1. Structures of selected organocatalyst **I-XI** used in previous organocatalyzed C-H bond activation.[3-5]

The *inter*-molecular direct arylation of unactivated arenes has been mainly reported to be catalyzed by N,N-bidentate ligands. Few examples of O,O-bidentate ligand has been reported to execute *intra*-molecular direct arylation reactions. Therefore, in our efforts to prepare bioactive heterocycles through novel synthetic strategies[6a-b] and to search for new metal-free/organocatalytic system;[6c-d] we anticipated that reaction catalyzed by N,O-bidentate ligand could effectively generate coupled product in excellent yields. Thus, based on above hypothesis, without neglecting N,N- and O,O-bidentate ligands, we plan to carry out extensive investigation for the search of new organocatalyst [possibly with N,O-bidentate ligand(s)] which can effectively facilitate both *inter*-as well as *intra*-molecular organocatalyzed direct arylation of unactivated arenes in a cost-effective manner under ambient reaction conditions. Herein, we uncovered 1-(2-hydroxyethyl)-piperazine as a new, cost-effective, highly efficient organocatalyst which promotes both *inter*- as well as *intra*-molecular direct $C(_{sp}{}^2)$–H arylation of unactivated arenes in the presence of potassium *tert*-butoxide. Both inter-molecular as well as intra-molecular direct arylation underwent smoothly to furnish biaryls and phenanthridinones (scaffold chosen in the present study), respectively. To the best of our knowledge, this is the first report by any organocatalyst reported in the literature which gives detailed extensive investigations (comprehensive optimization studies, substrate scope, gram-scale synthesis, kinetic isotopic studies, competition experiments, ICP-MS data studies, one-pot double direct arylation etc.) of both *inter*- as well as *intra*-molecular direct $C(_{sp}{}^2)$–H arylation of unactivated arenes in a single representation.

Results and Discussion

Inter-molecular Organocatalyzed C(sp^2)-H direct arylation of unactivated arenes

4-iodotoluene **1a** and extrapure anhydrous benzene **2** was selected as starting materials for the optimization of *inter*-molecular organocatalyzed C(sp^2)–H direct arylation of unactivated arenes (Table 1). Initially, the screening of organocatalyst (**A**-**M**) was carried out for the optimization study involving reaction of **1a** with **2** to furnish 4-methylbiphenyl **3a** (Table 1, entry 1-13, figure 2). The choice of the organocatalyst were based on previous findings and most of the ligands have either N,N-/O,O- or N,O-coordinating atoms between two carbon atoms. While the catalyst **A**, **D**, **J** and **M** were found ineffective to furnish biaryl product **3a** (Table 1, entry 1, 4, 10 and 13); the organocatalyst **C**, **E**, **H**, and **L** furnished **3a** in >50% yields (Table 1, entry 3, 5, 8 and 12). Rest of the organocatlayst were able to afford **3a** in lower yields (Table 1, entry 2, 6-7, 9 and 11). No conversion of **1a** into **3a** was observed when the reaction was carried out in the absence of an organocalalyst (Table 1, entry 14). Therefore, after screening of several commercially available organocatalysts **A**-**M**, [1-(2-hydroxyethyl)-piperazine] i.e., Catalyst **E** having N,O–coordinating atoms between two carbon atoms was found to be the best organocatalyst which afforded 4-methylbiphenyl **3a** in 72% yield (Table 1, entry 5). It has been

observed that 2-(1H-imidazole-1-yl)ethan-1-ol (catalyst **F**), piperazine (catalyst **H**), and [2,2'-(piperazine-1,4-diyl)bis(ethan-1-ol)] (catalyst **G**) were found less effective than 2-(piperazin-1-yl)ethan-1-ol (catalyst **E**) (Table-1, entry 5-8). Once oragnocatalyst is optimized, then, screening of various aprotic polar solvents such as DMF, DMSO, DMA were carried out in which 4 equiv. of **2** was taken (Table 1 entry 15-18). These solvents were not found effective in enhancing the yield of the reaction.

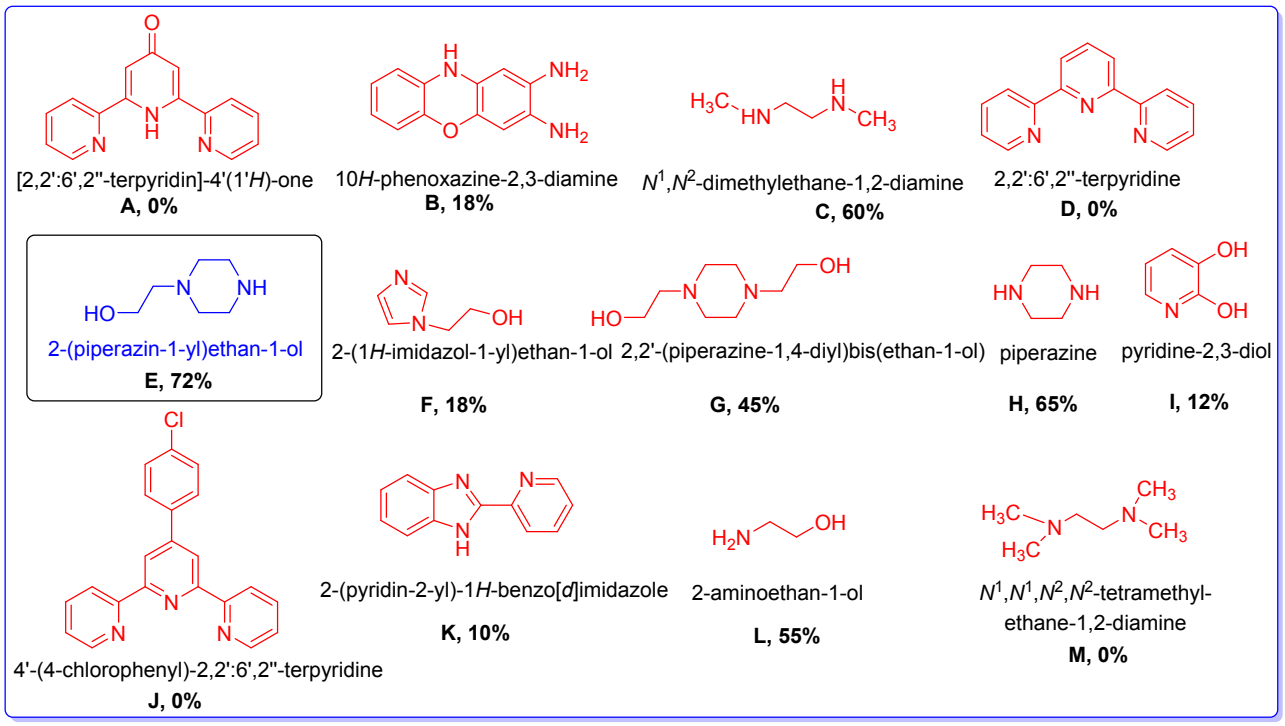


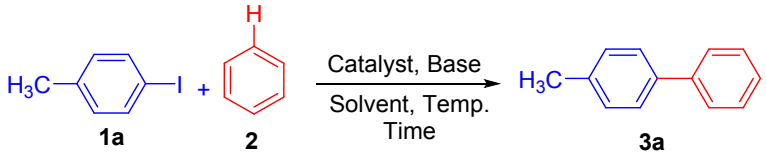
Figure 2. Structures of different organocatalyst **A-M** used in this study.

Subsequently, various bases such as LiO^{t}Bu, NaO^{t}Bu, KOH, K_2CO_3, and LiHMDS etc. were screened (Table 1, entry 19-23). Using 20 mol% of Catalyst E in benzene (4 mL), potassium *tert*-butoxide was found to be the best efficient base for the synthesis of **3a** (Table 1, entry 18). Other bases such as LiO^{t}Bu, NaO^{t}Bu, KOH, K_2CO_3 were found ineffective (Table 1, entry 19-23). An increase or decrease in gram equivalents of base do not have beneficial effect on the yield of the reaction (Table 1, entry 24-25). Then, the study towards variation of mol% of catalyst E {1-(2-hydroxyethyl)-piperazine} along with increase in temperature (100 °C) and time (24 h) and 3 equivalents of KO^{t}Bu was carried out (Table 1, entry 26-27). It was found that the reaction of **1a** with **2** to furnish **3a** underwent effectively in 85% isolated yield using 10 mol% of catalyst E as compared to the reaction where 20 mol% of cat. E was used (Table 1, entry 26-27).[5d] The formation of thick reddish reaction mixture using 20 mol% of cat. E might be the probable cause for the low yield of the reaction. However, using 10 mol% of cat. E, there is comparatively very less formation of thick reddish mixture. Eventually, decrease in the yield of the reaction was also observed when 5 mol% of cat. E was utilized keeping all the other parameters same (Table 1, entry 28). Overall, *10 mol % of Catalyst E {1-(2-hydroxyethyl)-piperazine}, 3*

equivalents of KO^{t}Bu dissolved in 4 mL of benzene at 100 °C for 24 h was found to be the best optimized reaction conditions for inter-molecular organocatalyzed direct arylation reaction.

Using optimized reaction conditions, several substituted aryl/heteroaryl halides **1a-v** were reacted with benzene **2** in presence of catalyst E and potassium tert-butoxide at 100 °C for 24 h furnished substituted biaryls **3a-v** upto 89% yields (Scheme 1).

Table 1. Optimization study: *Inter*-molecular Organocatalyzed C(sp^2)-H direct arylation of aryl halides unactivated benzene.[a]



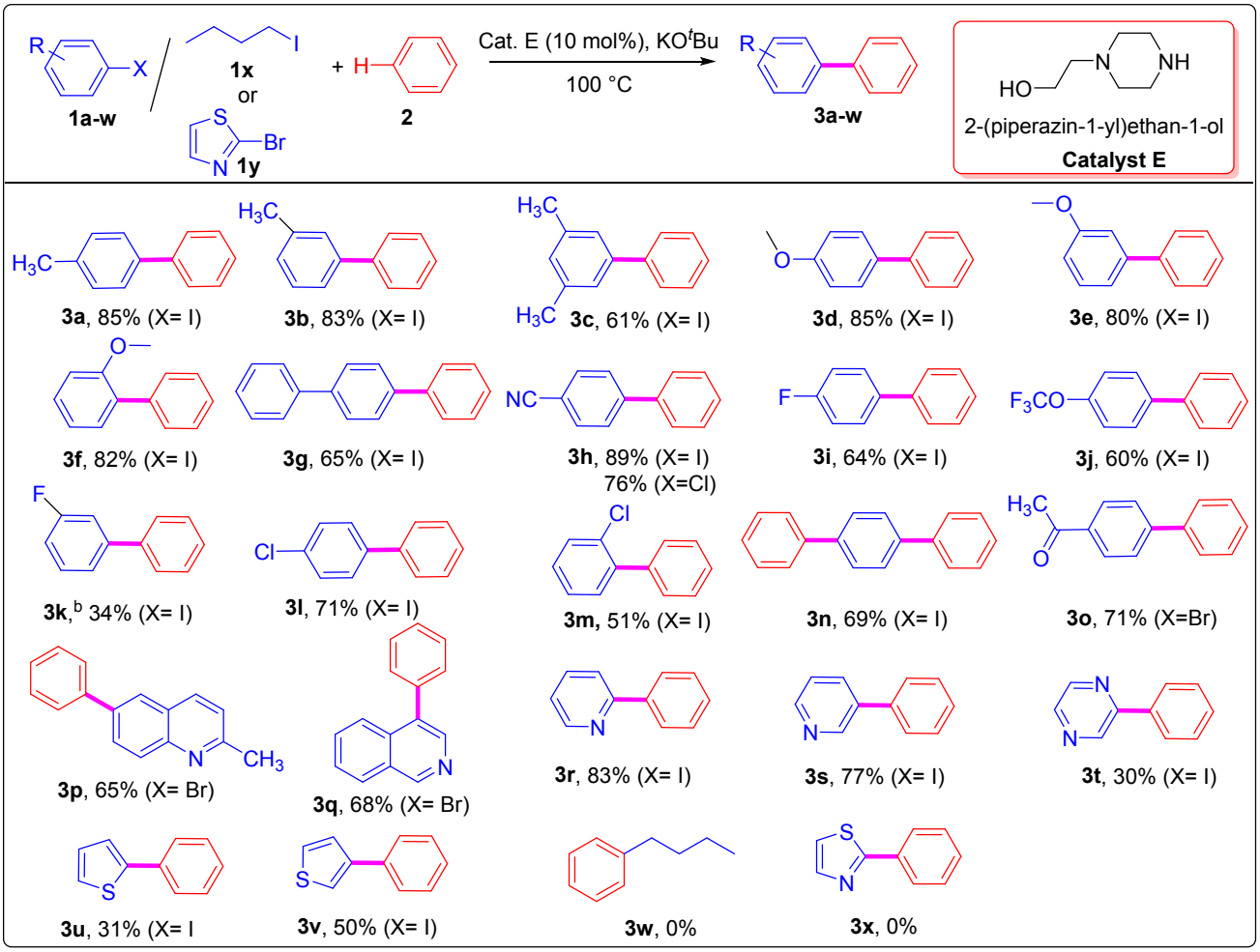
entry	Catalyst	solvent	Base	Temp [^{o}C]	Time [h]	Yield [%][b]
1.	A	benzene	KO^{t}Bu	80	13	trace
2.	B	benzene	KO^{t}Bu	80	13	18
3.	C	benzene	KO^{t}Bu	80	13	60
4.	D	benzene	KO^{t}Bu	80	13	trace
5.	E	benzene	KO^{t}Bu	80	13	72
6.	F	benzene	KO^{t}Bu	80	13	18
7.	G	benzene	KO^{t}Bu	80	13	45
8.	H	benzene	KO^{t}Bu	80	13	65
9.	I	benzene	KO^{t}Bu	80	13	12
10.	J	benzene	KO^{t}Bu	80	13	trace
11.	K	benzene	KO^{t}Bu	80	13	10
12.	L	benzene	KO^{t}Bu	80	13	55
13.	M	benzene	KO^{t}Bu	80	13	Trace
14.	-------	benzene	KO^{t}Bu	80	13	0
15.	E	DMF[c]	KO^{t}Bu	110	13	trace
16.	E	DMSO[c]	KO^{t}Bu	120	13	48
17.	E	DMA[c]	KO^{t}Bu	130	13	trace
18.	E	DMSO[c]	KO^{t}Bu	RT	24	55
19.	E	benzene	LiO^{t}Bu	80	13	0
20.	E	benzene	NaO^{t}Bu	80	13	0
21.	E	benzene	KOH	80	13	0
22.	E	benzene	K_2CO_3	80	13	0
23.	E	benzene	Li-HMDS	80	13	8
24.	E	benzene	KO^{t}Bu(4)	80	13	60
25.	E	benzene	KO^{t}Bu(2)	80	13	65
26.	E	benzene	KO^{t}Bu	100	24	76
27.	**E**[d]	benzene	**KO^{t}Bu**	**100**	**24**	**85**
28.	E[e]	benzene	KO^{t}Bu	100	24	65

[a]The reaction was carried out using **1a** (0.5 mmol), and benzene **2a** (4 mL) in the presence of catalyst and base (1.5 mmol) in sealed tubes., [b]isolated yield, [c] 4 equiv. of benzene was taken along with 2 mL of the solvent. [d]10 mol% of cat. E. [e]5 mol% of cat. E.

The yields of the reaction showed wide range of values and were found satiffactorily with both electron-donating group (EDG) and electron-withdrawing group (EWG) on aryl halides (**3a-m**). The electron-

donating methyl group at *p*- as well as *m*-position of **1a** and **1b** furnished biaryl coupling product **3a** and **3b** in 85% and 83% yields, respectively. However, introduction of two CH_3 group (**3c**) diminishes the yield of the reaction. Similarly, *o*-/*m*-/*p*-OMe group containing iodobenzene also furnished coupled product (**3d-f**) in excellent yields. Here, it is to be noted that the sterically hindered biaryl product **3f** was formed in 82% yield from *o*-OMe iodobenzene **1f**. Furthermore, terphenyl **3g** or **3n** have been synthesized either from biphenyl iodide **1g** or from diiodobenzene in significant yields. Like electron-donating groups, arylhalide containing electron-withdrawing groups such as CN, F, OCF_3 etc. also furnished the desired product in reasonably sufficient yields (**3h-j**) except **3k** where *m*-terphenyl is obtained in 30% yield. In contrast, the reaction of *p*-fluoroiodobenzene **1i** furnished the *p*-terphenyl in only trace amount. In addition, *p*-chloro and *m*-chloro –iodobenzene **1l** and **1m** furnished **3l** and **3m** in 71% and 51% yields, respectively. However, there is a formation of *o*-/*m*-/*p*-terphenyls in significant yields in the case of haloiodobenzene X–Ar–I (X = Cl, Br, I) which has been explained in Table 2.

Scheme 1. Substrate scope: 1-(2-hydroxyethyl)-piperazine-catalyzed biaryl coupling with aryl iodides/bromides /chlorides.[a]

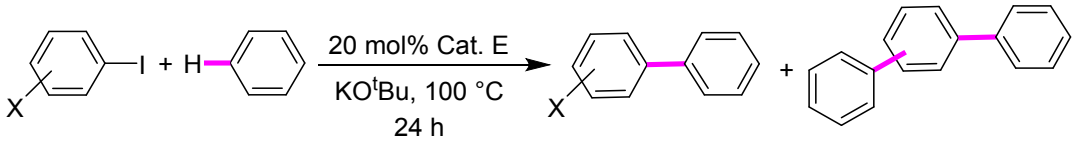


[a]*Reaction conditions*: The reaction was carried out under a nitrogen atmosphere using an aryl halide (**1a-y**: 0.5 mmol), benzene (**2**: 4 mL), KO^{t}Bu (1.5 mmol), and 1-(2-hydroxyethyl)-piperazine (Cat. **E**: 0.05 mmol) in a sealed tube for 24 h. [b]Conversion of **1k** to Compound **6** in 30% yield.

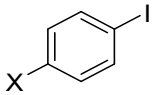
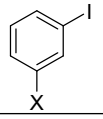
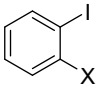
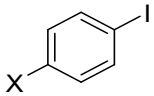
Similarly, functionalized bromoarene **1o** on direct arylation furnished functionalized biaryls **3o** in 71% yield. Some heteroaryl halides (X = Br, I) such as quinoline, isoquinoline, pyridine, pyrazine, thiophene etc. furnished heterobiaryls **3p-v** in moderate to high yields (up to 83%). It was also noticed that the reaction behaves differently with unsubstituted halobenzenes (X = Cl, Br). Chlorobenzene on reaction with **2** do not undergo direct arylation to furnish biaryl under optimal reaction conditions. However, bromobenzene on reaction with **2** furnished biaryl in only 20% yield. Overall, it can be interpreted that inspite of having electron-donating (EDG) and electron-withdrawing (EWG) group in the starting substrate; the reaction facilitates smooothy in relatively significant yields. The aliphatic iodoalkyl **1w** and iodo-thiazole **1x** was ineffective to accomplished the desired product **3w** and **3x,** respectively, under optimized reaction conditions.

To further explore the substrate scope of our optimized methodology, several dihalobenzenes **4a-i** substituted at *ortho*-, *meta*- and *para*-positions were subjected to direct double arylation under optimized reaction conditions which furnished mono-arylated **1g**/**5a-f**/**3l**/**3m** as well as bis-arylated products **3n**/**6**/**7** in good to moderate yields (Table 2).

Table 2. Substrate scope: 1-(2-hydroxyethyl)-piperazine catalyzed direct double arylation of dihalobenzenes with unsubstituted benzene.[a]



4a-i **2** **1g / 5a-f / 3l / 3m** **3n / 6 / 7**

entry	substrate		Product (yield %)	
			Biaryl	Terphenyl
1.		**4a**, X = I	**1g** (7)	**3n** (69)
2.		**4b**, X = Br	**5a** (50)	**3n** (35)
3.		**4c**, X = Cl	**3l** (71)	**3n** (9)
4.		**4d**, X = I	**5b** (traces)	**6** (71)
5.		**4e**, X = Br	**5c** (25)	**6** (50)
6.		**4f**, X = Cl	**5d** (32)	**6** (26)
7.		**4g**, X = I	**5e** (63)	**7** (17)
8.		**4h**, X = Br	**5f** (34)	**7** (30)
9.		**4i**, X = Cl	**3m** (51)	**7** (31)
10.[b]		**4b**, X = Br	**5a** (25)	**3n** (67)

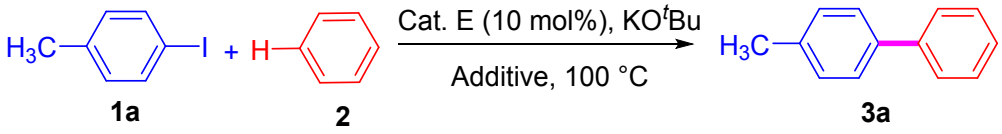
[a]*Reaction conditions*: The reaction was carried out under a nitrogen atmosphere using an aryl halide (**4a-i**: 0.5 mmol), benzene (**2**: 4 mL), KO^{t}Bu (1.5 mmol), and 1-(2-hydroxyethyl)-piperazine (Cat. **E**: 0.05 mmol) in a sealed tube for 24 h. [b]5 equivalents of KO^{t}Bu was used.

Different *para*-substituted halo-iodobenzenes **4a-c** (X = I, Br, Cl) reacted with **2** under optimized reaction conditions showed variation in the yield of the mono-arylated and bis-arylated products

depending upon the bond energies of the C–X bond (Table 2, entry 1-3). 1,4-Diiodobenzene **4a** on reaction with **2** furnished biaryl (mono-arylated) **1g** and terphenyl (bis-arylated) **3n** in 7% and 69% yields, respectively (Table 2, entry 1). However, 1-bromo-4-iodobenzene **4b** reacted with **2** under optimized conditions and furnished biaryl **5a** and terphenyl **3n** in 50% and 35% yields, respectively (Table 2, entry 2). Contrary to **4a**, 1-chloro-4-iodobenzene **4c** (having relatively stronger C–Cl bond) gives biaryl **3l** and terphenyl **3n** in 71% and 9% yields, respectively (Table 2, entry 3). Similar variation in the yield of biaryl and terphenyl was observed in the case of meta-substituted halo-iodoarenes **4d-f** (X = I, Br, Cl). While mono-arylated products **5b** and **5d** were obtained in lower yield in the case of *m*-diiodobenzene **4d** and higher yield in the case of *m*-chloro-iodobenzene **4f**, respectively; bis-arylated product **6** was obtained in higher yield in the case of *m*-diiodobenzene **4d** and lower yield in the case of *m*-chloro-iodobenzene **4f** (Table 2, entry 4 and 6). In addition, **5c** and **6** were obtained in average yields in the case of *m*-bromo-iodobenzene (Table 2, entry 5).

Sterically hindered *ortho*-Substituted halo-iodobenzenes **4g-i** undergoes this reaction in contrast to *para*- and *meta*-substituted halo-iodobenzenes **4a-c** and **4d-f**. 1,2-Diiodobenzene **4g** on reaction with **2** furnished biaryl (mono-arylated) **5e** and terphenyl (bis-arylated) **7** in 63% and 17% yields, respectively (Table 2, entry 7). However, 2-bromo-1-iodobenzene **4h** reacted with **2** under optimized conditions and furnished biaryl **5f** and terphenyl **7** in 34% and 30% yields, respectively (Table 2, entry 8). Contrary to **4g**, 1-chloro-1-iodobenzene **4i**, (having relatively stronger C–Cl bond) gives biaryl **3m** and terphenyl **7** in 51% and 31% yields, respectively (Table 2, entry 9). Thus, the newly developed catalyst potentially activates two C-H bond to effectively facilitate organocatalyzed double direct arylation. The most important characteristic feature of our reaction was observed with *m*-fluoro-iodoarenes as illustrated in Scheme 1 where *meta*-flouro-iodoarenes **1k**, inspite of having strong C–F bond, was subjected to direct arylation under optimized reaction conditions afforded meta-diarylated product **6** in 12% yield. It was also observed that increasing the amount of KO^{t}Bu from 3 equivalents to 5 equivalents increases the yield of the bis-arylated product (Table 2, entry 10).

Table 3. Role of radicals/cation in direct arylation reactions.



1a **2** **3a**

entry	Additive	Yield (%)[a]
1.	No radical scavenger	85
2.	TEMPO (10 mol %)	12%
3.	TEMPO (100 mol %)	0

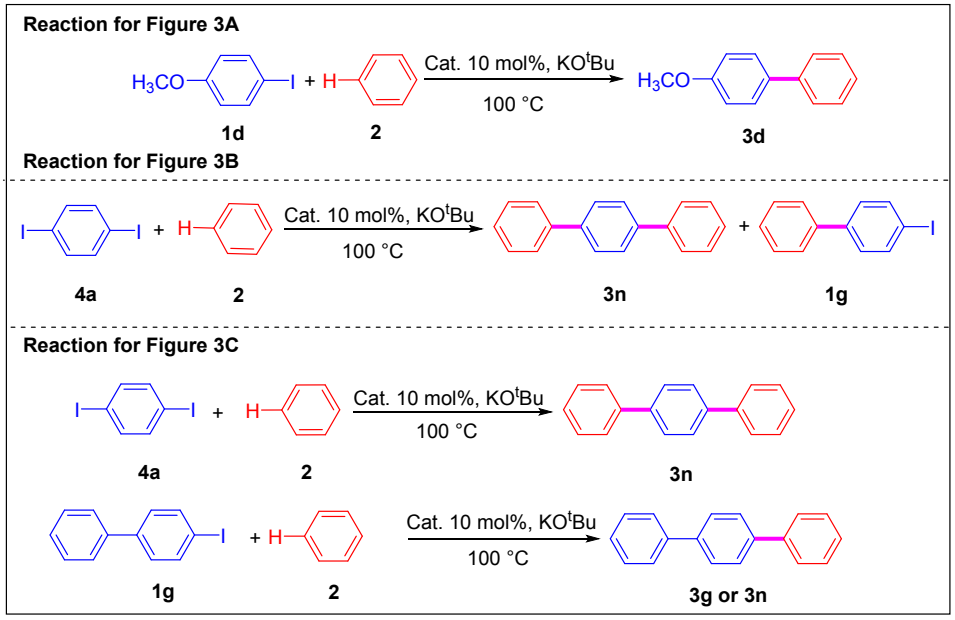
4.	18-crown-6 (3 equiv.)	27%

[a]Isolated yield.

Based on previous investigations,[7] we then examined experimentally the plausible mechanism of the 1-(2-hydroxyethyl)-piperazine catalyzed direct C(sp^2)–H arylation reaction and the possible role of free-radicals involved in it. **1a** was reacted with **2** under optimized reaction conditions in the presence of TEMPO (10 mol%) which furnished **3a** in only 12% yield (Table 3, entry 2). However, without radical scavenger, **3a** was obtained in 85% yield (Table 3, entry 1). Similarly, when the same reaction was carried out in presence of 100 mol% of TEMPO; the reaction was aborted and **3a** was not formed at all (Table 3, entry 3). However, our efforts to isolate any TEMPO adduct with the aryl radical was not successful. Then, we also figure out the role of K^+ cation (coming from the base KO^{t}Bu). **1a** was reacted with **2** under optimized reaction conditions using 18-crown-6 in stoichiometric amount in order to trap the K^+ cation during the course of the reaction; it was found that a significantly low conversion of **3a** (27%) was observed which underlines the importance of KO^{t}Bu. Thus, it can be speculated that the alkali metal cation is possibly playing a role in this transformation.

The reaction profile comparative study was carried out to understand the reactivity of substituted iodobenzenes with unactivated benzene with the passage of time in order to study its overall effects on the yield of the reaction. Therefore, **1d** was reacted with **2** under optimized conditions which afforded **3d** and plot against %yield versus time was generated (Scheme 2, Figure 3A). It was observed that the yield of the organocatalytic direct arylation reaction was increased with the passage of time (Figure 3A).

Scheme 2. Reaction profile comparative study: reactivity vs time.[a]



[a]*Reaction conditions*: The reaction was carried out under a nitrogen atmosphere using an aryl halide (**1d/4a/1g**: 0.5 mmol), benzene (**2**: 4 mL), KO^{t}Bu (1.5 mmol), and 1-(2-hydroxyethyl)-piperazine (Cat. **E**: 0.05 mmol) in a sealed tube for 24 h.

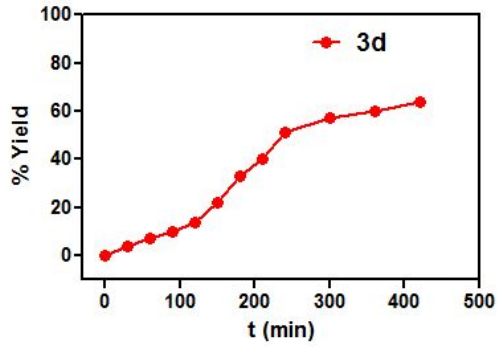


Figure 3A

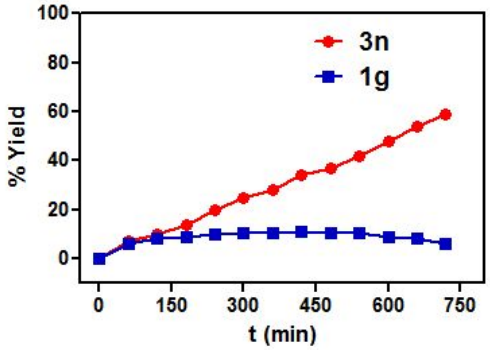


Figure 3B

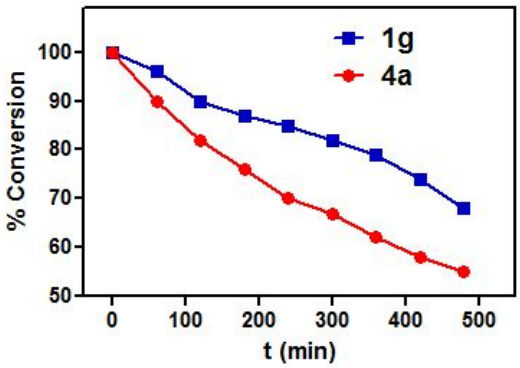


Figure 3c

Figure 3. (A) Reaction profile of the direct arylation of **1d** with benzene to furnish **3d**. (B) Distribution of *bis*-arylated **3n** and monoarylated **1g** with the interval of time during the reaction of **4a** with benzene. (C) The reaction profiles (amount of **1g** or **4a** and time of response) of the direct arylations of benzene with **4a** and **1g**, respectively.

Then, the comparative study of the yield of **1g** and **3n** was performed by carrying out the reaction of **4a** with **2** under optimized reaction conditions and plot against %conversion versus time was generated. It was noticed that the yield of bis-arylated product **3n** increased with the passage of time (over 12 hours). However, the yield of the monoarylated product **1g** was restricted upto 7% with the passage of time (Scheme 2, Figure 3B). This indicates that, unless otherwise noted, the diarylated product formation occurs faster as compared to monoarylated product. In addition, we also further prove the reactivity order of biphenyl iodide **1g** with diiodobenzene **4a** to furnish terphenyl **3g** or **3n** and performed competitive reactions separately. It was delineated that the reactivity of **1g** to furnish **3g** is less than that of **4a** (Scheme 2, Figure 3C).Kinetic isotope experiment was performed by reacting **1a** with a equalmolar mixture of benzene and benzene-D_6. The $k_{H/D}$ was found to be 1.12 which confirms that C−H bond cleavage does not constitute a rate-limiting step (for details, see SI).

A plausible mechanism has been depicted in figure 4. The catalytic cycle gets initiated via coordination of K^+ cation of KO^{t}Bu with –OH and –NH groups of catalyst E which formed the KO^{t}Bu-Catalyst E complex **7** which transfer the single electron to Ar-I (**1**) to form the radical anoin **8**. This radical anion **8** transformed to aryl radical **9** which, then, added to benzene to afford the cyclohexadienyl radical **10**.

Single elecctron oxidation of **10** by radical cation **11** gives cation **13**, which is deprotonated by t-BuO$^-$ to give desired coupling product **3** and t-BuOH. Complex **12** reacts with KO^{t}Bu to regenerate the complex **7**.

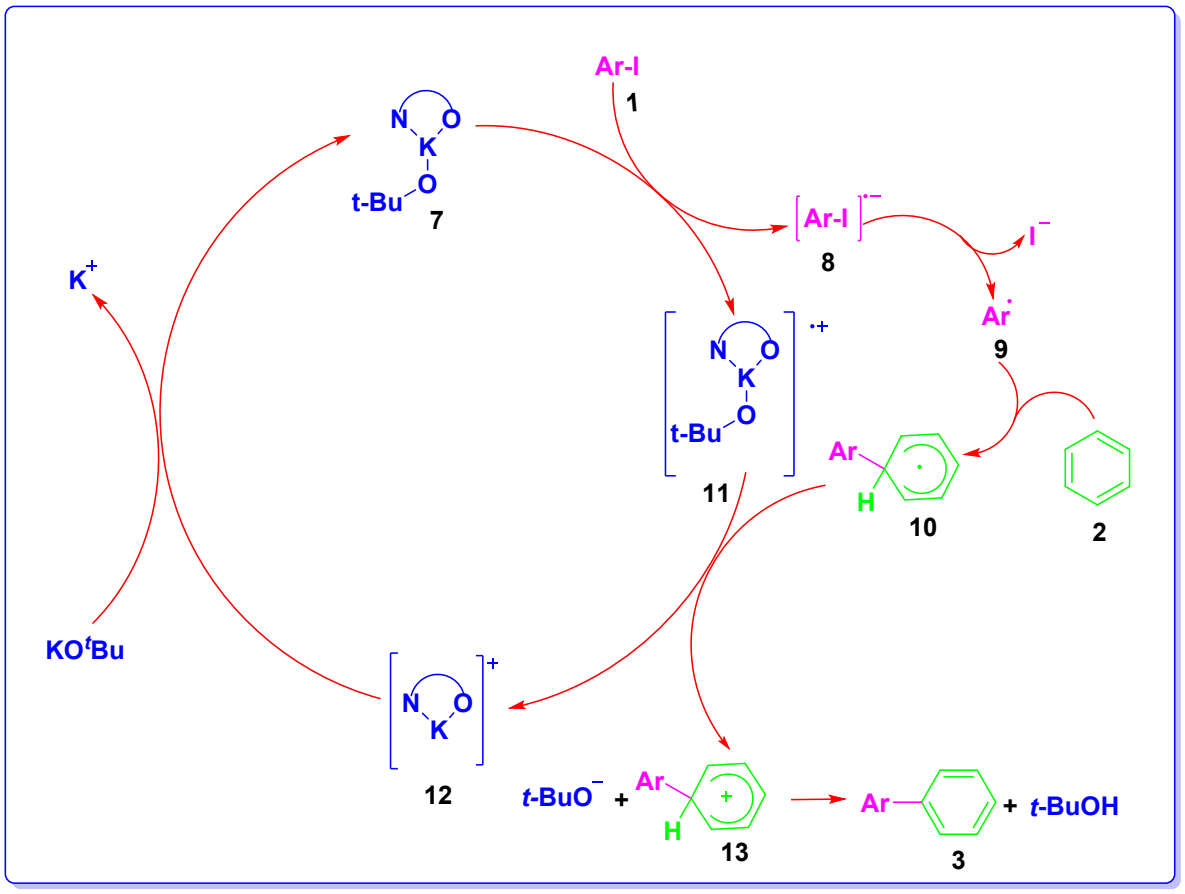
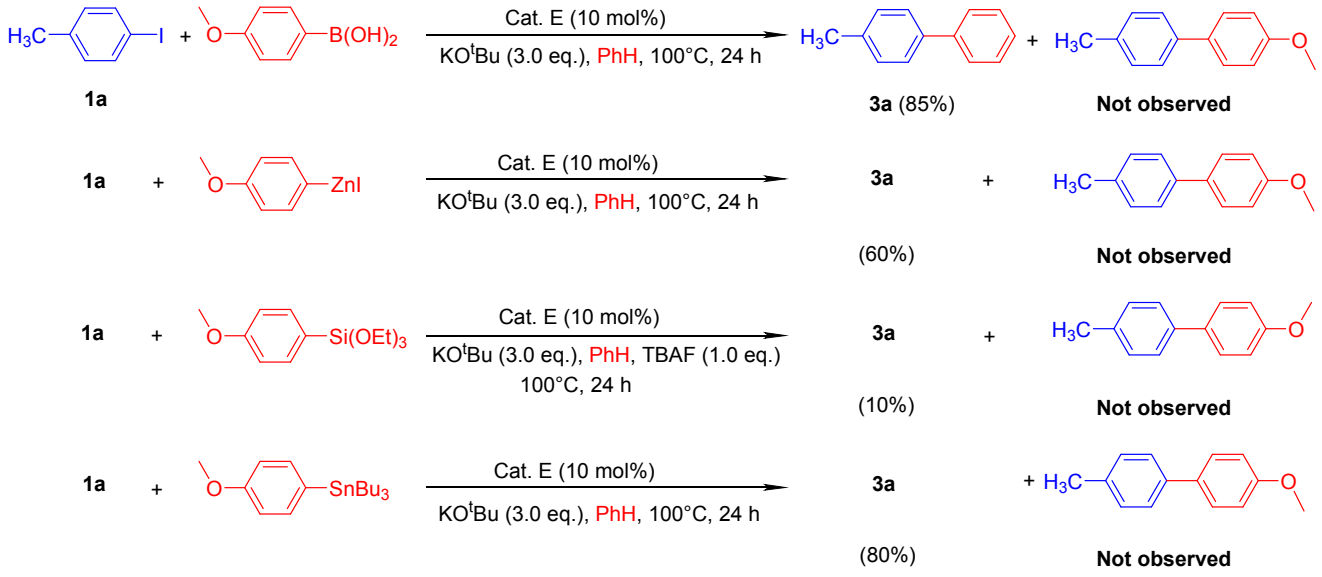


Figure 4: Plausible mechanism for *inter*-molecular organocatalyzed C(sp^2)-H direct arylation reaction.

Scheme 3. Traditional cross couplings with general reaction partners in the reaction mixture under optimized reaction conditions.



We had also carried out some traditional cross-coupling reactions with Ar-$B(OH)_2$, ArZnI, Ar-$Si(OEt)_3$, Ar-$Sn(Bu)_3$ under our optimized organo-catalyzed reaction conditions. However, there is no observation of any cross-coupled product which illustrates that our methodology was working through SET mechanism rather than any transition metal-mediated cross coupling pathway (Scheme 3).

The ICP-MS analysis of the *catalyst E* (procured from Sigma aldrich), the base *KO^{t}Bu* (procured from TCI), and *the reaction mixture* obtained after the completion of our optimized reaction was further investigated to check the presence of transition metals such as Fe, Co, Cu, Rh, Ag, Ni, Ru, Zn, Pd etc. The ICP-MS data revealed that all these transition metals (Fe, Co, Cu, Rh, Ag, Ni, Ru, Zn, Pd) were detected in <1.4 ppb level except Fe (28.23-30.04 ppb) and Zn (19.56-24.25 ppb) which indicates the exclusion of the possibility of transition metal-catalyzed C(sp^2)-H direct arylation reaction (for details, see SI).

Intra-molecular Organocatalyzed C(sp^2)-H direct arylation of unactivated arenes

Phenanthridinone, a well-known tricyclic bioactive heterocycle, was selected as a model substrate to illustrate the intra-molecular organocatalyzed C(sp^2)-H direct arylation with unactivated arenes. This scaffold is present in several bioactive natural products[8] and are blended with a wide range of biological activities.[9] Several phenanthridinones such as **14-22** showed potent bioactivities such as antitumor, anti-HIV, and antileukemic, inhibition of DNA topoisomerase, PARP inhibitors etc (Figure 5).

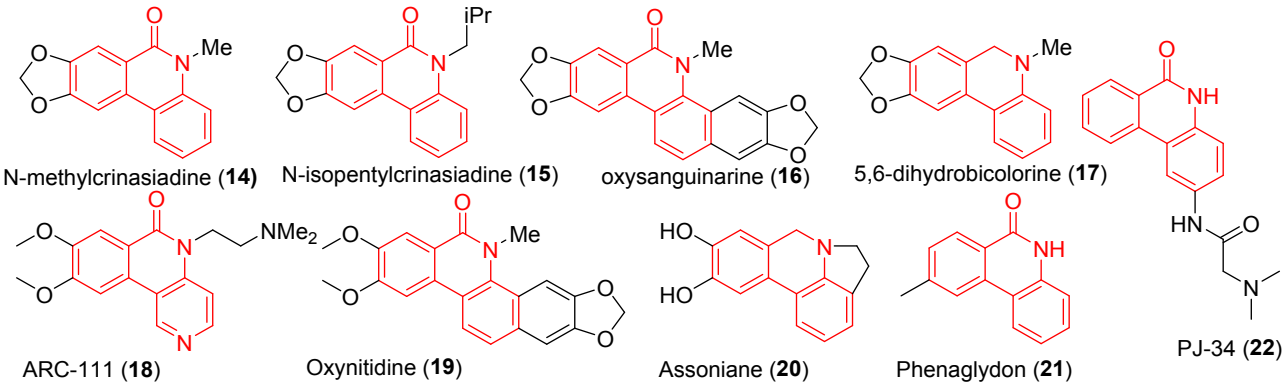
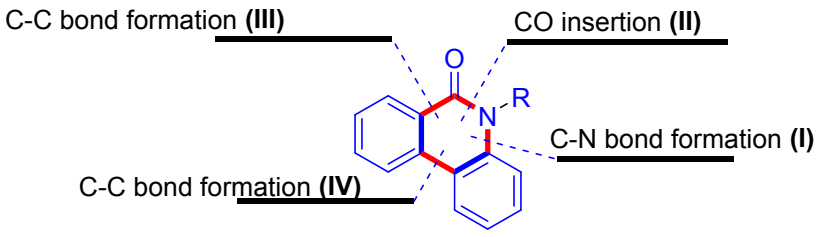


Figure 5. Structures of few bioactive phenanthridinone-based natural products and synthetic molecules.

Several methodologies have been reported in the literature for the synthesis of phenanthridinones *via* either transition-metal-catalysis (Pd, Rh, Cu) or radical-mediated catalysis[9-13] either *via* C–C/C–N bond formation (I, III, IV),[11,14] or *via* aminocarbonylation CO insertion (II)[12] (Scheme 4).

Scheme 4. Synthetic approaches to phenanthridinone skeleton.



In continuation to metal-catalysis, few organocatalytic/metal-free/radical-initiated methodologies have also been reported in the literature.[5c,5h, 14-15] However, the phenanthridinones synthesis *via* C(sp^2)–H direct activation using cost-effective organocatalyst which can catalyze both *inter*- as well as *intra*-molecular direct arylation of unactivated arenes/heteroarenes is certainly a promising area of investigation. Herein, we report the cost-effective, transition-metal-free, *intra*-molecular organocatalyzed synthesis of phenanthridinones using 2-(piperazin-1-yl)ethan-1-ol as an organocatalyst, the same catalyst used in *inter*-molecular organocatalyzed C(sp^2)-H direct arylation with unactivated arenes.

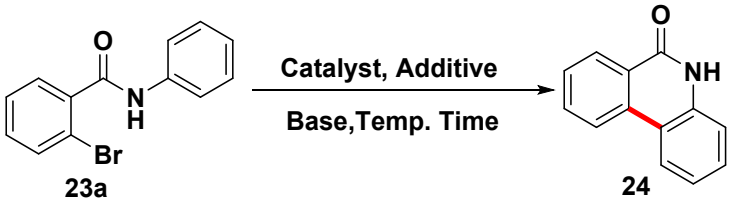
Initially, we started optimization study of *intra*-molecular organocatalyzed C(sp^2)-H direct arylation taking 2-bromo-N-phenylbenzamide **23a** as the starting material to construct phenanthridinones (Table 4). Therefore, using optimized reaction conditions obtained during *inter*-molecular organocatalyzed direct arylation, **23a** was reacted with 10 mol% of catalyst E in benzene in the presence of KO^{t}Bu (3. Equiv.) at 100 °C for 24 h which furnished the desired cyclized product phenanthridinone **24** in only 27% yield (Table 4. Entry 1). Since we obtained less yield in entry 1; after extensive literature search, we plan to execute the same reaction using 40 mol% of catalyst E in benzene in the presence of KO^{t}Bu (3. Equiv.) at 150 °C for 24 h which furnished **24** in 65% yield (Table 4, entry 2).

In order to further increase the yield of **24**, as we did for *inter*-molecular optimization studies, the catalytic screening (40 mol%) of other organocatalyst **A-D** and **F-M** were also carried out. However, all these catalyst furnished cyclized product **24** only in 10-26% yield range. Thereafter, the screening of different solvents such as mesitylene, toluene, cyclohexane, 1,4-dioxane, DMF, DMSO etc. were carried out (Table 4, entry 3-8). While the reaction in mesitylene and toluene using 40 mol% of Cat. E and KO^{t}Bu (3 equiv.) at 150 °C for 24 h furnished **24** in 68% and 59% yields, respectively; other solvents have detrimental effect on the yield of the reaction (Table 4, entry 3-8). Since, the inter-molecular organocatalyzed direct arylation involves free-radical pathway; we screened the same reaction in the presence of $K_2S_2O_8$ as an additive. The formation of **24** does not takes place at all (Table 4, entry 9).

In our endeavor to develop new catalytic system for the synthesis of bioactive heterocycles in our lab;[6i-j] we noticed that the mixture of two bases can be used in C–C bond forming reactions for the improvement of the yield of the reaction.[6j] Based on these facts, organic bases (0.4 equiv.) such as TEA, Triton-B, *n*-methyl aniline, DMAP, DABCO etc. were utilized as an additive in the same reaction conditions reported in entry 3 (Table 4, entry 10-14). Intriguingly, it was observed that out of all bases screened, DMAP furnished the desired product in 89% isolated yield (Table 4, entry 13). Other additives do not show promising results in improving the yield of the reaction. In addition, other strong bases such as LiO^{t}Bu, Li-HMDS and weak bases (K_2CO_3) were also screened keeping all the other reaction conditions same as given in entry 3 (Table 4, entry15-17). It was observed that the use of bases

other than KO^{t}Bu have a negative effect on the yield of the reaction. Furthermore, it was also found that increasing or decreasing the gram equivalents of KO^{t}Bu leads to slight decrease in the yield of the reaction keeping same all the other reaction conditions (Table 4, entry 18-19). To further check the importance of catalyst; a reaction without catalyst E was carried out (Table 4, entry 20). It has been noticed that no conversion of **23a** into **24** takes place which further emphasize the importance of newly discovered organocatalyst. In addition, decreasing the time interval of the reaction or catalyst loading eventually leads to decrease in overall yield of the reaction (Table 4, entry 21-22). Succinctly, *40 mol % of catalyst E {1-(2-hydroxyethyl)-piperazine}, 3 equivalents of KO^{t}Bu along with DMAP (40 mol%) in 4 mL of mesitylene at 150 °C for 24 h was found to be the best optimized reaction conditions for the intra-molecular organocatalyzed C(sp^2)-H direct arylation reaction*.

Table 4. Optimization study: *Intra*-molecular organocatalyzed C(sp^2)-H direct cyclization of 2-bromo-N-phenylbenzamide.[a]

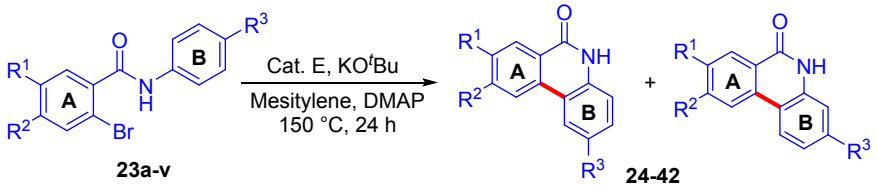


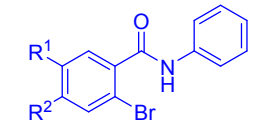
23a 24

Entry	Catalyst (40 mol %)	Solvent	Additive (equiv.)	Base (3 equiv.)	Temp. (°C)	Time(h)	Yield (%)[b]
1.	E[c]	Benzene	----	KO^{t}Bu	100	24	27
2.	E[d]	Benzene	----	KO^{t}Bu	150	24	65
3.	E	Mesitylene	----	KO^{t}Bu	150	24	68
4.	E	Toluene	----	KO^{t}Bu	150	24	59
5.	E	cyclohexane	----	KO^{t}Bu	150	24	21
6.	E	1,4-dioxane	----	KO^{t}Bu	150	24	26
7.	E	DMF	----	KO^{t}Bu	150	24	>5
8.	E	DMSO	----	KO^{t}Bu	150	18	25
9.	E	Mesitylene	$K_2S_2O_8$	KO^{t}Bu	150	24	00
10.	E	Mesitylene	TEA (0.4)	KO^{t}Bu	150	24	61
11.	E	Mesitylene	Triton B (0.4)	KO^{t}Bu	150	24	58
12.	E	Mesitylene	n-methyl aniline (0.4)	KO^{t}Bu	150	24	63
13.	**E**	**Mesitylene**	**DMAP (0.4)**	**KO^{t}Bu**	150	**24**	**89**
14.	E	Mesitylene	DABCO (0.4)	KO^{t}Bu	150	24	55
15.	E	Mesitylene	DMAP (0.4)	LiO^{t}Bu	150	24	7
16.	E	Mesitylene	DMAP (0.4)	Li-HMDS	150	24	10
17.	E	Mesitylene	DMAP (0.4)	K_2CO_3	150	24	5
18.	E	Mesitylene	DMAP (0.4)	KO^{t}Bu (4.0)	150	24	84
19.	E	Mesitylene	DMAP (0.4)	KO^{t}Bu (2.0)	150	24	64
20.	**----**	**Mesitylene**	**DMAP (0.4)**	**KO^{t}Bu (3.0)**	150	**24**	**00**
21.	E	Mesitylene	DMAP (0.4)	KO^{t}Bu (3.0)	150	18	75[e]
22.	E	Mesitylene	DMAP (0.4)	KO^{t}Bu (3.0)	150	24	70[f]

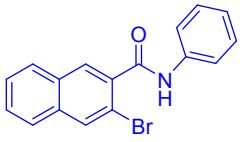
[a]Reaction conditions: **23a** (0.25 mmol), KO^{t}Bu (0.75 mmol), Catalyst 40 mol%, and additive 40 mol% (entry 8-21) were dissolved in solvents (as given in table) and heated at 150 °C for 24 h under a N_2 atmosphere in a sealed tube. [b]Isolated yields. [c]Catalyst E (10 mol%). [d]Other organocatalysts **A-D** and **F-M** furnished **24** in 10-26% yield range. [e]Time 18h. [f]Catalyst 20 mol%.

Scheme 5. Substrate scope: Organocatlyzed direct C-H activation of 2-halobenzamide to construct phenanthridinone[a]

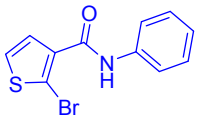




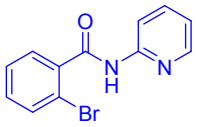
23a, R^1 = H, R^2 = H
23b, R^1 = CH_3, R^2 = H
23c R^1 = OCH_3, R^2 = OCH_3
23d, R^1 = Br, R^2 = H
23u, R^1 = NO_2, R^2 = H



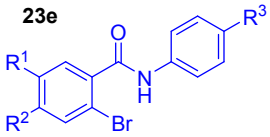
23e



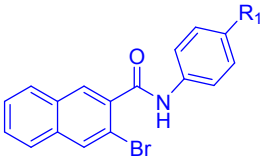
23f



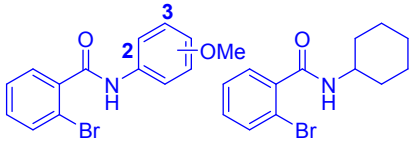
23g



23h, R^1 = H, R^2 = H, R^3 = CH_3
23i, R^1 = H, R^2 = H, R^3 = OCH_3
23j, R^1 = H, R^2 = H, R^3 = Cl
23k, R^1 = CH_3, R^2 = H, R^3 = CH_3
23l, R^1 = CH_3, R^2 = H, R^3 = OCH_3
23m, R^1 = CH_3, R^2 = H, R^3 = Cl
23n, R^1 = OCH_3, R^2 = OCH_3, R^3 = CH_3

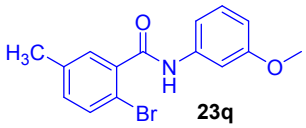


23r,R^1 = CH_3
23s, R^1 = OCH_3; **23t**, R^1 = Cl,

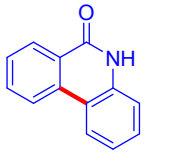


23o, 2-OMe**, 23p,** 3-OMe

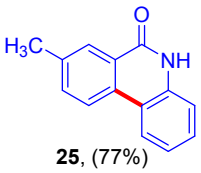
23v



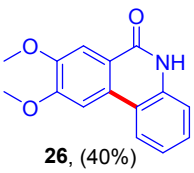
23q



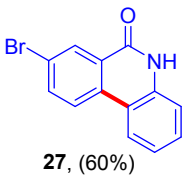
24, (89%), (94%)[c]



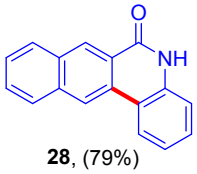
25, (77%)



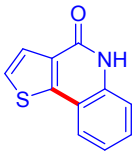
26, (40%)



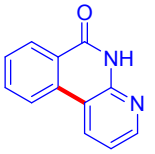
27, (60%)



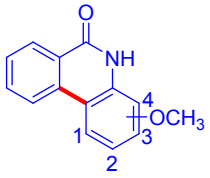
28, (79%)



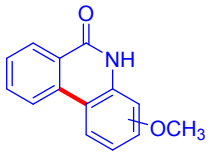
29, (30%)



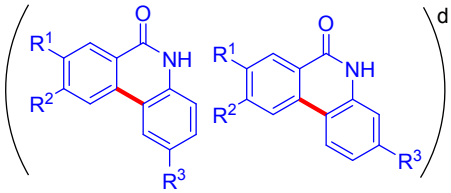
30, (55%)



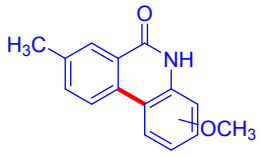
38a, **32b** and **38b** (74%), (1.0:0.50:0.35)
38a 1-OMe; **32b**, 2-OMe; **38b**, 4-OMe



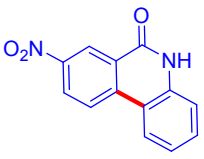
38a and **38b**, (70%), (1.0:0.30)
38a, 1-OMe, **38b**, 4-OMe



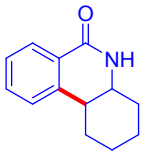
31a, R^1 = H, R^2 = H, R^3 = CH_3 and **31b**, R^1 = H, R^2 = H, R^3 = CH_3, (80 %), (1.0:0.46
32a, R^1 = H, R^2 = H, R^3 = OCH_3 and **32b**, R^1 = H, R^2 = H, R^3 = OCH_3, (94%), (1.0:0.85)
33a, R^1 = H, R^2 = H, R^3 = Cl and **33b**, R^1 = H, R^2 = H, R^3 = Cl, (53%), (1.0:0.50)
34a, R^1 = CH_3, R^2 = H, R^3 = CH_3 and **34b**, R^1 = CH_3, R^2 = H, R^3 = CH_3, (82%), (1.0:0.72)
35a, R^1 = CH_3, R^2 = H, R^3 = OCH_3 and **35b**, R^1 = CH_3, R^2 = H, R^3 = OCH_3, (80%), (1.0:0.64
36a, R^1 = CH_3, R^2 = H, R^3 = Cl and **36b**, R^1 = CH_3, R^2 = H, R^3 = Cl, (37%), (1.0:0.51)
37, R^1 =OCH_3, R^2 = OCH_3, R^3 = CH_3, (25%)



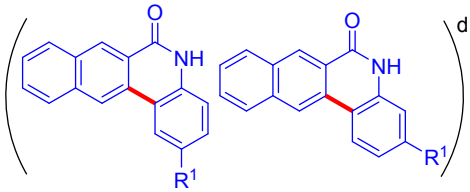
39a, **35b** and **39b** (82%), (1.0:0.68:1.6)
39a 1-OMe; **35b**, 2-OMe; **39b**, 4-OMe



43, (0%)



44, (0%)



40a, R^1 = CH_3 and **40b**, R^1 = CH_3, (87%), (1.0:0.25)
41a, R^1 = OCH_3 and **41b**, R^1 = OCH_3, (76%), (1.0:0.60
42a, R^1 = Cl (37%) and **42b**, R^1 = Cl, (20%), (1.0:0.54)

[a]Reaction conditions: **23a-v** (0.5 mmol), KO^{t}Bu (1.5 mmol), Catalyst E (40 mol%), and DMAP (40 mol%) were mixed in mesitylene and heated at 150 °C for 24 h under N_2 atmosphere in a sealed tube. [b]Isolated yields. [c]2-Iodo-N-phenylbenzamide was used.[d]Combined/individual yields and ratio of diastereomeric mixtures are given in parentheses.

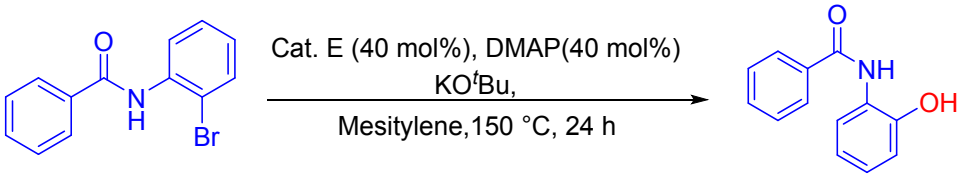
Utilizing the optimized conditions in hand, various substituted amides **23a-g** having substitutions at ring A and without substitution at ring B were subjected to *intra*-molecular cyclization using catalyst E (40 mol %) in the presence of KO^{t}Bu (3 equiv.) and DMAP (40 mol%) in mesitylene (4 mL) 150 °C for 24 h which furnished substituted phenanthridinones **24-30** upto 94% yield (Scheme 5). Similarly, amides **23h-q** having substitution at both ring A and B were subjected to intra-molecular cyclization using catalyst E (40 mol %) in the presence of KO^{t}Bu (3 equiv.) and DMAP (40 mol%) in mesitylene (4 mL) 150 °C for 24 h which furnished substituted phenanthridinones **31-42** upto 94% yield (Scheme 5). Extensive examination of the substrate scope revealed that amides having no substitution at ring B leads to the formation of single product; whereas amides having *o*-, *m*- or *p*-substitutions at ring B produced 5-*exo* and 6-*exo*/*endo* regioisomers as described earliar.[5c] The intramolecular cyclization of **23a** to **24** occurs in 89% and 94% yield from 2-bromo- and 2-iodo-derivatives of **23a**, respectively. The substrates having electron-donating groups (EDG) such as CH_3, OCH_3, and dimethoxy (**23b-c**, **23k-n**, **23q-s** etc. on aryl ring **A** were well tolerated and successfully cyclized into the corresponding phenanthridinones **25-26**, **34-37**, **38**, **40** and **41,** respectively in moderate to excellent yields. The substrate having bromo-group **23d** was found to be well-tolerated in benzene solvent to give the compound **27** in 60% yield. The electron-withdrawing group (EWG) having nitro group i.e., **23u** completely aborted the reaction and no cyclized product was obtained. The naphthalene and thiophene-based 2-bromo arylamide **23e-f** were also cyclized to **28** and **29** in 79% and 30% yield, respectively.

Then, we analyzed the substrate scopes in aryl ring B in order to understand the occurrence of regioselective isomer(s) in the organocatalyzed direct arylation. It has been interpreted that due to the *p*-substitution in ring B, irrespective of the electron-donating or electron-withdrawing groups; the major product obtained had 6-*exo*/*endo* regioselectivity whereas 5-*exo* regioisomer was obtained as a minor product. Thus, **23h**, having no substitution on ring A and the *p*-CH_3 substituents ($R_3 = CH_3$) on ring B, undergoes *intra*-molecular cyclization under optimized conditions afforded an inseparable mixture of **31a** (major) and **31b** (minor) in 1.0:0.46 ratio (as determined by ^{1}H NMR spectral data of mixture) in overall 80% combined yields. Similarly, **23i** having *p*-OMe substituents on ring B undergone *intra*-molecular direct arylation furnished an inseparable mixture of **32a** (major) and **32b** (minor) in 1.0:0.85 ratio in 94% combined yields.

Additionally, when the substrate having no substitution on ring A and *p*-Cl group on ring B i.e., **23j** was used, an inseparable mixture of **33a** and **33b** were isolated in the ratio of 1.0:0.50, respectively, in comparatively less yields (53%). Unlike compounds **31** and **32**, when the substrate having 5-CH_3 substitution on ring A and *p*-CH_3 group on ring B i.e., **23k** was used, an inseparable mixture of **34a** and

34b were isolated in the ratio of 1.0:0.72, respectively, in 82% yield. In contrast to compounds **31** and **32**, when the substrate having 5-CH_3 substitution on ring A and *p*-OCH_3 group on ring B i.e., **23l** was used, an inseparable mixture of **35a** and **35b** were isolated in the ratio of 1.0:0.64, respectively, in 80% yield. The substrate having 5-CH_3 substitution on ring A and *p*-chloro group on ring B i.e., **23m**, was subjected to *intra*-molecular cyclization under optimized reaction conditions, it furnished an inseparable mixture of **36a** and **36b** in the ratio of 1.0:0.51, respectively, in relatively lower (37%) yield. Similar was the case with the substrate **23n** which undertakes selective conversion to **37** in reasonably lower (25%) yield. In continuation, the substrates **23p**, having no substitution on ring A and *m*-OMe on ring B undergoes cyclization and furnished 5-*exo* regioisomer **38a** as the major product and 6-*exo*/*endo* regioisomer **38b** along with **32b** in 1.0:0.35:0.50:ratios. In the same way, the substrates **23o**, having no substitution on ring A and *o*-OMe on ring B undergoes cyclization and furnished 5-exo regioisomer **38a** as the major product and 6-*exo*/*endo* regioisomer **38b** in 1.0:0.30 ratio. Consequently, the substrates **23q**, having 5-CH_3 substitution on ring A and *m*-OMe on ring B undergoes cyclization and furnished 5-*exo* regioisomer **39a** as the major product and 6-*exo*/*endo* regioisomer **39b** along with **35b** in 1.0:0.68:1.6 ratios. The substrate **23r-t** which have naphthalene at ring A leads to the formation of **40-42** in 57-87% yields, respectively. Therefore, in brief, it can be understood that 1-(2-hydroxyethyl)-piperazine-catalyzed *intra*-molecular C(sp^2)-H direct arylation reaction proceeded smoothly and furnished the combined desired mixtures of regioisomers in significantly excellent yields.

Scheme 6. *Intra-molecular* organocatalyzed direct arylation of N-(2-bromophenyl)benzamide 23w: Cyclization attempt by reversing the bromo-substitution (as in the case of 2-bromo-N-phenylbenzamide).

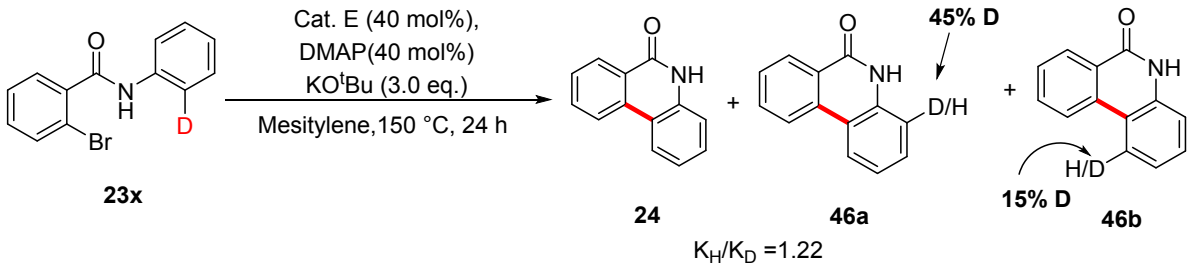


23w **45**

The substrate N-(2-bromophenyl)benzamide **23w** having Br-group on ring B, the opposite of **23a** where Br-group is on ring A, failed to undergo C-C coupling reaction under optimized reaction conditions (Scheme 6). Instead, the formation of N-(2-hydroxyphenyl)benzamide **45** takes place which illustrates that the cyclization is favoured *via* Br-group on ring A rather than on ring B.[5c]

As interpreted in the *inter*-molecular C-C coupling reaction, the SET mechanism might be also involved in the *intra*-molecular cyclization. The free-radical scavenging experiment was performed where **23a** was subjected to *intra*-molecular cyclization under optimized reaction conditions in the presence of 40 mol% TEMPO; **24** was obtained in only 35% yield. However, performing the same reaction in the presence of 100 mol% TEMPO stopped the reaction completely.

Scheme 7. Kinetic isotope experiment.



Kinetic isotope experiment was performed by reacting **23x** [deuterated at o-position of ring B (aniline part)], with optimized reaction conditions which furnished expected isotopic phenanthridinone products **24**, **46a** and **46b** (For the synthesis of **23x**, see experimental section). Since *ortho*-H/D is involved in the cyclization; the k_H/k_D was found to be 1.22 which confirms that C−H bond cleavage does not constitute a rate-limiting step (Scheme 7).

Plausible SET mechanism

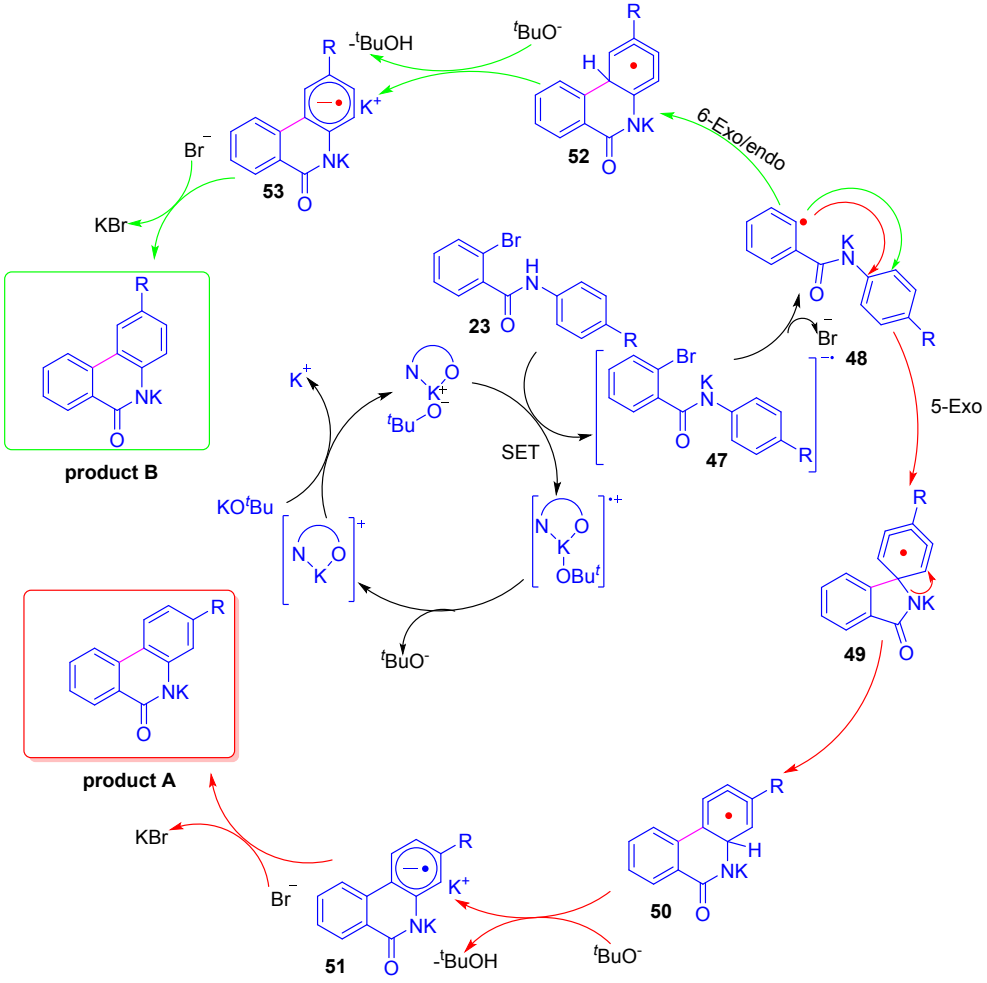


Figure 6. Proposed mechanism for the formation of **product A** and **B**.

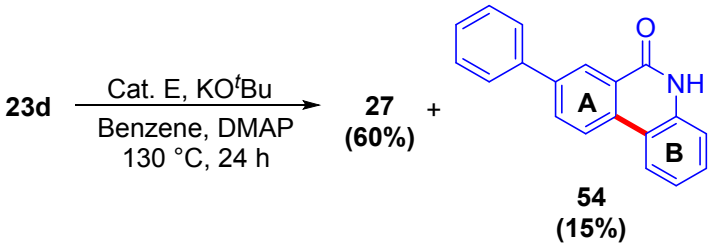
Basis on the above facts, the plausible mechanism is depicted in figure 6. The Catalyst E–KO^{t}Bu complex might directly donate a single electron to the 2-halo aryl amide **23** to form complex **47,** which further transformed into the radical species **48** with the elimination of bromide anion**.** The radical **48**,

then could attack on the aniline ring in a 6-*exo*/*endo* or 5-*exo-trig* manner to form the **52** or **49**, respectively.

Ring expansion of 5-*exo-trig* intermediates **49** might be giving more stable hexadienyl radical intermediate **50.** Hexadienyl radical intermediate **50** and **52** further deprotonated *via tert*-butoxy anion to form intermediate anion radical **51** and **53**, respectively. In the last step, these radical anions would undergo electron transfer to **23** to give respective products, KBr, and new radical **47**, thus continuing the radical chain with concomitant release of the product A and product B.

The ICP-MS analysis of the *catalyst E* (Procured from Sigma aldrich), *KO^{t}Bu* (Procured from TCI), and the *reaction mixture* (after the completion of the reaction) was carried out to investigate the presence of transition metals such as Fe, Co, Cu, Rh, Ag, Ni, Ru, Zn, Pd etc. The analytical data excludes the possibility of transition metal-catalyzed C-H bond activation as all these transition metals were detected at < 1.7 ppb level except Fe (28.23-42.53 ppb) and Zn (18.51-24.25ppb) (for details, see SI).

Scheme 8. One-pot double direct arylation.



Finally, the new catalyst was utilized to carry out both *inter*- as well as *intra*-molecular direct arylation reaction simultaneously in a one-pot. Thus, **23d** was reacted with benzene in the presence of Cat. E and KO^{t}Bu at 130 °C for 24 h which furnished double arylated *inter*- and *intra*-molecular product **54** in 15% yield along with the formation of bromo derivative of *intra*-molecular product **27** (Scheme 8). This further exemplifies the importance of one-pot dual arylation catalyzed by {1-(2-hydroxyethyl)-piperazine} as an organocatalyst.

Conclusion

In summary, we disclose the identification of 1-(2-hydroxylethyl) piperazine as a new cost-effective organocatalyst for the direct *inter*- as well as *intra*-molecular C-H bond activation of unactivated arenes to construct biaryls and phenanthridinones upto 94% yield. The protocol involves cost-effective organocatalyst (compared with a reported one) and was found well–tolerated under variable reaction conditions and feasible successfully with various Ar-X (X = I, Br, Cl) substrates. The wide substrate scope (aryl/heteroaryl), easy handling, gram-scale synthesis for both *inter*-/*intra*-molecular direct arylation using a single organocatalyst, kinetic studies further highlights the importance and versatile nature of the methodology as well as the efficacy of the newly developed organocatalyst. This finding

offers a novel organocatalyst for direct C-H activation toward the synthesis of biaryls-/phenthridinones-based bioactive heterocycles.

Experimental Details & Characterization Data

General information: All the reactions were carried out in screw cap glass reaction vial under argon atmosphere with magnetic stirring. Potassium *tert*-butoxide was purchased from TCI chemicals. Spectrochem and 1-(2-Hydroxyethyl) piperazine was brought from Sigma Aldrich and used without prior purification. Benzene was distilled over Na and benzophenone prior to use. All other reagents were procured from commercial source and used as received, unless otherwise stated. Column chromatography was performed over Merck silica-gel (particle size: 100-200 Mesh) procured from Merck (India). Hexane or hexane and ethyl acetate mixture was used as an eluting solvent in the column purification. Borosil glass column were used for purification. Thin layer chromatography was performed on Si 60 F_{254} which supplied from MERCK. ^{1}H NMR, ^{13}C NMR spectroscopy, HRMS, FT-IR were used to characterize all the compounds. ^{1}H NMR spectra were recorded on JEOL ECS-400 instrument (400 MHz). Chemical shifts were informed in parts per million (ppm) referenced to 0.0 ppm for Tetramethylsilane, 7.26 ppm for relative to residual $CHCl_3$ and 2.50 ppm for DMSO. ^{13}C NMR spectra were recorded on JEOL ECS-400 instrument (100 MHz) and were fully decoupled by broad band proton decoupling. Chemical shifts were reported in ppm referenced to the center line of a triplet at 77.16 ppm of Chloroform-d and 39.2 ppm for DMSO-D_6. High-resolution mass spectra (HRMS) were recorded on a Xevo G2-S Q Tof (Waters, USA) mass spectrometer. IR spectra were recorded on a FT-IR Spectrum 2 (Perkin-Elmer) spectrophotometer.

General procedure (GP1) for *inter*-molecular organocatalyzed C(sp^2)-H direct arylation (synthesis of 3a-v): An oven-dried sealed reaction vial was charged with cat. E (7 mg, 0.05 mmol) and KO^{t}Bu (0.168g, 1.5 mmol) under nitrogen gas atmosphere at room temperature. Aryl halide **1a-y** (0.5 mmol) and benzene **2** (4 ml) were added into the reaction vial and stirred at 100 ˚C (heated in oil bath) for 24 hr. The reaction mixture was allowed to cool to room temperature. Then, the reaction mixture was filtered through a celite bed and washed with ethyl acetate (3 × 10 mL). The combined filtrate was concentrated under vacuo to get crude compound which was further purified by silica-gel (100-200 mesh) column chromatography using either hexane alone or ethyl acetate/Hexane as an eluent which afforded the corresponding biaryl product **3a-v**.

Characterization data of biaryl coupling compounds 3a-v.

4-methyl-1,1'-biphenyl[3b] (**3a)**: The compound was synthesized according to the GP1 and purified through silica-gel column chromatography using the hexane as an eluent. R_f value: 0.72 (eluent: hexane); White solid; Yield: 85% (0.072 g) ; ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 7.63–7.60 (m, 2H), 7.55–7.52 (m, 2H), 7.48–7.44 (m, 2H), 7.38–7.34 (m, 1H), 7.30–7.26 (m, 2H), 2.42 (s, 3H); $^{13}C\{^{1}H\}$

NMR (100 MHz, Chloroform-*d*) δ: 141.3, 138.5, 137.1, 129.6, 128.8, 127.1, 127.1, 21.2.

3-methyl-1,1'-biphenyl[3b] (**3b)**: The compound was synthesized according to the GP1 and purified through silica-gel column chromatography using the hexane as an eluent. R_f value: 0.69 (eluent: hexane); White solid; Yield: 83% (0.070 g); ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 7.63–7.61 (m, 2H), 7.48–7.43 (m, 4H), 7.40–7.35 (m, 2H), 7.20 (d, *J* = 7.2 Hz, 1H), 2.46 (s, 3H); ^{13}C{^{1}H} (100 MHz, Chloroform-*d*) δ: 141.5, 141.3, 138.4, 128.8, 128.8, 128.1, 127.3, 124.4, 21.7.

3,5-dimethyl-1,1'-biphenyl[3d] (**3c)**: The compound was synthesized according to the GP1 and purified through silica-gel column chromatography using the hexane as an eluent. R_f value: 0.56 (eluent: hexane); White solid; Yield: 61% (0.056 g); ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 7.59 (d, *J* = 7.2 Hz, 2H), 7.45–7.41 (m, 2H), 7.35–7.32 (m, 1H), 7.23 (s, 2H), 7.01 (s, 1H), 2.40 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, Chloroform-*d*) δ: 141.5, 141.4, 138.3, 128.9, 128.7, 127.3, 127.2, 125.2, 21.5.

4-methoxy-1,1'-biphenyl[3b] **(3d)**: The compound was synthesized according to the GP1 and purified through silica-gel column chromatography using the hexane as an eluent. R_f value: 0.53 (eluent: hexane); White Solid; Yield: 85% (0.078 g); ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 7.58–7.53 (m, 4H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.34–7.30 (m, 1H), 7.00–6.98 (m, 2H), 3.87 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, Chloroform-*d*) δ: 159.2, 140.9, 133.9, 128.8, 128.2, 126.8, 126.8, 114.3, 55.4.

3-methoxy-1,1'-biphenyl[3b] **(3e)**: The compound was synthesized according to the GP1 and purified through silica-gel column chromatography using the hexane as an eluent. R_f value: 0.28 (eluent: hexane); Colorless liquid; Yield: 80% (0.074 g); ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 7.62–7.60 (m, 2H), 7.47–7.43 (m, 2H), 7.39–7.35 (m, 2H), 7.21–7.18 (m, 1H), 7.15–7.14 (m, 1H), 6.93–6.90 (m, 1H), 3.88 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, Chloroform-*d*) δ: 160.0, 142.9, 141.2, 129.8, 128.8, 127.5, 127.3, 119.8, 112.9, 112.8, 55.4.

2-methoxy-1,1'-biphenyl[3b] **(3f)**: The compound was synthesized according to the GP1 and purified through silica-gel column chromatography using the hexane as an eluent. R_f value: 0.17 (eluent: hexane); Colorless liquid; Yield: 82% (0.076 g); ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 7.56–7.54 (m, 2H), 7.46–7.41 (m, 2H), 7.36–7.32 (m, 3H), 7.06–7.00 (m, 2H), 3.82 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, Chloroform-*d*) δ: 156.5, 138.6, 131.0, 129.6, 128.7, 128.1, 127.0, 120.9, 111.3, 55.6.

1,1':4',1''-terphenyl[3b] (**3g or 3n)**: The compound was synthesized according to the GP1 and purified through silica-gel column chromatography using the hexane as an eluent. R_f value: 0.47 (eluent: hexane); White Solid Yield: 65% (0.075 g); ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 7.70–7.66 (m, 8H), 7.50–7.46 (m, 4H), 7.40–7.36 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, Chloroform-*d*) δ: 140.8, 140.2, 128.9, 127.6, 127.4, 127.1.

[1,1'-biphenyl]-4-carbonitrile[3b] **(3h)**: The compound was synthesized according to the GP1 and purified through silica-gel column chromatography using the hexane as an eluent. R_f value: 0.12 (eluent:

hexane); White Solid; Yield: 89% (0.080 g); ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 7.74–7.68 (m, 4H), 7.61–7.58 (m, 2H), 7.51–7.41 (m, 3H); ^{13}C{^{1}H} NMR (100 MHz, Chloroform-*d*) δ: 145.7, 139.3, 132.7, 129.22, 128.8, 127.8, 127.3, 119.1, 110.9.

4-fluoro-1,1'-biphenyl[3b] **(3i)**: The compound was synthesized according to the GP1 and purified through silica-gel column chromatography using the hexane as an eluent. R_f value: 0.61 (eluent: hexane); White solid; Yield: 64% (0.055 g); ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 7.58–7.53(m, 4H), 7.47–7.42 (m, 2H), 7.37–7.33 (m, 1H), 7.16–7.11 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, Chloroform-*d*) δ: 163.8 (d, $J_{C\text{-}F}$ = 244.8 Hz), 140.3, 137.4 (d, $J_{C\text{-}F}$ = 2.3Hz), 128.9, 128.8 (d, $J_{C\text{-}F}$ = 8.1 Hz) , 127.3 (d, $J_{C\text{-}F}$ = 8.6 Hz), 127.1, 115.8 (d, $J_{C\text{-}F}$ = 21.2 Hz).

4-(trifluoromethoxy)-1,1'-biphenyl[3d] **(3j)**: The compound was synthesized according to the GP1 and purified through silica-gel column chromatography using the hexane as an eluent. R_f value: 0.81(eluent: hexane); White solid; Yield: 60% (0.071 g); ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 7.63–7.55 (m, 4H), 7.48–7.44 (m, 2H), 7.40–7.35 (m, 1H), 7.30 (d, *J* = 8.0 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, Chloroform-*d*) δ: 148.7, 140.1, 139.9, 128.9, 128.5, 127.7, 127.2, 121.3, 120.6 (q, J = 255.9 Hz).

3-fluoro-1,1'-biphenyl[16b] (**3k**): The compound was synthesized according to the GP1 and purified through silica-gel column chromatography using the hexane as an eluent. R_f value: 0.60 (eluent: hexane); White solid; Yield: 34% (0.029 g); ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 7.62–7.60 (m, 2H), 7.50–7.45 (m, 2H), 7.43–7.39 (m, 3H), 7.35–7.32 (m, 1H), 7.10–7.05 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, Chloroform-*d*) δ: 164.6 (d, $J_{C\text{-}F}$ = 244.2 Hz), 143.7 (d, $J_{C\text{-}F}$ = 7.6 Hz), 140.1 (d, $J_{C\text{-}F}$ = 1.5 Hz), 130.4 (d, $J_{C\text{-}F}$ = 8.5 Hz), 129.0, 127.9, 127.2, 122.9 (d, $J_{C\text{-}F}$ = 2.5 Hz), 114.3, 114.0 (d, $J_{C\text{-}F}$ = 1.4 Hz).

4-chloro-1,1'-biphenyl[3d] **(3l)**: The compound was synthesized according to the GP1 and purified through silica-gel column chromatography using the hexane as an eluent. R_f value: 0.13 (eluent: hexane); White solid; Yield: 71% (0.067 g); ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 7.75 (d, *J* = 8.8 Hz, 2H), 7.56–7.52 (m, 2H), 7.45–7.41 (m, 3H), 7.34–7.31 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, Chloroform-*d*) δ: 140.8, 140.1, 137.9, 129.1, 128.9, 128.5, 127.8, 126.9.

2-chloro-1,1'-biphenyl[6c] **(3m)**: The compound was synthesized according to the GP1 and purified through silica-gel column chromatography using the hexane as an eluent. R_f value: 0.14 (eluent: hexane); Colorless liquid; Yield: 51% (0.048 g); ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 7.61–7.59 (m, 2H), 7.47–7.30 (m, 7H); ^{13}C{^{1}H} NMR (100 MHz, Chloroform-*d*) δ: 144.3, 141.3, 139.6, 130.2, 129.4, 128.8, 128.2, 128.0, 127.3, 127.3.

1-([1,1'-biphenyl]-4-yl)ethan-1-one[16a] (**3o**): The compound was synthesized according to the GP1 and purified through silica-gel column chromatography using the 3% ethyl acetate/hexane as an eluent. R_f value: 0.486 (eluent: 5% ethyl acetate/hexane); White solid; Yield: 71% (0.070 g); ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 8.05–8.03 (m, 2H), 7.70–7.68 (m, 2H), 7.65–7.62 (m, 2H), 7.49–7.46 (m, 2H), 7.43-

7.41 (m, 1H), 2.65 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, Chloroform-*d*) δ: 197.9, 145.9, 139.9, 135.9, 129.05, 129.0, 128.3, 127.4, 127.1, 26.8.

2-methyl-6-phenylquinoline[3d] (**3p**): The compound was synthesized according to the GP1 and purified through silica-gel column chromatography using the 8% ethyl acetate/hexane as an eluent. R_f value: 0.16 (eluent: 10% ethyl acetate/hexane); White solid; Yield: 65% (0.071 g); ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 8.08 (d, *J* = 8.8, 2H), 7.96–7.94 (m, 2H), 7.72–7.70 (m, 2H), 7.49 (t, *J* = 7.7 Hz, 2H), 7.39 (t, *J* = 7.2 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 1H), 2.77 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, Chloroform-*d*) δ: 159.1, 147.3, 140.5, 138.5, 136.4, 129.2, 129.1, 129.0, 127.6, 127.5, 126.7, 125.3, 122.5, 25.5.

4-phenylisoquinoline[3d] (**3q**): The compound was synthesized according to the GP1 and purified through silica-gel column chromatography using the 10% ethyl acetate/hexane as an eluent. R_f value: 0.16 (eluent: 10% ethyl acetate/hexane); Colorless liquid; Yield: 68% (0.07 g); ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 9.26 (s, 1H), 8.50 (s, 1H), 8.05–8.03 (m, 1H), 7.93–7.91 (m, 1H), 7.69–7.60 (m, 2H), 7.54–7.47 (m, 5H); $^{13}C\{^{1}H\}$ NMR (100 MHz, Chloroform-d) δ: 152.1, 142.9, 137.1, 134.3, 133.3, 130.6, 130.2, 128.7, 128.5, 128.0, 127.9, 127.2, 124.8.

2-phenylpyridine[3c] (**3r**): The compound was synthesized according to the GP1 and purified through silica-gel column chromatography using the 10% ethyl acetate/hexane as an eluent. R_f value: 0.47 (eluent: 10% ethyl acetate/hexane); Colorless liquid; Yield: 83% (0.064 g); ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 8.72–8.69 (m, 1H), 8.01–7.98 (m, 2H), 7.78–7.72 (m, 2H), 7.50–7.40 (m, 3H), 7.25–7.22 (m, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, Chloroform-d) δ: 157.5, 149.7, 139.4, 136.9, 129.1, 128.8, 127.0, 122.2, 120.7.

3-phenylpyridine[3c] (**3s**): The compound was synthesized according to the GP1 and purified through silica-gel column chromatography using the 10% ethyl acetate/hexane as an eluent. R_f value: 0.13 (eluent: 10% ethyl acetate/hexane); Brown liquid; Yield: 77% (0.060 g); ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 8.85 (dd, *J* = 2.4, 0.8 Hz, 1H), 8.59 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.89–7.86 (m, 1H), 7.60–7.57 (m, 2H), 7.50–7.46 (m, 2H), 7.43–7.35 (m, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, Chloroform-*d*) δ: 148.5, 148.4, 137.9, 136.7, 134.5, 129.2, 128.2, 127.2, 123.6.

2-phenylpyrazine[3c] (**3t**): The compound was synthesized according to the GP1 and purified through silica-gel column chromatography using the 7% ethyl acetate/hexane as an eluent. R_f value: 0.40 (eluent: 10% ethyl acetate/hexane); White solid; Yield: 30% (0.023 g); ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 9.04 (d, *J* = 1.6 Hz, 1H), 8.65–8.64 (m, 1H), 8.52 (d, *J* = 2.4 Hz, 1H), 8.03–8.01 (m, 2H), 7.54–7.48 (m, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, Chloroform-*d*) δ: 152.9, 144.3, 143.0, 142.4, 136.4, 130.0, 129.2, 127.0

2-phenylthiophene[16d] (**3u**): The compound was synthesized according to the GP1 and purified through silica-gel column chromatography using the hexane as an eluent. R_f value: 0.65 (eluent: hexane); White

solid; Yield: 31% (0.025 g); ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 7.64–7.62 (m, 2H), 7.41–7.37 (m, 2H), 7.33–7.27 (m, 3H), 7.10–7.08 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, Chloroform-*d*) δ: 144.5, 134.5, 128.9, 128.1, 127.6, 126.1, 124.9, 123.2.

3-phenylthiophene[3c] (**3v**): The compound was synthesized according to the GP1 and purified through silica-gel column chromatography using the hexane as an eluent. R_f value: 0.69 (eluent: hexane); White solid; Yield: 50% (0.040 g); ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 7.62–7.60 (m, 2H), 7.47–7.46 (m, 1H), 7.43–7.39 (m, 4H), 7.30 (t, *J* = 7.6 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, Chloroform-*d*) δ: 142.4, 135.9, 128.9, 127.2, 126.5, 126.4, 126.3, 120.4.

1,1':3',1''-terphenyl[3b] (**6**): The compound was synthesized according to the GP1 and purified through silica-gel column chromatography using the hexane as an eluent. R_f value: 0.50 (eluent: hexane); White Solid; Yield: 69% (0.079 g); ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 7.83 (d, *J* = 1.3 Hz, 1H), 7.68–7.66 (m, 4H), 7.61–7.60 (m, 2H), 7.55–7.47 (m, 5H), 7.41–7.37 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, Chloroform-*d*) δ: 141.9, 141.3, 129.3, 128.9, 127.5, 127.4, 126.3, 126.2.

1,1':2',1''-terphenyl[3b] (**7**): The compound was synthesized according to the GP1 and purified through silica-gel column chromatography using the hexane as an eluent. R_f value: 0.60 (eluent: hexane); Colorless liquid; Yield: 50% (0.058 g); ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 7.44–7.43 (m, 4H), 7.25–7.19 (m, 6H), 7.16–7.14 (m, 4H); ^{13}C{^{1}H} NMR (100 MHz, Chloroform-*d*) δ: 141.6, 140.7, 130.7, 130.0, 127.9, 127.6, 126.5.

General procedure for the gram-scale synthesis of compound 3d: An oven-dried sealed reaction tube was charged with cat. E (0.111 g, 0.85 mmol) and KO^{t}Bu (2.87 g, 25.64 mmol) under nitrogen gas atmosphere at room temperature. 4-Iodoanisole **1d** (2.0 g, 8.55 mmol) and benzene **2** (70 mL) were added into the reaction mixture and was allowed to stirr at 100 °C (heated in oil bath) for 24 h. After the completion of the reaction, the reaction mixture was allowed to cool to r.t; then, it was filtered through a celite pad and washed with ethyl acetate (3 × 20 mL). The combined filtrate was concentrated under vacuo to get crude compound which was further purified by silica-gel (100-200 mesh) column chromatography using hexane as an eluent which afforded **3d** (1.4 g, 7.60 mmol) as a white solid in 89% yield.

General procedure for the reaction for the examination of the role of KO^{t}Bu: An oven-dried sealed reaction vial was charged with Cat. E (7 mg, 0.05 mmol), KO^{t}Bu (0.168 g, 1.5 mmol) and 18-crown-6-ether (0.396 g, 1.5 mmol) under nitrogen gas atmosphere at room temperature. 4-Iodotoluene **1a** (0.109 g, 0.5 mmol) and benzene **2** (4 ml) was added into reaction vial and stirred at 100 ˚C (heated in oil bath) for 24 hr. After the completion of the reaction, the reaction mixture was allowed to cool to r.t; then, it was filtered through a celite pad and washed with ethyl acetate (3 × 10 mL). The combined filtrate was concentrated under vacuo to get crude compound which was further purified by silica-gel (100-200

mesh) column chromatography using either hexane as an eluent which afforded **3a** as a white solid in 23% (0.019g) yield.

General procedure for the free-radical reaction pathway: An oven-dried sealed reaction vial was charged with Cat. E (7 mg, 0.05 mmol), KO^{t}Bu (0.168 g, 1.5 mmol) and TEMPO (0.078 g, 0.5 mmol) under nitrogen gas atmosphere at room temperature. 4-Iodotoluene **1a** (0.5 mmol) and benzene **2** (4 ml) were added into the reaction vial and stirred at 100 ˚C (heated in oil bath) for 24 hr. After the completion of the reaction, the reaction mixture was cooled to room temperature. TLC observation of the TEMPO-assisted reaction indicates the non-formation of the desired product.

General procedure for the competition reaction between 1a and 1d: A mixture of cat. E (7.0 mg, 0.05 mmol), Potassium *t*-butoxide (168 mg, 1.5 mmol), 4-iodotoluene **1a** (109 mg, 0.5 mmol) 4-iodoanisole **1d** (117 mg, 0.5 mmol) and benzene **2** (4 mL) in a 10 mL oven-dried pressure-resistant tube was stirred at 100 °C (heated in oil bath) for 24 h. After the completion of the reaction, the reaction mixture was allowed to cool to r.t; then, it was filtered through a celite pad and washed with ethyl acetate (3 × 20 mL). The combined filtrate was concentrated under vacuo to get crude compound which was further purified by silica-gel (100-200 mesh) column chromatography using either hexane as an eluent which afforded **3a** and **3d** in 63% (0.053g) and 76% (0.070g) yields, respectively.

General procedure for the competition reaction between 1a and 1j: A mixture of cat. E (7.0 mg, 0.05 mmol), Potassium *t*-butoxide (168 mg, 1.5 mmol), 4-iodotoluene **1a** (109 mg, 0.5 mmol), 1-iodo-4-(trifluoromethoxy) benzene **1j** (144 mg, 0.5 mmol), and benzene **2** (4 mL) in a 10 mL oven-dried pressure-resistant tube was stirred at 100 °C (heated in oil bath) for 24 h. The reaction mixture was allowed to cool to r.t; then, it was filtered through a celite pad and washed with ethyl acetate (3 × 20 mL). The combined filtrate was concentrated under vacuo to get crude compound which was further purified by silica-gel (100-200 mesh) column chromatography using either hexane as an eluent which afforded **3a** and **3j** n 74% (0.062g) and 13% (0.016g) yields, respectively.

General procedure for the kinetic-isotope effect in the *inter*-molecular biaryl coupling: An oven dried reaction vial was charged with cat. E (7 mg, 0.05 mmol) and KO^{t}Bu (0.168 g, 1.5 mmol) under nitrogen gas atmosphere at room temperature. 1-iodotoluene **1a** (0.109 g, 0.5 mmol), benzene **2** (2 mL) and benzene-D_6 (2 mL) were added into the reaction vial. The reaction mixture was allowd to stirr at 100 °C (heated in oil bath) for 24 hr. After the completion of the reaction, the reaction mixture was allowed to cool to r.t; then, it was filtered through a celite pad and washed with ethyl acetate (3 × 20 mL). The combined filtrate was concentrated under vacuo to get crude compound which was further purified by silica-gel (100-200 mesh) column chromatography using either hexane alone or ethyl acetate/hexane as an eluent which afforded the desired product. The product distribution (K_H/K_D = 1.12) was analyzed by ^{1}H NMR.

General procedure[5c] (GP2) for the synthesis of substituted amides 23a-w

Compounds were prepared from the corresponding carboxylic acids and respective substituted amine. Substituted 2-bromo-benzoyl chlorides/benzoyl chlorides were prepared from respective benzoic acids (2.0 mmol) by refluxing with an excess of thionyl chloride (10.0 mmol) for 2-3 h. The excess amount of thionyl chloride was removed under vacuum. Then, additional dry THF was added to the reaction residue and again evaporated under reduced pressure to remove the traces amount of thionyl chloride. The resulted residue was used for the amide preparation without further purification. The substituted 2-bromo-benzoyl chlorides/benzoyl chloride (2.0 mmol) in DCM (10 mL) was added dropwise to a stirring solution of respective aniline (2.2 mmol,), Et_3N (4 mmol) and DMAP (0.2 mmol, 10 mol %) in DCM (15 mL) at 0-5 °C under nitrogen atmosphere. After the addition, the resulting mixture was allowed to room temperature and stirred for 6 h. The reaction was quenched with water at 0 °C and diluted with DCM (20 mL). The resulting solution was sequentially washed by aqueous HCl (15 mL, 1.0 M), saturated aqueous $NaHCO_3$ (15 mL) and brine (15 mL). The organic phase was dried over anhydrous Na_2SO_4 and then evaporated under vacuum. The residue was purified by column chromatography to afford the corresponding substituted amide **23a-v** for phenanthridinones synthesis. Compounds 2-bromo-*N*-phenylbenzamide[17a] **23a**, 2-bromo-4,5-dimethoxy-*N*-phenylbenzamide[17b] **23c**, *N*-((2-bromothiophen-3-yl)methyl)aniline[5c] **23f**, 2-bromo-*N*-(pyridin-2-yl)benzamide[17c] **23g**, 2-bromo-*N*-(p-tolyl)benzamide[17a] **23h**, 2-bromo-*N*-(4-methoxyphenyl)benzamide[17a] **23i**, 2-bromo-*N*-(4-chlorophenyl)benzamide[17a] **23j**, 2-bromo-4,5-dimethoxy-*N*-(p-tolyl)benzamide[17b] **23n**, 2-bromo-*N*-(2-methoxyphenyl)benzamide[17a] **23o**, 2-bromo-*N*-(3-methoxyphenyl)benzamide[17d] **23p**, 2-bromo-5-nitro-*N*-phenylbenzamide[17f] **23u** and 2-bromo-*N*-cyclohexylbenzamide[17e] **23v** are known compounds.

Characterization data of substrates amides (23b, 23d-e, 23k-m and 23q-s)

2-bromo-5-methyl-N-phenylbenzamide (**23b**): The compound was synthesized according to the GP2 and purified through silica-gel column chromatography using the ethyl acetate/hexane (05:95) as an eluent. R_f value: 0.71 (eluent: 30% ethyl acetate/hexane); White solid; Yield: 81% (0.470 g); ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 7.68 – 7.63 (m, 3H), 7.51 – 7.48 (m, 2H), 7.40 – 7.36 (m, 2H), 7.19 – 7.13 (m, 2H), 2.34 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, Chloroform-*d*) δ: 165.7, 138.1, 137.6, 137.4, 133.4, 132.7, 130.7, 129.2, 124.9, 120.1, 115.8, 20.9; HRMS (ESI/QTOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{13}BrNO$ 290.0175; found 289.0176.

2,5-dibromo-N-phenylbenzamide (**23d**): The compound was synthesized according to the GP2 and purified through silica-gel column chromatography using the ethyl acetate/hexane (08:92) as an eluent. R_f value: 0.78 (eluent: 30% ethyl acetate/hexane); White Solid; Yield: 65% (0.462 g); ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 7.79 (d, *J* = 2.0 Hz, 1H), 7.62 (d, *J* = 7.6 Hz, 3H), 7.52 – 7.44 (m, 2H), 7.39 (t, *J* = 8.0 Hz, 2H), 7.19 (t, *J* = 7.6 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, Chloroform-*d*) δ: 164.0, 155.9,

139.4, 137.2, 135.0, 134.7, 132.8, 129.3, 129.3, 125.3, 121.9, 120.2, 117.9; HRMS (ESI/QTOF) m/z: $[M + H]^+$ calcd for $C_{13}H_{10}Br_2NO$ 353.9124; found 353.9128.

3-bromo-N-phenyl-2-naphthamide (**23e**): The compound was synthesized according to the GP2 and purified through silica-gel column chromatography using the ethyl acetate/hexane (15:75) as an eluent. R_f value: 0.75 (eluent: 30% ethyl acetate/hexane); Light brown solid; Yield: 70% (0.457 g); ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 8.15 (d, J = 7.2 Hz, 2H), 7.88 (d, J = 7.6 Hz, 1H), 7.79 (d, J = 8.0 Hz, 2H), 7.69 (d, J = 7.6 Hz, 2H), 7.61 – 7.55 (m, 2H), 7.43–7.39 (m, 2H), 7.19 (t, J = 7.2 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, Chloroform-*d*) δ: 165.6, 137.7, 135.0, 134.8, 132.5, 131.6, 129.8, 129.3, 128.5, 127.4, 126.9, 124.9, 120.2, 115.8; HRMS (ESI/QTOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{12}Br_2NO$ 326.0175; found 326.0172.

2-bromo-5-methyl-N-(p-tolyl) benzamide (**23k**): The compound was synthesized according to the GP2 and purified through silica-gel column chromatography using the ethyl acetate/hexane (10:90) as an eluent. R_f value: 0.71 (eluent: 30% ethyl acetate/hexane); White solid; Yield: 82% (0.50 g); ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 7.60 (s, 1H), 7.53 – 7.47 (m, 4H), 7.18 (d, *J* = 8.4 Hz, 2H), 7.174 – 7.11 (m, 1H), 2.35 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, Chloroform-*d*) δ: 165.6, 138.0, 137. 6, 135.0, 134.6, 133.3, 132.6, 130.7, 129.7, 120.2, 115.8, 21.0, 20.9; HRMS (ESI/QTOF) m/z: $[M + H]^+$ calcd for $C_{15}H_{14}BrNO$ 304.0332; found 304.0337.

2-bromo-N-(4-methoxyphenyl)-5-methylbenzamide (**23l**): The compound was synthesized according to the GP2 and purified through silica-gel column chromatography using the ethyl acetate/hexane (20:80) as an eluent. R_f value: 0.52 (eluent: 30% ethyl acetate/hexane); White solid; Yield: 59% (0.378 g); ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 7.62 (s, 1H), 7.56 – 7.52 (m, 2H), 7.49 – 7.46 (m, 2H), 7.11 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.91 (d, *J* = 9.2 Hz, 2H), 3.81 (s, 3H), 2.34 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, Chloroform-*d*) δ: 165.6, 156.9, 138.1, 137.6, 133.4, 133.3, 132.6, 130.8, 130.7, 122.0, 115.9, 114.4, 55.6, 20.9; HRMS (ESI/QTOF) m/z: $[M + H]^+$ calcd for $C_{15}H_{14}BrNO_2$ 320.0281; found 320.0285.

2-bromo-N-(4-chlorophenyl)-5-methylbenzamide (**23m**): The compound was synthesized according to the GP2 and purified through silica-gel column chromatography using the ethyl acetate/hexane (15:75) as an eluent. R_f value: 0.72 (eluent: 30% ethyl acetate/hexane); White solid; Yield: 67% (0.435 g); ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 7.74 (s, 1H), 7.59 (d, J = 8.8 Hz, 2H), 7.50 – 7.45 (m, 2H), 7.33 (d, J = 8.8 Hz, 2H), 7.13 (dd, J = 8.0, 2.0 Hz, 1H), 2.34 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, Chloroform-*d*) δ: 165.7, 138.2, 137.1, 136.2, 133.5, 132.9, 130.7, 129.9, 129.3, 121.4, 115.8, 20.9; HRMS (ESI/QTOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{12}BrClNO$ 323.9786; found 323.9791.

2-bromo-N-(3-methoxyphenyl)-5-methylbenzamide (**23q**): The compound was synthesized according to the GP2 and purified through silica-gel column chromatography using the ethyl acetate/hexane (20:80) as an eluent. R_f value: 0.60 (eluent: 30% ethyl acetate/hexane);White solid; Yield: 60% (0.384 g); ^{1}H

NMR (400 MHz, Chloroform-*d*) δ: 7.70 (s, 1H), 7.50 – 7.41 (m, 3H), 7.28 – 7.24 (m, 1H), 7.14 – 7.08 (m, 2H), 6.74 (dd, *J* = 8.4, 2.0 Hz, 1H), 3.83 (s, 3H), 2.34 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, Chloroform-*d*) δ: 165.7, 160.4, 138.9, 138.1, 137.5, 133.4, 132.7, 130.7, 129.9, 115.9, 112.2, 110.9, 105.8, 55.5, 20.9; HRMS (ESI/QTOF) m/z: $[M + H]^+$ calcd for $C_{15}H_{14}BrNO_2$ 320.0281; found 320.0283.

3-bromo-N-(p-tolyl)-2-naphthamide (**23r**): The compound was synthesized according to the GP2 and purified through silica-gel column chromatography using the ethyl acetate/hexane (15:75) as an eluent. R_f value: 0.72 (eluent: 30% ethyl acetate/hexane); Light brown solid; Yield: 72% (0.490 g); ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 8.11 (s, 2H), 7.85 – 7.75 (m, 3H), 7.56 – 7.55 (m, 4H), 7.19 (d, *J* = 7.6 Hz, 2H), 2.36 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, Chloroform-*d*) δ: 165.6, 135.2, 134.8, 134.7, 132.5, 131.6, 129.78, 129.7, 128.5, 128.5, 127.4, 126.9, 120.3, 115.9, 21.1; HRMS (ESI/QTOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{15}BrNO$ 340.0332; found 340.0335.

3-bromo-N-(4-methoxyphenyl)-2-naphthamide (**23s**): The compound was synthesized according to the GP2 and purified through silica-gel column chromatography using the ethyl acetate/hexane (20:80) as an eluent. R_f value: 0.54 (eluent: 30% ethyl acetate/hexane); Light brown solid; Yield: 67% (0.477 g); ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 8.11 (d, J = 6.0 Hz, 2H), 7.85 (d, J = 7.6 Hz, 1H), 7.76 (d, J = 5.2 Hz, 2H), 7.59 – 7.53(m, 4H), 6.92 (d, J = 8.4 Hz, 2H), 3.82 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, Chloroform-*d*) δ: 165.5, 156.9, 135.1, 134.7, 132.4, 131.6, 130.8, 129.7, 128.5, 128.4, 127.3, 126.9, 122.0, 115.9, 114.3, 55.6; HRMS (ESI/QTOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{15}BrNO_2$ 356.0281; found 356.0285.

3-bromo-N-(4-chlorophenyl)-2-naphthamide (**23t**): The compound was synthesized according to the GP2 and purified through silica-gel column chromatography using the ethyl acetate/hexane (10:90) as an eluent. R_f value: 0.81 (eluent: 30% ethyl acetate/hexane); Light brown solid; Yield: 64% (0.462 g); ^{1}H NMR (400 MHz, Chloroform-*d*) δ: 8.13 (d, J = 7.2 Hz, 2H), 7.88 – 7.77 (m, 3H), 7.65 – 7.56 (m, 4H), 7.35 (d, J = 8.8 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, Chloroform-*d*) δ: 165.6, 136.2, 134.9, 134.6, 132.6, 131.5, 129.9, 129.9, 129.3, 128.6, 128.5, 127.5, 126.9, 121.4, 115.6; HRMS (ESI/QTOF) m/z: $[M + H]^+$ calcd for $C_{13}H_{11}BrClNO$ 359.9786; found 359.9790.

General procedure (GP3) for *intra*-molecular organocatalyzed C(sp^2)-H direct arylation (Synthesis of phenanthridines 24-42): 2-bromo-N-phenylbenzamide/ substituted 2-bromo-N-phenylbenzamide (0.5 mmol), potassium *tert*-butoxide (168 mg, 1.5 mmol), 1-(2-hydroxyl ethyl) piperazine (0.2 mmol) and additive DMAP (0.2 mmol) were added in mesitylene (4 mL) in a sealed tube. Then, the reaction mixture was degassed with N_2 gas and heated at 150 °C (heated in oil bath) for 24 h. After the completion of the reaction, the reaction mixture was allowed to cool to r.t and dissolved in 5% methanol: chloroform (10 ml) and then, filtered through a celite pad and washed with 5% MeOH:

chloroform (3 × 10 mL). The combined filtrate was concentrated under vacuo to get crude compound which was further purified by silica-gel (100-200 mesh) column chromatography using MeOH: $CHCl_3$ or EtOAc: Hexane as an eluent which afforded the desired product.

Characterization data of phenanthridinones compounds (**24-42**).

Phenanthridin-6(5*H*)-one[5c] (**24**): The compound was synthesized according to the GP3 and purified through silica-gel column chromatography using the ethyl acetate/hexane (1:3) as an eluent. R_f value: 0.46 (eluent: 5% MeOH/$CHCl_3$); White solid; Yield: 89% (0.089 g); ^{1}H NMR (400 MHz, DMSO-d_6) δ:11.68 (s, 1H), 8.51 (d, *J* = 8.0 Hz, 1H), 8.39 (d, *J* = 8.0 Hz, 1H), 8.32 (d, *J* = 7.9 Hz, 1H), 7.87–7.83 (m, 1H), 7.64 (t, *J* = 7.6 Hz, 1H), 7.50–7.47 (m, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.26 (t, *J* = 7.6 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ: 161.3, 137.1, 134.7, 133.3, 130.1, 128.5, 128.00, 126.2, 123.8, 123.16, 122.8, 118.1, 116.6; HRMS (ESI/QTOF) m/z: [M + H] $^+$ calcd for $C_{13}H_{10}NO$ 196.0757; found 196.0759; FT-IR (KBr); 3021, 1604, 1363, 1226, 725, 622 cm^{-1}.

8-methylphenanthridin-6(5*H*)-one[12b] (**25**): The compound was synthesized according to the GP3 and purified through silica-gel column chromatography using the ethyl acetate/hexane (1:3) as an eluent. R_f value: 0.43 (eluent: 5% MeOH/$CHCl_3$); White Solid; Yield: 77% (0.081 g); ^{1}H NMR (400 MHz, DMSO-d_6) δ:11.59 (s, 1H), 8.36 (d, *J* = 8.4 Hz, 1H), 8.30 (d, *J* = 8.0 Hz, 1H), 8.09 (s, 1H), 7.64 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.44–7.40 (m, 1H), 7.32–7.30 (m, 1H), 7.23–7.19 (m, 1H), 2.45 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ: 161.3, 138.1, 136.7, 134.5, 132.3, 129.6, 127.7, 126.1, 123.5, 123.2, 122.7, 118.2, 116.5, 21.5; HRMS (ESI/QTOF) *m/z*: [M + H]$^+$ calcd for $C_{14}H_{12}NO$, 210.0913; found 210.0914; FT-IR (KBr); 2854, 1667, 1358, 1208, 886, 744, 658, 445 cm^{-1}.

8,9-dimethoxyphenanthridin-6(5*H*)-one[5c] (**26**): The compound was synthesized according to the GP3 and purified through silica-gel column chromatography using the MeOH/$CHCl_3$ (1:99) as an eluent. R_f value: 0.76 (eluent: 5% MeOH/$CHCl_3$); White Solid; Yield: 40% (0.051 g); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.56 (s, 1H), 8.35 (d, *J* = 8.0 Hz, 1H), 7.84 (s, 1H), 7.67 (s, 1H), 7.40–7.37 (m, 1H), 7.29 (d, *J* = 8.4 Hz, 1H), 7.22–7.18 (m, 1H), 3.98 (s, 3H), 3.86 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ: 160.9, 153.7, 149.9, 136.5, 129.5, 129.0, 123.7, 122.4, 119.8, 118.1, 116.4, 108.3, 104.6, 56.6, 56.0; HRMS (ESI/QTOF) m/z: [M + H]$^+$ calcd for $C_{15}H_{14}NO_3$ 256.0968; found 256.0970; IR (KBr); 2921, 1646, 1602, 1514, 1373, 1207, 1099, 840, 754, 585 cm^{-1}.

8-bromophenanthridin-6(5*H*)-one[16d] **(27)**: The compound was synthesized according to the GP3 and purified through silica-gel column chromatography using the MeOH/$CHCl_3$ (1:99) as an eluent. R_f value: 0.76 (eluent: 10% MeOH/$CHCl_3$); White Solid; Yield: 60% (0.082 g); ^{1}H NMR (400 MHz, DMSO-d_6); δ 11.65 (s, 1H), 8.47 (d, *J* = 8.0 Hz, 1H), 8.35 (d, *J* = 7.6 Hz, 1H), 8.28 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.84–7.79 (m, 1H), 7.63–7.58 (m, 1H), 7.48–7.43 (m, 1H), 7.34–7.31(m, 1H), 7.25–7.20 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ: 161.3, 137.0, 134.8, 133.4, 130.1, 128.5, 127.9, 126.16, 123.8,

123.1, 122.8, 118.1, 116.6; HRMS (ESI/QTOF) m/z: $[M + H]^+$ calcd for $C_{13}H_9BrNO$ 273.9862; found 273.9858; FT-IR (KBr); 2920, 1642, 1600, 1518, 1372, 1207, 844, 752, 588 cm^{-1}

Benzo[*j*]phenanthridin-6(5*H*)-one[5c] **(28)**: The compound was synthesized according to the GP3 and purified through silica-gel column chromatography using the MeOH/$CHCl_3$ (1:99) as an eluent. R_f value: 0.66 (eluent: 10% MeOH/$CHCl_3$); White Solid; Yield: 79% (0.097 g); ^1H NMR (400 MHz, DMSO-d_6) δ: 11.57 (s, 1H), 9.09 (s, 1H), 8.98 (s, 1H), 8.54 (d, *J* = 8.0 Hz, 1H), 8.20 (dd, *J* = 19.6, 8.0 Hz, 2H), 7.73–7.62 (m, 2H), 7.50–7.47 (m, 1H), 7.36–7.27 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ: 161.6, 136.9, 135.4, 132.3, 130.9, 130.0, 129.7, 129.1, 129.0, 128.6, 127.3, 124.0, 122.9, 122.1, 118.4, 116.8; HRMS (ESI/QTOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{12}NO$ 246.0913; found 224.0915; FT-IR (KBr); 3030, 1623, 1665, 1369, 1227, 754, 470 cm^{-1}.

Thieno[3,2-*c*]quinolin-4(5*H*)-one[5c] **(29)**: The compound was synthesized according to the GP3 and purified through silica-gel column chromatography using the MeOH/$CHCl_3$ (1:99) as an eluent. R_f value: 0.66 (eluent: 5% MeOH/$CHCl_3$); White Solid; Yield: 30% (0.030 g); ^1H NMR (400 MHz, DMSO-d_6) δ: 11.71 (s, 1H), 7.80 (d, *J* = 7.6 Hz, 1H), 7.74 (d, *J* = 5.2 Hz, 1H), 7.54 (d, *J* = 5.2 Hz, 1H), 7.46–7.42 (m, 1H), 7.39–7.32 (m, 1H), 7.20 (t, *J* = 8.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ: 158.7, 146.1, 136.70, 131.6, 129.9, 127.2, 125.6, 123.9, 122.9, 122.0, 116.7; HRMS (ESI/QTOF) m/z: $[M + H]^+$ calcd for $C_{11}H_7NOS$ 202.2553; found 202.2550; FT-IR (KBr); 2925, 1647, 1610, 1521, 1370, 1209, 1101, 845, 752, 589 cm^{-1}.

Benzo[*c*][1,8]naphthyridin-6(5*H*)-one[5c] **(30):** The compound was synthesized according to the GP3 and purified through silica-gel column chromatography using the MeOH/$CHCl_3$ (1:99) as an eluent. R_f value: 0.35 (eluent: 10% MeOH/$CHCl_3$); White Solid; Yield: 55% (0.054 g); ^1H NMR (400 MHz, DMSO-d_6) δ: 12.03 (s, 1H), 8.82 (dd, *J* = 8.0, 1.2 Hz, 1H), 8.55 (d, *J* = 8.0 Hz, 1H), 8.50 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.33 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.91–7.87 (m, 1H), 7.71–7.67 (m, 1H), 7.33 (dd, *J* = 8.0, 4.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ: 162.2, 149.9, 148.7, 133.6, 133.5, 132.6, 129.1, 128.1, 126.3, 123.6, 119.1, 113.7; HRMS (ESI/QTOF) m/z: $[M + H]^+$ calcd for $C_{12}H_9N_2O$, 197.0709; found 197.0713; FT-IR (KBr); 2955, 1668, 1745, 1340, 1201, 1035,766 cm^{-1}.

2-methylphenanthridin-6(5*H*)-one[13c] (**31a**) and 3-methylphenanthridin-6(5*H*)-one[5c,16e] (**31b)**: The compound was synthesized according to the GP3 and purified through silica-gel column chromatography using the MeOH/$CHCl_3$ (1:49) as an eluent. R_f value: 0.43 (eluent: 5% MeOH/$CHCl_3$); White solid; Yield: 80% (0.084 g); Spectral data was interpreted with both isomers; ^1H NMR (400 MHz, DMSO-d_6) δ: 10.77 (s, 2H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.46–7.42 (m, 1H), 7.37 (s, 1H), 7.03–6.98 (m, 2H), 6.81 (d, *J* = 7.6 Hz, 1 H), 6.78–6.75 (m, 1H), 6.48 (d, *J* = 8.4 Hz, 1H), 6.43 (d, *J* = 8.4 Hz, 1H), 6.32 (s, 1H), 6.26 (d, *J* = 8.0 Hz, 1H), 1.59 (s, 3H), 1.56 (s, 3H); $^{13}C\{^1H\}$ NMR(100 MHz, DMSO-d_6) δ: 161.5, 161.2, 139.9, 137.1, 134.9, 134.7,

133.3, 133.2, 131.8, 131.1, 128.3, 128.0, 127.9, 126.3, 125.8, 124.1, 123.7, 123.6, 123.1, 122.9, 117.9, 116.5, 115.7, 21.7, 21.2; HRMS (ESI/QTOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{12}NO$, 210.0913; found 210.0917; FT-IR (KBr); 2919, 2852, 1650, 1606, 1362, 762, 648, 449 cm^{-1}.

2-methoxyphenanthridin-6(5*H*)-one[5c] (**32a)** and 3-methoxyphenanthridin-6(5*H*)-one[5c,16e] (**32b)**: The compound was synthesized according to the GP3 and purified through silica-gel column chromatography using the ethyl acetate/hexane (3:7) as an eluent. R_f value: 0.35 (eluent: 5% MeOH/$CHCl_3$); White solid; Yield: 94% (0.106 g); Spectral data was interpreted with both isomers; ^1H NMR (400 MHz, DMSO-d_6) δ: 11.58 (s, 1H), 11.57 (s, 1H), 8.56 (d, *J* = 8.2 Hz, 1H), 8.39 (d, *J* = 8.0 Hz, 1H), 8.33–8.31 (m, 1H) , 8.31–8.26 (m, 2H), 7.88 (d, *J* = 2.4 Hz, 1H), 7.86–7.79 (m, 2H), 7.65 (t, *J* = 7.6 Hz, 1H), 7.57–7.54 (m, 1H), 7.31 (d, *J* = 8.8 Hz, 1H), 7.15 (dd, *J* = 8.8 Hz, 2.4 Hz, 1H), 6.91–6.89 (m, 1H), 6.87 (d, *J* = 2.4 Hz, 1H), 3.88 (s, 3H), 3.84 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ: 161.7, 160.9, 155.3, 138.6, 135.1, 134.6, 133.2, 133.1, 131.2, 128.5, 127.9, 127.2, 126.4, 125.3, 124.9, 123.5, 122.6, 118.8, 118.3, 117.8, 111.6, 110.7, 106.7, 100.0, 56.2, 55.8; HRMS (ESI/QTOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{12}NO_2$ 226.0863; found 226.0865; FT-IR (KBr); 2951, 1667, 1741, 1361, 1211, 1036, 1036, 766 cm^{-1}.

2-chlorophenanthridin-6(5*H*)-one[5c,16e] (**33a)** and 3-chlorophenanthridin-6(5*H*)-one[16e] (**33b)**: The compound was synthesized according to the GP3 and purified through silica-gel column chromatography using the ethyl acetate/hexane (1:4) as an eluent. R_f value: 0.38 (eluent: 5% MeOH/$CHCl_3$); White solid; Yield: 53% (0.061 g); Spectral data was interpreted with both isomers; ^1H NMR (400 MHz, DMSO-d_6) δ: 11.81 (s, 1H), 11.69 (s, 1H), 8.58 (d, *J* = 8.4 Hz, 1H), 8.52 (d, *J* = 8.4 Hz, 1H), 8.49 (d, *J* = 2.0 Hz, 1H), 8.40 (d, *J* = 8.0 Hz, 1H), 8.33 (d, *J* = 7.2 Hz, 1H), 7.89–7.85 (m, 2H,), 7.71–7.67 (m, 1H), 7.67–7.63 (m, 1H), 7.56–7.53 (m, 1H), 7.51–7.48 (m, 1H), 7.38 (s, 1 H), 7.36 (s, 1H), 7.29–7.25 (m, 1H) $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ:161.3, 161.1, 137.1, 135.9, 134.8, 133.7, 133.5, 133.3, 130.1, 129.9, 129.2, 128.5, 127.9, 127.1, 126.3, 126.2, 123.8, 123.7, 123.3, 123.2, 122.8, 119.7, 118.4, 118.1, 116.6; HRMS (ESI/QTOF) m/z: $[M + H]^+$ calcd for $C_{13}H_9ClNO$, 230.0367; found 230.0365; FT-IR (KBr); 2859, 1677, 1609, 1363, 1098, 813, 718, 478 cm^{-1}.

2,8-dimethylphenanthridin-6(5*H*)-one (**34a)** and 3,8-dimethylphenanthridin-6(5*H*)-one[11c] (**34b)**: The compound was synthesized according to the GP3 and purified through silica-gel column chromatography using the ethyl acetate/hexane (3:7) as an eluent. R_f value: 0.66 (eluent: 5% MeOH/$CHCl_3$); White Solid; Yield: 82% (0.092 g); Spectral data was interpreted with both isomers; ^1H NMR (400 MHz, DMSO-d_6) δ: 11.51 (s, 1H), 11.50 (s, 1H), 8.34 (d, *J* = 8.4 Hz, 1H), 8.30 (d, *J* = 8.4 Hz, 1H), 8.18 (d, *J* = 8.4 Hz, 1H), 8.12 (s, 1H), 8.07 (d, *J* = 6.0 Hz, 2H), 7.64–7.60 (m, 2H), 7.25–7.19 (m, 2H), 7.10 (s, 1H), 7.03 (d, *J* = 8.0 Hz, 1H), 2.44 (s, 3H), 2.43 (s, 3H), 2.37 (s, 3H), 2.34 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ: 161.5, 161.2, 139.4, 137.9, 137.6, 136.6, 134.6, 134.4, 134.4,

132.5, 132.3, 131.67, 130.6, 127.7, 127.7, 126.2, 125.7, 123.9, 123.4, 123.3, 123.1, 122.9, 118.0, 116.4, 115.9, 21.6, 21.4, 21.2; HRMS (ESI/QTOF) m/z: $[M + H]^+$ calcd for $C_{15}H_{14}NO$ 224.1070; found 224.1073; FT-IR (KBr); 2903, 1665, 1357, 1212, 818, 643, 452 cm^{-1}.

2-methoxy-8-methylphenanthridin-6(5*H*)-one (**35a)** and 3-methoxy-8-methylphenanthridin-6(5*H*)-one (**35b)**: The compound was synthesized according to the GP3 and purified through silica-gel column chromatography using the MeOH/$CHCl_3$ (1:99) as an eluent. R_f value: 0.35 (eluent: 5% MeOH/$CHCl_3$); White Solid; Yield: 80% (0.096 g); Spectral data was interpreted for both isomers; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.51 (s, 1H), 11.50 (s, 1H), 8.44 (d, *J* = 8.4 Hz, 1H), 8.26 (d, *J* = 8.4 Hz, 1H), 8.23 (d, *J* =8.8, 1H), 8.12 (s, 1H), 8.06 (s, 1H), 7.82 (d, *J* = 2.8 Hz, 1H), 7.67 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.62 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.28 (d, *J* = 9.2 Hz, 1H), 7.10 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.88 (d, *J* = 2.4 Hz, 1H), 6.85 (dd, *J* = 8.8, 2.4 Hz, 1H), 3.86 (s, 3H), 3.81 (s, 3H), 2.50 (s, 3H), 2.45 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ: 161.7, 160.9, 160.5, 155.3, 138.2, 138.2, 136.8, 134.5, 134.2, 132.5, 132.2, 130.9, 127.8, 127.6, 126.3, 124.9, 124.9, 123.5, 122.6, 118.9, 117.8, 117.7, 111.8, 110.5, 106.5, 100.0, 56.1, 55.8, 21.5, 21.4; HRMS (ESI/QTOF) m/z: $[M + H]^+$ calcd for $C_{15}H_{14}NO_2$ 240.1019; found 240.1021; FT-IR (KBr); 2925, 1670, 1596, 1403, 1056, 776, 665 cm^{-1}

2-chloro-8-methylphenanthridin-6(5*H*)-one (**36a)** and 3-chloro-8-methylphenanthridin-6(5*H*)-one[11c] (**36b)**: The compound was synthesized according to the GP3 and purified through silica-gel column chromatography using the ethyl acetate/hexane (1:4) as an eluent. R_f value: 0.53 (eluent: 5% MeOH/$CHCl_3$); White Solid; Yield: 37% (0.045 g); Spectral data was interpreted for both isomers; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.73 (s, 1H), 11.60 (s, 1H), 8.42 (d, *J* = 8.4 Hz, 1H), 8.40 (d, *J* = 2.4 Hz, 1H), 8.36 (d, *J* = 8.0 Hz, 1H), 8.31 (d, *J* = 8.0 Hz, 1H), 8.09 (s, 2H), 7.67–7.63 (m, 2H), 7.46 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.44–7.40 (m, 1H), 7.32 (d, *J* = 8.8 Hz, 1H), 7.23–7.19 (m, 1H), 2.46 (s, 3H).2.46 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ: 161.3, 161.1, 139.0, 138.1, 136.7, 135.5, 134.6, 134.5, 132.3, 131.3, 129.6, 129.4, 127.7, 127.0, 126.2, 126.1, 123.7, 123.5, 123.2, 123.1, 122.7, 119.8, 118.3, 118.2, 116.5, 21.5; HRMS (ESI/QTOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{11}ClNO$ 244.0524; found 244.0526; FT-IR (KBr); 2920, 1676, 1355, 1231, 814, 639, 492 cm^{-1}.

8,9-dimethoxy-2-methylphenanthridin-6(5*H*)-one (**37)**: The compound was synthesized according to the GP2 and purified through silica-gel column chromatography using the MeOH/$CHCl_3$ (1:99) as an eluent. R_f value: 0.44 (eluent: 5% MeOH: $CHCl_3$); White solid; Yield: 25% (0.034 g); Isolation: Silica-gel column (eluent: 1 % MeOH/$CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.52 (s, 1H), 8.20 (s, 1H), 7.86 (s, 1H), 7.70 (s, 1H), 7.26–7.21 (m, 2H), 4.02 (s, 3H), 3.89 (s, 3H), 2.42 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ: 160.8, 153.6, 149.8, 134.4, 131.4, 130.1, 129.5, 123.4, 119.9, 117.9, 116.3, 108.3, 104.5, 56.6, 56.0, 21.2; HRMS (ESI/QTOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{16}NO_3$ 270.1125; found 270.1123; FT-IR (KBr); 2921, 1646, 1603, 1503, 1207, 1094, 835, 728, 686 cm^{-1}.

1-methoxyphenanthridin-6(5*H*)-one[5c,16e] (**38a)** and 3-methoxyphenanthridin-6(5*H*)-one[5c,16e] (**32b)**: The compound was synthesized according to the GP3 and purified through silica-gel column chromatography using the MeOH/$CHCl_3$ (1:99) as an eluent. R_f value: 0.33 (eluent: 5% MeOH/$CHCl_3$); White solid; Yield: 34% (0.038 g); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.65 (s, 1H), 11.53 (s, 1H), 9.13 (d, *J* = 8.4 Hz, 1H), 8.34–8.03 (m, 2H), 8.22 (d, *J* = 8.4 Hz, 1H), 7.78–7.72 (m, 2H), 7.58–7.36 (m, 3H), 6.99 (d, *J* = 8.0 Hz, 1H), 6.88–6.80 (m, 2H), 3.98 (s, 3H), 3.78 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ: 161.7, 161.2, 160.8, 158.8, 138.8, 138.6, 135.0, 134.6, 133.3, 132.9, 130.2, 128.1, 127.9, 127.7, 127.5, 127.2, 126.2, 125.2, 124.9, 122.5, 111.6, 110.6, 109.5, 107.6, 105.6, 100.0, 56.4, 55.8; HRMS (ESI/QTOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{12}NO_2$ 226.0863; found 226.867.

4-methoxyphenanthridin-6(5*H*)-one[16e] (**38b**): The compound was synthesized according to the GP3 and purified through silica-gel column chromatography using the MeOH/$CHCl_3$ (1:99) as an eluent. R*f* value: 0.51 (eluent: 5% MeOH/$CHCl_3$); White Solid; Yield: 40% (0.045 g); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.52 (s, 1H), 8.44 (d, *J* = 8.0 Hz, 1H), 8.31–8.29 (m, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.84–7.80 (m, 1H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.21–7.11 (m, 2H), 3.89 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ: 160.8, 146.8, 134.8, 133.4, 128.6, 128.1, 126.7, 126.4, 123.6, 122.7, 118.6, 115.4, 111.0, 56.6; HRMS (ESI/QTOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{12}NO_2$ 226.0863; found 226.868; FT-IR (KBr); 2952, 1665, 1752, 1364, 1207, 1064, 728 cm^{-1}.

1-methoxy-8-methylphenanthridin-6(5*H*)-one **(39a)**: The compound was synthesized according to the GP2 and purified through silica-gel column chromatography using the MeOH/$CHCl_3$ (1:99) as an eluent. R_f value: 0.44 (eluent: 5%MeOH/$CHCl_3$); White Solid; Yield: 25% (0.030 g); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.59 (s, 1H), 9.02 (d, *J* = 8.8Hz, 1H), 8.14 (d, *J* = 1.2 Hz, 1H), 7.59 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.36 (t, *J* = 8.0 Hz, 1H), 6.98–6.96 (m, 1H), 6.87 (d, *J* = 8.0 Hz, 1H), 3.99 (s, 3H), 2.44 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ: 161.2, 158.6, 138.4, 137.1, 134.1, 132.1, 129.7, 128.1, 127.5, 126.2, 109.5, 107.7, 105.5, 56.4, 21.3; HRMS (ESI/QTOF) m/z: $[M + H]^+$ calcd for $C_{15}H_{14}NO_2$ 240.1019; found 240.1022

3-methoxy-8-methylphenanthridin-6(5*H*)-one **(35b)**: The compound was synthesized according to the GP3 and purified through silica-gel column chromatography using the MeOH/$CHCl_3$ (1:99) as an eluent. R_f value: 0.35 (eluent: 5% MeOH/$CHCl_3$); White Solid; Yield: 17% (0.020 g); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.48 (s, 1H), 8.25–8.20 (m, 2H), 8.03 (s, 1H), 7.61–7.58 (m, 1H), 6.85–6.81 (m, 2H), 3.79 (s, 3H), 2.43 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ: 161.6, 160.5, 138.2, 136.8, 134.5, 132.6, 127.7, 125.0, 124.9, 122.6, 115.6, 111.8, 110.6, 106.2, 100.0, 91.9, 55.8, 21.4; HRMS (ESI/QTOF) m/z: $[M+H]^+$ calcd for $C_{15}H_{14}NO_2$ 240.1019; found 240.1023.

4-methoxy-8-methylphenanthridin-6(5*H*)-one (**39b**): The compound was synthesized according to the GP3 and purified through silica-gel column chromatography using the MeOH/$CHCl_3$ (1:99) as an

eluent. R_f value: 0.67 (eluent: 5% MeOH/$CHCl_3$); White Solid; Yield: 40% (0.048 g); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.46 (s, 1H), 8.33 (d, J = 8.4 Hz, 1H), 8.11 (s, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.65–7.63 (m, 1H), 7.17 (t, J = 8.0 Hz, 1H), 7.09 (dd, J = 8.0, 0.8 Hz, 1H), 3.89 (s, 3H), 2.45 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ: 160.8, 146.7, 138.3, 134.6, 132.3, 127.8, 126.3, 123.6, 122.7, 118.7, 115.2, 110.6, 56.6, 21.4; HRMS (ESI/QTOF) m/z: $[M + H]^+$ calcd for $C_{15}H_{14}NO_2$ 240.1019; found 240.1025

2-methylbenzo[*j*]phenanthridin-6(5*H*)-one (**40a)** and 3-methylbenzo[*j*]phenanthridin-6(5*H*)-one[16f] (**40b)**: The compound was synthesized according to the GP3 and purified through silica-gel column chromatography using the MeOH/$CHCl_3$ (1:99) as an eluent. R_f value: 0.46 (eluent: 5% MeOH/$CHCl_3$); White Solid; Yield: 87% (0.113 g); Spectral data was interpreted for both isomers; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.51 (s, 1H), 11.49 (s, 1H), 9.07 (s, 1H), 9.02 (s, 1H), 8.96 (s, 1H), 8.95 (s, 1H), 8.40 (d, J = 8.0 Hz, 1H), 8.35 (s, 1H), 8.24–8.14 (m, 4H), 7.73–7.68 m, 2H), 7.65–7.60 (m, 2H), 7.32–7.29 (m, 1H), 7.25(d, J = 8.4 Hz, 1H), 7.15–7.11 (m, 2H), 2.45 (s, 3H), 2.39 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ: 161.5, 139.8, 136.9, 135.4, 135.4, 134.7, 132.1, 131.9, 130.9, 129.6, 129.1, 128.9, 128.6, 128.5, 127.2, 127.0, 124.7, 124.1, 123.9, 121.9, 121.6, 118.3, 116.7, 116.1, 21.6, 21.3; HRMS (ESI/QTOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{14}NO$ 260.1070; found 260.1072; FT-IR (KBr); 2927, 1740, 1661, 1367, 1222, 876, 758, 653, 468 cm^{-1}.

2-methoxybenzo[*j*]phenanthridin-6(5*H*)-one[16f] (**41a)** and **3**-methoxybenzo[*j*]phenanthridin-6(5*H*)-one[16f](**41b**): The compound was synthesized according to the GP3 and purified through silica-gel column chromatography using the MeOH/$CHCl_3$ (2:98) as an eluent. R_f value: 0.59 (eluent: 10% MeOH/$CHCl_3$); White Solid; Yield: 76% (0.105 g); Spectral data was interpreted for both isomers; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.44 (s, 1H), 11.41 (s, 1H), 9.10 (s, 1H), 8.93 (s, 1H), 8.89 (s, 2H), 8.4 (d, J = 8.4 Hz, 1H), 8.19–8.07 (m, 3H), 8.08 (d, J = 8.0 Hz, 1H), 8.0 (d, J = 2.4 Hz, 1 H), 7.70–7.64 (m, 2H), 7.60–7.53 (m, 2H), 7.26 (d, J = 8.8 Hz, 1H), 7.09 (dd, J = 8.8, 2.8 Hz, 1H), 6.89–6.86 (m, 2H), 3.88 (s, 3H), 3.80 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ: 161.2, 155.5, 142.7, 138.4, 135.6, 135.3, 135.2, 132.1, 130.9, 130.9, 130.8, 129.7, 129.1, 128.9, 128.6, 128.3, 127.3, 125.5, 125.5, 124.7, 123.8, 122.4, 120.9, 119.2, 117.9, 117.9, 113.2, 111.8, 110.4, 107.3, 56.2, 55.9; HRMS (ESI/QTOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{14}NO_2$ 276.1019; found 276.1023; FT-IR (KBr); 2898, 1674, 1502, 1368, 1043, 875, 750, 471 cm^{-1}.

2-chlorobenzo[*j*]phenanthridin-6(5*H*)-one (**42a**): The compound was synthesized according to the GP3 and purified through silica-gel column chromatography using the MeOH/$CHCl_3$ (1:99) as an eluent. R_f value: 0.76 (eluent: 10% MeOH/$CHCl_3$); White Solid; Yield: 37% (0.052 g); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.67 (s, 1H), 9.10 (s, 1H), 8.97 (s, 1H), 8.56 (d, J = 8.8 Hz, 1H), 8.24 (d, J = 8.4 Hz, 1H), 8.17 (d, J = 8.0 Hz, 1H), 7.76–7.72 (m, 1H), 7.68–7.64 (m, 1H), 7.39 (d, J = 2.4 Hz, 1H), 7.35–

7.33 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ: 161.6, 138.1, 135.4, 134.0, 132.2, 130.1, 129.7, 129.3, 129.2, 128.6, 127.5, 125.9, 124.2, 122.8, 122.4, 117.5, 116.0; FT-IR (KBr); 2916, 1670, 1600, 1369, 749, 667, 429 cm^{-1}; HRMS (ESI/QTOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{11}ClNO$ 280.0524; found 280.0528.

3-chlorobenzo[*j*]phenanthridin-6(5*H*)-one (**42b)**: The compound was synthesized according to the GP3 and purified through silica-gel column chromatography using the MeOH/$CHCl_3$ (1:99) as an eluent. R_f value: 0.66 (eluent: 10% MeOH/$CHCl_3$); White solid; Yield: 20% (0.028 g); ^1H NMR (400 MHz, DMSO-d_6) δ: 11.65 (s, 1H), 9.15 (s, 1H), 8.93 (s, 1H), 8.58 (d, *J* = 2.4 Hz, 1H), 8.20 (d, *J* = 8.4 Hz, 1H), 8.14 (d, *J* = 8.0 Hz, 1H), 7.72–7.68 (m, 1H), 7.64–7.60 (m, 1H), 7.49 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.33 (d, *J* = 8.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ: 161.5, 135.8, 135.4, 132.4, 129.8, 129.7, 129.2, 128.7, 127.6, 127.2, 124.3, 123.6, 122.9, 120.2, 118.6; FT-IR (KBr); 3378, 2916, 1678, 1628, 1365, 807, 747, 501 cm^{-1}; HRMS (ESI/QTOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{11}ClNO$ 280.0524; found 280.0527.

N-(2-hydroxyphenyl)benzamide[16g] (**45)**: The compound was synthesized according to the GP3 and purified through silica-gel column chromatography using the ethyl acetate/hexane (20:80) as an eluent. R_f value: 0.73 (eluent: 10% MeOH/$CHCl_3$); Light brown solid; Yield: 58% (0.062 g); ^1H NMR (400 MHz, DMSO-d_6) δ: 9.75 (br, 1H), 9.49 (s, 1H), 7.94 – 7.92 (m, 2H), 7.64 – 7.62 (m, 1H), 7.56 – 7.54 (m, 1H), 7.51 – 7.47 (m, 2H), 7.02 – 6.98 (m, 1H), 6.88 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.81 – 6.77 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 165.7, 149.9, 134.9, 132.2, 129.0, 128.0, 126.4, 126.2, 124.7, 119.5, 116.5; HRMS (ESI/QTOF) m/z: $[M + H]^+$ calcd for $C_{13}H_{12}NO_2$ 214.0863; found 214.0867.

8-phenylphenanthridin-6(5H)-one (**54**): The compound was synthesized according to the GP3 and purified through silica-gel column chromatography using the ethyl acetate/hexane (10:90) as an eluent. R_f value: 0.52 (eluent: 20% ethyl acetate/hexane); Light brown solid; Yield: 15% (0.020 g); ^1H NMR (400 MHz, DMSO-d_6) δ: 11.75 (br, 1H), 8.57 (d, *J* = 8.4 Hz, 1H), 8.42 (d, *J* = 8.0 Hz, 1H), 8.01 (d, *J* = 1.7 Hz, 1H), 7.62 – 7.60 (m, 1H), 7.52 – 7.37 (m, 4H), 7.30 – 7.26 (m, 2H), 6.98 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 160.9, 140.1, 137.5, 136.5, 136.5, 135.1, 134.1, 132.9, 129.6, 128.2, 127.7, 125.8, 123.3, 123.1, 122.5, 117.5, 116.2; HRMS (ESI/QTOF) m/z: $[M + H]^+$ calcd for $C_{19}H_{14}NO$ 272.1070; found 272.1076.

General procedure for the gram-scale synthesis of phenanthridine 24: 2-bromo-N-phenylbenzamide (1.50 g, 5.43 mmol), potassium *t*-butoxide (1.3g, 16.29 mmol), 1-(2-hydroxyl ethyl) piperazine (0.283g, 2.17 mmol) and additive DMAP (0.265g, 2.17 mmol) were added in mesitylene (4 mL) in a sealed tube. This reaction mixture was then degassed with N_2 gas and heated at 150 °C (heated in oil bath) for 24 h. After the completion of the reaction, the reaction mixture was allowed to cool to r.t and dissolved in 5% methanol: chloroform (10 mL) and then, filtered through a celite pad and washed with 5% MeOH/$CHCl_3$ (3 × 10 mL). The combined filtrate was concentrated under vacuo to get crude compound

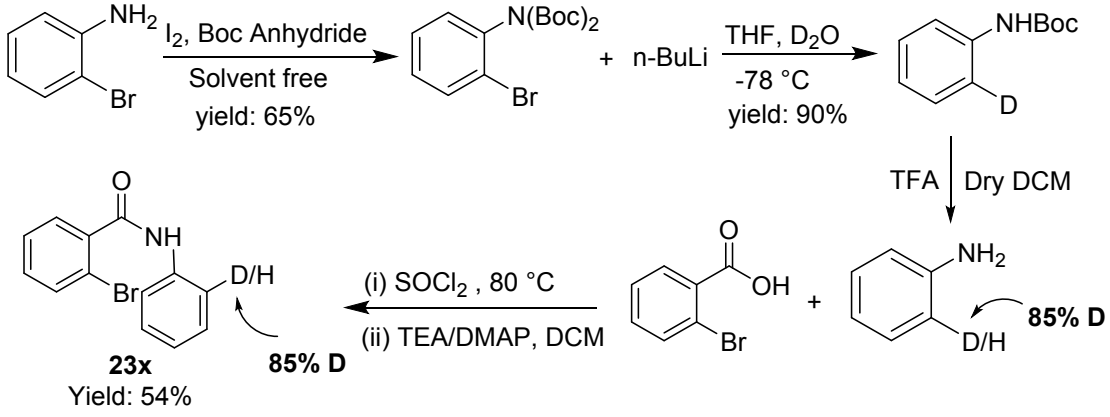
which was further purified by silica-gel (100-200 mesh) column chromatography using DCM/EtOAc as an eluent which afforded the phenanthridinone **24** in 80% yields.

Attempt to *intra*-molecular organocatalyzed synthesis with substrate 23w

N-(2-bromophenyl)benzamide (0.5 mmol), potassium *tert*-butoxide (168 mg, 1.5 mmol), 1-(2-hydroxyl ethyl) piperazine (0.2 mmol) and additive DMAP (0.2 mmol) were added in mesitylene (4 mL) in a sealed tube. This reaction mixture was degassed with N_2 gas for 20-25 min and then heated the reaction mixture at 150 °C (heated in oil bath) for 24 h. The progress of the reaction was monitored by TLC. The reaction mixture was dissolved in 5% MeOH/$CHCl_3$ solution (20 mL) and filtered the reaction mixture over celite bed. The organic filtrate was washed with 5% MeOH/$CHCl_3$ solution (3 × 10 mL). The filtrated solvent was evaporated under vacuo to get crude mass which was purified by silica-gel column chromatography using 3% EtOAc: DCM as an eluting solvent to afford the N-(2-hydroxyphenyl) benzamide **45** (58 mg, 0.27 mmol) in 54% yield as a white solid.

General procedure for the free-radical reaction pathway in *intra*-molecular C(sp^2)-H direct arylation: 2-bromo-N-phenylbenzamide **23a** (0.5 mmol), potassium *tert*-butoxide (168 mg, 1.5 mmol), 1-(2-hydroxyl ethyl) piperazine (0.2 mmol), TEMPO (0.5 mmol or 0.2 mmol) and additive DMAP (0.2 mmol) were added in mesitylene (4 mL) in a sealed tube. This reaction mixture was then degassed with N_2 gas and heated at 150 °C (heated in oil bath). As the reaction progresses, it was found that a 40 mol% TEMPO furnished phenanthridinone in only 35% yield; however, the stoichiometric amount of TEMPO completely aborted the reaction.

General Procedure for the synthesis of the substrate 23x for kinetic isotopic study.



(i) *Procedure for the synthesis of tert-butyl 2-bromophenyl (tert-butyl carbamate) carbamate*: A catalytic amount of iodine (10 mol %) was added to the magnetically stirred solution of 2-bromo aniline (10 mmol) and $(Boc)_2O$ (15 mmol) under solvent-free conditions at room temperature. After stirring the reaction mixture for the 3h, diethyl ether (100 mL) was added. The reaction mixture was washed with 5% $Na_2S_2O_3$ solution in water (2 × 50 mL) and then with saturated $NaHCO_3$ (2 × 50 mL) and dried over anhyd. Na_2SO_4. The filtrated solvent was evaporated under reduced pressure. The crude product was

purified by silica-gel column chromatography (60–120, 5% EtOAc/hexane) to afford the di-*tert*-butyl (2-bromophenyl) carbamate product with the 65% (2.42 g) isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.58 (dd, J = 8.0, 1.2 Hz, 1H), 7.32 – 7.28 (m, 1H), 7.21 – 7.14 (m, 2H), 1.38 (s, 18H).

(ii) *Procedure for the synthesis of tert-butyl (phenyl-2-d) carbamate*: *n*-BuLi (6.05 mmol) was added to a magnetically stirred mixture of *tert*-butyl 2-bromophenyl (tert-butyl carbamate) carbamate (1.0 g, 2.68 mmol) in dry THF at -78 °C under N_2 atmosphere and maintained for 1h. Then, heavy water (D_2O) was added slowly while maintaining the temperature at -78 °C. Then, the temperature of the reaction mixture was raised to 0 °C and monitored the reaction on TLC in 5% EtOAc/Hexane. The reaction mixture solvent was evaporated under vacuum and crude product was purified by column chromatography using EtOAc/Hexane (5:95) to get light yellow solid in 90% (0.468 g) isolated yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35 – 7.32 (m, 1H), 7.29 – 7.25 (m, 2H), 7.04– 7.00 (m, 1H), 6.46 (s, 1H), 1.51 (s, 9H).

(iii) *Procedure for the synthesis of benzen-2-d-amine*: To a solution of *tert*-butyl (phenyl-2-d) carbamate (0.430 g, 2.21 mmol) in anhyd. dichloromethane (15 mL); trifluoroacetic acid (3.5 mL) was added and stirred for 1 h at rt. Then, the excess reagent and solvent were evaporated under reduced pressure. The resulted sticky viscous mass was neutralized by sat. $NaHCO_3$ solution and extracted with dichloromethane (3 × 15 mL), then with brine (2 × 10 mL), dried over anhyd. Na_2SO_4 and evaporated under reduced pressure. The crude compound was further used without purification.

(iv) *Procedure for the synthesis of 2-bromo-N-(phenyl-2-d) benzamide* (**23x**): 2-bromobenzoyl chloride was prepared from 2-bromobenzoic acid (0.404 g, 2.01 mmol) by refluxing with an excess of thionyl chloride (1.30 ml, 10.04 mmol) for 2-3 h. The excess amount of thionyl chloride was removed under vacuum. Then, additional dry THF was added to the reaction residue and again evaporated under reduced pressure to remove the traces amount of thionyl chloride. The resulted residue was used for the amide preparation without further purification. The substituted benzoyl chloride (2.00 mmol) in DCM (10 mL) was added dropwise to a magnetically stirring solution of benzen-2-*d*-amine (2.21 mmol), Et_3N (0.914 ml, 6.03 mmol) and DMAP (0.049 g, 0.40 mmol) in DCM (15 mL) at 0-5°C under nitrogen atmosphere. After the addition, the resulting mixture was warmed to room temperature and stirred the reaction mixture for 6 h. The reaction mixture was quenched with dropwise addition of water (5 mL) at 0 ^{o}C and diluted with DCM (20 mL). The resulting solution was washed with aq. HCl (15 mL, 1.0 M), then with saturated aqueous $NaHCO_3$ (15 mL), then with water (3 × 15 mL), then with brine (2 × 10 mL), dried over anhyd. Na_2SO_4 and evaporated under reduced pressure. The crude residue was purified by column chromatography to afford **23x** (0.296 g, 53% isolated yield) as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.71 (s, 1H), 7.64 – 7.29 (m, 7H), 7.18 – 7.14 (m, 1H).

Kinetic isotope effect experiment for the *intra*-molecular C-H arylation: 2-bromo-N-(phenyl-2-*d*) benzamide **23x** (0.2 g, 0.7216 mmol), potassium *t*-butoxide (0.242 g, 2.1649 mmol), 1-(2-hydroxyl

ethyl) piperazine (0.037 g, 0.2886 mmol) and additive DMAP (0.035 g, 0.2886 mmol) were added in mesitylene (4 mL) in a sealed tube. This reaction mixture degassed with N_2 gas and heated at 150 °C (heated in oil bath) for 24 h. After the completion of the reaction, the reaction mixture was allowed to cool to r.t and dissolved in 5% methanol: chloroform (10 mL) and then, filtered through a celite pad and washed with 5% MeOH: chloroform (3 × 10 mL). The combined filtrate was concentrated under vacuo to get crude compound which was further purified by silica-gel (100-200 mesh) column chromatography using DCM/EtOAc (9: 1) as an eluent which afforded the cyclized products **24**, **46a** and **46b** as a white solid. The product distribution (K_H/K_D = 1.22) was analyzed by ^{1}H NMR.

Associated Content

Supporting information

ICP-MS analysis of various metals in organocatalyst E; K_H/K_D determination; ^{1}H NMR and ^{13}C NMR spectral data of compound **3a-w**, **6**, **7**, **23b**, **23d-e**, **23k-m**, **23q-s**, **23x**, **24-42**, **45**, **46a-b**, **54**, Di-Boc protected 2-bromo aniline and *tert*-butyl (phenyl-2-d)carbamate. The supporting information is available on free of charge on ACS website

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Notes

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Keywords: • Organocatalyst • Cross-coupling • Direct arylation • C-H bond activation • Metal-free synthesis • SET mechanism

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