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Substrate Switchable Pathway for Selective Construction of Bridged Dibenzo[b,f][1,5]diazocines and Bridged Spiromethanodibenzo[*b*,*e*]azepines

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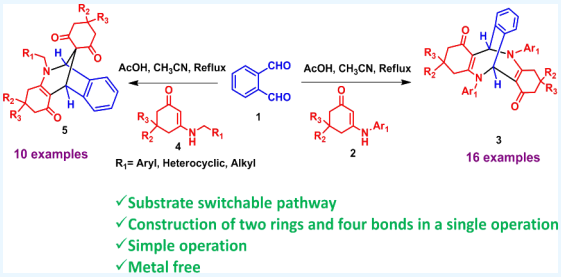
ABSTRACT: An operationally simple method for the synthesis of bridged dibenzo[b,f][1,5]diazocines and bridged spiromethanodibenzo[*b*,*e*]-azepines exhibiting bridged eight-membered and seven-membered molecular architecture is reported. This unique approach is based on substrate selective mechanistic pathway, including an unprecendented aerial oxidation-driven mechanism for the synthesis of bridged spiromethanodibenzo[*b*,*e*]azepines. The reaction is highly atom economic, and in addition, it allows the construction of two rings and four bonds in a single operation under metal-free condition. The easy availability of β enaminone and ortho phathalaldehyde as starting materials and the simple operation make this approach suitable for the preparation of important dibenzo[b,f][1,5]diazocine and spiromethanodibenzo[*b*,*e*]-azepine cores.



INTRODUCTION

Construction of a rigid molecule with a defined curvature is a challenging theme for organic chemists by virtue of rapidly growing supramolecular chemistry research area. Molecular cages,[1] capsules[2] and tweezers[3] are some most imposing supramolecular assemblies for in-depth exploration for future study. Among the molecular building blocks, material chemists have explored a bridged variant of diaryldibenzo[b,f][1,5]-diazocines, termed as Tröger's base, which has a chiral aromatic cage structure with the ability to host guests and as a result acts as a supramolecular receptor.[4] Additionally, several benzo[b,f][1,5]diazocines have shown antiviral, cholesterol-lowering, and hormone-like activities.[5] The unique structure of Tröger's base elaborates a number of unique applications like fluorescent probe,[6] photophysical activity,[7] catalysis,[8] and medicinal chemistry.[9] Thus, bridged variants of supramolecular building blocks have an enormous utilization in the diversified field of chemistry. Synthesis of Tröger's base involves direct condensation between aniline and paraformldehyde. Numerous Tröger's base analogues have been synthesized[4,10a,b] and used in the development of synthetic receptors,[10c,d] template synthesis of fullerene derivatives,[10e] investigation of intramolecular interactions, asymmetric transformations,[10f] and so forth. There are a number of synthetic strategies toward diazocines approached through the condensation reaction of 2-aminobenzophenones.[11] Wan and co-workers[12] developed dibenzo[b, f][1,5]-diazocines in good yields from acid-catalyzed cyclization of 2-benzoylbenzoyl azides. For further development of efficient synthetic procedures for this class of compounds, Sridharan group[13] in 2016 reported the synthesis of epiminodibenzo[*b*,*f*][1,5]diazocines from 2-aminoarylaldehydes reacted with arylamines in the presence of $Yb(OTf)_3$. Recently, epoxydibenzo[b,f][1,5]diazocines were synthesized from fluorinated o-aminophenones.[14] In contrast, to the best of our knowledge, no efficient synthetic approach toward benzenodibenzo[b,f][1,5]diazocine has been developed so far.

1- benzazepines and dibenzo[*b*,*e*]azepines exist as core structures of several natural products and pharmaceuticals, such as ACE inhibitor (benazepril), competitive vasopressin receptor antagonist (tolvaptan), antidepressants (mianserin and mirtazapine), and antidiuretics agent (fedovapagon).[15] Because of the attractive biological importance of benzoazepines, many approaches are made to access this class of compounds via NHC/transition metal-catalyzed annulations,[16a,b] Pictet−Spengler reaction,[16c] transition metal-catalyzed C−H functionalization and oxidative cross-coupling[16d,e] and cascade[1,5] hydride transfer/cyclization.[16f,g] In between several synthetic approaches of diversified dibenzo[*b*,*e*]-azepines, as far as we know, synthesis of spiromethano-bridged dibenzo[*b*,*e*]azepine was not reported elsewhere. Spiromethano-bridged dibenzo[*b*,*e*]azepine having a unique V-shaped rigid structure exhibited distinctive potential for asymmetric catalysis, molecular recognition, and optoelectronics property.

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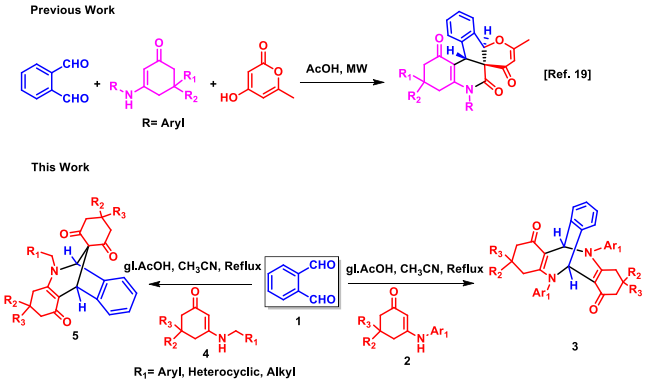
For these reasons, sustainable, practical methods for the synthesis of bent molecules are still highly desirable.

Multicomponent domino reactions (MDRs), being one of the most effective methods, can implement high levels of diversity giving rise to complex molecular structures by simultaneous bond formation from simple substrates to improve the synthetic outcome.[17] Our group have developed a series of MDRs that offer easy approach toward multiple functionalized compounds of chemical and pharmaceutical interest.[18] From our study on MDRs, we report here a novel construction of a new scaffold containing benzeneo-bridged dibenzo[b,f][1,5]diazocine from bicylization of cyclic enaminones of aryl amines with *ortho* phthaladehyde (OPA). Cyclic enaminones of benzyl amines and aliphatic amines undergo condensation with OPA by an unprecedented aerobic oxidation toward spiromethanodibenzo[*b*,*e*]azepine. By using multicomponent annulations of enaminones with OPA and 4-hydroxy-6-methyl-2Hpyran-b2-one, Li and co-workers[19] reported the synthesis of pyrano[3′,2′:2,3]indeno[2,1-*c*]-quinolines (Scheme 1). In contrast to the previous report,

Scheme 1. Synthesis of Bridged Dibenzo[b,f][1,5]diazocine and Bridged Spiromethanodibenzo[*b*,*e*]azepine Derivatives

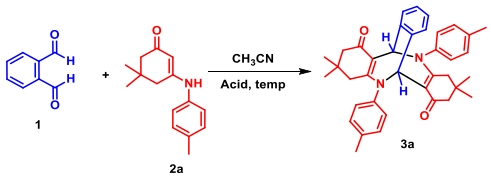


our reaction developed for the first time bridged dibenzo[b,f]-[1,5]diazocine and bridged spiromethanodibenzo[*b*,*e*]azepine through an interesting substrate switchable pathway (Scheme 1).

RESULTS AND DISCUSSION

Recently, we have reported the synthesis of 7-acetamido tetrahydroindole derivatives via trifluoro acetic acid (TFA)-promoted allylic amidation of cyclic enaminone of dimedone, aryl glyoxals, and acetonitrile.[20] During this investigation, we were drawn to study a model reaction between cyclic enaminone 5,5-dimethyl-3-(p-tolylamino)cyclohex-2-enone **2a** and OPA (**1**) in acid-catalyzed condition. Under our experimental condition, 20 mol % TFA and 1.00:1.00 molar ratio of two substrates combine in CH_3CN medium to form the autocondensation product 3,3,9,9-tetramethyl-5,11-di-p-tolyl-3,4,5,6,9,10,11,12-octahydro-6,12 [1,2]benzenodibenzo-[b,f][1,5]diazocine-1,7(2H,8H)-dione (**3a**) (Table 1 entry 1). The structure of **3a** was confirmed by NMR and HRMS analyses. Due to the formation of the autocondensation product, optimization of the reaction was performed under 1.00:2.00 molar ratio of OPA **1** and cyclic enaminone **2**. In an effort to increase the yield of the reaction, the reaction was optimized with several Bronsted acids like TFA, glacial AcOH, benzoic acid, and methane sulphonic acid and a number of

Table 1. Optimization of Reaction Condition[a]



entry	acid catalyst (mol %)	solvent	temperature (°C)	%yield[b]
1[c]	TFA (20)	CH_3CN	80	57
2	TFA (20)	CH_3CN	80	70
3	glacial AcOH (20)	CH_3CN	80	88
4	$PhCO_2H$ (20)	CH_3CN	80	58
5	CH_3SO_3H (20)	CH_3CN	80	65
6	$FeCl_3$ (20)	CH_3CN	80	46
7	$ZnCl_2$ (20)	CH_3CN	80	50
8	$AlCl_3$ (20)	CH_3CN	80	54
9	CuCl (20)	CH_3CN	80	40
10	glacial AcOH (20)	EtOH	80	75
11	glacial AcOH (50)	CH_3CN	80	72
12	glacial AcOH (50)	EtOH	80	60
13	glacial AcOH (20)	1,2-DCE	90	61
14	glacial AcOH (20)	THF	90	53
15	glacial AcOH (20)	toluene	100	trace
16	glacial AcOH (20)	DMF	100	30
17	glacial AcOH (20)	DCM	45	42
18	glacial AcOH (20)	water	90	trace
19	glacial AcOH (20)	CH_3CN	rt	20
20[d]	no catalyst	CH_3CN	80	24

[a]Reaction conditions: A mixture **1** (0.5 mmol) and **2a** (1 mmol) was reacted in various solvents and in various acid catalysts equipped with a reflux condenser in open air within 6 h time span. [b]Percentage of yield. [c]Mixture **1** (0.5 mmol) and **2a** (0.5 mmol) was reacted in a reflux condenser within 6 h time span. [d]Reaction time: 15 h.

Lewis acid catalysts like $FeCl_3$, $ZnCl_2$, $AlCl_3$, and CuCl (shown in Table 1). It was found that the reaction was completed in 5−6 h in the presence of 20 mol % of glacial AcOH catalyst at 80 °C, and a maximum yield of 88% was observed. Further increasing the loading of the catalyst was found to be disadvantageous for the product yield (entries 11, 12). We screened different solvents, and we noticed that when EtOH, 1, 2-DCE, or THF was used in the reaction at different reaction temperatures, product **3a** was obtained in moderate yields. Only trace yield was obtained in nonpolar solvents toluene (Table 1 entry 15), and with the use of high boiling solvent DMF, the reaction yield is extremely low at 100 °C (Table 1 entry 16). With low boiling solvent DCM, the reaction gave a moderate yield (Table 1 entry 17). However, using water as a solvent furnished lesser yield of the product. This may be due to the low solubility of starting materials in water. It was also observed that at room temperature, a very slight amount of autocondensation product was isolated (Table 1 entry 19), indicating that a high temperature is necessary in this reaction. The best result was found with the use of CH_3CN as the solvent at 70−80 °C temperature, supporting the fact that the solvent plays an important role in this reaction. The reaction proceeded very slowly in the absence of any acid promoter and yielded only slight amounts of the desired product after a prolonged reaction time (Table 1 entry 20).

With the optimal conditions secured, the scope of the method was explored. Extensive application of *β*-enaminones as 1,3-bidonours is developed for the construction of nitrogen-

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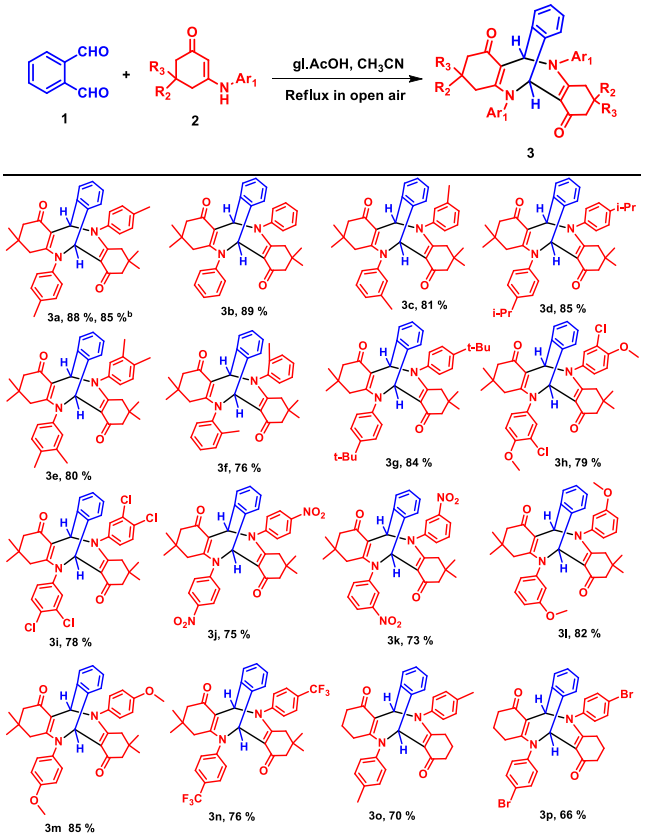
containing heterocycles. We subsequently explored the scope of the N-substituted enaminone in this reaction. Various enaminones of aryl amines were employed for preliminary investigation, and it was found that aryl amine-bearing electron-rich (4-Me, 4-OMe, 3-Me, 3-OMe, 2-Me, and 3, 4-dimethyl) and electron-deficient (4-NO_2, 3-NO_2, and 4-CF_3) were smoothly converted to the corresponding products in moderate-to-good yields (Table 2). Also halo-substituted N-

Table 2. Substrate Scope of Compound 3[a]



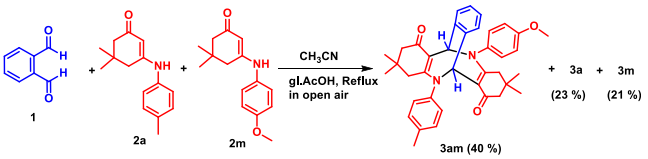
[a]Reaction conditions: A mixture **1** (0.5 mmol) and cyclic enaminone of aryl amine (**2**) (1 mmol) was reacted in CH_3CN as solvent (6 mL); reflux in open air equipped with a reflux condenser [b]Gram scale yield.

aryl enamines (3-chloro-4-methoxy-3, 4-dichloro, and 4-Br) were found to furnish desired products in good yields (65−79%) which provided possibilities of further functionalization. To further explore the versatility of this protocol, cyclic 1, 3-dione part of cyclic enaminones was varied. It was seen than apart from cyclic enaminones of dimedone, cyclic enamines of 1, 3 cyclohexane dione provided good yields of the final product (Table 2, **entry 3o, 3p**).

With excellent results in the autocondensation process, further investigations were directed to cross-condensation (Scheme 2). A successful cross-condensation by mixing **2a** and 3-((4-methoxyphenyl)amino)-5,5-dimethylcyclohex-2-enone (**2m**) with **1** enables the isolation of cross-condensation product (**3am**) with two autocondensation products **3a** and **3m**.

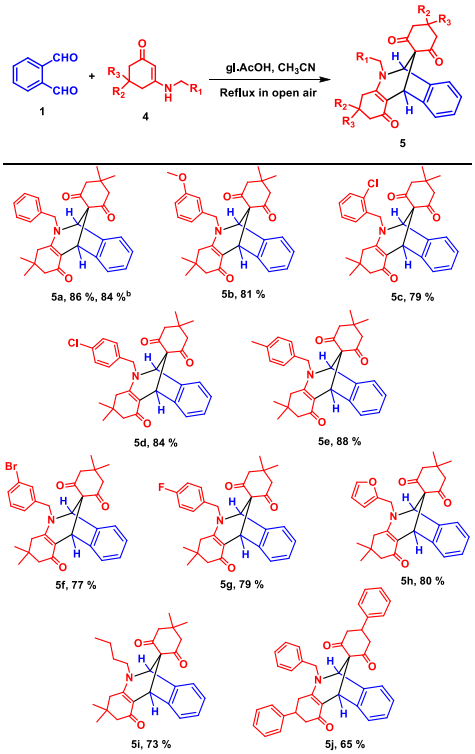
Next, we turned our attention to survey the fate of the reaction with N-substituted enaminones of various substituted benzyl amines and aliphatic amines. Surprisingly, it was

Scheme 2. Cross-Condensation of 1 with Two Different Cyclic Enaminones of Aryl Amine



observed that under the similar reaction condition, cyclic enaminones of substituted benzyl amines furnish spiromethanodibenzo[*b*,*e*]azepines. The structure of the corresponding product was confirmed by ^{1}HNMR, ^{13}CNMR, HRMS, and X-ray crystallographic analyses. The scope of this method was examined by varying N-substituted enaminones. Different electronic substitutions on the aryl ring of benzyl amines were well scrutinized (Table 3). Benzyl amines

Table 3. Substrate Scope of Compound 5[a]



[a]Reaction conditions: A mixture **1** (0.5 mmol) and cyclic enaminone of substituted benzyl amine (**2**) (1 mmol) was reacted in CH_3CN as solvent (6 mL); reflux in open air equipped with a reflux condenser. [b]Gram scale yield.

containing electron-donating (4-Me, 3-OMe) and electron-withdrawing halo substitutions (2-Cl, 4-Cl, 3-Br, 4-F) provided the desired product spiromethanodibenzo[*b*,*e*]azepines smoothly. Again, cyclic enamines of furfurylamines produced the desired product with good yield (Table 3, entry **5h**). Also, cyclic enaminones of the aliphatic amine (butyl amine) was well explored toward spiromethanodibenzo[*b*,*e*]azepines derivatives (Table 3, entry **5i**).

The proposed mechanism of benzenodibenzo[b,f][1,5]-diazocine synthesis is very straight forward (Scheme 3). At first, Michael addition of 2 moles of cyclic enaminone with the two aldehyde groups of **1** takes place to form intermediate **A**

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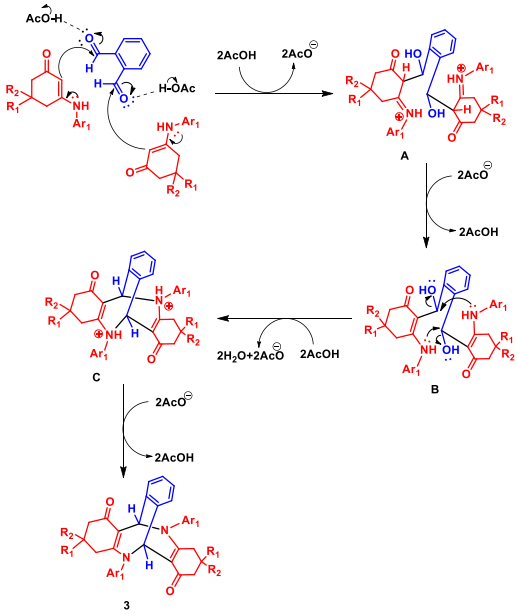
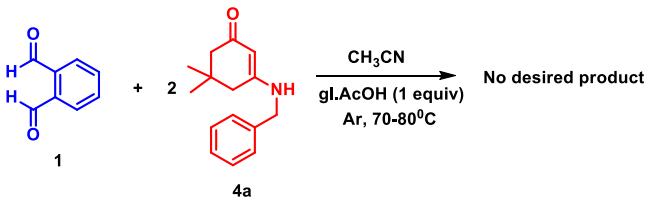
Scheme 3. Plausible Mechanism of the Reaction for 3



with the help of acid catalyst gl.AcOH. Then, intramolecular cyclization and subsequent deprotonation generate benzenodibenzo[b,f][1,5]diazocine derivatives.

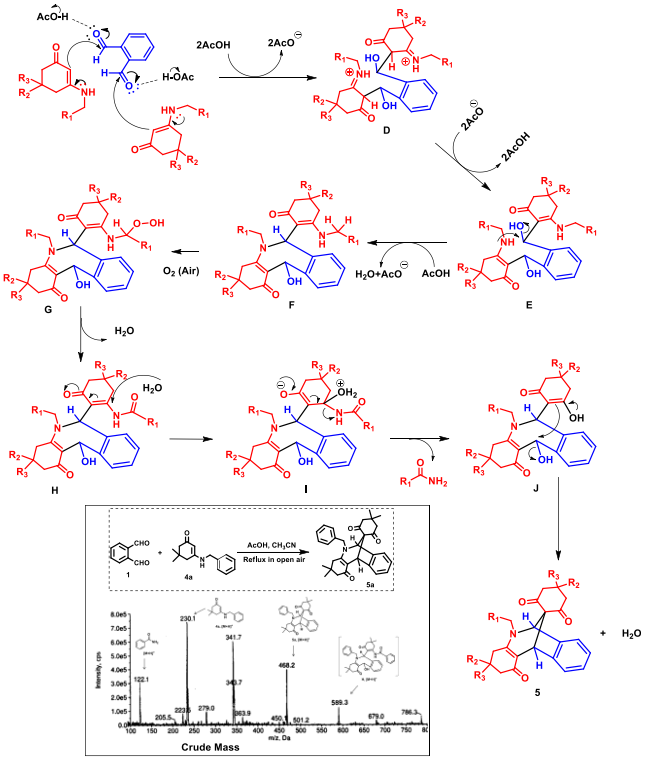
Next, to gain insight about the formation of spiromethanodibenzo[*b*,*e*]azepines derivatives, we carry out a control experiment by reacting **1** and 3-(benzylamino)-5,5-dimethylcyclohex-2-enone (**4a**) under an argon atmosphere, and it was noticed that no desired product was obtained in the argon atmosphere, indicating the aerial oxidation process during the course of the reaction (Scheme 4).

Scheme 4. Control Experiment



According to the outcome of the control experiment, a plausible mechanism is outlined in Scheme 5. At first, a moles of cyclic enaminone undergoes Michael addition with the two aldehyde groups of **1** to form intermediate **D** in the acid-catalyzed condition. Thereafter, intramolecular cyclization occurs toward seven-membered intermediate **F**. Then, aerial oxidation of one benzylic position of **F** generates intermediate **H** with the removal of one water molecule. The water molecule undergoes Michael addition with intermediate **H**, and subsequent elimination of one amide molecule generates intermediate **J**, which on intramolecular ring closure produces bridged spiromethanodibenzo[*b*,*e*]azepines derivatives (**5**). The different reaction pathway for cyclic enaminone of aliphatic amine can be described by ready C−H activation of sp^3 C−H through aerial oxidation. This C−H activation is fast enough that no cylization takes place to form eight-membered intermediate from **F**. Also due to strong electron withdrawal from the enone part of cyclic enaminone of aliphatic amine, availability of lone pair of N atom reduces. On the other hand,

Scheme 5. Plausible Mechanism of the Reaction for 5



for cyclic enaminone of aryl amine, there are two competitive electron pulls (both from the aryl moeity and the enone part) from the N lone pair; hence, availability of the N lone pair increases, and for the cyclic enamine of aryl amine, double cyclization takes place leading to eight-membered intermediate. In order to establish this unprecedented aerobic oxidation mediated pathway, we carry out a mass spectrometric analysis of the crude reaction mixture after few hours of reaction, and it was observed that benzamide and intermediate **H** were identified in crude mass (LC−MS) along with the unreacted reactant and the final product (Scheme 5). This study clearly indicates that the reaction goes through aerobic oxidation of one benzylic position.

The molecular structure of bridged dibenzo[b,f][1,5]-diazocines (**3**) and bridged spiromethanodibenzo[*b*,*e*]azepines (**5**) were fully characterized by ^{1}H, ^{13}C NMR spectroscopy and HRMS analyses. The identification of bridgehead protons of compounds **3** and **5** were done by ^{1}H−^{1}H COSY NMR experiment of compounds **3a** and **5e** (Supporting Information 1). The formation of compounds **3a** (**CCDC NO.** 2233860) and **5a** (**CCDC NO.** 2233874) were further confirmed by single-crystal X-ray diffraction analysis (Figure 1).

CONCLUSIONS

In conclusion, we have successfully developed substrate-specific construction of bridged dibenzo[b,f][1,5]diazocines and bridged spiromethanodibenzo[*b*,*e*]azepines. This reaction could be performed by following a straightforward procedure (only mixing the substrate and the acid catalyst) and is applicable to the synthesis of bridged seven- and eight-membered molecular architecture with various substituents on the aromatic ring. We note that this established methodology, in contrast with the previous approaches, refrains from using transition metal catalysts and and operates using readily

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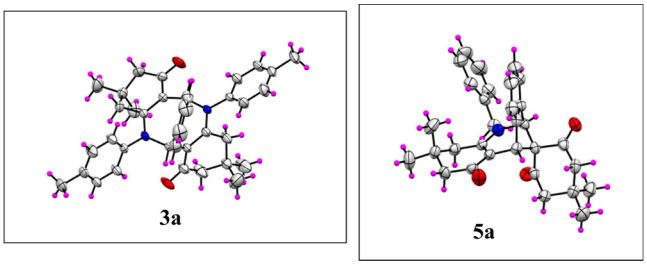

Figure 1. ORTEP representation of **3a** (**CCDC NO.** 2233860) and **5a** (**CCDC NO.** 2233874).

available starting materials. Because of the emerging appreciated importance of dibenzo[b,f][1,5]diazocines and dibenzo[*b*,*e*]azepines in supramolecular and pharmaceutical contexts, it is envisioned that this reaction would find wider applications and motivate further studies in due course.

EXPERIMENTAL SECTION

General Information of Materials and Instruments. All commercially available chemicals were purchased from Aldrich, USA or Spectrochem, India and used without further purification. All solvents were used as received. The progress of the reaction was checked by glass sheet precoated TLC with silica gel (with binder, 300 mesh, Spectrochem), and column chromatography was performed using silica gel (100−200 mesh). Bruker 300 and 400 MHz instruments were used for obtaining ^{1}H and ^{13}C NMR spectra at 300, 400, 75, and 100 MHz, respectively. Chemical shifts are reported in parts per million (ppm) downfield from an internal TMS (tetramethylsilane) reference. Coupling constants (*J*) are reported in hertz (Hz), and spin multiplicities are represented by the symbols s (singlet), brs (broad singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). HRMS with an ESI resource were acquired using a Waters XEVO-G2S Q TOF mass spectrometer. A 2400 Series II CHNS Analyzer, Perkin Elmer USA was used for elemental analyses. Melting points were recorded with an open capillary on an electrical melting point apparatus, and the single-crystal structures of the synthesized compounds were confirmed by an X-ray crystallography experiment on a Bruker SMART diffractometer.

General Procedure for the Synthesis of Compound ***3***. A typical procedure for the synthesis of compound **3a**. **1** (67 mg, 0.5 mmol), **2a** (229 mg, 1 mmol), and glacial acetic acid (20 mol %) were added to 6 mL of CH_3CN in a dry 10 mL round-bottomed flask equipped with a reflux condenser. Then, the reaction mixture was refluxed in an open atmosphere at 80−90 °C on water bath equipped with a reflux condenser for 5−6 h. After reaching the equilibrium, which was monitored by TLC, the reaction mixture was cooled to room temperature and diluted with 10 mL of water and extracted with EtOAc (3 × 10 mL). The organic layer was combined and washed with brine and dried over anhydrous Na_2SO_4. After the solvent was removed under reduced pressure, the crude product was purified by column chromatography using 100−200 mesh silica gel and petroleum ether−ethyl acetate mixture as the eluent to afford the desired product **3a** (244 mg, 88% yield).

The compounds **3b**−**3p** are synthesized according to same procedure as the general synthesis of **3**, where **1** and *β*-enaminone of aryl amine (**2**) are taken in 1:2 molar equivalent.

Gram Scale Synthesis of ***3a***. **1** (402 mg, 3 mmol), **2a** (1.37 g, 6 mmol), and glacial acetic acid (20 mol %) were added to 25 mL of CH_3CN in a dry 100 mL round-bottomed flask equipped with a reflux condenser. Then, the reaction mixture was refluxed in an open atmosphere at 80−90 °C on water bath equipped with a reflux condenser for 5−6 h. After reaching the equilibrium, which was monitored by TLC, the reaction mixture was cooled to room temperature and diluted with 100 mL of water and extracted with EtOAc (3 × 100 mL). The organic layer was combined and washed with brine and dried over anhydrous Na_2SO_4. After the solvent was removed under reduced pressure, the crude product was purified by column chromatography using 100−200 mesh silica gel and petroleum ether−ethyl acetate mixture as the eluent to afford the desired product **3a** (1.41 g, 85% yield).

Characterization of Compounds 3a−3p and 3am. *3,3,9,9-Tetramethyl-5,11-di-p-tolyl-3,4,5,6,9,10,11,12-octahydro-6,12-[1,2]benzenodibenzo[b,f][1,5]diazocine-1,7-(2H,8H)-dione (**3a**)*. White solid, yield: 244 mg, 88%; R_f: 0.3 (15% ethyl acetate in petroleum ether); m.p. = 257−258 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.06 (brs, 2H), 7.34 (brs, 2H), 7.17−7.14 (m, 2H), 6.91−6.85 (m, 4H), 6.10−6.04 (m, 4H), 2.37 (s, 6H), 2.33−2.26 (m, 4H), 2.03 (ABq, *J* = 15.9 Hz, 4H), 0.93 (s, 6H), 0.89 (s, 6H) ppm. ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) d: δ = 194.4, 160.8, 142.0, 136.6, 135.2, 130.2, 128.5, 127.8, 127.4, 126.9, 126.5, 108.3, 64.3, 50.3, 44.3, 31.5, 28.1, 26.8, 20.7 ppm. HRMS (ESI/TOF-Q) *m*/*z*: $[M + H]^+$ calcd for $[C_{38}H_{41}N_2O_2]$: 557.3168; found: 557.3169.

*3,3,9,9-Tetramethyl-5,11-diphenyl-3,4,5,6,9,10,11,12-octahydro-6,12-[1,2]benzenodibenzo[b,f][1,5]diazocine-1,7-(2H,8H)-dione (**3b**)*. White solid, yield: 235 mg, 89%; R_f: 0.3 (15% ethyl acetate in petroleum ether); m.p. = 250−251 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.22 (d, *J* = 8 Hz, 2H), 7.56 (t, *J* = 8 Hz, 2H), 7.31−7.27 (m, 2H), 7.16−7.11 (m, 4H), 6.86−6.84 (m, 2H), 6.21 (d, *J* = 8 Hz, 2H), 6.07 (s, 2H), 2.37−2.27 (m, 4H), 2.16 (d, *J* = 16 Hz, 2H), 1.90 (d, *J* = 16 Hz, 2H), 0.93 (s, 6H), 0.89 (s, 6H) ppm. ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) d: δ = 195.1, 161.1, 144.8, 135.3, 130.0, 128.5, 127.9, 127.6, 127.1, 126.9, 108.9, 64.6, 50.6, 44.6, 31.9, 28.5, 27.2 ppm. HRMS (ESI/TOF-Q) *m*/*z*: $[M + H]^+$ calcd for $[C_{36}H_{37}N_2O_2]$: 529.2855; found: 529.2858.

*3,3,9,9-Tetramethyl-5,11-di-m-tolyl-3,4,5,6,9,10,11,12-octahydro-6,12-[1,2]benzenodibenzo[b,f][1,5]diazocine-1,7-(2H,8H)-dione (**3c**)*. White solid, yield: 225.3 mg, 81%; R_f: 0.3 (15% ethyl acetate in petroleum ether); m.p. = 236−237 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.10−7.99 (m, 2H), 7.43 (brs, 1H), 7.15−7.08 (m, 4H), 7.01−6.99 (m, 1H), 6.86 (s, 2H), 6.06−5.98 (m, 4H), 2.52 (s, 3H), 2.38−2.26 (m, 4H), 2.20−2.16 (m, 4H), 1.90 (d, *J* = 15.9 Hz, 2H), 1.77 (s, 1H), 0.94 (s, 6H), 0.91 (s, 6H) ppm. ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) d: δ = 195.2, 161.1, 144.9, 135.6, 128.8, 127.9, 127.8, 126.9, 125.5, 124.8, 109.3, 64.8, 50.9, 44.8, 32.0, 28.5, 27.3 ppm. HRMS (ESI/TOF-Q) *m*/*z*: $[M + H]^+$ calcd for $[C_{38}H_{41}N_2O_2]$: 557.3168; found: 557.3176.

*5,11-Bis(4-Isopropylphenyl)-3,3,9,9-tetramethyl-3,4,5,6,9,10,11,12-octahydro-6,12-[1,2]benzenodibenzo[b,f]-[1,5]diazocine-1,7(2H,8H)-dione (**3d**)*. White solid, yield: 260 mg, 85%; R_f: 0.3 (15% ethyl acetate in petroleum ether); m.p. = 253−254 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.02 (brs, 2H), 7.40 (brs, 2H), 7.20−7.17 (m, 2H), 6.97−6.92 (brs, 2H), 6.91−6.88 (m, 2H), 6.14−6.05 (m, 4H), 2.93 (quintate, *J* = 6.9 Hz, 2H), 2.33 (ABq, *J* = 16.5 Hz, 4H), 2.12 (d, *J* = 15.9 Hz, 2H), 1.92 (d, *J* = 15.9 Hz, 2H), 1.29 (s, 6H), 1.26 (s, 6H), 0.94 (s, 6H), 0.90 (s, 6H) ppm. ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$)

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d: δ = 194.6, 161.6, 147.9, 142.5, 135.6, 127.9, 127.0, 108.4, 64.6, 50.5, 44.7, 33.7, 31.9, 28.6, 27.2, 23.9, 23.8 ppm. HRMS (ESI/TOF-Q) *m/z*: $[M + H]^+$ calcd for $[C_{42}H_{49}N_2O_2]$: 613.3794; found: 613.3799.

5,11-Bis(3,4-dimethylphenyl)-3,3,9,9-tetramethyl-3,4,5,6,9,10,11,12-octahydro-6,12-[1,2]benzenodibenzo[b,f][1,5]diazocine-1,7(2H,8H)-dione (**3e**). White solid, yield: 233 mg, 80%; R_f: 0.3 (15% ethyl acetate in petroleum ether); m.p. = 230−231 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.02 (s, 1H), 7.90−7.87 (m, 1H), 7.28 (s, 1H), 7.15 (brs, 2H), 6.87 (brs, 3H), 6.04−5.99 (m, 3H), 5.90 (d, *J* = 6.9 Hz, 1H), 2.42 (s, 3H), 2.31−2.27 (m, 10H), 2.17 (d, *J* = 16.2 Hz, 2H), 2.06 (s, 3H), 1.91 (d, *J* = 15.9 Hz, 2H), 0.94 (s, 6H), 0.90 (s, 6H) ppm. ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) d: δ = 194.9, 161.6, 142.6, 138.5, 136.7, 135.7, 131.1, 129.4, 129.1, 128.5, 127.8, 127.0, 125.7, 125.0, 108.6, 64.9, 50.7, 44.8, 32.0, 28.7, 27.3, 20.1, 19.5 ppm. HRMS (ESI/TOF-Q) *m/z*: $[M + H]^+$ calcd for $[C_{40}H_{45}N_2O_2]$: 585.3481; found: 585.3488.

3,3,9,9-Tetramethyl-5,11-di-o-tolyl-3,4,5,6,9,10,11,12-octahydro-6,12-[1,2]benzenodibenzo[b,f][1,5]diazocine-1,7-(2H,8H)-dione (**3f**). White solid, yield: 211 mg, 76%; R_f: 0.3 (15% ethyl acetate in petroleum ether); m.p. = 212−213 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.13 (d, *J* = 7.8 Hz, 2H), 7.40 (t, *J* = 7.2 Hz, 2H), 7.32−7.26 (m, 1H), 7.24−7.19 (m, 3H), 7.04 (d, *J* = 7.5 Hz, 2H), 6.95−6.93 (m, 2H), 6.06 (s, 2H), 2.43−2.28 (m, 10H), 1.91 (ABq, *J* = 16.2 Hz, 4H), 0.95 (s, 6H), 0.90 (s, 6H) ppm. ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) d: δ = 194.4, 162.0, 143.5, 135.8, 135.5, 130.6, 129.9, 128.4, 127.8, 127.7, 126.8, 106.9, 65.1, 50.4, 43.9, 31.5, 28.4, 27.9, 16.2 ppm. HRMS (ESI/TOF-Q) *m/z*: $[M + H]^+$ calcd for $[C_{38}H_{41}N_2O_2]$: 557.3168; found: 557.3175.

5,11-Bis(4-(tert-butyl)phenyl)-3,3,9,9-tetramethyl-3,4,5,6,9,10,11,12-octahydro-6,12-[1,2]benzenodibenzo[b,f][1,5]diazocine-1,7(2H,8H)-dione (**3g**). White solid, yield: 268.9 mg, 84%; R_f: 0.3 (15% ethyl acetate in petroleum ether); m.p. = 245−246 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.00−7.93 (m, 2H), 7.58−7.48 (m, 2H), 7.21−7.13 (m, 4H), 6.92−6.90 (m, 2H), 6.15−6.06 (m, 4H), 2.34 (ABq, *J* = 16.8 Hz, 4H), 2.13 (d, *J* = 15.6 Hz, 2H), 1.92 (d, *J* = 15.9 Hz, 2H), 1.36−1.34 (m, 18H), 0.95 (s, 6H), 0.90 (s, 6H) ppm. ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) d: δ = 194.6, 161.7, 150.3, 142.2, 135.7, 127.9, 127.1, 108.3, 64.5, 50.5, 44.7, 34.6, 32.0, 31.4, 28.7, 27.2 ppm. HRMS (ESI/TOF-Q) *m/z*: $[M + H]^+$ calcd for $[C_{44}H_{53}N_2O_2]$: 641.4107; found: 641.4109.

5,11-Bis(3-chloro-4-methoxyphenyl)-3,3,9,9-tetramethyl-3,4,5,6,9,10,11,12-octahydro-6,12-[1,2]benzenodibenzo[b,f][1,5]diazocine-1,7(2H,8H)-dione (**3h**). White solid, yield: 259 mg, 79%; R_f: 0.3 (20% ethyl acetate in petroleum ether); m.p. = 261−262 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.36 (s, 1H), 8.06 (d, *J* = 8.8 Hz, 1H), 7.20 (brs, 2H), 7.09 (d, *J* = 8.8 Hz, 1H), 6.89 (s, 2H), 6.65 (d, *J* = 8.8 Hz, 1H), 6.26 (s, 1H), 6.07−6.04 (m, 1H), 5.95 (s, 2H), 3.96−3.89 (m, 6H), 2.38−2.29 (m, 4H), 2.18−2.12 (m, 2H), 1.89 (d, *J* = 16 Hz, 2H), 0.94 (s, 6H), 0.92 (s, 6H) ppm. ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) d: δ = 195.1, 171.1, 160.7, 154.1, 137.9, 135.2, 130.3, 129.1, 128.2, 127.0, 126.8, 123.5, 121.6, 112.8, 111.0, 109.2, 65.0, 60.3, 56.3, 56.2, 50.5, 44.7, 32.0, 28.6, 28.5, 27.3, 27.1, 21.0, 14.1 ppm. HRMS (ESI/TOF-Q) *m/z*: $[M + H]^+$ calcd for $[C_{38}H_{39}Cl_2N_2O_4]$: 657.2287; found: 657.2295.

5,11-Bis(3,4-dichlorophenyl)-3,3,9,9-tetramethyl-3,4,5,6,9,10,11,12-octahydro-6,12-[1,2]benzenodibenzo[b,f][1,5]diazocine-1,7(2H,8H)-dione (**3i**). White solid, yield: 259 mg, 78%; R_f: 0.3 (20% ethyl acetate in petroleum ether); m.p. = 258−259 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.17−8.06 (m, 1H), 7.66−7.47 (m, 2H), 7.20 (brs, 3H), 6.89−6.87 (m, 2H), 6.32 (brs, 1H), 6.05−5.97 (m, 3H), 2.34 (s, 4H), 2.21−2.17 (m, 2H), 1.87 (d, *J* = 15.6 Hz, 2H), 0.94 (s, 12H) ppm. ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) d: δ = 195.5, 167.6, 160.3, 143.9, 139.7, 139.0, 134.9, 133.0, 132.6, 131.4, 130.7, 130.4, 130.1, 128.7, 128.5, 127.6, 127.1, 124.4, 122.7, 120.6, 118.2, 110.1, 65.1, 53.4, 50.7, 50.5, 44.7, 32.2, 28.4, 27.3 ppm. HRMS (ESI/TOF-Q) *m/z*: $[M + H]^+$ calcd for $[C_{36}H_{33}Cl_4N_2O_2]$: 665.1296; found: 665.1299.

3,3,9,9-Tetramethyl-5,11-bis(4-nitrophenyl)-3,4,5,6,9,10,11,12-octahydro-6,12-[1,2]benzenodibenzo[b,f][1,5]diazocine-1,7(2H,8H)-dione (**3j**). White solid, yield: 231.8 mg, 75%; R_f: 0.3 (25% ethyl acetate in petroleum ether); m.p. = 249−250 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.32−7.94 (m, 6H), 7.70−7.53 (m, 1H), 7.16−7.14 (m, 2H), 6.83−6.80 (m, 2H), 6.35 (brs, 1H), 6.12 (s, 2H), 2.37 (s, 4H), 2.28 (d, *J* = 15.9 Hz, 2H), 1.87 (d, *J* = 15.9 Hz, 2H), 0.96 (s, 6H), 0.95 (s, 6H) ppm. ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) d: δ = 196.0, 159.9, 150.2, 146.0, 134.8, 128.7, 128.4, 126.9, 125.1, 111.7, 65.4, 50.8, 44.9, 32.4, 28.2, 27.3 ppm. HRMS (ESI/TOF-Q) *m/z*: $[M + H]^+$ calcd for $[C_{36}H_{35}N_4O_6]$: 619.2556; found: 619.2561.

3,3,9,9-Tetramethyl-5,11-bis(3-nitrophenyl)-3,4,5,6,9,10,11,12-octahydro-6,12-[1,2]benzenodibenzo[b,f][1,5]diazocine-1,7(2H,8H)-dione (**3k**). White solid, yield: 225 mg, 73%; R_f: 0.3 (20% ethyl acetate in petroleum ether); m.p. = 238−239 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.74−8.51 (m, 2H), 8.18−8.15 (m, 2H), 8.05−7.95 (m, 1H), 7.69−7.56 (m, 2H), 7.19−7.16 (m, 3H), 6.86−6.83 (m, 2H), 6.07 (s, 2H), 2.37 (s, 4H), 2.22 (d, *J* = 15.9 Hz, 2H), 1.86 (d, *J* = 15.9 Hz, 2H), 0.95−0.86 (s, 12H) ppm. ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) d: δ = 195.7, 159.9, 145.6, 134.7, 132.8, 130.0, 128.7, 126.9, 124.4, 122.0, 118.7, 110.8, 65.2, 50.6, 44.8, 32.3, 31.5, 28.4, 27.2 ppm. HRMS (ESI/TOF-Q) *m/z*: $[M + H]^+$ calcd for $[C_{36}H_{35}N_4O_6]$: 619.2556; found: 619.2566.

5,11-Bis(3-methoxyphenyl)-3,3,9,9-tetramethyl-3,4,5,6,9,10,11,12-octahydro-6,12-[1,2]benzenodibenzo[b,f][1,5]diazocine-1,7(2H,8H)-dione (**3l**). White solid, yield: 241.2 mg, 82%; R_f: 0.3 (20% ethyl acetate in petroleum ether); m.p. = 244−245 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.93 (brs, 1H), 7.78 (brs, 1H), 7.45 (brs, 1H), 7.15 (q, *J* = 3.3 Hz, 2H), 7.01 (brs, 1H), 6.86−6.83 (m, 4H), 6.08 (s, 2H), 5.79−5.74 (m, 2H), 4.01 (s, 3H), 3.61 (s, 3H), 2.39−2.32 (m, 4H), 2.27−2.19 (m, 2H), 1.94 (d, *J* = 15.9 Hz, 2H), 0.95 (s, 6H), 0.91 (s, 6H) ppm. ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) d: δ = 195.2, 161.1, 146.0, 135.6, 127.9, 127.0, 120.0, 114.3, 112.7, 109.2, 64.7, 55.6, 50.9, 44.7, 32.0, 28.4, 27.3 ppm. HRMS (ESI/TOF-Q) *m/z*: $[M + H]^+$ calcd for $[C_{38}H_{41}N_2O_4]$: 589.3066; found: 589.3070.

5,11-Bis(4-methoxyphenyl)-3,3,9,9-tetramethyl-3,4,5,6,9,10,11,12-octahydro-6,12-[1,2]benzenodibenzo[b,f][1,5]diazocine-1,7(2H,8H)-dione (**3m**). White solid, yield: 250 mg, 85%; R_f: 0.3 (20% ethyl acetate in petroleum ether); m.p. = 234−235 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11−8.08 (m, 2H), 7.19−7.17 (m, 2H), 7.07−7.05 (m, 2H), 6.89−6.87 (m, 2H), 6.66−6.63 (m, 2H), 6.15−6.12 (m, 2H), 6.01 (s, 2H), 3.83 (s, 6H), 2.37−2.35 (m, 1H), 2.31 (d, *J* = 7.2 Hz, 3H), 2.12 (d, *J* = 16 Hz, 2H), 1.91 (d, *J* = 15.6 Hz, 2H), 0.94 (s, 6H), 0.90 (s, 6H) ppm. ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) d: δ = 194.9, 161.2, 158.4, 138.0, 135.7, 129.8, 128.6, 127.8, 126.9, 115.0, 113.5, 108.6, 64.9, 55.4, 50.8, 44.7, 31.9,

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28.6, 27.3 ppm. HRMS (ESI/TOF-Q) *m/z*: $[M + H]^+$ calcd for $[C_{38}H_{41}N_2O_4]$: 589.3066; found: 589.3069.

(6R)-3,3,9,9-Tetramethyl-5,11-bis(4-(trifluoromethyl)-phenyl)-3,4,5,6,9,10,11,12-octahydro-6,12-[1,2]-benzenodibenzo[b,f][1,5]diazocine-1,7(2H,8H)-dione (**3n**). White solid, yield: 252 mg, 76%; R_f: 0.3 (20% ethyl acetate in petroleum ether); m.p. = 207−208 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.42 (brs, 1H), 8.06 (d, J = 8.4 Hz, 1H), 7.83−7.79 (m, 1H), 7.71 (d, J = 8.8 Hz, 1H), 7.57 (d, J = 8 Hz, 1H), 7.47−7.36 (m, 2H), 7.22−7.20 (m, 2H), 6.88−6.86 (m, 2H), 6.33 (brs, 1H), 6.07 (s, 2H), 2.48−2.38 (m, 4H), 2.22 (s, 1H), 2.18 (s, 1H), 1.89 (d, J = 16 Hz, 2H), 0.96 (s, 6H), 0.95 (s, 6H) ppm. ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) d: δ = 195.1, 161.7, 147.4, 139.8, 134.8, 132.6, 129.5 (C−F, $2J_{C-F}$ = 32.7 Hz), 128.6, 127.1, 126.3 (C−F, $3J_{C-F}$ = 3.6 Hz), 123.8 (C−F, $1J_{C-F}$ = 270.6 Hz), 124.4, 122.7, 118.6, 109.8, 65.0, 50.5, 50.2, 44.8, 32.2, 28.4, 27.2 ppm. HRMS (ESI/TOF-Q) *m/z*: $[M + H]^+$ calcd for $[C_{38}H_{35}F_6N_2O_2]$: 665.2602; found: 665.2608.

5,11-Di-p-tolyl-3,4,5,6,9,10,11,12-octahydro-6,12-[1,2]-benzenodibenzo[b,f][1,5]diazocine-1,7(2H,8H)-dione (**3o**). White solid, yield: 175 mg, 70%; R_f: 0.3 (15% ethyl acetate in petroleum ether); m.p. = 210−211 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.44 (d, J = 7.2 Hz, 2H), 7.35−7.30 (m, 2H), 7.25−7.23 (m, 3H), 7.13 (d, J = 7.2 Hz, 2H), 7.04 (d, J = 7.5 Hz, 3H), 6.17 (s, 2H), 2.43 (s, 6H), 2.30−2.19 (m, 2H), 2.07−2.03 (m, 3H), 1.88 (brs, 5H), 1.84−1.76 (m, 2H) ppm. ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) d: δ = 191.4, 154.3, 144.4, 138.4, 138.0, 136.6, 130.5, 128.8, 127.9, 126.9, 119.6, 119.1, 109.8, 62.8, 40.4, 40.0, 35.8, 26.9, 21.6, 21.1 ppm. HRMS (ESI/TOF-Q) *m/z*: $[M + H]^+$ calcd for $[C_{34}H_{33}N_2O_2]$: 501.2542; found: 501.2549.

(6R)-5,11-Bis(4-bromophenyl)-3,4,5,6,9,10,11,12-octahydro-6,12-[1,2]benzenodibenzo[b,f][1,5]diazocine-1,7-(2H,8H)-dione (**3p**). White solid, yield: 207 mg, 66%; R_f: 0.3 (15% ethyl acetate in petroleum ether); m.p. = 210−211 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.73 (m, 1H), 7.59 (d, J = 7.8 Hz, 3H), 7.43 (d, J = 6.6 Hz, 1H), 7.34−7.21 (m, 4H), 7.10 (d, J = 7.2 Hz, 1H), 7.04 (d, J = 7.8 Hz, 2H), 6.15 (s, 1H), 6.03 (s, 1H), 2.45−2.40 (m, 1H), 2.34 (m, 1H), 2.27−2.12 (m, 3H), 2.06−2.04 (m, 3H), 1.90 (brs, 1H), 1.81−1.74 (m, 3H) ppm. ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) d: δ = 191.8, 153.0, 144.5, 139.7, 136.3, 133.1, 129.8, 128.9, 128.8, 127.0, 122.0, 119.5, 119.1, 110.9, 64.5, 37.1, 36.0, 27.7, 26.9, 21.7 ppm. HRMS (ESI/TOF-Q) *m/z*: $[M + H]^+$ calcd for $[C_{32}H_{27}Br_2N_2O_2]$: 629.0439; found: 629.0447.

5-(4-Methoxyphenyl)-3,3,9,9-tetramethyl-11-(p-tolyl)-3,4,5,6,9,10,11,12-octahydro-6,12-[1,2]benzenodibenzo[b,f]-[1,5]diazocine-1,7(2H,8H)-dione (**3am**). White solid, yield: 114 mg, 40%; R_f: 0.3 (20% ethyl acetate in petroleum ether); m.p. = 239−240 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10−8.05 (m, 2H), 7.35−7.32 (m, 1H), 7.18−7.13 (m, 2H), 7.07−7.04 (m, 1H), 6.91−6.85 (m, 3H), 6.64−6.61 (m, 1H), 6.14−6.09 (m, 2H), 6.04 (s, 1H), 6.00 (s, 1H), 3.82 (s, 3H), 2.36 (s, 3H), 2.30 (d, J = 6.8 Hz, 3H), 2.25−2.09 (m, 3H), 1.92−1.87 (m, 2H), 0.93−0.92 (m, 6H), 0.88 (s, 6H) ppm. ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) d: δ = 194.9, 194.8, 161.1, 161.0, 158.4, 142.4, 137.9, 136.9, 135.7, 135.6, 130.6, 129.8, 128.9, 128.6, 128.3, 127.8, 127.4, 126.9, 114.9, 113.4, 108.8, 108.6, 64.8, 64.7, 55.3, 50.8, 50.7, 44.6, 31.9, 31.8, 28.5, 27.2, 21.1 ppm. HRMS (ESI/TOF-Q) *m/z*: $[M + H]^+$ calcd for $[C_{38}H_{41}N_2O_3]$: 573.3117; found: 573.3119.

Procedure for the Synthesis of Compound **5a**. A typical procedure for the synthesis of compound **5a**. **1** (67 mg, 0.5 mmol), **4a** (229 mg, 1 mmol), and glacial acetic acid (20 mol %) were added to 6 mL of CH_3CN in a dry 10 mL round-bottomed flask equipped with a reflux condenser. Then, the reaction mixture was refluxed in an open atmosphere at 80−90 °C on water bath equipped with a reflux condenser for 5−6 h. After reaching the equilibrium, which was monitored by TLC, the reaction mixture was cooled to room temperature and diluted with 10 mL of water and extracted with EtOAc (3 × 10 mL). The organic layer was combined and washed with brine and dried over anhydrous Na_2SO_4. After the solvent was removed under reduced pressure, the crude product was purified by column chromatography using 100−200 mesh silica gel and petroleum ether−ethyl acetate mixture as the eluent to afford the desired product **5a** (200 mg, 86% yield).

The compounds **5b**−**5j** are synthesized according to same procedure as the general synthesis of **3** where **1** and β-enaminone of aliphatic amine (**4**) are taken in 1:2 molar equivalent.

Gram Scale Synthesis of **5a**. **1** (402 mg, 3 mmol), **4a** (1.37 g, 6 mmol) and glacial acetic acid (20 mol %) were added to 25 mL of CH_3CN in a dry 100 mL round-bottomed flask equipped with a reflux condenser. Then, the reaction mixture was refluxed in an open atmosphere at 80−90 °C on water bath equipped with a reflux condenser for 5−6 h. After reaching the equilibrium, which was monitored by TLC, the reaction mixture was cooled to room temperature and diluted with 100 mL of water and extracted with EtOAc (3 × 100 mL). The organic layer was combined and washed with brine and dried over anhydrous Na_2SO_4. After the solvent was removed under reduced pressure, the crude product was purified by column chromatography using 100−200 mesh silica gel and petroleum ether−ethyl acetate mixture as the eluent to afford the desired product **5a** (1.12 g, 80% yield).

Characterization of Compounds 5a−5j. *5-Benzyl-3,3,4′,4′-tetramethyl-3,4,5,6-tetrahydro-1H-spiro[6,11-methanodibenzo[b,e]azepine-12,1′-cyclohexane]-1,2′,6′(2H,11H)-trione* (**5a**). White solid, yield: 200 mg, 86%; R_f: 0.3 (30% ethyl acetate in petroleum ether); m.p. = 209−210 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38−7.36 (m, 3H), 7.20−7.17 (m, 2H), 7.15−7.09 (m, 2H), 7.00−6.95 (m, 1H), 6.48 (d, J = 7.5 Hz, 1H), 5.06 (s, 1H), 4.92 (d, J = 16.2 Hz, 1H), 4.74 (s, 1H), 4.62 (d, J = 16.5 Hz, 1H), 3.12 (d, J = 13.5 Hz, 1H), 3.03 (d, J = 12.3 Hz, 1H), 2.34−2.05 (m, 6H), 1.26 (s, 3H), 0.98 (s, 3H), 0.83 (s, 3H), 0.81 (s, 3H) ppm. ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) d: δ = 203.7, 202.9, 190.1, 156.3, 141.4, 139.0, 136.0, 128.7, 128.6, 128.0, 126.8, 122.8, 121.0, 74.6, 63.9, 55.5, 52.1, 51.5, 49.0, 47.0, 32.7, 31.1, 30.7, 28.8, 27.9, 26.3 ppm. HRMS (ESI/TOF-Q) *m/z*: $[M + H]^+$ calcd for $[C_{31}H_{34}NO_3]$: 468.2538; found: 468.2542.

5-(3-Methoxybenzyl)-3,3,4′,4′-tetramethyl-3,4,5,6-tetrahydro-1H-spiro[6,11-methanodibenzo[b,e]azepine-12,1′-cyclohexane]-1,2′,6′(2H,11H)-trione (**5b**). White solid, yield: 201 mg, 81%; R_f: 0.3 (30% ethyl acetate in petroleum ether); m.p. = 200−201 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.28 (t, J = 4.2 Hz, 1H), 7.15−7.10 (m, 2H), 7.04−7.00 (m, 1H), 6.88 (d, J = 7.8 Hz, 1H), 6.78 (d, J = 7.5 Hz, 1H), 6.69 (s, 1H), 6.63 (d, J = 7.2 Hz, 1H), 5.06 (s, 1H), 4.88 (d, J = 16.5 Hz, 1H), 4.74 (s, 1H), 4.60 (d, J = 16.5 Hz, 1H), 3.71 (s, 3H), 3.12 (d, J = 13.5 Hz, 1H), 3.03 (d, J = 12.3 Hz, 1H), 2.30−2.05 (m, 6H), 1.26 (s, 3H), 0.97 (s, 3H), 0.83 (s, 3H), 0.79 (s, 3H) ppm. ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) d: δ = 203.7, 202.8, 190.4, 159.9, 156.2, 141.4, 139.0, 137.7, 129.8, 126.8, 122.9, 121.0, 119.9, 113.9, 112.7, 106.5, 74.5, 64.1, 55.5, 55.1,

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52.0, 51.5, 49.1, 47.0, 40.0, 32.7, 31.1, 30.7, 28.9, 27.7, 26.3 ppm. HRMS (ESI/TOF-Q) *m/z*: $[M + H]^+$ calcd for $[C_{32}H_{36}NO_4]$: 498.2644; found: 498.2648.

5-(2-Chlorobenzyl)-3,3,4′,4′-tetramethyl-3,4,5,6-tetrahydro-1H-spiro[6,11-methanodibenzo[b,e]azepine-12,1′-cyclohexane]-1,2′,6′(2H,11H)-trione (**5c**). White solid, yield: 198 mg, 79%; R_f: 0.3 (30% ethyl acetate in petroleum ether); m.p. = 214−215 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45−7.42 (m, 1H), 7.34−7.30 (m, 1H), 7.29−7.24 (m, 1H), 7.23−7.20 (m, 1H), 7.19−7.16 (m, 2H), 7.07−7.02 (m, 1H), 6.65 (d, J = 7.5 Hz, 1H), 5.08 (s, 1H), 4.93 (d, J = 17.1 Hz, 1H), 4.76−4.70 (m, 2H), 3.12 (d, J = 13.5 Hz, 1H), 3.04 (d, J = 12.6 Hz, 1H), 2.26−2.05 (m, 6H), 1.27 (s, 3H), 0.96 (s, 3H), 0.84 (s, 3H), 0.79 (s, 3H) ppm. ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) d: δ = 203.6, 202.8, 190.6, 156.6, 141.4, 139.0, 133.7, 133.3, 130.0, 129.8, 127.0, 126.9, 122.7, 121.2, 106.9, 74.6, 64.1, 53.5, 52.1, 51.5, 49.2, 47.0, 39.7, 32.7, 31.1, 30.7, 28.6, 27.9, 26.3 ppm. HRMS (ESI/TOF-Q) *m/z*: $[M + H]^+$ calcd for $[C_{31}H_{33}ClNO_3]$: 502.2149; found: 502.2154.

5-(4-Chlorobenzyl)-3,3,4′,4′-tetramethyl-3,4,5,6-tetrahydro-1H-spiro[6,11-methanodibenzo[b,e]azepine-12,1′-cyclohexane]-1,2′,6′(2H,11H)-trione (**5d**). White solid, yield: 210 mg, 84%; R_f: 0.3 (30% ethyl acetate in petroleum ether); m.p. = 220−221 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35−7.32 (m, 2H), 7.15−7.11 (m, 4H), 7.05−7.01 (m, 1H), 6.63 (d, J = 7.6 Hz, 1H), 5.05 (s, 1H), 4.83 (d, J = 16.8 Hz, 1H), 4.69 (s, 1H), 4.59 (d, J = 16.4 Hz, 1H), 3.11 (d, J = 13.4 Hz, 1H), 3.02 (d, J = 12.4 Hz, 1H), 2.27−2.11 (m, 5H), 2.05−2.01 (m, 1H),1.25 (s, 3H), 0.96 (s, 3H), 0.82 (s, 3H), 0.79 (s, 3H) ppm. ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) d: δ = 203.5, 202.7, 190.4, 155.9, 141.3, 138.8, 134.6, 133.7, 129.0, 128.8, 128.7, 126.9, 122.5, 121.1, 106.7, 74.4, 63.9, 54.7, 53.3, 51.9, 51.4, 49.0, 48.9, 39.9, 32.6, 31.0, 30.6, 28.5, 27.9, 26.1 ppm. HRMS (ESI/TOF-Q) *m/z*: $[M + H]^+$ calcd for $[C_{31}H_{33}ClNO_3]$: 502.2149; found: 502.2152.

3,3,4′,4′-Tetramethyl-5-(4-methylbenzyl)-3,4,5,6-tetrahydro-1H-spiro[6,11-methanodibenzo[b,e]azepine-12,1′-cyclohexane]-1,2′,6′(2H,11H)-trione (**5e**). White solid, yield: 211.7 mg, 88%; R_f: 0.3 (30% ethyl acetate in petroleum ether); m.p. = 216−217 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.18 (d, J = 8.1 Hz, 2H), 7.14−7.12 (m, 2H), 7.08 (d, J = 8.1 Hz, 2H), 7.03−6.97 (m, 1H), 6.54 (d, J = 7.5 Hz, 1H), 5.06 (s, 1H), 4.86 (d, J = 16.2 Hz, 1H), 4.74 (s, 1H), 4.58 (d, J = 16.2 Hz, 1H), 3.12 (d, J = 13.8 Hz, 1H), 3.04 (d, J = 12.3 Hz, 1H), 2.40 (s, 3H), 2.33−2.08 (m, 6H), 1.27 (s, 3H), 0.98 (s, 3H), 0.84 (s, 3H), 0.82 (s, 3H) ppm. ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) d: δ = 203.7, 202.8, 190.3, 156.1, 141.4, 139.0, 137.7, 132.9, 129.3, 128.6, 127.9, 126.8, 122.9, 120.9, 106.3, 74.5, 63.7, 55.2, 52.1, 51.5, 49.1, 47.1, 40.1, 32.7, 31.1, 30.7, 28.8, 27.9, 26.3, 21.1 ppm. HRMS (ESI/TOF-Q) *m/z*: $[M + H]^+$ calcd for $[C_{32}H_{36}NO_3]$: 482.2695; found: 482.2699.

5-(3-Bromobenzyl)-3,3,4′,4′-tetramethyl-3,4,5,6-tetrahydro-1H-spiro[6,11-methanodibenzo[b,e]azepine-12,1′-cyclohexane]-1,2′,6′(2H,11H)-trione (**5f**). White solid, yield: 209 mg, 77%; R_f: 0.3 (30% ethyl acetate in petroleum ether); m.p. = 221−223 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35 (d, J = 8.4 Hz, 2H), 7.15−7.12 (m, 4H), 7.07−7.01 (m, 1H), 6.64 (d, J = 7.5 Hz, 1H), 5.05 (s, 1H), 4.83 (d, J = 16.5 Hz, 1H), 4.69 (s, 1H), 4.60 (d, J = 16.8 Hz, 1H), 3.12 (d, J = 13.5 Hz, 1H), 3.03 (d, J = 12.3 Hz, 1H), 2.28−2.13 (m, 5H), 2.06 (s, 1H), 1.26 (s, 3H), 0.96 (s, 3H), 0.83 (s, 3H), 0.80 (s, 3H) ppm. ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) d: δ = 203.5, 202.8, 190.5, 155.9, 141.3, 138.9, 134.7, 133.7, 129.1, 128.8, 128.7, 126.9, 122.6, 121.1, 106.7, 74.5, 63.9, 54.7, 52.0, 51.4, 49.0, 46.9, 40.0, 32.7, 31.0, 30.7, 28.6, 27.9, 26.2 ppm. HRMS (ESI/TOF-Q) *m/z*: $[M + H]^+$ calcd for $[C_{31}H_{33}BrNO_3]$: 546.1644; found: 546.1647.

5-(4-Fluorobenzyl)-3,3,4′,4′-tetramethyl-3,4,5,6-tetrahydro-1H-spiro[6,11-methanodibenzo[b,e]azepine-12,1′-cyclohexane]-1,2′,6′(2H,11H)-trione (**5g**). White solid, yield: 191 mg, 79%; R_f: 0.3 (30% ethyl acetate in petroleum ether); m.p. = 205−206 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.20−7.14 (m, 4H), 7.10−7.02 (m, 3H), 6.56 (d, J = 7.2 Hz, 1H), 5.05 (s, 1H), 4.85 (d, J = 16.2 Hz, 1H), 4.70 (s, 1H), 4.59 (d, J = 16.2 Hz, 1H), 3.12 (d, J = 13.5 Hz, 1H), 3.03 (d, J = 12.3 Hz, 1H), 2.31−2.24 (m, 2H), 2.18 (d, J = 4.2 Hz, 3H), 2.13−2.10 (m, 1H), 1.27 (s, 3H), 0.98 (s, 3H), 0.82 (s, 6H) ppm. ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) d: δ = 203.6, 202.8, 190.4, 162.4 (C−F, $1J_{C-F}$ = 245.2 Hz), 155.8, 141.3, 138.9, 131.8 (C−F, $3J_{C-F}$ = 3.1 Hz), 130.9, 129.5 (C−F, $3J_{C-F}$ = 8.1 Hz), 128.7, 126.9, 122.5, 121.1, 115.6 (C−F, $2J_{C-F}$ = 21.4 Hz), 106.5, 74.5, 63.7, 54.5, 52.0, 51.4, 49.0, 47.0, 40.0, 32.7, 31.0, 30.7, 28.7, 28.0, 26.2 ppm. HRMS (ESI/TOF-Q) *m/z*: $[M + H]^+$ calcd for $[C_{31}H_{33}FNO_3]$: 486.2444; found: 486.2448.

5-(Furan-2-ylmethyl)-3,3,4′,4′-tetramethyl-3,4,5,6-tetrahydro-1H-spiro[6,11-methanodibenzo[b,e]azepine-12,1′-cyclohexane]-1,2′,6′(2H,11H)-trione (**5h**). White solid, yield: 182 mg, 80%; R_f: 0.3 (30% ethyl acetate in petroleum ether); m.p. = 205−206 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41−7.40 (m, 1H), 7.12−7.11 (s, 2H), 7.04−7.00 (m, 1H), 6.62 (d, J = 7.2 Hz, 1H), 6.45−6.44 (m, 2H), 5.03 (s, 1H), 4.81−4.75 (m, 2H), 4.55 (d, J = 16.4 Hz, 1H), 3.13 (d, J = 13.6 Hz, 1H), 3.02 (d, J = 12.4 Hz, 1H), 2.35−2.12 (m, 6H), 1.27 (s, 3H), 0.99 (s, 3H), 0.84−0.83 (m, 6H) ppm. ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) d: δ = 203.7, 202.7, 190.5, 155.4, 149.8, 142.8, 141.2, 138.8, 128.6, 127.1, 122.2, 120.9, 110.4, 109.5, 106.2, 74.4, 63.2, 51.9, 51.5, 49.0, 47.6, 47.0, 39.7, 32.5, 31.0, 30.9, 30.7, 28.6, 28.1, 26.2 ppm. HRMS (ESI/TOF-Q) *m/z*: $[M + H]^+$ calcd for $[C_{29}H_{32}NO_4]$: 458.2331; found: 458.2338.

5-Butyl-3,3,4′,4′-tetramethyl-3,4,5,6-tetrahydro-1H-Spiro-[6,11-methanodibenzo[b,e]azepine-12,1′-cyclohexane]-1,2′,6′(2H,11H)-trione (**5i**). White solid, yield: 158 mg, 73%; R_f: 0.3 (30% ethyl acetate in petroleum ether); m.p. = 176−177 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32−7.28 (m, 1H), 7.18 (s, 3H), 5.07 (s, 1H), 4.78 (s, 1H), 3.47 (t, J = 7.5 Hz, 2H), 3.13 (d, J = 13.8 Hz, 1H), 3.03 (d, J = 12.3 Hz, 1H), 2.20−2.02 (m, 6H), 1.88−1.77 (m, 2H), 1.40−1.30 (m, 2H), 1.27 (s, 3H), 1.02 (t, J = 7.2 Hz, 3H), 0.95 (s, 3H), 0.86−0.82 (m, 6H) ppm. ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) d: δ = 203.7, 202.1, 190.4, 157.4, 141.1, 139.2, 129.0, 127.3, 121.8, 121.6, 74.8, 63.4, 51.9, 51.4, 46.9, 39.6, 32.5, 31.1, 30.7, 27.8, 26.2, 20.1, 13.8 ppm. HRMS (ESI/TOF-Q) *m/z*: $[M + H]^+$ calcd for $[C_{28}H_{36}NO_3]$: 434.2695; found: 434.2699.

5-Benzyl-3,4′-diphenyl-3,4,5,6-tetrahydro-1H-spiro[6,11-methanodibenzo[b,e]azepine-12,1′-cyclohexane]-1,2′,6′(2H,11H)-trione (**5j**). White solid, yield: 183 mg, 65%; R_f: 0.3 (25% ethyl acetate in petroleum ether); m.p. = 212−213 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40−7.31 (m, 8H), 7.26−7.22 (m, 7H), 7.10 (d, J = 6.9 Hz, 2H), 7.03 (t, J = 7.8 Hz, 1H), 6.51 (d, J = 7.8 Hz, 1H), 5.25 (s, 1H), 4.86−4.83 (m, 2H), 4.62 (d, J = 15 Hz, 1H), 3.35−3.29 (m, 2H), 3.00−2.98 (m, 1H), 2.89−2.84 (m, 1H), 2.78−2.72 (m, 1H), 2.66−2.63 (m, 3H), 2.59−2.55 (m, 1H), 2.50−2.41 (m, 1H) ppm. ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) d: δ = 202.7, 202.3, 190.3, 156.4, 143.0, 138.6, 135.6, 129.1, 128.8, 128.7, 128.6, 128.5, 128.1, 127.5, 127.1, 126.9, 126.8, 122.8, 121.3, 107.7, 75.6,

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63.1, 55.1, 47.1, 45.8, 42.2, 39.7, 37.6, 34.1, 19.1 ppm. HRMS (ESI/TOF-Q) *m/z*: $[M + H]^+$ calcd for $[C_{39}H_{34}NO_3]$: 564.2538; found: 564.2549.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c01046.

^1H, ^{13}C NMR spectra of all synthesized compounds, crude mass of reaction mixture, 2D NMR spectra of **3a** and **5e**, and X-ray ORTEP diagram for **3a** and **5a** (PDF)

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Notes

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