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Direct Access to Bridged Tetrahydroquinolines and Chromanes via $InCl_3$-Catalyzed Sequential Three-Component Cascade

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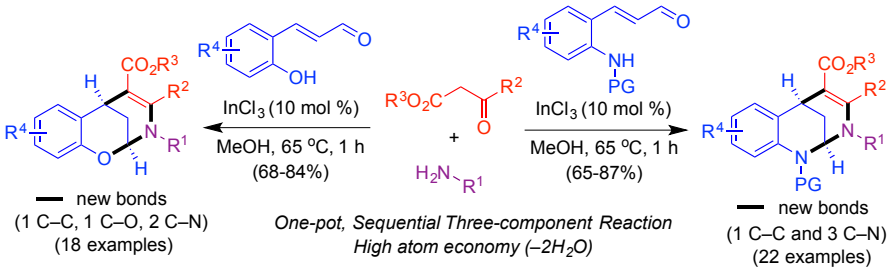
Supporting Information Placeholder



ABSTRACT: A sequential three-component cascade process was developed for the synthesis of bridged tetrahydroquinolines and chromanes bearing 2,6-methanobenzo[*d*][1,3]diazocine and 2,6-methanobenzo[*g*][1,3]oxazocine scaffolds, respectively, in good yields from readily available materials. The $InCl_3$ catalyzed reaction progressed *via* enamine formation, Michael addition, intramolecular cyclization, and intramolecular iminium ion cyclization steps. Notably, this high atom economic approach ($–2H_2O$) allowed the generation of four new bonds (1 C–C & 3 C–N or 1 C–C, 1 C–O & 2 C–N) and two heterocyclic rings in a single operation.

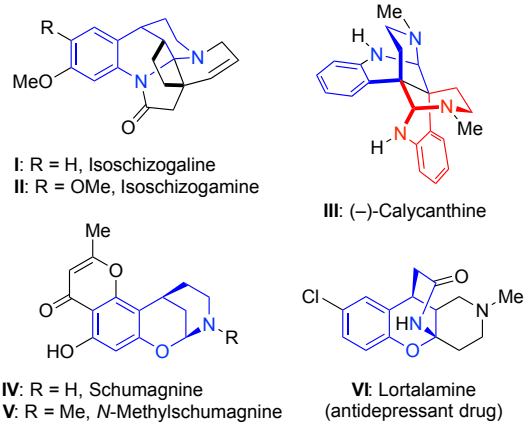
INTRODUCTION

The general approaches involved in modern drug discovery include target-oriented and diversity-oriented syntheses. The major objective of the diversity-oriented synthesis remains the synthesis of structurally complex and diverse small molecules for the identification of therapeutic targets.[1] The multicomponent and domino or cascade reactions, generally named as multibond-forming reactions, have been recognized as potential tools for the synthesis of privileged structural scaffolds by generating structural complexity and diversity.[2,3] In multicomponent reactions, three or more reactants combine to deliver a product that incorporate significant portions of all the reactants. Some of the classical multicomponent reactions have been developed in the 19th century that include Strecker reaction,[4] Hantzsch dihydropyridine synthesis,[5] and Biginelli dihydropyrimidine synthesis,[6] and other notable conventional multicomponent reactions remain Mannich,[7] Passerini,[8] and Ugi reactions.[9] After the discovery of Ugi's four-component bis-amide synthesis, tremendous effort has been devoted to the development of novel multicomponent reactions for the synthesis of diverse biologically significant compounds.[3] These multicomponent reactions, including sequential multicomponent reactions, offer high atom and step economy, operational simplicity, waste minimization, and several other advantages. These reactions allow the construction of complex biologically significant molecules starting from simple precursors by generating more than one covalent bonds and rings, comprising several sequential reactions, in a single synthetic operation.[10,11]

Among the privileged structural scaffolds that provide ligands for diverse receptors,[12] the 1,2,3,4-tetrahydroquinole ring system is prevalent in a large number of natural and synthetic compounds of biological significance.[13] In particular, the bicyclic 2,6-methanobenzo[*d*][1,3]diazocine framework is present in several alkaloids, exemplified by isoschizogaline **I**,[14] isoschizogamine **II**,[15] and (–)-calycanthine **III**[16] (Figure 1). Furthermore, tetrahydroquinolines and their fused analogs are known to act as chemotherapeutic agents including antiviral, antimalarial, antibacterial, antitumoral etc., and pharmacodynamic agents *i.e.* membrane receptors, steroid and non-steroid hormone receptors, enzyme inhibitors, and antagonists and agonists of various ion channels.[13] Comparable to 2,6-methanobenzo[*d*][1,3]diazocine framework, the bicyclic 2,6-methanobenzo[*g*][1,3]oxazocine scaffold is also pre-

sent in many interesting bioactive natural products and pharmaceuticals, represented by schumagnine **IV**,[17] *N*-methylschumagnine **V**,[17] and the antidepressant drug lortalamine **VI**.[18] and consequently few attractive strategies have been demonstrated in literature to access the related bicyclic chromane derivatives.[19]

Figure 1. Selected Examples of Natural and Biologically Relevant 2,6-Methanobenzo[*d*][1,3]diazocines and 2,6-Methanobenzo[*g*][1,3]oxazocines.



I: R = H, Isoschizogaline
II: R = OMe, Isoschizogamine

III: (–)-Calycanthine

IV: R = H, Schumagnine
V: R = Me, *N*-Methylschumagnine

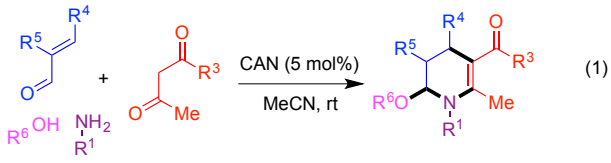
VI: Lortalamine
(antidepressant drug)

RESULTS AND DISCUSSION

Owing to the biological significance of tetrahydroquinolines and chromanes, we envisioned to develop a simple one-pot, three-component approach for the synthesis of bicyclic tetrahydroquinoline derivatives bearing a 2,6-methanobenzo[*d*][1,3]diazocine fragment, and their chromane analogs. A decade ago, a four-component strategy was developed for the synthesis of 6-alkoxy-1,4,5,6-tetrahydropyridines involving cerium(IV) ammonium nitrate (CAN) catalyzed reaction between primary amines, 1,3-dicarbonyl compounds, α,β-unsaturated aldehydes and alcohols (Scheme 1, eq. 1).[20] The mechanism of this approach involves initial formation of β-enaminones from primary amines and 1,3-dicarbonyl compounds followed by Michael addition with α,β-unsaturated aldehydes, subsequent intramolecular cyclization, and final nucleophilic displacement of the hydroxy group by the alcohol. The proposed synthesis of bicyclic tetrahydroquinolines **4** (X = NR) with a 2,6-methanobenzo[*d*][1,3]diazocine fragment could be achieved by introducing an *ortho*-amino group in the α,β-unsaturated aldehydes **3** and exclude the external nucleophile *i.e.* the alcohol (Scheme 1, eq. 2). The potential restrictions of the proposed approach include (i) the geometrical constrains of intermediate **A** in the final intramolecular nucleophilic cyclization step and (ii) the competitive intramolecular cyclization of the *ortho*-amino group with the adjacent ester functionality to deliver the corresponding lactam. Further, the methodology could be extended to the synthesis of bicyclic chromane derivatives *i.e.* 2,6-methanobenzo[*g*][1,3]oxazocines **6** (X = O) starting from *ortho*-hydroxycinnamaldehydes **5**. In 1986, Kim has reported the rearrangement of Hantzsch ester 4-(2-aminophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylic acid diethyl ester into the corresponding diazocine derivative in 28% yield in pyridine under reflux conditions along with two other products.[21] Encouraged by this result, we began our optimization studies for the one-pot synthesis of bicyclic tetrahydroquinolines using *n*-butylamine **1a**, methyl acetoacetate **2a**, and (*E*)-4-methyl-*N*-(2-(3-oxoprop-1-en-1-yl)phenyl)benzenesulfonamide **3a** as model substrates in the presence of 10 mol% of previously studied CAN[22] as the catalyst in ethanol at room temperature. To our delight, as shown in Table 1, entry 1, the expected bicyclic tetrahydroquinoline **4a** bearing a 2,6-methanobenzo[*d*][1,3]diazocine moiety was obtained in 24% yield without traces of the competitive lactam. The reaction rate was increased at elevated temperature (65 ^{o}C) and the yield was improved significantly (Table 1, entry 1, 63%). With an aim to further improve the product yield, a set of Lewis acids including $InCl_3$, $BiCl_3$, $Yb(OTf)_3$, $Sc(OTf)_3$ and AgOTf, and copper salts CuCl and $CuCl_2$ were screened at 65 ^{o}C (entries 2-8). Among the tested catalysts, $InCl_3$ and $Yb(OTf)_3$ were superior, yielding 74% and 76% of the desired product **4a**, respectively (entries 2 and 4). Encouraged by these preliminary results, screening of solvents was performed by fixing

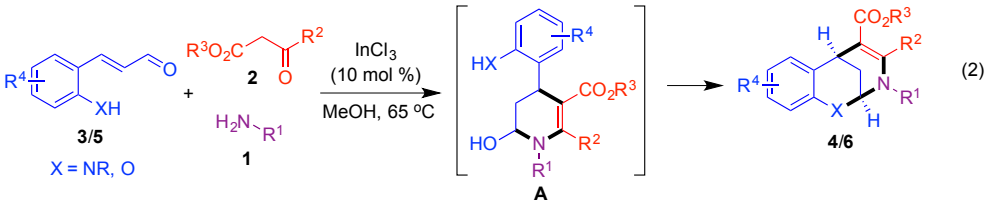
Scheme 1. Multicomponent Synthesis of Tetrahydropyridines and Envisioned Synthesis of Bridged Heterocycles

Previous work: Four-component synthesis of 6-alkoxy-1,4,5,6-tetrahydropyridines (Sridharan, Maiti and Menéndez, 2009)



(1)

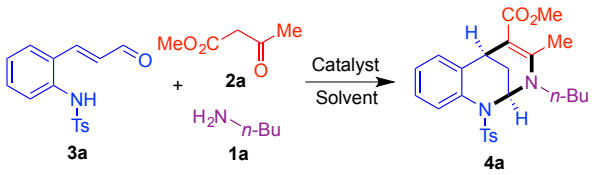
This work: Three-component synthesis of bridged tetrahydroquinolines and chromanes (2,6-methanobenzo[*d*][1,3] diazocines and 2*H*-2,6-methanobenzo[*g*][1,3]oxazocines)



(2)

Sequential formation of 6-hydroxy-1,4,5,6-tetrahydropyridine-intramolecualr iminium ion cyclization

Table 1. Optimization of Reaction Conditions[a]



entry	catalyst (10 mol %)	solvent	time (h)	**4a** (%)[b]
1	CAN	EtOH	3	63 (24)[c]
2	$InCl_3$	EtOH	2.5	74
3	$BiCl_3$	EtOH	3	56
4	$Yb(OTf)_3$	EtOH	3	76
5	$Sc(OTf)_3$	EtOH	3	68
6	AgOTf	EtOH	4	55
7	$CuCl_2$	EtOH	3	66
8	CuCl	EtOH	3	62
9	$Yb(OTf)_3$	MeOH	2	78
10	$Yb(OTf)_3$	*i*-PrOH	2	71
11	$Yb(OTf)_3$	THF	2	55
12	$Yb(OTf)_3$	MeCN	2	66
13	$Yb(OTf)_3$	DCM	2	59
14	$Yb(OTf)_3$	DCE	2	74
15	$Yb(OTf)_3$	DMSO	3	59
16	$Yb(OTf)_3$	DMF	3	58
17	$Yb(OTf)_3$	Toluene	4	65
18	$InCl_3$	MeOH	1	83[d]
19	$InCl_3$	DCE	3	75
20	No catalyst	MeOH	10	-[e]

[a]Unless otherwise noted, all reactions were carried out with **1a** (1.2 mmol), **2a** (1.0 mmol) and **3a** (1.0 mmol) with catalyst (10 mol %) in 6 mL solvent at 65 °C. [b]Isolated yield. [c]Reaction was carried out at rt for 6 h, and incomplete conversion was observed. [d]Optimized reaction condition. [e]Small quantity of intermediate enamine was observed in the crude ^{1}H-NMR spectrum.

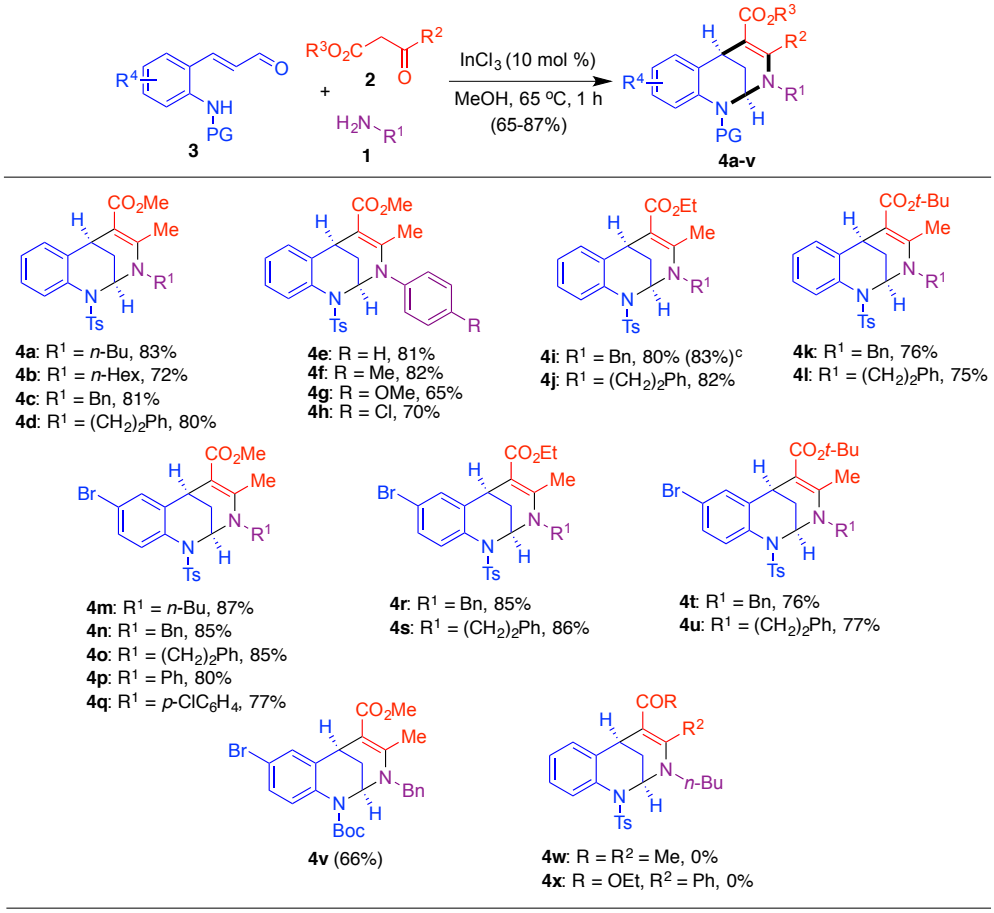
$Yb(OTf)_3$ as the catalyst, and the study revealed that MeOH (entry 9, 78%) was the high yielding solvent compared to other tested solvents such as *i*-PrOH, THF, MeCN, DCM, DCE, DMSO, DMF and toluene (entries 10-17). Gratifyingly, switching the catalyst to $InCl_3$ (10 mol%) in MeOH showcased further significant improvement in yield and reaction rate. The reaction was completed in just one hour delivering the product **4a** in 83% yield (entry 18). Another high yielding solvent DCE (entry 14) was also tested in the presence of $InCl_3$, however, the results were inferior to MeOH (entry 19). Finally, when the reaction was performed in the absence of any catalyst in MeOH, only a small quantity of the intermediate β-enaminone obtained from *n*-butylamine **1a** and methyl acetoacetate **2a** was detected in the crude ^{1}H-NMR spectrum of the reaction mixture (entry 20). Consequently, we selected entry 18 (10 mol% of $InCl_3$, MeOH, 65 °C) as the optimized reaction condition for the subsequent studies.

With the optimized condition in hand, the scope and generality of the three-component cascade process was demonstrated involving a variety of primary amines **1**, β-ketoesters **2** and *ortho*-amino α,β-unsaturated aldehydes **3** for the synthesis of bicyclic tetrahydroquinolines **4** (Scheme 2). At the outset, the effect of primary amines **1** including alkyl and arylamines was investigated. The combination of methyl acetoacetate, unsubstituted (*E*)-4-methyl-*N*-(2-(3-oxoprop-1-en-1-yl)phenyl) benzenesulfonamides, and alkyl amines such as *n*-butylamine, *n*-hexylamine, benzylamine and phenethylamine furnished the corresponding 2,6-methanobenzo[*d*][1,3]diazocines **4a-d** in good yields (72-83%). Likewise, aniline (**4e**, 81%) and arylamines bearing electron-releasing (*p*-Me, **4f**, 82%; *p*-OMe, **4g**, 65%), and -withdrawing (*p*-Cl, **4h**, 70%) substituents delivered the *N*-aryl substituted products in moderate to good yields. Interestingly, when ethyl and *t*-butyl acetoacetates were employed as substrates in combination with benzylamine and phenethylamine, the reaction proceeded smoothly to furnish the corresponding products **4i-l** in good yields (75-82%). Here, the yields of *t*-butyl acetoacetate reactions were slightly inferior (75-76%) to that of their ethyl counterparts (80-82%).

Next, we examined the effect of substituent on *ortho*-amino α,β-unsaturated aldehyde **3**, and it revealed that the presence of electron-withdrawing substituent (Br) afforded the products in slightly better yields compared to the unsubstituted analogue. The reactions between bromo substituted *ortho*-amino α,β-unsaturated aldehyde, methyl acetoacetate, and primary amines including *n*-butylamine, benzylamine, phenethylamine, aniline and *p*-chloroaniline delivered the products **4m-q** in high yields (77-87%). The reactivity of ethyl and *t*-butyl acetoacetates was comparable to the unsubstituted derivatives (**4r-u**, 76-86%). Finally, the *N*-Boc protected *ortho*-amino α,β-unsaturated aldehyde was also tested under the optimized reaction conditions to access the corresponding product **4v** in 66% yield. In general, the reactivity of alkyl amines were superior to that of arylamines that could be attributed to the high nucleophilicity of alkyl amines to deliver the initial β-enaminone intermediates effectively. One of the limitations of this strategy is that the reaction failed to deliver the corresponding products when we replaced β-ketoesters by β-diketones. The reaction between acetyl acetone, benzylamine, and aldehyde **3a** delivered a complex mixture under the standard conditions. When the reaction was monitored carefully, the β-enaminone intermediate was formed initially, and after addition of aldehyde **3a**, slow decomposition took place. This was the case when ethyl 3-oxo-3-phenylpropanoate (R^2 = Ph, R^3 = Et) was used as the substrate (**4w** and **4x**). The structure and stereochemistry of the bicyclic tetrahydroquinolines **4** were established from spectral studies and single crystal analysis of a representative compound **4n** (CCDC number: 1993226).

Next, we conceptualized a similar strategy to access bicyclic chromanes **6** bearing a 2,6-methanobenzo[*g*][1,3]oxazocine scaffold by replacing *ortho*-amino α,β-unsaturated aldehydes **3** by the *ortho*-hydroxy analog **5** (Scheme 3). The Biginelli reaction

Scheme 2. Scope and Limitations of the Three-Component Synthesis Bridged Tetrahydroquinolines[a,b]



[a]Reaction conditions: **1** (1.2 mmol), **2** (1.0 mmol), **3** (1.0 mmol), $InCl_3$ (10 mol %), MeOH (6 mL), 65 °C.
[b]Isolated yields. [c]Reaction was performed with isolated β-enaminone intermediate and **3a**.

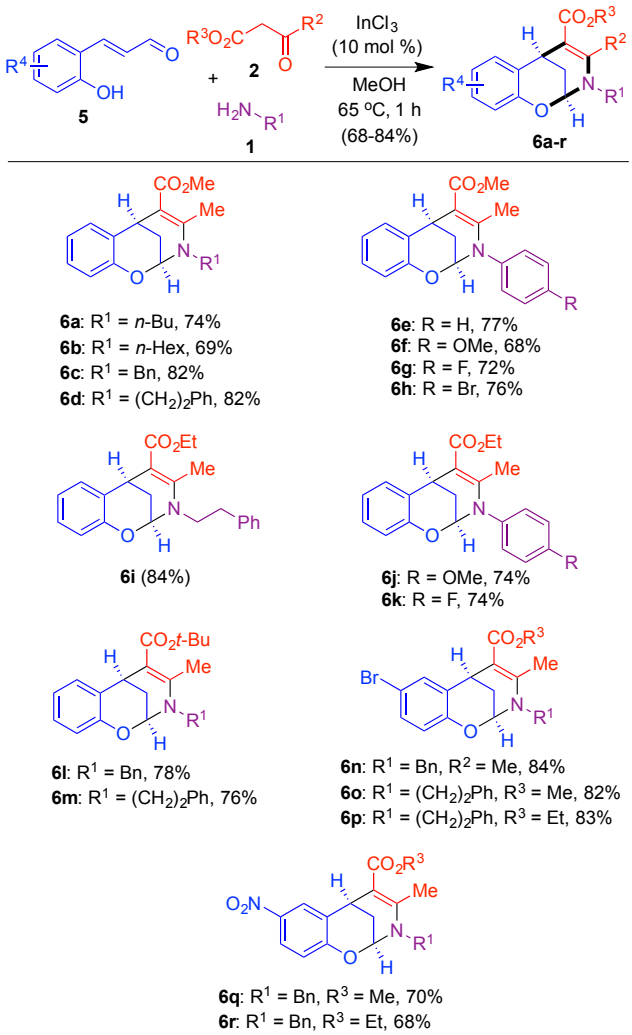
between salicylaldehydes, active methylene compounds and urea/thiourea was also identified as a direct approach for the synthesis of related chromane-fused bicyclic compounds.[23]

The three-component cascade reaction between primary amines **1**, β-ketoesters **2**, and *ortho*-hydroxy α,β-unsaturated aldehydes **5** was investigated by employing the previously established reaction conditions *i.e.* 10 mol% $InCl_3$ in MeOH at 65 °C to access 2,6-methanobenzo[*g*][1,3]oxazocines **6**. As summarized in Scheme 3, the reaction tolerated a wide range of primary amines including *n*-butylamine (**6a**, 74%) and *n*-hexylamine (**6b**, 69%), benzylamine (**6c**, **6l**, **6n**, **6q**, **6r**; 68-84%) and phenethylamine (**6d**, **6i**, **6m**, **6o, 6p**; 76-84%) delivering the corresponding products in good yields. Aryl amines bearing both electron-releasing (*p*-OMe) and -withdrawing (*p*-F, *p*-Br) groups were also equally effective (**6e-h**, **6j, 6k**), and furnished the products in 68-77% yields. In order to show the generality of the protocol, the influence of β-ketoesters such as methyl, ethyl and *tert*-butyl acetoacetate was assayed, and comparable yields were observed in all the cases. The reaction was also tolerated bromo (**6n-p**; 82-84%) and nitro (**6q, r**; 68-70%) substituents on *ortho*-hydroxy α,β-unsaturated aldehyde moiety, and the reaction times and yields were similar to those observed for unsubstituted system. It should be mentioned here that Světlík and co-workers reported the synthesis of few related compounds in poor yields with limited substrate scope.[24]

We have proposed a mechanism involving enamine formation, Michael addition, intramolecular cyclization and intramolecular iminium ion cyclization steps for the three-component reaction between primary amines **1**, β-ketoesters **2** and *ortho*-amino/hydroxy α,β-unsaturated aldehydes **3**/**5** for the synthesis of the bicyclic tetrahydroquinolines and chromanes (Scheme 4). Initial $InCl_3$ catalyzed reaction between primary amine **1** and β-ketoester **2** generates the β-enaminone intermediate **A**,[25] which undergoes Michael addition with compound **3**/**5** to deliver intermediate **B**. Successive $InCl_3$ catalyzed intramolecular cyclization provides 6-hydroxy-1,4,5,6-tetrahydropyridine intermediate **C**.[20,26] Final iminium ion (**D**) generation and intramolecular cyclization steps furnished the desired products. The observed *cis* stereochemistry in 2,4-positions could be explained *via* the cyclization of intermediate **D2**, where the geometry of this intermediate was visualized based on the single crystal structure of the product. In a separate experiment, isolated β-enaminone **A**, derived from benzylamine and ethyl acetoacetate, was treated with α,β-unsaturated aldehyde **3a** under the optimized reaction conditions, wherein the corresponding bridged tetrahydroquinoline **4i** was isolated in 83% yield. This experi-

ment supports the involvement of the β-enaminone intermediate in the three-component reaction.

Scheme 3. Scope and Limitations of the Three-Component Synthesis Bridged Chromanes[a,b]

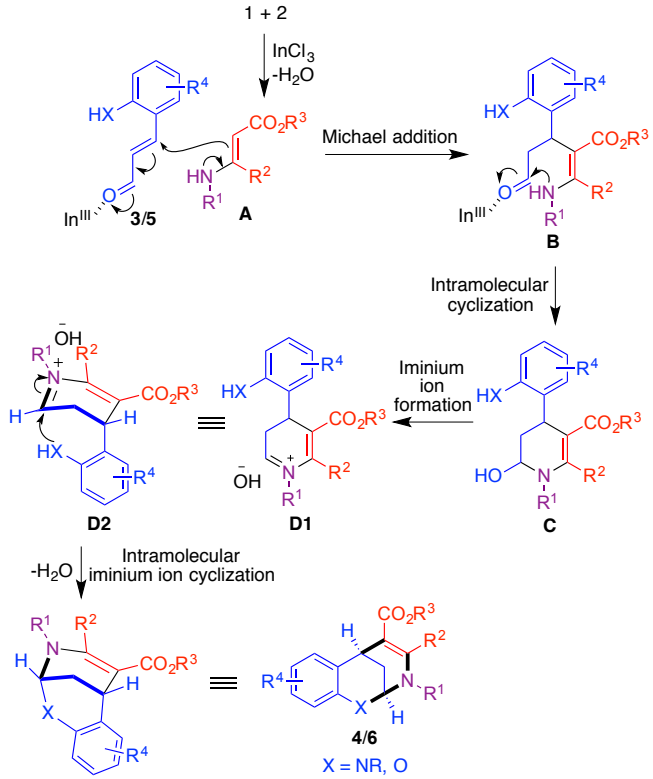


[a]Reaction conditions: **1** (1.2 mmol), **2** (1.0 mmol), **5** (1.0 mmol), $InCl_3$ (10 mol %), MeOH (6 mL), 65 °C. [b]Isolated yields.

CONCLUSIONS

In conclusion, we have developed an efficient $InCl_3$ catalyzed three-component strategy for the synthesis of bridged tetrahydroquinolines and chromanes in good yields under mild reaction conditions. The reactions showed high atom economy leaving only two molecules of water as the side product and generated four new bonds (1 C–C & 3 C–N or 1 C–C, 1 C–O & 2 C–N) and two heterocyclic rings in a single operation. Mechanistically, the three-component reaction proceeds *via* enamine formation, Michael addition, intramolecular cyclization and intramolecular iminium ion cyclization sequence. The bicyclic 2,6-methanobenzo[*d*][1,3]diazocine and 2,6-methanobenzo[*g*][1,3]oxazocine scaffolds were constructed *via* formation of 6-hydroxy-1,4,5,6-tetrahydropyridine followed by intramolecular nucleophilic cyclization.

Scheme 4. Proposed Mechanism



EXPERIMENTAL SECTION

General information. All reagents and solvents were purchased from commercial suppliers (Avra, Alfa Aesar, Sigma-Aldrich, CDH, Merck) and used without further purification. The reactions were monitored by thin layer chromatography using Merck silica gel 60 F_{254} and visualized by UV detection or using *p*-anisaldehyde stain or molecular iodine. Silica gel (230-400 mesh) was used for flash column chromatography. Melting points were recorded on a melting point apparatus in capillaries and are uncorrected. ^1H and ^{13}C-NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 at room temperature on a BruckerAvance 300 spectrometer operating at 300 MHz for ^1H and 75 MHz for ^{13}C. Chemical shifts (δ) are expressed in ppm using TMS as an internal standard and coupling constants (J) are given in Hz. Infrared (IR) spectra were obtained using an Agilent Cary630 FTIR Spectrometer with a diamond ATR accessory for solid and liquid samples, requiring no sample preparation and the major frequencies were reported in cm^{-1}. Elemental analyses were determined at the CAI de Microanálisis Elemental, Universidad Complutense, by using a Leco 932 CHNS combustion microanalyzer.

General Procedure for the Synthesis of Compounds 3/5a-c.[11b] A stirred mixture of 2-amino or 2-hydroxyarylaldehydes (3.0 mmol, 1.0 equiv.) and Wittig ylide 2-(triphenyl-λ^5-phosphanylidene)acetaldehyde (3.6 mmol, 1.2 equiv.) in toluene (10 mL) was heated at 90 °C in an oil bath for 3 h. After completion of the reaction, the reaction mixture was cooled to room temperature, solvent was evaporated to dryness, and the crude mixture was purified by flash column chromatography elut-

ing with petroleum ether-ethyl acetate mixture (90:10 to 80:20, v/v) to obtain compounds **3/5a-c**.

*(E)-4-Methyl-N-(2-(3-oxoprop-1-en-1-yl)phenyl)benzenesulfonamide (**3a**).*[19a] Purification by flash column chromatography on silica gel eluting with petroleum ether-ethyl acetate mixture (90:10 to 80:20, v/v) afforded the title compound as off-white solid; mp: 147-148 °C; yield: 0.669 g, 74%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.50 (d, *J* = 7.5 Hz, 1H), 7.70 (d, *J* = 2.1 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.40-7.48 (m, 2H), 7.25-7.28 (m, 3H), 7.01 (d, *J* = 8.7 Hz, 1H), 6.43-6.53 (m, 2H), 2.40 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 193.9, 147.4, 144.5, 135.6, 134.8, 131.8, 131.3, 129.9, 128.2, 127.9, 127.4, 21.5.

*(E)-N-(4-Bromo-2-(3-oxoprop-1-en-1-yl)phenyl)-4-methylbenzenesulfonamide (**3b**).*[27] Purification by flash column chromatography on silica gel eluting with petroleum ether-ethyl acetate mixture (90:10 to 80:20, v/v) afforded the title compound as off-white solid; mp: 168-170 °C; yield: 0.935 g, 82%;^{1}H NMR (300 MHz, $CDCl_3$): δ 9.49 (d, *J* = 7.5 Hz, 1H), 7.70 (d, *J* = 2.4 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.40-7.48 (m, 2H), 7.26 (d, *J* = 8.1 Hz, 2H), 7.02 (d, *J* = 8.4 Hz, 1H), 6.70 (brs, 1H), 6.47 (dd, *J* = 15.9, 7.5 Hz, 1H), 2.40 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 193.2, 145.3, 144.8, 135.3, 134.5, 133.6, 133.2, 130.8, 130.2, 130.0, 129.7, 127.4, 121.7, 21.6.

tert-Butyl (E)-(4-bromo-2-(3-oxoprop-1-en-1-yl)phenyl)carbamate (**3c**).[28] Purification by flash column chromatography on silica gel eluting with petroleum ether-ethyl acetate mixture (90:10 to 80:20, v/v) afforded the title compound as off-white solid; mp: 142-144 °C; yield: 0.764 g, 78%; 1H NMR (300 MHz, CDCl3): δ 9.74 (d, J = 7.5 Hz, 1H), 7.66 (d, J = 2.1 Hz, 1H), 7.62-7.65 (m, 1H), 7.50-7.57 (m, 2H), 6.62-6.70 (m, 1H), 6.42 (brs, 1H), 1.53 (s, 9H); 13C{1H} NMR (75 MHz, CDCl3): δ 193.0, 152.8, 145.5, 135.6, 134.4, 131.0, 130.1, 128.4, 125.4, 118.0, 81.8, 28.3.

*(E)-3-(2-Hydroxyphenyl)acrylaldehyde (**5a**).*[29] Purification by flash column chromatography on silica gel eluting with petroleum ether-ethyl acetate mixture (90:10 to 80:20, v/v) afforded the title compound as white solid; mp: 119-120 °C; yield: 0.324 g, 73 %; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.68 (d, *J* = 8.1 Hz, 1H), 7.50 (dd, *J* = 16.2 Hz, 1H), 7.31 (td, *J* = 8.1, 1.5 Hz, 1H), 7.07 (d, *J* = 8.1 Hz, 1H), 6.95-7.03 (m, 1H), 6.90 (d, *J* = 8.4 Hz, 1H), 6.80 (s, 1H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 195.8, 155.8, 149.8, 132.8, 130.1, 129.1, 121.3, 120.9, 116.6.

*(E)-3-(5-Bromo-2-hydroxyphenyl)acrylaldehyde (**5b**).*[29] Purification by flash column chromatography on silica gel eluting with petroleum ether-ethyl acetate mixture (90:10 to 80:20, v/v) afforded the title compound as pale brown solid; mp: 145-146 °C; yield: 0.525 g, 77 %; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.69 (d, *J* = 7.8 Hz, 1H), 7.69 (d, *J* = 15.9 Hz, 1H), 7.62 (d, *J* = 2.4 Hz, 1H), 7.38 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.88 (dd, *J* = 16.2, 7.8 Hz, 1H), 6.76 (d, *J* = 8.7 Hz, 1H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$/DMSO-d_6): δ 193.9, 155.8, 147.1, 134.3, 130.5, 128.5, 122.6, 118.0, 110.9.

*(E)-3-(2-Hydroxy-5-nitrophenyl)acrylaldehyde (**5c**).*[29] Purification by flash column chromatography on silica gel eluting with petroleum ether-ethyl acetate mixture (90:10 to 80:20, v/v) afforded the title compound as pale brown solid; mp: 154-158 °C; yield: 0.394 g, 68%; ^{1}H NMR (300 MHz, $CDCl_3$/DMSO-d_6): δ 9.71 (d, *J* = 7.8 Hz, 1H), 8.40 (d, *J* = 2.4 Hz, 1H), 8.12 (dd, *J* = 9.3, 27 Hz, 1H), 7.78 (d, *J* = 16.2 Hz, 1H), 7.08 (d, *J* = 9.0 Hz, 1H), 6.92 (dd, *J* = 16.2, 7.8 Hz, 1H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$/DMSO-d_6): δ 194.0, 162.6, 146.4, 140.2, 130.1, 127.2, 124.9, 121.3, 116.7.

General Procedure for the Synthesis of Bridged Tetrahydroquinolines 4a-v. To a stirred solution of primary amine **1** (1.2 mmol, 1.2 equiv.) in MeOH (6 mL) was added β-ketoester **2** (1.0 mmol, 1.0 equiv.) and $InCl_3$ (10 mol%). The reaction mixture was stirred at room temperature for 20 minutes. To this reaction mixture 2-aminoarylaldehyde **3** (1.0 mmol, 1.0 equiv.) was added, and the reaction mixture was stirred at 65 °C in an oil bath for 1 h. After completion of the reaction, the mixture was diluted with water (6 mL), extracted with ethyl acetate (3 × 6 mL), and washed with brine (6 mL). The organic layer was separated, dried over anhydrous sodium sulphate, and concentrated in vacuum. The crude product was purified through silica column chromatography using petroleum ether-ethyl acetate as eluent (90:10 to 85:15, v/v).

*(±) Methyl-3-butyl-4-methyl-1-tosyl-1,2,3,6-tetrahydro-2,6-methanobenzo[d][1,3]diazocine-5-carboxylate (**4a**).* Purification by flash column chromatography on silica gel eluting with petroleum ether-ethyl acetate mixture (90:10 to 85:15, v/v) afforded the title compound as off-white solid; mp: 140-142 °C; yield: 0.377 g, 83%; IR (neat): 3423.9, 2922.6, 1717.3, 1681.6, 1629.5, 1458.9, 1367.3, 1286.2, 1206.3, 1106.9, 1082.8 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.82 (d, *J* = 8.4 Hz, 1H), 7.66 (d, *J* = 7.8 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 7.25 (d, *J* = 7.2 Hz, 1H), 7.10 (t, *J* = 7.2 Hz, 1H), 6.97 (t, *J* = 7.2 Hz, 1H), 5.96 (s, 1H), 4.04 (s, 1H), 3.60 (s, 3H), 3.43 (t, *J* = 7.5 Hz, 2H), 2.34 (s, 3H), 2.30 (s, 3H), 1.68-1.72 (m, 1H), 1.52-1.56 (m, 3H), 1.24-1.34 (m, 2H), 0.94 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 167.8, 153.3, 144.0, 136.1, 132.9, 132.6, 129.7, 129.0, 127.0, 126.4, 124.8, 122.4, 100.9, 67.5, 50.6, 47.7, 31.3, 30.0, 21.5, 20.1, 15.9, 13.9; Anal Calcd $C_{25}H_{30}N_2O_4S$: C, 66.05; H, 6.65; N, 6.16. Found: C, 65.70; H, 6.57; N, 6.08.

*(±) Methyl-3-hexyl-4-methyl-1-tosyl-1,2,3,6-tetrahydro-2,6-methanobenzo[d][1,3]diazocine-5-carboxylate (**4b**).* Purification by flash column chromatography on silica gel eluting with petroleum ether-ethyl acetate mixture (90:10 to 85:15, v/v) afforded the title compound as pale yellow solid; mp: 88-90 °C; yield: 0.347 g, 72%; IR (neat): 3426.1, 2926.8, 1711.4, 1686.2, 1631.0, 1456.3, 1361.9, 1284.5, 1204.8, 1101.8, 1082.2 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00 (d, *J* = 8.4 Hz, 1H), 7.51 (d, *J* = 8.1 Hz, 2H), 7.29-7.34 (m, 1H), 7.18 (d, *J* = 8.1 Hz, 2H), 7.08-7.14 (m, 1H), 6.97-7.02 (m, 1H), 5.83 (s, 1H), 4.11 (s, 1H), 3.70 (s, 3H), 3.33-3.69 (m, 2H), 2.36 (s, 3H), 2.32 (s, 3H), 1.60-1.63 (m, 4H), 1.25-1.51 (m, 6H), 0.91-0.93 (m, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 167.8, 153.3, 144.0, 136.1, 132.9, 132.6, 129.7, 129.0, 127.0, 126.4, 124.7, 122.4, 100.9, 67.5, 50.6, 48.0, 31.5, 30.0, 29.2, 26.6, 25.1, 22.6, 21.5, 16.0, 14.0; Anal Calcd for $C_{27}H_{34}N_2O_4S$: C, 67.19; H, 7.10; N, 5.80. Found: C, 66.86; H, 6.89; N, 5.64.

*(±) Methyl-3-benzyl-4-methyl-1-tosyl-1,2,3,6-tetrahydro-2,6-methanobenzo[d][1,3]diazocine-5-carboxylate (**4c**).* Purification by flash column chromatography on silica gel eluting with petroleum ether-ethyl acetate mixture (90:10 to 85:15, v/v) afforded the title compound as off-white solid; mp: 166-168 ^{o}C; yield: 0.395 g, 81%; IR (neat): 3426.8, 2977.8, 2926.6, 1676.1, 1578.7, 1451.7, 1348.5, 1208.9, 1166.3, 1109.8 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.94 (d, *J* = 8.4 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.28-7.38 (m, 4H), 7.11-7.22 (m, 5H), 7.00 (t, *J* = 7.5 Hz, 1H), 5.74 (s, 1H), 4.83 (d, *J* = 17.7 Hz, 1H), 4.72 (d, *J* = 17.7, 1H), 4.20 (s, 1H), 3.72 (s, 3H), 2.34 (s, 3H), 2.32 (s, 3H), 1.73 (dt, *J* = 12.3, 2.4 Hz, 1H), 1.51 (dt, *J* = 12.3, 2.4 Hz, 1H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 167.8, 153.3, 144.1, 137.7, 135.9, 132.3, 129.9, 129.7, 129.1, 128.9, 127.3, 127.0, 126.6, 126.5, 126.1, 124.9, 122.6, 101.5, 68.0, 50.8, 30.1, 24.9, 21.5, 16.2; Anal Calcd for $C_{28}H_{28}N_2O_4S$: C, 68.83; H, 5.78; N, 5.73. Found: C, 68.67; H, 5.73; N, 5.65.

*(±) Methyl-4-methyl-3-phenethyl-1-tosyl-1,2,3,6-tetrahydro-2,6-methanobenzo[d][1,3]diazocine-5-carboxylate (**4d**).* Purification by flash column chromatography on silica gel eluting with petroleum ether-ethyl acetate mixture (90:10 to 85:15, v/v) afforded the title compound as off-white solid; mp: 160-162 ^{o}C; yield: 0.402 g, 80%; IR (neat): 3426.9, 2938.9, 1676.8, 1561.1, 1430.9, 1349.9, 1260.3, 1213.0, 1159.0, 1056.8 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.01 (d, *J* = 8.1 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.28-7.37 (m, 6H), 7.18 (d, *J* = 8.1, 2H), 7.11 (td, *J* = 7.5, 1.8 Hz, 1H), 6.98-7.03 (m, 1H), 5.73 (s, 1H), 4.10 (s, 1H), 3.79-3.89 (m, 1H), 3.59-3.73 (m, 4H), 2.82-3.02 (m, 2H), 2.36 (s, 3H), 2.35 (s, 3H), 1.53-1.58 (m, 1H), 1.35 (dt, *J* = 12.6, 2.1 Hz, 1H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 167.7, 153.0, 144.1, 138.3, 136.1, 132.9, 132.5, 129.8, 129.1, 129.0, 128.7, 127.0, 126.6, 126.5, 124.8, 122.5, 101.4, 67.7, 50.7, 49.6, 35.9, 30.0, 24.8, 21.6, 15.9; Anal Calcd for $C_{29}H_{30}N_2O_4S$: C, 69.30; H, 6.02; N, 5.57. Found: C, 68.91; H, 5.95; N, 5.51.

*(±) Methyl-4-methyl-3-phenyl-1-tosyl-1,2,3,6-tetrahydro-2,6-methanobenzo[d][1,3]diazocine-5-carboxylate (**4e**).* Purification by flash column chromatography on silica gel eluting with petroleum ether-ethyl acetate mixture (90:10 to 85:15, v/v) afforded the title compound as pale brown solid; mp: 131-133 ^{o}C; yield: 0.384 g, 81%; IR (neat): 3296.3, 2955.4, 2919.7, 1676.8, 1567.8, 1489.7, 1338.4, 1211.1, 1163.8, 1071.3 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62-7.68 (m, 2H), 7.36-7.44 (m, 5H), 7.33 (d, *J* = 8.4 Hz, 1H), 7.22 (dd, *J* = 8.1, 2.4 Hz, 1H), 7.13 (d, *J* = 5,4 Hz, 2H), 7.04-7.09 (m, 2H), 6.26 (s, 1H), 4.30 (s, 1H), 3.75 (s, 3H), 2.34 (s, 3H), 1.96-2.01 (m, 5H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 167.7, 152.7, 143.7, 142.5, 136.8, 132.4, 129.6, 129.3, 127.7, 127.3, 127.0, 126.5, 125.3, 124.8, 122.3, 121.6, 104.0, 69.7, 50.9, 30.3, 26.4, 21.5, 19.0; Anal Calcd for $C_{27}H_{26}N_2O_4S$: C, 68.33; H, 5.52; N, 5.90. Found: C, 68.02; H, 5.65; N, 5.70.

*(±) Methyl-4-methyl-3-(p-tolyl)-1-tosyl-1,2,3,6-tetrahydro-2,6-methanobenzo[d][1,3]diazocine-5-carboxylate (**4f**).* Purification by flash column chromatography on silica gel eluting with petroleum ether-ethyl acetate mixture (90:10 to 85:15, v/v) afforded the title compound as off-white solid; mp: 128-132 ^{o}C; yield: 0.400 g, 82%; IR (neat): 3282.3, 2940.9, 1684.5, 1577.5, 1481.0, 1331.6, 1211.1, 1156.1, 1080.9 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70 (d, *J* = 7.2 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.40 (dd, *J* = 7.2, 1.5 Hz, 1H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 8.1 Hz, 2H), 7.02-7.13 (m, 4H), 6.93 (d, *J* = 8.4 Hz, 1H), 6.20 (s, 1H), 4.29 (s, 1H), 3.74 (s, 3H), 2.40 (s, 3H), 2.37 (s, 3H), 2.35 (s, 3H), 1.89-2.03 (m, 2H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 167.8; 153.1, 143.7, 143.6, 137.5, 136.8, 136.2, 135.2, 133.9, 133.0, 132.5, 129.8, 129.6, 129.2, 127.3, 127.1, 126.4, 124.8, 122.4, 122.3, 103.6, 69.8, 50.9, 30.3, 26.4, 21.5, 21.2, 20.9, 18.9; Anal Calcd for $C_{28}H_{28}N_2O_4S$: C, 68.83; H, 5.78; N, 5.73. Found: C, 68.46; H, 5.83; N, 5.54.

*(±) Methyl-3-(4-methoxyphenyl)-4-methyl-1-tosyl-1,2,3,6-tetrahydro-2,6-methanobenzo[d][1,3]diazocine-5-carboxylate (**4g**).* Purification by flash column chromatography on silica gel eluting with petroleum ether-ethyl acetate mixture (90:10 to 85:15, v/v) afforded the title compound as brown gummy solid; yield: 0.343 g, 65%; IR (neat): 3287.1, 2941.6, 1686.4, 1579.3, 1489.8, 1337.9, 1210.8, 1156.7, 1080.7 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.1 Hz, 1H), 7.35-7.41 (m, 3H), 7.01-7.22 (m, 4H), 6.94-6.97 (m, 1H), 6.70-6.83(m, 3H), 6.15 (s, 1H), 4.28 (s, 1H), 3.80 (s, 3H), 3.74(s, 3H), 2.35 (s, 3H), 1.91-2.05 (m, 5H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 167.7, 158.9, 153.2, 143.7, 136.8, 135.2, 133.0, 132.5, 129.6, 129.5, 129.2, 127.1, 126.4, 124.8, 122.4, 114.9, 103.3, 70.0, 55.4, 50.8, 30.2, 26.4, 21.5, 18.8; Anal Calcd for $C_{28}H_{28}N_2O_5S$: C, 66.65; H, 5.59; N, 5.55. Found: C, 66.44; H, 5.65; N, 5.45.

*(±) Methyl-3-(4-chlorophenyl)-4-methyl-1-tosyl-1,2,3,6-tetrahydro-2,6-methanobenzo[d][1,3]diazocine-5-carboxylate (**4h**).* Purification by flash column chromatography on silica gel eluting with petroleum ether-ethyl acetate mixture (90:10 to 85:15, v/v) afforded the title compound as pale yellow solid; mp: 194-195 ^{o}C; yield: 0.356 g, 70%; IR (neat): 3301.1, 2910.7, 1665.4, 1566.2, 1489.7, 1338.6, 1216.5, 1140.0, 1076.6 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70 (d, *J* = 8.1 Hz, 1H), 7.35-7.40 (m, 5H), 7.17-7.24 (m, 2H), 7.13 (d, *J* = 7.8 Hz, 2H), 6.98-7.10 (m, 2H), 6.16 (s, 1H), 4.30 (s, 1H), 3.75 (s, 3H), 2.37 (s, 3H), 1.95-2.00 (m, 5H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 167.6, 152.1, 143.9, 141.0, 136.5, 133.4, 132.8, 132.3, 129.4, 129.3, 129.2, 127.2, 127.0, 126.6, 125.0, 122.6, 104.9, 69.5, 51.0, 30.2, 26.3, 21.5, 18.9; Anal Calcd for $C_{27}H_{25}ClN_2O_4S$: C, 63.71; H, 4.95; N, 5.50. Found: C, 63.52; H, 4.89; N, 5.33.

*(±) Ethyl -3-benzyl-4-methyl-1-tosyl-1,2,3,6-tetrahydro-2,6-methanobenzo[d][1,3]diazocine-5-carboxylate (**4i**).* Purification by flash column chromatography on silica gel eluting with petroleum ether-ethyl acetate mixture (90:10 to 85:15, v/v) afforded the title compound as pale brown solid; mp: 169-170 ^{o}C; yield: 0.402 g, 80%; IR (neat): 3423.9, 2976.6, 2938.9, 1676.8, 1570.7, 1450.2, 1348.6, 1206.2, 1160.9, 1106.9, 1050.0 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$/DMSO-d_6): δ 8.00 (d, *J* = 8.4 Hz, 1H), 7.45 (d, *J* = 8.1 Hz, 2H), 7.40 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.28-7.37 (m, 3H), 7.11-7.16 (m, 5H), 7.03 (td, *J* = 7.5, 1.2 Hz, 1H), 5.74 (s, 1H), 4.83 (d, *J* = 17.7 Hz, 1H), 4.77 (d, *J* = 17.7 Hz, 1H), 4.11-4.24 (m, 3H), 2.34 (s, 3H), 2.33 (s, 3H), 1.73 (dt, *J* = 12.6, 2.7 Hz, 1H),

1.47-1.54 (m, 1H), 1.33 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$/DMSO-d_6): δ 172.8, 157.6, 149.0, 142.5, 140.5, 137.7, 137.2, 134.6, 133.8, 133.6, 132.0, 131.1, 130.7, 129.6, 127.2, 106.5, 72.9, 64.0, 55.6, 34.6, 29.6, 26.3, 20.8, 19.4; Anal Calcd for $C_{29}H_{30}N_2O_4S$: C, 69.30; H, 6.02; N, 5.57. Found: C, 68.93; H, 5.97; N, 5.44.

*(±) Ethyl-4-methyl-3-phenethyl-1-tosyl-1,2,3,6-tetrahydro-2,6-methanobenzo[d][1,3]diazocine-5-carboxylate (**4j**).* Purification by flash column chromatography on silica gel eluting with petroleum ether-ethyl acetate mixture (90:10 to 85:15, v/v) afforded the title compound as off-white solid; mp: 155-156 °C; yield: 0.423 g, 82%; IR (neat): 3426.8, 2936.4, 1677.3, 1562.0, 1436.8, 1351.4, 1268.4, 1210.3, 1160.9, 1058.3 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.02 (d, *J* = 8.4 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.29-7.37 (m, 6H), 7.17 (d, *J* = 8.4 Hz, 2H), 7.11 (td, *J* = 8.7, 1.8 Hz, 1H), 7.00 (t, *J* = 7.5 Hz, 1H), 5.73 (s, 1H), 4.07-4.22 (m, 3H), 3.78-3.89 (m, 1H), 3.49-3.68 (m, 1H), 2.81-3.02 (m, 2H), 2.36 (s, 6H), 1.54-1.56 (m, 1H), 1.25-1.38 (m, 4H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 167.3, 152.8, 144.1, 138.3, 136.1, 132.9, 132.5, 129.7, 129.1, 129.0, 128.7, 127.0, 126.6, 124.8, 122.5, 67.7, 59.3, 49.5, 35.9, 29.9, 24.8, 21.6, 14.7; Anal Calcd for $C_{30}H_{32}N_2O_4S$: C, 69.74; H, 6.24; N, 5.42. Found: C, 69.39; H, 6.11; N, 5.33.

*(±) tert-Butyl-3-benzyl-4-methyl-1-tosyl-1,2,3,6-tetrahydro-2,6-methanobenzo[d][1,3]diazocine-5-carboxylate (**4k**).* Purification by flash column chromatography on silica gel eluting with petroleum ether-ethyl acetate mixture (90:10 to 85:15, v/v) afforded the title compound as off-white solid; mp: 146-148 °C; yield: 0.403 g, 76%; IR (neat): 3426.9, 2967.4, 2924.5, 1659.9, 1565.8, 1476.4, 1346.0, 1267.4, 1138.6, 1100.4 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.01 (d, *J* = 8.1 Hz, 1H), 7.41-7.46 (m, 3H), 7.28-7.38 (m, 3H), 7.11-7.17 (m, 5H), 7.01-7.06 (m, 1H), 5.72 (s, 1H), 4.81 (d, *J* = 17.7 Hz, 1H), 4.69 (d, *J* = 17.7 Hz, 1H), 4.17 (s, 1H), 2.34 (s, 3H), 2.30 (s, 3H), 1.73 (dt, *J* = 12.6, 3.0 Hz, 1H), 1.46-1.57 (m, 10H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 166.9, 152.0, 144.1, 137.9, 136.1, 133.1, 132.5, 128.9, 128.8, 127.2, 127.0, 126.4, 126.1, 124.7, 122.7, 103.1, 79.1, 68.0, 50.6, 30.3, 28.7, 25.0, 21.5, 16.2; Anal Calcd for $C_{31}H_{34}N_2O_4S$: C, 70.16; H, 6.46; N, 5.28. Found: C, 69.93; H, 6.35; N, 5.14.

*(±) tert-Butyl-4-methyl-3-phenethyl-1-tosyl-1,2,3,6-tetrahydro-2,6-methanobenzo[d][1,3]diazocine-5-carboxylate (**4l**).* Purification by flash column chromatography on silica gel eluting with petroleum ether-ethyl acetate mixture (90:10 to 85:15, v/v) afforded the title compound as off-white solid; mp: 123-125 °C; yield: 0.408 g, 75%; IR (neat): 3431.7, 2971.8, 2932.2, 1671.9, 1580.4, 1450.21352.8, 1216.0, 1163.8, 1104.0 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.02 (d, *J* = 8.4 Hz, 1H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.40 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.25-7.36 (m, 5H), 7.18 (d, *J* = 8.1 2H), 7.08 (td, *J* = 7.2, 1.5 Hz, 1H), 7.01 (td, *J* = 7.5, 1.2 Hz, 1H), 5.74 (s, 1H), 4.07 (s, 1H), 3.75-3.86 (m, 1H), 3.56-3.66 (m, 1H), 2.81-3.00 (m, 2H), 2.36 (s, 3H), 2.34 (s, 3H), 1.52-1.55 (m, 10H), 1.33-1.38 (m, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 167.0, 151.7, 144.0, 138.4, 136.2, 133.0, 132.7, 129.7, 129.1, 128.7, 127.0, 126.6, 126.4, 124.7, 122.6, 103.1, 79.0, 67.8, 49.5, 35.9, 30.2, 28.7, 24.8, 21.6, 15.9; Anal Calcd for $C_{32}H_{36}N_2O_4S$: C, 70.56; H, 6.66; N, 5.14. Found: C, 70.33; H, 6.69; N, 5.03.

*(±) Methyl-8-bromo-3-butyl-4-methyl-1-tosyl-1,2,3,6-tetrahydro-2,6-methanobenzo[d][1,3]diazocine-5-carboxylate (**4m**).* Purification by flash column chromatography on silica gel eluting with petroleum ether-ethyl acetate mixture (90:10 to 85:15, v/v) afforded the title compound as pale brown solid; mp: 122-124 °C; yield: 0.464 g, 87%; IR (neat): 3427.4, 2929.6, 1719.4, 1689.8, 1463.9, 1359.5, 1286.2, 1209.4, 1103.2, 1082.9 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.88 (d, *J* = 9.0 Hz, 1H), 7.50 (d, *J* = 8.1 Hz, 2H), 7.45 (d, *J* = 2.1 Hz, 1H), 7.19-7.23 (m, 3H), 5.79 (s, 1H), 4.07 (s, 1H), 3.71 (s, 3H), 3.33-3.58 (m, 2H), 2.38 (s, 3H), 2.33 (s, 3H), 1.54-1.60 (m, 3H), 1.36-1.43 (m, 3H), 0.98 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 153.6, 144.3, 135.8, 134.7, 132.2, 131.7, 129.9, 129.3, 127.0, 124.1, 117.9, 100.4, 67.4, 50.7, 47,7, 31.3, 30.0, 24.8, 21.6, 20.1, 15.9, 13.9; Anal Calcd for $C_{25}H_{29}BrN_2O_4S$: C, 56.29; H, 5.48; N, 5.25. Found: C, 55.92; H, 5.51; N, 5.11.

*(±) Methyl-3-benzyl-8-bromo-4-methyl-1-tosyl-1,2,3,6-tetrahydro-2,6-methanobenzo[d][1,3]diazocine-5-carboxylate (**4n**).* Purification by flash column chromatography on silica gel eluting with petroleum ether-ethyl acetate mixture (90:10 to 85:15, v/v) afforded the title compound as off-white solid; mp: 186-187 °C; yield: 0.482 g, 85%; IR (neat): 3428.8, 2945.7, 2917.7, 2257.3, 1717.3, 1561.1, 1428.9, 1354.7, 1208.2, 1160.9, 1106.9 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.88 (d, *J* = 9.0 Hz, 1H), 7.50 (d, *J* = 2.4 Hz, 1H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.28-7.38 (m, 3H), 7.21-7.26 (m, 1H), 7.18 (d, *J* = 8.1 Hz, 2H), 7.12 (d, *J* = 6.3 Hz, 2H), 5.71 (s, 1H), 4.82 (d, *J* = 17.4 Hz, 1H), 4.72 (d, *J* = 17.4 Hz, 1H), 4.16 (s, 1H), 3.74 (s, 3H), 2.36 (s, 3H), 2.34 (s, 3H), 1.71 (dt, *J* = 12.9, 2.7 Hz, 1H), 1.40-1.47 (m, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 167.5, 153.5, 144.4, 137.5, 135.6, 134.4, 132.3, 131.8, 129.9, 129.4, 128.9, 127.4, 127.0, 126.0, 124.3, 118.0, 101.0, 67.9, 50.9, 50.8, 30.1, 24.6, 21.6, 16.2; Anal Calcd for $C_{28}H_{27}BrN_2O_4S$: C, 59.26; H, 4.80; N, 4.94. Found: C, 58.95; H, 4.76; N, 4.88.

*(±) Methyl-8-bromo-4-methyl-3-phenethyl-1-tosyl-1,2,3,6-tetrahydro-2,6-methanobenzo[d][1,3]diazocine-5-carboxylate (**4o**).* Purification by flash column chromatography on silica gel eluting with petroleum ether-ethyl acetate mixture (90:10 to 85:15, v/v) afforded the title compound as off-white solid; mp: 145-147 °C; yield: 0.494 g, 85%; IR (neat): 3427.8, 2971.4, 2921.6, 1677.8, 1566.3, 1480.3, 1339.4, 1259.4, 1223.2, 1158.7, 1068.5 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.91 (d, *J* = 9.0 Hz, 1H), 7.46 (dd, *J* = 5.4, 2.7 Hz, 1H), 7.27-7.38 (m, 6H), 7.19-7.24 (m, 4H), 5.66 (s, 1H), 4.06 (s, 1H), 3.59-3.87 (m, 5H), 2.82-3.00 (m, 2H), 2.38 (s, 3H), 2.37 (s, 3H), 1.51-1.57 (m, 1H), 1.23-1.30 (m, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 167.5, 153.2, 144.4, 138.1, 135.7, 134.6, 132.2, 131.7, 129.9, 129.4, 129.1, 128.7, 127.0, 126.7, 124.2, 118.0, 100.9, 67.6, 50.8, 49.6, 35.9, 29.9, 24.4, 21.6, 15.8; Anal Calcd for $C_{29}H_{29}BrN_2O_4S$: C, 59.90; H, 5.03; N, 4.82. Found: C, 59.70; H, 4.89; N, 4.73.

*(±) Methyl-8-bromo-4-methyl-3-phenyl-1-tosyl-1,2,3,6-tetrahydro-2,6-methanobenzo[d][1,3]diazocine-5-carboxylate (**4p**).* Purification by flash column chroma-

tography on silica gel eluting with petroleum ether-ethyl acetate mixture (90:10 to 85:15, v/v) afforded the title compound as off-white solid; mp: 167-168 ^{o}C; yield: 0.443 g, 80%; IR (neat): 3431.7, 2962.1, 2934.1, 1679.6, 1563.0, 1476.2, 1349.9, 1215.9, 1170.6, 1078.0 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59 (d, *J* = 9.0 Hz, 1H), 7.53 (d, *J* = 2.4 Hz, 1H), 7.32-7.48 (m, 6H), 7.20 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.13 (d, *J* = 8.4 Hz, 2H), 6.22 (s, 1H), 4.26 (s, 1H), 3.76 (s, 3H), 2.36 (s, 3H), 1.99-2.05 (m, 4H), 1.87 (dq, *J* = 12.6, 2.1 Hz, 1H); ^{13}C{^{1}H} NMR (75 MHz, DMSO/$CDCl_3$): δ* 167.4; 153.0, 144.0, 142.3, 134.6, 132.3, 131.9, 129.8, 129.5, 127.8, 127.0, 123.9, 117.9, 103.5, 69.5, 51.0, 30.2, 26.0, 21.5, 19.0; Anal Calcd for $C_{27}H_{25}BrN_2O_4S$: C, 58.59; H, 4.55; N, 5.06. Found: C, 58.24; H, 4.63; N, 5.02. *Two aromatic carbons merged with others.

*(±) Methyl-8-bromo-3-(4-chlorophenyl)-4-methyl-1-tosyl-1,2,3,6-tetrahydro-2,6-methanobenzo[d][1,3]diazocine-5-carboxylate (**4q**).* Purification by flash column chromatography on silica gel eluting with petroleum ether-ethyl acetate mixture (90:10 to 85:15, v/v) afforded the title compound as off-white solid; mp: 176-178 ^{o}C; yield: 0.452 g, 77%; IR (neat): 3391.7, 2958.0, 2917.1, 1679.3, 1566.2, 1493.3, 1336.2, 1211.3, 1159.8, 1069.3 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61 (d, *J* = 9.0 Hz, 1H), 7.51 (d, *J* = 2.4 Hz, 1H), 7.35-7.38 (m, 4H), 7.22 (dd, *J* = 9.0, 2.7 Hz, 1H), 7.16 (d, *J* = 8.1 Hz, 2H), 6.12 (s, 1H), 4.25 (s, 1H), 3.76 (s, 3H), 2.38 (s, 3H), 1.96-2.03 (m, 4H), 1.86-1.93 (m, 1H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ* 167.3, 152.3, 144.3, 140.7, 136.1, 134.4, 133.6, 132.0, 131.9, 129.8, 129.6, 127.0, 124.1, 118.0, 104.4, 69.4, 51.1, 30.1, 26.0, 21.6, 18.9; Anal Calcd for $C_{27}H_{24}BrClN_2O_4S$: C, 55.16; H, 4.11; N, 4.76. Found: C, 55.89; H, 4.10; N, 4.67. *Two aromatic carbons merged with others.

*(±) Ethyl-3-benzyl-8-bromo-4-methyl-1-tosyl-1,2,3,6-tetrahydro-2,6-methanobenzo[d][1,3]diazocine-5-carboxylate (**4r**).* Purification by flash column chromatography on silica gel eluting with petroleum ether-ethyl acetate mixture (90:10 to 85:15, v/v) afforded the title compound as colourless solid; mp: 178-180 ^{o}C; yield: 0.494 g, 85%; IR (neat): 3427.6, 2944.5, 2257.1, 1717.9, 1559.3, 1429.4, 1332.1, 1209.3, 1168.1, 1106.6 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88 (d, *J* = 8.7 Hz, 1H), 7.57 (d, *J* = 2.4 Hz, 1H), 7.43 (d, *J* = 8.1 Hz, 2H), 7.28-7.38 (m, 3H), 7.23 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.12-7.19 (m, 4H), 5.71 (s, 1H), 4.81 (d, *J* = 17.4 Hz, 1H), 4.72 (d, *J* = 17.7 Hz, 1H), 4.21-4.30 (m, 1H), 4.10-4.18 (m, 2H), 2.36 (s, 3H), 2.35 (s, 3H), 1.72 (dt, *J* = 12.6, 3.3 Hz, 1H), 1.40-1.47 (m, 1H), 1.36 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 167.0, 153.4, 144.4, 137.5, 135.6, 134.5, 132.3, 131.9, 128.9, 127.4, 127.0, 126.1, 124.3, 117.9, 101.1, 67.9, 59.5, 50.8, 30.0, 24.6, 21.6, 16.1, 14.7; Anal Calcd for $C_{29}H_{29}BrN_2O_4S$: C, 59.90; H, 5.03; N, 4.82. Found: C, 59.53; H, 4.92; N, 4.71.

*(±) Ethyl-8-bromo-4-methyl-3-phenethyl-1-tosyl-1,2,3,6-tetrahydro-2,6-methanobenzo[d][1,3]diazocine-5-carboxylate (**4s**).* Purification by flash column chromatography on silica gel eluting with petroleum ether-ethyl acetate mixture (90:10 to 85:15, v/v) afforded the title compound as off-white solid; mp: 144-146 ^{o}C; yield: 0.512 g, 86%; IR (neat): 3423.9, 2974.6, 2924.5, 1671.9, 1570.7, 1476.2, 1336.5, 1258.3, 1219.8, 1160.9, 1066.7 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.91 (d, *J* = 9 Hz, 1H), 7.52 (d, *J* = 3.6 Hz, 1H), 7.47 (d, *J* = 7.2 Hz, 2H), 7.27-7.38 (m, 4H), 7.19-7.22 (m, 3H), 5.66 (s, 1H), 4.23-4.28 (m, 1H), 4.05-4.20 (m, 3H), 3.60-3.84 (m, 2H), 2.82-2.96 (m, 2H), 2.39 (s, 3H), 2.38 (s, 3H), 1.52-1.60 (m, 1H), 1.35 (t, *J* = 7.2 Hz, 3H), 1.23-1.29 (m, 1H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 167.0, 153.1, 144.4, 138.1, 135.7, 134.7, 132.2, 131.8, 129.9, 129.3, 129.1, 128.7, 127.0, 126.7, 124.2, 117.9, 101.0, 67.7, 59.4, 49.6, 35.9, 29.8, 24.3, 21.6, 15.7, 14.7; Anal Calcd for $C_{30}H_{31}BrN_2O_4S$: C, 60.50; H, 5.25; N, 4.70. Found: C, 60.19; H, 5.12; N, 4.59.

*(±) tert-Butyl-3-benzyl-8-bromo-4-methyl-1-tosyl-1,2,3,6-tetrahydro-2,6-methanobenzo[d][1,3]diazocine-5-carboxylate (**4t**).* Purification by flash column chromatography on silica gel eluting with petroleum ether-ethyl acetate mixture (90:10 to 85:15, v/v) afforded the title compound as off-white solid; mp: 153-154 ^{o}C; yield: 0.463 g, 76%; IR (neat): 3427.7, 2971.6, 1671.4, 1566.3, 1480.8, 1351,0, 1266.6, 1147.9, 1103.7 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89 (d, *J* = 9 Hz, 1H), 7.61 (d, *J* = 2.4 Hz, 1H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.29-7.38 (m, 3H), 7.23 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.13-7.19 (m, 4H), 5.69 (s, 1H), 4.79 (d, *J* = 17.7 Hz, 1H), 4.70 (d, *J* = 17.7 Hz, 1H), 4.09 (s, 1H), 2.36 (s, 3H), 2.31 (s, 3H), 1.73 (dt, *J* = 12.6, 2.7 Hz, 1H), 1.55 (s, 9H), 1.42 (dt, *J* = 12.6, 2.1 Hz, 1H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 166.6, 152.4, 144.3, 137.7, 135.7, 134.6, 132.3, 131.7, 129.8, 129.1, 128.9, 127.3, 127.0, 126.1, 124.4, 117.9, 102.5, 79.4, 67.9, 50.6, 30.3, 28.7, 24.5, 21.6, 16.0; Anal Calcd for $C_{31}H_{33}BrN_2O_4S$: C, 61.08; H, 5.46; N, 4.60. Found: C, 60.77; H, 5.38; N, 4.52.

*(±) tert-Butyl-8-bromo-4-methyl-3-phenethyl-1-tosyl-1,2,3,6-tetrahydro-2,6-methanobenzo[d][1,3]diazocine-5-carboxylate (**4u**).* Purification by flash column chromatography on silica gel eluting with petroleum ether-ethyl acetate mixture (90:10 to 85:15, v/v) afforded the title compound as off-white solid; mp: 158-160 ^{o}C; yield: 0.480 g, 77%; IR (neat): 3426.9, 2969.8, 2924.5, 1670.0, 1565.9, 1476.2, 1349.9, 1265.0, 1146.5, 1102.1 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.91 (d, *J* = 9.0 Hz, 1H); 7.59 (d, *J* = 2.1 Hz, 1H), 7.46 (d, *J* = 8.1 Hz, 2H), 7.29-7.35 (m, 4H), 7.20 (d, *J* = 8.4 Hz, 4H), 5.66 (s, 1H), 4.00 (s, 1H), 3.74-3.84 (m, 1H), 3.56-3.66 (m, 1H), 2.90-3.00 (s, 3H), 2.37 (s, 3H), 2.36 (s, 3H), 1.54-1.58 (m, 10H), 1.23-1.28 (m, 1H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 166.6, 152.1, 144.3, 138.2, 135.8, 134.8, 132.2, 131.7, 129.9, 129.1, 128.7, 127.0, 126.6, 124.3, 117.8, 102.5, 79.3, 67.7, 49.5, 35.9, 30.1, 28.7, 24.3, 21.6, 15.7; Anal Calcd for $C_{32}H_{35}BrN_2O_4S$: C, 61.63; H, 5.66; N, 4.49. Found: C, 61.33; H, 5.54; N, 4.33.

*(±) 1-(tert-Butyl) 5-methyl-3-benzyl-8-bromo-4-methyl-3,6-dihydro-2,6-methanobenzo[d][1,3]diazocine-1,5(2H)-dicarboxylate (**4v**).* Purification by flash column chromatography on silica gel eluting with petroleum ether-ethyl acetate mixture (90:10 to 85:15, v/v) afforded the title compound as off-white solid; mp: 110-114 ^{o}C; yield: 0.348 g, 66%; IR (neat): 3397.9, 2979.5, 2932.2, 1710.6, 1679.7, 1570.7, 1390.4, 1369, 1315.2, 1213.0, 1165.8, 1094.4 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62 (d, *J* = 9.0 Hz, 1H), 7.54 (d, *J* = 2.4 Hz, 1H), 7.24-7.33

(m, 3H), 7.18 (dd, *J* = 9.0, 2.4 Hz, 1H), 7.02 (d, *J* = 6.6 Hz, 2H), 5.90 (s, 1H), 4.74 (d, *J* = 17.7 Hz, 1H), 4.66 (d, *J* = 17.7 Hz, 1H), 4.37 (s, 1H), 3.79 (s, 3H), 2.35 (s, 3H), 2.13 (dt, *J* = 12.3, 2.1 Hz, 1H), 1.95 (dt, *J* = 12.3, 2.7 Hz, 1H), 1.30 (s, 9H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 167.7, 154.2, 152.5, 137.8, 133.8, 133.7, 131.2, 128.7, 128.6, 127.2, 125.6, 124.5, 116.2, 101.6, 82.3, 65.3, 51.6, 50.9, 30.6, 28.1, 26.7, 16.0; Anal Calcd for $C_{26}H_{29}BrN_2O_4$ C, 60.82; H, 5.69; N, 5.46. Found: C, 60.61; H, 5.50; N, 5.33.

Procedure for the Synthesis of Compound 4a in 3 mmol Scale. To a stirred solution of *n*-butylamine **1a** (3.6 mmol, 0.263 g) in MeOH (20 mL) was added methyl acetoacetate **2a** (3.0 mmol, 0.348 g) and $InCl_3$ (10 mol%, 0.066 g). The reaction mixture was stirred at room temperature for 20 minutes. To this reaction mixture, (*E*)-4-methyl-*N*-(2-(3-oxoprop-1-en-1-yl)phenyl)benzenesulfonamide **3a** (3.0 mmol, 0.904 g) was added, and the reaction mixture was stirred at 65 °C in an oil bath for 1 h. After completion of the reaction, the mixture was diluted with water (20 mL), extracted with ethyl acetate (3 × 15 mL), and washed with brine. The organic layer was separated, dried over anhydrous sodium sulphate, and concentrated in vacuum. The crude product **4a** was purified through silica column chromatography using petroleum ether-ethyl acetate as eluent (90:10 to 85:15, v/v). Yield: 79% (1.08 g).

General Procedure for the Synthesis of Bridged Chromanes 6a-r. To a stirred solution of primary amine **1** (1.2 mmol, 1.2 equiv.) in MeOH (6 mL) was added β-ketoester **2** (1.0 mmol, 1.0 equiv.) and $InCl_3$ (10 mol%). The reaction mixture was stirred at room temperature for 20 minutes. To this reaction mixture 2-hydroxyarylaldehyde **5** (1.0 mmol, 1.0 equiv.) was added and the reaction was stirred at 65 °C in an oil bath for 1 h. After completion of the reaction, the reaction mixture was diluted with water (6 mL), extracted with ethyl acetate (3 × 6 mL), and washed with brine (6 mL). The organic layer was separated, dried over anhydrous sodium sulphate, and concentrated in vacuum. The crude product was purified through silica column chromatography using petrolium ether-ethyl acetate as eluent (90:10 to 85:15, v/v).

*(±) Methyl-3-butyl-4-methyl-3,6-dihydro-2H-2,6-methanobenzo[g][1,3]oxazocine-5-carboxylate (**6a**).* Purification by flash column chromatography on silica gel eluting with petroleum ether-ethyl acetate mixture (90:10 to 85:15, v/v) afforded the title compound as off-white solid; mp: 104-105 °C; yield: 0.223 g, 74%; IR (neat): 3433.6, 2945.7, 2927.4, 1674.9, 1559.2, 1484.9, 1428.9, 1248.7, 1222.6, 1115.6, 1087.7 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.33 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.06 (td, *J* = 7.8, 1.8 Hz, 1H), 6.81-6.86 (m, 2H), 5.35 (s, 1H), 4.19 (s, 1H), 3.75 (s, 3H), 3.47-3.57 (m, 1H), 3.27-3.38 (m. 1H), 2.38 (s, 3H), 2.11 (dt, *J* = 12.9, 3.0 Hz, 1H), 1.79 (dt, *J* = 12.6, 2.7 Hz, 1H), 1.50-1.66 (m, 2H), 1.25-1.39 (m, 2H), 0.94 (t, *J* = 7.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 168.1, 153.1, 150.8, 128.9, 127.8, 127.1, 102.1, 81.3, 50.7, 49.5, 32.2, 28.0, 25.9, 20.1, 15.7, 13.9; Anal Calcd for $C_{18}H_{23}NO_3$ C, 71.73; H, 7.69; N, 4.65. Found: C, 71.35; H, 7.68; N, 4.57.

*(±) Methyl-3-hexyl-4-methyl-3,6-dihydro-2H-2,6-methanobenzo[g][1,3]oxazocine-5-carboxylate (**6b**).* Purification by flash column chromatography on silica gel eluting with petroleum ether-ethyl acetate mixture (90:10 to 85:15, v/v) afforded the title compound as brown solid; mp: 76-77 °C; yield: 0.227 g, 69%; IR (neat): 3434.8, 2974.1, 2958.0, 1684.4, 1588.9, 1427.9, 1329.0, 1208.1, 1157.3, 1106.5 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.33 (dd, *J* = 7.2, 1.5 Hz, 1H), 7.06 (td, *J* = 8.1, 1.5 Hz, 1H), 6.80-6.86 (m, 2H), 5.35 (s, 1H), 4.19 (s, 1H), 3.75 (s, 3H), 3.46-3.57 (m, 1H), 3.20-3.37 (m, 1H), 2.39 (s, 3H), 2.11 (dt, *J* = 12.6, 3.0 Hz, 1H), 1.56-1.82 (m, 5H), 1.25-1.29 (m, 4H), 0.87-0.91 (m, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 168.1, 153.1, 150.8, 128.8, 127.8, 127.0, 120.5, 116.2, 102.0, 81.3, 50.7, 49.7, 31.5, 30.0, 28.0, 26.6, 25.9, 22.6, 15.7, 14.0; Anal Calcd for $C_{20}H_{27}NO_3$: C, 72.92; H, 8.26; N, 4.25. Found: C, 72.70; H, 8.17; N, 4.24.

*(±) Methyl-3-benzyl-4-methyl-3,6-dihydro-2H-2,6-methanobenzo[g][1,3]oxazocine-5-carboxylate (**6c**).* Purification by flash column chromatography on silica gel eluting with petroleum ether-ethyl acetate mixture (90:10 to 85:15, v/v) afforded the title compound as brown solid; mp: 99-101 °C; yield: 0.275 g, 82%; IR (neat): 3426.9, 2938.9, 1674.9, 1564.9, 1456.9, 1424.2, 1328.7, 1224.6, 1165.8, 1118.5, 1056.8 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$/DMSO-d_6): δ 7.25-7.40 (m, 4H), 7.14 (d, *J* = 6.9 Hz, 2H), 7.07 (td, *J* = 7.8, 1.5 Hz, 1H), 6.87 (dd, *J* = 7.2, 0.9 Hz, 1H), 6.81 (d, *J* = 8.1 Hz, 1H), 5.34 (s, 1H), 4.76 (s, 2H), 4.28 (s, 1H), 3.76 (s, 3H), 2.34 (s, 3H), 2.16 (dt, *J* = 12.9, 2.7 Hz, 1H), 1.93 (dt, *J* = 12.6, 2.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$/DMSO-d_6): δ 167.2, 152.4, 150.2, 137.3, 128.5, 128.2, 127.0, 126.6, 126.5, 125.3, 120.0, 115.7, 102.0, 80.5, 51.5, 50.4, 27.3, 25.2, 15.4; Anal Calcd for $C_{21}H_{21}NO_3$: C, 75.20; H, 6.31; N, 4.18. Found: C, 75.05; H, 6.23; N, 4.09.

*(±) Methyl-4-methyl-3-phenethyl-3,6-dihydro-2H-2,6-methanobenzo[g][1,3]oxazocine-5-carboxylate (**6d**).* Purification by flash column chromatography on silica gel eluting with petroleum ether-ethyl acetate mixture (90:10 to 85:15, v/v) afforded the title compound as off-white solid; mp: 122-123 °C; yield: 0.286 g, 82%; IR (neat): 3443.3, 3023.8, 2942.8, 1681.6, 1561.2, 1482.9, 1423.2, 1251.6, 1158.0, 1115.6, 1046.2 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.31-7.35 (m, 2H), 7.22-7.29 (m, 2H), 7.17-7.20 (m, 2H), 7.04-7.09 (m, 1H), 6.82-6.87 (m, 2H), 5.25 (s, 1H), 4.19 (s, 1H), 3.72-3.83 (m, 4H), 3.54-3.64 (m, 1H), 2.93-3.02 (m, 1H), 2.75-2.85 (m, 1H), 2.40 (s, 3H), 2.07 (dt, *J* = 12.6, 2.7 Hz, 1H), 1.77 (dt, *J* = 12.6, 2.7 Hz, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 168.1, 152.7, 150.8, 138.5, 128.9, 128.7, 127.8, 127.1, 126.7, 120.6, 116.3, 102.8, 81.7, 51.4, 50.8, 36.8, 28.0, 25.8, 15.6; Anal Calcd for $C_{22}H_{23}NO_3$: C, 75.62; H, 6.63; N, 4.01. Found: C, 75.54; H, 6.59; N, 4.03.

*(±) Methyl-4-methyl-3-phenyl-3,6-dihydro-2H-2,6-methanobenzo[g][1,3]oxazocine-5-carboxylate (**6e**).* Purification by flash column chromatography on silica gel eluting with petroleum ether-ethyl acetate mixture (90:10 to 85:15, v/v) afforded the title compound as off-white solid; mp: 161-162 °C; yield: 0.247 g, 77%; IR (neat): 3417.2, 2945.7, 1676.8, 1563.0, 1484.9, 1406.8, 1321.9, 1211.0, 1104.4, 1073.2 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$):

δ 7.31-7.42 (m, 4H), 7.07-7.13 (m, 3H), 6.88 (td, *J* = 7.2, 1.2 Hz, 1H), 6.84 (d, *J* = 8.1 Hz, 1H), 5.62 (s, 1H), 4.30 (s, 1H), 3.79 (s, 3H), 2.26 (dt, *J* = 12.6, 2.7 Hz, 1H), 2.04-2.11 (m, 4H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$): δ* 168.1, 152.2, 150.9, 143.7, 129.5, 128.9, 127.8, 127.6, 127.2, 120.7, 116.4, 104.2, 82.5, 50.9, 28.1, 26.2, 18.7; Anal Calcd for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36. Found: C, 74.39; H, 5.99; N, 4.32. *One aromatic carbon is merged with others.

*(±) Methyl-3-(4-methoxyphenyl)-4-methyl-3,6-dihydro-2H-2,6-methanobenzo[g][1,3]oxazocine-5-carboxylate (**6f**).* Purification by flash column chromatography on silica gel eluting with petroleum ether-ethyl acetate mixture (90:10 to 85:15, v/v) afforded the title compound as colourless solid; mp: 178-180 °C; yield: 0.239 g, 68%; IR (neat): 3436.5, 2943.8, 1674.9, 1561.1, 1509.0, 1321.9, 1219.8, 1110.8, 1076.1 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39 (dd, *J* = 7.5, 1.5 Hz, 1H); 7.10 (td, *J* = 8.1, 1.8 Hz, 1H), 6.88-7.02 (m, 4H), 6.84 (d, *J* = 8.1 Hz, 2H), 5.54 (s, 1H), 4.29 (s, 1H), 3.83 (s, 3H), 3.78 (s, 3H), 2.24 (dt, *J* = 12.6, 3.0 Hz, 1H), 2.03-2.09 (m, 4H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$): δ 168.1, 158.8, 152.7, 150.9, 136.4, 128.9, 127.9, 127.2, 120.7, 116.4, 114.6, 103.7, 82.7, 55.5, 50.8, 28.1, 26.2, 18.5; Anal Calcd for $C_{21}H_{21}NO_4$: C, 71.78; H, 6.02; N, 3.99. Found: C, 71.85; H, 5.90; N, 3.89.

*(±) Methyl-3-(4-fluorophenyl)-4-methyl-3,6-dihydro-2H-2,6-methanobenzo[g][1,3]oxazocine-5-carboxylate (**6g**).* Purification by flash column chromatography on silica gel eluting with petroleum ether-ethyl acetate mixture (90:10 to 85:15, v/v) afforded the title compound as colourless solid; mp: 152-153 °C; yield: 0.244 g, 72%; IR (neat): 3437.8. 2931.3, 1684.3, 1571.2, 1509.8, 1326.4, 1219.7, 1108.6, 1079.2 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.08-7.13 (m, 5H), 6.89 (td, *J* = 7.5, 1.2 Hz, 1H), 6.83 (d, *J* = 8.1 Hz, 1H), 5.55 (s, 1H), 4.29 (s, 1H), 3.79 (s, 3H), 2.25 (dt, *J* = 12.9, 3.0 Hz, 1H), 2.03-2.10 (m, 4H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$): δ 168.0; 161.7 (d, *J* = 246 Hz), 151.9, 150.7, 139.6 (d, *J* = 3.0 Hz), 130.6, 128.9, 127.8, 127.3, 120.8, 116.4, 116.3 (d, *J* = 22.5 Hz), 104.6, 82.6, 50.9, 28.1, 26.2, 18.6; Anal Calcd for $C_{20}H_{18}FNO_3$: C, 70.78; H, 5.35; N, 4.13. Found: C, 70.53; H, 5.40; N, 4.04.

*(±) Methyl-3-(4-bromophenyl)-4-methyl-3,6-dihydro-2H-2,6-methanobenzo[g][1,3]oxazocine-5-carboxylate (**6h**).* Purification by flash column chromatography on silica gel eluting with petroleum ether-ethyl acetate mixture (90:10 to 85:15, v/v) afforded the title compound asoff-white solid; mp: 127-128 °C; yield: 0.304 g, 76%; IR (neat): 3419.6, 2944.3, 1676.8, 1566.3, 1481.3, 1408.7, 1328.1, 1210.5, 1101.8, 1071.6 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52 (d, *J* = 8.7 Hz, 2H), 7.38 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.10 (td, *J* = 7.8, 1.5 Hz, 1H), 7.00 (d, *J* = 7.8 Hz, 2H), 6.89 (dd, *J* = 7.5, 1.2 Hz, 1H), 6.81 (d, *J* = 8.1 Hz, 1H), 5.58 (s, 1H), 4.29 (s, 1H), 3.79 (s, 3H), 2.25 (td, *J* = 12.6, 2.7 Hz, 1H), 2.03-2.10 (m, 4H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$): δ 167.9, 151.5, 150.7, 142.7, 132.7, 130.6, 128.9, 127.6, 127.4, 121.4, 120.9, 116.4, 105.2, 82.4, 51.0, 28.1, 26.2, 18.7; Anal Calcd for $C_{20}H_{18}BrNO_3$: C, 60.01; H, 4.53; N, 3.50. Found: C, 59.85; H, 4.60; N, 3.49.

*(±) Ethyl-4-methyl-3-phenethyl-3,6-dihydro-2H-2,6-methanobenzo[g][1,3]oxazocine-5-carboxylate (**6i**).* Purification by flash column chromatography on silica gel eluting with petroleum ether-ethyl acetate mixture (90:10 to 85:15, v/v) afforded the title compound as pale yellow solid; mp: 108-109 °C; yield: 0.305 g, 84%; IR (neat): 3443.3, 3028.8, 2949.3, 1684.4, 1561.3, 1480.3, 1428.6, 1253.2, 1154.6, 1116.0, 1096.8, 1076.3 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$/DMSO-d_6): δ 7.18-7.35 (m, 6H), 7.03-7.08 (m, 1H), 6.81-6.85 (m, 2H), 5.27 (s, 1H), 4.12-4.28 (m, 3H), 3.73-3.83 (m, 1H), 3.57-3.65 (m, 1H), 2.93-3.02 (m, 1H), 2.75-2.85 (m, 1H), 2.39 (s, 3H), 2.06 (dt, *J* = 12.6, 2.7 Hz, 1H), 1.79 (dt, *J* = 12.3, 2.4 Hz, 1H), 1.38 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$/DMSO-d_6): δ 167.3, 152.2, 150.6, 138.4, 128.6, 128.5, 127.7, 126.9, 126.5, 120.3, 116.0, 102.7, 81.5, 59.1, 51.2, 36.6, 27.7, 25.5, 15.4, 14.6; Anal Calcd for $C_{23}H_{25}NO_3$: C, 76.01; H, 6.93; N, 3.85. Found: C, 75.76; H, 6.83; N, 3.76.

*(±) Ethyl-3-(4-methoxyphenyl)-4-methyl-3,6-dihydro-2H-2,6-methanobenzo[g][1,3]oxazocine-5-carboxylate (**6j**).* Purification by flash column chromatography on silica gel eluting with petroleum ether-ethyl acetate mixture (90:10 to 85:15, v/v) afforded the title compound as off-white solid; mp: 150-151 °C; yield: 0.270 g, 74%; IR (neat): 3426.9, 2979.9, 2945.7, 1676.8, 1561.1, 1484.9, 1320.0, 1211.1, 1108.8, 1064.5 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42 (dd, *J* = 7.5, 1.5 Hz, 1H); 7.07-7.12 (m, 3H), 6.83-6.92 (m, 4H), 5.55 (s, 1H), 4.18-4.30 (m, 3H), 3.83 (s, 3H), 2.23 (dt, *J* = 12.6, 3.0 Hz, 1H), 2.04-2.10 (m, 4H), 1.39 (t, *J* = 6.9 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$): δ* 167.7, 158.8, 152.5, 150.9, 136.5, 128.9, 128.0, 127.2, 120.6, 116.4, 114.6, 103.8, 82.7, 59.5, 55.5, 28.1, 26.2, 18.5, 14.7; Anal Calcd for $C_{22}H_{23}NO_4$: C, 72.31; H, 6.34; N, 3.83. Found: C, 71.95; H, 6.31; N, 3.79. *One aromatic carbon is merged with others.

*(±) Ethyl-3-(4-fluorophenyl)-4-methyl-3,6-dihydro-2H-2,6-methanobenzo[g][1,3]oxazocine-5-carboxylate (**6k**).* Purification by flash column chromatography on silica gel eluting with petroleum ether-ethyl acetate mixture (90:10 to 85:15, v/v) afforded the title compound as off-white solid; mp: 154-155 °C; yield: 0.265 g, 74%; IR (neat): 3436.5, 2981.3, 1681.6, 1570.7, 1507.1, 1323.8, 1211.1, 1106.9, 1071.3 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.07-7.13 (m, 5H), 6.89 (td, *J* = 7.5, 1.2 Hz, 1H), 6.83 (d, *J* = 8.1 Hz, 1H), 5.56 (s, 1H), 4.18-4.31 (m, 3H), 2.25 (dt, *J* = 12.6, 2.7 Hz, 1H), 2.03-2.11 (m, 4H), 1.39 (t, *J* = 6.9 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$): δ 167.5, 161.7 (d, *J* = 246 Hz), 151.7, 150.8, 139.6 (d, *J* = 3.0 Hz), 128.9, 127.8, 127.3, 120.8, 116.4, 116.3 (d, *J* = 22.5 Hz), 104.8, 82.6, 59.6, 28.1, 26.2, 18.5, 14.7; Anal Calcd for $C_{21}H_{20}FNO_3$: C, 71.37; H, 5.70; N, 3.96. Found: C, 71.03; H, 5.50; N, 3.74.

*(±) tert-Butyl-3-benzyl-4-methyl-3,6-dihydro-2H-2,6-methanobenzo[g][1,3]oxazocine-5-carboxylate (**6l**).* Purification by flash column chromatography on silica gel eluting with petroleum ether-ethyl acetate mixture (90:10 to 85:15, v/v) afforded the title compound as off-white solid; mp: 76-78 °C; yield: 0.294 g, 78%; IR (neat): 3422.1, 2974.7, 2960.2, 1684.5, 1570.7, 1428.9, 1336.4, 1222.6, 1118.5, 1052.0 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.24-7.36 (m, 3H), 7.15

(d, *J* = 7.2 Hz, 2H), 7.09 (td, *J* = 8.1, 1.8 Hz, 1H), 6.88 (dd, *J* = 7.2, 1.2 Hz, 1H), 6.83 (d, *J* = 8.1 Hz, 1H), 5.29 (s, 1H), 4.72 (s, 2H), 4.26 (s, 1H), 2.32 (s, 3H), 2.14 (dt, *J* =12.9, 3.0 Hz, 1H), 1.92 (dt, *J* = 12.6, 2.7 Hz, 1H), 1.58 (s, 9H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$): δ 167.2, 150.9, 138.2, 128.8, 127.8, 127.2, 127.1, 126.0, 120.6, 116.4, 104.3, 80.9, 79.1, 51.7, 28.8, 28.3, 25.9, 16.0; Anal Calcd for $C_{24}H_{27}NO_3$: C, 76.36; H, 7.21; N, 3.71. Found: C, 76.15; H, 7.16; N, 3.49.

*(±) tert-Butyl-4-methyl-3-phenethyl-3,6-dihydro-2H-2,6-methanobenzo[g][1,3]oxazocine-5-carboxylate (**6m**).* Purification by flash column chromatography on silica gel eluting with petroleum ether-ethyl acetate mixture (90:10 to 85:15, v/v) afforded the title compound as off-white solid; mp: 83-84 °C; yield: 0.297g, 76%; IR (neat): 3427.6, 2977.8, 1688.4, 1570.8, 1429.7, 1331.8, 1221.8, 1114.5, 1058.7 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38 (d, *J* = 7.2 Hz, 1H), 7.29-7.34 (m, 2H), 7.18-7.23 (m, 3H), 7.06 (td, *J* = 7.8, 1.5 Hz, 1H), 6.82-6.87 (m, 2H), 5.24 (s, 1H), 4.16 (s, 1H), 3.71-3.81 (m, 1H), 3.51-3.61 (m, 1H), 2.91-3.01 (m, 1H), 2.73-2.83 (m, 1H), 2.38 (s, 3H), 2.05 (dt, *J* = 12.6, 2.7 Hz, 1H), 1.78 (dt, *J* = 12.6 Hz, 1H), 1.57 (s, 9H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$): δ 167.3, 151.5, 150.8, 138.7, 128.8, 128.7, 127.9, 127.1, 126.6, 120.5, 116.3, 104.6, 81.8, 79.1, 51.3, 36.9, 28.8, 28.3, 25.9, 15.6; Anal Calcd for $C_{25}H_{29}NO_3$: C, 76.70; H, 7.47; N, 3.58. Found: C, 76.47; H, 7.42; N, 3.51.

*(±) Methyl-3-benzyl-8-bromo-4-methyl-3,6-dihydro-2H-2,6-methanobenzo[g][1,3]oxazocine-5-carboxylate (**6n**).* Purification by flash column chromatography on silica gel eluting with petroleum ether-ethyl acetate mixture (90:10 to 85:15, v/v) afforded the title compound asoff-white solid; mp: 165-166 °C; yield: 0.348 g, 84%; IR (neat): 3440.4, 2960.2, 2944.8, 1679.7, 1576.5, 1471.4, 1421.3, 1333.5, 1201.4, 1167.7, 1123.3, 1102.1 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47 (d, *J* = 2.4 Hz, 1H), 7.29-7.36 (m, 3H), 7.17 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.11 (d, *J* = 6.9 Hz, 2H), 6.69 (d, *J* = 8.4 Hz, 1H), 5.31 (s, 1H), 4.73 (s, 2H), 4.25 (s, 1H), 3.80 (s, 3H), 2.36 (s, 3H), 2.12 (dt, *J* = 12.9, 2.7 Hz, 1H), 1.91 (dt, *J* = 12.9, 2.7 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$): δ 167.8, 153.4, 150.1, 137.8, 131.5, 130.0, 129.7, 128.9, 127.4, 125.9, 118.2, 112.8, 102.3, 81.1, 52.1, 51.0, 28.0, 25.6, 16.0; Anal Calcd for $C_{21}H_{20}BrNO_3$: C, 60.88; H, 4.87; N, 3.38. Found: C, 60.36; H, 4.81; N, 3.35.

*(±) Methyl-8-bromo-4-methyl-3-phenethyl-3,6-dihydro-2H-2,6-methanobenzo[g][1,3]oxazocine-5-carboxylate (**6o**).* Purification by flash column chromatography on silica gel eluting with petroleum ether-ethyl acetate mixture (90:10 to 85:15, v/v) afforded the title compound as off-white solid; mp: 114-116 °C; yield: 0.351g, 82%; IR (neat): 3444.6, 2969.3, 2948.8, 1684.7, 1576.6, 1427.3, 1336.6, 1203.0, 1168.1, 1121.8, 1102.4, 1056.1 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44 (d, *J* = 2.4 Hz, 1H), 7.23-7.34 (m, 2H), 7.13-7.22 (m, 4H), 6.71 (d, *J* = 8.7 Hz, 1H); 5.22 (s, 1H), 4.15 (s, 1H), 3.71-3.88 (m, 4H), 3.53-3.64 (m, 1H), 2.91-3.00 (m, 1H), 2.74-2.84 (m, 1H), 2.41 (s, 3H), 2.02 (dt, *J* = 12.9, 3.0 Hz, 1H), 1.76 (dt, *J* = 12.9, 2.7 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$): δ 167.8, 152.9, 150.0, 138.4, 131.4, 130.0, 129.9, 128.8, 128.7, 126.8, 118.1, 112.7, 102.3, 81.8, 51.4, 50.9, 36.8, 27.9, 25.4, 15.6; Anal Calcd for $C_{22}H_{22}BrNO_3$: C, 61.69; H, 5.18; N, 3.27. Found: C, 61.44; H, 5.07; N, 3.08.

*(±) Ethyl-8-bromo-4-methyl-3-phenethyl-3,6-dihydro-2H-2,6-methanobenzo[g][1,3]oxazocine-5-carboxylate (**6p**).* Purification by flash column chromatography on silica gel eluting with petroleum ether-ethyl acetate mixture (90:10 to 85:15, v/v) afforded the title compound as off-white solid; mp: 79-80 °C; yield: 0.367 g, 83%; IR (neat): 3448.6, 2969.4, 2947.3, 1681.7, 1566.8, 1430.3, 1338.4, 1203.6, 1169.0, 1129.1, 1106.8, 1054.3 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49 (d, *J* = 2.4 Hz, 1H), 7.23-7.34 (m, 3H), 7.17-7.22 (m, 2H), 7.14 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.71 (d, *J* = 8.7 Hz, 1H), 5.23 (s, 1H), 4.14-4.32 (m, 3H), 3.70-3.79 (m, 1H), 3.53-3.63 (m, 1H), 2.91-3.00 (m, 1H), 2.76-2.84 (m, 1H), 2.42 (s, 3H), 2.02 (dt, *J* = 12.6, 2.7 Hz, 1H), 1.77 (dt, *J* = 12.9, 2.7 Hz, 1H), 1.40 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$): δ 167.4, 152.7, 150.1, 138.4, 131.5, 129.9, 129.8, 128.8, 128.7, 126.7, 118.0, 112.6, 102.5, 81.9, 59.5, 51.5, 36.8, 27.9, 25.4, 15.5, 14.7; Anal Calcd for $C_{23}H_{24}BrNO_3$: C, 62.45; H, 5.47; N, 3.17. Found: C, 62.13; H, 5.42; N, 3.18.

*(±) Methyl-3-benzyl-4-methyl-8-nitro-3,6-dihydro-2H-2,6-methanobenzo[g][1,3]oxazocine-5-carboxylate (**6q**).* Purification by flash column chromatography on silica gel eluting with petroleum ether-ethyl acetate mixture (90:10 to 85:15, v/v) afforded the title compound as yellow solid; mp: 146-148 °C; yield: 0.266 g, 70%; IR (neat): 3426.9, 2979.5, 2943.8, 1658.5, 1570.7, 1510.9, 1421.3, 1333.5, 1232.3, 1108.9, 1084.8 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.28 (d, *J* = 2.7 Hz, 1H), 8.0 (dd, *J* = 9.0, 3.0 Hz, 1H), 7.29-7.38 (m, 3H), 7.12 (d, *J* = 6.9 Hz, 2H), 6.87 (d, *J* = 9.0 Hz, 1H), 5.43 (s, 1H), 4.76 (s, 2H), 4.36 (s, 1H), 3.83 (s, 3H), 2.39 (s, 3H), 2.15 (dt, *J* = 12.9, 3.0 Hz, 1H), 2.02 (dt, *J* = 12.9, 2.7 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$/DMSO-d_6): δ 167.0, 156.6, 152.6, 140.8, 137.0, 128.5, 128.0, 127.0, 125.5, 124.5, 122.8, 116.5, 101.7, 81.7, 52.0, 50.6, 27.6, 24.7, 15.4; Anal Calcd for $C_{21}H_{20}N_2O_5$: C, 66.31; H, 5.30; N, 7.36. Found: C, 66.05; H, 5.40; N, 3.49.

*(±) Ethyl-3-benzyl-4-methyl-8-nitro-3,6-dihydro-2H-2,6-methanobenzo[g][1,3]oxazocine-5-carboxylate (**6r**).* Purification by flash column chromatography on silica gel eluting with petroleum ether-ethyl acetate mixture (90:10 to 85:15, v/v) afforded the title compound as yellow gummy solid; yield: 0.268g, 68%; IR (neat): 3428.6, 2978.0, 2944.5, 2848.6, 1656.4, 1571.8, 1514.6, 1422.4, 1329.4, 1109.1, 1088.5 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.35 (d, *J* = 2.7 Hz, 1H), 8.00 (dd, *J* = 9.0, 2.7 Hz, 1H), 7.29-7.38 (m, 3H), 7.13 (d, *J* = 6.9 Hz, 2H), 6.87 (d, *J* = 9.0 Hz, 1H), 5.43 (s, 1H), 4.75 (s, 2H), 4.18-4.37 (m, 3H), 2.40 (s, 3H), 2.15 (dt, *J* = 12.9, 3.0 Hz, 1H), 2.03 (dt, *J* = 12.9, 2.7 Hz, 1H), 1.47 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$): δ 167.0, 157.0, 152.9, 141.4, 137.5, 129.0, 128.4, 127.6, 126.0, 125.2, 123.2, 116.8, 102.4, 82.1, 60.0, 52.3, 28.0, 25.2, 15.8, 14.6; Anal Calcd for $C_{22}H_{22}N_2O_5$: C, 66.99; H, 5.62; N, 7.10. Found: C, 66.63; H, 5.50; N, 7.14.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Copies of ^{1}H and ^{13}C NMR spectra of all compounds, and X-ray crystallographic data of compound **4n** (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) For a review, see: Schreiber, S. L. Target-Oriented and Diversity-Oriented Organic Synthesis in Drug Discovery. *Science* **2000**, *287*, 1964–1969.

(2) For selected reviews on domino/cascade reactions, see: (a) Ardkhean, R.; Caputo, D. F. J.; Morrow, S. M.; Shi, H.; Xiong, Y.; Anderson, E. A. Cascade Polycyclizations in Natural Product Synthesis. *Chem. Soc. Rev.* **2016**, *45*, 1557–1569. (b) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G Cascade Reactions in Total Synthesis. *Angew. Chem. Int. Ed*. **2006**, *45*, 7134–7186. (c) Tietze, L. F. Domino Reactions in Organic Synthesis. *Chem. Rev*. **1996**, *96*, 115–136. (d) Parsons, P. J.; Penkett, C. S.; Shell, A. Tandem Reactions in Organic Synthesis: Novel Strategies for Natural Product Elaboration and the Development of New Synthetic Methodology. *Chem. Rev*. **1996**, *96*, 195–206.

(3) For selected recent reviews on multicomponent reactions, see: (a) Neochoritis, C. G.; Zhao, T.; Dömling, A. Tetrazoles via Multicomponent Reactions. *Chem. Rev.* **2019**, *119*, 1970–2042. (b) Zhi, S.; Ma, X.; Zhang, W. Consecutive Multicomponent Reactions for the Synthesis of Complex Molecules. *Org. Biomol. Chem*. **2019**, *17*, 7632–7650. (c) Estévez, V.; Villacampa, M.; Menéndez, J. C. Recent Advances in the Synthesis of Pyrroles by Multicomponent Reactions. *Chem. Soc. Rev*. **2014**, *43*, 4633–4657.

(4) Strecker, A. Ueber die künstliche Bildung der Milchsäure und einen neuen, dem Glycocoll homologen Körper; *Ann. Chem. Pharm*. **1850**, *75*, 27–45.

(5) Hantzsch, A. Condensationsprodukte aus Aldehydammoniak und ketonartigen Verbindungen. *Chem. Ber*. **1881**, *14*, 1637–1638.

(6) (a) Biginelli, P. Ueber Aldehyduramide des Acetessigäthers. *Chem. Ber*. **1891**, *24*, 1317–1319. (b) Biginelli, P. Ueber Aldehyduramide des Acetessigäthers. II. *Chem. Ber*. **1891**, *24*, 2962–2967.

(7) Mannich, C.; Krösche, W. Ueber ein Kondensationsprodukt aus Formaldehyd, Ammoniak und Antipyrin. *Arch. Pharm.* **1912**, *250*, 647–667.

(8) Passerini, M. Sopra gli Isonitrili (I). Composto del *p*-Isonitril-azobenzolo con Acetone ed Acido Acetico. *Gazz. Chim. Ital.* **1921**, *51*, 126–129.

(9) Ugi, I.; Meyr, R.; Fetzer U.; Steinbrückner, C. Versammlungsberichte. *Angew. Chem.* **1959**, *71*, 373–388.

(10) For some recent examples of multicomponent reactions for the synthesis of heterocycles, see: (a) Vivekanand, T.; Vachan, B. S.; Karuppasamy, M.; Muthukrishnan, I.; Maheswari, C. U.; Nagarajan, S.; Bhuvanesh, N.; Sridharan, V. Diastereoselective ABB′ Three-Component Synthesis of Highly Functionalized Spirooxindoles Bearing Five Consecutive Asymmetric Carbons. *J. Org. Chem*. **2019**, *84*, 4009–4016. (b) Muthukrishnan, I.; Vachan, B. S.; Karuppasamy, M.; Eniyaval, A.; Maheswari, C. U.; Nagarajan, S.; Menéndez, J. C.; Sridharan, V. Heterogeneous Amberlyst-15-Catalyzed Synthesis of Complex Hybrid Heterocycles Containing [1,6]-Naphthyridine Under Metal-Free Green Conditions. *Org. Biomol. Chem*. **2019**, *17*, 6872–6879. (c) Echemendía, R.; Silva, G. P.; Kawamura, M. Y.; de la Torre, A. F.; Corrêa, A. G.; Ferreira, M. A. B.; Rivera, D. G.; Paixão, M. W. A Stereoselective Sequential Organocascade and Multicomponent Approach for the Preparation of Tetrahydropyridines and Chimeric Derivatives. *Chem. Commun*. **2019**, *55*, 286–289. (d) Samala, S.; Ryu, D. H.; Song, C. E.; Yoo, E. J. Multicomponent Dipolar Cycloadditions: Efficient Synthesis of Polycyclic Fused Pyrrolizidines *via* Azomethine Ylides. *Org. Biomol. Chem*. **2019**, *17*, 1773–1777. (e) Liu, Y.-Y.; Yu, X.-Y.; Chen, J.-R.; Qiao, M.-M.; Qi, X.; Shi, D.-Q.; Xiao, W.-J. Visible-Light-Driven Aza-*ortho*-quinone Methide Generation for the Synthesis of Indoles in a Multicomponent Reaction. *Angew. Chem. Int. Ed*. **2017**, *56*, 9527–9531. (f) Wang, C.; Lai, J.; Chen, C.; Li, X.; Cao, H. Ag-Catalyzed Tandem Three-Component Reaction Toward the Synthesis of Multisubstituted Imidazoles *J. Org. Chem*. **2017**, *82*, 13740–13745. (g) Qiu, G.; Wang, Q.; Zhu, J. Palladium-Catalyzed Three-Component Reaction of Propargyl Carbonates, Isocyanides, and Alcohols or Water: Switchable Synthesis of Pyrroles and Its Bicyclic Analogues. *Org. Lett*. **2017**, *19*, 270–273.

(11) For some recent examples of cascade or domino reactions, for the synthesis of heterocycles, see: (a) Vinoth, P.; Karuppasamy, M.; Vachan, B. S.; Muthukrishnan, I.; Maheswari, C. U.; Nagarajan, S.; Pace, V.; Roller, A.; Bhuvanesh, N. Sridharan, V**.** Palladium-Catalyzed Regioselective *Syn*-Chloropalladation–Olefin Insertion–Oxidative Chlorination Cascade: Synthesis of Dichlorinated Tetrahydroquinolines. *Org. Lett*. **2019**, *21*, 3465–3469. (b) Karuppasamy, M.; Vachan, B. S.; Vinoth, P.; Muthukrishnan, I.; Nagarajan, S. Ielo, L.; Pace, V.; Banik, S.; Maheswari, C. U.; Sridharan, V. Direct Access to 9-Chloro-1*H*-benzo[*b*]furo[3,4-*e*]azepin-1-ones via Palladium(II)-Catalyzed Intramolecular *syn*-Oxypalladation/Olefin Insertion/sp^2-C–H Bond Activation Cascade. *Org. Lett*. **2019**, *21*, 5784–5788. (c) Vachan, B. S.; Ramesh, A.; Karuppasamy, M.; Muthukrishnan, I.; Nagarajan, S.; Menéndez, J. C.; Maheswari, C. U.; Sridharan, V. Oxidant-Free, Three-Component Synthesis of 7-Amino-6*H*-benzo[*c*]chromen-6-ones Under Green Conditions. *RSC Adv*. **2019**, *9*, 32946–32953. (d) Yang, S.-M.; Karanam, P.; Wang, M.; Jang, Y.-J.; Yeh, Y.-S.; Tseng, P.-Y.; Ganapuram, M. R.; Liou, Y.-C.; Lin, W. A Vinylogous Michael Addition-Triggered Quadruple Cascade Reaction for the Enantioselective Generation of Multiple Quaternary Stereocenters. *Chem. Commun*. **2019**, *55*, 1398–1401. (e) Kroc, M. A.; Markiewicz, M.; Pace, W. H.; Wink, D. J.; Anderson, L. L. Catalyst-Controlled Cascade Synthesis of Bridged Bicyclic Tetrahydrobenz[*b*]azepine-4-ones. *Chem. Commun.* **2019**, *55*, 2309–2312. (f) Alonso-Marañón, L.; Sarandeses, L. A.; Mar-

tínez, M. M.; Sestelo, J. P. Synthesis of Fused Chromenes by the Indium(III)-Catalyzed Cascade Hydroarylation/Cycloisomerization Reactions of Polyyne-Type Aryl Propargyl Ethers. *Org. Chem. Front*. **2018**, *5*, 2308–2312. (g) Parua, S.; Das, S.; Sikari, R.; Sinha, S.; Paul, N. D. One-Pot Cascade Synthesis of Quinazolin-4(3*H*)-ones via Nickel-Catalyzed Dehydrogenative Coupling of *o*-Aminobenzamides with Alcohols. *J. Org. Chem*. **2017**, *82*, 7165–7175. (h) Zhang, S.; Cheng, B.; Wang, S.-A.; Zhou, L.; Tung, C.-H.; Wang, J.; Xu, Z. Gold-Catalyzed Cycloisomerization/1,5-H Migration/Diels–Alder Reaction Cascade: Synthesis of Complex Nitrogen-Containing Heterocycles.*Org. Lett.* **2017**, *19*, 1072–1075.

(12) Yet, L. Privileged Structures in Drug Discovery: Medicinal Chemistry and Synthesis, 1st Ed., Wiley, 2018.

(13) For comprehensive reviews of tetrahydroquinolines, see: (a) Muthukrishnan, I.; Sridharan, V.; Menéndez, J. C. Progress in the Chemistry of Tetrahydroquinolines. *Chem. Rev*. **2019**, *119*, 5057–5191. (b) Sridharan, V.; Suryavanshi, P. A.; Menéndez, J. C. Advances in the Chemistry of Tetrahydroquinolines.*Chem. Rev*. **2011**, *111*, 7157–7259.

(14) (a) Renner, U.; Kernweisz, P. Alkaloide aus *Schizozygia caffaeoides*. Experientia **1963**, *19*, 244–246. (b) Miura, Y.; Hayashi, N.; Yokoshima, S.; Fukuyama, T. Total Synthesis of (**–**)-Isoschizogamine, *J. Am. Chem. Soc*. **2012**, *134*, 11995–11997.

(15) (a) Hájíček, J.; Taimr, J.; Buděšínský, M. Revised structure of Isoschizogamine. *Tetrahedron Lett*. **1998**, *39*, 505–508. (b) Hubbs, J. L.; Heathcock, C. H. Total Synthesis of (±)-Isoschizogamine. *Org. Lett*. **1999**, *1*, 1315–1317.

(16) Movassaghi, M.; Schmidt, M. A. Concise Total Synthesis of (–)-Calycanthine, (+)-Chimonanthine, and (+)-Folicanthine. *Angew. Chem. Int. Ed*. **2007**, *46*, 3725–3728 and references cited therein.

(17) Houghton, P. J.; Hairong, Y. Further Chromone Alkaloids from *Schumanniophyton magnificum*. *Planta Med*. **1987**, *53*, 262–264.

(18) Biała, J.; Czarnocki, Z. Maurin, J. K. Diastereoselective Synthesis of Lortalamine Analogs *Tetrahedron: Asymmetry* **2002**, *13*, 1021–1023 and references cited therein.

(19) (a) Lv, X.-J.; Chen, Y.-H.; Liu, Y.-K. Two Competitive but Switchable Organocatalytic Cascade Reaction Pathways: The Diversified Synthesis of Chiral Acetal-Containing Bridged Cyclic Compounds. *Org. Lett*. **2019**, *21*, 190–195. (b) Chen, Y.-H.; Lv, X.-J.; You, Z.-H.; Liu, Y.-K. Asymmetric Organocatalyzed Reaction Sequence To Synthesize Chiral Bridged and Spiro-Bridged Benzofused Aminals via Divergent Pathways. *Org. Lett.* **2019**, *21*, 5556–5561. (c) Borade, B. R.; Nomula, R.; Gonnade, R. G.; Kontham, R. Fe(III)-Catalyzed Diastereoselective Friedel–Crafts Alkylation–Hemiketalization–Lactonization Cascade for the Synthesis of Polycyclic Bridged 2-Chromanol Lactones. *Org. Lett.* **2019**, *21*, 2629–2633. (d) Du, J.-Y.; Ma, Y.-H.; Meng, F.-X.; Chen, B.-L.; Zhang, S.-L.; Li, Q.-L.; Gong, S.-W.; Wang, D.-Q.; Ma, C.-L. Lewis Acid Catalyzed Tandem 1,4-Conjugate Addition/Cyclization of in Situ Generated Alkynyl *o*-Quinone Methides and Electron-Rich Phenols: Synthesis of Dioxabicyclo[3.3.1]nonane Skeletons. *Org. Lett.* **2018**, *20*, 4371–4374. (e) Liu, H.; Wang, Y.; Guo, X.; Huo, L.; Xu, Z.; Zhang, W.; Qiu, S.; Yang, B.; Tan, H. A Bioinspired Cascade Sequence Enables Facile Assembly of Methanodibenzo[*b*,*f*][1,5]dioxocin Flavonoid Scaffold. *Org. Lett.* **2018**, *20*, 546–549. (f) Guo, J.; Bai, X.; Wang, Q.; Bu, Z. Diastereoselective Construction of Indole-Bridged Chroman Spirooxindoles through a TfOH-Catalyzed Michael Addition-Inspired Cascade Reaction. *J. Org. Chem.* **2018**, *83*, 3679–3687. (g) Ransborg, L. K.; Overgaard, M.; Hejmanowska, J.; Barfüsser, S.; Jørgensen, K. A.; Albrecht, Ł. Asymmetric Formation of Bridged Benzoxazocines through an Organocatalytic Multicomponent Dienamine-Mediated One-Pot Cascade. *Org. Lett.* **2014**, *16*, 4182–4185. (h) Sahn, J. J.; Martin, S. F. Facile Syntheses of Substituted, Conformationally-Constrained Benzoxazocines and Benzazocines via Sequential Multicomponent Assembly and Cyclization. *Tetrahedron Lett.* **2011**, *52*, 6855–6858.

(20) Sridharan, V.; Maiti, S.; Menéndez, J. C. A Very Efficient Cerium(IV) Ammonium Nitrate Catalyzed, Four-Component Synthesis of Tetrahydropyridines and Its Application in the Concise Generation of Functionalized Homoquinolizine Frameworks. *Chem. Eur. J*. **2009**, *15*, 4565–4572.

(21) Kim, D. H. Rearrangements of 4-(2-Aminophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylic acid diethyl ester. *J. Heterocyclic Chem.* **1986**, *23*, 1471–1474.

(22) For a review on cerium(IV) ammonium nitrate as a catalyst in organic synthesis, see: Sridharan, V.; Menéndez, J. C. Cerium(IV) Ammonium Nitrate as a Catalyst in Organic Synthesis. *Chem. Rev*. **2010**, *110*, 3805–3849.

(23) (a) Sedova1, V. F.; Krivopalov, V. P.; Shkurko, O. P.; Unexpected Transformations of 11-Acetyl-8-bromo-2-methyl-5,6-dihydro-2*H*-2,6-methano-1,3,5-benzoxadiazocin-4(3*H*)-one(thione). *Chem. Heterocycl. Compd*. **2017**, *53*, 1163–1166. (b) Sedova, V. F.; Krivopalov, V. P.; Shkurko, O. P. Synthesis and Intramolecular Transformations of 8-Substituted 11-Nitro-2-phenyl-5,6-dihydro-2*H*-2,6-methanobenzo[*g*][1,3,5]oxadiazocin-4(*3H*)-one diastereomers. *Russ. Chem. Bull. Int. Ed*. **2016**, *65*, 215–222. (c) Kulakov, V.; Talipov, S. A.; Shulgau, Z. T.; Seilkhanov, T. M. Synthesis, Structure, and Antiradical Activity of New Methano[1,3]Thiazolo[2,3-*d*][1,3,5]Benzoxa-Diazocine Derivatives. *Chem. Heterocycl. Compd.* **2015**, *50,* 1478–1486. (d) Sedova, V. F.; Krivopalov, V. P.; Gatilov, Y. V.; Shkurko, O. P. Synthesis and Intramolecular Conversion of Substituted 2-Methyl-11-nitro-5,6-dihydro-2*H*-2,6-methanobenzo[*g*][1,3,5] oxadiazocin-4(3*H*)-ones in Different Solvents. *Russ. Chem. Bull. Int. Ed*. **2014**, *63*, 1378–1385. (e) Tkachenko, V. V.; Muravyova, E. A.; Desenko, S. M.; Shishkin, O. V.; Shishkina, S. V.; Sysoiev, D. O.; Müller, T. J. J. Chebanov, V. A. The Unexpected Influence of Aryl Substituents in *N*-Aryl-3-oxobutanamides on the Behavior of their Multicomponent Reactions with 5-Amino-3-methylisoxazole and Salicylaldehyde. *Beilstein J. Org. Chem*. **2014**, *10*, 3019–3030. (f) Sedova, V. F.; Krivopalov, V. P.; Gatilov, Y. V.; Shkurko, O. P. 2-Methyl-11-nitro-5,6-dihydro-2*H*-2,6-methano- 1,3,5-benzoxadiazocin-4(3*H*)-one: Synthesis, Crystal Structure and Tautomerism in Dipolar Aprotic Solvents. *Mendeleev Commun*. **2013**, *23*, 176–178.

(24) (a) Světlík, J.; Goljer, I.; Tureček, F. Oxygen-Bridged Tetrahydropyridines, Hexahydropyridines, and Dihydropyridones *via* a Hantzsch-like Synthesis with 4-(2-hydroxyphenyl)but-3-en-2-one. *J. Chem. Soc. Perkin Trans. I* **1990**, 1315–1318. (b) Světlík, J. Formation of Oxygen-Bridged Heterocycles in the Hantzsch Synthesis with 4-(2-Hydroxyphenyl)but-3-en-2-one. *J. Chem. Soc. Perkin Trans. I* **1988**, 2053–2058.

(25) Sridharan, V.; Avendaño, C.; Menéndez, J. C. General, Mild and Efficient Synthesis of β-Enaminones Catalyzed by Ceric Ammonium Nitrate. *Synlett* **2007**, 881–884.

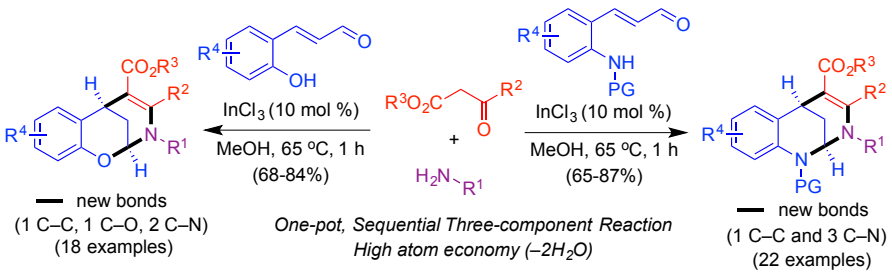
(26) For a related cyclization, see: Vinoth, P.; Prasad, P. S. R.; Vivekanand, T.; Maheswari, C. U.; Nagarajan, S.; Menéndez, J. C.; Sridharan, V. Expedient, Catalyst-Free, Three-Component Synthesis of Fused Tetrahydropyridines in Water. *RSC Adv*. **2015**, *5*, 81881–81888.

(27) Heo, S.; Kim, S.; Kim, S.-G. Organocatalytic Enantioselective Conjugate Addition–Cyclization Domino Reactions of *o*-*N*-Protected Aminophenyl α,β-Unsaturated Aldehydes. *Tetrahedron Lett.* **2013**, *54*, 4978–4981.

(28) Kim, C.; Kim, S.-G. Construction of Chiral Cyclopropane-Fused Tetrahydroquinolines: Enantioselective Organocatalytic Michael/Alkylation Domino Reaction and One-Pot aza-Cyclization *Tetrahedron: Asymmetry* **2014**, *25*, 1376–1382.

(29) Maity, R.; Pan, S. C. Organocatalytic Asymmetric Michael/Hemiacetalization/Acyl Transfer Reaction of α-Nitroketones with o-Hydroxycinnamaldehydes: Synthesis of 2,4-Disubstituted Chromans. *Org. Biomol.Chem*. **2018**, *16*, 1598–1608.

TOC


InCl3 (10 mol %)
MeOH, 65 ºC, 1 h
(68-84%)
InCl3 (10 mol %)
MeOH, 65 ºC, 1 h
(65-87%)
new bonds
(1 C–C, 1 C–O, 2 C–N)
(18 examples)
One-pot, Sequential Three-component Reaction
High atom economy (–2H2O)
new bonds
(1 C–C and 3 C–N)
(22 examples)