RESEARCH ARTICLE

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Chemodivergent temperature-controlled switchable iron-catalysed annulation of *o*-vinylaniline with isatin derivatives†

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Chemodivergent approaches strive to enable achieving regioselective and site-divergent transformations of multiple products from identical, readily accessible starting materials by changing the reaction parameters, but are challenging due to the complexity of precisely controlling the chemodiversity. Herein, we report a novel FeCl₃-catalyzed one-pot strategy involving switching the temperature to enable the selective synthesis of 5-methyl-7-phenyldibenzo[*b,h*][1,6] naphthy-ridin-6(5*H*)-one or 3-phenyl-1*H*-indole from o-vinylaniline and *N*-substituted isatin. Notably, the reaction exhibits temperature-controlled chemodivergence, selectively yielding either intramolecular or intermolecular products. This approach demonstrates a wide substrate scope, affording structurally diverse scaffolds under mild conditions. Furthermore, it provides an efficient route for synthesizing symmetrical urea derivatives and offers a potential pathway for directly synthesizing tryptanthrin and related bioactive molecules.

Introduction

Transition-metal–catalysed annulation reactions are powerful tools for constructing fused poly-heterocyclic compounds, and these frameworks are important due to their prevalence in natural products, pharmaceuticals, and functional materials.[1] Among these reactions, transition-metal–catalysed chemodivergent reactions have attracted particularly considerable attention due to the selective formation of multiple products from the same starting materials achieved by varying reaction conditions such as catalyst, temperature, or solvent.[2] This approach maximizes resource efficiency while providing access to structurally diverse compounds, which is valuable in medicinal chemistry and material science. Despite manifold benefits, this type of synthesis is entangled with onerous challenges, such as designing the ideal starting material, finding appropriate reaction condition, and most importantly, targeting a specific route as well as the product concurrently.[3]

In particular, interest in the 1,6-naphthyridine nucleus has grown significantly due to its presence as a core structural motif in various biologically active alkaloids and in potential therapeutic agents, such as JAK inhibitors[4a] and telomerase

inhibitors[4b] (Fig. 1).[4] The planar and rigid structure of this nucleus enhances its binding affinity with biological targets, including enzymes, receptors, and nucleic acids. As a result, compounds containing this scaffold are of high value in medicinal chemistry. Furthermore, their intrinsic fluorescence properties make them useful for DNA labeling, while their favorable photophysical characteristics position them as promising candidates for organic photovoltaic applications.[5] Similarly, indoles also constitute a prominent class of heterocycle scaffolds in drug discovery, and are valued for their structural diversity and potent pharmacological activities, including anticancer, antibacterial, and antifungal properties, making them crucial in medicinal chemistry.[6]
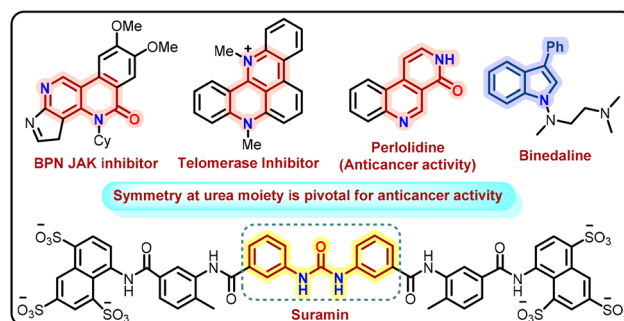
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Fig. 1 Representative symmetrical urea derivative and [1,6]-naphthyridine skeletons with potential biological applications.

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Despite the promising applications of naphthyridinones and 3-phenylindoles, the development of corresponding efficient and straightforward synthetic methodologies remains a challenge. Many of the conventional approaches carried out over the past few decades for synthesising [1,6]naphthyridin-6 (5*H*)-one and 3-phenyl-1*H*-indoles have required the pre-functionalisation of starting materials, necessitating the introduction of specific functional groups to activate substrates for subsequent transformations. This process typically requires multiple steps, such as halogenation, oxidation, or the installation of directing groups, which increases the overall reaction time, and the multi-step transformations often involve the use of expensive reagents, harsh reaction conditions, and stoichiometric amounts of chemical oxidants, making the process relatively unsustainable and inefficient.[7] Synthesizing polycyclic ring systems in a single synthetic operation is a practical challenge but also a crucial goal in modern organic synthesis.[8] Recently, the Wang group reported an iron-catalysed intramolecular C–H amination for the synthesis of N–H carbazoles and indoles using indolin-2-one as a ligand under aerial oxidation.[9] Conversely, the classical synthesis of urea derivatives often involves hazardous reagents like phosgene or its derivatives, progressing through an isocyanate intermediate, while greener alternatives such as the use of carbonates and carbonyldiimidazole, and catalytic oxidative carbonylation using carbon monoxide have been developed.[10]

Considering the challenges mentioned above, we thought to produce the above-mentioned targeted products by using a chemodivergent approach. As a part of our research[11] interest and focusing on the potential features of iron-catalysed cyclization reactions, herein we report an unprecedented set of iron-catalysed chemodivergent reactions between an o-vinylaniline with isatin derivatives. By appropriately modifying reaction parameters, diverse products could be formed from the same starting material, demonstrating specifically the great potency of iron-catalyzed aerobic oxidative annulation using air as the oxidant for synthesizing 5-methyl-7-phenyldibenzo[*b,h*][1,6] naphthyridin-6(5*H*)-one and indoles from unprotected primary amines. This process involves Fe(III)/Fe(II) single-electron transfer (SET) and offers a green, efficient method, which could be easily controlled by temperature, delivering either an intramolecular product or intermolecular product. In this respect, our methodology is also applicable towards the synthesis of symmetrical urea derivatives, accomplished by changing the isatin derivative (Scheme 1).

Results and discussion

We started our study by using 2-(1-phenylvinyl) aniline **1a** as the model substrate to react with *N*-methyl isatin **2a**. The results are summarised in Table 1. Initially, we attempted the reaction without a catalyst at room temperature in 1,4-dioxane, but the product did not form. Even upon increasing the reaction temperature, the formation of the desired product was not observed. When compounds **1a** and **2a** were treated with FeCl₃
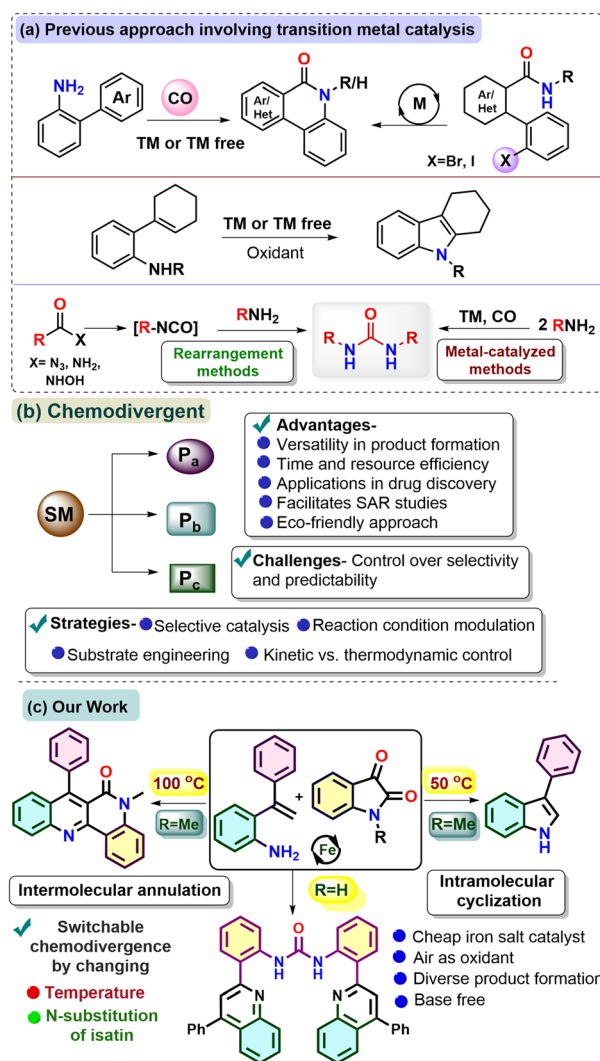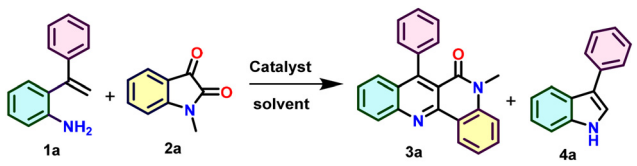

Scheme 1 Previous work, chemodivergence and present work.

in 1,4-dioxane at 50 °C, the reaction predominantly yielded the intramolecularly cyclised product **4a**, doing so in 78% yield (Table 1, entry 1). Notably, as the reaction temperature was increased from 80 to 100 °C, a clear shift in selectivity was observed favouring the formation of the intermolecularly annulated product **3a**, while the yield of intramolecularly cyclized product **4a** progressively decreased (Table 1, entries 2–4).

This result suggested that at higher temperatures, the reaction overcame the kinetic barrier, allowing the system to reach thermodynamic equilibrium, and hence form the thermodynamically favoured product **3a**. To further optimise the reaction, we investigated a range of Lewis acids as alternative catalysts (Table 1, entries 5–9) to enhance both selectivity and yield. Of the tested catalysts, only ZnCl₂ and FeCl₃ effectively facilitated the formation of annulated product **3a**. That is, the other catalysts, including TFA, CeCl₃·7H₂O, Cu(OAc)₂, and AlCl₃, failed to promote the selective formation of annulated product **3a**. In the absence of an iron catalyst, no annulated or

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Table 1   Selected optimization studies[a]

Sl. no.	Catalyst	Additives	Solvent	Temperature	3a yield[b]	4a yield[b]
1	FeCl$_3$	—	1,4-Dioxane	50 °C	n.d.	78%
2	FeCl$_3$	—	1,4-Dioxane	80 °C	30%	45%
3	FeCl$_3$	—	1,4-Dioxane	90 °C	85%	>10%
4	FeCl$_3$	—	1,4-Dioxane	100 °C	90%	Trace
5	AlCl$_3$	—	1,4-Dioxane	100 °C	n.d.	20%
6	TFA	—	1,4-Dioxane	100 °C	n.d.	10%
7	ZnCl$_2$	—	1,4-Dioxane	100 °C	40%	Trace
8	CeCl$_3$·7H$_2$O	—	1,4-Dioxane	100 °C	n.d.	Trace
9	Cu(OAc)$_2$	—	1,4-Dioxane	100 °C	n.d.	n.d.
10	—	—	1,4-Dioxane	100 °C	n.d.	n.d.
11	FeCl$_3$	CuBr	1,4-Dioxane	100 °C	10%	n.d.
12	FeCl$_3$	DDQ	1,4-Dioxane	100 °C	n.d.	n.d.
13	FeCl$_3$	—	Toluene	100 °C	60%	10%
14	FeCl$_3$	—	CH$_3$CN	100 °C	85%	Trace
15	FeCl$_3$	—	DCE	100 °C	84%	Trace
16	FeCl$_3$	—	Isopropanol	100 °C	69%	n.d.
17	FeCl$_3$	—	DMSO	100 °C	n.d.	n.d.
18[c]	FeCl$_3$	—	1,4-Dioxane	100 °C	30%	Trace
19[d]	FeCl$_3$	—	1,4-Dioxane	100 °C	90%	Trace

[a] Reactions condition **1a** (0.5 mmol), **2a** (0.5 mmol), and catalyst (20 mol%) in 2 ml of solvent for 12 hours. [b] Isolated yield. [c] Under N$_2$ atmosphere. [d] Catalyst (10 mol%).

cyclized product was formed (Table 1, entry 10). When the reaction was performed in the presence of an additive like DDQ or CuBr, no fruitful result was observed (Table 1, entries 11 and 12). Additionally, changing the solvent to 1,2-dichloroethane (DCE), toluene, acetonitrile, and isopropanol led to moderate yields of annulated product **3a**, whereas no annulated product was formed when using DMSO (Table 1, entries 13–17). The yield of the annulated product **3a** dropped drastically to 30% when the reaction was conducted under a nitrogen atmosphere instead of air (entry 18 *vs.* entry 4), highlighting the role of air in enhancing the oxidation/aromatization of product **3a**. Based on these observations and optimisation of catalyst loading, it was determined that (10 mol%) FeCl$_3$ in 1,4-dioxane under an air atmosphere at 100 °C provided the best conditions for making the annulation product **3a**, while (20 mol%) FeCl$_3$ in 1,4-dioxane under an air atmosphere at 50 °C favoured the formation of the cyclised product **4a**. With these optimised conditions in hand, we proceeded to investigate the scope of the reaction.

In the initial stage of our investigation of the substrate scope for synthesizing 7-phenyldibenzo[*b*,*h*][1,6]naphthyridin-6(5*H*)-one **3** under the standard intermolecular annulation reaction condition, a series of *N*-substituted isatin derivatives were synthesised, incorporating methyl, ethyl, benzyl, and phenyl groups. The benzyl-substituted derivatives containing F and OMe groups were well tolerated under the reaction conditions, whereas the CN-substituted derivative failed to deliver the annulated product **3d′**. Furthermore, isatin derivatives

bearing various substituents at the 5-position, such as Me, OMe, F, and Br, successfully provided the corresponding products (**3i–p, z**), specifically in 71–90% yields. Additionally, we investigated variations in the aryl ring of compound **1a** under standard conditions, which yielded moderate to good yields of the respective products (**3q–y**). However, 5-nitro isatin failed to give the desired product.

To further investigate the substrate scope, we utilized isatin derivatives bearing bulky isopropyl and long aliphatic pentyl *N*-protecting groups. These derivatives successfully delivered in good yields the annulated products **3a′** and **3b′**, respectively, demonstrating the robustness of the synthetic methodology toward steric and structural variations in the *N*-protecting groups. In particular, the presence of an electron-withdrawing group at the *para* position of the benzyl group, as well as a terminal acyclic chain in the *N*-protected isatin derivatives, may have been interfering with or deactivating the cyclization pathway. The structure of compound **3q** was confirmed by the results of a single-crystal X-ray diffraction analysis (see details in ESI†) (Scheme 2).

We also investigated the substrate scope for synthesizing 3-phenyl indoles **4**, under the standard intramolecular cyclization conditions. Initially, we studied a set of **1a** derivatives substituted with ethyl, isopropyl, n-butyl, tri-methoxy, OMe, F, and Cl groups; they delivered indole derivatives of compound **4** in moderate to good yields at a temperature of 50 °C (Scheme 3).

Furthermore, additional experiments were carried out to better understand the reaction mechanism (Scheme 4). The
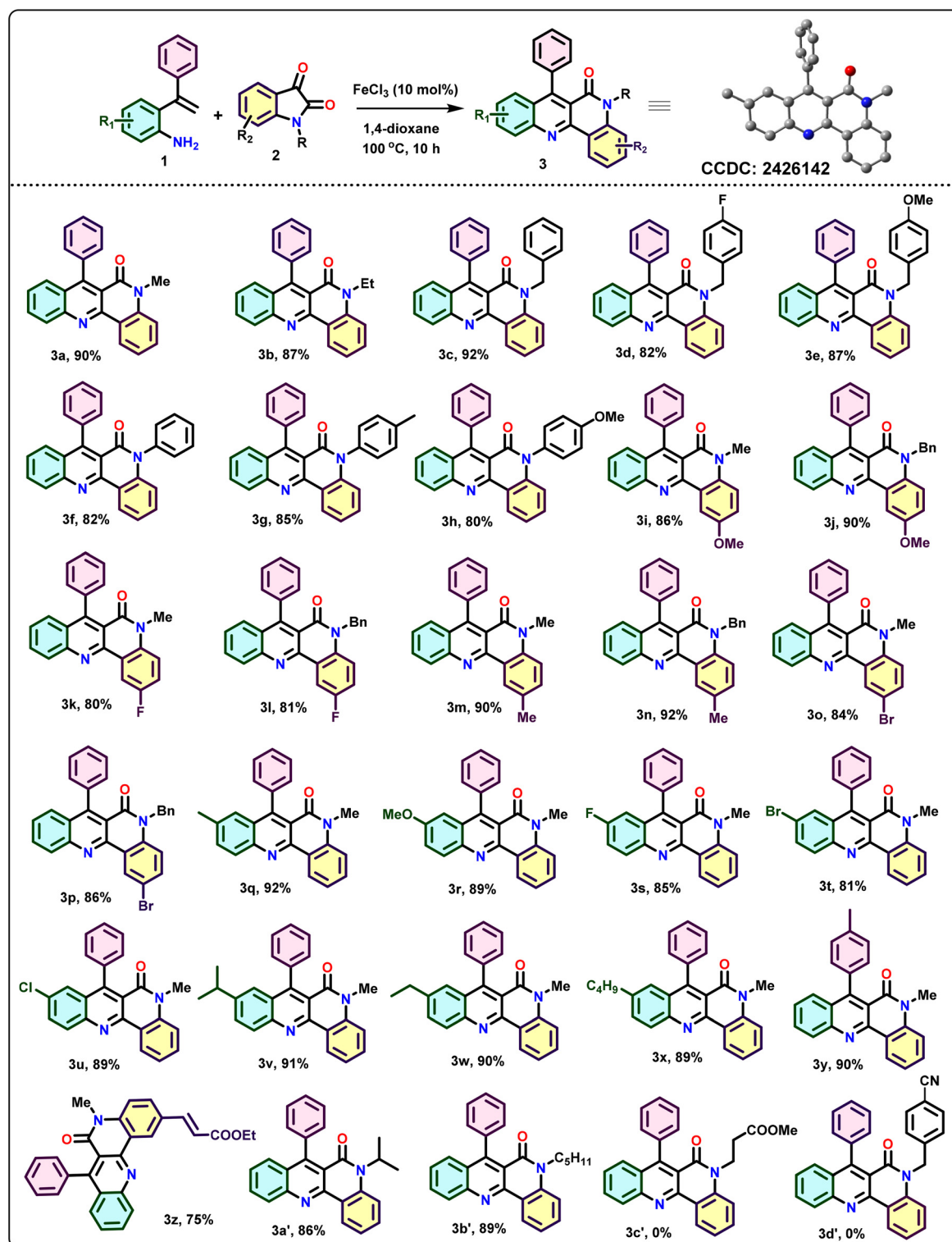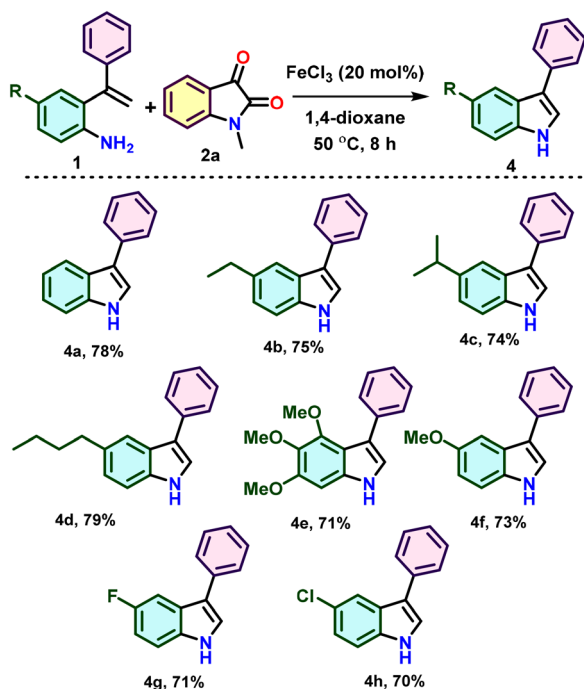
Scheme 2 Substrate scope for synthesizing 7-phenyldibenzo[*b*,*h*][1,6]naphthyridin-6(5*H*)-one.

reaction was inhibited, with only trace amount of product formed, when the radical scavenger 2,2,6,6-tetramethyl-piperidinyloxy (TEMPO) was included. Additionally, formation of the TEMPO adduct **5** was confirmed by the results of HRMS

analysis. We also examined UV absorption spectroscopy data of FeCl₃ with isatin substrate; these results clearly showed that in the reaction mixture, isatin derivatives combined with iron salt and formed a complex (Fig. 2).
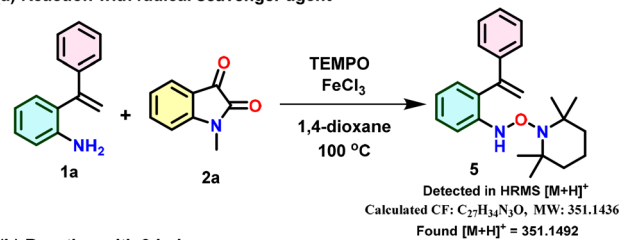
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Scheme 3 Substrate scope for synthesizing 3-phenyl indoles.

Scheme 4 Control experiments.

Fig. 2 UV spectra of FeCl₃, **2**, **2a**, FeCl₃ + **2**, and FeCl₃ + **2a** each in 1,4-dioxane solvent.
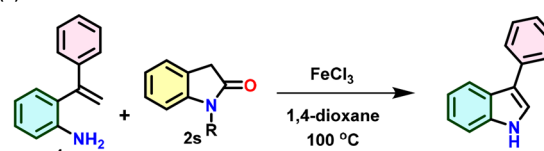
These results suggested that isatin, by chelating with Fe(III/II), may act as a radical donor and be an effective hydrogen scavenger, as presented in Scheme 5. The results provided evidence for a reaction mechanism proceeding *via* a single-electron transfer (SET) pathway. To understand the importance of isatin, we performed the reaction with indolin-2-one **2s** instead of isatin; only cyclized **4a** product was observed at 100 °C. When *N*-methyl-substituted aniline derivatives **6** were treated with **2** under the standard conditions, no cyclized product **7** was obtained. Furthermore, we investigated the reaction conditions with deuterated aniline substrate **8**; here, the annulated product **3a** with a good yield was observed. Conversely, in the reaction without isatin derivative, no cyclized product **4a** was observed (Scheme 4e), which confirmed that the reaction started with formation of an isatin iron complex.

Based on the above experiments and previous literature,[12] we propose a reaction mechanism involving two distinct pathways (Scheme 5). Pathway (a) involves intramolecular cyclisation, leading to the formation of product **4a**, whereas pathway (b) proceeds through intermolecular annulation, resulting in the formation of product 3a. Initially, isatin derivatives partially chelate with FeCl₃, forming intermediate **A**, which undergoes aerial oxidation *via* a single-electron transfer (SET) process, extracting an electron from the aniline derivative. This step generates a reactive intermediate that undergoes intramolecular cyclisation, followed by aromatisation at 50 °C, delivering compound **4a**. In contrast, at 100 °C, the nitrogen of the aniline derivative attacks the C3 position of isatin, leading to the formation of intermediate **C**. This intermediate undergoes a [1 + 6] annulation, forming a spiro compound, which sub-
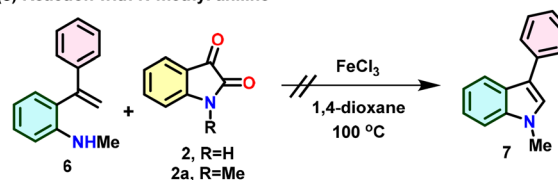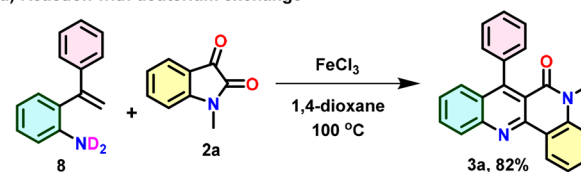
sequently undergoes ring expansion and aerial oxidation, affording compound **3a**.
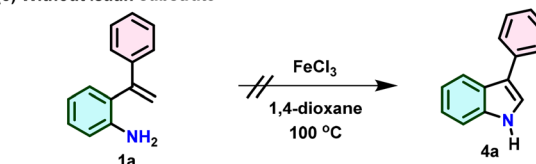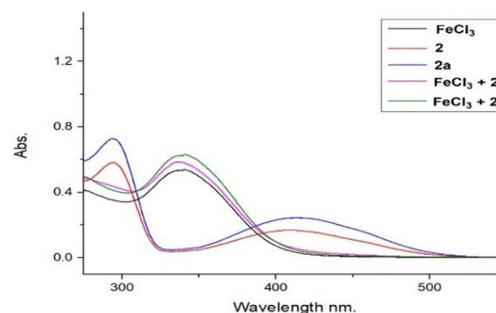
Under the optimal annulation reaction conditions, we next examined the reaction of isatin **2** with compound **1a**.

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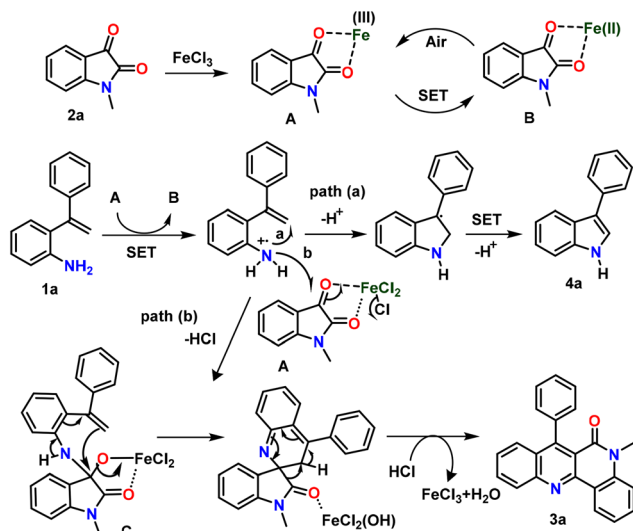
Scheme 5 Plausible mechanism.

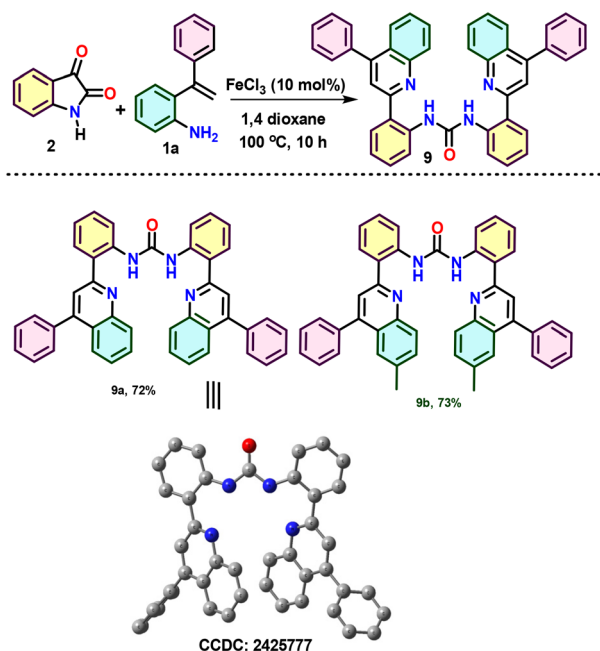Interestingly, we achieved the selective synthesis of 1,3-bis(2-(4-phenylquinolin-2-yl)phenyl)urea **9a** with a 72% yield (Scheme 6).

The structure of compound **9a** was confirmed by the results of single-crystal X-ray diffraction analysis (see details in the ESI†). Notably, the developed methodology was found to also be compatible with the synthesis of symmetrical urea derivatives, an important class of compounds with significant biological and photophysical properties.[13]
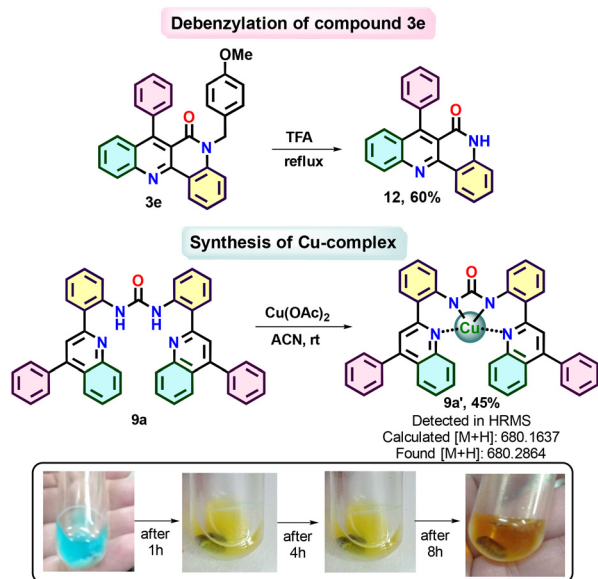
In addition, treatment of compound **2** with isatoic anhydride **10** under standard annulated reaction conditions generated tryptanthrin **11**, which is a naturally occurring plant alkaloid with anti-inflammatory and anticancer activities. This methodology highlighted a one-pot method for synthesizing tryptanthrin. Further derivatization of compound **11** enabled the synthesis of diverse bioactive molecules and natural products. Condensation of compound **11** with hydroxylamine hydrochloride under basic conditions yielded compound **11b** (90%), which has been shown to exhibit inhibitory activity. Reduction of compound **11** with NaBH$_4$ provided compound **11c** (95%), known for its anti-TMV activity. Additionally, treatment of compound **11** with methyl 2-bromoacetate and Zn dust in THF at 66 °C resulted in the formation of the natural product phaitanthrin-B (**11d**), while reaction with K$_2$CO$_3$ in acetone afforded phaitanthrin-A (**11e**). Nitration of **11** produced compound **11f**, which has been shown to be an antimicrobial agent (Scheme 7).[14]

We investigated the practicality of this methodology by extending it to the de-benzylation of compound **3e** using trifluoroacetic acid, followed by the synthesis of 1,6-naphthyridone **12**, which is a core moiety of phenanthridone-containing natural products. Additionally, we synthesized a Cu(ɪɪ) complex by treating a symmetrical urea derivative with Cu(OAc)$_2$ in acetonitrile at room temperature, observing a continuous colour change in the reaction mixture over time. The formation of the Cu complex was confirmed by the results of an HRMS analysis (see details in the ESI†) (Scheme 8).

Scheme 6 Synthesis of urea derivatives.
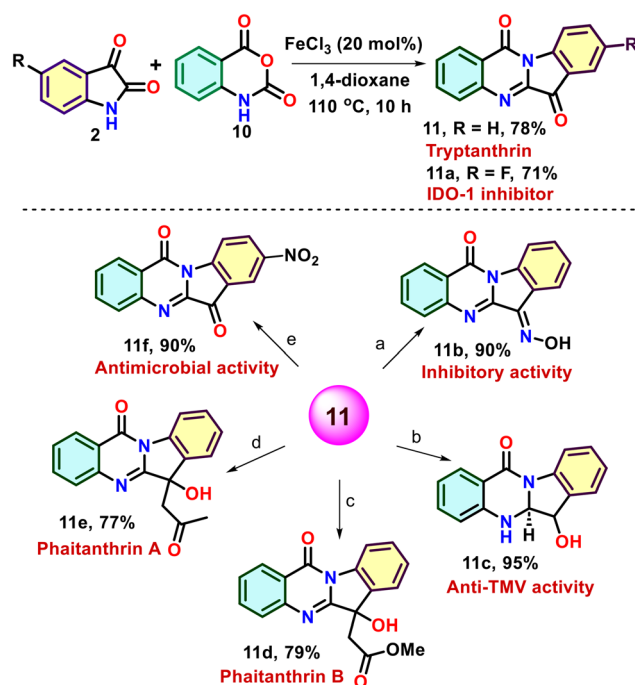
Scheme 7 Synthesis of tryptanthrin, phaitanthrin-A, phaitanthrin-B and bioactive compounds. Reaction conditions: (a) NH$_2$OH·HCl, pyridine, 60 °C; (b) NaBH$_4$, AcOH, 15 °C; (c) methyl 2-bromoacetate, Zn dust, THF, 66 °C; (d) K$_2$CO$_3$, acetone, rt; (e) (i) H$_2$SO$_4$, 0 °C; (ii) HNO$_3$, 0 °C.

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Scheme 8 Synthetic transformation and application of methodology.

Conclusion

We have successfully developed a novel FeCl$_3$-catalyzed one-pot strategy for the selective synthesis of 5-methyl-7-phenyl-dibenzo[b,h][1,6]naphthyridin-6(5H)-one or 3-phenyl-1H-indole from o-vinylaniline and N-substituted isatin by switching the temperature. This method exhibits temperature-dependent chemodivergence, enabling the controlled formation of either intramolecularly or intermolecularly derived products. Notably, the reaction demonstrates wide substrate scope, and efficiently produces structurally diverse scaffolds under mild conditions. Additionally, this methodology can also be extended to being applicable towards one-pot synthesis of symmetrical urea derivatives and tryptanthrin. The late-stage transformations enhance its potential for synthesizing biologically active compounds and natural products. Given its efficiency and synthetic utility, we anticipate that this methodology will be widely adopted in organic synthesis. Ongoing studies in our laboratory aim to further expand its scope and investigate new applications.

Data availability

The data supporting this article have been included as part of the ESI.†

Crystallographic data for compound **3q** [CCDC 2426142] and **9a** [CCDC 2425777] can be obtained free of charge *via* **www.ccdc.cam.ac.uk/data_request/cif**, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

Conflicts of interest

There are no conflicts of interest.

Acknowledgements

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