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From Isocyanides to Iminonitriles via Silver-mediated Sequential Insertion of C(sp³)–H Bond

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SUMMARY

Heterocycles are prevalent constituents of many marketing drugs and biologically active molecules to meet modern medical challenges. Isocyanide insertion into C(sp³)–H bonds is challenging especially for the construction of quaternary carbon centers. Herein, we describe an efficient strategy for the synthesis of α-iminonitrile substituted isochromans and tetrahydroisoquinolines (THIQs) with quaternary carbon centers through silver-triflate-mediated sequential isocyanide insertion of C(sp³)–H bonds, where isocyanide acts as the crucial “CN” and “imine” sources. The produced α-iminonitriles have extensive applications as valuable synthetic building blocks for pharmacologically interesting heterocycles. This protocol could be further applied for the synthesis of iminonitrile-decorated phenanthridines and azapyrene. Interestingly, a remarkable aggregation-induced emission (AIE) effect was first observed for an iminonitrile-decorated pyrene derivative, which may open a particular area for iminonitrile applications in materials science.

INTRODUCTION

Isochromans and tetrahydroisoquinolines (THIQs) are prevalent in many biologically active compounds including marketing drugs (Figure 1A) (Scott and Williams, 2002; Ennis et al., 1998). For example, peniciditrinin B is well known for its potent antioxidant activity (Clark et al., 2006; Lu et al., 2008). Solifenacin (VES-Icare) is a muscarinic antagonist indicated for the treatment of overactive bladder with associated problems such as increased urination frequency and urge incontinence (Ohtake et al., 2004; Cardozo et al., 2004). In general, the functionalization of the C1 position of both scaffolds is important for their biologically activities. The site-selective C1 mono-functionalization of isochromans and THIQs has been extensively studied, which commonly involved the formation of oxonium/iminium ions or α-heteroatom carbon-centered radicals initiated by irradiation or treatment with an oxidant (Yoo et al., 2009; Zhou et al., 2017; Bartling et al., 2016; Lin et al., 2017; Muramatsu and Nakano, 2014; Muramatsu et al., 2013; Zhang et al., 2013; Meng et al., 2014). Although isochromans and THIQs with quaternary C1 carbons are of high potentials in drug discovery, represented by CJ-17493 (Shishido et al., 2008) and trabectedin (Germano et al., 2013; Demetri et al., 2009; Grosso et al., 2007), they still provide significant synthetic challenges to chemists. The C1 difunctionalization of isochromans and THIQs is limited in scope and commonly requires multiple steps using active Grignard or organolithium reagents (Figure 1B) (Guo et al., 2017; Li and Coldham, 2014).

Isocyanides have proven to be versatile C1 building blocks in organic synthesis and invoked ever-growing synthetic efforts, owing to their unique electronic configuration capable of reacting with electrophiles, nucleophiles, and radicals easily (Boyarsky et al., 2015; Qiu et al., 2013; Song and Xu, 2017; Giustiniano et al., 2017). Although many challenges still remain due to the high energy barrier of activating the chemically inert C–H bonds regioselectively, the synergy from the combination of isocyanide insertion and C–H bond activation offers an efficient and powerful tool to establish complicated reactions and construct useful substances (Song and Xu, 2017). Numerous results have been reported on isocyanide insertions with C(sp²)–H or C(sp)–H bond. However, isocyanide insertion into C(sp³)–H bonds is challenging especially for the construction of quaternary carbon centers, since the pioneering intramolecular isocyanide insertion into benzylic C(sp³)–H bonds by Jones in the late 1980s (Jones and Kosar, 1986). Recently, a photolytic mono-amidation reaction of isochroman was achieved by Maruoka group through nucleophilic attack of excess amounts of isocyanide into the in situ generated oxocarboxocation intermediate with phenylidone bis(trifluoroacetate) (Figure 1C) (Sakamoto et al., 2015). In 2007, Zhu and co-workers reported an oxidative
Ugi-type multicomponent reaction for the C1 monofunctionalization of THIQs (Figure 1C) (Ngouansavanh and Zhu, 2007). In these reports, no C1 disubstitution, leading to quaternary products could be observed from isochromans and THIQs.

α-Iminonitriles were generally prepared using highly toxic metal cyanides with multi-steps (Gualtierotti et al., 2012; You et al., 2014; Fontaine et al., 2008, 2009; Amos et al., 2003; De Corte et al., 1987; Surmont et al., 2009; Verhé et al., 1980; Maruoka et al., 1983), whereas improved synthetic method could be achieved by isocyanide insertion into C(=N) bond (Tobisu et al., 2007) or C–H bond (Chen et al., 2016).

In view of the high bioactivities of isochromans and THIQs as well as our recent development of isocyanide chemistry (Huang et al., 2014; Fang et al., 2014; Hong et al., 2017), we herein report an unprecedented

**Figure 1. C1-Functionalization of Isochromans, THIQs, and Dihydrophenanthridines**

(A) Prevalence of C1 functionalized isochromans and THIQs motifs in marketing drugs and biologically active molecules.

(B) Traditional methods for the construction of the quaternary C1 carbons are limited in scope and usually require multiple steps and active Grignard or organolithium reagents.

(C) Reported reactions of isochromans and THIQs with isocyanides usually lead to C1 mono-functionalized amides.

(D) Silver-mediated sequential isocyanide insertion of C(sp3)–H bond of isochromans, THIQs, and dihydrophenanthridines affords quaternary mono-/dual α-iminonitrile substituted products or phenanthridines, where the isocyanide acts as both “imine” and “CN” sources. The photograph was taken under ultraviolet (UV) lamp (365 nm) for an iminonitrile-decorated azapyrene with remarkable AIE effect.

This Work: Isocyanides to carbimidoxy cyanides via silver-mediated sequential insertion of C(sp3)–H Bonds

- Facile access to α-iminonitriles
- Quaternary carbon center construction
- 1BuNC as both “C=N” and “CN” sources
- Sequential C(sp3)–H isocyanide insertion
- Valuable synthetic building blocks
- A novel AIEgen
### Table 1. Optimization of Reaction Conditions

| Entry | Catalyst (mol%) | Isocyanide (equiv) | Solvent | Temp. (°C) | Yield (%) |
|-------|----------------|-------------------|---------|------------|-----------|
| 1     | /              | 5.0               | PhCl    | 80         | 47        |
| 2     | CuCl (10)      | 5.0               | PhCl    | 80         | 27        |
| 3     | FeCl₃ (10)     | 5.0               | PhCl    | 80         | 36        |
| 4     | Ag₂CO₃ (10)    | 5.0               | PhCl    | 80         | 44        |
| 5     | AgNO₃ (10)     | 5.0               | PhCl    | 80         | 38        |
| 6     | AgTFA (10)     | 5.0               | PhCl    | 80         | 39        |
| 7     | AgOAc (10)     | 5.0               | PhCl    | 80         | 42        |
| 8     | AgOTf (10)     | 5.0               | PhCl    | 80         | 61        |
| 9     | AgOTf (10)     | 5.0               | DCE     | 80         | 35        |
| 10    | AgOTf (10)     | 5.0               | DMF     | 80         | NP        |
| 11    | AgOTf (10)     | 5.0               | DMSO    | 80         | NP        |
| 12    | AgOTf (10)     | 5.0               | CH₃CN   | 80         | NP        |
| 13    | AgOTf (10)     | 5.0               | dioxane | 80         | trace     |
| 14    | AgOTf (10)     | 5.0               | toluene | 80         | 52        |
| 15    | AgOTf (10)     | 5.0               | CH₂Cl₂  | 20         | 22        |
| 16    | AgOTf (5)      | 5.0               | PhCl    | 80         | 51        |
| 17    | AgOTf (20)     | 5.0               | PhCl    | 80         | 50        |
| 18    | AgOTf (10)     | 5.0               | PhCl    | 80         | 54        |
| 19    | AgOTf (10)     | 5.0               | PhCl    | 80         | 22        |
| 20    | AgOTf (10)     | 6.0               | PhCl    | 80         | 56        |
| 21    | AgOTf (10)     | 4.0               | PhCl    | 80         | 54        |
| 22    | AgOTf (10)     | 3.0               | PhCl    | 80         | 36        |
| 23    | AgOTf (10)     | 5.0               | PhCl    | 100        | 44        |
| 24    | AgOTf (10)     | 5.0               | PhCl    | 60         | 39        |
| 25    | AgOTf (10)     | 5.0               | PhCl    | 80         | 52        |
| 26    | AgOTf (10)     | 5.0               | PhCl    | 80         | 54        |

*Reaction conditions: 1a (0.3 mmol), catalyst (10 mol%), DDQ (2.0 equiv), solvent (3.0 mL), 3 h, under a nitrogen atmosphere. DDQ = 2,3-dichloro-5,6-dicyanobenzoquinone. NP = no product.

Yields of isolated products are given.

*(E)-N-tert-butyl-1-cyanoisochroman-1-carbimidoyl cyanide (2a‘) was also isolated in 17% yield.

*DDQ (3.0 equiv) was used.

*DDQ (1.0 equiv) was used.

*Under an oxygen atmosphere.

*Under an air atmosphere. H atoms of the X-ray structure were omitted for clarity.
silver-mediated sequential isocyanide insertion of C(sp³)–H bonds to afford mono- or dual α-iminonitrile substituted isochromans and THIQs, as well as aromatized phenanthridines and azapyrene (Figure 1D). The significance of the given chemistry is as follows: (1) the formation of α-iminonitriles was first realized by the synergistically cascade isocyanide insertion via C–H bond activation, where the isocyanide was used as both the crucial “CN” and “imine” sources; (2) it is the first example to construct pharmacologically relevant α-iminonitrile substituted isochromans and THIQs with quaternary carbon centers through direct C(sp³)–H bond isocyanide insertion; (3) a remarkable aggregation-induced emission (AIE) effect was first observed for as-prepared α-iminonitrile substituted pyrene derivative, which may open a particular area for iminonitrile applications in materials science; (4) the α-iminonitrile substituted products are valuable synthetic building blocks for facile access of pharmacologically interesting heterocycles.

RESULTS AND DISCUSSION

Reaction Optimization

We started our investigation by exploring the reaction of isochroman (1a) with tert-butyl isocyanide in chlorobenzene at 80°C in the presence of DDQ under a nitrogen atmosphere. To our surprise, a dual α-iminonitrile substituted isochroman 2a was isolated in 47% yield, without observation of any direct cyanated products (Table 1, entry 1) (Xu et al., 2012; Hong et al., 2014; Peng et al., 2012). Various metal catalysts were next tested, including CuCl, FeCl₃ and silver salts (entries 2–8), and the desired product 2a was obtained in 61% yield when AgOTf was applied (entry 8). Screening of the other solvents indicated chlorobenzene to be the suitable choice (entries 8–15). An extensive screening of the amounts of AgOTf (entries 16 and 17), DDQ (entries 18 and 19) and tert-butyl isocyanide (entries 20–22), temperature (entries 23 and 24), and the atmosphere (entries 25 and 26) revealed that the use of 10 mol% of AgOTf and two equivalents of DDQ in chlorobenzene at 80°C under a nitrogen atmosphere provided the most suitable conditions.
With the optimized reaction conditions in hand, a variety of isochromans were examined as shown in Figure 2. Substrates bearing different functional groups on the aryl ring, regardless of their substitution patterns, were compatible with this reaction and provided the corresponding products in moderate to good yields (2b–2i). The reaction was not limited to simple isochromans, but naphthyl- or thienyl-fused substrates also gave the desired di-α-iminonitrile substituted products in moderate yields (2j–2m). Isochromans with 3- or 4-substituent could afford the spiro- (2n–2p); 3,3-dialkyl (2q); 3-aryl (2r); 4-alkyl (2s); and 3,4-fused (2t) products in moderate to good yields. Notably, when symmetrical 1H,3H-benzo[de]isochromene (1u) bearing two potential benzyl C(sp3)-H bond insertion positions was applied in this reaction, only one position was attacked and afforded the product 2u predominately.

To further explore the scope and generality of this method, C1 mono-substituted isochromans were next explored for this insertion reaction with elevated temperature at 100°C. As illustrated in Figure 3, substrates with aryl groups, regardless of the substituent position on the aryl rings, provided the corresponding products in good yields (4a–4f). Similarly, 1-naphthyl or 1-thienyl isochromans afforded the desired products 4g and 4h, respectively. The identity of 4h was determined by spectral analysis and further confirmed by X-ray crystallographic analysis. Moreover, 4-methyl-1-phenyl-isochroman (3i) could be employed in this transformation and afforded the product 4i in 79% yield with a diastereomeric ratio of 3.3:1 as determined by proton NMR. Intriguingly, 6H-benzo[c]-chromene derivative 4j could be isolated almost quantitatively, which may be attributed to the perfect stabilization of generated oxocarbenium ion (Meng et al., 2014; Jung and Floreancig, 2009) by the electron delocalization of conjugated system. Owing to the similar reason, isocyanide insertion will occur selectively on the more sterically hindered C1-position, instead of C3-position, to form isochroman 4k in 74% yield. Furthermore, the less reactive 1-methyl-isochroman substrate also afforded the α-iminonitrile product 4l in 60% yield at C1-position.

Substrate Scope of THIQs

The optimized conditions for isochromans could be further applicable to THIQs. Interestingly, in this case, only one α-iminonitrile group and a nitrile group were installed to the C1 position in comparison to the introduction of two α-iminonitriles for isochromans. As shown in Figure 4, THIQs bearing various substituents or functional groups on the aryl ring were smoothly converted into the corresponding products in moderate to excellent yields (6a–6l). Similarly, the expected products were obtained for THIQs analogues with fused heterocycle (6m) or extended π-systems (6n). THIQs with modified piperidine rings also

Figure 3. Substrate Scope of Isochroman
Reaction conditions: 3a–3l (0.3 mmol), tBuNC (5.0 equiv), AgOTf (10 mol%), DDQ (2.0 equiv), PhCl (3.0 mL), 19–24 h, under a nitrogen atmosphere, at 100°C. Yields of isolated products are given. H atoms in the X-ray structure were omitted for clarity.
afforded the desired spiro- or fused products (6o–6r). The replacement of the tosyl group by benzoyl groups gave similar results (6s–6t), whereas the use of acetyl group led to an unidentified mixture. However, when the tosyl group was replaced by methanesulfonyl group, a separable mixture of 6u and 6u' was obtained, which indicates that the existed more steric hindrance of tosyl group may prohibit the introduction of the second α-iminonitrile group. The different results of THIQs and isochromans may also attribute to the existence of the protecting group on THIQs, which sterically prohibits the introduction of the second α-iminonitrile group.

Substrate Scope of Dihydrophenanthridines

To our surprise, 5-tosyl-5,6-dihydro-phenanthridine (7a) under the same conditions gave aromatized phenanthridine 8a with the elimination of the tosyl group. Functional groups such as methyl, halogen, phenyl, and alkynyl could be tolerated (8b–8e) (Figure 5). The structure of the product 8b was confirmed by X-ray crystallographic analysis. Interestingly, the dihedral angle of the phenanthridine plane and the α-iminonitrile plane is 41°, which suggests an effective conjugation between the α-iminonitrile and the phenanthridine. Attributed to the strong tendency toward aromatization of dihydrophenanthridine substrates, phenanthridines without substituents at the C6 position were observed in the reaction as a main byproduct, which lead to the formation of 8 in moderate yields. It should be noted that phenanthridines and their derivatives are of great interest in medicinal chemistry and materials science due to their potent biological activities and optoelectronic properties (Ishikawa, 2001; Dubost et al., 2012; Stevens et al., 2008).

Synthetic Applications of the Products

To demonstrate the synthetic utility of the given approach, we next turned our attention to the application of the current protocols, as depicted in Figure 6. Products (2a and 4l) derived from isochromans were
selected as examples. The corresponding isochroman carboxylate derivatives (9a–9c) could be easily obtained from a-iminonitrile 4l in the presence of alumina or by treatment with hydrochloride solution, respectively. Exposure of 4l to hydroxylamine in ethanol leads to the formation of a-cyanooxime 9d in good yield. Notably, isochromans with aminoquinoxaline (9e), benzothiazole (9f), or benzoxazole (9g) substitutions at C1 position could be synthesized smoothly from a-iminonitrile 4l, which provides a shortcut for pharmacologically interesting isochromanyl heterocycles. Iminonitrile substituted isochromans (2a and 4l) are also proven to be excellent cyanating reagents, for example, direct C–H bond cyanation of 2-phenylpyridine or 2-phenylpyrimidine could be achieved to afford cyano products 9i (Xu et al., 2012; Hong et al., 2014) or 9j (Xu et al., 2012; Peng et al., 2012) efficiently, together with the formation of quaternary carbon centered amide (9a) or diamide (9h) in high yields, which is very difficult to obtain with general methods. Similarly, 1-(pyrimidin-2-yl)-1H-indole could be cyanated with 2a to give the corresponding nitrile product 9k in 50% yield (Xu et al., 2012).

Application in Materials

Luminescent materials are the basis of many high-tech innovations such as organic light-emitting diodes (OLEDs), biological probes, dyes, and chemical sensors. Pyrene, a flat aromatic molecule, exhibits excellent fluorescent properties and has found numerous applications in many fields (Duarte and Müllen, 2011). Therefore, we plan to prepare a a-iminonitrile-decorated pyrene derivative 11 by this newly developed method in order to investigate the effect of the introduced a-iminonitrile functional group on the optical properties. To our delight, compound 11 was successfully obtained through a two-fold isocyanide insertion to the C(sp3)–H bonds of 10 (Figure 7A). The optical properties of 11 were next investigated. It is well-known that most of pyrene derivatives are highly emissive in solution, whereas the emission is weak in the solid state due to the detrimental aggregation-caused quenching (ACQ). To our surprise, compound 11 was non-emissive when dissolved in organic solvents such as THF, but the solid showed bright green luminescence (λem = 528 nm, Figure 7B and Video S1). It underwent a further dramatic change from a non-emissive state in THF to highly emissive aggregated states in THF/water mixtures when the water content exceeded 60 vol% (Figures 7C, 7D, and S4); this phenomenon is a hallmark of the aggregation-induced emission (AIE) effect (Mei et al., 2015; Hong et al., 2011; Luo et al., 2001). In comparison, parent 4,9-diaza-pyrene (Mosby, 1957), without a-iminonitrile substituent, is emissive in pure organic solvent (Figure S2), and no apparent AIE effect was observed. These results indicate that a-iminonitrile substituent might be an interesting AIEgen when appended to π-extended aromatic compounds. Furthermore, compound 11 showed a considerable bathochromic shift (63 nm) vs. parent 4,9-diaza-pyrene both in the solid state (Figure S3), which disclosed that iminonitrile substituted isochromans would be an excellent chromophore for tuning the color of emissive materials.
Mechanistic Studies

To gain insight into the mechanism of this transformation, several control experiments were carried out as shown in Figure 8. Both isocyanide (Xu et al., 2012; Hong et al., 2014; Peng et al., 2012) and DDQ (Zhang et al., 2012) have been reported as effective cyanide sources in the literatures. To address the possible “CN” source in the reaction, the o- or p-chloranil, which has the similar character to DDQ except for the absence of cyanide groups, was used to replace DDQ under the optimized conditions. In the presence of o-chloranil, the desired products (2a, 4a and 4l) could also be afforded (Figure 8, Reactions A and B), albeit in relatively lower yields, which may be due to the different oxidative capacity between o-chloranil and DDQ. It was reported that DDQ has a higher reduction potential (0.6 V vs SCE) than o- and p-chloranil (0.14 and 0.02 V vs SCE, respectively) (Rathore and Kochi, 1998; Fukuzumi et al., 1993), which indicates that DDQ is a more powerful oxidant. When p-chloranil was used for the reaction of 3j, iminonitrile 4j could be afforded in 71% yield (Figure 8, Reaction C). When cyclohexyl- or 2,6-dimethylphenyl isocyanide was used instead, which are rarely used as “CN” source, no iminonitrile substituted isochromans could be isolated in the presence of DDQ. These results may rule out the possibility of DDQ as the main source of “CN.” Furthermore, the distribution of the cyanated products (2a, 2a’ and 12) was sensitive to the amount of the isocyanide with the same amount of DDQ as an oxidant (Figure 8, Reaction D), which suggested the isocyanide as the “CN” source rather than DDQ. Interestingly, mono α-iminonitrile substituted isochroman was not obtained under these conditions.

The electrospray ionization mass spectroscopy (ESI-MS) has been used as an effective method for the characterization of reaction intermediates, which provides direct evidence for the reaction mechanism.
To further probe the progress of this cascade transformation, we monitored the reaction mixture of isochroman 1a, tBuNC, DDQ, and AgOTf in dichloromethane at room temperature by ESI-MS and electrospray ionization tandem mass spectrometry (ESI-MS/MS) techniques (for details, see Transparent Methods and Figures S9–S12). At the early stage of the reaction (30 min), the corresponding signal of some important ionic reactive species, such as intermediate B at m/z 133, D at m/z 299, [E + H]^+ at m/z 243, G at m/z 324, and H at m/z 407, were observed in the positive ion ESI-MS spectrum of the reaction mixture (Figure 9B and S9–S12 and Schemes S1–S4). These results and the corresponding proposed dissociation pathways provide strong evidence for the reaction key intermediates.

Although a detailed reaction pathway remains to be clarified, a plausible mechanism for this reaction was proposed on the basis of above preliminary results (Figure 9A). A radical pathway might be ruled out as the reaction could not be inhibited by a typical radical scavenger 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO). Initially, isochroman A was oxidized by DDQ in a reversible process to form the highly reactive benzyloxy cation intermediate B (Jung and Floreancig, 2009), followed by the isocyanide addition to give the nitrilium ion intermediate C. The role of silver triflate may be accounted for the formation of coordinated silver-isocyanide complex to improve the nucleophilic reactivity of isocyanide (Gao et al., 2013; Liu et al., 2015; Álvarez-Corral et al., 2008). The attack by a second molecule of isocyanide on cation C afforded intermediate D (Tobisu et al., 2007; Saegusa et al., 1969), which would furnish the double isocyanide insertion product E via the leaving of tert-butyl cation by means of β-scission of the imidoyl cation (Saegusa et al., 1969).
et al., 1969; Xia and Ganem, 2002). The compound E (R = H) may generate the cation F rapidly as it has never been isolated during the reaction. Following the above procedure again, finally, the bis-iminonitrile product 2a could be obtained smoothly from intermediate H.

**Conclusion**

We have developed a direct synthesis of iminonitrile substituted isochromans and THIQs with quaternary carbon centers through silver-mediated sequential isocyanide insertion of C(sp³)-H bonds. The isocyanide is the typical precursor of α-iminonitrile and is conceived to play a two-fold role as both the crucial “CN” and “imine” sources. Mechanistic studies by ESI-MS and ESI-MS/MS techniques revealed that the reaction probably proceeded through nitrilium ion as the key intermediate. The given approach provided a convenient and practical method for the construction of synthetic meaningful α-iminonitrile skeleton in moderate to good yields with preferred substrate adaptability. The α-iminonitriles are not only valuable building blocks for the synthesis of pharmacologically interesting heterocycles but also potential chromophores for tuning the optical behavior of emissive materials, leading to an interesting AIEgen when appended to π-extended aromatics.

**Limitations of the Study**

The substrates with strong electron-withdrawing groups such as CF₃ and CN on the aryl rings are not suitable under standard conditions. Substrates with moderate electron-withdrawing halogens gave relatively lower yields. THIQs with free N-H bond or other protecting groups such as Boc and Ac gave trace amount of the desired products or complex mixtures. 1,3-Dihydroisobenzofuran and isoindoline also gave complicated mixture.
METHODS
All methods can be found in the accompanying Transparent Methods supplemental file.

DATA AND CODE AVAILABILITY
The structures of 2a, 4h, 6a, and 8b reported in this article have been deposited in the Cambridge Crystallographic Data Center under accession numbers CCDC: 1533930, 1534967, 1829908, and 1829633.

SUPPLEMENTAL INFORMATION
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AUTHOR CONTRIBUTIONS
B.X. directed the research, conceived and developed the concepts, and provided overall supervision. B.X. and Q.T. wrote the manuscript and prepared the Supplemental Information. H.C., H.L., and R.Y. performed the experiments. B.L. performed the analysis of X-ray single crystal diffraction. H.W. and Y.G. investigated the intermediates by ESI-MS. Q.T. and H.L. investigated the AIE effect. All authors contributed to write the manuscript. H.C. and H.L. contributed equally to this work.

DECLARATION OF INTERESTS
The authors declare no competing interests.

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Figure 9. Plausible Mechanism and the Detection of the Key Intermediates by ESI-MS
(A) Proposed mechanism for imino nitrile substituted isochromans.
(B) The ESI-MS spectra of the intermediates in the reaction at the early stage of the reaction. Most of the proposed intermediates were detected.
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Supplemental Information

From Isocyanides to Iminonitriles
via Silver-mediated Sequential
Insertion of C(sp$^3$)–H Bond

Huiwen Chi, Hao Li, Bingxin Liu, Rongxuan Ye, Haoyang Wang, Yin-Long Guo, Qitao Tan, and Bin Xu
**Transparent Methods**

**General Information**

All reagents and metal catalysts were obtained from commercial sources without further purification, and commercially available solvents were purified before use. All new compounds were fully characterized. All melting points were taken on a WRS-1A or a WRS-1B Digital Melting Point Apparatus without correction. Infrared spectra were obtained using an AVATAR 370 FT-IR spectrometer. \(^1\)H, \(^{13}\)C, and \(^{19}\)F NMR spectra were recorded with a Bruker AV-500 spectrometer operating at 500 MHz, 125 MHz and 470 MHz, respectively, with chemical shift values being reported in ppm relative to chloroform (\(\delta = 7.26\) ppm), dimethyl sulfoxide (\(\delta = 2.50\) ppm) or TMS (\(\delta = 0.00\) ppm) for \(^1\)H NMR, with chloroform (\(\delta = 77.16\) ppm), dimethyl sulfoxide (\(\delta = 39.52\) ppm) or acetone (\(\delta = 29.84\) ppm) for \(^{13}\)C NMR; and \(\text{C}_6\text{F}_6\) (\(\delta = -164.9\) ppm) for \(^{19}\)F NMR. Mass spectra and high resolution mass spectra (HRMS) were recorded with an Agilent 5975N using an Electron impact (EI) or Electrospray ionization (ESI) techniques. For mechanistic study, the electrospray ionization mass spectrometry (ESI-MS) and the subsequent tandem mass spectrometry (ESI-MS/MS) experiments were performed in Thermo TSQ Quantum Access™ triple-quadrupole mass spectrometer. Ultraviolet spectra were measured on a PEGeneral spectrometer. Fluorescence spectra were recorded on a LS-55 spectrometer. Silica gel plate GF254 were used for thin layer chromatography (TLC) and silica gel H or 300–400 mesh were used for flash column chromatography. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise indicated.

**Experimental Procedures**

**Synthesis and Characterization of Isochroman Substrates, Related to Figure 2 and Figure 3.**

Isochroman 1a is commercial available, and 1b, 1d-1f, 1j and 1s-1u were prepared according to the known methods (Zhou et al., 2013). Substrate 3a-3b, 3d-3e, 3i and 3k-3l were prepared according to the reported procedures (Muramatsu and Nakano, 2014). The spectra of the prepared substrates are consistent with the reported data. Other isochroman substrates are prepared as shown below.

![Diagram](image)

7-Phenylisochroman (1c): To a flask containing K\(_2\)CO\(_3\) (138.2 mg, 1.0 mmol), Pd(PPh\(_3\))\(_4\) (14.4 mg, 1.25 mol%) and phenylboronic acid (67.1 mg, 0.55 mmol) in the aqueous solution of dioxane (5.0 mL) was added 7-bromoisochroman (1e) (106.0 mg, 0.5 mmol). The mixture was heated to 90 °C under N\(_2\) for 8.5 h. Upon completion, the reaction mixture was cooled down to room temperature, diluted with ethyl acetate (10 mL) and washed with brine (2 × 30 mL). The combined organic phase was dried over Na\(_2\)SO\(_4\) and purified by column chromatography on silica gel to give product 1c as white solid (101.3 mg, 96%). M.p. 60-62 °C; IR (KBr, cm\(^{-1}\)):
5-Phenylisochroman (1g): Following the general procedure as for 1c, the reaction mixture of 5-bromoisochroman (254.4 mg, 1.2 mmol), phenylboronic acid (161.0 mg, 1.3 mmol), K₂CO₃ (331.7 mg, 2.4 mmol) and Pd(PPh₃)₄ (34.7 mg, 0.03 mmol) in the aqueous solution of dioxane (8.0 mL) was stirred at 90 °C for 14 h to afford product 1g (204.0 mg, 81%) as white solid. M.p. 46-48 °C; IR (KBr, cm⁻¹): 2934, 2854, 1955, 1569, 1432, 1237, 1108, 1060, 999, 799, 757, 699; ¹H NMR (CDCl₃, 500 MHz): δ 7.41 (t, J = 7.5 Hz, 2H), 7.36-7.31 (m, 3H), 7.24 (t, J = 8.0 Hz, 1H), 7.13 (d, J = 7.5 Hz, 1H), 7.00 (d, J = 7.5 Hz, 1H), 4.86 (s, 2H), 3.89 (t, J = 5.7 Hz, 2H), 2.72 (t, J = 5.7 Hz, 2H); ¹³C NMR (CDCl₃, 125 MHz): 142.6, 140.0, 135.3, 132.3, 131.3, 127.3, 126.0, 124.5, 123.5, 111.4, 68.1, 65.4, 27.8; LC-MS (ESI) m/z 217 [M+NH₄⁺]; HRMS (ESI) m/z calcd for C₁₃H₁₃O₂ [M⁺] 201.0910, found 201.0909.

5-(Furan-3-yl)isochroman (1h): Following the general procedure as for 1c, the reaction mixture of 5-bromoisochroman (196.1 mg, 0.9 mmol), furan-3-ylboronic acid (110.9 mg, 1.0 mmol), K₂CO₃ (229.4 mg, 1.8 mmol) and Pd(PPh₃)₄ (24.0 mg, 0.03 mmol) in the aqueous solution of dioxane was stirred at 90 °C for 8.5 h to afford product 1h (86.5 mg, 54%) as white solid. M.p. 37-39 °C; IR (KBr, cm⁻¹): 2933, 2850, 1602, 1255, 1237, 1157, 1105, 1061, 1019, 873, 753, 725; ¹H NMR (CDCl₃, 500 MHz): δ 7.50 (d, J = 13.0 Hz, 2H), 6.96 (d, J = 6.5 Hz, 1H), 6.57 (s, 1H), 4.83 (s, 2H), 3.95 (t, J = 5.7 Hz, 2H), 2.85 (t, J = 5.5 Hz, 2H); ¹³C NMR (CDCl₃, 125 MHz): 142.6, 140.0, 135.3, 132.3, 131.3, 127.3, 126.0, 124.5, 123.5, 111.4, 68.1, 65.4, 27.8; LC-MS (ESI) m/z 217 [M+NH₄⁺]; HRMS (ESI) m/z calcd for C₁₃H₁₃O₂ [M⁺] 201.0910, found 201.0909.

Butyl-3-(isochroman-5-yl)acrylate (1i): To a test tube containing 5-bromoisochroman (63.6 mg, 0.3 mmol), Pd(OAc)₂ (6.8 mg, 0.03 mmol) and Ph₃P (15.8 mg, 0.06 mmol) in DMF (3.0 mL), butyl acrylate (46.2 mg, 0.36 mmol) and TMEDA (69.7 mg, 0.6 mmol) were added. The mixture was heated to 125 °C under N₂ and stirred for 19 h. Upon completion, the reaction
mixture was cooled down to room temperature, diluted with ethyl acetate (10 mL) and washed with water (3 × 15 mL). The combined organic phase was dried over Na₂SO₄ and purified by column chromatography on silica gel to give product 1i (86.8 mg, 100%) as colorless liquid. IR (KBr, cm⁻¹): 2959, 2864, 1712, 1634, 1459, 1308, 1263, 1222, 1172, 1114, 984, 786; ¹H NMR (CDCl₃, 500 MHz): δ 7.89 (d, J = 16.0 Hz, 1H), 7.44 (d, J = 7.5 Hz, 1H), 7.17 (t, J = 7.7 Hz, 1H), 6.99 (d, J = 7.5 Hz, 1H), 6.36 (d, J = 16.0 Hz, 1H), 4.76 (s, 2H), 4.20 (t, J = 6.7 Hz, 2H), 4.00 (t, J = 5.7 Hz, 2H), 2.91 (t, J = 5.5 Hz, 2H), 1.71-1.65 (m, 2H), 1.46-1.39 (m, 2H), 0.96 (t, J = 7.5 Hz, 3H); ¹³C NMR (CDCl₃, 125 MHz): 167.0, 141.0, 135.6, 133.4, 132.7, 126.2, 126.1, 124.7, 120.0, 68.0, 65.1, 64.5, 30.7, 25.9, 19.2, 13.7; LC-MS (ESI) m/z 261 [M+H]⁺; HRMS (ESI) m/z calcd for C₁₆H₂₁O₃ [M+H]⁺ 261.1485, found 261.1483.

1,4-Dihydro-2H-benzo[f]isochromene (1k): To a flask containing lithium aluminum hydride (683.1 mg, 18.0 mmol) in dry THF (30 mL) was slowly added 2-(naphthalen-1-yl)acetic acid (2.79 g, 15.0 mmol) at 0 °C over a period of 1 h. Then the reaction mixture was warmed to room temperature and refluxed for 30 min. The excess lithium aluminum hydride was hydrolyzed by slow addition of 20% aqueous sodium hydroxide solution (20 mL). After filtration through a thin pad of celite, the filtrate was extracted with ethyl acetate (3 × 30 mL) and washed with brine (2 × 20 mL). The combined organic phase was dried over Na₂SO₄ and purified by column chromatography on silica gel to give 2-(naphthalen-1-yl)ethanol (2.25 g, 87%) as colorless liquid. A mixture of the 2-(naphthalen-1-yl)ethanol (1.37 g, 8 mmol), (chloromethoxy)ethane (1.13 g, 12 mmol) and N,N-diisopropylethylamine (2.07 g, 16 mmol) in dry dichloromethane (24 mL) was stirred for 6.5 h under N₂ at room temperature. The reaction mixture was then washed with brine (2 × 50 mL), dried over Na₂SO₄ and the solvent was removed in vacuo. The given crude acetal (0.69 g, 3.0 mmol) was dissolved in dry CH₃CN (9 mL) and trimethylsilyl trifluoromethanesulfonate (TMSOTf) (0.8 g, 3.6 mmol) was added at 0 °C. The reaction was carried out under N₂ for 14 h and quenched by the addition of NaHCO₃ (1.0 M, 10 mL). The organic phase was washed with brine (2 × 20 mL), dried with Na₂SO₄ and purified by column chromatography on silica gel to give product 1k (421.8 mg, 66% yield for three steps) as white solid. M.p. 66-67 °C; IR (KBr, cm⁻¹): 3053, 2923, 2845, 2812, 1590, 1507, 1388, 1305, 1106, 1069, 990, 807, 737; ¹H NMR (CDCl₃, 500 MHz): δ 7.92 (d, J = 8.5 Hz, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.69 (d, J = 8.5 Hz, 1H), 7.56-7.53 (m, 1H), 7.50-7.47 (m, 1H), 7.11 (d, J = 8.5 Hz, 1H), 4.92 (s, 2H), 4.15 (t, J = 5.7 Hz, 2H), 3.17 (t, J = 5.5 Hz, 2H); ¹³C NMR (CDCl₃, 125 MHz): 132.3, 132.1, 132.0, 126.8, 128.3, 126.8, 126.1, 126.2, 125.3, 122.9, 122.5, 68.3, 65.2, 25.1; EI-MS m/z (%): 184 (100) [M⁺], 183 (20), 154 (55), 153 (35), 152 (32); HRMS (EI) m/z calcd for C₁₃H₁₂O [M⁺] 184.0888, found 184.0884.

4,7-Dihydro-5H-thieno[2,3-c]pyran (1l) (Gonzalez-de-Castro et al., 2014): The product 1l was prepared following the general procedure as for 1k. The reaction mixture of 2-(thiophen-3-yl)acetic acid (710.0 mg, 5.0 mmol) and lithium aluminum hydride (474.4 mg,
12.5 mmol) in dry THF (15 mL) was stirred at 0 °C for 8 h to afford 2-(thiophen-3-yl)ethan-1-ol as a crude. Then the mixture of the 2-(thiophen-3-yl)ethan-1-ol (640.2 mg, 5.0 mmol), (chloromethoxy)ethane (695 μL, 7.5 mmol) and N,N-diisopropylethylamine (1.6 mL, 10.0 mmol) in dry dichloromethane (15 mL) was stirred for 23 h under N₂ at room temperature to afford crude acetal product. Finally, the reaction mixture of acetal (258.1 mg, 1.5 mmol) and TMSOTf (50 μL, 0.26 mmol) in dry CH₃CN (9.0 mL) was stirred at 0 °C for 15 h to afford product 1l (46.4 mg, 22% yield for three steps) as a pale yellow liquid. IR (KBr, cm⁻¹): 2919, 2844, 1446, 1385, 1154, 1091, 1020, 974, 704; ¹H NMR (CDCl₃, 500 MHz): δ 7.15 (d, J = 5.0 Hz, 1H), 6.83 (d, J = 5.0 Hz, 1H), 4.83 (s, 2H), 3.95 (t, J = 5.7 Hz, 2H), 2.77-2.74 (m, 2H); ¹³C NMR (CDCl₃, 125 MHz): 132.7, 127.0, 122.5, 65.6, 65.0, 26.1; EI-MS m/z (%): 140 (100) [M⁺], 110 (72).

6,7-Dihydro-4H-thieno[3,2-c]pyran (1m): The product 1m was prepared following the general procedure as for 1k. The reaction mixture of 2-(thiophen-2-yl)acetic acid (1.1 g, 8.0 mmol) and lithium aluminum hydride (542.0 mg, 14.3 mmol) in dry Et₂O (30 mL) was stirred at 0 °C for 40 min, then refluxed for 6.5 h to afford 2-(thiophen-2-yl)ethan-1-ol as a crude. Then the mixture of the 2-(thiophen-2-yl)ethan-1-ol (947.4 mg, 7.4 mmol), (chloromethoxy)ethane (1.0 mL, 11.1 mmol) and N,N-diisopropylethylamine (2.5 mL, 14.8 mmol) in dry dichloromethane (30 mL) was stirred for 16 h under N₂ at room temperature to afford crude acetal product. Finally, the reaction mixture of acetal (279.1 mg, 1.5 mmol) and TMSOTf (130 μL, 0.68 mmol) in dry CH₃CN (9.0 mL) was stirred at 0 °C for 13.5 h to afford product 1m (71.7 mg, 32% yield for three steps) as pale yellow liquid. IR (KBr, cm⁻¹): 3102, 2924, 2848, 1446, 1397, 1325, 1228, 1095, 1072, 966, 851, 705; ¹H NMR (CDCl₃, 500 MHz): δ 7.14 (d, J = 5.5 Hz, 1H), 6.76 (d, J = 5.0 Hz, 1H), 4.76 (t, J = 1.2 Hz, 2H), 4.00 (t, J = 5.5 Hz, 2H), 2.91 (t, J = 5.5 Hz, 2H); ¹³C NMR (CDCl₃, 125 MHz): 133.7, 132.2, 123.6, 122.7, 66.5, 64.9, 25.5; EI-MS m/z (%): 140 (52) [M⁺], 110 (100); HRMS (EI) m/z calcd for C₇H₈OS [M⁺] 140.0296, found 140.0294.

Spiro[cyclobutane-1,3'-isochroman] (1n): To a two-neck round bottom flask equipped with a reflux condenser under N₂ containing magnesium turnings (1.5 g, 60.0 mmol) in Et₂O (15 mL) and a particle of iodine was added dropwise (bromomethyl)benzene (5.1 g, 30.0 mmol) in Et₂O (15 mL) over 1 h. The mixture was stirred for 5 h under reflux. It was then allowed to cool to room temperature and transferred by syringe into a vial sealed with rubber stopper under a positive pressure of N₂. To a stirring solution of cyclobutanone (560.7 mg, 8.0 mmol) in dry Et₂O (24.0 mL), benzylmagnesium bromide (1.0 M in Et₂O, 12 mL) was added at 0 °C under N₂. Upon completion, water was added and the solution was extracted with ethyl acetate. The combined organic phase was washed with brine, dried over Na₂SO₄ and evaporated in vacuum to give the crude product 1-benzycyclobutan-1-ol for further use. Following the general procedure as for 1k, the mixture of crude 1-benzycyclobutan-1-ol (1.13 g), (chloromethoxy)ethane (973 μL, 10.5 mmol) and N,N-diisopropylethylamine (2.3 mL, 14.0
mmol) in dry dichloromethane (24 mL) was stirred for 5 h under N₂ at room temperature. After reaction, the purified acetal (586.4 mg, 33% yield for two steps) was obtained by silica gel column chromatography. The reaction mixture of acetal (550.4 mg, 2.5 mmol) and TMSOTf (526 μL, 2.75 mmol) in dry CH₂CN (9.0 mL) was stirred at 0 °C, then warmed to room temperature and stirred for 10.5 h to afford product 1n (284.4 mg, 61%) as colorless liquid. IR (KBr, cm⁻¹): 2976, 2933, 2835, 1692, 1550, 1532, 1505, 1266, 1091, 1047, 744; ¹H NMR (CDCl₃, 500 MHz): δ 7.17-7.11 (m, 3H), 6.98 (d, J = 8.5 Hz, 1H), 4.79 (s, 2H), 2.92 (s, 2H), 2.25-2.18 (m, 2H), 1.96-1.85 (m, 3H), 1.75-1.69 (m, 1H); ¹³C NMR (CDCl₃, 125 MHz): 134.3, 132.7, 129.4, 126.3, 125.9, 123.9, 75.4, 63.3, 37.2, 32.4, 12.4; LC-MS (ESI) m/z 175 [M+H]+; HRMS (ESI) m/z calcd for C₁₂H₁₅O [M+H]+ 175.1117, found 175.1117.

Spire[cyclopentane-1,3'-isochroman] (1o): The product 1o was prepared following the general procedure as for 1n. The reaction mixture of cyclopentanone (672.0 mg, 8.0 mmol) and benzylmagnesium bromide (1.0 M in Et₂O, 12 mL) in dry Et₂O (24 mL) was stirred at 0 °C, then warmed to room temperature and stirred for 16 h to afford 1-benzylcyclopentan-1-ol as a crude. Then a mixture of the crude 1-benzylcyclopentan-1-ol (1.41 g), (chloromethoxy)ethane (1.1 mL, 12 mmol) and N,N-diisopropylethylamine (2.6 mL, 16 mmol) in dry dichloromethane (24 mL) was stirred for 5 h under N₂ at room temperature. After reaction, the purified acetal (580.2 mg, 29% yield for two steps) was obtained by silica gel column chromatography. Finally, the reaction mixture of acetal (749.3 mg, 3.2 mmol) and TMSOTf (0.68 mL, 3.52 mmol) in dry CH₃CN (11 mL) was stirred at 0 °C, then warmed to room temperature and stirred for 14 h to afford product 1o (232.2 mg, 39%) as colorless liquid. IR (KBr, cm⁻¹): 2954, 1494, 1448, 1208, 1081, 744; ¹H NMR (CDCl₃, 500 MHz): δ 7.17-7.13 (m, 2H), 7.09-7.07 (m, 1H), 4.80 (s, 2H), 2.81 (s, 2H), 1.91-1.87 (m, 2H), 1.83-1.79 (m, 2H), 1.69-1.63 (m, 2H), 1.54-1.48 (m, 2H); ¹³C NMR (CDCl₃, 125 MHz): 134.2, 133.6, 129.0, 126.1, 125.8, 123.9, 82.4, 63.3, 37.9, 36.4, 23.8; EI-MS m/z (%): 188 (12) [M⁺], 104 (100); HRMS (EI) m/z calcd for C₁₃H₁₆O [M⁺] 188.1201, found 188.1197.

Spire[cyclohexane-1,3'-isochroman] (1p): The product 1p was prepared following the general procedure as for 1n. The reaction mixture of cyclohexanone (783.0 mg, 8.0 mmol) and benzylmagnesium bromide (1.0 M in Et₂O, 12 mL) in dry Et₂O (24 mL) was stirred at 0 °C, then warmed to room temperature and stirred for 16 h to afford 1-benzylcyclohexan-1-ol as a crude. Then a mixture of the crude 1-benzylcyclohexan-1-ol (1.32 g), (chloromethoxy)ethane (973.0 μL, 10.5 mmol) and N,N-diisopropylethylamine (2.3 mL, 14.0 mmol) in dry dichloromethane (24 mL) was stirred for 5 h under N₂ at room temperature. After reaction, the purified acetal (761.6 mg, 40% yield for two steps) was obtained by silica gel column chromatography. Finally, the reaction mixture of acetal (570.8 mg, 2.3 mmol) and TMSOTf (444 μL, 2.53 mmol) in dry CH₃CN (9.0 mL) was stirred at 0 °C, then warmed to room temperature and stirred for 10.5 h to afford product 1p (343.2 mg, 79%) as white solid. M.p. 50-52 °C; IR (KBr, cm⁻¹): 3032, 2850, 1444, 1075, 1026, 951, 748; ¹H NMR (CDCl₃, 500 MHz): δ 7.16-7.13 (m, 2H), 7.08-7.06 (m,
1H), 7.00-6.98 (m, 1H), 4.76 (s, 2H), 2.68 (s, 2H), 1.76-1.73 (m, 2H), 1.67-1.58 (m, 3H), 1.51-1.33 (m, 5H); 13C NMR (CDCl₃, 125 MHz): 134.3, 132.7, 129.2, 126.2, 125.7, 123.9, 71.6, 62.1, 38.8, 34.8, 26.0, 21.9; LC-MS (ESI) m/z 203 [M+H]⁺; HRMS (ESI) m/z calcd for C₁₄H₁₉O [M+H]⁺ 203.1430, found 203.1430.

3,3-Dimethylisochroman (1q): The product 1q was prepared following the general procedure as for 1n. The reaction mixture of acetone (0.44 mL, 6.0 mmol) and benzylmagnesium bromide (1.0 M in Et₂O, 9 mL) in dry Et₂O (18 mL) was stirred at 0 °C, then warmed to room temperature and stirred for 5 h to afford product 2-methyl-1-phenylpropan-2-ol (636.0 mg, 71%). Then a mixture of the 2-methyl-1-phenylpropan-2-ol (630.4 mg, 4.2 mmol), (chloromethoxy)ethane (589 μL, 6.3 mmol) and N,N-diisopropylethylamine (1.4 mL, 8.4 mmol) in dry dichloromethane (12 mL) was stirred for 13 h under N₂ at room temperature to afford crude product acetal. Finally, the reaction mixture of acetal (624.4 mg, 3.0 mmol) and TMSOTf (638 μL, 3.3 mmol) in dry CH₃CN (9.0 mL) was stirred at 0 °C, then warmed to room temperature and stirred for 20 h to afford product 1q (248.4 mg, 51% yield for two steps) as pale yellow oil. IR (KBr, cm⁻¹): 2968, 2925, 2847, 1549, 1500, 1456, 1368, 1212, 1080, 742; ¹H NMR (CDCl₃, 500 MHz): δ 7.18-7.14 (m, 2H), 7.09-7.07 (m, 1H), 7.03-6.99 (m, 1H), 4.80 (s, 2H), 2.72 (s, 2H), 1.29 (s, 6H); 13C NMR (CDCl₃, 125 MHz): 133.9, 133.0, 129.1, 126.3, 125.8, 123.9, 70.8, 63.0, 39.6, 26.4; EI-MS m/z (%): 162 (5) [M⁺], 147 (5), 105 (12), 104 (100); HRMS (EI) m/z calcd for C₁₁H₁₄O [M⁺] 162.1045, found 162.1048.

3-Phenylisochroman (1r): The product 1r was prepared following the general procedure as for 1n. The reaction mixture of benzaldehyde (530.6 mg, 5.0 mmol) and benzylmagnesium bromide (0.5 M in Et₂O, 15 mL) in dry Et₂O (10 mL) was stirred at 0 °C, then warmed to room temperature and stirred for 5.5 h to afford product 1,2-diphenylethan-1-ol (359.4 mg, 36%). Then a mixture of the 1,2-diphenylethan-1-ol (356.6 mg, 1.8 mmol), (chloromethoxy)ethane (0.25 mL, 2.7 mmol) and N,N-diisopropylethylamine (595 μL, 3.6 mmol) in dry dichloromethane (6 mL) was stirred for 19 h under N₂ at room temperature to afford acetal product (402.5 mg, 87%). Finally, the reaction mixture of acetal (402.2 mg, 1.57 mmol) and TMSOTf (334 μL, 3.3 mmol) in dry CH₃CN (6.0 mL) was stirred at 0 °C, then warmed to room temperature and stirred for 17 h to afford product 1r (213.8 mg, 65%) as white solid. M.p. 75-76 °C; IR (KBr, cm⁻¹): 3024, 2910, 2851, 1487, 1444, 1367, 1084, 1027, 984, 735, 695; ¹H NMR (CDCl₃, 500 MHz): δ 7.18-7.14 (m, 2H), 7.09-7.07 (m, 1H), 7.03-6.99 (m, 1H), 4.80 (s, 2H), 2.72 (s, 2H), 1.29 (s, 6H); 13C NMR (CDCl₃, 125 MHz): 142.1, 134.5, 133.5, 128.8, 128.5, 127.7, 126.5, 125.9, 124.2, 76.9, 68.7, 36.1; EI-MS m/z (%): 210 (5) [M⁺], 105 (12), 104 (100); HRMS (EI) m/z calcd for C₁₅H₁₄O [M⁺] 210.1045, found 210.1044.
7-Methyl-1-phenylisochroman (3c): Following the procedure as for 3f (see below), the reaction mixture of 7-methylisochroman (59.2 mg, 0.4 mmol), 2,3-dichloro-5,6-dicyano-benzoquinone (DDQ) (18.2 mg, 0.08 mmol), [bis(trifluoroacetoxy)iodo]benzene (PIFA) (172.0 mg, 0.4 mmol) in dry 1,2-dichloroethane (4.0 mL) was stirred at 80 °C under N₂ for 3.5 h, then phenyl- magnesium iodide was added at -15 °C and kept stirring for another 4.5 h to afford product 3c (44.6 mg, 50%) as pale yellow oil. IR (KBr, cm⁻¹): 3027, 2961, 2919, 2852, 2723, 1606, 1499, 1453, 1274, 1090, 1020, 806, 748, 701; ¹H NMR (CDCl₃, 500 MHz): δ 7.46-7.41 (m, 5H), 7.16 (d, J = 8.0 Hz, 1H), 7.09 (d, J = 8.0 Hz, 1H), 6.68 (s, 1H), 5.80 (s, 1H), 4.30-4.26 (m, 1H), 4.02-3.97 (m, 1H), 3.20-3.18 (m, 1H), 2.88-2.84 (m, 1H), 2.29 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz): 142.4, 137.1, 135.5, 130.9, 129.0, 128.7, 128.5, 128.1, 127.6, 127.3, 79.7, 64.0, 28.6, 21.1; EI-MS m/z (%): 224 (100) [M⁺], 223 (45), 209 (45), 178 (42), 147 (80), 119 (42); HRMS (EI) m/z calcd for C₁₆H₁₆O [M⁺] 224.1201, found 224.1205.

5-Methyl-1-(p-tolyl)isochroman (3f): To a two-neck round bottom flask equipped with a reflux condenser under N₂ containing magnesium turnings (466.6 mg, 19.2 mmol) in Et₂O (4.0 mL) was added 1-iodo-4-methylbenzene (3.5 g, 16.0 mmol) in Et₂O (4.0 mL) dropwise over 0.5 h. The mixture was stirred for 5.5 h under reflux. After cooling to room temperature, the produced p-tolylmagnesium iodide was then transferred by syringe into a vial sealed with rubber stopper under a positive pressure of N₂. The mixture of 5-methylisochroman (59.2 mg, 0.4 mmol), DDQ (18.2 mg, 0.08 mmol) and PIFA (172.0 mg, 0.4 mmol) in dry 1,2-dichloroethane (4.0 mL) in a test tube was stirred at 80 °C for 4 h under N₂, then p-tolylmagnesium iodide (2.0 M in Et₂O, 0.4 mL, 0.8 mmol) was added to the suspension at -15 °C. After stirring vigorously for 4 h at -15 °C, the reaction mixture was quenched with saturated aqueous NaHCO₃ and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na₂SO₄ and purified by column chromatography on silica gel to give product 3f (42.5 mg, 45%) as white solid. M.p. 70-71 °C; IR (KBr, cm⁻¹): 2929, 2872, 2812, 1909, 1462, 1266, 1106, 1061, 1011, 825, 796, 755; ¹H NMR (CDCl₃, 500 MHz): δ 7.18 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 8.0 Hz, 2H), 7.05 (d, J = 7.0 Hz, 1H), 6.98 (t, J = 7.5 Hz, 1H), 6.61 (d, J = 8.0 Hz, 1H), 5.71 (s, 1H), 4.22-4.18 (m, 1H), 3.96-3.91 (m, 1H), 2.92-2.89 (m, 1H), 2.73-2.69 (m, 1H), 2.34 (s, 3H), 2.28 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz): 139.4, 137.7, 137.3, 136.1, 132.4, 129.0, 128.8, 127.8, 125.3, 124.6, 79.5, 63.4, 26.4, 21.2, 19.0; LC-MS (ESI) m/z 239 [M+H⁺]; HRMS (ESI) m/z calcd for C₁₇H₁₇O [M+H+] 239.1430, found 239.1429.
1-(Naphthalen-1-yl)isochroman (3g): Following the general procedure as for 3f, the reaction mixture of isochroman (53.7 mg, 0.4 mmol), DDQ (18.2 mg, 0.08 mmol), PIFA (172.0 mg, 0.4 mmol) in dry 1,2-dichloroethane (4.0 mL) was stirred at 80 °C under N\textsubscript{2} for 4 h, then naphthalen-1-ylmagnesium bromide was added at -15 °C and kept stirring for another 4 h to afford product 3g (40.2 mg, 39%) as pale yellow solid. M.p. 122-123 °C; IR (KBr, cm\textsuperscript{-1}): 3019, 2972, 2923, 2874, 1589, 1495, 1450, 1363, 1263, 1080, 1040, 783, 740; \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 500 MHz): \(\delta\) 8.22-8.20 (m, 1H), 7.89-7.87 (m, 1H), 7.84 (d, \(J = 8.5\) Hz, 1H), 7.49-7.47 (m, 2H), 7.43-7.40 (m, 1H), 7.31 (d, \(J = 7.0\) Hz, 1H), 7.26-7.19 (m, 2H), 7.04 (t, \(J = 7.0\) Hz, 1H), 6.76 (d, \(J = 7.5\) Hz, 1H), 6.42 (s, 1H), 4.24-4.20 (m, 1H), 4.05-4.00 (m, 1H), 3.22-3.20 (m, 1H), 2.99-2.94 (m, 1H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 125 MHz): 137.4, 137.2, 134.3, 133.8, 131.7, 129.0, 128.8, 128.6, 128.1, 126.7, 126.5, 126.2, 126.0, 125.6, 124.9 (2), 77.7, 63.7, 28.8; EI-MS m/z (%): 261 (20), 260 (100) [M\textsuperscript{+}], 259 (42), 133 (21); HRMS (EI) m/z calcd for C\textsubscript{19}H\textsubscript{16}O [M\textsuperscript{+}] 260.1201, found 260.1199.

1-(3-Bromothiophen-2-yl)isochroman (3h): After stirring the mixture of 5-methylisochroman (59.2 mg, 0.4 mmol), DDQ (18.2 mg, 0.08 mmol) and PIFA (172.0 mg, 0.4 mmol) in dry 1,2-dichloroethane (4.0 mL) in a test tube at 80 °C for 4 h under N\textsubscript{2}, 3-bromothiophene (78.3 mg, 0.48 mmol) was added to the suspension at room temperature. After stirring vigorously for 14 h at room temperature, the reaction mixture was purified by column chromatography on silica gel to give product 3h (34.0 mg, 28%) as white solid. M.p. 86-87 °C; IR (KBr, cm\textsuperscript{-1}): 2967, 2921, 2851, 1731, 1458, 1262, 1094, 1016, 869, 804, 742, 701; \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 500 MHz): \(\delta\) 7.27 (d, \(J = 5.5\) Hz, 1H), 7.09 (d, \(J = 7.0\) Hz, 1H), 7.04 (t, \(J = 7.5\) Hz, 1H), 7.00 (d, \(J = 5.0\) Hz, 1H), 6.75 (d, \(J = 7.5\) Hz, 1H), 6.18 (s, 1H), 4.31-4.27 (m, 1H), 4.02-3.97 (m, 1H), 2.96-2.90 (m, 1H), 2.71 (dt, \(J = 16.7\) Hz, 3.8 Hz, 1H), 2.28 (s, 3H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 125 MHz): 140.7, 136.2, 136.1, 132.0, 129.5, 128.5, 126.2, 125.7, 124.2, 110.8, 73.6, 63.9, 26.2, 19.0; EI-MS m/z (%): 310 (39) [M (\textsuperscript{81}Br)+], 308 (40) [M (\textsuperscript{79}Br)+], 229 (100), 201 (65), 184 (45); HRMS (EI) m/z calcd for C\textsubscript{14}H\textsubscript{13}OSBr [M\textsuperscript{+}] 307.9870, found 307.9871.

6-Phenyl-6H-benzo[c]chromene (3j): Following the general procedure as for 3f, the reaction mixture of 6H-benzo[c]chromene (182.1 mg, 0.4 mmol), DDQ (18.2 mg, 0.08 mmol), PIFA
(172.0 mg, 0.4 mmol) in dry 1,2-dichloroethane (4.0 mL) was stirred at 80 °C under N₂ for 3 h, then phenylmagnesium iodide was added at -15 °C and kept stirring for another 9 h to afford product 3j (79.0 mg, 77%) as white solid. M.p. 74-75 °C; IR (KBr, cm⁻¹): 3065, 3026, 2923, 1594, 1487, 1439, 1235, 1000, 743, 693, 607; ¹H NMR (CDCl₃, 500 MHz): δ 7.81-7.78 (m, 2H), 7.44-7.36 (m, 6H), 7.29-7.24 (m, 2H), 7.08 (td, J = 7.6, 1.0 Hz, 1H), 7.06-7.04 (m, 1H), 6.89 (d, J = 7.5 Hz, 1H), 6.20 (s, 1H); ¹³C NMR (CDCl₃, 125 MHz): 153.7, 139.6, 134.0, 130.1, 129.6, 128.5 (2), 128.4, 128.1, 127.6, 126.3, 123.1, 122.8, 122.1, 117.9, 79.7; EI-MS m/z (%): 258 (55) [M⁺], 257 (28), 181 (100); HRMS (EI) m/z calcd for C₁₉H₁₄O [M⁺] 258.1035.

C1 Functionalization of Isochromans, Related to Figure 2 and Figure 3.

(1E,1E)-N,N'-Di-tert-butylisochroman-1,1-bis(carbimidoyl) cyanide (2a):
To a test tube, 1a (39 μL, 0.3 mmol), tBuNC (170 μL, 1.5 mmol), AgOTf (7.8 mg, 0.03 mmol), DDQ (139.0 mg, 0.6 mmol), and dry PhCl (3.0 mL) were added in the glove box. The reaction mixture was stirred at 80 °C under N₂ for 3 h as monitored by TLC. Upon completion, the reaction mixture was cooled down to room temperature. After removed the solvent, the residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 100 : 1) to give product 2a (64.1 mg, 61%) as white solid. M.p. 113-115 °C; IR (KBr, cm⁻¹): 2979, 2216, 1643, 1476, 1464, 1208, 914, 754; ¹H NMR (CDCl₃, 500 MHz): δ 7.29-7.27 (m, 1H), 7.19-7.15 (m, 2H), 6.90 (d, J = 7.5 Hz, 1H), 4.05 (t, J = 5.7 Hz, 2H), 2.97 (t, J = 5.5 Hz, 2H), 1.39 (s, 18H); ¹³C NMR (CDCl₃, 125 MHz): 139.7, 134.8, 130.0, 129.2, 128.9, 128.4, 127.8, 125.5, 111.2, 85.0, 62.0, 59.1, 29.1, 28.2; LC-MS (ESI) m/z 351 [M+H⁺]; HRMS (ESI) m/z calcd for C₂₁H₂₇ON₄ [M+H⁺] 351.2179, found 351.2186.

(1E,1E)-N,N'-Di-tert-butyl-7-methylisochroman-1,1-bis(carbimidoyl) cyanide (2b):
Following the general procedure as for 2a, the reaction mixture of 1b (44.5 mg, 0.3 mmol), tBuNC (170 μL, 1.5 mmol), AgOTf (7.8 mg, 0.03 mmol), and DDQ (139.0 mg, 0.6 mmol) in dry PhCl (3.0 mL) was stirred at 80 °C under N₂ for 4.5 h to afford product 2b (79.3 mg, 73%) as white solid. M.p. 123-125 °C; IR (KBr, cm⁻¹): 2977, 2216, 1647, 1509, 1467, 1367, 1234, 1213, 1110, 1029, 948, 810; ¹H NMR (CDCl₃, 500 MHz): δ 7.07 (s, 2H), 6.69 (s, 1H), 4.02 (t, J = 5.5 Hz, 2H), 2.92 (t, J = 5.5 Hz, 2H), 2.28 (s, 3H), 1.39 (s, 18H); ¹³C NMR (CDCl₃, 125 MHz): 139.7, 134.8, 130.0, 129.2, 128.4, 127.8, 125.5, 111.2, 85.0, 62.0, 59.1, 29.1, 28.2; LC-MS (ESI) m/z 365 [M+H⁺]; HRMS (ESI) m/z calcd for C₂₂H₂₉ON₄ [M+H⁺] 365.2336, found 365.2332.
(1E,1E)-N,N'-Di-tert-butyl-7-phenylisochroman-1,1-bis(carbimidoyl) cyanide (2c):
Following the general procedure as for 2a, the reaction mixture of 1c (63.0 mg, 0.3 mmol), tBuNC (170 μL, 1.5 mmol), AgOTf (7.8 mg, 0.03 mmol), and DDQ (139.0 mg, 0.6 mmol) in dry PhCl (3.0 mL) was stirred at 80 °C under N₂ for 4.5 h to afford product 2c (81.7 mg, 64%) as white solid. M.p. 124–125 °C; IR (KBr, cm⁻¹): 2977, 2216, 1638, 1475, 1364, 1202, 1108, 762, 693; ¹H NMR (CDCl₃, 500 MHz): δ 7.53–7.51 (m, 3H), 7.45 (t, J = 7.5 Hz, 2H), 7.36 (t, J = 7.2 Hz, 1H), 7.28 (d, J = 8.0 Hz, 1H), 7.18 (s, 1H), 4.11 (t, J = 5.2 Hz, 2H), 3.03 (t, J = 5.2 Hz, 2H), 1.43 (s, 18H); ¹³C NMR (CDCl₃, 125 MHz): 140.7, 139.6, 138.4, 133.8, 129.5, 128.8, 128.1, 127.3, 126.8, 111.1, 85.1, 62.0, 59.1, 29.0, 27.8; LC-MS (ESI) m/z 427 [M+H]^⁺; HRMS (ESI) m/z calcd for C₂₇H₃₁ON₄ [M+H]^⁺ 427.2492, found 427.2489.

(1E,1E)-N,N'-Di-tert-butyl-7-methoxyisochroman-1,1-bis(carbimidoyl) cyanide (2d):
Following the general procedure as for 2a, the reaction mixture of 1d (50.7 mg, 0.3 mmol), tBuNC (170 μL, 1.5 mmol), AgOTf (7.8 mg, 0.03 mmol), and DDQ (139.0 mg, 0.6 mmol) in dry PhCl (3.0 mL) was stirred at 80 °C under N₂ for 4.5 h to afford product 2d (71.9 mg, 63%) as white solid. M.p. 124–125 °C; IR (KBr, cm⁻¹): 2977, 1727, 1645, 1483, 1454, 1366, 1212, 1104, 1029, 959, 820; ¹H NMR (CDCl₃, 500 MHz): δ 7.10 (d, J = 8.5 Hz, 1H), 6.85 (dd, J = 8.0, 2.5 Hz, 1H), 6.46 (d, J = 2.0 Hz, 1H), 4.03 (t, J = 5.4 Hz, 2H), 3.72 (s, 3H), 2.90 (t, J = 5.4 Hz, 2H), 1.40 (s, 18H); ¹³C NMR (CDCl₃, 125 MHz): 157.0, 139.6, 138.4, 130.6, 129.9, 128.6, 126.9, 115.3, 114.5, 111.0, 85.0, 62.1, 59.0, 55.2, 29.0, 27.8; LC-MS (ESI) m/z 381 [M+H]^⁺; HRMS (ESI) m/z calcd for C₂₂H₂₉O₂N₄ [M+H]^⁺ 381.2285, found 381.2293.

(1E,1E)-7-Bromo-N,N'-di-tert-butylisochroman-1,1-bis(carbimidoyl) cyanide (2e):
Following the general procedure as for 2a, the reaction mixture of 1e (65.6 mg, 0.3 mmol), tBuNC (170 μL, 1.5 mmol), AgOTf (7.8 mg, 0.03 mmol), and DDQ (139.0 mg, 0.6 mmol) in dry PhCl (3.0 mL) was stirred at 80 °C under N₂ for 4.5 h to afford product 2e (44.1 mg, 34%) as white solid. M.p. 108–110 °C; IR (KBr, cm⁻¹): 2975, 1727, 1645, 1483, 1454, 1366, 1212, 1089, 756, 697; ¹H NMR (CDCl₃, 500 MHz): δ 7.39 (dd, J = 8.5, 2.0 Hz, 1H), 7.07 (d, J = 8.0 Hz, 1H), 7.01 (d, J = 2.0 Hz, 1H), 4.02 (t, J = 5.5 Hz, 2H), 2.92 (t, J = 5.5 Hz, 2H), 1.40 (s, 18H); ¹³C NMR (CDCl₃, 125 MHz): 139.1, 133.6, 132.8, 131.4, 130.6, 129.8, 118.8, 110.8, 84.5, 61.7, 59.2, 28.9, 27.6; LC-MS (ESI) m/z (%): 431 (100) [M(^81Br)+H]^⁺, 429 (96) [M(^79Br)+H]^⁺; HRMS
(1E,1E)-N,N'-Di-tert-butyl-5-methylisochroman-1,1-bis(carbimidoyl) cyanide (2f):  
Following the general procedure as for 2a, the reaction mixture of 1f (44.4 mg, 0.3 mmol), tBuNC (170 μL, 1.5 mmol), AgOTf (7.8 mg, 0.03 mmol), and DDQ (139.0 mg, 0.6 mmol) in dry PhCl (3.0 mL) was stirred at 80 °C under N₂ for 3.5 h to afford product 2f (71.3 mg, 65%) as white solid. M.p. 103-105 °C; IR (KBr, cm⁻¹): 2976, 2220, 1643, 1467, 1367, 1211, 1096, 1028, 782; ¹H NMR (CDCl₃, 500 MHz): δ 7.14 (d, J = 7.0 Hz, 1H), 7.08 (t, J = 7.5 Hz, 1H), 6.75 (d, J = 8.0 Hz, 1H), 4.06 (t, J = 5.5 Hz, 2H), 2.82 (t, J = 5.7 Hz, 2H), 2.27 (s, 3H), 1.39 (s, 18H); ¹³C NMR (CDCl₃, 125 MHz): 139.8, 136.4, 133.3, 129.7, 127.7, 127.4, 124.8, 111.1, 85.1, 61.6, 58.9, 28.9, 25.6, 19.1; LC-MS (ESI) m/z 365 [M+H]^+; HRMS (ESI) m/z calcd for C₂₂H₂₉ON₄ [M+H]^+ 365.2336, found 365.2333.

(1E,1E)-N,N'-Di-tert-butyl-5-phenylisochroman-1,1-bis(carbimidoyl) cyanide (2g):  
Following the general procedure as for 2a, the reaction mixture of 1g (63.0 mg, 0.3 mmol), tBuNC (170 μL, 1.5 mmol), AgOTf (7.8 mg, 0.03 mmol), and DDQ (139.0 mg, 0.6 mmol) in dry PhCl (3.0 mL) was stirred at 80 °C under N₂ for 5 h to afford product 2g (85.1 mg, 67%) as white solid. M.p. 112-113 °C; IR (KBr, cm⁻¹): 2973, 2217, 1645, 1462, 1366, 1211, 1106, 1059, 755, 701; ¹H NMR (CDCl₃, 500 MHz): δ 7.44-7.41 (m, 2H), 7.38-7.34 (m, 3H), 7.26-7.23 (m, 2H), 6.95-6.93 (m, 1H), 3.94 (t, J = 5.5 Hz, 2H), 2.83 (t, J = 5.2 Hz, 2H), 1.42 (s, 18H); ¹³C NMR (CDCl₃, 125 MHz): 141.9, 140.3, 139.7, 132.7, 129.7, 129.3, 129.2, 128.2, 127.7, 127.2, 125.0, 111.2, 85.2, 62.0, 59.0, 29.0, 27.3; LC-MS (ESI) m/z 427 [M+H]^+; HRMS (ESI) m/z calcd for C₂₇H₃₁ON₄ [M+H]^+ 427.2492, found 427.2485.

(1E,1E)-N,N'-Di-tert-butyl-5-(furan-3-yl)isochroman-1,1-bis(carbimidoyl) cyanide (2h):  
Following the general procedure as for 2a, the reaction mixture of 1h (60.1 mg, 0.3 mmol), tBuNC (170 μL, 1.5 mmol), AgOTf (7.8 mg, 0.03 mmol), and DDQ (139.0 mg, 0.6 mmol) in dry PhCl (3.0 mL) was stirred at 80 °C under N₂ for 12 h to afford product 2h (83.2 mg, 67%) as
white solid. M.p. 114-115 °C; IR (KBr, cm\(^{-1}\)): 3130, 2977, 2216, 1641, 1506, 1466, 1364, 1234, 1210, 1108, 1055, 791, 749; \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 7.53 (s, 1H), 7.49 (s, 1H), 7.31 (d, \(J = 7.5\) Hz, 1H), 7.20 (t, \(J = 7.7\) Hz, 1H), 6.88 (d, \(J = 7.5\) Hz, 1H), 6.57 (s, 1H), 4.00 (t, \(J = 5.2\) Hz, 2H), 2.96 (t, \(J = 5.2\) Hz, 2H), 1.40 (s, 18H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): 142.8, 140.2, 139.7, 132.9, 132.5, 129.4, 129.3, 127.9, 125.1, 124.2, 111.4, 111.1, 85.2, 61.9, 59.0, 29.0, 27.3; LC-MS (ESI) m/z 417 [M+H]\(^+\); HRMS (ESI) m/z calcd for C\(_{25}\)H\(_{29}\)O\(_2\)N\(_4\) [M+H]\(^+\) 417.2285, found 417.2298.

\(\text{(E)-Butyl 3-(1,1-bis((E)-(tert-butylimino)(cyano)methyl)isochroman-5-yl)acrylate (2i):}\)

Following the general procedure as for 2a, the reaction mixture of 1i (78.1 mg, 0.3 mmol), \(\text{tBuNC (170 μL, 1.5 mmol), AgOTf (7.7 mg, 0.03 mmol), and DDQ (139.0 mg, 0.6 mmol)}\) in dry PhCl (3.0 mL) was stirred at 80 °C under N\(_2\) for 12 h to afford product 2i (62.0 mg, 43%) as white solid. M.p. 88-90 °C; IR (KBr, cm\(^{-1}\)): 2970, 1723, 1640, 1483, 1461, 1367, 1311, 1232, 1173, 1096, 1027, 977, 791; \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 7.90 (d, \(J = 16.0\) Hz, 1H), 7.55 (d, \(J = 7.5\) Hz, 1H), 7.21 (t, \(J = 7.7\) Hz, 1H), 6.92 (d, \(J = 7.5\) Hz, 1H), 6.38 (d, \(J = 15.5\) Hz, 1H), 4.21 (t, \(J = 6.5\) Hz, 2H), 4.06 (t, \(J = 5.7\) Hz, 2H), 3.04 (t, \(J = 5.5\) Hz, 2H), 1.71-1.66 (m, 2H), 1.45-1.42 (m, 2H), 1.39 (s, 18H), 0.96 (t, \(J = 7.2\), 3H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): 166.7, 140.6, 139.5, 134.1, 133.6, 128.4, 126.7, 125.4, 120.8, 110.9, 85.1, 64.5, 61.3, 59.1, 30.7, 28.9, 25.5, 19.2, 13.7; LC-MS (ESI) m/z 477 [M+H]\(^+\); HRMS (ESI) m/z calcd for C\(_{28}\)H\(_{37}\)O\(_3\)N\(_4\) [M+H]\(^+\) 477.2860, found 477.2854.

\(\text{(1E,1E)-N,N'-Di-tert-butyl-3,4-dihydro-1H-benzo[g]isochromene-1,1-bis(carbimidoyl) cyanide (2j):}\)

Following the general procedure as for 2a, the reaction mixture of 1j (55.2 mg, 0.3 mmol), \(\text{tBuNC (170 μL, 1.5 mmol), AgOTf (7.8 mg, 0.03 mmol), and DDQ (139.0 mg, 0.6 mmol)}\) in dry PhCl (3.0 mL) was stirred at 80 °C under N\(_2\) for 4.5 h to afford product 2j (60.8 mg, 51%) as white solid. M.p. 175-177 °C; IR (KBr, cm\(^{-1}\)): 2978, 2215, 1645, 1467, 1364, 1206, 1096, 1061, 914, 814, 751; \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 7.79 (d, \(J = 8.0\) Hz, 1H), 7.76 (d, \(J = 8.0\) Hz, 1H), 7.67 (d, \(J = 9.0\) Hz, 1H), 7.36 (t, \(J = 7.2\) Hz, 1H), 7.31-7.26 (m, 2H), 4.09 (t, \(J = 5.7\) Hz, 2H), 3.17 (t, \(J = 5.5\) Hz, 2H), 1.36 (s, 18H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): 166.7, 140.6, 139.5, 134.1, 133.6, 128.4, 126.7, 125.4, 120.8, 110.9, 85.1, 64.5, 61.3, 59.1, 30.7, 28.9, 25.5, 19.2, 13.7; LC-MS (ESI) m/z 401 [M+H]\(^+\); HRMS (ESI) m/z calcd for C\(_{25}\)H\(_{29}\)ON\(_4\) [M+H]\(^+\) 401.2336, found 401.2335.
(1E,1E)-N,N'-Di-tert-butyl-1,2-dihydro-4H-benzo[f]isochromene-4,4-bis(carbimidoyl) cyanide (2k):
Following the general procedure as for 2a, the reaction mixture of 1k (55.2 mg, 0.3 mmol), tBuNC (170 μL, 1.5 mmol), AgOTf (7.7 mg, 0.03 mmol), and DDQ (139.0 mg, 0.6 mmol) in dry PhCl (3.0 mL) was stirred at 80 °C under N₂ for 4.5 h to afford product 2k (69.5 mg, 58%) as white solid. M.p. 140–142 °C; IR (KBr, cm⁻¹): 2978, 2220, 1643, 1464, 1367, 1209, 1099, 1062; ¹H NMR (CDCl₃, 500 MHz): δ 7.99 (d, J = 8.0 Hz, 1H), 7.85–7.83 (m, 1H), 7.64 (d, J = 9.0 Hz, 1H), 7.59–7.53 (m, 2H), 7.00 (d, J = 9.0 Hz, 1H), 4.20 (t, J = 5.5 Hz, 2H), 3.33 (t, J = 5.5 Hz, 2H), 1.40 (s, 18H); ¹³C NMR (CDCl₃, 125 MHz): 139.7, 132.8, 131.6, 128.5, 126.6, 126.4, 126.3, 125.3 (2), 123.1, 111.0, 85.3, 61.4, 59.2, 29.0, 24.7; LC-MS (ESI) m/z 401 [M+H]⁺; HRMS (ESI) m/z calcd for C₂₂H₂₉O₄N₄ [M+H]⁺ 401.2336, found 401.2335.

(1E,1E)-N,N'-Di-tert-butyl-4,5-dihydro-7H-thieno[2,3-c]pyran-7,7-bis(carbimidoyl) cyanide (2l):
Following the general procedure as for 2a, the reaction mixture of 1l (42.0 mg, 0.3 mmol), tBuNC (170 μL, 1.5 mmol), AgOTf (7.7 mg, 0.03 mmol), and DDQ (139.0 mg, 0.6 mmol) in dry PhCl (3.0 mL) was stirred at 80 °C under N₂ for 10 h to afford product 2l (44.5 mg, 42%) as white solid. M.p. 110–112 °C; IR (KBr, cm⁻¹): 3101, 2976, 2215, 1642, 1468, 1367, 1236, 1208, 1064, 1020, 956, 891, 738; ¹H NMR (CDCl₃, 500 MHz): δ 7.39 (d, J = 5.0 Hz, 1H), 6.89 (d, J = 5.0 Hz, 1H), 4.07 (t, J = 5.5 Hz, 2H), 2.88 (t, J = 5.2 Hz, 2H), 1.40 (s, 18H); ¹³C NMR (CDCl₃, 125 MHz): 139.7, 132.8, 131.6, 128.5, 126.6, 126.4, 126.3, 125.3 (2), 123.1, 111.0, 85.3, 61.4, 59.2, 29.0, 24.7; LC-MS (ESI) m/z 357 [M+H]⁺; HRMS (ESI) m/z calcd for C₁₉H₂₅O₃N₄S [M+H]⁺ 357.1744, found 357.1739.

(1E,1E)-N,N'-Di-tert-butyl-6,7-dihydro-4H-thieno[3,2-c]pyran-4,4-bis(carbimidoyl) cyanide (2m):
Following the general procedure as for 2a, the reaction mixture of 1m (42.0 mg, 0.3 mmol), tBuNC (170 μL, 1.5 mmol), AgOTf (7.7 mg, 0.03 mmol), and DDQ (139.0 mg, 0.6 mmol) in dry PhCl (3.0 mL) was stirred at 80 °C under N₂ for 7.5 h to afford product 2m (41.2 mg, 39%) as white solid. M.p. 103–105 °C; IR (KBr, cm⁻¹): 3116, 2972, 2212, 1642, 1466, 1366, 1236, 1209, 1087, 1017, 948, 867, 724; ¹H NMR (CDCl₃, 500 MHz): δ 7.09 (d, J = 5.0 Hz, 1H), 6.65 (d, J =
5.0 Hz, 1H), 4.07 (t, J = 5.5 Hz, 2H), 3.01 (t, J = 5.2 Hz, 2H), 1.39 (s, 18H); $^{13}$C NMR (CDCl$_3$, 125 MHz): 139.1, 137.0, 127.7, 126.7, 122.2, 110.8, 84.6, 62.1, 59.1, 29.0, 24.9; LC-MS (ESI) m/z 357 [M+H]$^+$; HRMS (ESI) m/z calcd for C$_{19}$H$_{25}$ON$_4$S [M+H]$^+$ 357.1744, found 357.1741.

(1'E,1'E)-$N'$,$N''$-Di-tert-butylspiro[cyclobutane-1,3'-isochroman]-1',1'-bis(carbimidoyl) cyanide (2n):

Following the general procedure as for 2a, the reaction mixture of 1n (52.3 mg, 0.3 mmol), tBuNC (170 μL, 1.5 mmol), AgOTf (7.7 mg, 0.03 mmol), and DDQ (139.0 mg, 0.6 mmol) in dry PhCl (3.0 mL) was stirred at 80 °C under N$_2$ for 5.5 h to afford product 2n (62.0 mg, 53%) as white solid. M.p. 82-83 °C; IR (KBr, cm$^{-1}$): 2976, 2217, 1645, 1462, 1364, 1211, 1108, 1072, 754; $^1$H NMR (CDCl$_3$, 500 MHz): δ 7.30-7.27 (m, 1H), 7.21-7.16 (m, 2H), 6.90 (d, J = 8.0 Hz, 1H), 3.06 (s, 2H), 2.32-2.25 (m, 2H), 1.92-1.84 (m, 3H), 1.66-1.60 (m, 1H), 1.37 (s, 18H); $^{13}$C NMR (CDCl$_3$, 125 MHz): 140.2, 133.9, 130.2, 129.4, 128.4, 127.4, 111.3, 1072.754; LC-MS (ESI) m/z 391 [M+H]$^+$; HRMS (ESI) m/z calcd for C$_{24}$H$_{31}$ON$_4$[M+H]$^+$ 391.2492, found 391.2491.

(1'E,1'E)-$N'$,$N''$-Di-tert-butylspiro[cyclopentane-1,3'-isochroman]-1',1'-bis(carbimidoyl) cyanide (2o):

Following the general procedure as for 2a, the reaction mixture of 1o (56.4 mg, 0.3 mmol), tBuNC (170 μL, 1.5 mmol), AgOTf (7.7 mg, 0.03 mmol), and DDQ (139.0 mg, 0.6 mmol) in dry PhCl (3.0 mL) was stirred at 80 °C under N$_2$ for 4.5 h to afford product 2o (62.0 mg, 53%) as white solid. M.p. 75-77 °C; IR (KBr, cm$^{-1}$): 2970, 2224, 1649, 1462, 1363, 1211, 1106, 921, 758; $^1$H NMR (CDCl$_3$, 500 MHz): δ 7.28-7.26 (m, 1H), 7.19-7.16 (m, 2H), 6.99 (d, J = 8.0 Hz, 1H), 2.99 (s, 2H), 1.94-1.92 (m, 4H), 1.66-1.64 (m, 2H), 1.54-1.50 (m, 2H), 1.37 (s, 18H); $^{13}$C NMR (CDCl$_3$, 125 MHz): 140.6, 135.2, 130.5, 128.9, 128.3, 127.2, 125.2, 111.3, 85.5, 84.2, 58.6, 38.0 (2), 28.8, 23.2; LC-MS (ESI) m/z 405 [M+H]$^+$; HRMS (ESI) m/z calcd for C$_{25}$H$_{33}$ON$_4$[M+H]$^+$ 405.2649, found 405.2649.

(1'E,1'E)-$N'$,$N''$-Di-tert-butylspiro[cyclohexane-1,3'-isochroman]-1',1'-bis(carbimidoyl) cyanide (2p):
Following the general procedure as for 2a, the reaction mixture of 1p (60.7 mg, 0.3 mmol), \(^{1}{\text{BuNC}}\) (170 μL, 1.5 mmol), AgOTf (7.7 mg, 0.03 mmol), and DDQ (139.0 mg, 0.6 mmol) in dry PhCl (3.0 mL) was stirred at 80 °C under \(N_2\) for 5.5 h to afford product 2p (72.5 mg, 57%) as white solid. M.p. 119-120 °C; IR (KBr, cm\(^{-1}\)): 2936, 2212, 1644, 1455, 1366, 1236, 1209, 1070, 752; \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 7.27 (t, \(J = 7.7\) Hz, 1H), 7.19-7.14 (m, 2H), 6.97 (d, \(J = 8.0\) Hz, 1H), 2.90 (s, 2H), 1.77-1.71 (m, 4H), 1.52-1.42 (m, 6H), 1.37 (s, 18H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): 140.5, 134.0, 130.2, 129.1, 128.4, 127.3, 125.2, 111.7, 83.7, 75.8, 58.6, 38.6, 28.8, 25.7, 22.4; LC-MS (ESI) m/z 419 [M+H]\(^+\); HRMS (ESI) m/z calcd for C\(_{26}\)H\(_{35}\)ON\(_4\) [M+H]\(^+\) 419.2805, found 419.2799.

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\text{(1E,1E)-N,N'-Di-tert-butyl-3,3-dimethylisochroman-1,1-bis(carbimidoyl) cyanide (2q):}
\]
Following the general procedure as for 2a, the reaction mixture of 1q (48.6 mg, 0.3 mmol), \(^{1}{\text{BuNC}}\) (170 μL, 1.5 mmol), AgOTf (7.7 mg, 0.03 mmol), and DDQ (139.0 mg, 0.6 mmol) in dry PhCl (3.0 mL) was stirred at 80 °C under \(N_2\) for 5 h to afford product 2q (60.1 mg, 53%) as white solid. M.p. 101-103 °C; IR (KBr, cm\(^{-1}\)): 2979, 2212, 1646, 1465, 1371, 1208, 1076, 921, 758; \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 7.27-7.23 (m, 1H), 7.16 (t, \(J = 7.5\) Hz, 1H), 7.12 (d, \(J = 7.5\) Hz, 1H), 6.97 (d, \(J = 7.5\) Hz, 1H), 2.86 (s, 2H), 1.34 (s, 18H), 1.31 (s, 6H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): 140.6, 134.2, 130.3, 129.1, 128.5, 125.2, 111.4, 83.8, 74.3, 58.5, 40.1, 28.8, 28.3; LC-MS (ESI) m/z 379 [M+H]\(^+\); HRMS (ESI) m/z calcd for C\(_{23}\)H\(_{31}\)ON\(_4\) [M+H]\(^+\) 379.2492, found 379.2491.

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\text{(1E,1E)-N,N'-Di-tert-butyl-3-phenylisochroman-1,1-bis(carbimidoyl) cyanide (2r):}
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Following the general procedure as for 2a, the reaction mixture of 1r (63.0 mg, 0.3 mmol), \(^{1}{\text{BuNC}}\) (170 μL, 1.5 mmol), AgOTf (7.7 mg, 0.03 mmol), and DDQ (139.0 mg, 0.6 mmol) in dry PhCl (3.0 mL) was stirred at 80 °C under \(N_2\) for 5.5 h to afford product 2r (79.9 mg, 62%) as white solid. M.p. 145-146 °C; IR (KBr, cm\(^{-1}\)): 2975, 2216, 1646, 1457, 1367, 1233, 1210, 1069, 916, 748, 692; \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 7.55 (d, \(J = 7.5\) Hz, 2H), 7.42 (t, \(J = 7.5\) Hz, 2H), 7.36-7.33 (m, 1H), 7.33-7.30 (m, 1H), 7.23 (t, \(J = 6.7\) Hz, 2H), 6.99 (d, \(J = 7.5\) Hz, 1H), 4.78 (dd, \(J = 11.5, 2.5\) Hz, 1H), 3.34-3.28 (m, 1H), 3.03 (dd, \(J = 16.5, 2.5\) Hz, 1H), 1.44 (s, 9H), 1.37 (s, 9H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): 140.1, 139.7, 139.5, 135.1, 129.8, 129.1, 128.6, 128.5, 128.3, 128.2, 127.5, 126.3, 125.9, 125.7, 111.6, 110.6, 86.2, 73.5, 59.3, 58.8, 35.6, 29.0 (2); LC-MS (ESI) m/z 427 [M+H]\(^+\); HRMS (ESI) m/z calcd for C\(_{27}\)H\(_{31}\)ON\(_4\) [M+H]\(^+\) 427.2492, found 427.2493.
(1E,1E)-N,N'-Di-tert-butyl-4-methylisochroman-1,1-bis(carbimidoyl) cyanide (2s):
Following the general procedure as for 2a, the reaction mixture of 1s (44.4 mg, 0.3 mmol), t-BuNC (170 μL, 1.5 mmol), AgOTf (7.7 mg, 0.03 mmol), and DDQ (139.0 mg, 0.6 mmol) in dry PhCl (3.0 mL) was stirred at 80 °C under N₂ for 5 h to afford product 2s (59.7 mg, 55%) as white solid. M.p. 126-127 °C; IR (KBr, cm⁻¹): 2974, 2212, 1644, 1474, 1368, 1234, 1211, 1113, 981, 959, 755; ¹H NMR (CDCl₃, 500 MHz): δ 7.32-7.29 (m, 1H), 7.26 (d, J = 5.0 Hz, 1H), 7.18-7.15 (m, 1H), 6.88 (d, J = 7.5 Hz, 1H), 3.96 (dd, J = 11.0, 3.5 Hz, 1H), 3.87 (dd, J = 11.5, 4.0 Hz, 1H), 2.98-2.92 (m, 1H), 1.45 (d, J = 7.0 Hz, 3H), 1.36 (s, 9H), 1.33 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz): 140.1, 139.6, 139.5, 129.7, 128.5, 128.3, 127.0, 125.2, 111.4, 110.9, 85.4, 67.4, 59.1, 58.8, 32.0, 28.9, 20.1; LC-MS (ESI) m/z 365 [M+H]+; HRMS (ESI) m/z calcd for C₂₂H₂₉ON₄ [M+H]+ 365.2336, found 365.2332.

(6E,6E)-N,N'-Di-tert-butyl-6H-benzo[c]chromene-6,6-bis(carbimidoyl) cyanide (2t):
Following the general procedure as for 2a, the reaction mixture of 1t (54.7 mg, 0.3 mmol), t-BuNC (170 μL, 1.5 mmol), AgOTf (7.7 mg, 0.03 mmol), and DDQ (139.0 mg, 0.6 mmol) in dry PhCl (3.0 mL) was stirred at 80 °C under N₂ for 5.5 h to afford product 2t (87.1 mg, 73%) as white solid. M.p. 158-159 °C; IR (KBr, cm⁻¹): 2978, 2216, 1645, 1471, 1446, 1364, 1236, 1204, 1059, 1035, 752; ¹H NMR (CDCl₃, 500 MHz): δ 7.81 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.50 (t, J = 7.7 Hz, 1H), 7.36 (t, J = 7.5 Hz, 1H), 7.30-7.27 (m, 1H), 7.21 (d, J = 8.0 Hz, 1H), 7.10 (t, J = 7.5 Hz, 1H), 7.02 (d, J = 8.0 Hz, 1H), 1.33 (s, 18H); ¹³C NMR (CDCl₃, 125 MHz): 150.3, 137.2, 130.0, 129.1, 128.9, 128.2, 127.0, 126.8, 123.3, 122.9, 122.7, 121.8, 118.7, 110.7, 86.6, 59.3, 28.9, 20.1; LC-MS (ESI) m/z 399 [M+H]+; HRMS (ESI) m/z calcd for C₂₅H₂₇ON₄ [M+H]+ 399.2179, found 399.2178.

(1E,1E)-N,N'-Di-tert-butyl-1H,3H-benzo[de]isochromene-1,1-bis(carbimidoyl) cyanide (2u):
Following the general procedure as for 2a, the reaction mixture of 1u (51.1 mg, 0.3 mmol), t-BuNC (170 μL, 1.5 mmol), AgOTf (7.7 mg, 0.03 mmol), and DDQ (139.0 mg, 0.6 mmol) in dry
PhCl (3.0 mL) was stirred at 80 °C under N₂ for 12 h to afford product 2u (53.7 mg, 46%) as white solid. M.p. 146-148 °C; IR (KBr, cm⁻¹): 2975, 2216, 1641, 1464, 1365, 1207, 1068, 1037, 821, 766; ¹H NMR (CDCl₃, 500 MHz): δ 7.89 (d, J = 8.0 Hz, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.53-7.47 (m, 2H), 7.26-7.25 (m, 1H), 7.12 (d, J = 7.0 Hz, 1H), 5.20 (s, 2H), 1.42 (s, 18H); ¹³C NMR (CDCl₃, 125 MHz): 139.2, 132.9, 129.6, 128.8, 127.2, 126.1, 125.7, 125.6, 125.4, 125.1, 120.8, 111.0, 85.7, 64.7, 59.3, 29.0; LC-MS (ESI) m/z 387 [M+H]+; HRMS (ESI) m/z calcd for C₂₄H₂₇NO₄ [M+H]+ 387.2179, found 387.2176.

(E)-N-(tert-Butyl)-1-phenylisochroman-1-carbimidoyl cyanide (4a):

To a sealed tube, 3a (63.1 mg, 0.3 mmol), tBuNC (170 μL, 1.5 mmol), AgOTf (7.7 mg, 0.03 mmol), and DDQ (139.0 mg, 0.6 mmol) in dry PhCl (3.0 mL) were added in the glove box. The mixture was stirred at 100 °C for 19 h under N₂. The reaction mixture was cooled down to room temperature and purified by column chromatography on silica gel to give product 4a (64.5 mg, 68%) as white solid. M.p. 121-123 °C; IR (KBr, cm⁻¹): 2973, 2208, 1643, 1482, 1449, 1361, 1213, 1092, 1048, 919, 758, 695; ¹H NMR (CDCl₃, 500 MHz): δ 7.31-7.27 (m, 4H), 7.23-7.18 (m, 4H), 7.05 (d, J = 8.0 Hz, 1H), 4.04-4.00 (m, 1H), 3.90-3.85 (m, 1H), 3.18-3.12 (m, 1H), 2.88-2.84 (m, 1H), 1.40 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz): 143.1, 141.7, 134.7, 132.8, 129.3, 129.2, 128.9, 127.9, 127.7, 127.6, 125.5, 111.9, 84.9, 60.6, 58.5, 29.0, 28.3; LC-MS (ESI) m/z 319 [M+H]+; HRMS (ESI) m/z calcd for C₂₁H₂₃NO₂ [M+H]+ 319.1805, found 319.1802.

(E)-N-(tert-Butyl)-5-methyl-1-phenylisochroman-1-carbimidoyl cyanide (4b):

Following the general procedure as for 4a, the reaction mixture of 3b (67.3 mg, 0.3 mmol), tBuNC (170 μL, 1.5 mmol), AgOTf (7.7 mg, 0.03 mmol), and DDQ (139.0 mg, 0.6 mmol) in dry PhCl (3.0 mL) was stirred at 100 °C for 24 h to afford product 4b (67.1 mg, 67%) as white solid. M.p. 127-128 °C; IR (KBr, cm⁻¹): 2977, 2216, 1636, 1482, 1461, 1365, 1233, 1208, 1093, 1053, 920, 784, 697; ¹H NMR (CDCl₃, 500 MHz): δ 7.31-7.28 (m, 3H), 7.23-7.21 (m, 2H), 7.16 (d, J = 7.0 Hz, 1H), 7.10 (t, J = 7.5 Hz, 1H), 6.90 (d, J = 8.0 Hz, 1H), 4.06-4.02 (m, 1H), 3.84-3.79 (m, 1H), 2.98-2.96 (m, 1H), 2.70-2.65 (m, 1H), 2.30 (s, 3H), 1.39 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz): 143.3, 141.7, 136.8, 133.4, 132.3, 129.3, 129.1, 127.9, 127.5, 126.8, 125.0, 112.0, 85.2, 60.2, 58.5, 29.0, 25.9, 19.2; LC-MS (ESI) m/z 333 [M+H]+; HRMS (ESI) m/z calcd for C₂₂H₂₅NO₂ [M+H]+ 333.1961, found 333.1961.
(E)-N-(tert-Butyl)-7-methyl-1-phenylisochroman-1-carbimidoyl cyanide (4c):
Following the general procedure as for 4a, the reaction mixture of 3c (68.7 mg, 0.3 mmol), tBuNC (170 μL, 1.5 mmol), AgOTf (7.7 mg, 0.03 mmol), and DDQ (139.0 mg, 0.6 mmol) in dry PhCl (3.0 mL) was stirred at 100 °C for 24 h to afford product 4c (72.8 mg, 73%) as white solid. M.p. 153-154 °C; IR (KBr, cm⁻¹): 2983, 2203, 1636, 1497, 1452, 1365, 1209, 1083, 1048, 921, 756, 695; ¹H NMR (CDCl₃, 500 MHz): δ 7.30-7.28 (m, 3H), 7.19-7.17 (m, 2H), 7.11-7.06 (m, 2H), 6.82 (s, 1H), 3.99-3.95 (m, 1H), 3.81-3.76 (m, 1H), 3.10-3.08 (m, 1H), 2.74 (dt, J = 16.0, 3.7 Hz, 1H), 2.27 (s, 3H), 1.38 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz): 143.2, 141.7, 135.0, 132.4, 131.8, 129.4, 129.2 (2), 128.7, 127.9, 127.6, 112.0, 84.9, 60.6, 58.5, 29.0, 27.9, 21.2; LC-MS (ESI) m/z 333 [M+H]+; HRMS (ESI) m/z calcd for C₂₂H₂₅ON₂ [M+H]+ 333.1961, found 333.1967.

(1H)-N-(tert-Butyl)-1-(o-tolyl)isochroman-1-carbimidoyl cyanide (4d):
Following the general procedure as for 4a, the reaction mixture of 3d (67.3 mg, 0.3 mmol), tBuNC (170 μL, 1.5 mmol), AgOTf (7.7 mg, 0.03 mmol), and DDQ (139.0 mg, 0.6 mmol) in dry PhCl (3.0 mL) was stirred at 100 °C for 24 h to afford product 4d (70.7 mg, 71%) as white solid. M.p. 112-113 °C; IR (KBr, cm⁻¹): 2973, 2930, 2212, 1636, 1477, 1457, 1366, 1210, 1093, 1046, 919, 752; ¹H NMR (CDCl₃, 500 MHz): δ 7.28 (t, J = 7.5 Hz, 1H), 7.23-7.17 (m, 4H), 7.03-6.99 (m, 2H), 6.77 (d, J = 7.5 Hz, 1H), 4.03-3.99 (m, 1H), 3.76-3.71 (m, 1H), 3.21-3.17 (m, 1H), 2.77-2.74 (m, 1H), 2.32 (s, 3H), 1.39 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz): 143.2, 139.5, 138.1, 135.3, 132.8, 132.2, 130.6, 129.5 (2), 128.1, 127.7, 125.4, 124.3, 111.9, 86.1, 60.2, 58.4, 28.9, 28.1, 22.2; LC-MS (ESI) m/z 333 [M+H]+; HRMS (ESI) m/z calcd for C₂₂H₂₅ON₂ [M+H]+ 333.1961, found 333.1968.

(1H)-N-(tert-Butyl)-1-(m-tolyl)isochroman-1-carbimidoyl cyanide (4e):
Following the general procedure as for 4a, the reaction mixture of 3e (67.3 mg, 0.3 mmol), tBuNC (170 μL, 1.5 mmol), AgOTf (7.7 mg, 0.03 mmol), and DDQ (139.0 mg, 0.6 mmol) in dry PhCl (3.0 mL) was stirred at 100 °C for 21 h to afford product 4e (74.7 mg, 75%) as white solid. M.p. 123-125 °C; IR (KBr, cm⁻¹): 2971, 2208, 1646, 1480, 1358, 1208, 1091, 1048, 922, 755, 699; ¹H NMR (CDCl₃, 500 MHz): δ 7.26-7.24 (m, 1H), 7.20-7.14 (m, 3H), 7.10 (d, J = 7.5 Hz, 1H), 7.05-7.01 (m, 2H), 7.00 (d, J = 8.0 Hz, 1H), 4.00-3.96 (m, 1H), 3.94-3.90 (m, 1H), 3.11-3.06 (m, 1H), 2.92-2.86 (m, 1H), 2.31 (s, 3H), 1.40 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz): 143.2, 141.6, 137.3, 134.5, 133.1, 129.5, 129.4, 129.2, 128.7, 127.6, 127.5, 125.9, 125.4, 111.9, 84.8, 60.7, 58.5, 29.1, 28.4, 21.6; LC-MS (ESI) m/z 333 [M+H]+; HRMS (ESI) m/z calcd for C₂₂H₂₅ON₂ [M+H]+ 333.1961, found 333.1957.
(E)-N-(tert-Butyl)-5-methyl-1-(p-tolyl)isochroman-1-carbimidoyl cyanide (4f):
Following the general procedure as for 4a, the reaction mixture of 3f (71.5 mg, 0.3 mmol), tBuNC (170 μL, 1.5 mmol), AgOTf (7.7 mg, 0.03 mmol), and DDQ (139.0 mg, 0.6 mmol) in dry PhCl (3.0 mL) was stirred at 100 °C for 22 h to afford product 4f (81.1 mg, 78%) as white solid. M.p. 122-123 °C; IR (KBr, cm⁻¹): 2974, 2964, 2870, 2220, 1642, 1508, 1456, 1365, 1234, 1096, 1056, 918, 811, 773; ¹H NMR (CDCl₃, 500 MHz): δ 7.14 (d, J = 7.5 Hz, 1H), 7.09-7.06 (m, 5H), 6.87 (d, J = 8.0 Hz, 1H), 4.03-3.99 (m, 1H), 3.83-3.78 (m, 1H), 2.98-2.93 (m, 1H), 2.69-2.64 (m, 1H), 2.33 (s, 3H), 2.28 (s, 3H), 1.38 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz): 143.4, 138.8, 137.5, 136.6, 133.4, 132.6, 129.2, 129.0, 128.2, 126.8, 124.9, 112.0, 85.0, 60.1, 58.4, 29.0, 25.9, 21.1, 19.2; LC-MS (ESI) m/z 347 [M+H]+; HRMS (ESI) m/z calcd for C₂₃H₂₇ON₂ [M+H]+ 347.2118, found 347.2128.

(E)-N-(tert-Butyl)-1-(naphthalen-1-yl)isochroman-1-carbimidoyl cyanide (4g):
Following the general procedure as for 4a, the reaction mixture of 3g (78.1 mg, 0.3 mmol), tBuNC (170 μL, 1.5 mmol), AgOTf (7.7 mg, 0.03 mmol), and DDQ (139.0 mg, 0.6 mmol) in dry PhCl (3.0 mL) was stirred at 100 °C for 23 h to afford product 4g (76.5 mg, 69%) as white solid. M.p. 141-143 °C; IR (KBr, cm⁻¹): 2977, 2216, 1640, 1598, 1453, 1362, 1229, 1202, 1090, 1050, 910, 785, 745, 632; ¹H NMR (CDCl₃, 500 MHz): δ 8.17-8.15 (m, 1H), 7.84-7.82 (m, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.45-7.43 (m, 2H), 7.34-7.32 (m, 1H), 7.28 (d, J = 7.5 Hz, 1H), 7.24-7.21 (m, 2H), 7.11 (d, J = 7.5 Hz, 1H), 6.91 (d, J = 7.0 Hz, 1H), 4.08-4.04 (m, 1H), 3.73-3.68 (m, 1H), 3.34-3.28 (m, 1H), 2.72 (d, J = 16.0 Hz, 1H), 1.22 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz): 143.0, 137.7, 135.6, 134.6, 132.6, 131.0, 129.9, 129.8, 129.6, 128.5 (2), 128.0, 125.6, 125.1, 125.0, 123.6, 111.9, 86.3, 60.2, 58.3, 28.7, 28.1; LC-MS (ESI) m/z 369 [M+H]+; HRMS (ESI) m/z calcd for C₂₅H₂₅ON₂ [M+H]+ 369.1961, found 369.1957.

(E)-1-(3-Bromothiophen-2-yl)-N-(tert-butyl)-5-methylisochroman-1-carbimidoyl cyanide (4h):
Following the general procedure as for 4a, the reaction mixture of 3h (92.4 mg, 0.3 mmol),
BuNC (170 μL, 1.5 mmol), AgOTf (7.7 mg, 0.03 mmol), and DDQ (139.0 mg, 0.6 mmol) in dry PhCl (3.0 mL) was stirred at 100 °C for 24 h to afford product 4h (72.3 mg, 58%) as white solid. M.p. 153-155 °C; IR (KBr, cm⁻¹): 3088, 2972, 2927, 1942, 1734, 1645, 1462, 1356, 1225, 1086, 1050, 868, 772, 740; ¹H NMR (CDCl₃, 500 MHz): δ 7.21-7.19 (m, 1H), 7.14-7.11 (m, 3H), 7.03 (d, J = 5.0 Hz, 1H), 4.20-4.16 (m, 1H), 3.85-3.79 (m, 1H), 3.08-3.01 (m, 1H), 2.63-2.59 (m, 1H), 2.28 (s, 3H), 1.41 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz): 140.3, 139.8, 137.0, 133.6, 132.4, 132.3, 130.1, 125.5, 125.4, 125.1, 111.5, 110.2, 58.5, 28.9, 25.5, 19.2; LC-MS (ESI) m/z (%): 419 (78) [M⁺(81Br)+H⁺], 417 (100) [M⁺(79Br)+H⁺]; HRMS (ESI) m/z calcd for C₂₀H₂₂ON₂BrS [M⁺H⁺]+ 417.0631, found 417.0630.

(E)-N(tert-Butyl)-4-methyl-1-phenylisochroman-1-carbimidoyl cyanide (4i):
Following the general procedure as for 4a, the reaction mixture of 3i (44.5 mg, 0.3 mmol), BuNC (170 μL, 1.5 mmol), AgOTf (7.7 mg, 0.03 mmol), and DDQ (139.0 mg, 0.6 mmol) in dry PhCl (3.0 mL) was stirred at 100 °C for 24 h to afford product 4i (79.4 mg, 79%) as white solid. M.p. 113-114 °C; IR (KBr, cm⁻¹): 2972, 2207, 1640, 1483, 1450, 1365, 1230, 1211, 1109, 1045, 749, 699; ¹H NMR (CDCl₃, 500 MHz): δ 7.33-7.11 (m, 8H), 7.03 (d, J = 7.8 Hz, 0.23H), 6.97 (d, J = 7.8 Hz, 0.76H), 3.96 (dd, J = 11.5, 4.7 Hz, 0.78H), 3.80 (dd, J = 11.8, 3.8 Hz, 0.24H), 3.69 (dd, J = 11.5, 2.4 Hz, 0.23H), 3.64 (dd, J = 11.5, 6.5 Hz, 0.77H), 3.15-3.08 (m, 0.78H), 2.85-2.84 (m, 0.23H), 1.51 (d, J = 7.0 Hz, 0.79H), 1.39 (s, 6.96H), 1.37 (s, 2.13H), 1.34 (d, J = 7.0 Hz, 2.45H); ¹³C NMR (CDCl₃, 125 MHz): 140.6, 139.6, 132.6, 131.5, 129.5, 129.4, 129.2, 128.5, 128.1, 128.0, 127.9, 127.7 (2), 127.4, 125.5, 125.2, 111.9, 85.5, 85.2, 66.7, 65.9, 58.6, 58.5, 32.4, 31.7, 29.0 (2), 21.8, 18.6; LC-MS (ESI) m/z 333 [M⁺H⁺]+; HRMS (ESI) m/z calcd for C₂₂H₂₅ON₂Br [M⁺H⁺]+ 333.1961, found 333.1960.

(E)-N(tert-Butyl)-6-phenyl-6H-benzo[c]chromene-6-carbimidoyl cyanide (4j):
Following the general procedure as for 4a, the reaction mixture of 3j (77.5 mg, 0.3 mmol), BuNC (170 μL, 1.5 mmol), AgOTf (7.7 mg, 0.03 mmol), and DDQ (139.0 mg, 0.6 mmol) in dry PhCl (3.0 mL) was stirred at 100 °C for 23 h to afford product 4j (107.8 mg, 98%) as white solid. M.p. 142-144 °C; IR (KBr, cm⁻¹): 2969, 2207, 1640, 1483, 1450, 1365, 1230, 1211, 1109, 1045, 749-7.20 (m, 3H), 7.08 (t, J = 7.2 Hz, 1H), 6.84 (d, J = 7.5 Hz, 1H), 1.21 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz): 151.3, 140.7, 138.1, 133.1, 130.0, 129.6, 129.0, 128.6, 128.3, 128.0, 127.8, 127.3, 123.1, 122.9, 122.3, 119.0, 111.5, 86.8, 58.7, 28.8; LC-MS (ESI) m/z 367 [M⁺H⁺]; HRMS (ESI) m/z calcd for C₂₅H₂₃ON₂ [M⁺H⁺]+ 367.1805, found 367.1804.
(E)-N-(tert-Butyl)-1-phenyl-1H,3H-benzo[de]isochromene-1-carbimidoyl cyanide (4k):
Following the general procedure as for 4a, the reaction mixture of 3k (73.9 mg, 0.3 mmol), tBuNC (170 μL, 1.5 mmol), AgOTf (7.7 mg, 0.03 mmol), and DDQ (139.0 mg, 0.6 mmol) in dry PhCl (3.0 mL) was stirred at 100 °C for 23 h to afford product 4k (78.4 mg, 74%) as white solid. M.p. 153-155 °C; IR (KBr, cm⁻¹): 2964, 2856, 2212, 1631, 1446, 1364, 1230, 1205, 1059, 822, 768, 690; ¹H NMR (CDCl₃, 500 MHz): δ 7.89 (d, J = 8.5 Hz, 1H), 7.81 (d, J = 8.5 Hz, 1H), 7.51 (t, J = 7.7 Hz, 1H), 7.46 (t, J = 7.7 Hz, 1H), 7.30-7.29 (m, 3H), 7.19 (t, J = 6.5 Hz, 2H), 7.16-7.15 (m, 2H), 5.11 (t, J = 15.0 Hz, 1H), 4.90 (d, J = 14.5 Hz, 1H), 1.41 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz): 142.5, 139.8, 133.1, 131.2, 130.4, 129.1, 128.2 (2), 127.9, 126.8, 126.7, 125.7, 125.1, 124.6, 120.6, 111.9, 85.8, 63.8, 58.7, 29.1; LC-MS (ESI) m/z 355 [M+H]⁺; HRMS (ESI) m/z calcd for C₂₄H₂₃ON₂ [M+H]⁺ 355.1805, found 355.1801.

(E)-N-(tert-Butyl)-1-methylisochroman-1-carbimidoyl cyanide (4l):
Following the general procedure as for 4a, the reaction mixture of 3l (44.5 mg, 0.3 mmol), tBuNC (170 μL, 1.5 mmol), AgOTf (7.7 mg, 0.03 mmol), and DDQ (139.0 mg, 0.6 mmol) in dry PhCl (3.0 mL) was stirred at 100 °C for 24 h to afford product 4l (46.5 mg, 60%) as pale yellow oil. IR (KBr, cm⁻¹): 2975, 2212, 1645, 1460, 1368, 1232, 1109, 1031, 756; ¹H NMR (CDCl₃, 500 MHz): δ 7.23-7.14 (m, 3H), 6.99-6.97 (m, 1H), 4.17-4.13 (m, 1H), 4.03-3.98 (m, 1H), 3.15-3.09 (m, 1H), 2.75 (dt, J = 16.0, 3.5 Hz, 1H), 1.68 (s, 3H), 1.40 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz): 143.0, 135.6, 134.3, 129.1, 127.3, 126.5, 126.4, 111.7, 80.6, 60.8, 58.0, 29.1, 28.8, 25.3; LC-MS (ESI) m/z 257 [M+H]⁺; HRMS (ESI) m/z calcd for C₁₆H₂₁ON₂ [M+H]⁺ 257.1645, found 257.1645.

Synthesis and Characterization of 1,2,3,4-Tetrahydroisoquinolines, Related to Figure 4.
Compounds 5a (Sullivan et al., 2014), 5k (Pingaew et al., 2013), 5s (Michael et al., 2010) and 5u (Park et al., 2008) were prepared by known method. Other tetrahydroisoquinolines were prepared as shown below.
7-Methyl-2-tosyl-1,2,3,4-tetrahydroisoquinoline (5b):

To a solution of 5b’ (135.2 mg, 1.0 mmol), Et₃N (0.28 mL, 2.0 mmol) and dichloromethane (3 mL) was added a solution of TsCl (228 mg, 1.2 mmol) in dichloromethane (3 mL). After stirred at room temperature for 6 h, the reaction was quenched with 2M HCl (15 mL) and extracted with dichloromethane (3 × 15 mL). The combined organic phase was washed with saturated Na₂CO₃ solution (15 mL) and brine (15 mL), dried over Na₂SO₄. The resulting solution was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 5 : 1) to give 5b” (259.1 mg, 90%), which was directly used for the next step without further purification.

To a mixture of 5b” (259.1 mg, 0.9 mmol) and (HCHO)ₙ (81 mg, 2.7 mmol) was added H₂SO₄/AcOH = 1 : 4 (5 mL). After stirred at room temperature for 12 h, the reaction was quenched with water (20 mL) and extracted with dichloromethane (3 × 15 mL). The combined organic phase was washed with saturated Na₂CO₃ solution (15 mL) and brine (15 mL), dried over Na₂SO₄. The resulting solution was concentrated under reduced pressure, and the residue was recrystallized to give pure product 5b (225.0 mg, 83%) as a white solid. M.p. 164-165 °C; IR (KBr, cm⁻¹): 3022.4, 2863.4, 2829.4, 1935.1, 1588.2, 1502.1, 1455.0, 1338.9, 1161.9; ¹H NMR (CDCl₃, 500 MHz): δ 7.72 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 6.99-6.92 (m, 2H), 6.84 (s, 1H), 4.21 (s, 2H), 3.33 (t, J = 5.9 Hz, 2H), 2.88 (t, J = 5.9 Hz, 2H), 2.42 (s, 3H), 2.27 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz): δ 143.7, 136.03, 133.44, 131.56, 130.11, 129.78, 128.75, 127.86, 127.70, 126.90, 47.62, 43.97, 28.60, 21.63, 21.08; EI-MS m/z (%): 146.1 (100), 301.1 (14) [M]+; HRMS (EI) m/z calcd for C₁₇H₁₉NO₂S [M]+ 301.1136, found 301.1139.

7-Phenyl-2-tosyl-1,2,3,4-tetrahydroisoquinoline (5c):

To a mixture of 5g (219.8 mg, 0.6 mmol), phenylboronic acid (110 mg, 0.9 mmol), K₂CO₃ (231 mg, 1.8 mmol), Pd(OAc)₂ (6.7 mg, 0.03 mmol), PPh₃ (31.5 mg, 0.12 mmol) were added MeOH (1.2 mL) and dioxane (0.6 mL). After stirred at 80 °C for 5 h under N₂, the reaction mixture was filtered, and the filter residue was washed with ethyl acetate. The resulting solution was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 5 : 1) to give pure product 5c (149.5 mg, 69%) as a white solid. M.p. 164-165 °C; IR (KBr, cm⁻¹): 3022.4, 2863.4, 2829.4, 1935.1, 1588.2, 1502.1, 1455.0, 1338.9, 1161.9; ¹H NMR (CDCl₃, 500 MHz): δ 7.75 (d, J = 8.2 Hz, 2H), 7.52 (d, J = 7.6 Hz, 2H), 7.42 (t, J = 7.6 Hz, 2H), 7.38-7.30 (m, 4H), 7.25 (s, 1H), 7.16 (d, J = 8.0 Hz, 1H), 4.31 (s, 2H), 3.39 (t, J = 5.9 Hz, 2H), 2.97 (t, J = 5.9 Hz, 2H), 2.42 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz): δ 143.73, 136.03, 133.44, 131.56, 130.11, 129.78, 128.75, 127.86, 127.70, 126.90, 47.62, 43.97, 28.60, 21.63, 21.08; EI-MS m/z (%): 146.1 (100), 301.1 (14) [M]+; HRMS (EI) m/z calcd for C₂₂H₂₁NO₂S [M]+ 363.1293, found 363.1288.
7-Methoxy-2-tosyl-1,2,3,4-tetrahydroisoquinoline (5d):

To a solution of 5d' (736 mg, 5 mmol) and THF (1 mL) in three-necked bottle was added BH$_3$·THF (1M in THF, 15 mL) under N$_2$. After stirred at 75 °C overnight, the reaction was quenched with MeOH (5 mL) carefully, and concentrated under reduced pressure. After dichloromethane (8 mL), Et$_3$N (1.4 mL, 10 mmol) and pyridine (0.8 mL, 10 mmol) were added to this residue, a solution of TsCl (1.14 g, 6 mmol) in dichloromethane (8 mL) was added, and the mixture was stirred at room temperature overnight. The reaction was quenched with 2 M HCl (15 mL), extracted with dichloromethane (3 × 15 mL). The combined organic phase was washed with saturated Na$_2$CO$_3$ solution (15 mL) and brine (15 mL), dried over Na$_2$SO$_4$. The resulting solution was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 5 : 1) to give 5d'' (811.6 mg, 53% for two steps) without further purification. To a solution of 5d'' (305.4 mg, 1 mmol) in dichloromethane (2.4 mL) was added BF$_3$·OEt$_2$ (225 μL, 3 mmol) and aq. HCHO (37%) (93 μL). After stirred at room temperature for 2 h, the reaction was quenched with water (10 mL), and extracted with dichloromethane (3 × 10 mL). The combined organic phase was washed with brine (15 mL), and dried over Na$_2$SO$_4$. The resulting solution was concentrated under reduced pressure. And the residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 5 : 1) to give product 5d (114.8 mg, 36%) as a white solid. M.p. 115-117 °C; IR (KBr, cm$^{-1}$): 2925.4, 2849.8, 1609.2, 1503.6, 1457.5, 1337.4; $^1$H NMR (CDCl$_3$, 500 MHz): δ 7.72 (d, $J = 8.3$ Hz, 2H), 7.32 (d, $J = 8.2$ Hz, 2H), 6.98 (d, $J = 8.4$ Hz, 1H), 6.71 (dd, $J = 8.5$, 2.6 Hz, 1H), 6.55 (d, $J = 2.6$ Hz, 1H), 4.21 (s, 2H), 3.75 (3H, s), 3.33 (t, $J = 5.9$ Hz, 2H), 2.85 (t, $J = 5.9$, 2H), 2.42 (s, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz): δ 158.16, 143.78, 133.49, 132.78, 129.89, 129.83, 127.87, 125.28, 113.35, 111.05, 55.44, 47.82, 44.13, 28.19, 21.66; EI-MS m/z (%): 134.1 (100), 317.1 (32) [M]$^+$; HRMS (EI) m/z calcd for C$_{17}$H$_{19}$NO$_3$S [M]$^+$ 317.1086, found 317.1087.

7-Fluoro-2-tosyl-1,2,3,4-tetrahydroisoquinoline (5e):

To a solution of 5e' (675 mg, 5 mmol) and THF (1 mL) in a three-necked bottle was added BH$_3$·THF (1M in THF, 15 mL) under N$_2$. After stirred at 75 °C overnight, the reaction was quenched with MeOH (5 mL) carefully, and concentrated under reduced pressure. After dichloromethane (8 mL), Et$_3$N (1.4 mL, 10 mmol) and pyridine (0.8 mL, 10 mmol) were added to this residue, a solution of TsCl (1.14 g, 6 mmol) in dichloromethane (8 mL) was dropped, and stirred at room temperature overnight. The reaction was quenched with 2 M HCl (15 mL), extracted with dichloromethane (3 × 15 mL). The combined organic phase was washed with saturated Na$_2$CO$_3$ solution (15 mL) and brine (15 mL), and dried over Na$_2$SO$_4$. The resulting solution was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 5 : 1) to give product 5e (114.8 mg, 36%) as a white solid. M.p. 115-117 °C; IR (KBr, cm$^{-1}$): 2925.4, 2849.8, 1609.2, 1503.6, 1457.5, 1337.4; $^1$H NMR (CDCl$_3$, 500 MHz): δ 7.72 (d, $J = 8.3$ Hz, 2H), 7.32 (d, $J = 8.2$ Hz, 2H), 6.98 (d, $J = 8.4$ Hz, 1H), 6.71 (dd, $J = 8.5$, 2.6 Hz, 1H), 6.55 (d, $J = 2.6$ Hz, 1H), 4.21 (s, 2H), 3.75 (3H, s), 3.33 (t, $J = 5.9$ Hz, 2H), 2.85 (t, $J = 5.9$, 2H), 2.42 (s, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz): δ 158.16, 143.78, 133.49, 132.78, 129.89, 129.83, 127.87, 125.28, 113.35, 111.05, 55.44, 47.82, 44.13, 28.19, 21.66; EI-MS m/z (%): 134.1 (100), 317.1 (32) [M]$^+$; HRMS (EI) m/z calcd for C$_{17}$H$_{19}$NO$_3$S [M]$^+$ 317.1086, found 317.1087.
organic phase was washed with saturated Na₂CO₃ solution (15 mL) and brine (15 mL), and then dried over Na₂SO₄. The resulting solution was concentrated under reduced pressure. The residue was recrystallized (dichloromethane/hexane) to give pure product 5e (225.0 mg, 83%) as a white solid. M.p. 116-117 °C; IR (KBr, cm⁻¹): 2975.2, 2908.6, 1921.2, 1731.4, 1605.3, 1499.1, 1437.1; ¹H NMR (CDCl₃, 500 MHz): δ 7.72 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 8.2 Hz, 2H), 7.03 (dd, J = 8.5, 5.7 Hz, 1H), 6.84 (td, J = 8.5, 2.6 Hz, 1H), 6.71 (dd, J = 9.2, 2.5 Hz, 1H), 4.21 (s, 2H), 3.34 (t, J = 5.9 Hz, 2H), 2.88 (t, J = 5.9 Hz, 2H), 2.42 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz): δ 161.31 (d, ¹JC-F = 244.7 Hz), 143.96, 133.58 (d, ³JC-F = 7.6 Hz), 133.34, 130.43 (d, ³JC-F = 7.8 Hz), 129.90, 128.82 (d, ⁴JC-F = 2.8 Hz), 127.86, 114.15 (d, ²JC-F = 21.2 Hz), 112.95 (d, ²JC-F = 22.0 Hz), 47.58 (d, ³JC-F = 2.3 Hz), 43.87, 28.33, 21.66; EI-MS m/z (%): 150.1 (100), 305.1 (16) [M]+; HRMS (EI) m/z calcd for C₁₆H₁₆FNO₂S [M]+ 305.0886, found 305.0890.

7-Chloro-2-tosyl-1,2,3,4-tetrahydroisoquinoline (5f):
To a solution of 5f' (758 mg, 5 mmol) and THF (1 mL) in a three-necked bottle was added BH₃·THF (1 M in THF, 15 mL) under N₂. After stirred at 75 °C overnight, the reaction was quenched with MeOH (5 mL) carefully, and concentrated under reduced pressure. After dichloromethane (8 mL), Et₃N (1.4 mL, 10 mmol) and pyridine (0.8 mL, 10 mmol) were added in this residue, a solution of TsCl (1.14 g, 6 mmol) in dichloromethane (8 mL) was added, and the mixture was stirred at room temperature overnight. The reaction was quenched with 2 M HCl (15 mL), extracted with dichloromethane (3 × 15 mL). The combined organic phase was washed with saturated Na₂CO₃ solution (15 mL), brine (15 mL), and dried over Na₂SO₄. The resulting solution was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 5 : 1) to give 5f'' (850.4 mg, 55% for two steps). To a mixture of 5f'' (309.8 mg, 1 mmol) and (HCHO)n (90 mg, 3 mmol) was added H₂SO₄/AcOH = 3 : 2 (10 mL). After stirred at room temperature for 5 h, the reaction was quenched with water (20 mL), and extracted with dichloromethane (3 × 10 mL). The combined organic phase was washed with saturated Na₂CO₃ solution (15 mL), brine (15 mL), and dried over Na₂SO₄. The resulting solution was concentrated under reduced pressure. The residue was recrystallized (dichloromethane/Hexane) to give pure product (266.6 mg, 83%) as a white solid. M.p. 156-158 °C; IR (KBr, cm⁻¹): 3032.1, 2930.9, 2843.7, 1925.6, 1741.2, 1598.4, 1483.4, 1419.8, 1336.9, 1161.4; ¹H NMR (CDCl₃, 500 MHz): δ 7.70 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 7.9 Hz, 2H), 7.09 (d, J = 8.2 Hz, 1H), 7.05-6.95 (m, 2H), 4.18 (s, 2H), 3.32 (t, J = 5.6 Hz, 2H), 2.87 (t, J = 5.6 Hz, 2H), 2.41 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz): δ 143.95, 133.48, 133.20, 131.97, 131.66, 130.23, 129.86, 127.78, 127.03, 126.30, 47.32, 43.64, 28.39, 21.60; EI-MS m/z (%): 166.0 (100) [M-Ts]+; HRMS (EI) m/z calcd for C₁₆H₁₆ClNO₂S [M]+ 321.0590, found 321.0601.
**7-Bromo-2-tosyl-1,2,3,4-tetrahydroisoquinoline (5g):**

To a solution of 5g' (980 mg, 5 mmol) and THF (1 mL) in a three-necked bottle was added BH$_3$·THF (1 M in THF, 15 mL) under N$_2$. After stirred at 75 ºC overnight, the reaction was quenched with MeOH (5 mL) carefully, and concentrated under reduced pressure. After dichloromethane (8 mL) and Et$_3$N (1.4 mL, 10 mmol) were added to this residue, a solution of TsCl (1.14 g, 6 mmol) in dichloromethane (8 mL) was added, and the mixture was stirred at room temperature overnight. The reaction was quenched with 2 M HCl (15 mL), extracted with dichloromethane (3 × 15 mL). The combined organic phase was washed with saturated Na$_2$CO$_3$ solution (15 mL), brine (15 mL), and dried over Na$_2$SO$_4$. The resulting solution was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 5 : 1) to give 5g'' (884.2 mg, 50% for two steps). To a mixture of 5g'' (884.2 mg, 2.5 mmol) and (HCHO)$_n$ (225 mg, 7.5 mmol) was added H$_2$SO$_4$/AcOH = 3 : 2 (25 mL). After stirred at room temperature for 5 h, the reaction was quenched with water (40 mL). The mixture was filtered to collect residue solid. The residue was recrystallized (hexane/ethyl acetate) to give product 5g (737.3 mg, 81%) as a white solid. M.p. 160–161 ºC; IR (KBr, cm$^{-1}$): 3031.1, 2929.8, 2841.9, 1924.6, 1740.8, 1593.9, 1479.8, 1417.5, 1337.9, 1161.3; $^1$H NMR (CDCl$_3$, 500 MHz): δ 7.71 (d, $J = 8.2$ Hz, 2H), 7.32 (d, $J = 8.1$ Hz, 2H), 7.25 (d, $J = 8.6$ Hz, 1H), 7.18 (s, 1H), 6.95 (d, $J = 8.2$ Hz, 1H), 4.20 (s, 2H), 3.33 (t, $J = 5.9$ Hz, 2H), 2.86 (t, $J = 5.8$ Hz, 2H), 2.42 (s, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz): δ 143.99, 133.95, 133.30, 132.24, 130.57, 130.00, 129.91, 129.32, 127.85, 119.96, 47.23, 43.62, 28.52, 21.66; EI-MS m/z (%): 210.0 (100), 364 (8) [M$^{^{79}$Br}]+, 366 (10) [M$^{^{81}$Br}]+; HRMS (EI) m/z calcd for C$_{16}$H$_{16}$BrNO$_2$S [M]$^+$ 365.0085, found 365.0084.

**2-Tosyl-7-((trimethylsilyl)ethynyl)-1,2,3,4-tetrahydroisoquinoline (5h):**

To a mixture of 1g (219.8 mg, 0.6 mmol), Pd(PPh$_3$)$_2$Cl$_2$ (42.1 mg, 0.06 mmol) and Cul (11.4 mg, 0.06 mmol) in DMF (3 mL) were added ethynyltrimethylsilane (169 μL, 1.2 mmol) and Et$_3$N (169 μL, 1.8 mmol). After stirred at 50 ºC for 4 h, the reaction was quenched with saturated Na$_2$CO$_3$ solution, and extracted with EtOAc (10 mL) for three times. The combined organic phase were washed with water (3 × 10 mL), brine (10 mL), and dried over Na$_2$SO$_4$. The resulting solution was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 10 : 1) to give product 5h (138.2 mg, 60%) as a white solid. M.p. 39-41 ºC; IR (KBr, cm$^{-1}$): 3046.1, 2977.9, 2925.7, 2850.0, 1919.6, 1608.7, 1457.7, 1361.9, 1200.5, 1159.6; $^1$H NMR (CDCl$_3$, 500 MHz): δ 7.70 (d, $J = 8.0$ Hz, 2H), 7.32 (d, $J = 8.0$ Hz, 2H), 7.22 (d, $J = 7.8$ Hz, 1H), 7.15 (s, 1H), 7.00 (d, $J = 7.9$ Hz, 1H), 4.19 (s, 2H), 3.34 (t, $J = 5.7$ Hz, 2H), 2.89 (t, $J = 5.7$ Hz, 2H), 2.41 (s, 3H), 0.23 (s, 9H); $^{13}$C NMR (CDCl$_3$, 125 MHz): δ 143.91, 133.85, 133.37, 131.87, 130.31, 130.00, 129.87,
7-Pinacolboryl-2-tosyl-1,2,3,4-tetrahydroisoquinoline (5i):
To a seal tube was added 1g (256.4 mg, 0.7 mmol), Pd(dppf)Cl₂ (31 mg, 0.042 mmol), B₂pin₂ (200 mg, 0.78 mmol), KOAc (206 mg, 2.1 mmol) and dioxane (3 mL). After stirred at 100 °C for 2 h, the reaction was filtered by celite and washed with EtOAc. The solvent was removed under vacuum, and the residue was purified by flash column chromatography on silica gel to give pure product 5i (212.4 mg, 73%) as a white solid.

M.p. 133–134 °C; IR (KBr, cm⁻¹): 3046.1, 2977.9, 2925.7, 2850.0, 1919.6, 1608.7, 1457.7, 1361.9, 1200.5, 1159.6; ¹H NMR (CDCl₃, 500 MHz): δ 7.70 (d, J = 8.2 Hz, 2H), 7.56 (d, J = 7.6 Hz, 1H), 7.49 (s, 1H), 7.31 (d, J = 8.1 Hz, 2H), 7.08 (d, J = 7.6 Hz, 1H), 4.24 (s, 2H), 3.34 (t, J = 5.9 Hz, 2H), 2.93 (t, J = 5.7 Hz, 2H), 2.41 (s, 3H), 1.32 (s, 12H); ¹³C NMR (CDCl₃, 125 MHz): δ 143.78, 136.54, 133.34, 133.05, 132.97, 131.20, 129.78, 128.35, 127.87, 83.96, 47.56, 43.64, 29.24, 24.96, 21.63; EI-MS m/z (%): 258.2 (100), 411.2 (4) [M–H]+, 412.2 (14) [M]+; HRMS (EI) m/z calcd for C₂₂H₂₇NO₂SSi [M–H]+ 411.1790, found 411.1786.

5-Methyl-2-tosyl-1,2,3,4-tetrahydroisoquinoline (5j):
To a solution of 5j' (656 mg, 5 mmol) and THF (1 mL) in a three-necked bottle was added BH₃·THF (1 M in THF, 15 mL) under N₂. After stirred at 75 °C overnight, the reaction was quenched with MeOH (5 mL) carefully, and concentrated under reduced pressure. To the residue were added dichloromethane (8 mL), Et₃N (1.4 mL, 10 mmol) and pyridine (0.8 mL, 10 mmol), and a solution of TsCl (1.14 g, 6 mmol) in dichloromethane (8 mL) was added dropwise. After stirred at room temperature overnight, the reaction was quenched with 2M HCl (15 mL), extracted with dichloromethane (3 x 15 mL). The combined organic phase was washed with saturated Na₂CO₃ solution (15 mL), brine (15 mL), and dried over Na₂SO₄. The resulting solution was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 5 : 1) to give 5j'' (714.0 mg, 49% for two steps). To a mixture of 5j'' (289.4 mg, 1 mmol) and (HCHO)n (90 mg, 3 mmol) was added H₂SO₄/AcOH = 3 : 2 (10 mL). After stirred at room temperature for 5 h, the reaction was quenched with water (40 mL). The mixture was filtered to collect the solid. The residue was recrystallized (hexane/ethyl acetate) to give product 5j (273.4 mg, 91%) as a white solid. M.p. 160-162 °C; IR (KBr, cm⁻¹): 3029.4, 2925.7, 1922.7, 17.6.6, 1659.4, 1493.5, 1465.3, 1335.4, 1160.5; ¹H NMR (CDCl₃, 500 MHz): δ 7.73 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 8.2 Hz, 2H), 7.06 (t, J = 7.5 Hz, 1H), 7.01 (d, J = 7.2 Hz, 1H), 6.88 (d, J = 7.6 Hz, 1H), 4.22 (s, 2H), 3.36 (t, J = 6.0 Hz, 2H), 2.79 (t, J = 6.0 Hz, 2H), 2.42 (s, 3H), 2.19 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz): δ
6-Tosyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline (5I):

To a solution of 5I’ (806 mg, 5 mmol) and THF (1 mL) in three-necked bottle was added BH₃·THF (1 M in THF, 15 mL) under N₂. After stirred at 75 °C overnight, the reaction was quenched with MeOH (5 mL) carefully, and concentrated under reduced pressure. After dichloromethane (8 mL) and Et₃N (1.4 mL, 10 mmol) were added in this residue, a solution of TsCl (1.14 g, 6 mmol) in dichloromethane (8 mL) was added, and the mixture was stirred at room temperature overnight. The reaction was quenched with 2 M HCl (15 mL), extracted with dichloromethane (3 × 15 mL). The combined organic phase was washed with saturated Na₂CO₃ solution (15 mL), brine (15 mL), and dried over Na₂SO₄. The resulting solution was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 3 : 1) to give 5I” (850.4 mg, 55% for two steps). To a mixture of 5I” (302.1 mg, 0.94 mmol) and (HCHO)ₙ (84.6 mg, 2.82 mmol) was added MeOH (1 mL) and AcOH (9 mL). After stirred at 60 °C for 12 h, the reaction was quenched with water (20 mL), and extracted with dichloromethane (3 × 10 mL). The combined organic phase was washed with saturated Na₂CO₃ solution (15 mL), brine (15 mL), and dried over Na₂SO₄. The resulting solution was concentrated under reduced pressure. The residue was recrystallized (dichloromethane/hexane) to give product 5I (304.8 mg, 92%) as a white solid. M.p. 150-151 °C; IR (KBr, cm⁻¹): 3046.4, 2893.3, 2837.2, 1917.7, 1710.3, 1594.4, 1495.5, 1391.1, 1344.3, 1160.6; ¹H NMR (CDCl₃, 500 MHz): δ 7.70 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H), 6.51 (s, 1H), 4.12 (s, 2H), 2.80 (t, J = 5.9 Hz, 2H), 1.21 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz): δ 146.59, 146.36, 143.77, 133.39, 129.79, 127.81, 126.25, 124.55, 108.52, 106.20, 100.99, 47.64, 43.79, 28.91, 21.61; EI-MS m/z (%): 175.1 (100), 331.1 (14) [M⁺]; HRMS (EI) m/z calcd for C₁₇H₁₉NO₂S [M⁺] 331.0878, found 331.0877.

5-Tosyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (5m):

To a solution of 5m’ (616 mg, 5 mmol) and THF (1 mL) in three-necked bottle was added BH₃·THF (1 M in THF, 15 mL) under N₂. After stirred at 65 °C overnight, the reaction was quenched with MeOH (5 mL) carefully, and concentrated under reduced pressure. After dichloromethane (10 mL) and Et₃N (1.4 mL, 10 mmol) were added to this residue, a solution of TsCl (950 mg, 5 mmol) in dichloromethane (10 mL) was added dropwise, and stirred at room temperature for 6 h. The reaction was quenched with 2 M HCl (15 mL), extracted with
dichloromethane (3 × 15 mL). The combined organic phase was washed with saturated Na₂CO₃ solution (15 mL), brine (15 mL), and dried over Na₂SO₄. The resulting solution was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 3 : 1) to give 5m′′ (874.6 mg, 62% for two steps). To a mixture of 5m′′ (517.1 mg, 1.8 mmol) and (HCHO)ₙ (165.4 mg, 5.4 mmol) were added MeOH (4.5 mL) and AcOH (13.5 mL). After stirred at 60 °C for 12 h, the reaction was quenched with water (20 mL), and extracted with dichloromethane (3 × 10 mL). The combined organic phase was washed with saturated Na₂CO₃ solution (15 mL) and brine (15 mL), and then dried over Na₂SO₄. The resulting solution was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 3 : 1) to give product 5m (116.6 mg, 22%) as a white solid. M.p. 159-160 °C; IR (KBr, cm⁻¹): 3083.5, 3026.2, 2918.2, 2859.4, 1920.8, 1593.9, 1455.6, 1344.6; ¹H NMR (CDCl₃, 500 MHz): δ 7.71 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 8.1 Hz, 2H), 7.09 (d, J = 5.3 Hz, 1H), 6.71 (d, J = 5.1 Hz, 1H), 4.19 (s, 2H), 3.41 (t, J = 5.7 Hz, 2H), 2.90 (t, J = 5.7 Hz, 2H), 2.42 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz): δ 143.80, 133.77, 132.65, 130.69, 129.81, 127.70, 124.79, 123.70, 45.94, 43.99, 25.29, 21.62; EI-MS m/z (%): 110.0 (100), 293.1 (7) [M⁺]; HRMS (EI) m/z calcd for C₁₄H₁₅NO₂S₂ [M⁺] 293.0544, found 293.0547.

3-Tosyl-1,2,3,4-tetrahydrobenzo[f]isoquinoline (5n):
To a solution of 5n’ (836 mg, 5 mmol) and THF (1 mL) in a three-necked bottle was added BH₃·THF (1 M in THF, 15 mL) under N₂. After stirred at 75 °C overnight, the reaction was quenched with MeOH (5 mL) carefully, and concentrated under reduced pressure. After dichloromethane (8 mL), Et₃N (1.4 mL, 10 mmol) was added in this residue, the solution of TsCl (1.14 g, 6 mmol) in dichloromethane (8 mL) was added, and stirred at room temperature for 10 h. The reaction was quenched with 2 M HCl (15 mL), extracted with dichloromethane (3 × 15 mL). The combined organic phase was washed with saturated Na₂CO₃ solution (15 mL), brine (15 mL), and dried over Na₂SO₄. The resulting solution was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 3 : 1) to give product 5n (383.1 mg, 54%) as a white solid. M.p. 239-241 °C; IR (KBr, cm⁻¹): 3058.0, 2970.7, 2923.4, 2857.3, 2822.8, 1925.1, 1591.1, 1500.5, 1340.4, 1158.7; ¹H NMR (CDCl₃, 500 MHz): δ 7.86 (d, J = 8.3 Hz, 1H), 7.83-7.72 (m, 3H), 7.66 (d, J = 8.4 Hz, 1H), 7.52 (t, J = 7.2 Hz, 1H), 7.49 (t, J = 7.2 Hz, 1H), 7.34 (d, J = 8.0 Hz, 2H), 7.12 (d, J = 8.5 Hz, 1H), 4.36 (s, 2H), 3.49 (t, J = 5.9 Hz, 2H), 3.27 (t, J = 5.5 Hz, 2H), 2.42 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz): δ 143.90, 133.27, 132.43,
EI-MS m/z: 337.1 [M]+; HRMS (EI) m/z calcd for C_{20}H_{19}NO_{2}S [M]+ 337.1136, found 337.1133.

2'-Tosyl-2',3'-dihydro-1'H-spirocyclopropane-1,4'-isoquinoline (5o):

To a solution of NaH (60%) (640 mg, 16 mmol) and DMF (5.6 mL) was added dropwisely a solution of 2-phenylacetonitrile (937.1 mg, 8 mmol) in DMF (9.4 mL) at 0 °C under N₂ atmosphere. After stirred for 40 min, 1,2-dibromoethane (1.8 g, 9.6 mmol) was added dropwise, and kept stirred for 5 h. The reaction was quenched with water, and extracted with ethyl acetate (3 × 15 mL). The combined organic phase was washed with brine (15 mL), and dried over Na₂SO₄. The resulting solution was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 50 : 1) to give 5o' (541.8 mg, 47%) as a colorless liquid. To a solution of 5o' (716 mg, 5 mmol) and THF (1 mL) in a three-necked bottle was added BH₃·THF (1 M in THF, 15 mL) under N₂. After stirred at 75 °C overnight, the reaction was quenched with MeOH (5 mL) carefully, and concentrate under reduced pressure. After dichloromethane (8 mL), Et₃N (1.4 mL, 10 mmol) was added in this residue, a solution of TsCl (1.14 g, 6 mmol) in dichloromethane (8 mL) was added dropwise, and stirred at room temperature for 5 h. The reaction was quenched with 2 M HCl (15 mL), extracted with dichloromethane (3 × 15 mL). The combined organic phase was washed with saturated Na₂CO₃ solution (15 mL), brine (15 mL), and dried over Na₂SO₄. The resulting solution was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 5 : 1) to give 5o'' (903.5 mg, 60% for two steps). To a mixture of 5o'' (304.1 mg, 1 mmol) and (HCHO),n (90 mg, 3 mmol) was added H₂SO₄/AcOH = 1 : 4 (10 mL). After stirred at room temperature for 4 h, the reaction was quenched with water (40 mL). The mixture was filtered to collect the solid. The residue was recrystallized (hexane/ethyl acetate) to give product 5o (260.1 mg, 83%) as a white solid. M.p. 155-157 °C; IR (KBr, cm⁻¹): 3074.1, 2995.3, 2921.2, 2839.6, 1933.6, 1598.0, 1491.4, 1452.7, 1338.1; ¹H NMR (CDCl₃, 500 MHz): δ 7.70 (d, J = 8.1 Hz, 2H), 7.31 (d, J = 8.1 Hz, 2H), 7.17-7.05 (m, 2H), 7.02 (d, J = 7.3 Hz, 1H), 6.67 (d, J = 7.4 Hz, 1H), 4.35 (s, 2H), 3.14 (s, 2H), 2.42 (s, 3H), 1.05-0.91 (m, 4H); ¹³C NMR (CDCl₃, 125 MHz): δ 143.74, 138.35, 133.61, 132.02, 129.77, 127.91, 127.39, 126.18, 125.66, 121.71, 53.08, 48.83, 21.65, 19.54, 16.88; EI-MS m/z (%): 130.1 (100), 313.1 (9) [M]+; HRMS (EI) m/z calcd for C_{18}H_{19}NO_{2}S [M]+ 313.1136, found 313.1135.
2'-Tosyl-2',3'-dihydro-1'H-spiro[cyclobutane-1,4'-isoquinoline] (5p):
To a solution of NaH (60%) (960 mg, 24 mmol) and DMF (7 mL) was added a solution of 2-phenylacetonitrile (1.17 g, 10 mmol) in DMF (11 mL) dropwise at 0 °C under N₂ atmosphere. After stirred for 40 min, 1,3-dibromopropane (2.42 g, 12 mmol) was added dropwise, and kept stirred for 5 h. The reaction was quenched with water, extracted with ethyl acetate (3 × 15 mL). The combined organic phase was washed with brine (15 mL), and dried over Na₂SO₄. The resulting solution was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 50 : 1) to give 5p' (1.02 g, 65%) as colorless liquid. To a solution of 5p' (786 mg, 5 mmol) and THF (1 mL) in a three-necked bottle was added BH₃·THF (1 M in THF, 15 mL) under N₂. After stirred at 75 °C overnight, the reaction was quenched with MeOH (5 mL) carefully, and concentrated under reduced pressure. After dichloromethane (8 mL) and Et₃N (1.4 mL, 10 mmol) were added in to the residue, a solution of TsCl (1.14 g, 6 mmol) in dichloromethane (8 mL) was added dropwise, and stirred at room temperature for 5 h. The reaction was quenched with 2 M HCl (15 mL), extracted with dichloromethane (3 × 5 mL). The combined organic phase was washed with saturated Na₂CO₃ solution (15 mL) and brine (15 mL), and dried over Na₂SO₄. The resulting solution was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 5 : 1) to give 5p'' (815.8 mg, 52% for two steps). To a mixture of 5p'' (304.1 mg, 1 mmol) and (HCHO)ₙ (90 mg, 3 mmol) was added H₂SO₄/AcOH = 1 : 4 (10 mL), and stirred at room temperature for 4 h. After quenched with water (40 mL), the mixture was filtered to collect residue solid. The residue was recrystallized (hexane/ethyl acetate) to give the product 5p (301.2 mg, 92%) as a white solid. M.p. 175-176 °C; IR (KBr, cm⁻¹): 3063.1, 2980.5, 2937.1, 2843.0, 1593.1, 1489.6, 1337.3, 1162.9; ¹H NMR (CDCl₃, 500 MHz): δ 7.75 (d, J = 8.2 Hz, 2H), 7.56 (d, J = 7.8 Hz, 1H), 7.36 (d, J = 8.0 Hz, 2H), 7.26 (t, J = 7.5 Hz, 1H), 7.14 (t, J = 7.4 Hz, 1H), 6.98 (d, J = 7.6 Hz, 1H), 4.19 (s, 2H), 3.31 (s, 2H), 2.44 (s, 2H), 2.40-2.30 (m, 2H), 2.20-2.00 (m, 4H); ¹³C NMR (CDCl₃, 125 MHz): δ 143.78, 141.23, 133.29, 130.80, 129.84, 127.88, 127.41, 126.32, 126.07, 53.68, 48.49, 41.57, 32.88, 21.63, 15.17; EI-MS m/z (%): 143.1 (100), 327.1 (15) [M⁺]; HRMS (EI) m/z calcd for C₁₉H₂₁NO₂S [M⁺] 327.1293, found 327.1287.
2'-Tosyl-2',3'-dihydro-1'H-spirocyclopentane-1,4'-isoquinoline (5q):
To a solution of NaH (60%) (960 mg, 24 mmol) in DMF (7 mL) was added a solution of 2-phenylacetonitrile (1.17 g, 10 mmol) in DMF (11 mL) dropwise at 0 °C under N₂ atmosphere. After stirred for 40 min, 1,4-dibromobutane (2.59 g, 12 mmol) was added dropwise, and kept stirred for 5 h. The reaction was quenched by water, extracted with ethyl acetate (15 mL × 3). The combined organic phase was washed with brine (15 mL), and dried over Na₂SO₄. The resulting solution was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 50:1) to give 5q' (1.76 g, 99%) as colorless liquid. To a solution of 5q' (786 mg, 5 mmol) and THF (1 mL) in a three-necked bottle was added BH₃·THF (1 M in THF, 15 mL) under N₂. After stirred at 75 °C overnight, the reaction was quenched with MeOH (5 mL) carefully, and concentrated under reduced pressure. After dichloromethane (8 mL) and Et₃N (1.4 mL, 10 mmol) were added in this residue, a solution of TsCl (1.14 g, 6 mmol) in dichloromethane (8 mL) was added dropwise, and stirred at room temperature for 5 h. The reaction was quenched with 2 M HCl (15 mL), extracted with dichloromethane (3 × 15 mL). The combined organic phase was washed with saturated Na₂CO₃ solution (15 mL), brine (15 mL), and dried over Na₂SO₄. The resulting solution was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to give 5q'' (632.8 mg, 38% for two steps). To a mixture of 5q'' (240 mg, 0.73 mmol) and (HCHO)ₙ (66 mg, 2.2 mmol) was added H₂SO₄/AcOH = 1:4 (7.3 mL), and stirred at room temperature for 12 h. After quenched with water (40 mL), the mixture was filtered to collect residue solid. The residue was recrystallized (hexane/ethyl acetate) to give pure product 5q (224.1 mg, 98%) as a white solid. M.p. 161-163 °C; IR (KBr, cm⁻¹): 3035.1, 2953.7, 2861.7, 1923.6, 1593.2, 1468.7, 1450.3, 1340.7, 1219.0, 1162.3; ¹H NMR (CDCl₃, 500 MHz): δ 7.74 (d, J = 8.3 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 8.0 Hz, 1H), 7.19 (t, J = 7.3 Hz, 1H), 7.11 (dt, J = 7.6, 1.1 Hz, 1H), 6.98 (d, J = 7.6 Hz, 1H), 4.20 (s, 2H), 3.00 (s, 2H), 2.43 (s, 3H), 2.0-1.74 (m, 8H); ¹³C NMR (CDCl₃, 125 MHz): δ 143.75, 143.29, 133.34, 131.09, 129.85, 127.90, 127.38, 126.25, 126.13, 125.94, 53.63, 48.43, 46.86, 40.23, 26.10, 21.66; EI-MS m/z (%): 158.1 (100), 341.1 (24) [M⁺]; HRMS (EI) m/z calcd for C₂₀H₂₃NO₂S [M⁺] 341.1449, found 341.1453.

5-Tosyl-1,2,3,4,4a,5,6,10b-octahydropolanthridine (5r):
To the solution of 5r' (Cheng et al., 2016) (360 mg, 2 mmol) in pyridine (5 mL) was added TsCl
(570 mg, 3 mmol). After stirred at 40 °C overnight, the reaction was cooled to room temperature, then quenched with water (30 mL) and extracted with dichloromethane (3 x 15 mL). The combined organic phase was washed with water (2 x 20 mL), 2 M HCl (20 mL), saturated NaHCO₃ solution (20 mL) and brine (20 mL), then dried over Na₂SO₄. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 5 : 1) to give pure 5r'' as a white solid (552.9 mg, 84%). To a mixture 5r'' (306.3 mg, 0.93 mmol) and (HCHO)ₙ was added H₂SO₄/AcOH = 1 : 4 (10 mL) and stirred at room temperature for 12 h. The reaction was quenched with water (20 mL), then stirred for 20 min and filtered to collect the residue solid. The residue solid was washed with water and recrystallized (hexane/ethyl acetate) to give product 5r (272.4 mg, 86%) as a white solid. M.p. 100 - 102 °C; IR (KBr, cm⁻¹): 3058.5, 2925.6, 2857.4, 1597.1, 1493.0, 1454.2, 1386.8, 1336.3; ¹H NMR (CDCl₃, 500 MHz): δ 7.74 (d, J = 8.0 Hz, 2H), 7.34 - 7.24 (m, 3H), 7.22 (t, J = 7.5 Hz, 1H), 7.17 (t, J = 7.2 Hz, 1H), 7.07 (d, J = 7.4 Hz, 1H), 4.63 (d, J = 15.9 Hz, 1H), 4.32 (d, J = 15.8 Hz, 1H), 4.21 - 4.08 (m, 1H), 3.07 (s, 1H), 2.45 (d, J = 14.3 Hz, 1H), 2.40 (s, 3H), 1.75 - 1.63 (m, 1H), 1.62 - 1.20 (m, 5H), 1.15 - 1.00 (m, 1H); ¹³C NMR (CDCl₃, 125 MHz): δ 143.29, 137.30, 135.14, 132.34, 129.81, 127.22, 127.19, 126.35, 126.34, 126.06, 54.51, 44.01, 37.31, 27.86, 25.89, 25.41, 21.61, 19.87; ESI-MS m/z: 342.2 [M+H⁺]; HRMS (ESI) m/z calcd for C₂₀H₂₄N₂O₂S [M⁺+H]⁺ 342.1522, found 342.1521.

(3,4-Dihydroisoquinolin-2(1H)-yl)(4-nitrophenyl)methanone (5t):
To a solution of 1,2,3,4-tetrahydroisoquinoline (133.2 mg, 1 mmol), pyridine (0.24 mL, 3 mmol) and dichloromethane (5 mL) was added a solution of 4-nitrobenzoyl chloride (278.3 mg, 1.5 mmol) in dichloromethane (5 mL) dropwise. After stirred at room temperature overnight, the reaction was quenched with HCl (2 M, 10 mL), and then extracted with dichloromethane (15 mL) for three times. The combined organic phase was washed with saturated Na₂CO₃ solution (15 mL) and brine (15 mL), and then dried over Na₂SO₄. The resulting solution was concentrated under reduced pressure. The residue was purified by flash column chromatography on neutral alumina (petroleum ether/ethyl acetate/dichloromethane = 3 : 1 : 1) to give product 5t (201.6 mg, 71%) as a white solid. M.p. 100-102 °C; IR (KBr, cm⁻¹): 2974.2, 1930.6, 1628.8, 1593.2, 1520.3, 1386.8; ¹H NMR (CDCl₃, 500 MHz): δ 8.30 (s, 2H), 7.62 (s, 2H), 7.35 - 6.80 (m, 4H), 4.90 (s, 1H), 4.51 (s, 1H), 4.01 (s, 1H), 3.59 (s, 1H), 3.01 (s, 1H), 2.88 (s, 1H); ¹³C NMR (CDCl₃, 125 MHz) (rotational isomers): δ 168.70, 168.27, 148.60, 142.39, 142.27, 134.61, 133.50, 132.52, 132.20, 129.81, 128.31, 128.04, 127.42, 127.00, 126.90, 126.68, 125.95, 124.07, 49.78, 45.35, 44.94, 40.80, 29.62, 28.25; EI-MS m/z (%): 282.1 (100) [M⁺]; HRMS (EI) m/z calcd for C₁₆H₁₄N₂O₃ [M⁺] 282.1004, found 282.1012.
C1 Functionalization of 1,2,3,4-Tetrahydroisoquinolines, Related to Figure 4.

(Z)-N-(tert-Butyl)-1-cyano-2-tosyl-1,2,3,4-tetrahydroisoquinoline-1-carbimidoyl cyanide (6a):
To a mixture of 5a (86.2 mg, 0.3 mmol), DDQ (204.3 mg, 0.9 mmol) and AgOTf (11.6 mg, 0.045 mmol, 15 mol%) was added PhCl (4.5 mL) and tBuNC (134 μL, 1.2 mmol) in a glovebox. The reaction was stirred at 80 °C for 3 h under N₂ atmosphere. Upon completion, the reaction mixture was cooled down to room temperature and the solvent was removed under reduced pressure. Then, purification of the residue by column chromatography on silica gel (petroleum ether/ethyl acetate = 10 : 1) to give the desired product 6a (99.8 mg, 79%) as a white solid. M.p. 172-174 °C; IR (KBr, cm⁻¹): 2977.3, 2931.3, 2872.0, 2271.8, 1931.4, 1646.3, 1596.5, 1331.4, 1162.9; ¹H NMR (CDCl₃, 500 MHz): δ 7.88 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.4, 2H), 7.36-7.28 (m, 3H), 7.22 (d, J = 7.2, 1H), 4.23-4.15 (m, 1H), 3.35-3.25 (m, 1H), 3.10-3.01 (m, 1H), 2.87-2.79 (m, 1H), 2.45 (s, 3H), 1.52 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz): δ 145.35, 137.47, 134.74, 133.45, 130.01, 129.92, 129.88, 129.02, 128.53, 128.00, 127.76, 114.27, 110.00, 66.74, 59.31, 43.01, 29.04, 28.95, 21.80; ESI-MS m/z: 421.2 [M+H]⁺; HRMS (DART Positive) m/z calcd for C₂₃H₂₅N₄O₂S [M+H]⁺ 421.1693, found 421.1690.

(Z)-N-(tert-Butyl)-1-cyano-7-methyl-2-tosyl-1,2,3,4-tetrahydroisoquinoline-1-carbimidoyl cyanide (6b):
Following the general procedure for 6a, the reaction of 5b (90.4 mg, 0.3 mmol), DDQ (204.3 mg, 0.9 mmol), AgOTf (11.6 mg, 15 mol%) and tBuNC (134 μL, 1.2 mmol) in PhCl (4.5 mL) at 80 °C for 3 h afforded the desired product 6b as a white solid (98.6 mg, 76%). M.p. 181-183 °C; IR (KBr, cm⁻¹): 2974.7, 2925.4, 2868.0, 2266.8, 1914.4, 1646.3, 1599, 1362, 1164; ¹H NMR (CDCl₃, 500 MHz): δ 7.88 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 7.16-7.06 (m, 3H), 4.19-4.12 (m, 1H), 3.28-3.17 (m, 1H), 3.08-3.00 (m, 1H), 2.81-2.75 (m, 1H), 2.45 (s, 3H), 2.31 (s, 3H), 1.53 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz): δ 145.33, 137.89, 137.55, 133.58, 131.67, 130.93, 129.91, 129.83, 129.07, 128.27, 128.09, 114.40, 110.07, 66.70, 59.31, 43.18, 29.00, 28.65, 21.85, 21.26; ESI-MS m/z: 435.2 [M+H]⁺; HRMS (DART Positive) m/z calcd for C₂₃H₂₅N₄O₂S [M+H]⁺ 435.1849, found 435.1849.
Following the general procedure for 6a, the reaction of 5c (109.5 mg, 0.3 mmol), DDQ (204.3 mg, 0.9 mmol), AgOTf (11.6 mg, 15 mol%) and tBuNC (134 μL, 1.2 mmol) in PhCl (4.5 mL) at 80 °C for 3 h afforded the desired product 6c as a white solid (115.3 mg, 77%). M.p. 193-195 °C; IR (KBr, cm⁻¹): 2212, 1645, 1593, 1477, 1337, 1160; ¹H NMR (CDCl₃, 500 MHz): δ 7.91 (d, J = 8.2 Hz, 2H), 7.57 (d, J = 7.9 Hz, 1H), 7.52-7.30 (m, 9H), 4.25-4.16 (m, 1H), 3.39-3.26 (m, 1H), 3.15-3.05 (m, 1H), 2.88 (d, J = 16.0 Hz, 1H), 2.46 (s, 3H), 1.55 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz): δ 145.41, 141.24, 139.56, 137.50, 133.54, 133.46, 130.47, 129.93, 129.12, 129.06, 128.99, 128.78, 128.08, 126.95, 126.27, 114.28, 110.08, 66.89, 59.43, 43.10, 29.07, 28.77, 21.83; ESI-MS m/z: 497.2 [M+H]⁺; HRMS (DART Positive) m/z calcd for C₂₉H₂₉N₄O₂S [M+H]⁺ 497.2006, found 497.2005.

Following the general procedure for 6d, the reaction of 5d (95.1 mg, 0.3 mmol), DDQ (204.3 mg, 0.9 mmol), AgOTf (11.6 mg, 15 mol%) and tBuNC (134 μL, 1.2 mmol) in PhCl (4.5 mL) at 80 °C for 3 h afforded the desired product 6d as a white solid (135.3 mg, 99%). M.p. 177-178 °C; IR (KBr, cm⁻¹): 2979.7, 1936.6, 2249.7, 2219.1, 1644.6, 1607.7, 1503.1, 1338.5, 1279.0, 1203.3; ¹H NMR (CDCl₃, 500 MHz): δ 7.88 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.2 Hz, 1H), 6.90 (dd, J = 8.5, 2.6 Hz, 1H), 6.77 (d, J = 2.6 Hz, 1H), 4.18-4.11 (m, 1H), 3.76 (s, 3H), 3.24-3.14 (m, 1H), 3.07-2.99 (m, 1H), 2.80-2.72 (m, 1H), 2.45 (s, 3H), 1.54 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz): δ 159.02, 145.37, 137.54, 133.52, 131.03, 129.91, 129.23, 129.07, 126.67, 117.09, 114.22, 111.85, 110.02, 66.79, 59.39, 55.53, 43.33, 29.06, 28.22, 21.84; ESI-MS m/z: 451.2 [M+H]⁺; HRMS (DART Positive) m/z calcd for C₂₄H₂₇N₄O₃S [M+H]⁺ 451.1798, found 451.1798.

Following the general procedure for 6e, the reaction of 5e (91.6 mg, 0.3 mmol), DDQ (204.3 mg, 0.9 mmol), AgOTf (11.6 mg, 15 mol%) and tBuNC (134 μL, 1.2 mmol) in PhCl (4.5 mL) at 80 °C for 3 h afforded the desired product 6e as a white solid (55.9 mg, 43%). M.p. 125-128 °C; IR (KBr, cm⁻¹): 2982.3, 2925.8, 2865.2, 2219.7, 1918.0, 1645.6, 1501.2, 1350.4, 1276.6, 1200.8; ¹H NMR (CDCl₃, 500 MHz): δ 7.87 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.2 Hz, 1H), 6.77 (d, J = 2.6 Hz, 1H), 4.18-4.11 (m, 1H), 3.76 (s, 3H), 3.24-3.14 (m, 1H), 3.07-2.99 (m, 1H), 2.80-2.72 (m, 1H), 2.45 (s, 3H), 1.54 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz): δ 159.02, 145.37, 137.54, 133.52, 131.03, 129.91, 129.23, 129.07, 126.67, 117.09, 114.22, 111.85, 110.02, 66.79, 59.39, 55.53, 43.33, 29.06, 28.22, 21.84; ESI-MS m/z: 451.2 [M+H]⁺; HRMS (DART Positive) m/z calcd for C₂₉H₂₉N₄O₂S [M+H]⁺ 451.1798, found 451.1798.
\(^{19}\)F NMR (CDCl\(_3\), 470 MHz): \(\delta\) -112.0 (m, Ar-F); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 161.73 (d, \(^{1}\)J\(_{CF}\) = 248.2 Hz), 145.56, 137.27, 133.30, 131.72 (d, \(^{3}\)J\(_{CF}\) = 7.7 Hz), 130.56 (d, \(^{4}\)J\(_{CF}\) = 2.8 Hz), 130.26 (d, \(^{2}\)J\(_{CF}\) = 7.4 Hz), 129.97, 129.08, 66.63, 59.65, 43.13, 28.89, 28.49, 21.85; ESI-MS m/z: 439.2 [M+H]; HRMS (DART Positive) m/z calcd for C\(_{23}\)H\(_{34}\)FN\(_4\)O\(_2\)S [M+H]\(^+\) 439.1599, found 439.1599.

(Z)-\(\text{N-(tert-Butyl)-7-chloro-1-cyano-2-tosyl-1,2,3,4-tetrahydroisoquinoline-1-carbimidoyl cyanide (6f)}\):
Following the general procedure for 6a, the reaction of 5f (96.5 mg, 0.3 mmol), DDQ (204.3 mg, 0.9 mmol), AgOTf (11.6 mg, 15 mol%) and \(^1\)BuNC (134 \(\mu\)L, 1.2 mmol) in PhCl (4.5 mL) at 80 \(^\circ\)C for 3 h afforded the desired product 6f as a white solid (62.4 mg, 46%). M.p. 137-139 \(^\circ\)C; IR (KBr, cm\(^{-1}\)): 2982.5, 2927.9, 2218.4, 1922.3, 1643.8, 1485.1, 1348.8, 1164.7; \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 7.87 (d, \(J\) = 8.2 Hz, 2H), 7.39 (d, \(J\) = 8.1 Hz, 2H), 7.32 (dd, \(J\) = 8.1, 1.9 Hz, 1H), 7.29 (d, 1.9 Hz, 1H), 7.18 (d, \(J\) = 8.2 Hz, 1H), 4.22-4.13 (m, 1H), 3.29-3.17 (m, 1H), 3.07-2.97 (m, 1H), 2.86-2.76 (m, 1H), 2.45 (s, 3H), 1.54 (s, 9H); \(^1\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 145.60, 137.21, 133.80, 133.28, 133.22, 131.32, 130.39, 130.32, 129.99, 129.10, 127.84, 113.82, 109.87, 66.47, 59.68, 42.93, 28.98, 28.63, 21.86; ESI-MS m/z (%): 455.1 [M\(^+\)\(^{(35)Cl}\)]\(^+\) (100), 457.1 [M\(^+\)\(^{(37)Cl}\)]\(^+\) (36); HRMS (DART Positive) m/z calcd for C\(_{23}\)H\(_{24}\)ClN\(_4\)O\(_2\)S [M+H]\(^+\) 455.1303, found 455.1301.

(Z)-\(\text{7-bromo-N-(tert-butyl)-1-cyano-2-tosyl-1,2,3,4-tetrahydroisoquinoline-1-carbimidoyl cyanide (6g)}\):
Following the general procedure for 6a, the reaction of 5g (109.9 mg, 0.3 mmol), DDQ (204.3 mg, 0.9 mmol), AgOTf (11.6 mg, 15 mol%) and \(^1\)BuNC (134 \(\mu\)L, 1.2 mmol) in PhCl (4.5 mL) at 80 \(^\circ\)C for 3 h afforded the desired product 6g as a white solid (60.2 mg, 40%). M.p. 158-160 \(^\circ\)C; IR (KBr, cm\(^{-1}\)): 2977.0, 2932.9, 2245.6, 2220.7, 1925.7, 1645.9, 1593.0, 1483.3, 1338.5, 1209.5; \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 7.87 (d, \(J\) = 8.2 Hz, 2H), 7.39 (d, \(J\) = 8.1 Hz, 2H), 7.32 (dd, \(J\) = 8.1, 1.9 Hz, 1H), 7.29 (d, 1.9 Hz, 1H), 7.18 (d, \(J\) = 8.2 Hz, 1H), 4.22-4.13 (m, 1H), 3.29-3.17 (m, 1H), 3.07-2.97 (m, 1H), 2.86-2.76 (m, 1H), 2.45 (s, 3H), 1.54 (s, 9H); \(^1\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 145.60, 133.80, 133.28, 133.22, 131.32, 130.39, 130.32, 129.99, 129.10, 127.84, 113.82, 109.87, 66.47, 59.68, 42.93, 28.98, 28.63, 21.86; ESI-MS m/z (%): 455.1 [M\(^+\)\(^{(35)Br}\)]\(^+\) (100), 457.1 [M\(^+\)\(^{(37)Br}\)]\(^+\) (36); HRMS (DART Positive) m/z calcd for C\(_{23}\)H\(_{24}\)BrN\(_4\)O\(_2\)S [M+H]\(^+\) 455.1303, found 455.1301.
(Z)-N-(tert-Butyl)-1-cyano-2-tosyl-7-((trimethylsilyl)ethynyl)-1,2,3,4-tetrahydroisoquinoline-1-carbimidoyl cyanide (6h):

Following the general procedure for 6a, the reaction of 5h (115.1 mg, 0.3 mmol), DDQ (204.3 mg, 0.9 mmol), AgOTf (11.6 mg, 15 mol%) and tBuNC (134 μL, 1.2 mmol) in PhCl (4.5 mL) at 80 °C for 4 h afforded the desired product 6h as a white solid (86.2 mg, 57%). M.p. 185-187 °C; IR (KBr, cm⁻¹): 2969, 2878, 2156, 1648, 1598, 1494, 1358, 1169, 852; ¹H NMR (CDCl₃, 500 MHz): δ 7.87 (d, J = 8.4 Hz, 2H), 7.42-7.35 (m, 4H), 7.16 (d, J = 8.0 Hz, 1H), 4.20-4.12 (m, 1H), 3.30-3.20 (m, 1H), 3.09-3.00 (m, 1H), 2.86-2.78 (m, 1H), 2.45 (s, 3H), 1.54 (s, 9H), 0.24 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz): δ 145.50, 137.15, 134.88, 133.34, 132.99, 131.52, 129.97, 129.96, 129.07, 128.86, 123.32, 114.01, 109.92, 103.23, 96.19, 66.50, 59.60, 42.86, 28.98, 28.95, 21.84, -0.07; ESI-MS m/z: 517.2 [M+H]⁺; HRMS (DART Positive) m/z calcd for C₂₈H₃₃N₄O₂S [M+H]⁺ 517.2086, found 517.2086.

(Z)-N-(tert-Butyl)-1-cyano-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-tosyl-1,2,3,4-tetrahydroisoquinoline-1-carbimidoyl cyanide (6i):

Following the general procedure for 6a, the reaction of 5i (124.0 mg, 0.3 mmol), DDQ (204.3 mg, 0.9 mmol), AgOTf (11.6 mg, 15 mol%) and tBuNC (134 μL, 1.2 mmol) in PhCl (4.5 mL) at 80 °C for 3 h afforded the desired product 6i as a white solid (81.9 mg, 50%). M.p. 240-242 °C; IR (KBr, cm⁻¹): 2983.4, 2934.5, 2873.8, 2224.2, 1915.5, 1736.4, 1645.3, 1606.0, 1334.9, 1212.4; ¹H NMR (CDCl₃, 500 MHz): δ 7.89 (d, J = 8.2 Hz, 2H), 7.74 (s, 1H), 7.72 (dd, J = 7.6, 0.8 Hz, 1H), 7.38 (d, J = 8.1 Hz, 2H), 7.21 (d, J = 7.6 Hz, 1H), 4.16-4.09 (m, 1H), 3.31-3.21 (m, 1H), 3.14-3.06 (m, 1H), 2.88-2.80 (m, 1H), 2.45 (s, 3H), 1.54 (s, 9H), 1.33 (s, 6H), 1.29 (s, 6H); ¹³C NMR (CDCl₃, 125 MHz): δ 145.40, 137.38, 137.14, 135.69, 134.90, 133.46, 129.97, 129.33, 129.12, 128.01, 114.01, 109.92, 103.23, 96.19, 66.50, 59.60, 42.86, 28.98, 28.95, 21.85; ESI-MS m/z: 547.3 [M+H]⁺; HRMS (DART Positive) m/z calcd for C₂₉H₃₆BN₂O₂S [M+H]⁺ 546.2584, found 546.2579.

(Z)-N-(tert-Butyl)-1-cyano-5-methyl-2-tosyl-1,2,3,4-tetrahydroisoquinoline-1-carbimidoyl cyanide (6j):

Following the general procedure for 6a, the reaction of 5j (90.4 mg, 0.3 mmol), DDQ (204.3 mg,
0.9 mmol), AgOTf (11.6 mg, 15 mol%) and tBuNC (134 μL, 1.2 mmol) in PhCl (4.5 mL) at 80 °C for 3 h afforded the desired product 6j as a white solid (97.1 mg, 74%). M.p. 197-199 °C; IR (KBr, cm⁻¹): 2973.7, 2862.5, 2407.4, 2226.6, 1916.3, 1649.8, 1595.4, 1466.4, 1411.3; ¹H NMR (CDCl₃, 500 MHz): δ 7.87 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.3 Hz, 2H), 7.24-7.18 (m, 2H), 7.16-7.10 (m, 1H), 4.27-4.16 (m, 1H), 3.10-3.00 (m, 2H), 2.86-2.76 (m, 1H), 2.45 (s, 3H), 2.27 (s, 3H), 1.53 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz): δ 145.38, 137.69, 137.45, 133.38, 131.25, 129.90, 129.10, 128.58, 127.50, 125.50, 114.18, 110.01, 67.05, 59.31, 42.81, 28.97, 26.43, 21.84, 19.39; ESI-MS m/z: 435.2 [M+H]⁺; HRMS (DART Positive) m/z calcd for C₂₄H₂₇N₂O₂S [M+H]⁺ 435.1849, found 435.1848.

(Z)-N-(tert-Butyl)-1-cyano-6,7-dimethoxy-2-tosyl-1,2,3,4-tetrahydroisoquinoline-1-carbimidoyl cyanide (6k):

Following the general procedure for 6a, the reaction of 5k (104.2 mg, 0.3 mmol), DDQ (204.3 mg, 0.9 mmol), AgOTf (11.6 mg, 15 mol%) and tBuNC (134 μL, 1.2 mmol) in PhCl (4.5 mL) at 80 °C for 3 h afforded the desired product 6k as a white solid (142.6 mg, 99%). M.p. 194-196 °C; IR (KBr, cm⁻¹): 2977.3, 2936.6, 2250.9, 1658.9, 1453.6, 1269.3; ¹H NMR (CDCl₃, 500 MHz): δ 7.88 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.2 Hz, 2H), 6.68 (s, 1H), 6.63 (s, 1H), 4.17-4.10 (m, 1H), 3.88 (s, 3H), 3.81 (s, 3H), 3.26-3.16 (m, 1H), 3.08-3.00 (m, 1H), 2.76-2.68 (m, 1H), 2.45 (s, 3H), 1.52 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz): δ 150.42, 148.86, 145.37, 137.37, 133.52, 129.91, 129.08, 119.41, 114.39, 111.60, 110.07, 109.44, 66.44, 59.27, 56.13, 56.09, 43.08, 29.12, 28.64, 21.84; ESI-MS m/z: 481.2 [M+H]⁺; HRMS (DART Positive) m/z calcd for C₂₅H₂ₙN₂O₄S [M+H]⁺ 481.1904, found 481.1901.

(Z)-N-(tert-Butyl)-5-cyano-6-tosyl-5,6,7,8-tetrahydro[1,3]dioxolo[4,5-g]isoquinoline-5-carbimidoyl cyanide (6l):

Following the general procedure for 6a, the reaction of 5l (99.4 mg, 0.3 mmol), DDQ (204.3 mg, 0.9 mmol), AgOTf (11.6 mg, 15 mol%) and tBuNC (134 μL, 1.2 mmol) in PhCl (4.5 mL) at 80 °C for 3 h afforded the desired product 6l as a white solid (120.0 mg, 86%). M.p. 189-191 °C; IR (KBr, cm⁻¹): 2979.2, 2915.4, 2874.6, 2249.8, 2221.3, 1646.6, 1483.2, 1341.1, 1288.7; ¹H NMR (CDCl₃, 500 MHz): δ 7.86 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.2 Hz, 2H), 6.68 (s, 1H), 6.61 (s, 1H), 5.99 (dd, J = 5.9, 1.2 Hz, 2H), 4.17-4.09 (m, 1H), 4.24-4.13 (m, 1H), 3.05-2.96 (m, 1H), 2.74-2.66 (m, 1H), 2.44 (s, 3H), 1.52 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz): δ 149.25, 147.82, 145.38, 137.50, 133.44, 129.89, 129.34, 129.05, 120.85, 114.20, 110.05, 109.09, 106.83, 102.05, 66.79, 59.38, 43.06, 29.10, 29.02, 21.83; ESI-MS m/z: 465.2 [M+H]⁺; HRMS (DART Positive) m/z calcd for C₂₄H₂ₙN₂O₄S [M+H]⁺ 465.1591, found 465.1590.
(Z)-N-(tert-Butyl)-4-cyano-5-tosyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-4-carbimidoyl cyanide (6m):
Following the general procedure for 6a, the reaction of 5m (88.2 mg, 0.3 mmol), DDQ (204.3 mg, 0.9 mmol), AgOTf (11.6 mg, 15 mol%) and tBuNC (134 μL, 1.2 mmol) in PhCl (4.5 mL) at 80 °C for 3 h afforded the desired product 6m as a white solid (56.3 mg, 44%). M.p. 156-158 °C; IR (KBr, cm⁻¹): 2978.6, 2930.4, 2875.7, 2223.4, 1921.7, 1645.6, 1595.3, 1398.7, 1337.5, 1162.0; ¹H NMR (CDCl₃, 500 MHz): δ 7.88 (d, J = 8.0 Hz, 2H), 7.38 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 5.3 Hz, 1H), 6.77 (d, J = 5.4 Hz, 1H), 4.26-4.17 (m, 1H), 3.25-3.16 (m, 1H), 3.15-3.07 (m, 1H), 2.93 (d, J = 15.8 Hz, 1H), 2.45 (s, 3H), 1.52 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz): δ 145.50, 138.04, 136.66, 133.34, 129.95, 129.06, 126.81, 126.07, 124.28, 113.29, 109.79, 65.75, 59.41, 43.81, 29.03, 25.06, 21.83; ESI-MS m/z: 427.1 [M+H]+; HRMS (DART Positive) m/z calcd for C₂₁H₂₃N₄O₂S₂ [M+H]+ 427.1257, found 427.1256.

(Z)-N-(tert-Butyl)-4-cyano-3-tosyl-1,2,3,4-tetrahydrobenzo[f]isoquinoline-4-carbimidoyl cyanide (6n):
Following the general procedure for 6a, the reaction of 5n (101.2 mg, 0.3 mmol), DDQ (204.3 mg, 0.9 mmol), AgOTf (11.6 mg, 15 mol%) and tBuNC (134 μL, 1.2 mmol) in PhCl (4.5 mL) at 80 °C for 3 h afforded the desired product 6n as a white solid (111.3 mg, 79%). M.p. 212-214 °C; IR (KBr, cm⁻¹): 2977.3, 2932.9, 2226.7, 1915.8, 1643.0, 1353.3, 1200.9, 1164.5; ¹H NMR (CDCl₃, 500 MHz): δ 7.97 (d, J = 7.7 Hz, 1H), 7.92 (d, J = 8.2 Hz, 2H), 7.86 (d, J = 8.9 Hz, 1H), 7.80 (d, J = 8.9 Hz, 1H), 7.65-7.56 (m, 2H), 7.40 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 8.9 Hz, 1H), 4.41-4.32 (m, 1H), 3.55-3.35 (m, 2H), 3.21-3.10 (m, 1H), 2.46 (s, 3H), 1.54 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz): δ 145.50, 137.33, 133.34, 129.95, 129.06, 126.81, 126.07, 124.28, 113.29, 109.79, 65.75, 59.41, 43.81, 29.03, 25.06, 21.83; ESI-MS m/z: 471.2 [M+H]+; HRMS (DART Positive) m/z calcd for C₂₇H₂₉N₂O₂S₂ [M+H]+ 471.1849, found 471.1848.

(Z)-N-(tert-Butyl)-1'-cyano-2'-tosyl-2',3'-dihydro-1'H-spiro[cyclopropane-1,4'-isoquinoline]-1'-carbimidoyl cyanide (2o):
Following the general procedure for 6a, the reaction of 5o (94.0 mg, 0.3 mmol), DDQ (204.3
mg, 0.9 mmol), AgOTf (11.6 mg, 15 mol%) and tBuNC (134 μL, 1.2 mmol) in PhCl (4.5 mL) at 80 °C for 3 h afforded the desired product 6o as a white solid (108.3 mg, 81%). M.p. 192-195 °C; IR (KBr, cm⁻¹): 2980.4, 2228.0, 1921.0, 1645.3, 1489.5, 1334.7, 1164.6; ¹H NMR (CDCl₃, 500 MHz): δ 7.85 (d, J = 8.3 Hz, 2H), 7.37 (d, J = 8.2 Hz, 2H), 7.36-7.30 (m, 1H), 7.30-7.23 (m, 2H), 6.87 (d, J = 7.7 Hz, 1H), 3.49 (dd, J = 12.4, 0.8 Hz, 1H), 3.26 (d, J = 12.4 Hz, 1H), 2.45 (s, 3H), 1.53 (s, 9H), 1.47-1.38 (m, 1H), 1.18-1.04 (m, 1H), 1.00-0.90 (m, 2H); ¹³C NMR (CDCl₃, 125 MHz): δ 145.35, 139.77, 137.59, 133.50, 130.32, 129.88, 129.07, 129.02, 127.77, 127.06, 122.91, 114.14, 109.93, 67.74, 59.31, 51.54, 28.98, 21.84, 20.17, 19.78, 11.92; ESI-MS m/z: 447.2 [M+H]⁺; HRMS (DART Positive) m/z calcd for C₂₅H₂₇N₄O₂S [M+H]⁺ 447.1849, found 447.1848.

(Z)-N-(tert-Butyl)-1'-cyano-2'-tosyl-2',3'-dihydro-1'H-spirocyclobutane-1,4'-isoquinoline-1'-carbimidoyl cyanide (6p):
Following the general procedure for 6a, the reaction of 5p (98.0 mg, 0.3 mmol), DDQ (204.3 mg, 0.9 mmol), AgOTf (11.6 mg, 15 mol%) and tBuNC (134 μL, 1.2 mmol) in PhCl (4.5 mL) at 80 °C for 3 h afforded the desired product 6p as a white solid (92.6 mg, 67%). M.p. 158-161 °C; IR (KBr, cm⁻¹): 2979.4, 2936.5, 2863.9, 2220.7, 1692.2, 1648.5, 1482.7, 1356.2, 1165.5; ¹H NMR (CDCl₃, 500 MHz): δ 7.89 (d, J = 8.2 Hz, 2H), 7.66 (d, J = 7.9 Hz, 1H), 7.45 (t, J = 7.2 Hz, 1H), 7.40 (d, J = 8.2 Hz, 2H), 7.29 (t, J = 7.4 Hz, 1H), 7.22 (d, J = 7.9 Hz, 1H), 4.17 (d, J = 12.1 Hz, 1H), 3.03 (d, J = 12.1 Hz, 1H), 2.70-2.60 (m, 1H), 2.50-2.39 (m, 4H), 2.25-2.03 (m, 3H), 1.95-1.85 (m, 1H), 1.53 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz): δ 145.44, 142.52, 137.54, 133.34, 130.51, 129.89, 129.23, 127.67, 127.52, 127.48, 126.78, 114.01, 109.89, 67.58, 59.31, 51.82, 41.09, 34.82, 28.98, 28.85, 21.87, 15.17; ESI-MS m/z: 461.2 [M+H]⁺; HRMS (DART Positive) m/z calcd for C₂₆H₂₉N₄O₂S [M+H]⁺ 461.2006, found 461.2006.

(Z)-N-(tert-Butyl)-1'-cyano-2'-tosyl-2',3'-dihydro-1'H-spirocyclopentane-1,4'-isoquinoline-1'-carbimidoyl cyanide (6q):
Following the general procedure for 6a, the reaction of 5q (102.5 mg, 0.3 mmol), DDQ (204.3 mg, 0.9 mmol), AgOTf (11.6 mg, 15 mol%) and tBuNC (134 μL, 1.2 mmol) in PhCl (4.5 mL) at 80 °C for 3 h afforded the desired product 6q as a white solid (77.5 mg, 54%). M.p. 234-236 °C; IR (KBr, cm⁻¹): 2972.2, 2869.4, 2226.5, 1934.9, 1647.5, 1592.7, 1484.9, 1453.4, 1339.0, 1169.6; ¹H NMR (acetone-d₆, 500 MHz): δ 7.94 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 7.9 Hz, 1H), 7.52 (d, J = 8.2 Hz, 2H), 7.49 (t, J = 7.4 Hz, 1H), 7.38 (t, J = 7.3 Hz, 1H), 7.25 (d, J = 8.0 Hz, 1H), 3.92 (d, J = 12.6 Hz, 1H), 2.95 (d, J = 12.6 Hz, 1H), 2.47 (s, 3H), 2.31-2.24 (m, 1H),
2.24-2.14 (m, 1H), 2.00-1.78 (m, 3H), 1.75-1.60 (m, 3H), 1.55 (s, 9H); $^{13}$C NMR (acetone-$d_6$, 125 MHz): $\delta$ 146.59, 145.77, 138.75, 134.35, 131.56, 130.87, 130.22, 128.95, 128.42, 128.15, 114.55, 111.17, 68.45, 59.80, 52.34, 47.37, 41.77, 38.21, 29.12, 26.79, 25.99, 21.72; ESI-MS m/z: 475.2 [M+H]$^+$; HRMS (DART Positive) m/z calcd for C$_{27}$H$_{31}$N$_4$O$_2$S [M+H]$^+$ 475.2162, found 475.2158.

(Z)-N-(tert-Butyl)-6-cyano-5-tosyl-1,2,3,4,4a,5,6,10b-octahydrophenanthridine-6-carbimido cyanide (6r):

Following the general procedure for 6a, the reaction of 5r (102.5 mg, 0.3 mmol), DDQ (204.3 mg, 0.9 mmol), AgOTf (11.6 mg, 15 mol%) and tBuNC (134 μL, 1.2 mmol) in PhCl (4.5 mL) at 80 °C for 3 h afforded the desired product 6r as a white solid (101.1 mg, 71%, d.r. = 1:1 (determined by crude $^1$H NMR)). One of the isomers can be obtained through recrystallization in ethyl acetate and hexane. One isomer: M.p. 235-237 oC; IR (KBr, cm$^{-1}$): 2933.3, 2863.6, 2216.7, 1940.8, 1645.8, 1598.1, 1454.4; $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 8.02 (d, $J$ = 8.3 Hz, 2H), 7.47 (t, $J$ = 7.4 Hz, 1H), 7.41 (d, $J$ = 7.6 Hz, 1H), 7.37 (d, $J$ = 8.2 Hz, 2H), 7.34 (t, $J$ = 7.6 Hz, 1H), 7.21 (d, $J$ = 7.9 Hz, 1H), 4.05 (dt, $J$ = 12.2, 4.2 Hz, 1H), 3.12 (s, 1H), 2.51 (d, $J$=14.6 Hz, 1H), 2.45 (s, 3H), 1.96 (d, $J$ = 13.1 Hz, 1H), 1.79-1.66 (m, 2H), 1.52-1.47 (m, 1H), 1.43-1.31 (m, 2H), 1.25-1.12 (m, 1H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 144.97, 136.87, 136.30, 135.38, 130.56, 129.85, 129.59, 128.78, 127.92, 127.82, 126.26, 115.16, 110.51, 64.43, 57.80, 30.68, 29.15, 27.06, 25.95, 21.81, 19.32; ESI-MS m/z: 475.2 [M+H]$^+$; HRMS (DART Positive) m/z calcd for C$_{27}$H$_{31}$N$_4$O$_2$S [M+H]$^+$ 475.2162, found 475.2158.

(Z)-N-(tert-Butyl)-1-cyano-2-(4-methoxybenzoyl)-1,2,3,4-tetrahydroisoquinoline-1-carbimido cyanide (6s):

Following the general procedure for 6a, the reaction of 5s (80.0 mg, 0.3 mmol), DDQ (204.3 mg, 0.9 mmol), AgOTf (11.6 mg, 15 mol%) and tBuNC (134 μL, 1.2 mmol) in PhCl (4.5 mL) at 80 °C for 3 h afforded the desired product 6s as a white solid (75.0 mg, 62%). M.p. 158-160 oC; IR (KBr, cm$^{-1}$): 2979.6, 2937.5, 2220.7, 1646.4, 1605.2, 1508.6, 1242.9, 1369.9, 1250.1, 1174.6; $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.66-7.58 (m, 3H), 7.43-7.34 (m, 2H), 7.31-7.26 (m, 1H), 6.99 (d, $J$ = 8.7 Hz, 2H), 4.31-4.24 (m, 1H), 3.87 (s, 3H), 3.53-3.31 (m, 2H), 2.90-2.80 (m, 1H), 1.44 (s, 9H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 172.94, 162.23, 136.87, 136.30, 135.38, 130.56, 129.85, 129.59, 128.78, 127.92, 127.82, 126.26, 115.16, 110.51, 64.43, 59.78, 57.80, 36.53, 30.68, 29.15, 27.06, 25.95, 21.81, 19.32; ESI-MS m/z: 401.2 [M+H]$^+$; HRMS (DART Positive) m/z calcd for C$_{24}$H$_{25}$N$_4$O$_2$ [M+H]$^+$ 401.1972, found 401.1971.
(Z)-N-(tert-Butyl)-1-cyano-2-(4-nitrobenzoyl)-1,2,3,4-tetrahydroisoquinoline-1-carbimido
yl cyanide (6t):
Following the general procedure for 6a, the reaction of 5t (85.0 mg, 0.3 mmol), DDQ (204.3 mg, 0.9 mmol), AgOTf (11.6 mg, 15 mol%) and tBuNC (134 μL, 1.2 mmol) in PhCl (4.5 mL) at 80 °C for 3 h afforded the desired product 6t as a white solid (59.3 mg, 48%). M.p. 198-200 °C; IR (KBr, cm⁻¹): 2975.0, 2930.6, 2245.6, 2214.1, 1765.4, 1658.2, 1523.5, 1347.9; ¹H NMR (CDCl₃, 500 MHz): δ 8.37 (d, J = 8.6 Hz, 2H), 7.81 (d, J = 8.7 Hz, 2H), 7.66-7.60 (m, 1H), 7.44-7.37 (m, 2H), 7.32-7.27 (m, 1H), 4.07-4.00 (m, 1H), 3.55-3.46 (m, 1H), 3.39-3.28 (m, 1H), 2.91-2.82 (m, 1H), 1.44 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz): δ 170.70, 149.41, 140.13, 136.36, 134.91, 130.14, 129.78, 128.50, 128.42, 127.59, 124.45, 116.21, 109.98, 65.03, 59.67, 44.93, 29.05, 29.00; ESI-MS m/z: 416.2 [M+H]⁺; HRMS (DART Positive) m/z calcd for C₂₃H₂₂N₅O₃ [M+H]⁺ 416.1717, found 416.1717.

(Z)-N-(tert-buty1)-1-cyano-2-(methylsulfonyl)-1,2,3,4-tetrahydroisoquinoline-1-carbimido
yl cyanide (6u) and (1Z,1Z)-N,N′-di-tert-buty1-2-(methylsulfonyl)-3,4-dihydroisoquinoline-
1,1(2H)-bis(carbimidoyl) dicyanide (6u’):
To a test tube, 5u (63.4 mg, 0.3 mmol), tBuNC (136.0 μL, 1.2 mmol), AgOTf (11.6 mg, 0.045 mmol), DDQ (204.3 mg, 0.9 mmol) and dry chlorobenzene (3.0 mL) were added in a glove box. The mixture was stirred at 80 °C for 3 h under a nitrogen atmosphere as monitored by TLC. Upon completion of the reaction, the solution was cooled down to room temperature. After removal of the solvent, the residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 6 : 1 to 3 : 1) to give the product 6u (59.1 mg, 57 %) and 6u’ (20.5 mg, 16 %), respectively, as a yellow solid.

6u: M.p. 161-162 °C; IR (KBr, cm⁻¹): 3432.8, 2979.4, 2870.9, 2220.7, 1644.7, 1351.0, 1165.1, 964.0, 767.7, 495.3; ¹H NMR (CDCl₃, 500 MHz): δ 7.40-7.34 (m, 3H), 7.28 (d, J = 7.3 Hz, 1H), 4.22-4.18 (m, 1H), 3.40-3.33 (m, 1H), 3.27-3.22 (m, 1H), 3.20 (s, 3H), 2.95-2.91 (m, 1H), 1.44 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz): δ 137.56, 134.79, 130.13, 130.07, 128.19, 127.95, 127.72, 115.73, 109.64, 66.96, 59.32, 42.75, 37.56, 29.21, 28.87; ESI-MS m/z: 345.14 [M⁺H⁺]; HRMS (DART) m/z calcd for C₁₇H₁₉N₄O₂S [M⁺H⁺] 345.1380, found 345.1380.

6u’: M.p. 147-148 °C; IR (KBr, cm⁻¹): 3433.7, 2975.3, 2216.6, 1643.5, 1340.1, 1152.9, 1075.5, 777.0; ¹H NMR (CDCl₃, 500 MHz): δ 7.44-7.42 (m, 1H), 7.38-7.33 (m, 2H), 7.26-7.24 (m, 1H), 3.61 (t, J = 6.0 Hz, 2H), 3.14 (s, 3H), 3.02 (t, J =6.0 Hz, 2H), 1.46 (s, 18H); ¹³C NMR (CDCl₃, 125 MHz): δ 138.23, 135.59, 129.97, 129.52, 129.25, 129.13, 127.00, 111.52, 76.45, 59.44,
Synthesis and Characterization of 5,6-Dihydrophenanthridines, Related to Figure 5

8-Methyl-5-tosyl-5,6-dihydrophenanthidine (7b):
To a mixture of 2-bromoaniline (1.72 g, 10 mmol), p-tolylboronic acid (1.43 g, 10.5 mmol), Pd(PPh₃)₂Cl₂ (351 mg, 0.5 mmol), K₂CO₃ (5.53 g, 40 mmol) was added water (10 mL) and DMF (40 mL), then reduced pressure and backfilled with N₂. After stirred at 80 °C for 2 h, the mixture was cooled down to room temperature and filtered on diatomite. The filtrate was washed with water (2 x 15 mL) and brine (20 mL), and dried over Na₂SO₄. The resulting solution was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 50 : 1) to give pure 7b' (1.53 g, 83%). To a solution of 7b' (1.53 g, 8.34 mmol) in pyridine (15 mL) was added TsCl (1.75 g, 9.17 mmol) portionwise. After stirred at 60 °C for 12 h, pyridine was removed under vacuum. To this residue was added dichloromethane (20 mL) and 2 M HCl (20 mL). After stirred for 10 min, the mixture was extracted by dichloromethane (2 x 15 mL). The combined organic phase was washed with saturated Na₂CO₃ solution (15 mL) and brine (15 mL), and then dried over Na₂SO₄. The resulting solution was concentrated under reduced pressure to give crude 7b'' (2.39 g, 85%) without further purification.

To a mixture of 7b'' (1.687 g, 5 mmol) and (HCHO)ₙ (450 mg, 15 mmol) was added H₂SO₄ : AcOH = 1 : 4 (25 mL). After stirred at room temperature for 5 h, the reaction was quenched with water (50 mL), then filtered and washed with water for several times. The residue was collected and purified by flash column chromatography on basic alumina (petroleum ether/ethyl acetate/dichloromethane = 20 : 1 : 2) to give 7b (1.42 g, 81%) as a white solid. M.p. 150-152 °C; IR (KBr, cm⁻¹): 3038.3, 2989.5, 2908.9, 1915.7, 1591.6, 1476.7, 1341.7, 1200.2, 1158.1; ¹H NMR (CDCl₃, 500 MHz): δ 7.77 (dd, J = 7.9, 1.2 Hz, 1H), 7.54 (dd, J = 7.5, 1.4 Hz, 1H), 7.36-7.29 (m, 2H), 7.11 (d, J = 7.8 Hz, 2H), 6.96 (d, J = 8.3 Hz, 2H), 6.90 (d, J = 7.9 Hz, 1H), 6.87 (s, 1H), 6.69 (d, J = 8.1 Hz, 2H), 4.79 (s, 2H), 2.30 (s, 3H), 2.15 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz): δ 142.95, 137.92, 135.86, 134.88, 131.37, 130.85, 128.42, 128.37, 128.31, 128.18, 127.99, 127.47, 127.23, 126.80, 123.58, 123.02, 49.96, 21.38, 21.15; EI-MS m/z (%): 194.1 (100), 349.1 (17) [M⁺]; HRMS (EI) m/z calcd for C₂₁H₁₉NO₂S [M⁺] 349.1136, found 349.1140.
8-Bromo-5-tosyl-5,6-dihydrophenanthridine (7c):
To a mixture of 2-iodoaniline (2.2 g, 10 mmol), (4-bromophenyl)boronic acid (2.04 g, 10.2 mmol), Pd(PPh₃)₂Cl₂ (140.4 mg, 0.2 mmol), K₂CO₃ (5.52 g, 40 mmol) was added water (10 mL) and DMF (40 mL), then reduced pressure and backfilled with N₂. After stirred at 80 °C for 2 h, the mixture was cooled down to room temperature and filtered on diatomite. The filtrate was washed with water (2 × 15 mL) and brine (20 mL), and dried over Na₂SO₄. The resulting solution was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 50 : 1) to give pure 7c′ (2.16 g, 87%). To a solution of 7c′ (2.16 g, 8.7 mmol) in pyridine (15 mL) was added TsCl (2.00 g, 10.44 mmol) portionwise. After stirred at 60 °C for 9 h, pyridine was removed under vacuum. To this residue was added dichloromethane (20 mL) and 2M HCl (20 mL). After stirred for 10 min, the mixture was extracted by dichloromethane (2 × 15 mL). The combined organic phase was washed with saturated Na₂CO₃ solution (15 mL) and brine (15 mL), and then dried over Na₂SO₄. The resulting solution was concentrated under reduced pressure to give crude 7c'' (2.78 g, 80%) without further purification.

To a mixture of 7c'' (371.7 mg, 1 mmol) and (HCHO)ₙ (90 mg, 3 mmol) was added H₂SO₄/AcOH = 1 : 4 (10 mL). After stirred at room temperature for 24 h, the reaction was quenched with water (30 mL), and the mixture was extracted by dichloromethane (2 × 15 mL). The combined organic phase was washed with saturated Na₂CO₃ solution (15 mL) and brine (15 mL), and then dried over Na₂SO₄. The solvent was removed under vacuum, and the residue was purified by flash column chromatography on neutral alumina (petroleum ether/ethyl acetate/dichloromethane = 20 : 1 : 2) to give pure product 7c (159.3 mg, 38%) as a white solid.

M.p. 153-155 °C; IR (KBr, cm⁻¹): 3054.7, 2917.9, 1909.3, 1590.0, 1474.1, 1439.1, 1403.6, 1341.1; ¹H NMR (CDCl₃, 500 MHz): δ 7.78 (d, J = 7.9 Hz, 1H), 7.54 (d, J = 7.6 Hz, 1H), 7.21 (d, J = 8.2 Hz, 1H), 7.18 (s, 1H), 6.98 (d, J = 8.1 Hz, 2H), 6.76 (d, J = 8.0 Hz, 2H), 4.77 (s, 2H), 2.19 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz): δ 143.4, 136.0, 135.1, 133.2, 130.9, 130.7, 129.7, 129.2, 128.9, 128.4, 127.3, 127.2, 126.6, 126.9, 124.8, 124.6, 124.4, 123.8, 123.7, 121.9, 35.3, 24.3, 4.6; EI-MS m/z (%): 258.0 [M⁺], 413.0 (22) [M⁺]; HRMS (EI) m/z calcd for C₂₀H₁₆BrNO₂S [M⁺]: 413.0085, found 413.0080.
Phenyl-5-tosyl-5,6-dihydrophenanthridine (7d):
To a mixture of 7c (248.6 mg, 0.6 mmol), phenylboronic acid (88 mg, 0.72 mmol), K$_2$CO$_3$ (332 mg, 2.4 mmol), Pd(PPh$_3$)$_2$Cl$_2$ (21 mg, 0.03 mmol) were added water (0.6 mL) and DMF (2.4 mL). After stirred at 80 °C for 5 h under N$_2$, the reaction mixture was filtered, and the filter residue was washed with ethyl acetate. The resulting solution was concentrated under reduced pressure. The residue was purified by flash column chromatography on basic Al$_2$O$_3$ (petroleum ether/ethyl acetate = 10 : 1) to give product 7d (153.2 mg, 62%) as a white solid. M.p. 144-146 °C; IR (KBr, cm$^{-1}$): 3030.8, 2918.0, 1918.0, 1593.1, 1470.8, 1342.2, 1157.9, 1077.8; $^1$H NMR (CDCl$_3$, 500 MHz): δ 7.81 (d, $J$ = 7.5 Hz, 1H), 7.60 (d, $J$ = 7.2 Hz, 1H), 7.56-7.42 (m, 4H), 7.42-7.16 (m, 6H), 6.98 (d, $J$ = 7.6 Hz, 2H), 6.66 (d, $J$ = 7.5 Hz, 2H), 4.86 (s, 2H), 2.09 (s, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz): δ 143.09, 140.82, 140.31, 136.13, 134.73, 131.76, 130.45, 130.07, 129.53, 128.43, 128.43, 128.37, 127.77, 127.60, 127.22, 126.89, 126.27, 124.84, 123.78, 123.56, 50.05, 21.37; EI-MS m/z (%): 256.1 (100) [M–Ts]+, 301.1 (22) [M]+; HRMS (EI) m/z calcd for C$_{26}$H$_{21}$NO$_2$S [M]+ 411.1293, found 411.1289.

5-Tosyl-8-((trimethylsilyl)ethynyl)-5,6-dihydrophenanthridine (7e):
To a mixture of 7c (331.4 mg, 0.8 mmol), Pd(OAc)$_2$ (9.0 mg, 0.04 mmol), CuI (7.6 mg, 0.04 mmol) in a schlenk tube was added ethynyltrimethylsilane (340 μL, 2.4 mmol) and Et$_3$N (2.5 mL) under N$_2$. After stirred at 90 °C for 24 h, the reaction was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 10 : 1) to give 7e (196.4 mg, 57%) as a white solid. M.p. 162-164 °C; IR (KBr, cm$^{-1}$): 2958.2, 2142.1, 1597.0, 1466.2, 1434.4, 1240.9, 1160.0; $^1$H NMR (CDCl$_3$, 500 MHz): δ 7.78 (d, $J$ = 7.9 Hz, 1H), 7.54 (d, $J$ = 7.5 Hz, 1H), 7.38 (t, $J$ = 7.2 Hz, 1H), 7.32 (t, $J$ = 7.5 Hz, 1H), 7.22-7.10 (m, 3H), 6.97 (d, $J$ = 8.2 Hz, 2H), 6.74 (d, $J$ = 8.0 Hz, 2H), 4.78 (s, 2H), 2.17 (s, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz): δ 143.32, 136.26, 134.69, 131.38, 131.12, 131.08, 130.02, 129.53, 128.90, 128.59, 128.31, 127.58, 127.23, 124.00, 122.84, 122.69, 104.50, 95.78, 49.56, 21.43, 0.10; EI-MS m/z (%): 256.1 (100) [M–Ts]+, 431.1 (40) [M]+; HRMS (EI) m/z calcd for C$_{25}$H$_{25}$NO$_2$SSi [M]+ 431.1375, found 431.1372.
To a mixture of 2-bromo-5-methylaniline (930 mg, 5 mmol), \( \text{p-tolylboronic acid} \) (748 mg, 5.5 mmol), \( \text{Pd(PPh}_3\text{)Cl}_2 \) (70.1 mg, 0.1 mmol), \( \text{K}_2\text{CO}_3 \) (2.76 g, 20 mmol) was added water (10 mL) and DMF (40 mL), then reduced pressure and backfilled with \( \text{N}_2 \). After stirred at 80 °C for 2 h, the mixture was cooled down to room temperature and filtered on diatomite. The filtrate was washed with water (2 \( \times \) 15 mL) and brine (20 mL), and dried over \( \text{Na}_2\text{SO}_4 \). The resulting solution was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 50 : 1) to give \( 7f' \) (835.7 mg, 85%) . To a solution of \( 7f' \) (835.7 mg, 4.24 mmol) in pyridine (10 mL) was added \( \text{TsCl} \) (969 mg, 5.1 mmol) portionwise. After stirred at 60 °C for 12 h, pyridine was removed under vacuum. To this residue was added dichloromethane (20 mL) and 2 M HCl (20 mL). After stirred for 10 min, the mixture was extracted by dichloromethane (2 \( \times \) 15 mL). The combined organic phase was washed with saturated Na\(_2\)CO\(_3\) solution (15 mL) and brine (15 mL), and dried over Na\(_2\)SO\(_4\). The resulting solution was concentrated under reduced pressure to give crude \( 7f'' \) (1.32 g, 89%) without further purification.

To a mixture of \( 7f'' \) (351.5 mg, 1 mmol) and \( \text{(HCHO)}_n \) (90 mg, 3 mmol) was added \( \text{H}_2\text{SO}_4/\text{AcOH} = 1 : 10 \) (10 mL). After stirred at room temperature for 5 h, the reaction was quenched with water (20 mL), then filtered and washed with water for several times. The residue was collected and purified by flash column chromatography on neutral alumina (petroleum ether/ethyl acetate/dichloromethane = 20 : 1 : 2) to give pure product \( 7f \) (210.4 mg, 58%) as a white solid. M.p. 176-178 °C; IR (KBr, cm\(^{-1}\)): 3026.8, 2917.9, 2858.8, 1906.7, 1603.6, 1518.3, 1479.8, 1342.4, 1285.5, 1160.9; \(^1\text{H NMR (CDCl}_3, 500 MHz)\): \( \delta \) 7.59 (d, \( J = 0.5 \) Hz, 1H), 7.42 (d, \( J = 7.9 \) Hz, 1H), 7.12 (dd, \( J = 7.9, 1.1 \) Hz, 1H), 7.07 (d, \( J = 7.9 \) Hz, 1H), 6.97 (d, \( J = 8.3 \) Hz, 2H), 6.88 (d, \( J = 8.0 \) Hz, 1H), 6.84 (s, 1H), 6.70 (d, \( J = 7.9 \) Hz, 2H), 4.76 (d, 2H), 2.43 (s, 3H), 2.28 (s, 3H), 2.15 (s, 3H); \(^{13}\text{C NMR (CDCl}_3, 125 MHz)\): \( \delta \) 142.89, 138.13, 137.41, 135.76, 134.92, 131.00, 128.58, 128.56, 128.41, 128.33, 128.22, 128.12, 127.26, 126.75, 123.39, 122.71, 50.09, 21.47, 21.38, 21.12; EL-MS m/z (%): 208.1 (100), 363.1 (26) [M\(^+\)]; HRMS (EI) m/z calcd for C\(_{22}\)H\(_{21}\)NO\(_2\)S [M\(^+\)] 363.1293, found 363.1292.
3-Fluoro-8-methyl-5-tosyl-5,6-dihydrophenanthidine (7g):
To a mixture of 2-bromo-5-fluoroaniline (950 mg, 5 mmol), p-tolylboronic acid (1.02 g, 7.5 mmol), Pd(PPh₃)₂Cl₂ (175.5 mg, 0.25 mmol), K₂CO₃ (2.76 g, 20 mmol) was added water (5 mL) and DMF (20 mL), then reduced pressure and backfilled with N₂. After stirred at 80 °C for 2 h, the mixture was cooled down to room temperature and filtered on diatomite. The filtrate was washed with water (2 x 15 mL) and brine (20 mL), and dried over Na₂SO₄. The resulting solution was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 50 : 1) to give 7g' (977.3 mg, 97%). To a solution of 7g' (977.3 mg, 4.86 mmol) in pyridine (10 mL) was added TsCl (1.38 g, 7.29 mmol) portionwise. After stirred at 60 °C for 12 h, pyridine was removed under vacuum. To this residue was added dichloromethane (20 mL) and 2 M HCl (20 mL). After stirred for 10 min, the mixture was extracted by dichloromethane (2 x 15 mL). The combined organic phase was washed with saturated Na₂CO₃ solution (15 mL) and brine (15 mL), and dried over Na₂SO₄. The resulting solution was concentrated under reduced pressure to give crude 7g'' (1.43 g, 83%) without further purification.

To a mixture of 7g'' (351.5 mg, 1 mmol) and (HCHO)n (90 mg, 3 mmol) was added H₂SO₄/AcOH = 1 : 4 (10 mL). After stirred at room temperature for 12 h, the reaction was quenched with water (20 mL), then filtered and washed with water for several times. The residue was collected and purified by flash column chromatography on neutral alumina (petroleum ether/ethyl acetate/dichloromethane = 20 : 1 : 2) to give product 7g (286.7 mg, 78%) as a white solid. M.p. 152-153 °C; IR (KBr, cm⁻¹): 3034.3, 2916.6, 1918.5, 1603.4, 1481.5, 1334.2, 1279.1, 1160.0; ¹H NMR (CDCl₃, 500 MHz): δ 7.58-7.45 (m, 2H), 7.07 (d, J = 7.9 Hz, 1H), 7.05-6.97 (m, 3H), 6.91 (d, J = 8.0 Hz, 1H), 6.88 (s, 1H), 6.73 (d, J = 8.1 Hz, 2H), 4.79 (s, 2H), 2.30 (s, 3H), 2.18 (s, 3H); ¹⁹F NMR (CDCl₃, 470 MHz): δ -112.53 (m, Ar-F); ¹³C NMR (CDCl₃, 125 MHz): δ 161.90 (d, ¹J_C-F = 247.1 Hz), 143.27, 137.90, 137.27 (d, ³J_C-F = 11.0 Hz), 134.85, 130.81, 128.55, 128.51, 127.84, 127.24, 127.09 (d, ³J_C-F = 3.6 Hz), 126.83, 124.87 (d, ³J_C-F = 9.0 Hz), 122.81, 115.18 (d, ²J_C-F = 24.0 Hz), 114.76 (d, ²J_C-F = 21.6 Hz), 49.95, 21.44, 21.16; EI-MS m/z (%): 212.1 (100), 367.1 (25) [M⁺]; HRMS (El) m/z calcld for C₂₁H₁₈FNO₂S [M⁺] 367.1042, found 367.1034.
**3-Chloro-8-methyl-5-tosyl-5,6-dihydrophenanthridine (7h):**
To a mixture of 2-bromo-5-chloroaniline (1.03 g, 5 mmol), p-tolylboronic acid (1.02 g, 7.5 mmol), Pd(PPh₃)₂Cl₂ (175.5 mg, 0.25 mmol), K₂CO₃ (2.76 g, 20 mmol) was added water (5 mL) and DMF (20 mL), then reduced pressure and backfilled with N₂. After stirred at 80 °C for 2 h, the mixture was cooled down to room temperature and filtered on diatomite. The filtrate was washed with water (2 × 15 mL) and brine (20 mL), and dried over Na₂SO₄. The resulting solution was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 50 : 1) to give pure 7h’ (760.1 mg, 70%). To a solution of 7h’ (760.1 mg, 3.5 mmol) in pyridine (7 mL) was added TsCl (995 mg, 5.24 mmol) portionwise. After stirred at 60 °C for 12 h, pyridine was removed under vacuum. To this residue was added dichloromethane (20 mL) and 2 M HCl (20 mL). After stirred for 10 min, the mixture was extracted by dichloromethane (2 × 15 mL). The combined organic phase was washed with saturated Na₂CO₃ solution (15 mL) and brine (15 mL), and dried over Na₂SO₄. The resulting solution was concentrated under reduced pressure to give crude 7h’’ (1.43g, 83%) without further purification.

To a mixture of 7h’’ (371.7 mg, 1 mmol) and (HCHO)ₙ (90 mg, 3 mmol) was added H₂SO₄/ AcOH = 1 : 4 (10 mL). After stirred at room temperature for 12 h, the reaction was quenched with water (20 mL), then filtered and washed with water for several times. The residue was collected and purified by flash column chromatography on neutral alumina (petroleum ether/ethyl acetate/dichloromethane = 20 : 1 : 2) to give product 7h (340.7 mg, 89%) as a white solid. M.p. 152-153 °C; IR (KBr, cm⁻¹): 3030.2, 2915.9, 2855.3, 1906.9, 1591.2, 1465.0, 1337.5, 1158.4; ¹H NMR (CDCl₃, 500 MHz): δ 7.79 (d, J = 2.2 Hz, 1H), 7.46 (d, J = 8.5 Hz, 1H), 7.27 (dd, J = 8.5, 2.2 Hz, 1H), 7.08 (d, J = 7.9 Hz, 1H), 7.00 (d, J = 8.3 Hz, 2H), 6.91 (d, J = 7.9 Hz, 1H), 6.86 (s, 1H), 6.72 (d, J = 8.0 Hz, 2H), 4.76 (s, 2H), 2.29 (s, 3H), 2.16 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz): δ 143.28, 138.34, 136.82, 134.70, 133.70, 131.08, 129.33, 128.51, 128.49, 128.01, 127.67, 127.55, 127.19, 126.83, 124.60, 122.91, 49.82, 21.38, 21.15; EI-MS m/z (%): 227.0 (100), 385.1 (28) [M (³⁷Cl)]⁺, 383.1 (83) [M (³⁵Cl)]⁺; HRMS (El) m/z calcd for C₂₁H₁₆ClNO₂S [M⁺] 383.0747, found 383.0740.
2,8-Dimethyl-5-tosyl-5,6-dihydrophenanthridine (7i):
To a mixture of 2-bromo-4-methylaniline (930 mg, 5 mmol), p-tolylboronic acid (748 mg, 5.5 mmol), Pd(PPh₃)₂Cl₂ (70.1 mg, 0.1 mmol), K₂CO₃ (2.76 g, 20 mmol) was added water (10 mL) and DMF (40 mL), then reduced pressure and backfilled with N₂. After stirred at 80 °C for 2 h, the mixture was cooled down to room temperature and filtered on diatomite. The filtrate was washed with water (2 × 15 mL) and brine (20 mL), and dried over Na₂SO₄. The resulting solution was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 50 : 1) to give 7i' (838.8 mg, 85%). To a solution of 7i' (838.8 mg, 4.25 mmol) in pyridine (10 mL) was added TsCl (969 mg, 5.1 mmol) portionwise. After stirred at 60 °C for 12 h, pyridine was removed under vacuum. To this residue was added dichloromethane (20 mL) and 2 M HCl (20 mL). After stirred for 10 min, the mixture was extracted by dichloromethane (2 × 15 mL). The combined organic phase was washed with saturated Na₂CO₃ solution (15 mL) and brine (15 mL), and then dried over Na₂SO₄. The resulting solution was concentrated under reduced pressure to give crude 7i'' (1.36 g, 91%) without further purification.

To a mixture of 7i'' (351.5 mg, 1 mmol) and (HCHO)n (90 mg, 3 mmol) was added H₂SO₄ : AcOH = 1 : 4 (10 mL). After stirred at room temperature for 5 h, the reaction was quenched with water (20 mL), then filtered and washed with water for several times. The residue was collected and purified by flash column chromatography on basic alumina (petroleum ether/ethyl acetate/dichloromethane = 20 : 1 : 2) to give product 7i (312.7 mg, 86%) as a white solid. M.p. 183-185 °C; IR (KBr, cm⁻¹): 3033.5, 2918.5, 2859.4, 1909.5, 1645.3, 1483.0, 1343.6, 1281.9, 1159.0; ¹H NMR (CDCl₃, 500 MHz): δ 7.65 (d, J = 8.2 Hz, 1H), 7.34 (d, J = 1.2 Hz, 1H), 7.10 (d, J = 8.1 Hz, 1H), 6.97 (d, J = 8.0 Hz, 2H), 6.89 (d, J = 7.9 Hz, 1H), 6.84 (s, 1H), 6.70 (d, J = 8.0 Hz, 2H), 4.76 (s, 2H), 2.40 (s, 3H), 2.29 (s, 3H), 2.15 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz): δ 142.84, 137.72, 137.19, 134.88, 133.32, 131.33, 130.51, 128.80, 128.51, 128.33, 128.20, 127.93, 127.25, 126.78, 124.05, 122.94, 50.04, 21.47, 21.37, 21.12; EI-MS m/z (%): 208.1 (100), 363.1 (22) [M]+; HRMS (EI) m/z calcd for C₂₂H₂₁NO₂S [M]+ 363.1293, found 363.1295.
C1 Functionalization of 5,6-Dihydrophenanthridines, Related to Figure 5.

(Z)-N-(tert-Butyl)phenanthridine-6-carbimidoyl cyanide (8a):
Following the general procedure for 6a, the reaction of 7a (100.6 mg, 0.3 mmol), DDQ (204.3 mg, 0.9 mmol), AgOTf (11.6 mg, 15 mol%) and tBuNC (134 μL, 1.2 mmol) in PhCl (4.5 mL) at 80 °C for 3 h afforded the desired product 8a as a white solid (58.6 mg, 68%). M.p. 104-105 °C; IR (KBr, cm⁻¹): 3075, 2975, 2217, 1612, 1450, 1362, 1207, 937; ¹H NMR (CDCl₃, 500 MHz): δ 9.10 (d, J = 8.4 Hz, 1H), 8.69 (d, J = 8.3 Hz, 1H), 8.60 (d, J = 7.8 Hz, 1H), 8.31 (d, J = 7.8 Hz, 1H), 7.89 (t, J = 7.4 Hz, 1H), 7.83-7.74 (m, 2H), 7.72 (t, J = 7.4 Hz, 1H), 1.70 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz): δ 151.44, 142.74, 139.05, 134.01, 131.09, 131.05, 129.22, 128.97, 128.05, 127.73, 124.81, 123.82, 122.38, 122.12, 112.44, 59.94, 29.41; ESI-MS m/z: 288.1 [M+H]⁺; HRMS (DART Positive) m/z calcd for C₁₉H₁₈N₃ [M+H]⁺ 288.1495, found 288.1492.

(Z)-N-(tert-Butyl)-8-methylphenanthridine-6-carbimidoyl cyanide (8b):
To a mixture of 7b (104.7 mg, 0.3 mmol), DDQ (272.4 mg, 1.2 mmol) and AgOTf (11.6 mg, 15 mol%) was added PhCl (3.0 mL) and tBuNC (168 μL, 1.5 mmol) in glovebox. The reaction was stirred at 80 °C for 3 h under N₂ atmosphere. Upon completion, the reaction mixture was cooled down to room temperature and removed solvent under reduced pressure. Then, purified by column chromatography on basic Al₂O₃ (petroleum ether/ethyl acetate = 30 : 1) to give the desired product 8b (45.9 mg, 51%) as a white solid. M.p. 159-161 °C; IR (KBr, cm⁻¹): 2965.9, 2208.3, 1954.4, 1741.1, 1621.8, 1568.0, 1459.3, 1366.4, 1324.9; ¹H NMR (CDCl₃, 500 MHz): δ 8.90 (s, 1H), 8.59-8.50 (m, 2H), 8.31-8.25 (m, 1H), 7.80-7.68 (m, 3H), 2.59 (s, 3H), 1.71 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz): δ 151.10, 142.48, 139.03 138.06, 132.76, 131.95, 131.02, 128.68, 128.76, 127.18, 124.93, 123.97, 122.28, 121.95, 112.45, 59.94, 29.42, 22.18; EI-MS m/z (%): 245.1 (100), 301.2 (18) [M⁺]; HRMS (EI) m/z calcd for C₂₀H₁₉N₃ [M⁺] 301.1579, found 301.1584.

(Z)-8-Bromo-N-(tert-butyl)phenanthridine-6-carbimidoyl cyanide (8c):
Following the general procedure for 6a, the reaction of 7c (124.3 mg, 0.3 mmol), DDQ (204.3
mg, 0.9 mmol), AgOTf (11.6 mg, 15 mol%) and tBuNC (134 μL, 1.2 mmol) in PhCl (4.5 mL) at 80 °C for 3 h afforded the desired product 8c as a white solid (34.5 mg, 31%). M.p. 172 - 175 °C; IR (KBr, cm⁻¹): 2967.0, 2931.7, 2220.7, 1614.3, 1692.6, 1616.6, 1566.5; ¹H NMR (CDCl₃, 500 MHz): δ 9.47 (d, J = 2.0 Hz, 1H), 8.56 - 8.47 (m, 2H), 8.30 (dd, J = 8.2, 1.2 Hz, 1H), 7.95 (dd, J = 8.8, 2.0 Hz, 1H), 7.84-7.74 (m, 2H), 1.71 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz): δ 149.67, 142.66, 139.10, 134.17, 132.64, 131.33, 130.68, 129.65, 129.52, 124.96, 124.32, 124.08, 122.43, 121.97, 112.08, 60.13, 29.34; ESI-MS m/z (%): 366.1 [M⁺(⁸¹Br)+H]⁺ (81), 368.1 [M⁺(⁷⁵Br)+H]⁺ (100); HRMS (DART Positive) m/z calcd for C₁₉H₁₇N₃Br [M+H]⁺ 366.0600, found 366.0601.

(Z)-N-(tert-Butyl)-3,8-dimethylphenanthridine-6-carbimidoyl cyanide (8d):
Following the general procedure for 8b, the reaction of 7d (123.45 mg, 0.3 mmol), DDQ (272.4 mg, 1.2 mmol), AgOTf (11.6 mg, 15 mol%) and tBuNC (168 μL, 1.5 mmol) in PhCl (3 mL) at 80 °C for 3 h afforded the desired product 8d as a white solid (38.5 mg, 36%). M.p. 112 - 115 °C; IR (KBr, cm⁻¹): 2965.7, 2859.4, 2216.6, 1608.8, 1463.4, 1395.9; ¹H NMR (CDCl₃, 500 MHz): δ 9.55 (d, J = 1.3 Hz, 1H), 8.70 (d, J = 8.7 Hz, 1H), 8.58 (d, J = 7.7 Hz, 1H), 8.31 (d, J = 7.5 Hz, 1H), 8.13 (dd, J = 8.6, 1.5 Hz, 1H), 7.82-7.72 (m, 4H), 7.54 (t, J = 7.7 Hz, 2H), 7.44 (t, J = 7.4 Hz, 1H), 1.73 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz): δ 151.15, 142.71, 140.56, 140.41, 139.40, 132.97, 131.16, 129.97, 129.26, 129.18, 129.14, 128.07, 127.38, 126.05, 124.67, 124.27, 122.94, 122.14, 112.32, 59.90, 29.43; EI-MS m/z (%): 307.1 (100), 363.2 (33) [M⁺]; HRMS (EI) m/z calcd for C₂₅H₂₁N₃ [M⁺] 363.1735, found 363.1736.

(Z)-N-(tert-Butyl)-8-((trimethylsilyl)ethynyl)phenanthridine-6-carbimidoyl cyanide (8e):
Following the general procedure for 8b, the reaction of 7e (123.45 mg, 0.3 mmol), DDQ (272.4 mg, 1.2 mmol), AgOTf (11.6 mg, 15 mol%) and tBuNC (168 μL, 1.5 mmol) in PhCl (3 mL) at 80 °C for 3 h afforded the desired product 8e as a white solid (36.8 mg, 32%). M.p. 135 - 139 °C; IR (KBr, cm⁻¹): 2966.6, 2150.3, 1690.5, 1647.2, 1619.5, 1463.4, 1363.4; ¹H NMR (CDCl₃, 500 MHz): δ 9.55 (d, J = 1.3 Hz, 1H), 8.70 (d, J = 8.7 Hz, 1H), 8.58 (d, J = 7.7 Hz, 1H), 8.31 (d, J = 7.5 Hz, 1H), 8.13 (dd, J = 8.6, 1.5 Hz, 1H), 7.82-7.72 (m, 4H), 7.54 (t, J = 7.7 Hz, 2H), 7.44 (t, J = 7.4 Hz, 1H), 1.73 (s, 9H), 0.30 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz): δ 150.40, 142.88, 138.78, 133.38, 133.35, 132.13, 131.10, 129.51, 129.15, 124.33, 123.43, 122.86, 122.25, 122.21, 112.05, 104.63, 96.30, 59.96, 29.17, -0.11; EI-MS m/z (%): 327.1 (100), 383.2 (30) [M⁺]; HRMS (EI) m/z calcd for C₂₄H₂₅N₃Si [M⁺] 383.1818, found 383.1815.
(Z)-N-(tert-Butyl)-3,8-dimethylphenanthridine-6-carbimido yl cyanide (8f):
Following the general procedure for 8b, the reaction of 7f (108.9 mg, 0.3 mmol), DDQ (272.4 mg, 1.2 mmol), AgOTf (11.6 mg, 15 mol%) and tBuNC (168 μL, 1.5 mmol) in PhCl (3 mL) at 80 °C for 3 h afforded the desired product 8f as a white solid (46.2 mg, 49%). M.p. 159-161 °C; IR (KBr, cm⁻¹): 2970.1, 2909.2, 2212.4, 1619.9, 1565.2, 1470.6; ¹H NMR (CDCl₃, 500 MHz): δ 8.89 (s, 1H), 8.52 (d, J = 8.5 Hz, 1H), 8.43 (d, J = 8.4 Hz, 1H), 8.09 (s, 1H), 7.68 (dd, J = 8.5, 1.6 Hz, 1H), 7.56 (dd, J = 8.4, 1.6 Hz, 1H), 2.60 (s, 3H), 2.57 (s, 3H), 1.70 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz): δ 151.06, 142.64, 139.17, 138.98, 137.53, 132.69, 132.04, 130.72, 130.46, 127.11, 123.70, 122.64, 122.10, 121.73, 112.50, 59.87, 29.41, 22.16, 21.55; EI-MS m/z (%): 259.1 (100), 315.2 (36) [M]+; HRMS (EI) m/z calcd for C₂₁H₂₁N₃ [M]+ 315.1735, found 315.1738.

(Z)-N-(tert-Butyl)-3-fluoro-8-methylphenanthridine-6-carbimido yl cyanide (8g):
Following the general procedure for 6a, the reaction of 7g (110.2 mg, 0.3 mmol), DDQ (204.3 mg, 0.9 mmol), AgOTf (11.6 mg, 15 mol%) and tBuNC (134 μL, 1.2 mmol) in PhCl (4.5 mL) at 80 °C for 3 h afforded the desired product 8g as a white solid (44.3 mg, 46%). M.p. 162-164 °C; IR (KBr, cm⁻¹): 2966.8, 2927.6, 2220.2, 1620.7, 1575.9, 1472.7; ¹H NMR (CDCl₃, 500 MHz): δ 8.82 (s, 1H), 8.48 (dd, J = 9.1, 5.7 Hz, 1H), 8.44 (d, J = 8.4 Hz, 1H), 7.90 (dd, J = 9.5, 2.5 Hz, 1H), 7.68 (d, J = 8.3 Hz, 1H), 7.46 (td, J = 8.2, 1.8 Hz, 1H), 2.60 (s, 3H), 1.71 (s, 9H); ¹⁹F NMR (CDCl₃, 470 MHz): δ -111.95 (m, Ar-F); ¹³C NMR (CDCl₃, 125 MHz): δ 162.59 (d, J_{C,F} = 249.0 Hz), 152.24, 143.55 (d, J_{C,F} = 12.0 Hz), 138.67, 137.89, 133.14, 131.78, 127.22, 123.89 (d, J_{C,F} = 9.3 Hz), 123.48, 122.10, 112.50 (d, J_{C,F} = 2.2 Hz), 117.98 (d, J_{C,F} = 24.0 Hz), 115.17 (d, J_{C,F} = 20.7 Hz), 112.30, 60.09, 29.38, 22.12; EI-MS m/z (%): 263.1 (100), 319.2 (21) [M]⁺; HRMS (EI) m/z calcd for C₂₀H₁₈F₁N₃ [M]⁺ 319.1485, found 319.1484.

(Z)-N-(tert-Butyl)-3-chloro-8-methylphenanthridine-6-carbimido yl cyanide (8h):
Following the general procedure for 6a, the reaction of 7h (115.2 mg, 0.3 mmol), DDQ (204.3 mg, 0.9 mmol), AgOTf (11.6 mg, 15 mol%) and tBuNC (134 μL, 1.2 mmol) in PhCl (4.5 mL) at
80 °C for 3 h afforded the desired product 8h as a white solid (46.6 mg, 46%). M.p. 207-209 °C; IR (KBr, cm⁻¹): 2966.4, 2923.7, 1614.3, 1466.8, 1365.1; ¹H NMR (CDCl₃, 500 MHz): δ 8.82 (s, 1H), 8.40 (d, J = 8.5 Hz, 1H), 8.36 (d, J = 8.8 Hz, 1H), 8.20 (d, J = 2.0 Hz, 1H), 7.67 (dd, J = 8.4, 1.0 Hz, 1H), 7.61 (dd, J = 8.8, 2.1 Hz, 1H), 2.57 (s, 3H), 1.71 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz): δ 152.00, 142.87, 138.68, 138.39, 134.35, 133.10, 131.44, 129.87, 129.24, 127.26, 123.75, 123.25, 123.24, 122.09, 112.25, 60.08, 29.36, 22.17; EI-MS m/z (%): 279.1 (100), 337.1 (7) [M (³⁷Cl)], 335.1 (21) [M (³⁵Cl)]; HRMS (EI) m/z calcd for C₂₀H₁₈N₃Cl [M]⁺ 335.1189, found 335.1183.

(Z)-N-((tert-Butyl)-2,8-dimethylphenanthridine-6-carbimidoyl cyanide (8i): Following the general procedure for 8b, the reaction of 7h (108.9 mg, 0.3 mmol), DDQ (272.4 mg, 1.2 mmol), AgOTf (11.6 mg, 15 mol%) and tBuNC (168 μL, 1.5 mmol) in PhCl (3 mL) at 80 °C for 3 h afforded the desired product 8h as a white solid (29.1 mg, 31%). M.p. 139-140 °C; IR (KBr, cm⁻¹): 2970.6, 2915.2, 2212.4, 1899.3, 1743.5, 1609.2, 1567.8, 1462.8, 1233.3, 1200.3; ¹H NMR (CDCl₃, 500 MHz): δ 8.91 (s, 1H), 8.52 (d, J = 8.5 Hz, 1H), 8.30 (s, 1H), 8.16 (d, J = 8.3 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.57 (d, J = 8.3 Hz, 1H), 2.64 (s, 3H), 2.57 (s, 3H), 1.71 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz): δ 150.13, 140.85, 139.22, 139.14, 137.87, 132.48, 131.60, 130.75, 130.55, 127.10, 124.77, 124.06, 122.22, 121.55, 112.51, 59.80, 29.40, 22.35, 22.17; EI-MS m/z (%): 259.1 (100), 315.2 (38) [M]⁺; HRMS (EI) m/z calcd for C₂₀H₂₁N₃Cl [M]⁺ 315.1735, found 315.1728.

Synthetic applications of the α-Iminonitrile-decorated Isochromans, Related to Figure 6.

N-tert-Butyl-1-methylisochroman-1-carboxamide (9a): To a sealed tube containing Al₂O₃ (1.0 g) was added (E)-N-((tert-butyl)-1-methyl-isochroman-1-carbimidoyl cyanide 4l (51.3 mg, 0.2 mmol) in toluene (2.0 mL) and the mixture was stirred at 150 °C for 25 h. Upon completion, the reaction mixture was cooled down to room temperature and diluted with ethyl acetate. After filtration through a thin pad of celite, the solid was repeatedly rinsed with ethyl acetate (3 x 10 mL). Then the combined organic phase was evaporated in vacuum to give the crude product which was purified by column chromatography on silica gel to give product 9a (26.0 mg, 53%) as white solid. M.p. 52-54 °C; IR (KBr, cm⁻¹): 3364, 2977, 2931, 1665, 1510, 1450, 1363, 1286, 1235, 1109, 1041, 976, 745, 653; ¹H NMR (CDCl₃, 500 MHz): δ 7.67 (d, J = 9.0 Hz, 1H), 7.22-7.15 (m, 2H), 7.06 (d, J = 7.0 Hz, 1H), 6.72 (s, 1H), 3.98 (t, J = 5.7 Hz, 1H), 2.92-2.86 (m, 1H), 2.84-2.79 (m, 1H), 1.68 (s,
\[\text{Methyl 1-methylisochroman-1-carboxylate (9b):}\]

To a test tube containing (E)-N-(tert-butyl)-1-methylisochroman-1-carbimidoyl cyanide 4l (51.3 mg, 0.2 mmol) in MeOH (3.0 mL) was added 1M HCl (0.6 mL) and the mixture was stirred at room temperature for 10 h. Then water (30 mL) was added and the solution was extracted with ethyl acetate (3 × 10 mL). The combined organic phase was washed with brine and dried over Na$_2$SO$_4$. After that, the filtrate was evaporated in vacuum to give the crude product which was purified by column chromatography on silica gel to give 9b (30.1 mg, 73%) as pale yellow oil.

\[
\begin{align*}
\text{IR (KBr, cm}^{-1}\text{): 2949, 1738, 1446, 1250, 1117, 977, 742; H NMR (CDCl}_3\text{, 500 MHz): } & 7.43-7.41 (m, 1H), 7.22-7.20 (m, 2H), 7.12-7.10 (m, 1H), 4.15-4.07 (m, 2H), 3.74 (s, 3H), 3.04-2.97 (m, 1H), 2.74-2.69 (m, 1H), 1.74 (s, 3H); C NMR (CDCl}_3\text{, 125 MHz): } & 174.1, 136.2, 133.5, 128.7, 127.1, 126.8, 126.3, 78.3, 62.1, 52.5, 28.7, 27.9;
\end{align*}
\]

LC-MS (ESI) m/z 224 [M+NH$_4$]$^+$; HRMS (ESI) m/z calcd for C$_{12}$H$_{15}$O$_3$ 207.1016, found 207.1015.

\[\text{Methylisochroman-1-carboxylic acid (9c):}\]

(E)-N-(tert-butyl)-1-methylisochroman-1-carbimidoyl cyanide 4l (51.3 mg, 0.2 mmol) was subjected to hydrolysis in aqueous CH$_3$CN (80% v/v, 50 mL) containing 0.1 N HCl at room temperature for 2.5 h. Upon completion, water (50 mL) was added and the solution was extracted with dichloromethane (3 × 10 mL). The combined organic phase was washed with brine and dried over Na$_2$SO$_4$. After that, the filtrate was evaporated in vacuum to give the crude product which was purified by column chromatography on silica gel to give 9c (34.1 mg, 89%) as pale yellow oil.

\[
\begin{align*}
\text{IR (KBr, cm}^{-1}\text{): 2933, 2631, 1711, 1449, 1373, 1286, 1217, 1117, 740, 652; H NMR (CDCl}_3\text{, 500 MHz): } & 7.55-7.54 (m, 1H), 7.23-7.22 (m, 2H), 7.11-7.09 (m, 1H), 4.17-4.13 (m, 1H), 4.08-4.03 (m, 1H), 2.93-2.83 (m, 2H), 1.78 (s, 3H); C NMR (CDCl}_3\text{, 125 MHz): } & 176.7, 135.0, 133.1, 128.7, 127.5, 127.0, 126.8, 78.3, 61.9, 28.7, 27.9; LC-MS (ESI) m/z 210 [M+NH$_4$]$^+$; HRMS (ESI) m/z calcd for C$_{11}$H$_{16}$O$_3$N [M+NH$_4$]$^+$ 210.1125, found 210.1124.
\end{align*}
\]

\[\text{N-Hydroxy-1-methylisochroman-1-carbimidoyl cyanide (9d):}\]

To a sealed tube containing NH$_2$OH•HCl (16.7 mg, 0.24 mmol) and K$_2$CO$_3$ (41.5 mg, 0.3 mmol) was added (E)-N-(tert-butyl)-1-methylisochroman-1-carbimidoyl cyanide 4l (51.3 mg, 0.2 mmol) in EtOH (3.0 mL). The mixture was stirred at 100 °C for 4 h. Upon completion, the reaction mixture was cooled down to room temperature and diluted with ethyl acetate. After
filtration through a thin pad of celite, the solid was repeatedly rinsed with ethyl acetate (3 × 10 mL). Then the combined organic phase was evaporated in vacuum to give the crude product which was purified by column chromatography on silica gel to give product 9d (31.6 mg, 73%) as colorless oil. IR (KBr, cm⁻¹): 3133, 2988, 2865, 1619, 1482, 1375, 1286, 1091, 994, 754, 665; ¹H NMR (d₆-DMSO, 500 MHz): 6 13.41 (s, 1H), 7.23-7.17 (m, 3H), 7.13-7.11 (m, 1H), 4.00-3.96 (m, 1H), 3.81-3.77 (m, 1H), 2.88-2.83 (m, 1H), 2.76 (dt, J = 16.5, 9.5 Hz, 1H), 1.72 (s, 3H); ¹³C NMR (d₆-DMSO, 125 MHz): 137.1, 135.9, 134.0, 129.4, 127.8, 127.3, 126.6, 110.4, 76.7, 60.3, 28.4, 26.4; LC-MS (ESI) m/z 234 [M+NH₄]⁺; HRMS (ESI) m/z calcd for C₁₂H₁₆O₂N₃ [M+NH₄]⁺ 234.1237, found 234.1235.

3-[(1-Methylisochroman-1-yl)quinoxalin-2-amine (9e):
To a test tube containing benzene-1,2-diamine (26.0 mg, 0.24 mmol) and NaOAc (19.7 mg, 0.24 mmol), (E)-N-(tert-butyl)-1-methylisochroman-1-carbimidoxy cyanide 4l (51.3 mg, 0.2 mmol) in AcOH (2.0 mL) was added. The mixture was stirred at 120 °C for 7.5 h. Upon completion, the reaction mixture was poured into water (50 mL) and extracted with dichloromethane (3 × 10 mL). The combined organic phase was dried over anhydrous Na₂SO₄ and evaporated in vacuum to give the crude product which was purified by column chromatography on silica gel to give product 9e (30.3 mg, 52%) as yellow solid. M.p. 155-157 °C; IR (KBr, cm⁻¹): 3454, 2929, 1727, 1626, 1423, 1365, 1274, 1101, 1038, 756; ¹H NMR (CDCl₃, 500 MHz): 6 7.88 (d, J = 8.1 Hz, 1H), 7.60-7.53 (m, 2H), 7.40-7.37 (m, 1H), 7.21-7.15 (m, 2H), 7.11 (t, J = 7.4 Hz, 1H), 7.01 (d, J = 7.8 Hz, 1H), 5.89 (s, 2H), 4.31-4.25 (m, 1H), 4.14-4.10 (m, 1H), 3.14-3.08 (m, 1H), 2.96 (dt, J = 16.7, 4.3 Hz, 1H), 2.08 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz): 150.7, 147.9, 140.9, 138.0, 136.4, 132.1, 129.9, 129.2, 128.8, 127.5, 126.9, 126.1, 124.9, 124.5, 81.6, 60.6, 28.5, 26.2; EI-MS m/z (%): 291 (30) [M⁺], 263 (27), 147 (100), 129 (20); HRMS (EI) m/z calcd for C₁₈H₁₇N₃O [M⁺] 291.1372, found 291.1370.

2-[(1-Methylisochroman-1-yl)benzo[d]thiazole (9f):
Following the above procedure as for 5e, the reaction mixture of (E)-N-(tert-butyl)-1-methylisochroman-1-carbimidoxy cyanide 4l (51.3 mg, 0.2 mmol), 2-aminobenzenethiol (30.0 mg, 0.24 mmol), and NaOAc (19.7 mg, 0.24 mmol) in AcOH (2.0 mL) was stirred at 120 °C for 3 h to afford product 9f (22.9 mg, 41%) as white solid. M.p. 96-98 °C; IR (KBr, cm⁻¹): 2978, 2919, 1935, 1735, 1513, 1481, 1440, 1365, 1274, 1202, 1110, 1012, 762, 723; ¹H NMR (CDCl₃, 500 MHz): 6 8.03 (d, J = 8.0 Hz, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.64 (d, J = 7.0 Hz, 1H), 7.44 (t, J = 7.5 Hz, 1H), 7.33 (t, J = 7.5 Hz, 1H), 7.23-7.19 (m, 2H), 7.13 (d, J = 7.0 Hz, 1H), 4.13 (t, J = 5.5 Hz, 2H), 2.96 (t, J = 5.5 Hz, 2H), 2.08 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz): 178.3, 153.4,
2-(1-Methylisochroman-1-yl)benzo[d]oxazole (9g):
Following the above procedure as for 5e, the reaction mixture of (E)-N-(tert-butyl)-1-methylisochroman-1-carbimidoyl cyanide 4l (51.3 mg, 0.2 mmol), 2-aminophenol (26.2 mg, 0.24 mmol), and NaOAc (19.7 mg, 0.24 mmol) in AcOH (4.0 mL) was stirred at 120 °C for 4 h to afford product 9g (29.4 mg, 55%) as pale yellow oil. IR (KBr, cm⁻¹): 2987, 2934, 1738, 1556, 1451, 1282, 1242, 1104, 936, 841, 744; ¹H NMR (CDCl₃, 500 MHz): δ 7.75-7.74 (m, 1H), 7.52-7.50 (m, 1H), 7.33-7.30 (m, 3H), 7.25-7.19 (m, 3H), 4.18-4.15 (m, 2H), 3.10-3.08 (m, 1H), 2.88-2.84 (m, 1H), 2.07 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz): 168.0, 150.9, 140.7, 136.8, 133.4, 129.1, 127.4, 126.8, 126.4, 125.2, 124.3, 120.4, 110.9, 75.3, 61.8, 28.8, 28.4; LC-MS (ESI) m/z 266 [M+H]+; HRMS (ESI) m/z calcd for C₁₇H₁₆ONS [M+H]+ 266.1176, found 266.1174.

N,N'-di-tert-butylisochroman-1,1-dicarboxamide (9h):
To a sealed tube containing Pd(OAc)₂ (2.3 mg, 0.01 mmol), Cu(TFA)₂ (202.7 mg, 0.7 mmol) and (1E,1E)-N,N'-di-tert-butyl-isochroman-1,1-bis(carbimidoyl) cyanide 2a (84.1 mg, 0.24 mmol), 2-phenylpyridine (31.0 mg, 0.2 mmol) in THF (2.0 mL) was added. The mixture was stirred at 120 °C for 24 h. Upon completion, the reaction mixture was cooled down to room temperature and was purified by column chromatography on silica gel to give product 9h (67.1 mg, 84%) as white solid, together with 5i (26.3 mg, 73%) as pale yellow solid. M.p. 139-141 °C; IR (KBr, cm⁻¹): 3352, 2971, 1693, 1517, 1452, 1362, 1223, 1116, 1036, 746, 646; ¹H NMR (CDCl₃, 500 MHz): δ 7.90-7.88 (m, 1H), 7.23-7.21 (m, 2H), 7.09-7.08 (m, 1H), 7.05 (s, 2H), 4.24 (t, J = 5.5 Hz, 2H), 2.87 (t, J = 5.5 Hz, 2H), 1.31 (s, 18H); ¹³C NMR (CDCl₃, 125 MHz): 168.5, 133.0, 131.3, 128.6, 127.6, 127.5, 126.3, 81.4, 63.2, 51.2, 28.6, 28.5; LC-MS (DART) m/z 333 [M+H]+; HRMS (DART) m/z calcd for C₁₉H₂₉O₃N₂ [M+H]+ 333.2173, found 333.2171.

2-(Pyridin-2-yl)benzonitrile (9i) (Xu et al., 2012):
To a sealed tube containing Pd(OAc)₂ (2.3 mg, 0.01 mmol), Cu(TFA)₂ (115.8 mg, 0.4 mmol) and (E)-N-(tert-butyl)-1-methyl-isochroman-1-carbimidoyl cyanide 4l (61.5 mg, 0.24 mmol), 2-phenylpyridine (31.1 mg, 0.2 mmol) in THF (1.0 mL) was added. The mixture was stirred at...
120 °C for 23 h. Upon completion, the reaction mixture was cooled down to room temperature
and was purified by column chromatography on silica gel to give product 9i (27.1 mg, 75%) as
pale yellow solid, together with 5a (33.2 mg, 56%) as white solid. M.p. 42-43 °C; IR (KBr, cm⁻¹):
3062, 2923, 2856, 2224, 1956, 1579, 1460, 1432, 1300, 1155, 1100, 760; ¹H NMR (CDCl₃, 500
MHz): δ 8.75 (d, J = 4.5 Hz, 1H), 7.82–7.74 (m, 4H), 7.66 (t, J = 7.5 Hz, 1H), 7.47 (t, J = 7.5 Hz,
1H), 7.33–7.31 (m, 1H); ¹³C NMR (CDCl₃, 125 MHz): 155.2, 149.9, 143.4, 136.8, 134.1, 132.8,
129.9, 128.7, 123.3, 123.2, 118.7, 111.0; LC-MS (ESI) m/z 181 [M+H]+.

2-(Pyrimidin-2-yl)benzonitrile (9j) (Xu et al., 2012):
Following the above procedure as for 5i and 5h, the reaction mixture of Pd(OAc)₂ (2.3 mg,
0.01 mmol), Cu(TFA)₂ (202.7 mg, 0.7 mmol), (1E,1E)-N,N'-di-tert-butylisochroman-1,1-
bis(carbimidoyl) cyanide 2a (84.1 mg, 0.24 mmol) and 2-phenyl-pyrimidine (31.2 mg, 0.2 mmol) in
THF (2.0 mL) was stirred at 120 °C for 22 h to afford product 9j (26.7 mg, 67%) as white solid,
together with 9h (75.4 mg, 94%) as white solid. M.p. 140–141 °C; IR (KBr, cm⁻¹): 3422, 3039,
2922, 2220, 1644, 1555, 1412, 1365, 757; ¹H NMR (CDCl₃, 500 MHz): δ 8.91 (d, J = 4.5 Hz,
2H), 8.35 (dd, J = 8.0, 0.5 Hz, 1H), 7.84 (dd, J = 7.5, 1.0 Hz, 1H), 7.70 (td, J = 7.5, 1.0 Hz, 1H),
7.56 (td, J = 8.0, 1.5 Hz, 1H), 7.32 (t, J = 5.0 Hz, 1H); ¹³C NMR (CDCl₃, 125 MHz): 162.8,
157.3, 140.3, 135.0, 132.5, 130.4, 130.2, 120.1, 118.9, 111.8; EI-MS m/z (%): 181 (100) [M]+,
128 (96).

1-(Pyrimidin-2-yl)-1H-indole-2-carbonitrile (9k) (Xu et al., 2012):
Following the above procedure as for 5i and 5h, the reaction mixture of Pd(OAc)₂ (2.3 mg,
0.01 mmol), Cu(TFA)₂ (202.7 mg, 0.7 mmol), (1E,1E)-N,N'-di-tert-butylisochroman-1,1-
bis(carbimidoyl) cyanide 2a (84.1 mg, 0.24 mmol) and 1-(pyrimidin-2-yl)-1H-indole (39.0 mg, 0.2
mmol) in THF (2.0 mL) was stirred at 120 °C for 23 h to afford product 9k (22.1 mg, 50%) as
white solid, together with 9h (66.4 mg, 83%) as white solid. M.p. 124-125 °C; IR (KBr, cm⁻¹):
3436, 3104, 3036, 2360, 1571, 1439, 1338, 1254, 813, 735; ¹H NMR (CDCl₃, 500 MHz): δ 8.83
(d, J = 4.5 Hz, 2H), 8.69 (dd, J = 8.5, 0.5 Hz, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.52-7.48 (m, 1H),
7.47 (d, J = 0.5 Hz, 1H), 7.34-7.31 (m, 1H), 7.23 (t, J = 4.7 Hz, 1H); ¹³C NMR (CDCl₃, 125
MHz): 158.3, 156.5, 136.6, 127.7, 127.5, 123.5, 122.0, 120.9, 117.9, 116.1, 114.2, 108.9;
EI-MS m/z (%): 220 (100) [M]+.
Application for the Synthesis of Pyrene-based Materials, Related to Figure 7.

4,9-Ditosyl-4,5,9,10-tetrahydropyrido[2,3,4,5-imn]phenanthridine (10)

To a mixture of LiAlH₄ (760 mg, 20 mmol) and anhydrous 1,4-dioxane (20 mL) was added pyrido[2,3,4,5-imn]phenanthridine-5,10(4H,9H)-dione 10’ (472 mg, 2 mmol) (Gawlak and Robbins, 1964) at 0 °C under a nitrogen atmosphere. The mixture was stirred at 110 °C for 24 h. The reaction was quenched with saturated Na₂SO₄ solution after cooling to room temperature. The mixture was filtered and the residue was washed with dichloromethane (5 x 5 mL). Evaporation of the solvent gave the product 10” (344.9 mg, 83%) as a yellow solid, which was directly used for the next step without further purification. To a mixture of TsCl (912 mg, 4.8 mmol) and pyridine (8 mL) was added 10” at 0 °C under a nitrogen atmosphere. After stirred for 5 min, the reaction was transferred to a refrigerator at -20 °C overnight. Pyridine was removed on rotary evaporator, and the residue was dissolved in dichloromethane (15 mL), washed with 2 M HCl (15 mL). The aqueous phase was extracted by dichloromethane (3 x 15 mL). The combined organic phase was washed with saturated Na₂CO₃ (15 mL) solution and brine (15 mL) and dried over Na₂SO₄. The solvent was removed on a rotary evaporator and the residue was recrystallized by dichloromethane/Hexane (below 5 °C) to give the product 10 (527.3 mg, 64%) as a white solid. M.p. 213-215 °C; IR (KBr, cm⁻¹): 2922, 1914, 1599, 1447, 1344, 1294, 1161; ¹H NMR (CDCl₃, 500 MHz): δ 7.48 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 8.0 Hz, 4H), 7.19 (t, J = 7.5 Hz, 2H), 7.02 (d, J = 8.0 Hz, 4H), 6.92 (d, J = 7.5 Hz, 2H), 4.74 (s, 4H), 2.30 (s, 6H); ¹³C NMR (CDCl₃, 125 MHz): δ 144.23, 136.06, 134.28, 130.05, 129.46, 128.54, 127.00, 124.01, 122.85, 48.89, 21.58; ESI-MS m/z: 534.2 [M+NH₄]⁺; HRMS (DART Positive) m/z calcd for C₂₈H₂₈N₂O₄S₂ [M+H]⁺ 517.1250, found 517.1250.
To a mixture of 10 (51.7 mg, 0.1 mmol), DDQ (113.0 mg, 0.5 mmol), AgOTf (3.9 mg, 30 mol%), and PhCl (1.5 mL) was added 3^BuNC (90 µL, 0.8 mmol). The mixture was sealed and stirred at 80 °C under nitrogen atmosphere; the reaction was cooled to room temperature and the solvent was removed under reduced pressure. The residue was purified by column chromatography on basic Al₂O₃ (petroleum ether/dichloromethane = 2:1) to give the product 11 as a yellow solid (11.9 mg, 28%). M.p. >300 °C; IR (KBr, cm⁻¹): 2965.2, 2926.1, 2858.9, 2235.6, 1831.8, 1696.4, 1636.5, 1463.9; ^1H NMR (CDCl₃, 500 MHz): δ 9.64 (d, J = 8.0 Hz, 2H), 8.85 (d, J = 7.5 Hz, 2H), 8.34 (t, J = 7.5 Hz, 2H), 1.76 (s, 18H); ^13C NMR (CDCl₃, 125 MHz): δ 151.78, 140.48, 139.65, 131.76, 129.81, 128.14, 122.33, 122.11, 112.08, 60.28, 29.43; ESI-MS m/z: 421.2 [M+H]⁺; HRMS (ESI) m/z calcd for C₂₆H₂₅N₆ [M+H]⁺ 421.2135, found 421.2132.

Figure S1. UV-Vis absorption of compound 11 (red curve) and 4,9-diazapyrene (Black curve). c = 5×10⁻⁵ M in THF. Related to Figure 7.
**Figure S2.** Emission spectrum of 4,9-diazapyrene. $c = 2 \times 10^{-5}$ M in THF, excited at 330 nm. Related to **Figure 7**.

**Figure S3.** Emission spectra of 4,9-diazapyrene (blue curve) and compound 11 (red curve) in the solid state. Related to **Figure 7**.
Figure S4. Aggregation-induced Emission (AIE) of Compound 11. (A) PL spectra of 11 in THF/water mixtures with different fractions of water \( f_w \). Observation of the aggregation-induced emission (AIE): Stock solutions of 11 with a concentration of 200 μM in THF were first prepared; 1 mL aliquots of the stock solutions were transferred into 10 mL volumetric flasks; Appropriate amounts of THF were then added, after which water was added dropwise under vigorous stirring to furnish 20 μM solutions with defined fractions of water (0% to 90%). (B) Photographs taken under illumination of a UV lamp (365 nm). Related to Figure 7.

X-ray Crystallographic Analysis for 2a, 4h, 6a and 8b

Figure S5. Crystallographic data for 2a. 25% probability ellipsoids. \( \text{C}_{21}\text{H}_{26}\text{N}_{4}\text{O} \), M = 350.46, Monoclinic, P 21/c (No. 14), \( a = 13.460 \) (11) Å, \( b = 9.739 \) (8) Å, \( c = 16.398 \) (13) Å, \( \beta = 100.331 \) (10)°, \( V = 2115 \) (3) Å³, \( Z = 4 \), Crystal size: 0.24 × 0.22 × 0.18 mm, \( T = 293 \) K, \( R_1 = 0.0713 \) (I>4σ(I)), \( wR_2 = 0.2813 \) (all data), GOF = 1.048, reflections collected/unique: 11496 / 4758 (Rint = 0.0660), Data: 2565, restraints: 0, parameters: 236. CCDC 1533930 contains the supplemental crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Related to Table 1.
Figure S6. Crystallographic data for 4h. 25% probability ellipsoids; C_{20}H_{21}BrN_{2}OS, M = 417.36, monoclinic, P21/c (No. 14), a = 9.581 (5) Å, b = 13.015 (6) Å, c = 16.536 (8) Å, β = 106.114 (6)°, V = 1981 (2) Å³, Z = 4, Crystal size: 0.26 × 0.18 × 0.14 mm, T = 293 K, R₁ = 0.0351 (I>4σ(I)), wR₂ = 0.0905 (all data), GOF = 1.055, reflections collected/unique: 9979 / 3503 (Rint = 0.0246), Data: 2600, restraints: 0, parameters: 254. CCDC 1534967 contains the supplemental crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Related to Figure 3.

Figure S7. Crystallographic data for 6a. 25% probability ellipsoids; Chemical Formula: C_{23}H_{24}N_{4}O_{2}S, M = 420.52, monoclinic, P21/n, a = 9.745 (8) Å, b = 11.135 (9) Å, c = 20.716 (16) Å, β = 93.037 (11)°, V = 2245 (3) Å³, Z = 4, Crystal size: 0.24 × 0.15 × 0.12 mm, T = 293 K, R₁ = 0.0541 (I>4σ(I)), wR₂ = 0.1748 (all data), GOF = 1.050, reflections collected/unique: 9937/3942 (Rint = 0.0700), Data: 2417, restraints: 0, parameters: 271. CCDC 1829908 contains the supplemental crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Related to Figure 4.

Figure S8. Crystallographic data for 8b. 25% probability ellipsoids; Chemical Formula: C_{20}H_{19}N_{3}, M = 301.38, triclinic, P -1, a = 7.219 (9) Å, b = 9.096 (11) Å, c = 13.168 (16) Å, α = 79.250 (14)°, β = 83.431 (14)°, γ = 89.505(15)°, V = 844 (2) Å³, Z = 2, Crystal size: 0.21 × 0.18 × 0.14 mm, T = 293 K, R₁ = 0.0531 (I>4σ(I)), wR₂ = 0.1663 (all data), GOF = 1.058, reflections collected/unique: 5215/3694 (Rint = 0.0238), Data: 2421, restraints: 0, parameters: 209. CCDC 1829633 contains the supplemental crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Related to Figure 5.
Mechanistic Studies, Related to Figure 8 and Figure 9.

(A) Control Experiments, Related to Figure 8.

To a sealed tube were added 1a (40.2 mg, 0.3 mmol), tBuNC (170 μL, 1.5 mmol), AgOTf (7.8 mg, 0.03 mmol), o-chloranil (147.5 mg, 0.6 mmol) in dry PhCl (3.0 mL) in the glove box. The mixture was stirred at 100°C under N₂ for 24 h. Upon completion, the reaction mixture was cooled down to room temperature and purified by silica gel plate to give product 2a as white solid (6.8 mg, 6%).

To a test tube were added 3a (63.1 mg, 0.3 mmol), tBuNC (170 μL, 1.5 mmol), AgOTf (7.8 mg, 0.03 mmol), o-chloranil (147.5 mg, 0.6 mmol) in dry PhCl (3.0 mL) in the glove box. The mixture was stirred at 80°C under N₂ for 24 h. Upon completion, the reaction mixture was cooled down to room temperature and purified by column chromatography on silica gel to give product 4a as white solid (22.9 mg, 24%).

To a test tube were added 3l (44.4 mg, 0.3 mmol), tBuNC (170 μL, 1.5 mmol), AgOTf (7.8 mg, 0.03 mmol), o-chloranil (147.5 mg, 0.6 mmol) in dry PhCl (3.0 mL) in the glove box. The mixture was stirred at 80°C under N₂ for 24 h. Upon completion, the reaction mixture was cooled down to room temperature and was purified by column chromatography on silica gel to give product 4l as pale yellow oil (26.5 mg, 34%).

To a sealed tube were added 3j (77.5 mg, 0.3 mmol), tBuNC (170 μL, 1.5 mmol), AgOTf (7.8 mg, 0.03 mmol), p-chloranil (147.5 mg, 0.6 mmol) in dry PhCl (3.0 mL) in the glove box. The mixture was stirred at 100°C under N₂ for 24 h. Upon completion, the reaction mixture was cooled down to room temperature and purified by column chromatography on silica gel to give product 4j as pale yellow solid (78.3 mg, 71%).
To a test tube were added 3a (63.1 mg, 0.3 mmol), tBuNC (169 μL, 1.5 mmol), AgOTf (7.8 mg, 0.03 mmol), DDQ (139.0 mg, 0.6 mmol), and TEMPO (93.8 mg, 0.6 mmol) in dry PhCl (3.0 mL) in the glove box. The mixture was stirred at 100 °C under N₂ for 19 h. Upon completion, the reaction mixture was cooled down to room temperature and was purified by column chromatography on silica gel to give product 4a as pale yellow oil (63.3 mg, 66%). In the absence of the radical scavenger TEMPO, the yield was 68%. These results indicate that the radical pathway can probably been ruled out.

To a test tube were added 3j (77.4 mg, 0.3 mmol), tBuNC (169 μL, 1.5 mmol), AgOTf (7.9 mg, 0.03 mmol), DDQ (139.0 mg, 0.6 mmol), and TEMPO (93.8 mg, 0.6 mmol) in dry PhCl (3.0 mL) in the glove box. The mixture was stirred at 100 °C under N₂ for 24 h. Upon completion, the reaction mixture was cooled down to room temperature and was purified by column chromatography on silica gel to give product 4j as pale yellow oil (82.0 mg, ~100%). In the absence of the radical scavenger TEMPO, the yield was 98%. These results again indicate that the radical pathway can probably been ruled out.

(E)-N-(tert-Butyl)-1-cyanoisochroman-1-carbimidoxy cyanide (2a): To a sealed tube was added 1a (40.2 mg, 0.3 mmol), tBuNC (3.0 equiv), AgOTf (7.8 mg, 0.03 mmol), DDQ (139.0 mg, 0.6 mmol) in dry PhCl (3.0 mL) in the glove box. The mixture was stirred at 80 °C under N₂ for 3 h. Upon completion, the reaction mixture was cooled down to room temperature and purified by silica gel plate to give products 2a (36.8 mg, 35%), 2a⁻ (12.8 mg, 16%) and 6a (13.4 mg, 28%), respectively. colorless oil; IR (KBr, cm⁻¹): 2978, 2220, 1647, 1453, 1367, 1285, 1195, 1101, 1061, 762, 746; ¹H NMR (CDCl₃, 500 MHz): δ 7.37 (td, J = 7.5, 1.1 Hz, 1H), 7.31 (t, J = 7.5 Hz, 1H), 7.26 (d, J = 7.5 Hz, 1H), 7.18-7.17 (m, 1H), 4.43-4.39 (m, 1H), 4.13 (td, J = 11.8, 2.7 Hz, 1H), 3.32-3.25 (m, 1H), 2.75 (dd, J = 16.5, 2.0 Hz, 1H), 1.48 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz): 136.3, 134.3, 130.0, 129.9, 127.8, 127.7, 126.1, 116.3, 109.4, 80.2, 63.4, 59.7, 29.0, 27.3; LC-MS (ESI) m/z 268 [M+H]; HRMS (ESI) m/z calcd for C₁₆H₁₆ON₃ [M+H]⁺ 268.1444, found 268.1446.
Isochroman-1-carbonitrile (12) (Yan et al., 2014): white solid. M.p. 43-44 °C; IR (KBr, cm⁻¹): 3071, 3030, 2973, 2933, 2866, 2734, 2232, 2093, 1921, 1821, 1603, 1489, 1434, 1289, 1262, 1197, 1099, 992, 956, 892, 751; ¹H NMR (CDCl₃, 500 MHz): δ 7.31-7.26 (m, 2H), 7.22-7.17 (m, 2H), 5.65 (s, 1H), 4.19-4.10 (m, 2H), 3.05-3.01 (m, 1H); ¹³C NMR (CDCl₃, 125 MHz): 132.9, 129.4, 129.1, 128.7, 127.0, 125.4, 118.1, 65.3, 63.3, 27.2; EI-MS m/z (%): 159 (88) [M⁺], 131 (42), 129 (100), 102 (35), 77 (23).

(B) Mass Spectrometry, Related to Figure 9.

Experimental conditions

Tandem Mass spectrometry instrument:
The electrospray ionization mass spectrometry (ESI-MS) and the subsequent tandem mass spectrometry (ESI-MS/MS) experiments were performed in Thermo TSQ Quantum Access™ triple-quadrupole mass spectrometer (Thermo-Fisher Scientific, Waltham, MA, USA). The basic ESI-MS conditions were: spray voltage, 3000 V; capillary temperature, 275 °C; sheath gas pressure, 2 arb. units; aux gas pressure, 2 arb. units; the collision energy ranged from 5 to 30 eV depending on the dissociation capability of the precursor ions in MS/MS. Data acquisition and analysis were carried out with the Xcalibur software package (Version 2.0, Thermo Fisher Scientific).

General MS experimental conditions:
The concentration of the reaction solution was too high for direct ESI-MS analysis. Therefore, the concentrated reaction solutions in solvent CH₂Cl₂ were first filtered by 0.5 µm membrane and then were diluted 200 times with CH₂Cl₂ before ESI-MS analysis. The diluted CH₂Cl₂ solution was injected by a 500 µL air-tight syringe with speed of the diluted solution was set to 8 µL/min to ESI-MS. We carefully monitored the diluted reaction solution by ESI-MS and found some signals of the reactive intermediates. The electrospray ionization tandem mass spectrometry (ESI-MS/MS) method was performed to assign the possible structures of the reactive intermediates observed by ESI-MS.

Mass spectrometric experiment results

The Reaction Solution 1 was prepared by mixing 1a (39.0 µL, 0.3 mmol), 'BuNC (170.0 µL, 1.5 mmol), AgOTf (7.8 mg, 0.03 mmol), DDQ (139.0 mg, 0.6 mmol) in dry CH₂Cl₂ (3.0 mL). In order to get better and stable signal in ESI-MS analysis, the solvent PhCl at 80 °C (Eq. 1 in Scheme S1) was displaced by CH₂Cl₂ (Eq. 2 in Scheme S1) at room temperature. The synthetic experiments showed that the reaction could also work at such condition. The mixture was stirred at room temperature and ready for measurement in different reaction time.
Scheme S1. The typical reaction condition and the reaction condition for ESI-MS studying by using CH$_2$Cl$_2$ as solvent. Related to Figure 9

The corresponding signal of some important ionic reactive species in the early stage of the reaction, such as B at $m/z$ 133, D at $m/z$ 299, [E+H]$^+$ at $m/z$ 243 were observed in the positive ion ESI-MS spectrum of Reaction Solution 1 (Figure S1a). The possible structures of these intermediates were supposed in Scheme S2 and the ESI-MS/MS experiments for these species were performed and shown in Figure S2. Their proposed dissociation pathways supported their proposed structures (Scheme S3).

Scheme S2. The possible process of the cascade insertion reaction. Related to Figure 9.
Scheme S3. The proposed fragmentation patterns of the important ionic reactive intermediate D at m/z 299, which could give rise to [E+H]+ at m/z 243 by loss of isobutene. These results supported such structure assignments. Related to Figure 9.

Figure S9. (a) The ESI-MS spectrum in positive ion mode of the diluted Reaction Solution 1 at reaction time of 30 min; (b) the expanded ESI-MS spectrum in positive ion mode of Reaction Solution 1 at reaction time of 30 min. Related to Figure 9.
Figure S10. The ESI-MS/MS spectra in positive ion mode of ionic species from Reaction Solution 1: (a) at m/z 133; (b) at m/z 299; (c) at m/z 243. Related to Figure 9.
The corresponding signal of some important ionic reactive species in the early stage of the reaction, such as G at m/z 324, [2a'+H]^+ at m/z 268, and H at m/z 407 were observed in the positive ion ESI-MS spectrum of Reaction Solution 1 (Figure S1). The possible structures of these intermediates were supposed in Scheme S2 and the ESI-MS/MS experiments for these species were performed and shown in Figure S3. Their proposed dissociation pathways supported their proposed structures (Scheme S4).

Figure S11. The ESI-MS/MS spectra in positive ion mode of ionic species from Reaction Solution 1: (a) at m/z 324; (b) at m/z 268; (c) at m/z 407. Related to Figure 9.
Scheme S4. The proposed fragmentation patterns of the important ionic reactive intermediate H at m/z 407, which could give rise to signal of the product [2a+H]^+ at m/z 351 by loss of isobutene. These results supported such structure assignments. Related to Figure 9.

The corresponding signal of some negative ionic species in the reaction, such as CF₃SO₃⁻ at m/z 149, negative radical anion of DDQH⁻ at m/z 226 were observed in the negative ion ESI-MS spectrum of Reaction Solution 1 (Figure S4a). The ESI-MS/MS experiments of the negative radical anion of DDQH⁻ at m/z 226 was performed and shown in Figure S4b, which is proposed structure (Figure S4b).

Figure S12. (a) The ESI-MS spectrum in negative ion mode of the diluted Reaction Solution 1; (b) the ESI-MS/MS spectrum of the negative ion at m/z 226. Related to Figure 9.
Figure S13. $^1$H and $^{13}$C NMR spectra of 1c. Related to Figure 2.
Figure S14. $^1$H and $^{13}$C NMR spectra of 1g. Related to Figure 2.
1H NMR (500 MHz, CDCl₃)

13C NMR (125 MHz, CDCl₃)

Figure S15. ¹H and ¹³C NMR spectra of 1h. Related to Figure 2.
Figure S16. $^1$H and $^{13}$C NMR spectra of 1i. Related to Figure 2.
Figure S17. $^1$H and $^{13}$C NMR spectra of 1k. Related to Figure 2.
Figure S18. $^1$H and $^{13}$C NMR spectra of 1l. Related to Figure 2.
Figure S19. $^{1}$H and $^{13}$C NMR spectra of 1m. Related to Figure 2.
Figure S20. $^1$H and $^{13}$C NMR spectra of 1n. Related to Figure 2.
Figure S21. $^1$H and $^{13}$C NMR spectra of 1o. Related to Figure 2.
Figure S22. $^1$H and $^{13}$C NMR spectra of 1p. Related to Figure 2.
Figure S23. $^1$H and $^{13}$C NMR spectra of 1q. Related to Figure 2.
Figure S24. $^1$H and $^{13}$C NMR spectra of 1r. Related to Figure 2.
Figure S25. $^1$H and $^{13}$C NMR spectra of 3c. Related to Figure 3.
Figure S26. $^1$H and $^{13}$C NMR spectra of 3f. Related to Figure 3.
Figure S27. $^1$H and $^{13}$C NMR spectra of 3g. Related to Figure 3.
Figure S28. $^1$H and $^{13}$C NMR spectra of 3h. Related to Figure 3.
Figure S29. $^1$H and $^{13}$C NMR spectra of 3j. Related to Figure 3.
Figure S30. $^1$H and $^{13}$C NMR spectra of 2a. Related to Table 1.
Figure S31. $^1$H and $^{13}$C NMR spectra of 2b. Related to Figure 2.
Figure S32. $^1$H and $^{13}$C NMR spectra of 2c. Related to Figure 2.
Figure S33. $^1$H and $^{13}$C NMR spectra of 2d. Related to Figure 2.
Figure S34. $^1$H and $^{13}$C NMR spectra of 2e. Related to Figure 2.
Figure S35. $^1$H and $^{13}$C NMR spectra of 2f. Related to Figure 2.
Figure S36. $^1$H and $^{13}$C NMR spectra of 2g. Related to Figure 2.
Figure S37. $^1$H and $^{13}$C NMR spectra of 2h. Related to Figure 2.
Figure S38. $^1$H and $^{13}$C NMR spectra of 2i. Related to Figure 2.
Figure S39. $^1$H and $^{13}$C NMR spectra of 2j. Related to Figure 2.
Figure S40. $^1$H and $^{13}$C NMR spectra of 2k. Related to Figure 2.
Figure S41. $^1$H and $^{13}$C NMR spectra of 2l. Related to Figure 2.
Figure S42. $^1$H and $^{13}$C NMR spectra of 2m. Related to Figure 2.
Figure S43. $^1$H and $^{13}$C NMR spectra of 2n. Related to Figure 2.
Figure S44. $^1$H and $^{13}$C NMR spectra of 2o. Related to Figure 2.
Figure S45. $^1$H and $^{13}$C NMR spectra of 2p. Related to Figure 2.
Figure S46. $^1$H and $^{13}$C NMR spectra of 2q. Related to Figure 2.
Figure S47. $^1$H and $^{13}$C NMR spectra of 2r. Related to Figure 2.
Figure S48. $^1$H and $^{13}$C NMR spectra of 2s. Related to Figure 2.
Figure S49. $^1$H and $^{13}$C NMR spectra of 2t. Related to Figure 2.
Figure S50. $^1$H and $^{13}$C NMR spectra of 2u. Related to Figure 2.
Figure S51. $^1$H and $^{13}$C NMR spectra of 4a. Related to Figure 3.
Figure S52. $^1$H and $^{13}$C NMR spectra of 4b. Related to Figure 3.
Figure S53. $^1$H and $^{13}$C NMR spectra of 4c. Related to Figure 3.
Figure S54. $^1$H and $^{13}$C NMR spectra of 4d. Related to Figure 3.
Figure S55. $^1$H and $^{13}$C NMR spectra of 4e. Related to Figure 3.
Figure S56. $^1$H and $^{13}$C NMR spectra of 4f. Related to Figure 3.
Figure S57. $^1$H and $^{13}$C NMR spectra of 4g. Related to Figure 3.
Figure S58. $^1$H and $^{13}$C NMR spectra of 4h. Related to Figure 3.
Figure S59. $^1$H and $^{13}$C NMR spectra of 4i. Related to Figure 3.
Figure S60. $^1$H and $^{13}$C NMR spectra of 4j. Related to Figure 3.
Figure S61. $^1$H and $^{13}$C NMR spectra of 4k. Related to Figure 3.
Figure S62. $^1$H and $^{13}$C NMR spectra of 4I. Related to Figure 3.
Figure S63. $^1$H and $^{13}$C NMR spectra of 5a. Related to Figure 4.
Figure S64. $^1$H and $^{13}$C NMR spectra of 5b. Related to Figure 4.
Figure S65. $^1\text{H}$ and $^{13}\text{C}$ NMR spectra of 5c. Related to Figure 4.
Figure S66. $^1$H and $^{13}$C NMR spectra of 5d. Related to Figure 4.
Figure S67. $^1$H, $^{19}$F and $^{13}$C NMR spectra of 5e. Related to Figure 4.
Figure S68. $^1$H and $^{13}$C NMR spectra of 5f. Related to Figure 4.
Figure S69. $^1$H and $^{13}$C NMR spectra of 5g. Related to Figure 4.
Figure S70. $^1$H and $^{13}$C NMR spectra of 5h. Related to Figure 4.
Figure S71. $^1$H and $^{13}$C NMR spectra of 5i. Related to Figure 4.
Figure S72. $^1$H and $^{13}$C NMR spectra of 5j. Related to Figure 4.
Figure S73. $^1$H and $^{13}$C NMR spectra of 5l. Related to Figure 4.
Figure S74. $^1$H and $^{13}$C NMR spectra of 5m. Related to Figure 4.
Figure S75. $^1$H and $^{13}$C NMR spectra of 5n. Related to Figure 4.
Figure S76. $^1$H and $^{13}$C NMR spectra of 5o. Related to Figure 4.
Figure S77. $^1$H and $^{13}$C NMR spectra of 5p. Related to Figure 4.
Figure S78. $^1$H and $^{13}$C NMR spectra of 5q. Related to Figure 4.
Figure S79. $^1$H and $^{13}$C NMR spectra of 5r. Related to Figure 4.
Figure S80. $^1$H and $^{13}$C NMR spectra of 5t. Related to Figure 4.
Figure S81. $^1$H and $^{13}$C NMR spectra of 6a. Related to Figure 4.
Figure S82. $^1$H and $^{13}$C NMR spectra of 6b. Related to Figure 4.
Figure S83. $^1$H and $^{13}$C NMR spectra of 6c. Related to Figure 4.
Figure S84. $^1$H and $^{13}$C NMR spectra of 6d. Related to Figure 4.
Figure S85. $^1$H, $^{19}$F and $^{13}$C NMR spectra of 6e. Related to Figure 4.
Figure S86. $^1$H and $^{13}$C NMR spectra of 6f. Related to Figure 4.
Figure S87. $^1$H and $^{13}$C NMR spectra of 6g. Related to Figure 4.
Figure S88. $^1$H and $^{13}$C NMR spectra of 6h. Related to Figure 4.
Figure S89. $^1$H and $^{13}$C NMR spectra of 6i. Related to Figure 4.
Figure S90. $^1$H and $^{13}$C NMR spectra of 6j. Related to Figure 4.
Figure S91. $^1$H and $^{13}$C NMR spectra of 6k. Related to Figure 4.
Figure S92. $^1$H and $^{13}$C NMR spectra of 6l. Related to Figure 4.
Figure S93. $^1$H and $^{13}$C NMR spectra of 6m. Related to Figure 4.
Figure S94. $^1$H and $^{13}$C NMR spectra of 6n. Related to Figure 4.
Figure S95. $^1$H and $^{13}$C NMR spectra of 6o. Related to Figure 4.
Figure S96. $^1$H and $^{13}$C NMR spectra of 6p. Related to Figure 4.
Figure S97. $^1$H and $^{13}$C NMR spectra of 6q. Related to Figure 4.
Figure 598. $^1$H and $^{13}$C NMR spectra of 6r. Related to Figure 4.
Figure S99. $^1$H and $^{13}$C NMR spectra of 6s. Related to Figure 4.
Figure S100. $^1$H and $^{13}$C NMR spectra of 6t. Related to Figure 4.
Figure S101. $^1$H and $^{13}$C NMR spectra of 6u. Related to Figure 4.
Figure S102. $^1$H and $^{13}$C NMR spectra of 6u'. Related to Figure 4.
Figure S103. $^1$H and $^{13}$C NMR spectra of 7b. Related to Figure 5.
Figure S104. $^1\text{H}$ and $^{13}\text{C}$ NMR spectra of 7c. Related to Figure 5.
Figure S105. $^1$H and $^{13}$C NMR spectra of 7d. Related to Figure 5.
Figure S106. $^1$H and $^{13}$C NMR spectra of 7e. Related to Figure 5.
Figure S107. $^1$H and $^{13}$C NMR spectra of 7f. Related to Figure 5.
Figure S108. $^1$H, $^{19}$F and $^{13}$C NMR spectra of 7g. Related to Figure 5.
Figure S109. $^1$H and $^{13}$C NMR spectra of 7h. Related to Figure 5.
Figure S110. $^1$H and $^{13}$C NMR spectra of 7i. Related to Figure 5.
Figure S111. $^1$H and $^{13}$C NMR spectra of 8a. Related to Figure 5.
Figure S112. $^1$H and $^{13}$C NMR spectra of 8b. Related to Figure 5.
Figure S113. $^1$H and $^{13}$C NMR spectra of 8c. Related to Figure 5.
Figure S114. $^1$H and $^{13}$C NMR spectra of 8d. Related to Figure 5.
Figure S115. $^1$H and $^{13}$C NMR spectra of 8e. Related to Figure 5.
Figure S116. $^1$H and $^{13}$C NMR spectra of 8f. Related to Figure 5.
Figure S117. $^1$H, $^{19}$F and $^{13}$C NMR spectra of 8g. Related to Figure 5.
Figure S118. $^1$H and $^{13}$C NMR spectra of 8h. Related to Figure 5.
Figure S119. $^1$H and $^{13}$C NMR spectra of 8i. Related to Figure 5.
Figure S120. $^1$H and $^{13}$C NMR spectra of 9a. Related to Figure 6.
Figure S121. \( ^1H \) and \( ^{13}C \) NMR spectra of \( 9b \). Related to Figure 6.
Figure S122. $^1$H and $^{13}$C NMR spectra of 9c. Related to Figure 6.
Figure S123. $^1$H and $^{13}$C NMR spectra of 9d. Related to Figure 6.
Figure S124. $^1$H and $^{13}$C NMR spectra of 9e. Related to Figure 6.
Figure S125. $^1$H and $^{13}$C NMR spectra of 9f. Related to Figure 6.
Figure S126. $^1$H and $^{13}$C NMR spectra of 9g. Related to Figure 6.
Figure S127. $^1$H and $^{13}$C NMR spectra of 9h. Related to Figure 6.
Figure S128. $^1$H and $^{13}$C NMR spectra of 9i. Related to Figure 6.
Figure S129. $^1$H and $^{13}$C NMR spectra of 9j. Related to Figure 6.
Figure S130. $^1$H and $^{13}$C NMR spectra of 9k. Related to Figure 6.
Figure S131. $^1$H and $^{13}$C NMR spectra of 2a'. Related to Figure 8.
Figure S132. $^1$H and $^{13}$C NMR spectra of 10. Related to Figure 7.
Figure S133. $^1$H and $^{13}$C NMR spectra of 11. Related to Figure 7.
Figure S134. $^1$H and $^{13}$C NMR spectra of 12. Related to Figure 8.
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