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Synthesis of Highly Fused Pyrano[2,3-*b*]pyridines *via* Rh(III)-Catalyzed C-H Activation and Intramolecular Cascade Annulation under Room Temperature

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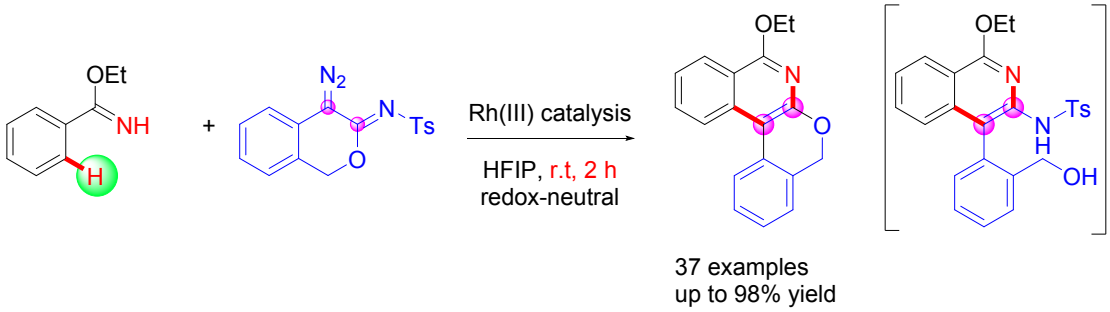
Graphic Abstract



37 examples
up to 98% yield

√ Good functional group tolerance and unique versatility
√ High efficiency and mild reaction conditions
√ Highly fused ring construction & moderate to excellent yields
√ Late-stage diversification of drugs possessing CN group

Abstract

A facile access to the polycyclic fused pyrano[2,3-*b*]pyridines has been established under room temperature *via* Rh(III)-catalyzed C-H bond activation and intramolecular cascade annulation. This strategy features high efficiency, unique versatility, and generality and it can occur under mild conditions in good to excellent yields. More importantly, this strategy can be extended to the late-stage functionalization of drugs possessing CN group.

Introduction

Fused pyrano[2,3-*b*]pyridines are essential privileged scaffolds in medicinal chemistry , exhibiting diversified biological activities including antimicrobial,[1] anti-Alzheimer,[2] anti-inflammatory and analgestic,[3] antirhinovirus,[4] and cannabinoid-1 receptor (CB1R) inverse agonist activity[5] (Figure 1). Additionally, substituted pyrano[2,3-*b*]pyridines have been applied as an effective ligand for C-H bond functionalization in organometallic chemistry.[6] To date, several classical synthetic methods had been reported to build these intriguing pyrano[2,3-*b*]pyridine motifs,[7] and representatively, Taylor's pioneering works on construction of the multi-substituted pyrano[2,3-*b*]pyridines were developed by

pre-preparation of a 1,2,4-triazines precursor in which electron-rich dienophiles, such as alkynes, were incorporated followed with an intramolecular Diels-Alder reaction under high temperature (Scheme 1a). However, these traditional strategies typically required harsh reaction conditions and started from highly functionalized starting materials, which lead to limited generality and low step economy. Thus, it is in high demand to develop more efficient synthetic strategies for the preparation of these important structural motifs.

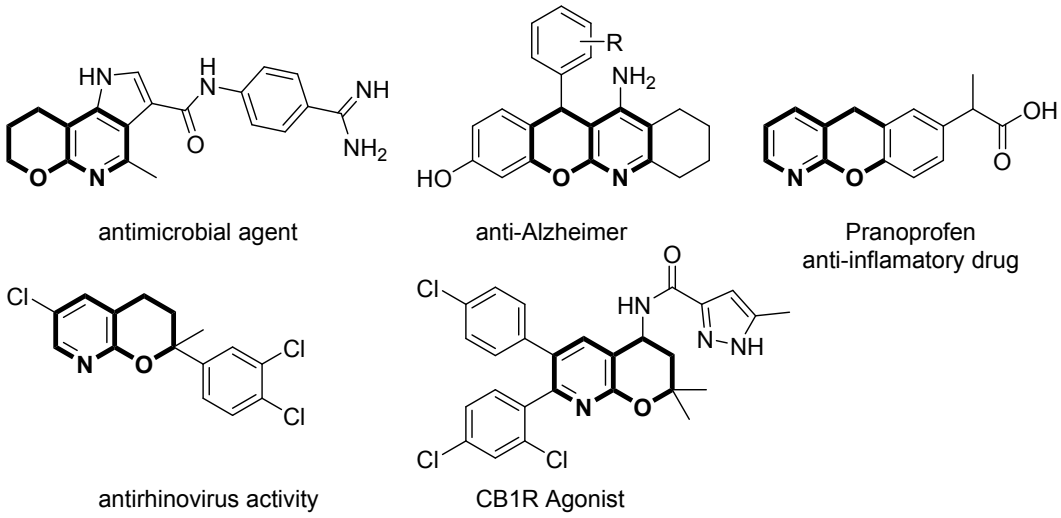
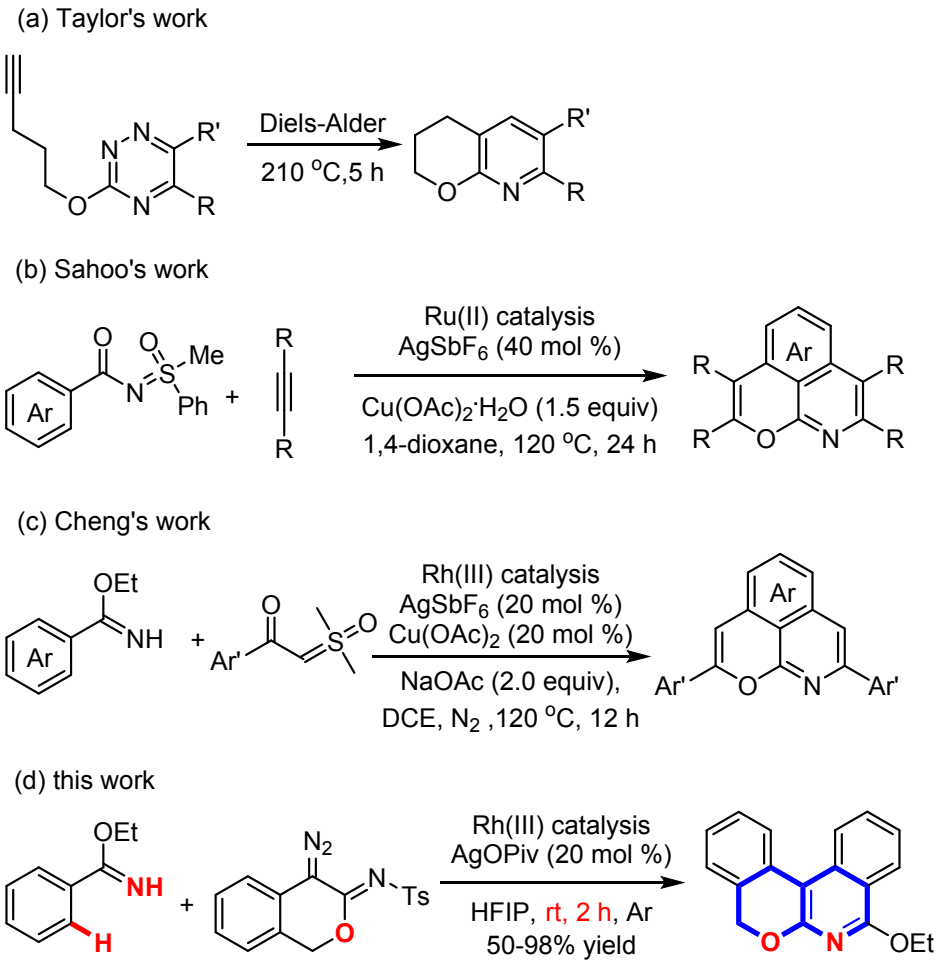


Figure 1. Representative biological compounds containing pyrano[2,3-*b*]pyridines motif

Transition-metal-catalyzed carbon-carbon and/or carbon-heteroatom bond formation through C-H bond activation have attracted attention and been proved to be an efficient tool for both construction of heterocyclic scaffolds and late-stage functionalization of biologically active agents.[8] Among these noble metals, Ru(II) and Rh(III) catalysts performed to be robust catalysts in C-H bond functionalization due to their high reaction efficiency and broad adaptability.[9] For instance, in 2018, the Sahoo's group achieved the construction of fused pyrano[2,3-*b*]pyridine scaffold through one-pot dual C-H bond activation and annulation of *o*-C-H bonds of arenes with cost-effective Ru(II) complex (Scheme 1b).[10] Almost simultaneously, Cheng and co-workers reported another strategy to build the similar

pyrano[2,3-*b*]pyridine skeleton *via* a Rh(III)-catalyzed domino double annulation of C-H bonds between sulfoxonium ylides and ethyl benzimidates (Scheme 1c).[11] In Cheng's study, the imidate moiety in benzimidates was presented as a powerful directing group (DG) which had been extensively exhibited in Rh(III)-catalyzed C-H bond functionalization reactions to establish versatile heterocyclic skeletons. [12] However, it is of note that most of these imidate assisted Rh(III)-catalyzed reactions have inevitably been carried out under high reaction temperature, which may limited their potential application.

Scheme 1. Pyrano[2,3-*b*]pyridine Construction



Within our continuous research effort on rapid construction of diverse drug-like heterocyclic skeletons *via* Rh(III)-catalyzed synthetic strategies,[13] we serendipitously found

that aryl imidates could smoothly couple with 4-diazoisochroman-3-imines to furnish the polycyclic fused pyrano[2,3-*b*]pyridines. The biggest advantage of this methodology is that desired products can be obtained with good to excellent yields (up to 98%) under room temperature along with broad generality and versatility (Scheme 1d). But coincidentally, during the period that our work has been finished and ready to submit, a similar work has been reported by Cheng.[14c] However, his strategy required a rather high reaction temperature (120 °C) and longer time (12 h) for the full conversion. On the contrary, our strategy could be achieved under room temperature in 2 h with good to excellent yields, and it also featured broad substrate generality, especially the strong electron-withdrawing groups, such as nitro group or trifluoromethyl group is also independently compatible for this transformation. Moreover, our strategy can be applied to the late-stage functionalization for different marketed drugs possessing CN group. Herein, we report our obtained results in detail.

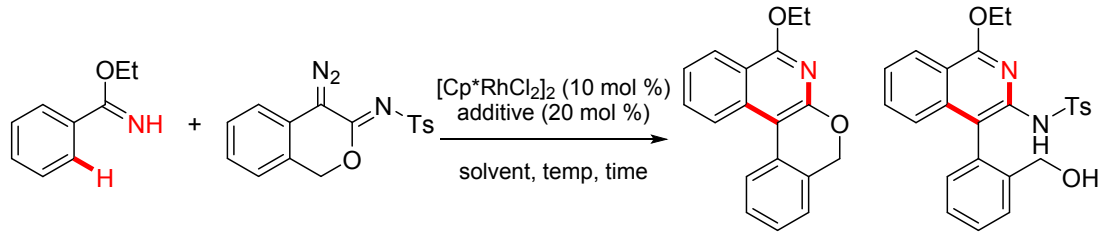
Results and Discussion

Taking into account the typical conditions used in Rh(III)-catalyzed reactions, we have chosen the following starting conditions for our studies: ethyl benzimidate (**1a**) and 4-diazoisochroman-3-imine (**2a**) were mixed in DCE in the presence of $[Cp^*RhCl_2]_2$ (10 mol %), $AgSbF_6$ (20 mol %) and CsOAc (1.0 equiv) and the resulting mixture was stirred at 80 °C for 12 h (Table 1, entry 1). The results displayed that a multiple substituted isoquinoline scaffold **4aa** was mainly attained in 75% yield, however, a product with strong fluorescence under UV-Vis (365 nm wavelength) was isolated with a yield of 10% (Table 1, entry 1). Further structure elucidation verified that it is a polycyclic fused pyrano[2,3-*b*]pyridine motif (**3aa**). Intrigued by this gratifying result, we implemented a

comprehensive screening of the reaction parameters and envisioned that **3aa** could be selectively afforded in a good yield. We first investigated the effects of $AgSbF_6$ and CsOAc, respectively. The results demonstrated that removal of $AgSbF_6$ lead to sharp decrease in the yield of **3aa** (Table 1, entry 2), but omission of CsOAc could give a better yield of **3aa** (Table 1, entry 3). These results indicated that $AgSbF_6$ was of great importance for this transformation. The reaction temperature was defined in the following explorations and we noticed that this process could be carried out smoothly under room temperature to afford **3aa** in 36% yield (Table 1, entry 4) but **4aa** was detected only in a trace yield. Solvents screening was subsequently carried out (Table 1, entries 5-11) and HFIP was optimal for the formation of **3aa** in 66% yield (Table 1, entry 8), whereas in EtOH **4aa** was predominantly afforded in 81% yield together with 11% of **3aa** (Table 1, entry 6). A series of additives was successively explored (Table 1, entries 12-19) and when displacing $AgSbF_6$ with AgOPiv, the yield of **3aa** was dramatically increased to 83% and only trace amount of **4aa** could be detected (Table 1, entry 14). We kept exploring the optimal reaction conditions. After adjusting the equivalent of **2a** to 1.5 fold and sealing the system in argon atmosphere, **3aa** was detected in 94% yield and subsequent studies revealed that it was no obvious discrepancy of the yield of **3aa** when independently ceased the reaction at 12 h and 6 h (Table 1, entries 21-22). Further study had confirmed that this process could finish its full conversion in only 2 h with **3aa** isolated in 93% yield (Table 1, entry 23). Afterwards, the amount of $[Cp^*RhCl_2]_2$ was also examined and when 5% of Rh(III) catalyst was presented, although with a slightly lower efficiency, compound **3aa** could still be detected in 86% yield (Table 1, entry 24) . However, only 50% of **3aa** was detected after altering the amount of $[Cp^*RhCl_2]_2$ to 2.5% (Table 1, entry 25) and

no more desired product was obtained under the absence of $[Cp^*RhCl_2]_2$, indicating the $[Cp^*RhCl_2]_2$ catalyst is necessary for this transformation (Table 1, entry 26).

Table 1. Optimization of the Reaction Conditions[a]



1a **2a** **3aa** **4aa**

entry	additive	solvent	temp (°C)	yield[b] (%) of **3aa**/**4aa**
1[c]	$AgSbF_6$/CsOAc	DCE	80	10 / 75
2	CsOAc	DCE	80	0 / 15
3	$AgSbF_6$	DCE	80	39 / 32
4	$AgSbF_6$	DCE	rt	36/trace
5	$AgSbF_6$	DMA	rt	6/79
6	$AgSbF_6$	EtOH	rt	11/81
7	$AgSbF_6$	TFE	rt	44/28
8	$AgSbF_6$	HFIP	rt	66/18
9	$AgSbF_6$	Toluene	rt	11/67
10	$AgSbF_6$	1,4-dioxane	rt	19/53
11	$AgSbF_6$	THF	rt	trace/32
12	$AgBF_4$	HFIP	rt	27/17
13	$AgNTf_2$	HFIP	rt	48/12

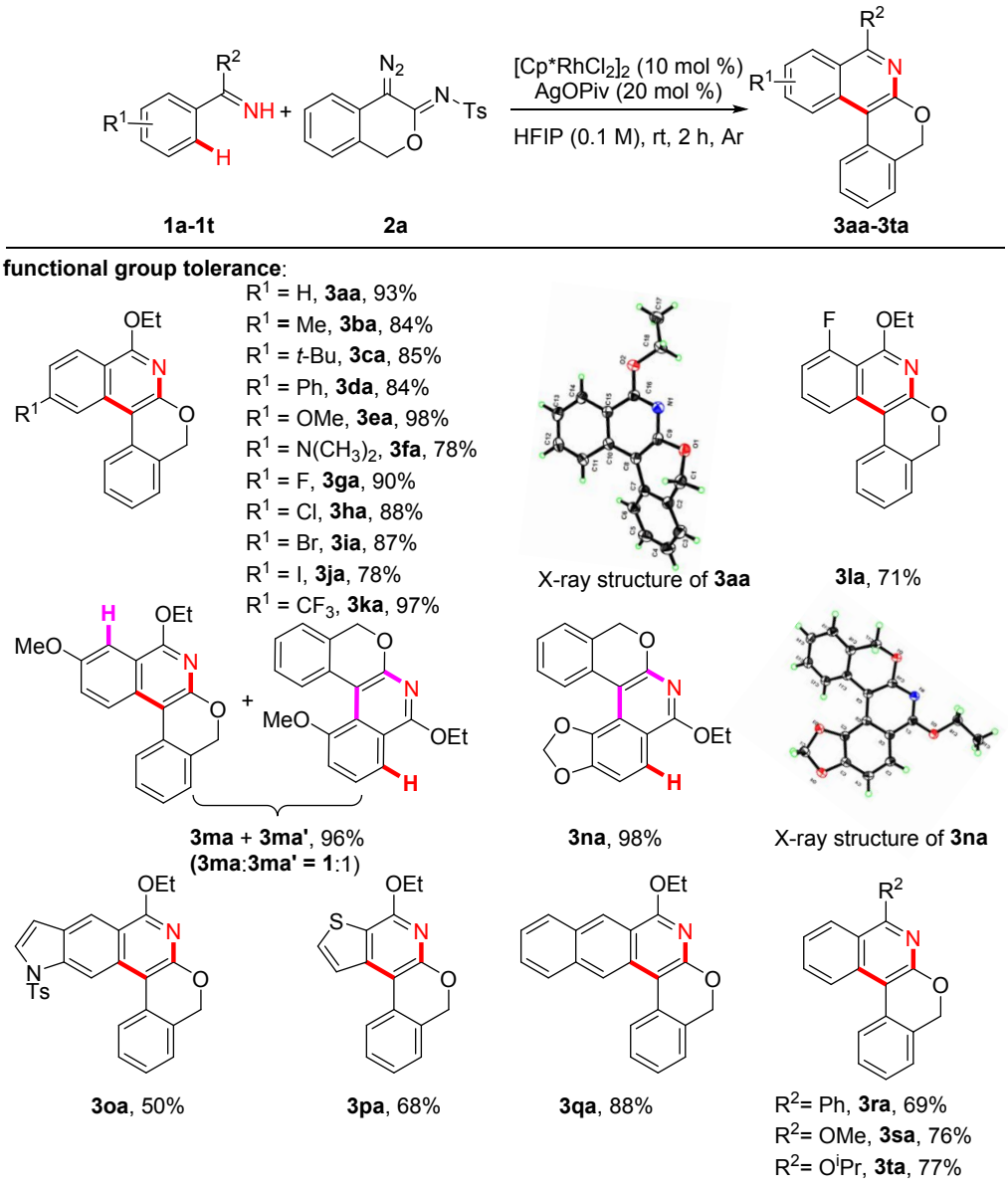
14	AgOPiv	HFIP	rt	83/trace
15	Ag_2CO_3	HFIP	rt	64/27
16	$AgPF_6$	HFIP	rt	43/14
17	AgOTf	HFIP	rt	57/8
18	AgOAc	HFIP	rt	64/12
19	AgTFA	HFIP	rt	59/13
20[d]	AgOPiv	HFIP	rt	86/ND
21[e]	AgOPiv	HFIP	rt	94/ND
22[e,f]	AgOPiv	HFIP	rt	94/ND
23[e,g]	AgOPiv	HFIP	rt	95(93)[h]/ND
24[e,g,i]	AgOPiv	HFIP	rt	86/ND
25[e,g,j]	AgOPiv	HFIP	rt	50/ND
26[e,g,k]	AgOPiv	HFIP	rt	N.R.

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), $[Cp^*RhCl_2]_2$ (10 mol %) and additive (20 mol %) in solvent (0.1 M) for 12 h under air. [b]Determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [c]1.0 equiv of CsOAc was supplemented**.** [d]Under Argon atmosphere. [e]1.5 equiv of **2a** was applied; the reaction was conducted under Argon atmosphere. [f]The reaction time was shorten to 6 h. [g]The reaction time was 2 h.[h]Isolated yield of **3aa.** [i]$[Cp^*RhCl_2]_2$ (5 mol %) was presented. [j]$[Cp^*RhCl_2]_2$ (2.5 mol %) was presented. [k]Without $[Cp^*RhCl_2]_2$.

With the optimal reaction conditions in hand, we first verified the substrate scope of aryl imidates (Table 2). Many aryl imidates with substituents installed on the *para* position of the

benzene ring were firstly examined and these derivatives bearing an electron-withdrawing group or electron-donating group react smoothly with **2a** to afford the fused pyrano[2,3-*b*]pyridine motifs (**3aa-3ka**) in good to excellent yields. And it is unambiguous of the molecular structure of **3aa** which was further verified by X-ray crystallography.[15] The *ortho*-substituted aryl imidate was additionally defined, furnishing the product in good yield (**3la**, 71%). Introduction of substituents to the *meta* position of benzene ring was also tolerated but without getting more products which cyclized on the less hindered site, two regioisomeric products **3ma** and **3ma'** were obtained in a total yield of 96% with an equivalent ratio. More surprisingly, when benzodioxole derivative was applied, mono-isomer that cyclization was occurred on the much hindered site was attained in a 98% yield (**3na**). The molecular structure of **3na** was subsequently confirmed with X-ray crystallography.[16] These results indicated that the electrostatic effect is the predominant factor which determined the regioselectivity of this transformation rather than the steric effect. Significantly, heterocycles bearing indole scaffold and thiophene were independently examined and the corresponding products **3oa** and **3pa** were obtained in 50% and 68% yields, respectively. Besides these heterocycles, naphthalene imidate was also compatible under standard reaction conditions and the desired product **3qa** could be afforded in 88% yield. Moreover, benzophenone NH imine (**3ra**) and other aryl imidate esters (**3sa-3ta**) were also tested and they were tolerated in this reaction albeit with a slightly lower efficiency.

Table 2. Substrate Scope with Aryl Imidates for Assymbly of 3[a,b]

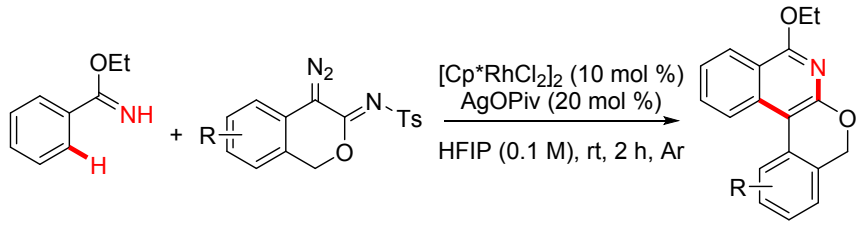


[a]Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), $[Cp^*RhCl_2]_2$ (10 mol %) and AgOPiv (20 mmol %) in HFIP (0.1 M) at ambient temperature for 2 h under Ar atmosphere; [b]Isolated yield

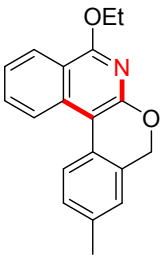
We next evaluated the substrate scope of the diazo coupling partner (Table 3) and the results revealed that electron-withdrawing or electron-donating groups incorporated derivatives were fully tolerated to this process and the desired products could be obtained in moderate to good yields. For example, when CH_3 or Cl was incorporated at the *para* position of benzene ring, the reaction could complete smoothly to afford **3ab** and **3ac** in 78% and 58%

yield, respectively. Other substituents such as F or CF_3 incorporated at the *para* position were also tolerated and the desired products were obtained in good yields (**3ad**, 66%; **3ae**, 80%). It was worth mentioning that substrate bearing NO_2 group was also compatible to furnish the product **3af** in 77% yield. *Meta* position incorporated starting materials were also scrutinized and they were all tolerated to the reaction by producing the desired products in good to excellent yields **(3ag-3al)**. For instance, **3ai** was obtained in 94% yield and **3ak**, which bearing a CF_3 group, was also attained in 91% yield. Substrate with benzodioxole moiety was also viable in this transformation albeit a slightly lower yield was detected (**3al**, 76%**)**.

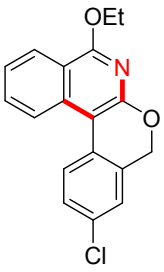
Table 3. Substrate Scope of 4-Diazoisochroman-3-imines[a,b]



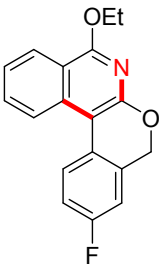
1a **2b-2l** **3ab-3al**



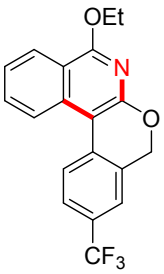
3ab, 78%



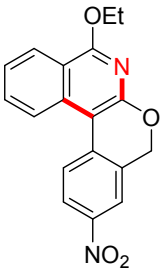
3ac, 58%



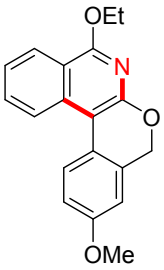
3ad, 66%



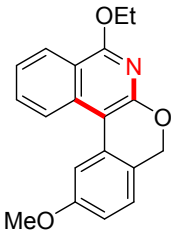
3ae, 80%



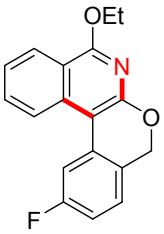
3af, 77%



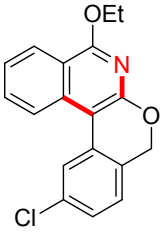
3ag, 70%



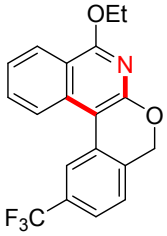
3ah, 79%



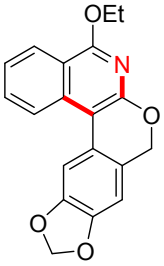
3ai, 94%



3aj, 82%



3ak, 91%



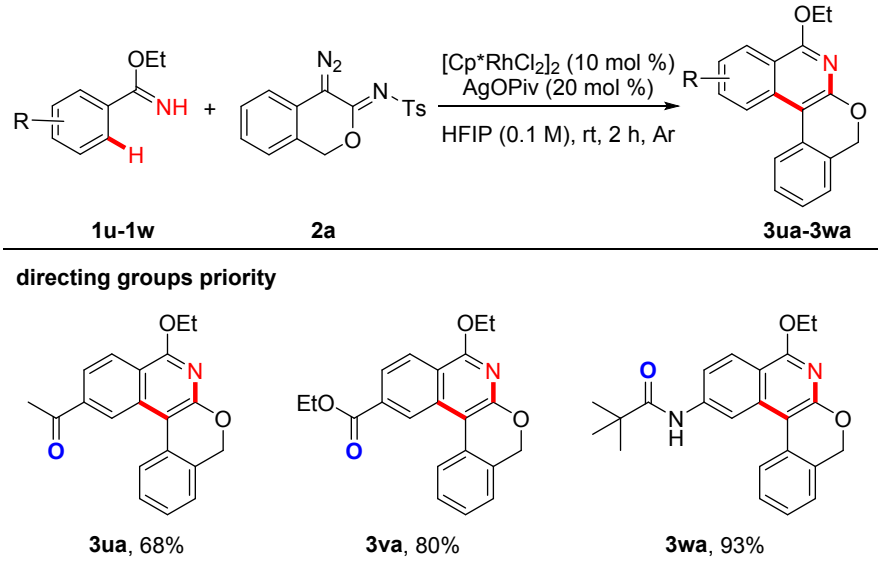
3al, 76%

[a]Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), $[Cp^*RhCl_2]_2$ (10 mol %) and AgOPiv (20 mmol %) in HFIP (0.1 M) at ambient temperature for 2 h under Ar atmosphere; [b]Isolated yield

After established a preliminary knowledge of the optimal reaction conditions and functional group tolerance, intrigued by the priority of directing groups, selected aryl imidates were further explored (**3ua-3wa**) and the results indicated that imine as directing group outcompeted ketone (**3ua**), ester (**3va**) and NHPiv (**3wa**) leading to the fused

pyrano[2,3-*b*]pyridine scaffold in a very high selective manner (Scheme 2).

Scheme 2. Directing Groups Priority of Imidates

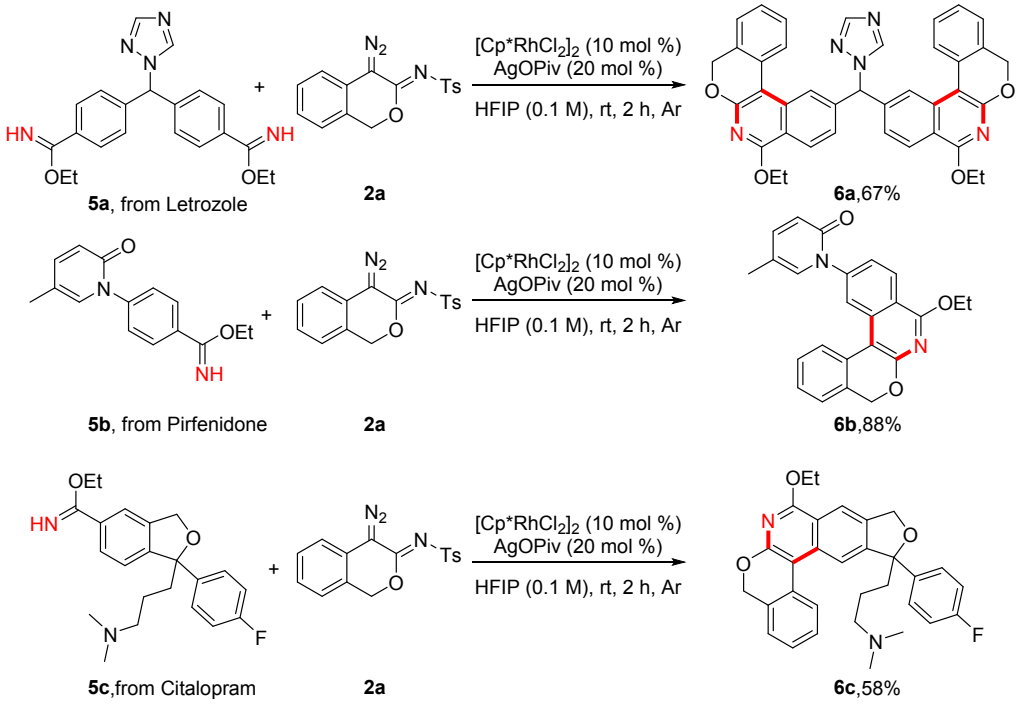


[a]Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), $[Cp^*RhCl_2]_2$ (10 mol %) and AgOPiv (20 mmol %) in HFIP (0.1 M) at ambient temperature for 2 h under Ar atmosphere; [b]Isolated yield

Intrigued by the highly fused heterocyclic product derived from our strategy, we have further explored the synthetic utility of this transformation on the late-stage functionalization for clinical drugs possessing CN group including Letrozole, Pirfenidone and Citalopram. After first transferring the CN group in these drugs into the corresponding imidates, a coupling reaction with **2a** was independently processed under standard conditions and the functionalized drug molecules could be obtained in moderate to good yields. These results indicated that the strategy could be extended to the late-stage functionalization of more clinical drugs possessing CN group for drug discovery (Scheme 3). In addition, gram-scale reaction was subsequently conducted with a maintained reaction efficiency (91% yield, for gram-scale reaction), which further demonstrated the potential synthetic utility of this

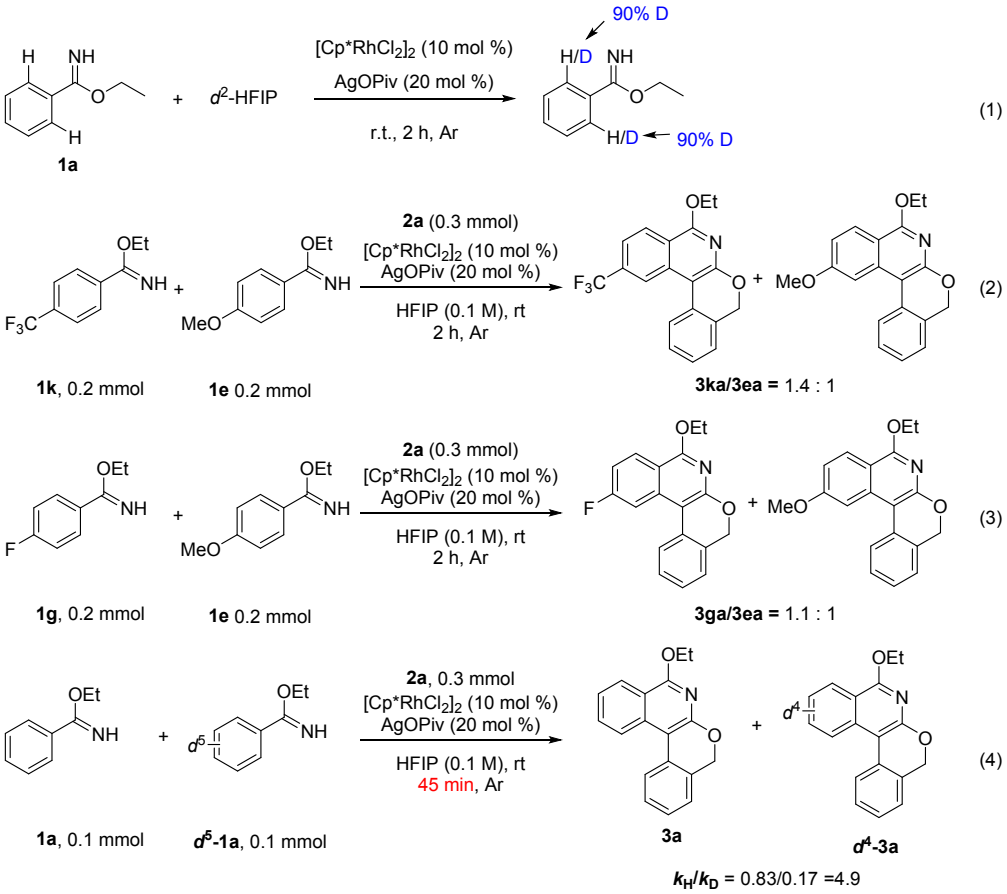
strategy.

Scheme 3. Late-stage Diversification of Drugs Possessing CN Group



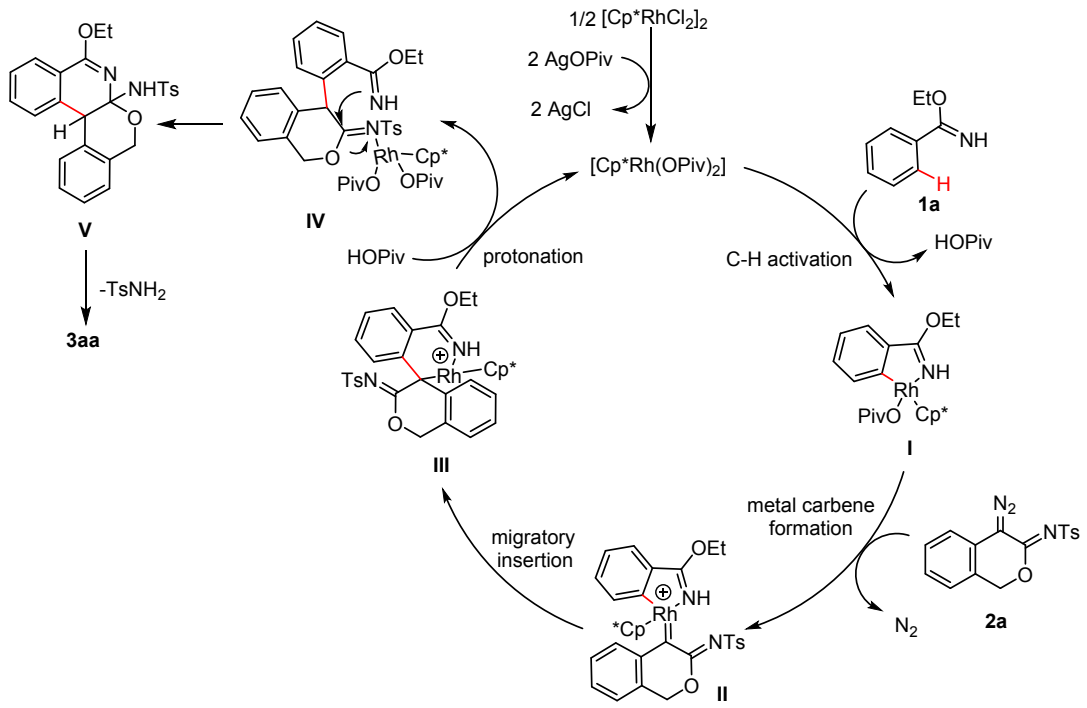
In order to gain insight into the preliminary mechanism of this reaction, several studies were independently performed. In the H/D exchange study, the reaction of **1a** in d^2-HFIP in the absence of substrate **2a** indicated that the C-H bond activation was reversible (Scheme 4, eq 1). Furthermore, the intermolecular competition experiments were parallel conducted between **1e** and **1k** or **1e** and **1g** under standard reaction conditions, respectively and the results both indicated that benzimidate that bearing an electron-withdrawing group reacted preferentially (Scheme 4, eq 2 and eq 3). Moreover, the kinetic isotope effect (KIE) experiment was performed using substrate **1a** and **1a-*d*^{5}** coupled with **2a** under standard reaction conditions at a low conversion (Scheme 4, eq 4). The KIE value of 4.9 indicated that the cleavage of C-H bond might be involved in the rate-determining step.

Scheme 4. Mechanistic Investigations



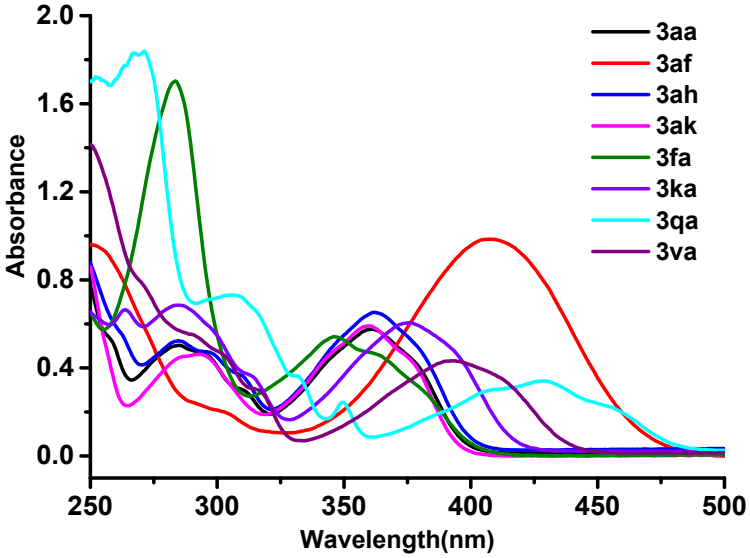
On the basis of these results and previous reports[14, 17], a plausible mechanism for the generation of **3aa** has been proposed (Scheme 5). $[Cp^*RhCl_2]_2$ was first activated by ligand exchange with AgOPiv to form $Cp^*Rh(OPiv)_2$ which coordinates with substrate **1a** to generate the rhodacyclic intermediate **I** *via* C-H bond activation following the release of HOPiv. Meanwhile, the active catalyst is coordinated with substrate **2a** following with exclusion of N_2 to yield the rhodium carbine intermediate **II** which subsequently undergoes intramolecular migratory insertion to afford the intermediate **III**. Protonolysis of the generated intermediate **III** finally triggers the formation of intermediate **IV**, which is sequentially proceeded via an intramolecular nucleophilic addition and elimination of $TsNH_2$ to eventually furnish the desired product **3aa** with a release of the Rh (III) species.

Scheme 5. Proposed Catalytic Cycle

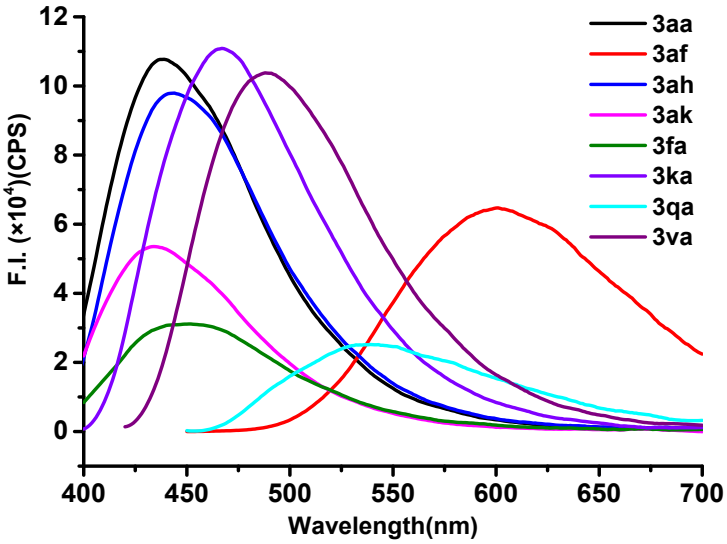


Taking into account the strong fluorescence of compound **3aa** under UV-Vis (365 nm wavelength) and in order to verify the fluorescent properties of these compounds, UV-Vis and fluorescence spectra were tested for chosen compounds (Scheme 6). Comparing with **3aa**, compound **3af** and **3qa** exhibited obvious red shift indicating a strong visible-light absorption property (407 nm for **3af**; 428 nm for **3qa**) (Scheme 6a). In fluorescence spectra, **3af** exhibited strong fluorescence emission peak at 600 nm while **3qa** also showed an emission peak at 535 nm. The other compounds including **3aa**, **3ah**, **3ak**, **3fa**, **3ka** and **3va** had a most similar range of the emission peak around 433-488 nm (Scheme 6b). After obtaining the absorbance and emission data of chosen compounds, Strokes' shift was calculated in Table 4 and it ranged from 73 nm for **3ak** to 193 nm of **3af**.

Scheme 6. UV-Vis and Fluorescence Spectra



(a) UV-Vis Spectra (5×10^{-5} M in DCM)



(b) Fluorescence Spectra (5×10^{-5} M in DCM)

Table 4. Absorption and Emission Data[a]

Compound	**3aa**	**3af**	**3ah**	**3ak**	**3fa**	**3ka**	**3qa**	**3va**
λ_{abs} (nm)	360	407	362	360	346	375	428	392
λ_{em} (nm)	438	600	443	433	448	466	535	488
Strokes' shift (nm)	78	193	81	73	102	91	107	96

[a]In DCM (5×10^{-5} M)

Conclusion

In conclusion, we have developed an efficient synthetic strategy for the rapid establishment of highly fused heterocyclic compound *via* Rh(III)-catalyzed C-H bond activation and cascade annulation under room temperature. This strategy featured broad synthetic generality, unique versatility and high efficiency. Gram-scale reaction was also carried out with maintained efficiency. In addition, this strategy is applicable in late-stage diversification of drugs possessing CN group, which provided a potential tool for the structural modification of biological active compounds.

Experimental Section

General Information. All reagents and solvents were purchased from commercial sources (J&K, TCI, Adamas-beta, etc.) and used as received without further purification. Dichloro(η5-pentamethylcyclopentadienyl)rhodium(III) dimer (99%) was purchased from Sinocompound Technology Co., Ltd. Analytical thin layer chromatography (TLC) was HSGF 254 (0.15-0.2 mm thickness). AgOPiv was prepared as a reported literature indicated.[18] ^{1}H and ^{13}C nuclear magnetic resonance spectra (NMR) were acquired on a Bruker 400 MHz or 500 MHz or 600 MHz NMR spectrometer. Chemical shifts (δ) were expressed in ppm using tetramethylsilane as an internal reference and the coupling constants (J) were indicated in Hz. The coupling constants were described as singlet (s), doublet (d), triplet (t), quartet (q),quintet (quint), broad (br) or multiplet (m). LRMS data was tested on a Thermo Fisher Finnigan LEQ with Electrospray Ionization (ESI). HRMS data was obtained on an Agilent G6520 Q-TOF with Electrospray Ionization (ESI). The UV-vis spectra were carried out on an Ocean Optics Maya 2000 Pro spectrometer. The fluorescence spectra were measured with a HORIBA Jobin

Yvon Fluoromax-4 fluorescence spectrometer.

General Procedure for the Synthesis of Substrate 1 (1a-1w) and 5 (5a-5c). 1r is commercially available and other aryl imidates were synthesized according to a reported literature.[19] Aryl nitrile (20 mmol, 1.0 equiv) was dissolved in alcohol (240 mmol, 12.0 equiv) in a round bottom flask. To the mixture was added AcCl (160 mmol, 8.0 equiv) over 30 min in an ice bath. After the addition, ice bath was removed and the reaction mixture was stirred at room temperature for 4-12 h. Solvent was removed under reduced pressure and the resulting solid was washed with EA (10 mL x 3 times). The solid was dissolved in EA (50.0 mL) and saturated $NaHCO_3$ solution was added dropwise until the pH of the solution is above 7. The organic layer was collected, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to yield the crude product which was further purified by flash chromatography to afford the desired product. Compounds **1a**[19], **1b**[20a], **1d**[20b], **1e**[19], **1g**[20c], **1h**[19], **1k**[20d], **1m**[20e], **1p**[20f], **1q**[20b], **1r**[20g], **1s**[20h], **1t**[20i] and d^5-**1a**[20j] are known compounds and the spectroscopic and physical data were completely matched with the characterization data from the literatures.

*Ethyl 4-(tert-butyl)benzimidate (**1c**)*. Colorless oil (350 mg, 78% yield); ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.73 (s, 1H), 7.75 (d, J = 8.5 Hz, 2H), 7.41 (d, J = 8.5 Hz, 2H), 4.26 (q, J = 7.1 Hz, 2H), 1.31 (t, J = 7.1 Hz, 3H), 1.25 (s, 10H); ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 165.3, 153.2, 129.5, 126.4, 125.0, 60.6, 34.3, 30.8, 14.1; LRMS (ESI): *m/z* 206.1 $[M + H]^+$; HRMS (ESI): calculated for $C_{13}H_{20}NO^+$ $[M + H]^+$: 206.1539, found: 206.1538.

*Ethyl 4-(dimethylamino)benzimidate (**1f**)*.White solid (2.2 g, 57% yield); m.p. 58.9-59.1 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.36 (s, 1H), 7.66 (d, J = 8.4 Hz, 2H), 6.68 (d, J = 9.0 Hz, 2H), 4.20 (q, J = 7.2 Hz, 2H), 2.94 (s, 6H), 1.30 (t, J = 7.2 Hz, 3H); ^{13}C{^{1}H}

NMR (151 MHz, DMSO-d_6): δ 165.5, 151.6, 127.9, 119.0, 111.0, 60.3, 39.7, 14.3; LRMS (ESI): *m/z* 193.1 $[M + H]^+$; HRMS (ESI): calculated for $C_{11}H_{17}N_2O$ $[M + H]^+$: 193.2335, found: 193.1331.

*Ethyl 4-bromobenzimidate (**1i**)*. Colorless oil (2.0 g, 44% yield); ^{1}H NMR (600 MHz, DMSO-d_6): δ 9.00 (s, 1H), 7.76 (d, J = 8.4 Hz, 2H), 7.63 (d, J = 8.4 Hz, 2H), 4.23 (q, J = 7.2 Hz, 2H), 1.30 (t, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6): δ 164.0, 131.4, 131.2, 128.8, 124.4, 61.0, 14.2; LRMS (ESI): *m/z* 228.0 $[M + H]^+$; HRMS (ESI): calculated for $C_9H_{11}NBrNO^+$ $[M + H]^+$: 228.0014, found: 228.0019.

*Ethyl 4-iodobenzimidate (**1j**)*. Colorless oil (3.6 g, 65% yield); m.p. 34.1-34.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.98 (s, 1H), 7.82 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 8.4 Hz, 2H), 4.22 (q, J = 7.2 Hz, 2H), 1.30 (t, J = 7.2 Hz, 4H); ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6): δ 164.3, 137.3, 131.5, 128.7, 98.2, 61.0, 14.2; LRMS (ESI): *m/z* 276.0 $[M + H]^+$; HRMS (ESI): calculated for $C_9H_{11}INO^+$ $[M + H]^+$: 275.9880, found: 275.9871.

*Ethyl 2-fluorobenzimidate (**1l**)*. Colorless oil (1.6 g, 48% yield); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.60 (d, J = 3.6 Hz, 1H), 77.61-7.57 (m, 1H), 7.53–7.48 (m, 1H), 7.31–7.24 (m, 2H), 4.24 (q, J = 7.2 Hz, 2H), 1.29 (t, J = 7.2Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 162.1, 159.4 (d, J = 250.2 Hz), 132.2 (d, J = 8.8 Hz), 129.3 (d, J = 2.4 Hz), 124.5 (d, J = 3.5 Hz), 121.7 (d, J = 11.5 Hz), 116.2 (d, J = 22.0 Hz), 60.93, 13.99; ^{19}F NMR (471 MHz, DMSO-d_6): δ -116.12 (d, J = 5.9 Hz); LRMS (ESI): *m/z* 168.1 $[M + H]^+$; HRMS (ESI): calculated for $C_9H_{11}FNO^+$ $[M + H]^+$: 168.0819, found: 168.0816.

*Ethyl benzo[d][1,3]dioxole-5-carbimidate (**1n**)*. White solid (2.8 g, 72% yield); m.p. 42.1-42.6 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.70 (s, 1H), 7.40 (d, J = 1.8 Hz, 1H), 7.37

(dd, J = 7.8, 1.8 Hz, 1H), 6.95 (d, J = 8.4 Hz, 1H), 6.08 (s, 2H), 4.20 (q, J = 7.2 Hz, 2H), 1.29 (t, J = 7.2 Hz, 4H); $^{13}C\{^{1}H\}$ NMR (151 MHz, DMSO-d_6): δ 164.3, 149.2, 147.5, 126.2, 121.5, 107.9, 107.0, 101.7, 60.8, 14.2; LRMS (ESI): *m/z* 194.0 $[M + H]^+$; HRMS (ESI): calculated for $C_{10}H_{12}NO_3^+$ $[M + H]^+$: 194.0812, found: 194.0807.

*Ethyl 1-tosyl-1H-indole-5-carbimidate (**1o**)*. Light yellow solid (1.1 g, 16% yield); m.p. 136.4-137.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.87 (s, 1H), 8.07 (d, J = 2.0 Hz, 1H), 7.97 (d, J = 8.8 Hz, 1H), 7.88-7.86 (m, 3H), 7.81 (dd, J = 8.8, 2.0 Hz, 1H), 7.38-7.36 (m, 2H), 6.92-6.90 (m, 1H), 4.24 (q, J = 7.2 Hz, 2H), 2.29 (s, 3H), 1.31 (t, J = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (126 MHz, DMSO-d_6): δ 165.5, 146.2, 135.6, 134.5, 130.8, 128.6, 128.3, 127.2, 123.9, 120.9, 113.3, 110.3, 61.4, 21.5, 14.7; LRMS (ESI): *m/z* 343.0 $[M + H]^+$; HRMS (ESI): calculated for $C_{18}H_{19}N_2O_3S^+$ $[M + H]^+$: 343.1111, found: 343.1113.

*Ethyl 4-acetylbenzimidate (**1u**)*. White solid (1.4 g, 37% yield); m.p. 42.6-43.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.15 (s, 1H), 8.02-7.99 (m, 2H), 7.95–7.93 (m, 2H), 4.26 (q, J = 7.2 Hz, 2H), 2.60 (s, 3H), 1.33 (t, J = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (151 MHz, DMSO-d_6): δ 197.6, 164.3, 138.2, 135.8, 128.3, 128.1, 127.7, 127.1, 61.2, 26.9, 14.2; LRMS (ESI): *m/z* 192.2 $[M + H]^+$; HRMS (ESI): calculated for $C_{11}H_{14}NO_2^+$ $[M + H]^+$: 192.1019, found: 192.1014.

*Ethyl 4-(ethoxy(imino)methyl)benzoate (**1v**)*. White solid (1.3g, 29% yield); m.p. 67.4-69.3 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.14 (s, 1H), 8.00 (d, J = 8.4 Hz, 2H), 7.94 (d, J = 8.4 Hz, 2H), 4.32 (q, J = 7.2 Hz, 2H), 4.26 (q, J = 7.2 Hz, 2H), 1.32 (t, J = 7.2 Hz, 6H); $^{13}C\{^{1}H\}$ NMR (151 MHz, DMSO-d_6): δ 165.2, 164.2, 136.0, 131.6, 129.2, 127.1, 61.2, 61.0,

14.1, 14.1; LRMS (ESI): *m/z* 222.1 $[M + H]^+$; HRMS (ESI): calculated for $C_{12}H_{16}NO_3^+$ $[M + H]^+$: 222.1125, found: 222.1120.

*Ethyl 4-pivalamidobenzimidate (**1w**).* White solid (2.4g, 48%); m.p. 122.5-123.7 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ 9.38 (s, 1H), 8.70 (s, 1H), 7.78–7.73 (m, 4H), 4.22 (q, J = 7.2 Hz, 2H), 1.32 (d, J = 7.2 Hz, 3H), 1.23 (s, 9H); ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6): δ 176.7, 164.8, 141.6, 127.8, 127.2, 126.5, 119.3, 60.7, 27.1, 14.3; LRMS (ESI): *m/z* 249.2 $[M + H]^+$; HRMS (ESI): calculated for $C_{14}H_{21}N_2O_2^+$ $[M + H]^+$: 249.1598, found: 249.1594.

*Diethyl 4,4'-(1H-1,2,4-triazol-1-ylmethanediyl)dibenzenecarboximidate (**5a**)*. White solid (465 mg, 72% yield); m.p. 102.7-103.4 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.90 (s, 2H), 8.64 (s, 1H), 8.09 (s, 1H), 7.82 (d, J = 8.0 Hz, 4H), 7.30 (d, J = 8.5 Hz, 4H), 7.23 (s, 1H), 4.24 (q, J = 7.1 Hz, 4H), 1.30 (t, J = 6.0 Hz, 7H); ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 164.7, 152.1, 144.6, 141.3, 131.9, 128.1, 127.1, 64.6, 60.9, 14.1; LRMS (ESI): *m/z* 378.2 $[M + H]^+$; HRMS (ESI): calculated for $C_{21}H_{24}N_5O_2^+$ $[M + H]^+$: 378.1925, found: 378.1927.

*Ethyl 4-(5-methyl-2-oxopyridin-1(2H)-yl)benzimidate (**5b**)*. White solid (178 mg, 82% yield); m.p. 129.5-131.0 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.03 (s, 1H), 7.94 (d, J = 8.0 Hz, 2H), 7.48 (d, J = 8.0 Hz, 2H), 7.45-7.44 (m, 1H), 7.39 (dd, J = 9.0, 2.5 Hz, 1H), 6.44 (d, J = 9.5 Hz, 1H), 4.36-4.26 (m, 2H), 2.05 (s, 3H), 1.34 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 164.3, 160.3, 143.2, 142.7, 135.6, 131.5, 127.5, 126.7, 120.2, 114.2, 61.0, 16.3, 14.1; LRMS (ESI): *m/z* 257.1 $[M + H]^+$; HRMS (ESI): calculated for $C_{15}H_{17}N_2O_2^+$ $[M + H]^+$: 257.1285, found: 257.1284.

*Ethyl 1-(3-(dimethylamino)propyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbimidate (**5c**)*. Light yellow oil (220 mg, 24%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.66 (d, J =

8.0 Hz, 1H), 7.58 (s, 1H), 7.44-7.42 (m, 2H), 7.30 (d, J = 8.0 Hz, 1H), 6.99-6.95 (m, 2H), 5.15 (dd, J = 23.0, 12.5 Hz, 2H), 4.29 (q, J = 7.0 Hz, 2H), 2.26–2.23 (m, 2H), 2.20–2.16 (m, 2H), 2.14 (s, 6H), 1.52-1.43 (m, 1H), 1.40 (t, J = 7.5 Hz, 3H), 1.36-1.27 (m, 1H); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): δ 166.9, 162.0 (d, J = 246.1 Hz), 147.0, 140.6 (d, J = 3.4 Hz), 139.7, 133.0, 126.9 (d, J = 7.9 Hz), 126.6, 121.9, 119.9, 115.2 (d, J = 21.3 Hz), 90.9 , 71.8, 61.9, 59.6, 45.3, 39.2, 22.2, 14.3; ^{19}F NMR (471 MHz, $CDCl_3$): δ -116.04; LRMS (ESI): *m/z* 371.1 $[M + H]^+$; HRMS (ESI): calculated for $C_{22}H_{28}FN_2O_2^+$ $[M + H]^+$: 371.2129, found: 371.2136.

General Procedure for the Preparation of Substrate 2 (2a-2l). Compound **2** was synthesized starting from (2-ethynylphenyl)methanols[21] according to a reported literature.[22] To a two-neck round bottom flask was successively added (2-ethynylphenyl)methanols (5.0 mmol, 1.0 equiv), CuBr (0.5 mmol, 0.1 equiv) and NEt_3 (10.0 mmol, 2.0 equiv) in anhydrous MeCN (50 mL, 0.1 M). The mixture was evacuated and refilled with Ar for 3 times. To the resulting mixture was slowly added *p*-toluenesulfonyl azide (75% in EA solution, 11.0 mmol, 2.2 equiv) over 10 min under Ar and the reaction was processed under room temperature for 4-6 h. Then the mixture was filtered through a pad of celite which was subsequently washed wish CH_2Cl_2 (30 mL x 3). The combined organic layer was washed wish saturated $NaHCO_3$ solution, dried over anhydrous Na_2SO_4 and removed under reduced pressure. The crude residue was purified by flash chromatography eluting with Hexane/EA/CH_2Cl_2 = 5:1:2 to get the desired product as a yellow solid. Compounds **2a**, **2c**-**2e**, **2g**-**2j**, and **2l** are known compounds whose spectroscopic and physical data were completely matched with the characterization data from the literature.[22]

N-(4-diazo-7-methylisochroman-3-ylidene)-4-methylbenzenesulfonamide ***(2b)***. Yellow solid (460 mg, 28% yield); m.p. 138.6-139.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, J = 8.4 Hz, 2H), 7.28-7.26 (m, 2H), 7.19-7.16 (m, 1H), 6.96 (s, 1H), 6.81 (d, J = 8.0 Hz, 1H), 5.26 (s, 2H), 2.41 (s, 3H), 2.33 (s, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 164.1, 143.6, 143.1, 139.4, 136.6, 130.4, 129.8, 129.3, 127.4, 126.6, 125.6, 124.6, 118.9, 117.4, 71.4, 21.7, 21.2; LRMS (ESI): *m/z* 342.1 $[M + H]^+$; HRMS (ESI): calculated for $C_{17}H_{16}N_3O_3S^+$ $[M + H]^+$: 342.0907, found: 342.0909.

N-(4-diazo-7-nitroisochroman-3-ylidene)-4-methylbenzenesulfonamide ***(2f)***. Yellow solid (370 mg, 32% yield); m.p. 172.0-173.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.24 (dd, J = 8.4, 2.4 Hz, 1H), 8.20 (d, J = 2.4 Hz, 1H), 7.77 (d, J = 8.4 Hz, 2H), 7.49 (d, J = 8.4 Hz, 1H), 7.38 (d, J = 8.0 Hz, 2H), 5.49 (s, 2H), 2.38 (s, 3H); ^{13}C{^{1}H} (151 MHz, DMSO-d_6): δ 162.9, 144.7, 142.9, 139.0, 129.4, 129.3, 129.2, 126.8, 125.6, 125.4, 124.2, 120.9, 120.4, 70.3, 67.1, 21.0; LRMS (ESI): *m/z* 373.0 $[M + H]^+$; HRMS (ESI): calculated for $C_{16}H_{13}N_4O_5S^+$ $[M + H]^+$: 373.0601, found: 373.0597.

N-(4-Diazo-6-(trifluoromethyl)isochroman-3-ylidene)-4-methylbenzenesulfonamide ***(2k)***. Yellow solid (300 mg, 56% yield); m.p. 151.8-154.3 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98 (d, J = 8.5 Hz, 2H), 7.55 (dd, J = 8.0, 1.6 Hz, 1H), 7.42-7.37 (m, 3H), 7.37 (s, 1H), 5.46 (s, 2H), 2.53 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 162.3, 143.4, 139.1, 132.3 (q, J = 8.1 Hz), 130.4, 129.4, 128.1, 127.4, 125.7, 125.6 (q, J = 273.4 Hz), 123.1 (q. J = 3.8 Hz), 122.7, 115.8 (q, J = 4.0 Hz), 70.7, 21.7; ^{19}F NMR (471 MHz, $CDCl_3$): δ -63.0; LRMS (ESI): *m/z* 396.0 $[M + H]^+$; HRMS (ESI): calculated for $C_{17}H_{13}F_3N_3O_3S^+$ $[M + H]^+$: 396.0624, found: 396.0623.

General Procedure for the Preparation of Compound 3. Substrate **2** (0.3 mmol, 1.5 equiv), $[Cp^*RhCl_2]_2$ (0.02 mmol, 12.4 mg, 0.1 equiv), AgOPiv (0.04 mmol, 8.4 mg, 0.2 equiv) were mixed in a Shlenk tube and to this mixture was added **1** (0.2 mmol, 1.0 equiv) in HFIP (2.0 mL, 0.1 M). The resulting mixture was filled with Ar and stirred at ambient temperature for 2 h. Upon completion of the reaction, the mixture was filtered through a pad of celite and washed with CH_2Cl_2 (10 mL x 3). The combined organic layer was concentrated under reduced pressure and the crude residue was purified by silica gel chromatography to give the desired product **3**.

*8-Ethoxy-5H-isochromeno[3,4-c]isoquinoline (**3aa**)*. White solid (51.6 mg, 93% yield); m.p. 94.8-96.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.38 (d, J = 8.4 Hz, 1H), 8.21 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 7.6 Hz, 1H), 7.81-7.78 (m, 1H), 7.52-7.48 (m, 1H), 7.46-7.41 (m, 2H), 7.33 (t, J = 7.6 Hz, 1H), 5.16 (s, 2H), 4.51 (q, J = 7.1, 2H), 1.43 (t, J = 7.1, 3H); ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 159.9, 157.2, 135.5, 131.9, 131.4, 129.7, 128.3, 126.5, 125.4, 124.6, 124.5, 124.4, 123.2, 116.6, 102.0, 68.7, 62.4, 14.3; LRMS (ESI): *m/z* 278.2 $[M + H]^+$; HRMS (ESI): calculated for $C_{18}H_{16}NO_2^+$ $[M + H]^+$: 278.1176, found: 278.1177.

*8-Ethoxy-11-methyl-5H-isochromeno[3,4-c]isoquinoline (**3ba**)*.White solid (49.0mg, 84% yield); m.p. 82.8-84.1 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.20-8.18 (m, 2H), 7.92 (d, J = 7.5 Hz, 1H), 7.45-7.40 (m, 1H), 7.29-7.28 (m, 2H), 7.25(dd, J = 8.5, 1.5 Hz, 1H), 5.17 (s, 2H), 4.60 (q, J = 7.0 Hz, 2H), 2.55 (s, 3H), 1.51 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 160.9, 157.8, 141.8, 136.7, 131.5, 130.9, 128.3, 126.3, 126.1, 125.3, 125.2, 124.8, 122.9, 115.9, 102.2, 69.8, 62.8, 22.5, 14.7; LRMS (ESI): *m/z* 292.2 $[M + H]^+$; HRMS (ESI): calculated for $C_{19}H_{18}NO_2^+$ $[M + H]^+$: 292.1332, found: 292.1328.

*11-Tert-butyl-8-ethoxy-5H-isochromeno[3,4-c]isoquinoline (**3ca**)*. Colorless oil (56.7 mg, 85% yield); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.39 (d, J = 2.0 Hz, 1H), 8.23 (d, J = 9.0 Hz, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.51 (dd, J = 8.5, 2.0 Hz, 1H), 7.45-7.42 (m, 1H), 7.30-7.29 (m, 2H), 5.18 (s, 2H), 4.61 (q, J = 7.0 Hz, 2H), 1.50 (t, J = 7.0 Hz, 3H), 1.44 (s, 9H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 160.9, 157.8, 154.6, 136.5, 131.6, 131.1, 128.4, 126.3, 125.4, 125.0, 124.7, 122.8, 119.1, 115.8, 102.8, 69.9, 62.8, 35.6, 31.3, 14.7; LRMS (ESI): m/z 334.3 $[M + H]^+$; HRMS (ESI): calculated for $C_{22}H_{24}NO_2^+$ $[M + H]^+$: 334.1802, found: 334.1804.

*8-Ethoxy-11-phenyl-5H-isochromeno[3,4-c]isoquinoline (**3da**)*: White solid (59.4 mg, 84% yield); m.p. 133.0-134.2 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.60 (s, 1H), 8.37 (d, J = 8.5 Hz, 1H), 7.96 (d, J = 8.0 Hz, 1H), 7.72 (d, J = 7.5 Hz, 2H), 7.66 (d, J = 8.5 Hz, 1H), 7.51 (t, J = 7.5 Hz, 2H), 7.43 (t, J = 8.5 Hz, 2H), 7.31-7.28 (m, 2H), 5.21 (s, 2H), 4.64 (q, J = 7.0 Hz, 2H), 1.54 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 160.9, 157.9, 144.0, 140.8, 136.7, 131.4, 130.7, 129.0, 128.4, 128.1, 127.6, 126.3, 125.8, 125.3, 124.8, 123.7, 121.6, 116.6, 102.7, 69.8, 62.9, 14.6; LRMS (ESI): *m/z* 354.2 $[M + H]^+$; HRMS (ESI): calculated for $C_{24}H_{20}NO_2^+$ $[M + H]^+$: 354.1489, found: 354.1495.

*8-Ethoxy-11-methoxy-5H-isochromeno[3,4-c]isoquinoline (**3ea**)*. White solid (60.2 mg, 98% yield); m.p. 161.2-161.6 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.20 (d, J = 9.0 Hz, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 2.0 Hz, 1H), 7.42-7.39 (m, 1H), 7.31 – 7.28 (m, 2H), 7.04 (dd, J = 9.0, 2.0 Hz, 1H), 5.17 (s, 2H), 4.58 (q, J = 7.0 Hz, 2H), 3.95 (s, 3H), 1.49 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 162.3, 160.9, 158.4, 138.4, 131.5, 131.1, 128.4, 127.1, 126.2, 125.4, 124.1, 115.4, 112.5, 103.5, 102.2, 69.8, 62.7, 55.5, 14.7; LRMS (ESI): *m/z* 308.2 $[M + H]^+$; HRMS (ESI): calculated for $C_{19}H_{18}NO_3^+$ $[M + H]^+$: 308.1281,

found: 308.1274.

*8-Ethoxy-N, N-dimethyl-5H-isochromeno[3,4-c]isoquinolin-11-amine (**3fa**)*. White solid (50.0 mg, 78% yield); m.p. 116.1-118.2 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.15 (d, J = 9.0 Hz, 1H), 8.09 (d, J = 7.8 Hz, 1H), 7.49 (s, 1H), 7.42-7.40 (m, 1H), 7.31-7.27 (m, 2H), 6.97 (dd, J = 9.6, 2.4 Hz, 1H), 5.17 (s, 2H), 4.59 (q, J = 7.2 Hz, 2H), 3.14 (s, 6H), 1.51 (t, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 161.0, 158.3, 152.3, 138.2, 131.6, 131.4, 128.1, 126.4, 125.7, 125.2, 123.8, 112.4, 109.4, 102.1, 101.3, 69.7, 62.4, 40.5, 14.8; LRMS (ESI): *m/z* 321.2 $[M + H]^+$; HRMS (ESI): calculated for $C_{20}H_{21}N_2O_2^+$ $[M + H]^+$: 321.1598, found: 321.1611.

*8-Ethoxy-11-fluoro-5H-isochromeno[3,4-c]isoquinoline (**3ga**)*. White solid (53.2 mg, 90% yield); m.p. 131.2-132.6 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.31 (dd, J = 9.0, 6.0 Hz, 1H), 8.02 (dd, J = 11.5, 2.5 Hz, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.44-7.41 (m, 1H), 7.32-7.28 (m, 2H), 7.17-7.13 (m, 1H), 5.18 (s, 2H), 4.60 (q, J = 7.0 Hz, 2H), 1.50 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 165 (d, J = 251.1 Hz), 160.9, 158.6, 138.2 (d, J = 10.6 Hz), 131.3, 130.4, 128.6, 128.4 (d, J = 10.2 Hz), 126.7, 125.4, 124.3, 114.7, 113.8 (d, J = 24.8 Hz), 108.0 (d, J = 23.3 Hz), 102.5 (d, J = 4.3 Hz), 69.9, 63.1, 14.6; ^{19}F NMR (471 MHz, $CDCl_3$): δ -106.9; LRMS (ESI): *m/z* 296.2 $[M + H]^+$; HRMS (ESI): calculated for $C_{18}H_{15}FNO_2^+$ $[M + H]^+$: 296.1081, found: 296.1080.

*11-Chloro-8-ethoxy-5H-isochromeno[3,4-c]isoquinoline (**3ha**)*. White solid (54.8 mg, 88% yield); m.p. 146.2-147.3 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.37 (d, J = 2.0 Hz, 1H), 8.22 (d, J = 9.0 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.46-7.42 (m, 1H), 7.35 (dd, J = 8.5, 2.0 Hz, 1H), 7.32-7.28 (m, 2H), 5.18 (s, 2H), 4.60 (q, J = 7.0 Hz, 2H), 1.50 (t, J = 7.0 Hz, 3H);

$^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): δ 160.9, 158.5, 138.2, 137.3, 131.4, 130.2, 128.6, 127.1, 126.7, 125.4, 124.9, 124.6, 122.8, 116.0, 102.1, 69.9, 63.2, 14.6; LRMS (ESI): *m/z* 312.2 $[M + H]^+$; HRMS (ESI): calculated for $C_{18}H_{15}ClNO_2^+$ $[M + H]^+$: 312.0786, found: 312.0781.

*11-bromo-8-ethoxy-5H-isochromeno[3,4-c]isoquinoline (**3ia**)*. White solid (62 mg, 87% yield); m.p. 137.9-139.2 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.55 (d, J = 1.5 Hz, 1H), 8.15 (d, J = 9.0 Hz, 1H), 7.84 (d, J = 7.5 Hz, 1H), 7.49 (dd, J = 9.0, 2.0 Hz, 1H), 7.46-7.43 (m, 1H), 7.33-7.28 (m, 2H), 5.18 (s, 2H), 4.59 (q, J = 7.0 Hz, 2H), 1.50 (t, J = 7.0 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): δ 161.0, 158.4, 137.6, 131.4, 130.2, 128.7, 127.5, 127.0, 126.9, 126.8, 126.0, 125.4, 124.6, 116.2, 102.0, 69.9, 63.2, 14.6; LRMS (ESI): *m/z* 356.2 $[M + H]^+$; HRMS (ESI): calculated for $C_{18}H_{15}BrNO_2^+$ $[M + H]^+$: 356.0281, found: 356.0280.

*8-Ethoxy-11-iodo-5H-isochromeno[3,4-c]isoquinoline (**3ja**)*. White solid (62.8 mg, 78% yield); m.p. 121.4-122.3 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.78 (s, 1H), 7.98 (d, J = 8.5 Hz, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.68 (d, J = 8.5 Hz, 1H), 7.46-7.43 (m, 1H), 7.33-7.28 (m, 2H), 5.17 (s, 2H), 4.59 (q, J = 7.0 Hz, 2H), 1.50 (t, J = 7.0 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): δ 161.1, 158.1, 137.7, 132.9, 132.5, 131.4, 130.1, 128.7, 126.7, 125.4, 124.7, 116.5, 101.6, 99.6, 69.9, 63.2, 14.6; LRMS (ESI): *m/z* 404.1 $[M + H]^+$; HRMS (ESI): calculated for $C_{18}H_{15}INO_2^+$ $[M + H]^+$: 404.0142, found: 404.0150.

*8-Ethoxy-11-(trifluoromethyl)-5H-isochromeno[3,4-c]isoquinoline (**3ka**)*. White solid (67.0 mg, 97% yield); m.p. 161.4-161.9 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.69 (s, 1H), 8.41 (d, J = 8.5 Hz, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.59 (dd, J = 9.0, 2.0 Hz, 1H), 7.48-7.45 (m, 1H), 7.35-7.30 (m, 2H), 5.21 (s, 2H), 4.63 (q, J = 7.0 Hz, 2H), 1.53 (t, J = 7.0 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): δ 160.6, 158.4, 135.6, 132.8 (q, J = 32.1 Hz), 131.3,

129.8, 128.7, 126.9, 126.5, 125.4, 124.5, 124.1 (q, J = 273.4 Hz), 121.0 (q, J = 4.7 Hz), 119.70 (q, J = 3.3 Hz), 118.9, 103.0, 69.8, 63.2, 14.4; ^{19}F NMR (471 MHz, $CDCl_3$): δ -62.89; LRMS (ESI): *m/z* 346.2 $[M + H]^+$; HRMS (ESI): calculated for $C_{19}H_{15}F_3NO_2^+$ $[M + H]^+$: 346.1049, found: 346.1046.

*8-Ethoxy-9-fluoro-5H-isochromeno[3,4-c]isoquinoline (**3la**)*. White solid (42.0 mg, 71% yield); m.p. 153.3-154.2 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.17 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.58 (td, J = 8.0, 5.5 Hz, 1H), 7.43-7.39 (m, 1H), 7.32-7.28 (m, 2H), 7.05 (ddd, J = 11.6, 8.0, 1.0 Hz, 1H), 5.18 (s, 2H), 4.61 (q, J = 7.0 Hz, 2H), 1.51 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 161.6, 160.2 (d, J = 5.7 Hz), 158.7 (d, J = 209.4 Hz) , 139.1, 131.7 (d, J = 9.6 Hz), 131.5, 130.5, 128.4, 126.7, 125.4, 124.9, 119.4 (d, J = 4.5 Hz), 110.2 (d, J = 21.9 Hz), 108.2 (d, J = 11.7 Hz), 102.2 (d, J = 2.9 Hz), 69.9, 63.3, 14.6; ^{19}F NMR (471 MHz, $CDCl_3$): δ -107.2 (d, J = 5.7 Hz); LRMS (ESI): *m/z* 296.2 $[M + H]^+$; HRMS (ESI): calculated for $C_{18}H_{15}FNO_2^+$ $[M + H]^+$: 296.1081, found: 296.1080.

*8-Ethoxy-10-methoxy-5H-isochromeno[3,4-c]isoquinoline(**3ma**) and 8-ethoxy-12-methoxy-5H-isochromeno[3,4-c]isoquinoline (**3ma'**)*. Colorless oil (59.0 mg, 96% yield); ^{1}H NMR (500 MHz, $CDCl_3$) selected signals for **3ma**: δ 8.33 (d, J = 9.5 Hz, 1H), 7.86 (d, J = 7.5 Hz, 1H), 7.59 (d, J = 2.5 Hz, 1H), 7.30-7.28 (m, 3H), 7.12 (d, J = 7.5 Hz, 1H), 5.19 (s, 2H), 4.62 (q, J = 7.0 Hz, 2H), 3.86 (s, 3H), 1.50 (t, J = 7.0 Hz, 3H); selected signals for **3ma'**: δ 7.93 (d, J = 8.5 Hz, 1H), 7.42-7.35 (m, 3H), 7.22-7.20 (m, 3H), 5.17 (s, 2H), 4.59 (q, J = 7.0 Hz, 2H), 3.96 (s, 3H), 1.52 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) for the mixtures: δ 161.7, 159.8, 158.7, 156.4, 156.2, 154.9, 131.9, 131.7, 131.5, 130.8, 129.3, 128.3, 128.2, 127.8, 126.9, 126.4, 125.4, 125.3, 125.2, 124.9, 124.6, 124.0, 123.4, 119.6, 118.7, 117.3,

111.2, 103.8, 102.9, 101.1, 70.1, 69.8, 63.0, 62.9, 55.6, 55.0, 14.8, 14.7; LRMS (ESI): *m/z* 308.2 $[M + H]^+$; HRMS (ESI): calculated for $C_{19}H_{18}NO_3^+$ $[M + H]^+$: 308.1281, found: 308.1283.

*8-ethoxy-5H-[1,3]dioxolo[4,5-g]isochromeno[3,4-c]isoquinoline (**3na**)*. White solid (63.0 mg, 98% yield); m.p. 166.4-168.1 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.98 (d, J = 8.4 Hz, 1H), 7.50 (dd, J = 7.8, 1.2 Hz, 1H), 7.36 (td, J = 7.8, 1.8 Hz, 1H), 7.25-7.24 (m, 1H), 7.24-7.21 (m, 1H), 7.09 (d, J = 8.4 Hz, 1H), 6.14 (s, 2H), 5.18 (s, 2H), 4.57 (q, J = 7.2 Hz, 2H), 1.49 (t, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 161.8, 158.9, 149.0, 140.0, 130.3, 129.8, 127.6, 127.0, 126.0, 124.3, 121.9, 121.1, 114.6, 108.1, 101.3, 98.7, 70.1, 63.1, 14.6; LRMS (ESI): *m/z* 322.2 $[M + H]^+$; HRMS (ESI): calculated for $C_{19}H_{16}NO_4^+$ $[M + H]^+$: 322.1074, found: 322.1073.

*8-Ethoxy-12-[(4-methylphenyl)sulfonyl]-5,12-dihydroisochromeno[3,4-c]pyrrolo[2,3-g]-isoquinoline (**3oa**)*. White solid (47.0 mg, 50% yield); m.p. 156.8-157.1 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.90 (s, 1H), 8.50 (d, J = 0.6 Hz, 1H), 7.91 (d, J = 7.8 Hz, 1H), 7.82 (d, J = 8.4 Hz, 2H), 7.73 (d, J = 3.6 Hz, 1H), 7.52-7.50 (m, 1H), 7.36-7.32 (m, 2H), 7.27 (d, J = 8.4 Hz, 2H), 6.81 (dd, J = 3.6, 0.6 Hz, 1H), 5.20 (s, 2H), 4.61 (q, J = 7.2 Hz, 2H), 2.34 (s, 3H), 1.51 (t, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 161.3, 157.1, 145.4, 137.9, 135.2, 133.4, 131.4, 131.0, 130.1, 129.1, 128.4, 127.2, 126.4, 125.4, 124.3, 118.1, 115.2, 109.2, 106.4, 102.3, 69.9, 63.0, 21.8, 14.7; LRMS (ESI): *m/z* 471.2 $[M + H]^+$; HRMS (ESI): calculated for $C_{27}H_{23}N_2O_4S^+$ $[M + H]^+$: 471.1373, found: 471.1379.

*4-Ethoxy-7H-isochromeno[3,4-b]thieno[3,2-d]pyridine (**3pa**)*. White solid (38.5 mg, 68% yield); m.p. 104.6-105.7 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87-7.84 (m, 2H), 7.76 (d,

J = 5.5 Hz, 1H), 7.41 (dt, *J* = 7.5, 2.0 Hz, 1H), 7.29 (dt, *J* = 7.5, 1.0 Hz, 1H), 7.24-7.23 (m, 1H), 5.22 (s, 2H), 4.60 (q, *J* = 7.0 Hz, 2H), 1.48 (t, *J* = 7.0 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): δ 158.4, 157.3, 145.3, 133.4, 130.9, 130.8, 128.7, 126.8, 125.1, 123.8, 122.8, 119.1, 104.6, 69.7, 63.0, 14.8; LRMS (EI): *m/z* 283; HRMS (EI): calculated for $C_{16}H_{13}NO_2S$ 283.0662, found: 283.0661.

*8-Ethoxy-5H-benzo[g]isochromeno[3,4-c]isoquinoline (**3qa**)*. Yellow solid (57.6 mg, 88% yield); m.p. 160.2-161.3 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.92 (s, 1H), 8.89 (s, 1H), 8.09 (d, *J* = 8.0 Hz, 1H), 8.05 (d, *J* = 8.5 Hz, 1H), 7.98 (d, *J* = 8.5 Hz, 1H), 7.58-7.55 (m, 1H), 7.50-7.46 (m, 2H), 7.32 (d, *J* = 4.5 Hz, 2H), 5.23 (s, 2H), 4.70 (q, *J* = 7.0 Hz, 2H), 1.59 (t, *J* = 7.0 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): δ 161.9, 157.0, 135.2, 132.4, 131.2, 131.1, 130.2, 129.3, 128.4, 128.0, 127.9, 126.3, 125.7, 125.4, 125.3, 124.5, 121.5, 117.8, 101.0, 70.0, 63.3, 14.7; LRMS (ESI): *m/z* 328.2 $[M + H]^+$; HRMS (ESI): calculated for $C_{22}H_{18}NO_2^+$ $[M + H]^+$: 328.1332, found: 328.1332.

*8-Phenyl-5H-isochromeno[3,4-c]isoquinoline (**3ra**)*. Yellow solid (42.7 mg, 69% yield); m.p. 146.1-147.3 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.56 (d, *J* = 8.5 Hz, 1H), 8.15 (d, *J* = 8.5 Hz, 1H), 8.03 (d, *J* = 8.0 Hz, 1H), 7.80-7.78 (m, 2H), 7.73-7.70 (m, 1H), 7.55-7.46 (m, 4H), 7.44-7.35 (m, 3H), 5.26 (s, 2H); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): δ 160.3, 157.9, 138.7, 135.5, 133.2, 130.7, 130.3, 129.9, 128.9, 128.8, 128.3, 128.2, 127.6, 126.3, 125.4, 124.9, 124.6, 124.0, 108.2, 69.5; LRMS (ESI): *m/z* 310.2 $[M + H]^+$; HRMS (ESI): calculated for $C_{22}H_{16}NO^+$ $[M + H]^+$: 310.1226, found: 310.1220.

*8-Methoxy-5H-isochromeno[3,4-c]isoquinoline (**3sa**)*. White solid (40 mg, 76% yield); m.p. 152.9-154.3 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.42 (d, *J* = 8.5 Hz, 1H), 8.28 (d, *J* = 8.0

Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.72-7.68 (m, 1H), 7.44-7.40 (m, 2H), 7.30-7.29 (m, 2H), 5.20 (s, 2H), 4.17 (s, 3H); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): δ 161.3, 157.6, 136.4, 131.6, 131.4, 130.7, 128.4, 126.5, 125.3, 125.2, 125.0, 124.3, 123.6, 117.7, 102.9, 69.9, 54.5; LRMS (ESI): *m/z* 286.1 $[M + Na]^+$; HRMS (ESI): calculated for $C_{17}H_{14}NO_2^+$ $[M + H]^+$: 264.1019, found: 264.1025.

*8-(propan-2-yloxy)-5H-isochromeno[3,4-c]isoquinoline (**3ta**)*. Colorless oil (45.0 mg, 77% yield); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.41 (d, *J* = 8.5 Hz, 1H), 8.31 (d, *J* = 8.5 Hz, 1H), 7.91 (d, *J* = 7.5 Hz, 1H), 7.68 (t, *J* = 7.5 Hz, 1H), 7.43-7.40 (m, 2H), 7.29 (d, *J* = 4.5 Hz, 2H), 5.64 (hept, *J* = 6.0 Hz, 1H), 5.19 (s, 2H), 1.48 (d, *J* = 6.0 Hz, 6H); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): δ 160.5, 157.6, 136.4, 131.4, 131.3, 130.8, 128.3, 126.3, 125.4, 125.2, 124.8, 124.0, 123.5, 118.1, 102.3, 69.8, 69.5, 22.2; LRMS (ESI): *m/z* 314.1 $[M + Na]^+$; HRMS (ESI): calculated for $C_{19}H_{18}NO_2^+$ $[M + H]^+$: 292.1332, found: 292.1335.

*1-(8-Ethoxy-5H-isochromeno[3,4-c]isoquinolin-11-yl)ethanone (**3ua**)*. Light yellow solid (43.4 mg, 68% yield); m.p. 130.1-131.8 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.99 (s, 1H), 8.35 (d, *J* = 8.5 Hz, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.86 (d, *J* = 7.5 Hz, 1H), 7.48-7.45 (m, 1H), 7.35-7.30 (m, 2H), 5.21 (s, 2H), 4.62 (q, *J* = 7.0 Hz, 2H), 2.73 (s, 3H), 1.52 (t, *J* = 7.0 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): δ 198.3, 160.8, 158.2, 138.9, 136.0, 131.5, 130.3, 128.8, 126.9, 125.5, 124.9, 124.8, 122.4, 119.6, 103.6, 70.0, 63.3, 27.1, 14.6; LRMS (ESI): *m/z* 320.2 $[M + H]^+$; HRMS (ESI): calculated for $C_{20}H_{18}NO_3^+$ $[M + H]^+$: 320.1281, found: 320.1284.

*Ethyl 8-ethoxy-5H-isochromeno[3,4-c]isoquinoline-11-carboxylate (**3va**)*. Light green solid (56.0 mg, 80% yield); m.p. 153.2-154.6 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.14 (d, *J* =

1.2 Hz, 1H), 8.34 (d, *J* = 8.4 Hz, 1H), 7.99 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.90 (d, *J* = 7.8 Hz, 1H), 7.46 (td, *J* = 7.8, 1.8 Hz, 1H), 7.34-7.30 (m, 2H), 5.21 (s, 2H), 4.62 (q, *J* = 7.2 Hz, 2H), 4.46 (q, *J* = 7.2 Hz, 2H), 1.52 (t, *J* = 7.2 Hz, 3H), 1.44 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$): δ 166.6, 160.8, 158.1, 135.8, 132.8, 131.4, 130.3, 128.7, 126.8, 126.1, 125.6, 125.4, 125.1, 123.7, 119.6, 103.4, 70.0, 63.3, 61.6, 14.6, 14.5; LRMS (ESI): *m/z* 372.2 $[M + Na]^+$; HRMS (ESI): calculated for $C_{21}H_{20}NO_4^+$ $[M + H]^+$: 350.1387, found: 350.1388.

N-(8-ethoxy-5H-isochromeno[3,4-c]isoquinolin-11-yl)-2,2-dimethylpropanamide ***(3wa)***. White solid (70.0 mg, 93% yield); m.p. 197.1-198.2 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.79 (d, *J* = 1.8 Hz, 1H), 8.23 (d, *J* = 9.0 Hz, 1H), 8.02 (d, *J* = 7.8 Hz, 1H), 7.55 (s, 1H), 7.50-7.47 (m, 1H), 7.39 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.28-7.27 (m, 2H), 5.16 (s, 2H), 4.58 (q, *J* = 7.2 Hz, 2H), 1.50 (t, *J* = 7.2 Hz, 3H), 1.36 (s, 9H); $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$): δ 176.4, 160.1, 157.6, 140.1, 136.8, 130.6, 130.1, 128.2, 125.8, 125.7, 124.6, 124.1, 116.8, 113.8, 111.9, 102.0, 69.3, 62.3, 39.5, 27.2, 14.1; LRMS (ESI): *m/z* 399.2 $[M + Na]^+$; HRMS (ESI): calculated for $C_{23}H_{25}N_2O_3^+$ $[M + H]^+$: 377.1860, found: 377.1858.

8-Ethoxy-3-methyl-5H-isochromeno[3,4-c]isoquinoline ***(3ab)***. White solid (45.5 mg, 78% yield); m.p. 67.6-68.1 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.39 (d, *J* = 8.5 Hz, 1H), 8.30 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.69-7.66 (m, 1H), 7.42-7.39 (m, 1H), 7.22 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.09 (d, *J* = 2.0 Hz, 1H), 5.15 (s, 2H), 4.61 (q, *J* = 7.0 Hz, 2H), 2.40 (s, 3H), 1.52 (t, *J* = 7.0 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): δ 160.6, 157.2, 136.3, 136.2, 131.6, 131.2, 129.0, 127.9, 126.0, 125.3, 124.8, 124.0, 123.6, 117.7, 102.6, 69.8, 62.8, 21.2, 14.7; LRMS (ESI): *m/z* 292.1 $[M + H]^+$; HRMS (ESI): calculated for $C_{19}H_{18}NO_2^+$ $[M + H]^+$: 292.1332, found: 292.1334.

*3-Chloro-8-ethoxy-5H-isochromeno[3,4-c]isoquinoline (**3ac**)*. White solid (36.2 mg, 58% yield); m.p. 154.3-155.6 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.31 (dd, J = 8.0, 1.5 Hz, 2H), 7.82 (d, J = 8.5 Hz, 1H), 7.72-7.68 (m, 1H), 7.45-7.42 (m, 1H), 7.37 (dd, J = 8.5, 2.5 Hz, 1H), 7.27 (d, J = 2.0 Hz, 1H), 5.13 (s, 2H), 4.60 (q, J = 7.0 Hz, 2H), 1.51 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 161.2, 157.5, 136.2, 133.0, 131.9, 131.6, 129.3, 128.4, 125.9, 125.5, 124.4, 123.3, 117.9, 101.9, 69.2, 63.1, 14.7; LRMS (ESI): *m/z* 312.1 $[M + H]^+$; HRMS (ESI): calculated for $C_{18}H_{15}ClNO_2^+$ $[M + H]^+$: 312.0786, found: 312.0792.

*8-Ethoxy-3-fluoro-5H-isochromeno[3,4-c]isoquinoline (**3ad**)*. White solid (39.0 mg, 66% yield); m.p. 122.5-123.4 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.34-8.30 (m, 2H), 7.86 (dd, J = 8.5, 5.0 Hz, 1H), 7.71-7.68 (m, 1H), 7.44-7.41 (m, 1H), 7.11 (td, J = 8.5, 3.0 Hz, 1H), 7.01 (dd, J = 8.0, 3.0 Hz, 1H), 5.14 (s, 2H), 4.60 (q, J = 7.0 Hz, 2H), 1.51 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 161.40 (d, J = 247.5 Hz), 160.9, 157.1, 136.2, 133.6 (d, J = 7.2 Hz), 131.5, 126.9 (d, J = 3.0 Hz), 126.3 (d, J = 7.9 Hz), 125.4, 124.3, 123.3, 117.8, 115.1 (d, J = 21.4 Hz), 112.6 (d, J = 22.6 Hz), 102.0, 69.3, 63.0, 14.7; ^{19}F NMR (471 MHz, $CDCl_3$): δ -115.7; LRMS (ESI): *m/z* 296.1 $[M + H]^+$; HRMS (ESI): calculated for $C_{18}H_{15}FNO_2^+$ $[M + H]^+$: 296.1081, found: 296.1081.

*8-Ethoxy-3-(trifluoromethyl)-5H-isochromeno[3,4-c]isoquinoline (**3ae**)*. White solid (55.2 mg, 80% yield); m.p. 117.7-119.6 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.35-8.31 (m, 2H), 7.99 (d, J = 8.5 Hz, 1H), 7.74-7.71 (m, 1H), 7.66-7.64 (m, 1H), 7.54 (d, J = 2.0 Hz, 1H), 7.47-7.44 (m, 1H), 5.21 (s, 2H), 4.62 (q, J = 7.0 Hz, 2H), 1.52 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 161.9, 158.4, 136.3, 134.4, 131.9, 131.6, 128.1 (q, J = 32.8 Hz),126.6 (q, J = 270.3 Hz), 125.6, 125.3 (q, J = 3.6 Hz), 124.7, 124.6, 123.2, 122.1 (q, J =

3.9 Hz), 117.9, 101.7, 69.4, 63.2, 14.6; ^{19}F NMR (471 MHz, $CDCl_3$): δ -62.3; LRMS (ESI): *m/z* 346.1 $[M + H]^+$; HRMS (ESI): calculated for $C_{19}H_{15}F_3NO_2^+$ $[M + H]^+$: 346.1049, found: 346.1051.

*8-Ethoxy-3-nitro-5H-isochromeno[3,4-c]isoquinoline (**3af**)*. Light yellow green solid (49.6 mg, 77% yield); m.p. 184.1-185.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.34-8.30 (m, 2H), 8.26 (dd, *J* = 8.5, 2.5 Hz, 1H), 8.17 (d, *J* = 2.5 Hz, 1H), 8.00 (d, *J* = 9.0 Hz, 1H), 7.78-7.74 (m, 1H), 7.50-7.47 (m, 1H), 5.24 (s, 2H), 4.63 (q, *J* = 7.0 Hz, 2H), 1.53 (t, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 162.8, 159.2, 145.6, 137.5, 136.1, 132.3, 131.7, 125.8, 125.0, 124.7, 124.0, 123.1, 120.7, 118.1, 101.5, 69.0, 63.5, 14.6; LRMS (ESI): *m/z* 323.1 $[M + H]^+$; HRMS (ESI): calculated for $C_{18}H_{15}N_2O_4^+$ $[M + H]^+$: 323.1026, found: 323.1033.

*8-Ethoxy-3-methoxy-5H-isochromeno[3,4-c]isoquinoline (**3ag**)*. White solid (43.0 mg, 70% yield); m.p. 133.4-135.2 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.36 (d, *J* = 8.4 Hz, 1H), 8.30 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 1H), 7.69-7.66 (m, 1H), 7.41 (dd, *J* = 7.8, 6.0 Hz, 1H), 6.96 (dd, *J* = 8.4, 3.0 Hz, 1H), 6.85 (d, *J* = 3.0 Hz, 1H), 5.15 (s, 2H), 4.60 (q, *J* = 7.2 Hz, 2H), 3.86 (s, 3H), 1.51 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 160.2, 158.4, 156.6, 136.2, 133.3, 131.2, 126.1, 125.3, 124.0, 123.5, 123.5, 117.7, 113.6, 111.1, 102.6, 69.9, 62.8, 55.6, 14.7; LRMS (ESI): *m/z* 308.1 $[M + H]^+$; HRMS (ESI): calculated for $C_{19}H_{18}NO_3^+$ $[M + H]^+$: 308.1281, found: 308.1280.

*8-Ethoxy-2-methoxy-5H-isochromeno[3,4-c]isoquinoline (**3ah**)*.White solid (48.6 mg, 79% yield); m.p. 98.8-99.6 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.42 (d, *J* = 8.4 Hz, 1H), 8.30 (d, *J* = 8.4 Hz, 1H), 7.71-7.68 (m, 1H), 7.46 (d, *J* = 2.4 Hz, 1H), 7.43-7.40 (m, 1H), 7.21 (d, *J*

= 8.4 Hz, 1H), 6.82 (dd, *J* = 8.4, 2.4 Hz, 1H), 5.13 (s, 2H), 4.61 (q, *J* = 7.2 Hz, 2H), 3.87 (s, 3H), 1.51 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$): δ 161.1, 159.8, 157.8, 136.4, 132.0, 131.5, 126.2, 125.4, 124.1, 124.0, 123.5, 117.8, 111.5, 111.0, 102.5, 69.5, 63.0, 55.6, 14.7; LRMS (ESI): *m/z* 308.2 $[M + H]^+$; HRMS (ESI): calculated for $C_{19}H_{18}NO_3^+$ $[M + H]^+$: 308.1281, found: 308.1282.

*8-Ethoxy-2-fluoro-5H-isochromeno[3,4-c]isoquinoline (**3ai**)*. White solid (55.5 mg, 94% yield); m.p. 109.3-110.2 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.35 (d, *J* = 8.5 Hz, 1H), 8.32-8.30 (m, 1H), 7.72 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H), 7.60 (dd, *J* = 11.0, 2.5 Hz, 1H), 7.46-7.42(m, 1H), 7.24 (dd, *J* = 8.5, 5.5 Hz, 1H), 6.97 (td, *J* = 8.5, 2.5 Hz, 1H), 5.15 (s, 2H), 4.61 (q, *J* = 7.2 Hz, 2H), 1.51 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): δ 163.0 (d, *J* = 244.5 Hz), 161.5, 157.9, 136.2, 132.8 (d, *J* = 8.8 Hz), 131.8, 126.9, 126.6 (d, *J* = 8.9 Hz), 125.5, 124.4, 123.1, 117.8, 112.9 (d, *J* = 22.2 Hz), 111.9 (d, *J* = 24.1 Hz), 101.9, 69.3, 63.1, 14.7; ^{19}F NMR (471 MHz, $CDCl_3$): δ -113.3; LRMS (ESI): *m/z* 296.1 $[M + H]^+$; HRMS (ESI): calculated for $C_{18}H_{15}FNO_2^+$ $[M + H]^+$: 296.1081, found: 296.1083.

*2-Chloro-8-ethoxy-5H-isochromeno[3,4-c]isoquinoline (**3aj**)*. White solid (97.0 mg, 82% yield); m.p. 115.6-116.2 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.34 (d, *J* = 8.5 Hz, 1H), 8.31 (d, *J* = 8.0 Hz, 1H), 7.87 (d, *J* = 2.0 Hz, 1H), 7.75-7.72 (m, 1H), 7.46-7.43 (m, 1H), 7.26-7.24 (m, 1H), 7.21 (d, *J* = 8.0 Hz, 1H), 5.13 (s, 2H), 4.61 (q, *J* = 7.0 Hz, 2H), 1.51 (t, *J* = 7.0 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): δ 161.5, 157.9, 136.1, 134.3, 132.6, 131.8, 129.6, 126.4, 126.2, 125.5, 124.7, 124.4, 123.1, 117.8, 101.6, 69.3, 63.1, 14.6; LRMS (ESI): *m/z* 312.1 $[M + H]^+$; HRMS (ESI): calculated for $C_{18}H_{15}ClNO_2^+$ $[M + H]^+$: 312.0786, found: 312.0787.

*8-Ethoxy-2-(trifluoromethyl)-5H-dibenzo[c,f]chromene (**3ak**)*. White solid (62.8 mg,

91% yield); m.p. 112.5-113.9 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.33 (d, J = 9.5 Hz, 2H), 8.14 (s, 1H), 7.77-7.74 (m, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.48-7.45 (m, 1H), 7.40 (d, J = 8.0 Hz, 1H), 5.21 (s, 2H), 4.62 (q, J = 7.0 Hz, 2H), 1.52 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 161.7, 158.1, 136.1, 134.7, 132.1, 131.7, 130.8 (q, J = 32.3 Hz), 125.7, 125.6, 124.6, 124.3 (q, J = 272.7 Hz), 123.1 (q, J = 3.9 Hz), 122.9, 121.3 (d, J = 3.9 Hz), 117.9, 101.6, 69.4, 63.2, 14.6; ^{19}F NMR (471 MHz, $CDCl_3$): δ -62.5; LRMS (ESI): *m/z* 346.2 $[M + H]^+$; HRMS (ESI): calculated for $C_{19}H_{15}F_3NO_2^+$ $[M + H]^+$: 346.1049, found: 346.1050.

*5-Ethoxy-8H-[1,3]dioxolo[6,7]isochromeno[3,4-c]isoquinoline (**3al**)*. White solid (48.8 mg, 76% yield); m.p. 130.1-131.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.32-8.28 (m, 2H), 7.69-7.66 (m, 1H), 7.42-7.39 (m, 2H), 6.78 (s, 1H), 6.01 (s, 2H), 5.07 (s, 2H), 4.60 (q, J = 7.0 Hz, 2H), 1.50 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 160.5, 157.0, 147.9, 146.2, 136.1, 131.3, 125.4, 125.1, 124.8, 124.1, 123.3, 117.7, 106.3, 105.9, 102.8, 101.4, 69.7, 62.9, 14.7; LRMS (ESI): *m/z* 322.1 $[M + H]^+$; HRMS (ESI): calculated for $C_{19}H_{16}NO_4^+$ $[M + H]^+$: 322.1074, found: 322.1075.

*N-{1-ethoxy-4-[2-(hydroxymethyl)phenyl]isoquinolin-3-yl}-4-methylbenzenesulfonamide (**4aa**)*. Product **4aa** was synthesized by mixing substrate **1a** (29.8 mg, 0.2 mmol, 1.0 equiv)**,** **2a** (65.5 mg, 0.2 mmol, 1.0 equiv), $[Cp^*RhCl_2]_2$ (12.4 mg, 0.02 mmol, 10 mmol %) and AgOPiv (8.4 mg, 0.04 mmol, 20 mmol %) in a Shlenk tube followed with EtOH (2.0 mL, 0.1 M). The resulting mixture was stirred under room temperature for 12 h in the air. Upon completion of the reaction, the mixture was filtered through a pad of celite and washed with CH_2Cl_2 (10 mL x 3). The combined organic layer was concentrated under reduced pressure and the residue was purified by silica gel chromatography to give the desired product **4aa**.

White solid (75.6 mg, 79% yield); m.p. 126.4-127.1 ℃; ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.69 (s, 1H), 8.07 (dd, J = 8.5, 1.0 Hz, 1H), 7.84 (d, J = 8.5 Hz, 2H), 7.71 (d, J = 8.0 Hz, 1H), 7.59-7.53 (m, 2H), 7.47-7.43 (m, 2H), 7.39 (d, J = 8.0 Hz, 2H), 7.13 (dd, J = 7.5, 1.0 Hz, 1H), 6.98 (d, J = 8.5 Hz, 1H), 4.29 (d, J = 13.8 Hz, 1H), 4.06-3.99 (m, 3H), 2.39 (s, 3H), 2.37 (s, 1H), 1.21 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 158.7, 142.7, 142.2, 141.1, 140.8, 138.7, 132.3, 131.9, 131.8, 129.6, 128.7, 127.6, 127.0, 126.1, 126.0, 124.4, 124.1, 116.4, 113.6, 62.6, 61.3, 21.4, 14.6; LRMS (ESI): *m/z* 471.2 $[M + Na]^+$; HRMS (ESI): calculated for $C_{25}H_{25}N_2O_4S^+$ $[M + H]^+$: 449.1530, found: 449.1535.

Gram-scale reaction for the synthesis of 3aa. To a 250 mL round bottom flask was successively added substrate **2a** (3.85g, 10.36 mmol, 1.5 equiv), $[Cp^*RhCl_2]_2$ (426.7 mg, 0.69 mmol, 10 mol %) and AgOPiv (288.6 mg, 1.38 mmol, 20 mol %). Then substrate **1a** (1.03 g, 6.90 mmol, 1.0 equiv) in 69.0 mL HFIP was subsequently supplemented and the resulting mixture was filled with Ar. After stirring at room temperature for 2 h, the mixture was filtered through a pad of celite and washed with CH_2Cl_2 (20 mL x 3). The organic layer was collected and concentrated under vacuum to yield the crude product which was further purified by flash chromatography eluting with Hexane/EA to afford the pure desired product **3aa** (1.74 g, 91% yield).

General Procedure for the Diversification of Clinical Drugs. Prodtuct **6** was prepared starting from substrate **5** by following the general procedure for the synthesis of compound **3**.

*11,11'-(1H-1,2,4-triazol-1-ylmethanediyl)bis(8-ethoxy-5H-isochromeno[3,4-c]isoquinoline) (**6a**)*. White solid (85.0 mg, 67% yield); m.p. 149.3-150.6 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.33 (d, J = 8.4 Hz, 2H), 8.15 (s, 1H), 8.10-8.09 (m, 2H), 8.08 (s, 1H), 7.47 (d, J =

7.8 Hz, 2H), 7.30 (dd, *J* = 8.4, 1.8 Hz, 2H), 7.23-7.19 (m, 4H), 7.16-7.13 (m, 2H), 7.12 (s, 1H), 5.15 (s, 4H), 4.61 (q, *J* = 7.2 Hz, 4H), 1.50 (t, *J* = 7.2 Hz, 6H); $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$): δ 160.6, 158.7, 152.7, 143.9, 140.5, 136.3, 131.2, 129.9, 128.2, 126.6, 126.3, 125.2, 124.3, 123.6, 123.4, 117.2, 102.6, 69.8, 67.9, 63.0, 14.5; LRMS (ESI): *m/z* 632.4 $[M - H]^-$; HRMS (ESI): calculated for $C_{39}H_{30}N_5O_4^-$ $[M - H]^-$: 632.2303, found: 632.2303.

1-(8-Ethoxy-5H-isochromeno[3,4-c]isoquinolin-11-yl)-5-methylpyridin-2(1H)-one ***(6b)***. White solid (67.7 mg, 88% yield); m.p. 104.2-105.8 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.40 (d, *J* = 8.5 Hz, 1H), 8.37 (d, *J* = 2.0 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.43-7.40 (m, 2H), 7.33 (dd, *J* = 9.5, 2.5 Hz, 1H), 7.28 (d, *J* = 4.5 Hz, 2H), 7.19-7.18 (m, 1H), 6.71 (d, *J* = 9.5 Hz, 1H), 5.19 (s, 2H), 4.62 (q, *J* = 7.0 Hz, 2H), 2.13 (s, 3H), 1.51 (t, *J* = 7.0 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): δ 161.8, 160.8, 158.4, 143.7, 143.2, 136.9, 135.0, 131.4, 130.3, 128.7, 126.9, 126.7, 125.4, 124.8, 122.7, 121.7, 121.3, 117.0, 115.7, 102.9, 69.9, 63.2, 17.3, 14.6; LRMS (ESI): *m/z* 385.3 $[M + H]^+$; HRMS (ESI): calculated for $C_{24}H_{21}N_2O_3^+$ $[M + H]^+$: 385.1547, found: 385.1550.

*3-[8-Ethoxy-12-(4-fluorophenyl)-10,12-dihydro-5H-furo[3,4-g]isochromeno[3,4-c]isoquinolin-12-yl]-N,N-dimethylpropan-1-amine(****6c****)*. Yellow solid (57.8 mg, 58% yield); m.p. 132.0-132.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.28 (s, 1H), 8.13 (s, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.53-7.50 (m, 3H), 7.35-7.29 (m, 2H), 7.03 (t, *J* = 8.5 Hz, 2H), 5.31 (d, *J* = 13.0 Hz, 1H), 5.23 (d, *J* = 13.0 Hz, 1H), 5.20-5.14 (m, 2H), 4.58 (q, *J* = 7.0 Hz, 2H), 3.09-3.03 (m, 2H), 2.67 (s, 6H), 2.52-2.46 (m, 1H), 2.35-2.29 (m, 1H), 1.86-1.77 (m, 2H), 1.48 (t, *J* = 7.0 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): δ 162.2 (d, *J* = 247.3 Hz), 160.7, 157.8, 148.3, 139.3, 136.4, 135.5, 131.5, 130.6, 128.9, 126.9, 126.8, 126.6, 125.5, 124.6, 117.9, 117.7, 116.2,

115.8, 115.6, 103.1, 90.2, 71.3, 69.9, 63.0, 57.9, 43.0, 38.3, 19.6, 14.6, 9.3; ^{19}F NMR (471 MHz, $CDCl_3$): δ -115.09 (d, J = 79.1 Hz); LRMS (ESI): *m/z* 499.3 $[M + H]^+$; HRMS (ESI): calculated for $C_{31}H_{32}FN_2O_3^+$ $[M + H]^+$: 499.2391, found: 499.2401.

Mechanistic Investigations

H/D exchange experiment. A mixture of **1a** (29.8 mg, 0.2 mmol, 1.0 equiv), $[Cp^*RhCl_2]_2$ (12.4 mg, 0.02 mmol, 10 mol %), AgOPiv (8.4 mg, 0.04 mmol, 20 mol%) and d^2-HFIP was added into a Shlenk tube and filled with Ar. The resulting mixture was stirred at room temperature for 2 h. Afterwards, the mixture was diluted with CH_2Cl_2 and filtered through a pad of celite, which was washed with CH_2Cl_2 for three times. The combined organic layer was collected and concentrated *in vacuo* to yield the crude product which was further purified by flash chromatography eluting with hexane/EA = 5 : 1 to afford the deuterium product as a light yellow oil. *H/D exchange occurred at the C2-position of benzimidate (90% D)*.

Competition experiment. To a mixture of **1e** (35.8 mg, 0.2 mmol, 1.0 equiv), **1k** (43.4 mg, 0.2 mmol, 1.0equiv) (if using **1g** to perform the experiment, **1g** (33.4 mg, 0.2 mmol, 1.0 equiv) was added), $[Cp^*RhCl_2]_2$ (12.4 mg, 0.02 mmol, 10% mol %) and AgOPiv (8.4 mg, 0.04 mmol, 20 mol % equiv) was added **2a** (98.2 mg, 0.3 mmol, 1.5 equiv) and HFIP (2.0 mL, 0.1 M). The resulting mixture was filled with Ar and stirred at room temperature for 2 h. After the reaction was completed, CH_2Cl_2 was added and the mixture was filtered through a pad of celite which was subsequently washed with CH_2Cl_2. The combined organic layer was concentrated under vacuum and purified by flash chromatography to yield the mixture of **3ea** and **3ka** (if **1g** was used, then **3ea** and **3ga** will be obtained). The ratio of products was

calculated according to ^{1}H NMR spectra (see SI).

Kinetic isotope effect (KIE) experiment. Compounds **1a** (15.0 mg, 0.1 mmol, 1.0 equiv) and ***d*^{5}-1a** (15.4 mg, 0.1 mmol, 1.0 equiv) were successively added to a mixture of $[Cp^*RhCl_2]_2$ (12.4 mg, 0.02 mmol, 10 mol %), AgOPiv (8.4 mg, 0.04 mmol, 20 mol %) and **2a** (98.2 mg, 0.3 mmol, 1.5 equiv) in HFIP (2.0 mL, 0.1 M). The resulting mixture was refilled with Ar and stirred at room temperature for 45 min. Then the reaction was stopped and filtered through a pad of celite which was subsequently washed with CH_2Cl_2 (10 mL x 3) and the combined organic layer was concentrated under reduced pressure. The mixture of **3aa** and ***d*^{4}-3aa** was isolated by flash chromatography eluting with Hexane/EA from 20:1 to 10:1. The KIE value was determined using ^{1}H NMR. (see SI)

Associated Content

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at http://pubs.acs.org.

^{1}H NMR and ^{13}C NMR spectra for all new compounds

X-ray crystallographic data of **3aa** and **3na**

Mechanistic study and intermolecular competition experiments

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Notes

The authors declare no conflict of interest.

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15. For details, see the Supporting Information. CCDC 1963986 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the

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16. For details, see the Supporting Information. CCDC 1963988 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre.

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