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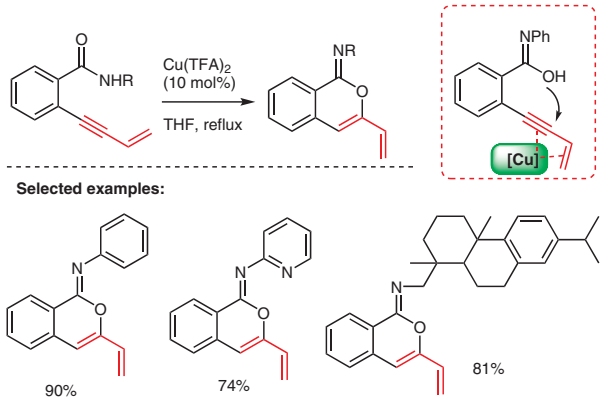
Copper-Catalyzed 6-*endo*-*dig* O-Cyclization of 2-(But-3-en-1-yn-1-yl)benzamide

Rui-Xiang Wang[*a]
Zhuang Fang[a]
Guanyinsheng Qiu[*b]
Wenlin Xie[c]
Jin-Biao Liu[*a]

[a] Department of chemistry, Jiangxi University of Science and Technology, 86 Hongqi Road, Ganzhou 341000, P. R. of China
liujinbiao@jxust.edu.cn
[b] College of Biological, Chemical Science and Engineering, Jiaxing University, 118 Jiahang Road, Jiaxing 314001, P. R. of China
qiuguanyinsheng@mail.zjxu.edu.cn
[c] School of Chemistry and Chemical Engineering, Hunan University of Science and Technology, Hunan 411201, P. R. of China



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Abstract The copper-catalyzed synthesis of 3-vinylisocoumarin-1-imine is reported. The transformation proceeds smoothly with good yields in THF and the regioselectivity was determined by a O-nucleophilic 6-*endo* cyclization. Studies on the mechanism indicate that copper trifluoroacetate serves as a Lewis acid, and the use of vinyl-connected 2-alkynylbenzamide is important for this O-nucleophilic 6-*endo* cyclization.

Key words copper catalysis, O-nucleophilic 6-*endo* cyclization, Lewis acid, vinyl-connected 2-alkynylbenzamide, isocoumarin

As a dual-functionalized synthon, 2-alkynylbenzamide has attracted increasing attention from the scientific community because of its synthetic versatility in annulative reactions.[1] Together with an improvement in reaction efficiency, we wished to explore the selectivity of N- versus O-nucleophilicity and 6-*endo*- versus 5-*exo* cyclization for 2-alkynylbenzamide-based chemistry. The N/O-nucleophilicity and 6-*endo*/5-*exo*-switch has been ascribed to the use of various reaction systems. Generally, base-mediated reactions of 2-alkynylbenzamide tend to undergo N-nucleophilic 5-*exo* cyclization,[2] and electrophilic cyclization of 2-alkynylbenzamide resulted in the formation of a mixture of O-nucleophilic 5-*exo* cyclization and O-nucleophilic 6-*endo* cyclization products.[3] Pleasingly, our recent work suggested that either an O-nucleophilic 5-*exo* reaction[4a] or an O-nucleophilic 6-*endo* reaction[4b] could be realized, respectively, when radical cyclization of 2-alkynylbenzamide was conducted.

In 2009, Liu and co-workers developed a silver-catalyzed cyclization of 2-alkynylbenzamide in which a distinctive O-nucleophilic 6-*endo* cyclization took place with the formation of isocoumarin-1-imine derivatives (Scheme 1a).[5] However, it was surprising that the reaction of substrates with *N*-alkyl protecting groups provided isocoumarin-1-imine in good yields, and *N*-aryl protecting substrates were not efficient reaction partners. For examples, the reaction of *N*-phenyl-2-phenylethynylbenzamide provided only *N*-phenylisocoumarin-1-imine **2a** in a 23% yield. Subsequently, many research groups also investigated O-nucleophilic 6-*endo* cyclization of 2-alkynylbenzamide.[6] To our surprise, silver salts have been used in most of the examples; other metal salt-catalyzed examples of O-nucleophilic 6-*endo* cyclization of 2-alkynylbenzamide remain rare.[7] Inspired by these reports, we wanted to explore O-nucleophilic 6-*endo* cyclization of 2-alkynylbenzamide under other metal catalysis with a view to expanding the scope of the reaction by making it compatible with substrates bearing various *N*-aryl protecting groups. Considering our ongoing interest in copper catalysis[8] and the high importance of the isocoumarin-1-imine core,[4,9] in this paper we would like to report the development of a copper-catalyzed O-nucleophilic 6-*endo*-cyclization of 2-alkynylbenzamide **1**.

A preliminary result from the copper chloride-catalyzed reaction of 2-alkynylbenzamide **1** suggested the substituent R in substrate **1** had a significant impact on the outcome of the reaction.[10] Although the expected O-nucleophilic 6-*endo* cyclization took place, the yields of isocoumarin-1-imine **2** varied depending on the use of the substituent R in 2-alkynylbenzamide **1**. As illustrated in Scheme 1b, the reaction of 2-phenylethynylbenzamide provided the desired product **2a** in 35% yield, whereas reaction

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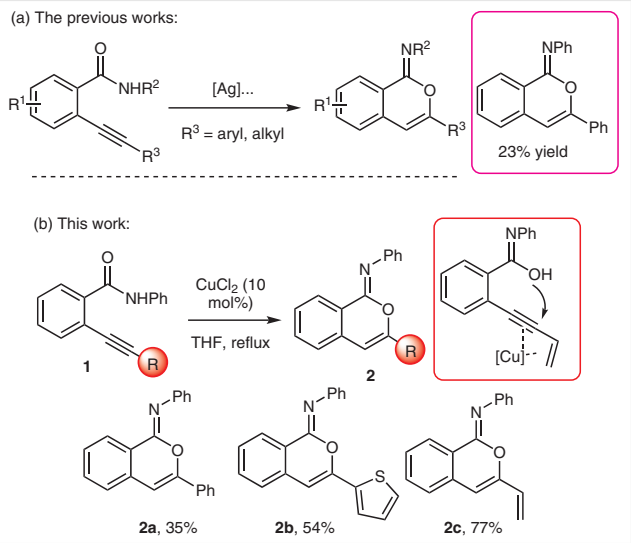


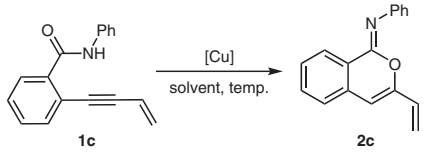
Scheme 1 Copper-catalyzed *ortho*-group-assisted 6-*endo*-*dig* cyclization of 2-alkynylbenzamide

of 2-(but-3-en-1-yn-1-yl)benzamide gave rise to the corresponding product **2c** in 77% yield without further reaction optimization. We assumed that the substituent R probably stabilized the resulting copper-involved species through a coordination effect during the process. Given the synthetic potential of the vinyl group for structural elaboration, we optimized the reaction of 2-(but-3-en-1-yn-1-yl)benzamide for the formation of 3-vinylisocoumarin-1-imines.

The optimization of the reaction is summarized in Table 1. We initially explored a range of copper sources including $Cu(OAc)_2$, $Cu(TFA)_2$, CuI and CuBr, and found that the use of $Cu(TFA)_2$ greatly improved the efficiency of the reaction to deliver the desired product **2c** in 90% yield (entry 3). Solvent screening suggested that tetrahydrofuran (THF) was optimal; other solvents including 1,4-dioxane, 1,2-dichloroethane (DCE), MeCN, toluene, and DMF did not deliver better yields (entries 6–10). Reducing either the reaction temperature or the copper loading had a negative impact on the outcome of the reaction (entries 11 and 12). As such, we established the optimized conditions as $Cu(TFA)_2$ (10 mol%), THF, and 60 °C.

With the optimized conditions in hand, we then explored the scope and generality of the reaction. The results are illustrated in Scheme 2. A range of vinyl group-connected substrates were compatible with the reaction conditions. For instance, the reaction of cyclohexene-linked substrate provided the desired product **2f** in a 75% yield. The screening of substituent R^1 showed that this substituent could be replaced with methyl, chloro, fluoro, or bromo groups, and the corresponding products **2g–j** were achieved in moderated to good yields. Interestingly, the reaction of 3-enynylnaphthalen-2-amide **1k** also worked well, leading to

Table 1 Initial Studies for the Reaction of Regioselective 6-*endo*-*dig* Cyclization of 2-Alkynylbenzamide[a]



Entry	[Cu] (0.1 equiv)	Solvent	*T* (°C)	Yield of **2c** (%)[b]
1	$CuCl_2$	THF	60	77
2	$Cu(OAc)_2$	THF	60	35
3	$Cu(TFA)_2$	THF	60	90
4	CuI	THF	60	62
5	CuBr	THF	60	68
6	$Cu(TFA)_2$	1,4-dioxane	60	85
7	$Cu(TFA)_2$	DCE	60	73
8	$Cu(TFA)_2$	MeCN	60	61
9	$Cu(TFA)_2$	toluene	60	67
10	$Cu(TFA)_2$	DMF	60	complex
11	$Cu(TFA)_2$	THF	r.t.	trace
12	$Cu(TFA)_2$[c]	THF	60	39

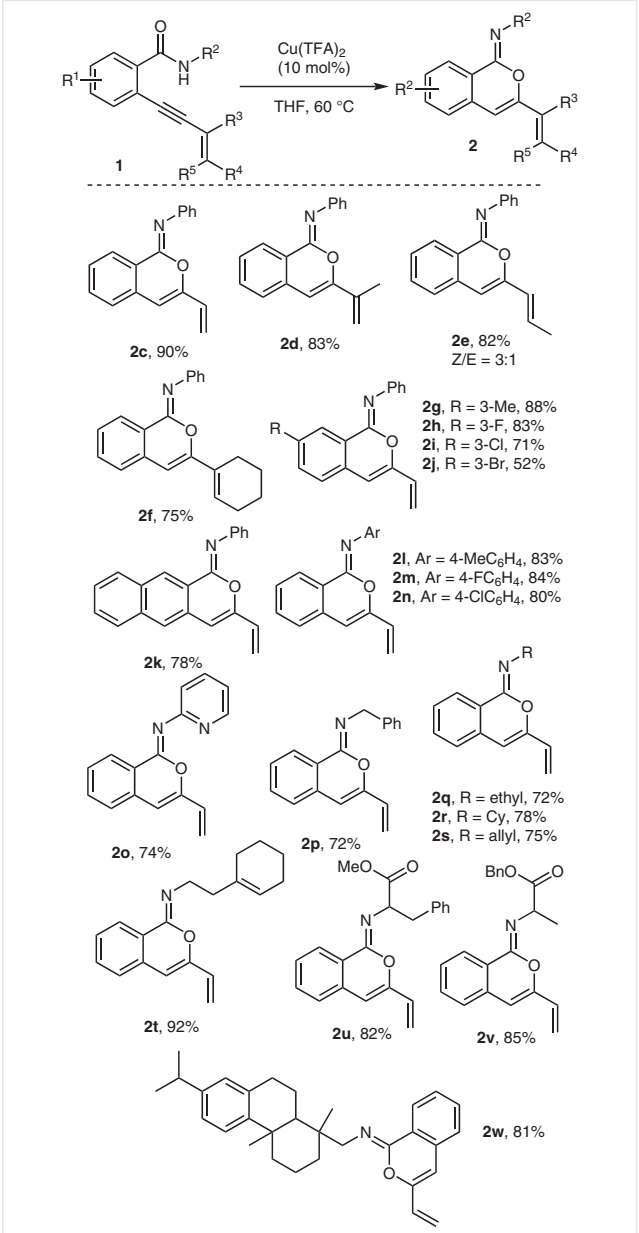
[a] Standard conditions: 2-(but-3-en-1-yn-1-yl)benzamide (**1c**; 0.2 mmol), copper catalysis (0.1 equiv), solvent (2 mL), overnight.
[b] Isolated yield based on 2-(but-3-en-1-yn-1-yl)benzamide (**1c**).
[c] $Cu(TFA)_2$ (0.05 equiv) was added.

the expected isocoumarin-1-imine **2k** in 78% yield. The structure of **2j** was confirmed by X-ray diffraction analysis (CCDC 1941980).[11]

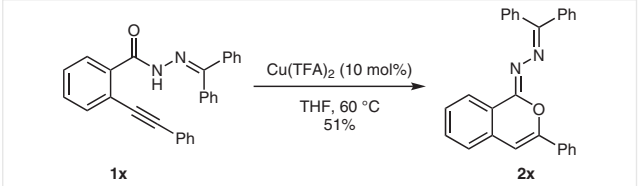
Subsequently, the substituent effect of N-protecting groups was also examined. From the results, the N-protecting group could be aryl, heteroaryl, alkyl, and complex molecular blocks. For example, *N*-pyridinyl-2-(but-3-en-1-yn-1-yl)benzamide was recognized as an efficient reaction partner, resulting in the formation of *N*-pyridinyl-3-vinylisocoumarin-1-imine (**2o**) in 74% yield. Other *N*-alkyl group-linked substrates were also suitable for the reactions, producing the corresponding products **2p–s** in 72–92% yield.

In particular, substrates with complex N-protecting groups were also compatible with the reaction. For instance, the reaction of the substrates with *N*-phenylalanine and *N*-alanine worked uniquely well, leading to the desired products **2u** and **2v** in 82% and 85% yields, respectively. The rosin amine-connected substrate was also a good reaction partner, producing the desired product **2w** in 81% yield.

Additionally, the reaction of *N*-imine-2-alkynylbenzamide **1x** was conducted under the standard conditions. As expected, the desired *N*-imineisocoumarin-1-imine **2x** was achieved in moderated yield (Scheme 3).

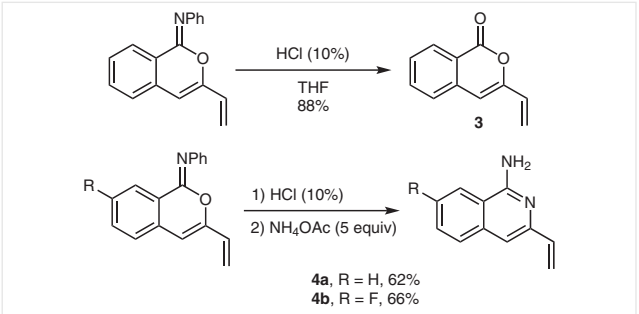


Scheme 2 Generation of isocoumarins **2** through a regioselective 6-*endo-dig* O-cyclization of 2-alkynylbenzamide. Isolated yields based on 2-alkynylbenzamide **1** are given.



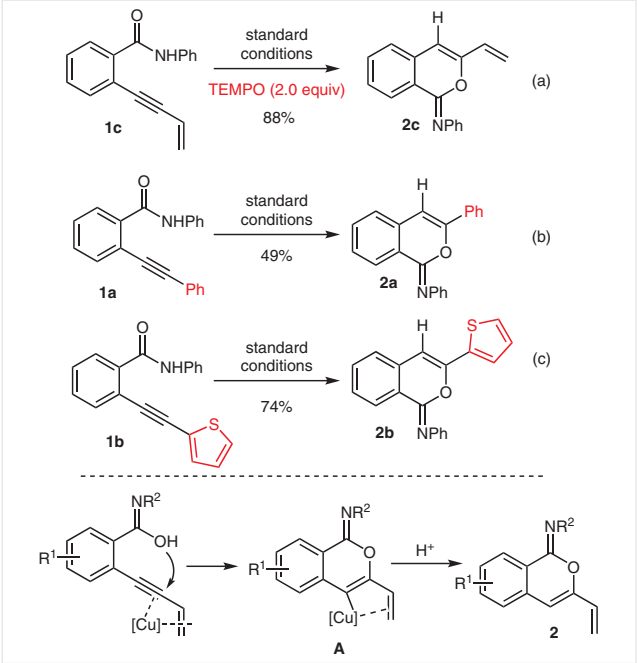
Scheme 3 Generation of *N*-imineisocoumarin-1-imine **2** through regioselective 6-*endo-dig* O-cyclization of *N*-imine-2-alkynylbenzamide. Isolated yield based on *N*-imine-2-alkynylbenzamide **1x** is given.

Subsequently, structural elaboration of 3-vinylisocoumarin-1-imine **2** was investigated. The results are presented in Scheme 4. Thus, 3-vinylisocoumarin **3** was readily accessible through hydrolysis of 3-vinylisocoumarin-1-imine **2c**. Moreover, 3-vinylisocoumarin **3**, generated in situ, was readily converted into 1-amino-3-vinylisoquinoline **4** in good yields.



Scheme 4 Synthetic applications of isocoumarin-1-imine. Isolated yields based on 3-vinylisocoumarin-1-imine **3** are given.

To gain insights into reaction mechanism, several control experiments were carried out. As presented in Scheme 5, the first trial was to confirm the role of the copper catalyst. A control reaction with 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) as an additive was conducted. The use of TEMPO did not made significant impact on the reaction, indicating the role of copper catalyst as a Lewis acid. We then examined whether the vinyl group assisted in the reaction. Under standard conditions we ran the reactions of



Scheme 5 Control experiments and proposed mechanism

N-phenyl-2-phenylethynylbenzamide, *N*-phenyl-2-(2-thiophene) ethynylbenzamide, and *N*-phenyl-2-(but-3-en-1-yn-1-yl)benzamide. As expected, the yield of *N*-phenyl-2-phenylethynylbenzamide was much lower than that of *N*-phenyl-2-(but-3-en-1-yn-1-yl)benzamide, thus suggesting a coordination effect of the vinyl group.

In light of these results, a plausible mechanism is proposed in Scheme 5. In this process, the copper salt serves as a Lewis acid to activate the triple bond. Nucleophilic addition then takes place through O-nucleophilic 6-*endo* and O-nucleophilic 5-*exo* reactions. Through O-nucleophilic 6-*endo* cyclization, intermediate **A** is formed, and subsequent protonation provides the final isocoumarin-1-imine **2**.

In conclusion, we have developed a copper-catalyzed O-nucleophilic 6-*endo*-*dig* cyclization of 2-(but-3-en-1-yn-1-yl)benzamide for the synthesis of 3-vinylisocoumarin-1-imine derivatives. Compared to the use of 2-arylethynylbenzamide as substrates, substrates with a 2-enynyl group were more efficient reaction partners. Studies on the mechanism indicated that the *ortho*-vinyl group serves as an assisting group, and the reaction proceeds through Lewis acid catalysis. The scope of the reaction showed that the N-protecting group in the substrates could be replaced by various aryl groups, alkyl groups, and even many complex building blocks. The copper-catalyzed O-nucleophilic 6-*endo*-*dig* cyclization of 2-(but-3-en-1-yn-1-yl)benzamide reported herein represents an important complement for silver-catalyzed O-nucleophilic 6-*endo*-*dig* cyclization of 2-(but-3-en-1-yn-1-yl)benzamide. Copper-catalyzed N-nucleophilic cyclization studies are ongoing in our laboratory, and the results will be reported in due course.

The solvents were distilled from standard drying agents. Unless otherwise stated, commercial reagents purchased from Aladdin and J&K® chemical companies were used without further purifcation. Purifcation of reaction products was carried out by flash chromatography using Qing Dao Sea Chemical Reagent silica gel (200–300 mesh). ^{1}H NMR spectra were recorded on a Bruker Avance III 400 (400 MHz) spectrometer and referenced internally to the residual proton resonance in $CDCl_3$ (δ = 7.26 ppm), or with tetramethylsilane (TMS, δ = 0.00 ppm) as the internal standard. Chemical shifts were reported as parts per million (ppm) in the δ scale downfeld from TMS. Multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet), dd (doublet of doublet), bs (broad singlet). Analytical TLC was performed using EM separations percolated silica gel 0.2 mm layer UV 254 fluorescent sheets.

1*H*-Isochromen-1-imines 2; General Procedure

The 2-(but-3-en-1-yn-1-yl)benzamide **1** (0.2 mmol) and $Cu(TFA)_2$ (10 mol%) were added to a test tube, and then solvent THF was added. The mixture was stirred at 60 °C overnight. After the consumption of substrate as indicated by TLC, the mixture was filtered , and the filtrate was concentrated in vacuo. The resulting crude product was purified by column chromatography by using an EtOAc/petroleum ether gradient mixture to afford the pure product **2**.

(*Z*)-*N*,3-Diphenyl-1*H*-isochromen-1-imine (2a)

Yield: 20.8 mg (35%); black solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.43 (d, *J* = 7.8 Hz, 1 H), 7.63–7.51 (m, 3 H), 7.47–7.43 (m, 3 H), 7.42–7.27 (m, 6 H), 7.20 (t, *J* = 7.3 Hz, 1 H), 6.70 (s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 151.6, 149.8, 146.8, 134.0, 132.5, 132.3, 129.5, 128.8, 128.2, 127.5, 125.7, 124.7, 123.7, 122.6, 100.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{16}NO^+$: 298.1226; found: 298.1222.

(*Z*)-*N*-Phenyl-3-(thiophen-2-yl)-1*H*-isochromen-1-imine (2b)

Yield: 32.7 mg (54%); yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.35 (d, *J* = 7.9 Hz, 1 H), 7.47–7.51 (m, 1 H), 7.34–7.41 (m, 3 H), 7.24–7.28 (m, 4 H), 7.19–7.20 (m, 1 H), 7.13 (t, *J* = 7.3 Hz, 1 H), 6.95–6.97 (m, 1 H), 6.51 (s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 149.2, 147.7, 146.4, 136.1, 133.8, 132.5, 128.7, 127.9, 127.6, 126.7, 125.4, 125.2, 123.8, 123.5, 122.7, 100.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{14}NOS^+$: 304.0791; found: 304.0795.

(*Z*)-*N*-Phenyl-3-vinyl-1*H*-isochromen-1-imine (2c)

Yield: 44.5 mg (90%); yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.25 (d, *J* = 7.9 Hz, 1 H), 7.38 (t, *J* = 7.5 Hz, 1 H), 7.32–7.22 (m, 3 H), 7.12–7.15 (m, 3 H), 7.04–6.97 (m, 1 H), 6.05–6.09 (m, 1 H), 5.98 (s, 1 H), 5.48 (d, *J* = 17.1 Hz, 1 H), 5.10 (d, *J* = 11.0 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 150.7, 149.6, 146.8, 133.9, 132.6, 129.0, 128.9, 128.5, 127.8, 125.8, 124.5, 123.9, 122.8, 117.5, 105.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{14}NO^+$: 248.1070; found: 248.1070.

(*Z*)-*N*-Phenyl-3-(prop-1-en-2-yl)-1*H*-isochromen-1-imine (2d)

Yield: 43.3 mg (83%); yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.37 (d, *J* = 7.9 Hz, 1 H), 7.47–7.51 (m, 1 H), 7.44–7.33 (m, 3 H), 7.27 (d, *J* = 7.9 Hz, 1 H), 7.24–7.16 (m, 2 H), 7.11 (t, *J* = 7.3 Hz, 1 H), 6.25 (s, 1 H), 5.44 (s, 1 H), 5.05 (s, 1 H), 1.97 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 152.0, 149.7, 146.8, 134.5, 133.8, 132.4, 128.7, 128.2, 127.4, 125.8, 124.0, 123.5, 122.4, 115.9, 102.1, 18.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{16}NO^+$: 262.1226; found: 262.1200.

N-Phenyl-3-[(*Z*)-prop-1-en-1-yl]-1*H*-isochromen-1-imine (2e) (*Z*/*E* = 3:1)

Yield: 42.8 mg (82%); brown liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.36 (d, *J* = 7.9 Hz, 1 H), 7.53–7.44 (m, 1 H), 7.41 (d, *J* = 8.2 Hz, 1 H), 7.38 (d, *J* = 4.3 Hz, 1 H), 7.34 (d, *J* = 7.7 Hz, 1 H), 7.31–7.27 (m, 1 H), 7.22–7.11 (m, 2 H), 7.06–7.09 (m, 1 H), 6.17–6.03 (m, 1 H), 5.96 (s, 1 H), 5.88–5.96 (m, 1 H), 1.77–1.79 (m, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 150.8, 149.7, 146.7, 134.2, 132.3, 131.9, 129.9, 128.7, 127.9, 127.5, 125.3, 123.6, 122.6, 121.9, 103.0, 18.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{16}NO^+$: 262.1226; found: 262.1264.

(*Z*)-3-(Cyclohex-1-en-1-yl)-*N*-phenyl-1*H*-isochromen-1-imine (2f)

Yield: 45.2 mg (75%); yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.33 (d, *J* = 7.9 Hz, 1 H), 7.48 (t, *J* = 7.5 Hz, 1 H), 7.43–7.30 (m, 3 H), 7.20–7.26 (m, 3 H), 7.10 (t, *J* = 7.3 Hz, 1 H), 6.26 (s, 1 H), 6.12 (s, 1 H), 2.26–2.02 (m, 4 H), 1.64–1.71 (m, 4 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 152.5, 150.0, 146.9, 134.3, 132.2, 128.6, 128.6, 128.5, 127.6, 127.4, 125.5, 123.7, 123.4, 122.4, 99.4, 25.7, 24.0, 22.3, 21.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{20}NO^+$: 302.1539; found: 302.1547.

(*Z*)-7-Methyl-*N*-phenyl-3-vinyl-1*H*-isochromen-1-imine (2g)

Yield: 46 mg (88%); yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20 (s, 1 H), 7.45–7.29 (m, 3 H), 7.25 (d, *J* = 7.6 Hz, 2 H), 7.09–7.15 (m, 2 H), 6.14–6.21 (m, 1 H), 6.10 (s, 1 H), 5.56 (d, *J* = 17.1 Hz, 1 H), 5.20 (d, *J* = 11.0 Hz, 1 H), 2.45 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 148.8, 145.6, 137.6, 132.5, 130.2, 127.7, 126.5, 124.6, 123.0, 122.6, 121.5, 115.7, 104.2, 20.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{16}NO^+$: 262.1226; found: 262.1248.

(*Z*)-7-Fluoro-*N*-phenyl-3-vinyl-1*H*-isochromen-1-imine (2h)

Yield: 44 mg (83%); yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 9.2 Hz, 1 H), 7.43–7.32 (m, 2 H), 7.28–7.21 (m, 2 H), 7.18–7.25 (m, 2 H), 7.09–7.13 (m, 1 H), 6.13–6.20 (m, 1 H), 6.05 (s, 1 H), 5.58 (d, *J* = 17.1 Hz, 1 H), 5.21 (d, *J* = 11.0 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 162.2 (d, *J* = 248.4 Hz), 149.9 (d, *J* = 2.9 Hz), 148.5 (s), 146.0 (s), 130.1 (d, *J* = 2.7 Hz), 128.7 (s), 128.6 (s), 127.6 (d, *J* = 7.9 Hz), 126.2 (d, *J* = 8.6 Hz), 124.0 (s), 122.6 (s), 120.3 (d, *J* = 23.1 Hz), 117.3 (s), 113.7 (d, *J* = 24.2 Hz), 104.3 (d, *J* = 1.5 Hz).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{13}FNO^+$: 266.0976; found: 266.0978.

(*Z*)-7-Chloro-*N*-phenyl-3-vinyl-1*H*-isochromen-1-imine (2i)

Yield: 38.5 mg (71%); yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.31 (d, *J* = 1.8 Hz, 1 H), 7.47–7.29 (m, 3 H), 7.23 (d, *J* = 7.4 Hz, 2 H), 7.09–7.13 (m, 2 H), 6.12–6.19 (m, 1 H), 6.02 (s, 1 H), 5.59 (d, *J* = 17.1 Hz, 1 H), 5.22 (d, *J* = 11.0 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 150.7, 148.1, 145.9, 134.0, 132.5, 132.1, 128.6, 127.3, 126.9, 125.6, 124.0, 122.6, 117.8, 104.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{13}ClNO^+$: 282.0680; found: 282.0662.

(*Z*)-7-Bromo-*N*-phenyl-3-vinyl-1*H*-isochromen-1-imine (2j)[11]

Yield: 33.8 mg (52%); yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.48 (d, *J* = 1.4 Hz, 1 H), 7.56–7.58 (m, 1 H), 7.36 (t, *J* = 7.8 Hz, 2 H), 7.23 (d, *J* = 7.5 Hz, 2 H), 7.17–7.00 (m, 2 H), 6.13–6.20 (m, 1 H), 6.03 (s, 1 H), 5.60 (d, *J* = 17.1 Hz, 1 H), 5.24 (d, *J* = 10.9 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 150.8, 147.9, 145.9, 135.4, 132.5, 130.2, 128.6, 127.0, 125.8, 124.0, 122.5, 121.9, 117.9, 104.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{13}BrNO^+$: 326.0175; found: 326.0191.

(*Z*)-*N*-Phenyl-3-vinyl-1*H*-benzo[*g*]isochromen-1-imine (2k)

Yield: 46.4 mg (78%); yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.41 (d, *J* = 8.7 Hz, 1 H), 8.28–8.10 (m, 1 H), 7.92–7.85 (m, 1 H), 7.82 (d, *J* = 8.7 Hz, 1 H), 7.68–7.54 (m, 2 H), 7.40 (t, *J* = 7.7 Hz, 2 H), 7.31 (d, *J* = 7.4 Hz, 2 H), 7.14 (t, *J* = 7.3 Hz, 1 H), 6.84 (s, 1 H), 6.31–6.38 (m, 1 H), 5.70 (d, *J* = 17.0 Hz, 1 H), 5.30 (d, *J* = 10.9 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 151.6, 150.2, 146.6, 135.0, 131.6, 129.0, 128.8, 128.7, 128.5, 128.1, 127.9, 127.0, 123.7, 123.3, 122.6, 121.6, 117.8, 100.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{16}NO^+$: 298.1226; found: 298.1228.

(*Z*)-*N*-(*p*-Tolyl)-3-vinyl-1*H*-isochromen-1-imine (2l)

Yield: 43.3 mg (83%); brown liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.35 (t, *J* = 9.3 Hz, 1 H), 7.47–7.51 (m, 1 H), 7.38 (t, *J* = 7.4 Hz, 2 H), 7.24–7.15 (m, 4 H), 6.18–6.25 (m, 1 H), 6.10 (s, 1 H), 5.67 (d, *J* = 17.1 Hz, 1 H), 5.25 (d, *J* = 11.0 Hz, 1 H), 2.37 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 150.5, 149.2, 143.6, 133.6, 133.2, 132.2, 129.2, 128.8, 128.3, 127.5, 125.6, 124.4, 122.7, 117.3, 105.2, 21.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{16}NO^+$: 262.1226; found: 262.1268.

(*Z*)-*N*-(4-Fluorophenyl)-3-vinyl-1*H*-isochromen-1-imine (2m)

Yield: 44.5 mg (84%); yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.33 (d, *J* = 7.9 Hz, 1 H), 7.47–7.51 (m, 1 H), 7.36–7.40 (m, 1 H), 7.32–7.14 (m, 3 H), 7.13–6.98 (m, 2 H), 6.17–6.24 (m, 1 H), 6.09 (s, 1 H), 5.60 (d, *J* = 17.1 Hz, 1 H), 5.24 (d, *J* = 11.0 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.4 (d, *J* = 241.8 Hz), 150.4 (s), 149.6 (s), 142.5 (d, *J* = 2.9 Hz), 133.6 (s), 132.4 (s), 128.8 (s), 128.3 (s), 127.5 (s), 125.7 (s), 124.1 (t, *J* = 8.6 Hz), 117.2 (s), 115.4 (s), 115.2 (s), 105.7 (s).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{13}FNO^+$: 266.0976; found: 266.0980.

(*Z*)-*N*-(4-Chlorophenyl)-3-vinyl-1*H*-isochromen-1-imine (2n)

Yield: 44.96 mg (80%); yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.31 (d, *J* = 7.9 Hz, 1 H), 7.48–7.52 (m, 1 H), 7.42–7.34 (m, 1 H), 7.35–7.26 (m, 2 H), 7.26–7.12 (m, 3 H), 6.16–6.23 (m, 1 H), 6.10 (s, 1 H), 5.58 (d, *J* = 17.1 Hz, 1 H), 5.23 (d, *J* = 11.0 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 150.4, 149.9, 145.1, 133.7, 132.5, 128.7, 128.4, 127.6, 125.7, 124.0, 117.3, 105.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{13}ClNO^+$: 282.0680; found: 282.0668.

(*Z*)-*N*-(Pyridin-2-yl)-3-vinyl-1*H*-isochromen-1-imine (2o)

Yield: 36.7 mg (74%); brown liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.54 (s, 1 H), 8.34 (d, *J* = 6.2 Hz, 2 H), 7.52–7.57 (m, 2 H), 7.41 (t, *J* = 7.6 Hz, 1 H), 7.25–7.30 (m, 2 H), 6.32–6.07 (m, 2 H), 5.55 (d, *J* = 17.2 Hz, 1 H), 5.24 (d, *J* = 11.0 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 150.9, 150.3, 144.6, 142.9, 133.8, 132.8, 129.8, 128.5, 127.7, 125.7, 123.7, 123.4, 117.5, 105.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{13}N_2O^+$: 249.1022; found: 249.1042.

(*Z*)-*N*-Benzyl-3-vinyl-1*H*-isochromen-1-imine (2p)

Yield: 37.6 mg (72%); brown liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.30 (d, *J* = 7.8 Hz, 1 H), 7.51 (d, *J* = 7.8 Hz, 2 H), 7.45 (t, *J* = 7.5 Hz, 1 H), 7.33–7.38 (m, 3 H), 7.26 (t, *J* = 7.1 Hz, 1 H), 7.20 (d, *J* = 7.7 Hz, 1 H), 6.28–6.34 (m, 1 H), 6.09 (s, 1 H), 5.92 (d, *J* = 17.1 Hz, 1 H), 5.39 (d, *J* = 10.9 Hz, 1 H), 4.81 (s, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 150.4, 150.3, 140.9, 132.9, 131.7, 129.4, 128.3, 128.1, 127.7, 127.0, 126.5, 125.5, 124.6, 116.6, 105.2, 49.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{16}NO^+$: 262.1226; found: 262.1232.

(*Z*)-*N*-Ethyl-3-vinyl-1*H*-isochromen-1-imine (2q)

Yield: 28.7 mg (72%); yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (d, *J* = 7.6 Hz, 1 H), 7.30 (t, *J* = 7.3 Hz, 1 H), 7.19 (t, *J* = 7.3 Hz, 1 H), 7.05 (d, *J* = 7.3 Hz, 1 H), 6.30–6.07 (m, 1 H), 5.91 (s, 1 H), 5.78 (d, *J* = 17.1 Hz, 1 H), 5.25 (d, *J* = 10.8 Hz, 1 H), 3.48–3.53 (m, 2 H), 1.23 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 150.3, 149.5, 132.7, 131.3, 129.4, 127.9, 126.5, 125.3, 124.6, 116.2, 104.8, 40.6, 15.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{14}NO^+$: 200.1070; found: 200.1098.

(*Z*)-*N*-Cyclohexyl-3-vinyl-1*H*-isochromen-1-imine (2r)

Yield: 25.3 mg (78%); brown liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (d, *J* = 7.8 Hz, 1 H), 7.30–7.34 (m, 1 H), 7.24–7.18 (m, 1 H), 7.07 (d, *J* = 7.6 Hz, 1 H), 6.17–6.24 (m, 1 H), 5.94 (s, 1 H), 5.82–5.70 (m, 1 H), 5.27 (d, *J* = 11.2 Hz, 1 H), 3.86–3.71 (m, 1 H), 1.86–1.70 (m, 4 H), 1.44–1.19 (m, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 150.4, 132.9, 131.3, 129.6, 127.9, 126.8, 125.3, 124.9, 116.1, 104.8, 54.6, 33.5, 26.0, 25.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{20}NO^+$: 254.1539; found: 254.1537.

(*Z*)-*N*-Allyl-3-vinyl-1*H*-isochromen-1-imine (2s)

Yield: 33.8 mg (80%); yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.22 (d, *J* = 7.9 Hz, 1 H), 7.43 (t, *J* = 7.5 Hz, 1 H), 7.31 (t, *J* = 7.6 Hz, 1 H), 7.17 (d, *J* = 7.7 Hz, 1 H), 6.35–6.21 (m, 1 H), 6.20–6.07 (m, 1 H), 6.05 (s, 1 H), 5.95–5.80 (m, 1 H), 5.34–5.39 (m, 2 H), 5.13–5.17 (m, 1 H), 4.21 (d, *J* = 5.6 Hz, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 150.3, 136.4, 132.8, 131.7, 129.4, 128.0, 126.8, 125.4, 124.5, 116.5, 115.0, 105.1, 48.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{14}NO^+$: 212.1070; found: 212.1076.

(*Z*)-*N*-[2-(Cyclohex-1-en-1-yl)ethyl]-3-vinyl-1*H*-isochromen-1-imine (2t)

Yield: 51.37 mg (92%); brown liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16 (d, *J* = 7.9 Hz, 1 H), 7.40–7.44 (m, 1 H), 7.34–7.27 (m, 1 H), 7.17 (d, *J* = 7.6 Hz, 1 H), 6.25–6.32 (m, 1 H), 6.04 (s, 1 H), 5.90 (d, *J* = 17.1 Hz, 1 H), 5.52 (s, 1 H), 5.37 (d, *J* = 11.0 Hz, 1 H), 3.62–3.66 (m, 2 H), 2.34 (t, *J* = 7.7 Hz, 2 H), 1.99–2.05 (m, 4 H), 1.70–1.48 (m, 4 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 150.4, 149.7, 136.5, 132.8, 131.5, 129.5, 128.0, 126.7, 125.4, 124.7, 121.9, 116.4, 105.0, 45.6, 38.9, 28.7, 25.3, 23.1, 22.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{22}NO^+$: 280.1696; found: 280.1686.

Methyl (*Z*)-3-Phenyl-2-[(3-vinyl-1*H*-isochromen-1-ylidene)amino]propanoate (2u)

Yield: 54.6 mg (82%); brown liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.30 (d, *J* = 7.7 Hz, 1 H), 7.43–7.47 (m, 1 H), 7.32–7.35 (m, 3 H), 7.30–7.23 (m, 2 H), 7.23–7.13 (m, 2 H), 6.17–6.24 (m, 1 H), 6.03 (s, 1 H), 5.81 (d, *J* = 17.1 Hz, 1 H), 5.33 (d, *J* = 11.0 Hz, 1 H), 4.77–4.80 (m, 1 H), 3.67 (s, 3 H), 3.19–3.31 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.4, 151.7, 150.2, 138.4, 132.9, 132.1, 129.5, 129.0, 128.2, 127.4, 126.4, 125.4, 124.0, 116.8, 105.3, 60.8, 51.9, 40.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{20}NO_3^+$: 334.1438; found: 334.1448.

Benzyl (*Z*)-2-[(3-Vinyl-1*H*-isochromen-1-ylidene)amino]propanoate (2v)

Yield: 56.6 g (85%); brown liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.29 (d, *J* = 7.9 Hz, 1 H), 7.51–7.42 (m, 1 H), 7.41–7.29 (m, 5 H), 7.29–7.12 (m, 2 H), 6.19–6.26 (m, 1 H), 6.07 (s, 1 H), 5.78 (d, *J* = 17.2 Hz, 1 H), 5.21–5.30 (m, 2 H), 5.15 (d, *J* = 12.4 Hz, 1 H), 4.73 (q, *J* = 7.0 Hz, 1 H), 1.60 (d, *J* = 7.0 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.9, 151.4, 150.3, 136.0, 132.9, 132.1, 129.0, 128.5, 128.1, 127.3, 125.5, 124.0, 116.8, 105.4, 66.4, 54.4, 19.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{20}NO_3^+$: 334.1438; found: 334.1430.

(*Z*)-*N*-[(7-Isopropyl-1,4*a*-dimethyl-1,2,3,4,4*a*,9,10,10*a*-octahydrophenanthren-1-yl)methyl]-3-vinyl-1*H*-isochromen-1-imine (2w)

Yield: 71.2 mg (81%); brown liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (d, *J* = 7.6 Hz, 1 H), 7.42 (t, *J* = 7.0 Hz, 1 H), 7.35–7.21 (m, 2 H), 7.17 (d, *J* = 7.5 Hz, 1 H), 7.06 (d, *J* = 7.5 Hz, 1 H), 6.93 (s, 1 H), 6.43–6.24 (m, 1 H), 6.04 (s, 1 H), 5.94 (d, *J* = 17.1 Hz, 1 H), 5.41 (d, *J* = 10.8 Hz, 1 H), 3.61 (d, *J* = 14.6 Hz, 1 H), 3.24 (d, *J* = 14.6 Hz, 1 H), 2.87 (d, *J* = 7.0 Hz, 3 H), 2.34 (d, *J* = 12.1 Hz, 1 H), 2.06–1.85 (m, 2 H), 1.85–1.65 (m, 3 H), 1.52 (d, *J* = 9.1 Hz, 2 H), 1.41–1.14 (m, 9 H), 1.09–1.04 (m, 4 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 150.5, 148.5, 147.9, 145.2, 135.3, 132.7, 131.3, 129.8, 128.0, 127.0, 125.2, 124.5, 123.8, 116.3, 104.9, 57.0, 45.2, 38.6, 37.7, 36.5, 33.5, 30.8, 25.7, 24.1, 24.1, 19.8, 19.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{31}H_{38}NO^+$: 440.2948; found: 440.2942.

(*Z*)-1-(Diphenylmethylene)-2-(3-phenyl-1*H*-isochromen-1-ylidene)hydrazine (2x)

Yield: 40.8 mg (51%); brown solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 7.8 Hz, 1 H), 7.92 (d, *J* = 7.9 Hz, 2 H), 7.87–7.89 (m, 2 H), 7.53–7.37 (m, 12 H), 7.27 (d, *J* = 9.5 Hz, 2 H), 6.70 (s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 162.1, 151.7, 150.1, 138.8, 135.8, 132.9, 132.5, 131.7, 129.7, 129.6, 129.5, 128.8, 128.7, 128.6, 128.2, 128.0, 127.8, 126.2, 125.5, 124.9, 122.8, 101.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{21}N_2O^+$: 401.1648; found: 401.1648.

3-Vinyl-1*H*-isochromen-1-one (3)

Yield: 30.3 mg (88%); yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.24–8.27 (m, 1 H), 7.65–7.69 (m, 1 H), 7.54–7.42 (m, 1 H), 7.39 (d, *J* = 7.8 Hz, 1 H), 6.42–6.24 (m, 2 H), 6.09 (d, *J* = 17.2 Hz, 1 H), 5.46 (d, *J* = 11.0 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 162.0, 152.1, 137.2, 134.8, 129.7, 128.5, 128.3, 125.9, 121.1, 118.7, 105.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_9O_2^+$: 173.0597; found: 173.0577.

3-Vinylisoquinolin-1-amine (4a)

Yield: 21.1 mg (62%); brown solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 8.3 Hz, 1 H), 7.67 (d, *J* = 8.2 Hz, 1 H), 7.59 (t, *J* = 7.5 Hz, 1 H), 7.44 (t, *J* = 7.6 Hz, 1 H), 6.97 (s, 1 H), 6.71–6.78 (m, 1 H), 6.28 (d, *J* = 17.1 Hz, 1 H), 5.40 (d, *J* = 10.7 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.81, 145.6–145.4 (m), 137.8, 135.5, 130.9, 127.4, 126.3, 123.1, 117.7, 117.1, 110.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{11}N_2^+$: 171.0917; found: 171.0929.

7-Fluoro-3-vinylisoquinolin-1-amine (4b)

Yield: 24.8 mg (66%); brown solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74–7.62 (m, 1 H), 7.34–7.41 (m, 2 H), 6.97 (s, 1 H), 6.70–6.77 (m, 1 H), 6.27 (d, *J* = 17.2 Hz, 1 H), 5.39 (d, *J* = 10.5 Hz, 1 H), 5.20 (s, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.4 (d, *J* = 247.8 Hz), 155.2 (s), 135.9 (s), 134.8 (s), 129.8 (d, *J* = 8.3 Hz), 120.5 (d, *J* = 24.4 Hz), 118.1 (d, *J* = 7.7 Hz), 118.2–114.9 (m), 110.9 (s), 107.4 (d, *J* = 21.7 Hz), 105.0 (s).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{10}FN_2^+$: 189.0823; found: 189.08.

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Supporting Information

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(11) CCDC 1941980 contains the supplementary 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/getstructures.