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Tandem Reactions

Copper-Catalyzed Tandem Amide *N*-Arylation and Regioselective Cyclization of 2-Alkynylbenzamides

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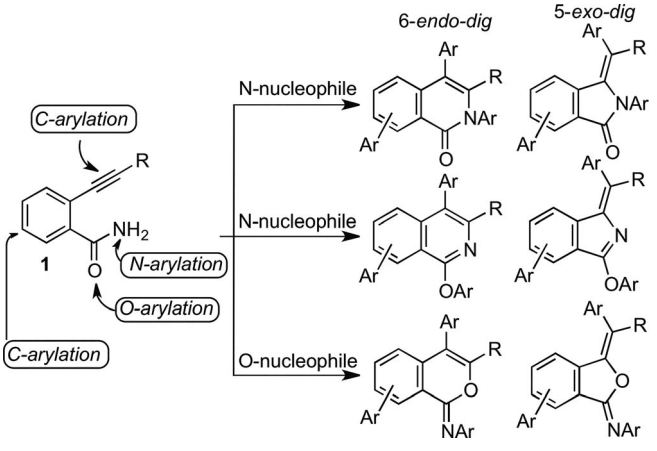
Abstract: A new approach to form iminoisocoumarins from readily available and stable 2-alkynylbenzamides was developed by using a tandem copper-catalyzed *N*-arylation and regioselective 6-*endo*-*dig* cyclization in the presence of diaryliodonium salts, a copper catalyst, and 2,6-di-*tert*-butylpyridine. The arylation occurred at the nitrogen atom rather than the oxygen atom of the amide group, the alkynyl carbon, or the benzene ring of the benzamide. Cyclization occurred through a preferential nucleophilic attack by the oxygen rather than the nitrogen atom of the amide group to produce iminoisocoumarin derivatives in good to moderate yields.

Introduction

The carbon-carbon triple bond is one of the most important functional groups in organic chemistry. In the past two decades, electrophile-promoted nucleophilic cyclizations of alkynes with the nucleophile in close proximity to the triple bond has proven valuable in synthetic applications for the construction of five- and six-membered ring compounds.[1] In this regard, a metal-catalyzed cyclization is an attractive method to construct oxygen- and nitrogen-heterocycles such as isoquinolines,[2] indoles,[3] furans,[4] pyrroles,[5] and coumarins[6] under mild conditions. On the other hand, a variety of cross-coupling reactions that use diaryliodonium salts have recently emerged.[7] Because of the electron-deficient character and hyperleaving ability of aryliodonio groups,[8] they can act as versatile arylating reagents for many nucleophiles. For example, the α-arylations of carbonyl compounds[9] and the arylations of arenes,[10] alkynes,[11] alkenes,[12] oxygen nucleophiles,[13] and nitrogen nucleophiles[14] have been reported.

As part of our continued interest in the synthesis of biologically interesting heterocyclic compounds, we focused on easily accessible and stable but less reactive 2-alkynylbenzamides **1**.[15] Compound **1** may be thought of having four reactive sites for a copper-catalyzed reaction with diaryliodonium salts, that is, arylation at a carbon atom of the aromatic ring, carboarylation of the carbon-carbon triple bond, and arylation at the nitrogen or oxygen atom of the amide group (Scheme 1). In addition, a transition-metal-catalyzed ring closure could occur through either a 6-*endo*-*dig* or 5-*exo*-*dig* cyclization process that proceeds through the nucleophilic attack of either the nitrogen or oxygen atom of the amide on the carbon-carbon triple bond. Herein, we describe a new copper-catalyzed tandem *N*-arylation and intramolecular regioselective ring-closing reaction of 2-alkynylbenzamide derivatives to give iminoisocoumarins. However, the *N*-arylation of benzamide with iodonium salts is rare, possibly because of the low electron density on the amide nitrogen atom.[14e] Furthermore, little work has been done with regard to the synthesis of iminoisocoumarins through the cyclization of 2-alkynylbenzamides with copper catalysts.[16]



Scheme 1. Product divergency.

Results and Discussion

First, we examined the viability of copper catalysts in this reaction. The reaction of alkyne **1a** with diphenyliodonium salt **2** in the presence of various copper catalysts was performed in $CDCl_3$ under nitrogen at 40 °C to give either no product or iminoisocoumarin **3a** in moderate yields (Table 1, Entries 1–5). Under acidic conditions, **3a** was accompanied by the corre-

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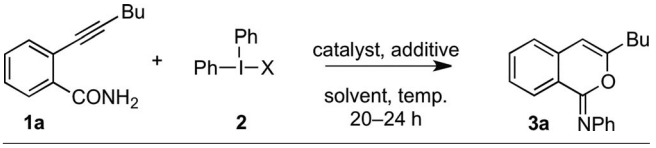
sponding hydrolysis product.[17] We were delighted to find that the addition of the bulky 2,6-di-*tert*-butylpyridine (DTBP) base in the presence of CuBr allowed the reaction to proceed smoothly and gave **3a** in good yield (Table 1, Entry 6). Screening the iodonium salts **2** [X = trifluoromethanesulfonate (OTf), BF_4, and PF_6] showed that diphenyliodonium triflate was the superior coupling partner (Table 1, Entries 6, 8, and 9). A higher yield of the desired **3a** was also obtained in DCE instead of $CDCl_3$ (Table 1, Entries 10 and 11). In the absence of a copper catalyst, the synthesis of *N*-arylated iminoisocoumarin **3a** was unsuccessful, and the starting benzamide **1a** was recovered (Table 1, Entry 12). The yield of the product was insufficient when 2 equiv. of DTBP, a higher reaction temperature, or other solvents were used (Table 1, Entries 13–18). The optimization results reveal that a copper-catalyzed *N*-arylation of the amide functional group occurs along with a 6-*endo-dig* cyclization reaction through a nucleophilic attack of the oxygen atom on the carbon-carbon triple bond.

Table 1. Results for the optimization of the reaction conditions.[a]

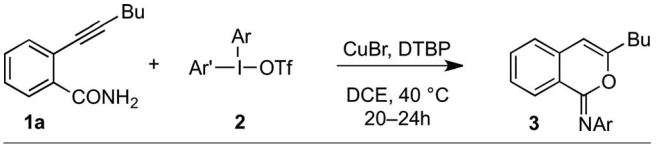


Entry	Catalyst [10 mol-%]	X	Solvent	DTBP [equiv.]	Temp. [°C]	Yield [%][b]
1	CuCl	OTf	$CDCl_3$	none	40	(48)[c]
2	CuBr	OTf	$CDCl_3$	none	40	(48)[c]
3	CuI	OTf	$CDCl_3$	none	40	(trace)[c]
4	$Cu(OAc)_2$	OTf	$CDCl_3$	none	40	0
5	$Cu(OTf)_2$	OTf	$CDCl_3$	none	40	(47)[c]
6	CuBr	OTf	$CDCl_3$	1.1	40	(85)[c]
7	$Cu(OTf)_2$	OTf	$CDCl_3$	1.1	40	(80)[c]
8	CuBr	BF_4	$CDCl_3$	1.1	40	(80)[c]
9	CuBr	PF_6	$CDCl_3$	1.1	40	(47)[c]
10	CuBr	OTf	$CDCl_3$	1.1	40	80
11	CuBr	OTf	DCE	1.1	40	80
12	none	OTf	DCE	1.1	40	0[d]
13	CuBr	OTf	DCE	2.2	40	75
14	CuBr	OTf	DCE	1.1	60	56
15	CuBr	OTf	DCE	1.1	80	36
16	CuBr	OTf	toluene	1.1	40	70
17	CuBr	OTf	THF[e]	1.1	40	15
18	CuBr	OTf	AcOEt	1.1	40	40

[a] Reactions were performed with **1a** (0.2 mmol) and **2** (0.22 mmol) at a concentration of 0.1 M. [b] Yield of isolated product is reported. [c] Determined by ^1H NMR spectroscopic analysis using 1,3,5-trimethoxybenzene as the internal standard. [d] Starting material **1a** was recovered in quantitative yield. [e] THF = tetrahydrofuran.

Having established the reaction conditions, we examined the transfer of the aryl group from a range of diaryliodonium salts (Table 2). We were pleased to find that some symmetrical diaryliodonium salts that have aryl groups with electron-donating or -withdrawing substituents were compatible in the aryl transfer reaction and gave the product in good yields (Table 2, Entries 1–4). Although the reason is unclear, the electron-rich bis(4-methoxyphenyl)iodonium bromide posed a problem (Table 2, Entry 5).[10a,11c,14a] Unsymmetrical aryl(mesityl)iodonium salts were also employed in this reaction, in which the two aryl groups competed to mainly give *N*-arylated iminoisocoumarins **3f** and **3g** along with a small amount of *N*-mesitylene iminoisocoumarin **3e** (Table 2, Entries 6 and 7). An alkynylphenyliodonium salt could not proceed in the desired reaction but gave a complex mixture (Table 2, Entry 8).

Table 2. Scope of aryl transfer reaction.



Entry	Ar	Ar′	X	Product	Yield [%]
1	4-MeC_6H_4	4-MeC_6H_4	OTf	**3b**	92
2	4-FC_6H_4	4-FC_6H_4	OTf	**3c**	77
3	4-$tBuC_6H_4$	4-$tBuC_6H_4$	PF_6	**3d**	78
4	2,4,6-$Me_3C_6H_2$	2,4,6-$Me_3C_6H_2$	OTf	**3e**	79
5	4-$MeOC_6H_4$	4-$MeOC_6H_4$	Br	–	0
6[a]	3-MeC_6H_4	2,4,6-$Me_3C_6H_2$	OTf	(**3e**) **3f**	(8) 80
7[a]	4-$CF_3C_6H_4$	2,4,6-$Me_3C_6H_2$	OTf	(**3e**) **3g**	(6) 79
8	-C≡C-Bu	Ph	BF_4	–	0

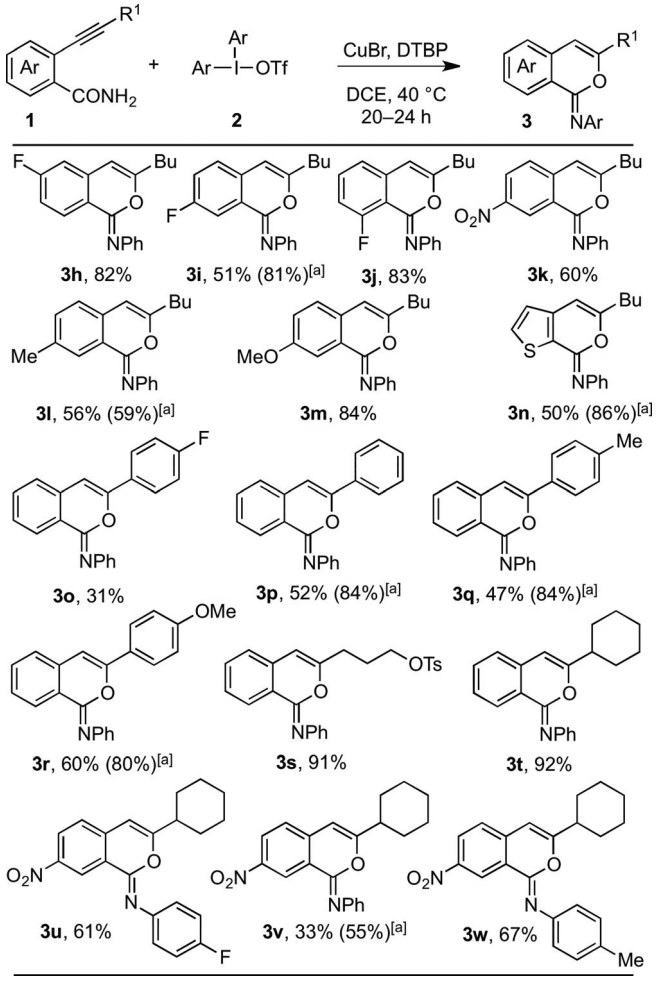
[a] The reaction was performed at 30 °C.

We next turned our attention to the scope of this arylation and cyclization reaction by using various aromatic amides with the symmetrical diaryliodonium triflates (Table 3). Benzamides **1** that have an alkyl group for R^1, which is bonded to the alkynyl sp-hybridized carbon, underwent facile arylation of the nitrogen atom followed by a ring-closing reaction to give the corresponding products (i.e., **3h**, **3j**, **3m**, **3s**, and **3t**) in excellent yields. On the other hand, benzamides that contain an aryl group for R^1 also produced the respective iminoisocoumarin but in a relatively low yield. The supplementation of the reaction mixture with additional diaryliodonium triflate, CuBr, and DTBP after 20–24 h increased the yields of **3i**, **3n**, **3p**, **3q**, and **3r**. An electron-withdrawing group at the 5-position of the aromatic ring of amide **1** had an unfavorable effect, which can be observed in the yields of **3i**, **3k**, **3u**, **3v**, and **3w**. The structures of iminoisocoumarins **3k**, **3q**, and **3u** were confirmed by X-ray crystallographic analysis.[18]

For a comparison, copper-catalyzed arylation reactions with organobismuth reagents were also developed.[19] As shown in Table 3, amide **1q** gave iminoisocoumarin **3q** in 47 % yield. We then tried the same reaction by using bismuthonium reagents in the presence of 10 mol-% CuBr in DCE (Table 4). When tetraphenylbismuthonium tetrafluoroborate was used, **3q** was obtained in moderate yields with or without the addition of DTBP at 80 °C (Table 4, Entries 1 and 2). Triphenylbismuthonium difluoride also gave **3q** but in a lower yield (Table 4, Entry 3).

Taking these observations into consideration, we tentatively proposed a reaction mechanism that includes the formation of the two discrete intermediates **4** and **5** (Scheme 2). In some instances, compound **5** was able to be isolated from the optimization experiments. Intermediate **4** can break down to give *N*-arylbenzamide **5** by reductive elimination of CuBr (Scheme 2, path A). Another route involves the copper-catalyzed heterocy-

Table 3. Scope of aromatic amide in tandem iminoisocoumarin synthesis.



[a] Additional **2** (0.22 mmol), CuBr (0.022 mmol), and DTBP (0.22 mmol) were added after 20–24 h. The reaction mixture was then stirred for 20–24 h at 40 °C.

clization of intermediate **4** through an intramolecular nucleophilic attack of the amide oxygen atom on the alkynyl carbon (Scheme 2, path B).

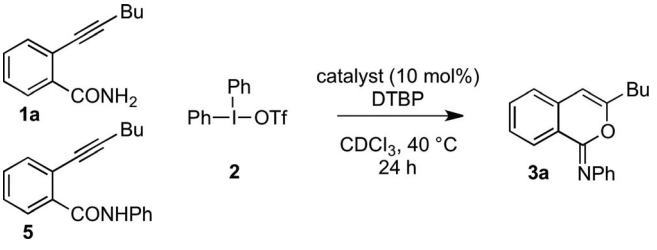
Table 4. Synthesis of iminoisocoumarin **3q** by using bismuthonium reagents.[a]

Entry	Bismuthonium reagent	DTBP [equiv.]	Yield [%]
1	Ph_4BiBF_4	1.1	65
2	Ph_4BiBF_4	0	54
3	Ph_3BiF_2	1.1	41

[a] Reactions were performed with **1q** (0.2 mmol), the bismuthonium reagent (0.22 mmol), and CuBr (10 mol-%) at a 0.1 M concentration in DCE at 80 °C for 24 h.

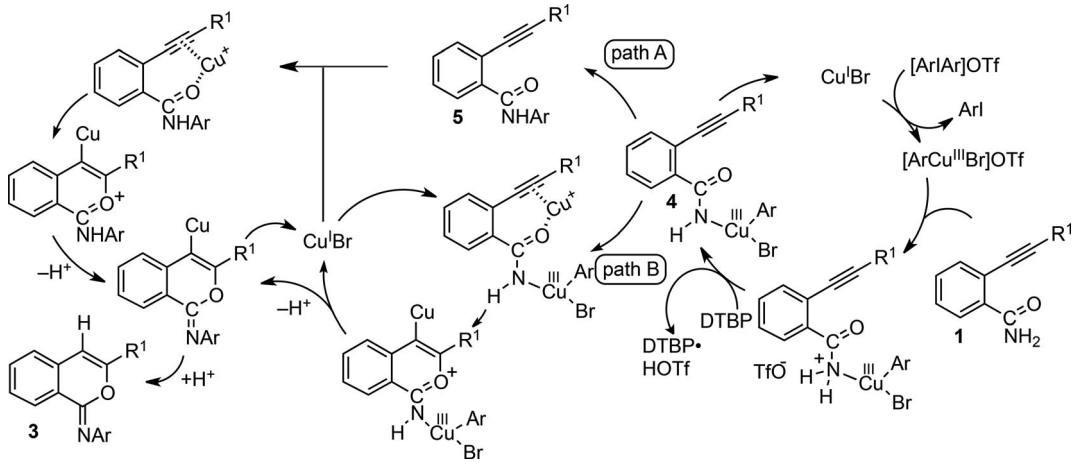
To obtain further insight into the mechanisms, some comparative studies were performed with amide **1a** and **5** (Table 5).[20] When CuBr or $CuBr_2$ was used as the catalyst, *N*-phenylamide **5** was recovered (Table 5, Entries 1–3).[21] Product **3a** was obtained in low yield under acidic conditions (Table 5,

Table 5. Comparative experiments.



Entry	**1a** [equiv.]	**5** [equiv.]	Catalyst [10 mol-%]	TfOH [equiv.]	**2** [equiv.]	DTBP [equiv.]	Yield [%][a]
1	0	1	CuBr	0	0	0	0
2[b]	0	1	CuBr	0	0	0	0
3	0	1	$CuBr_2$	0	0	0	0
4	0	1	–	1.1	0	0	21
5	0	1	CuBr	1.1	0	0	68
6	0	1	CuBr	0	1.1	0	66
7	0	1	CuBr	0	1.1	1.1	29
8	0.5	0.5	CuBr	0	1.1	1.1	81[c]

[a] Determined by ^1H NMR analysis by using 1,3,5-trimethoxybenzene as an internal standard. [b] Reaction was conducted under oxygen. [c] Determined by ^1H NMR analysis using dichloromethane as an internal standard.



Scheme 2. Proposed reaction mechanism.

Entry 4). The reaction of CuBr with TfOH or diphenyliodonium salt **2** gave **3a** in moderate yields (Table 5, Entries 5 and 6). The further addition of DTBP decreased the product yield (Table 5, Entry 7). The reaction that used 0.5 equiv. of both amide **1a** and **5** with CuBr, diphenyliodonium triflate **2**, and DTBP proceeded well to give **3a** in 81 % yield (Table 5, Entry 8). These results imply that not only *N*-phenylamide **5** but also in situ generated **4** could be reactive intermediates in paths A and B to produce iminoisocoumarin **3**.

Conclusions

In summary, we have developed a new approach to form iminoisocoumarins from readily available and stable 2-alkynylbenzamides by using a tandem Cu-catalyzed *N*-arylation and regioselective 6-*endo*-*dig* cyclization process in the presence of diaryliodonium salts, a copper catalyst, and 2,6-di-*tert*-butylpyridine. Arylation occurred at the nitrogen atom rather than the oxygen atom of the amide group, the alkynyl carbon, or the benzene ring, and cyclization occurred preferentially by nucleophilic attack of the oxygen rather than the nitrogen atom of the amide group to produce the iminoisocoumarins.

Experimental Section

General Methods: The ^{1}H and ^{13}C NMR spectroscopic data were recorded with a 600 MHz spectrometer. Chemical Shifts [δ (ppm)] are reported by using tetramethylsilane as the internal standard, and the NMR data are described as follows: chemical shift, multiplicity [s (singlet), d (doublet), t (triplet), q (quartet), br. (broad), and m (multiplet)], coupling constant [*J* (Hz)], relative integration value. Infrared spectra were obtained with an FT spectrometer. Mass spectroscopy experiments were performed on a double-focusing mass spectrometer by using EI as the ionization mode. Analytical thin layer chromatography was performed on Merck silica gel 60 F254 TLC plates.

General Procedure for the Synthesis of the 2-Alkynylbenzamide: To a solution of 2-bromo- or 2-iodobenzamide (1.0 mmol, 1.00 equiv.) in Et_3N (0.2 M) were added triphenylphosphine (0.02 equiv.), CuI (0.02 equiv.), $Pd(OAc)_2$ (0.02 equiv.), and the terminal alkyne (1.5 equiv.), and the resulting mixture was stirred at 70 °C under nitrogen. The progress of the reaction was monitored by TLC analysis to establish its completion. NH_4Cl solution was then added, and the mixture was extracted with chloroform (3×). The combined organic phases were dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. Chromatography of the residue on a silica gel column (hexane/ethyl acetate) afforded the corresponding 2-alkynylbenzamide. 2-Alkynylbenzamides **1a**,[15a] **1i**,[15d] **1k**,[15d] **1m**,[15d] **1n**,[22] **1p**,[23] **1q**,[15d] **1r**,[24] and **1s**[15d] are known compounds.

General Procedure for the Synthesis of the Iminoisocoumarin: To a solution of the 2-alkynylbenzamide (0.2 mmol, 1.00 equiv.) in DCE were added the diphenyliodonium trifluoromethanesulfonate (1.1 equiv.), CuBr (0.1 equiv.), and DTBP (1.1 equiv.), and the resulting mixture was stirred at 40 °C under nitrogen. The progress of the reaction was monitored by TLC analysis to establish its completion. Chromatography on a neutral silica gel column (hexane/ethyl acetate) afforded the corresponding iminoisocoumarin **3**. Iminoisocoumarins **3a**,[20] **3p**,[20] **3q**,[25] and **3r**[29] are known compounds.

***N*-Phenylbenzamide Derivative 5:** Known compound, see ref.[26]

4-Fluoro-2-(hex-1-ynyl)benzamide (1h): Pale yellow solid (179 mg, 82 % yield); m.p. 83–84 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.15 (dd, *J* = 8.2, 6.2 Hz, 1 H), 7.65 (br. s, 1 H), 7.17 (dd, *J* = 8.9, 2.1 Hz, 1 H), 7.09 (ddd, *J* = 8.9, 8.2, 2.1 Hz, 1 H), 6.35 (br. s, 1 H), 2.50 (t, *J* = 7.2 Hz, 2 H), 1.66–1.60 (m, 2 H), 1.52–1.46 (m, 2 H), 0.96 (dd, *J* = 7.6, 6.2 Hz, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 167.2, 163.7 (d, $J_{C,F}$ = 252.9 Hz), 133.0 (d, $J_{C,F}$ = 8.7 Hz), 130.3 (d, $J_{C,F}$ = 2.9 Hz), 123.3 (d, $J_{C,F}$ = 10.1 Hz), 120.2 (d, $J_{C,F}$ = 23.1 Hz), 115.7 (d, $J_{C,F}$ = 21.7 Hz), 99.2, 78.8 (d, $J_{C,F}$ = 2.9 Hz), 30.3, 22.1, 19.3, 13.6 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3503, 3035, 2962, 1669, 1605, 1585, 1366, 1267, 1174, 877, 697, 687, 684 cm^{-1}. MS (EI): *m*/*z* = 219 [M]$^+$. HRMS (EI): calcd. for $C_{13}H_{14}NOF$ 219.1059; found 219.1062.

2-Fluoro-6-(hex-1-ynyl)benzamide (1j): Pale yellow solid (195 mg, 89 % yield); m.p. 125–127 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.32–7.24 (m, 2 H), 7.04 (dd, *J* = 8.9, 8.2 Hz, 1 H), 6.21 (br. s, 1 H), 6.00 (br. s, 1 H), 2.43 (t, *J* = 7.2 Hz, 2 H), 1.62–1.56 (m, 2 H), 1.50–1.43 (m, 2 H), 0.94 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 166.0, 159.2 (d, $J_{C,F}$ = 250.0 Hz), 130.8 (d, $J_{C,F}$ = 10.1 Hz), 128.7 (d, $J_{C,F}$ = 2.9 Hz), 126.0 (d, $J_{C,F}$ = 17.3 Hz), 123.8 (d, $J_{C,F}$ = 5.8 Hz), 115.4 (d, $J_{C,F}$ = 23.1 Hz), 96.5, 77.2, 30.5, 22.0, 19.3, 13.6 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3521, 3404, 3008, 2962, 2936, 1684, 1609, 1589, 1564, 1467, 1458, 1368, 1283, 690 cm^{-1}. MS (EI): *m*/*z* = 219 [M]$^+$. HRMS (EI): calcd. for $C_{13}H_{14}NOF$ 219.1059; found 219.1053.

2-(Hex-1-ynyl)-5-methylbenzamide (1l): Pale yellow solid (32 mg, 15 % yield); m.p. 113–114 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.94 (s, 1 H), 7.75 (br. s, 1 H), 7.38 (d, *J* = 7.9 Hz, 1 H), 7.22 (d, *J* = 7.9 Hz, 1 H), 6.60 (br. s, 1 H), 2.48 (t, *J* = 7.2 Hz, 2 H), 2.38 (s, 3 H), 1.64–1.58 (m, 2 H), 1.51–1.44 (m, 2 H), 0.95 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 168.6, 138.4, 133.7, 133.7, 131.8, 130.8, 118.0, 97.0, 79.7, 30.5, 22.1, 21.3, 19.3, 13.6 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3499, 3378, 3037, 3007, 2961, 2934, 2875, 2864, 1669, 1608, 1587, 1488, 1467, 1419, 1380, 1354, 1237, 828 cm^{-1}. MS (EI): *m*/*z* = 215 [M]$^+$. HRMS (EI): calcd. for $C_{14}H_{17}NO$ 215.1310; found 215.1311.

2-[(4-Fluorophenyl)ethynyl]benzamide (1o): Pale yellow solid (116 mg, 97 % yield); m.p. 159–160 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.10 (dd, *J* = 7.6, 1.4 Hz, 1 H), 7.62 (d, *J* = 7.6 Hz, 1 H), 7.54–7.45 (m, 4 H), 7.32 (br. s, 1 H), 7.09 (dd, *J* = 8.9, 8.2 Hz, 2 H), 6.06 (br. s, 1 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 168.3, 163.0 (d, $J_{C,F}$ = 251.5 Hz), 134.7, 133.5 (t, $J_{C,F}$ = 8.7 Hz), 131.1, 130.2, 128.9, 120.0, 118.2 (d, $J_{C,F}$ = 4.3 Hz), 116.0 (d, $J_{C,F}$ = 21.7 Hz), 94.6, 87.4 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3509, 3393, 1670, 1602, 1584, 1508, 1373, 1238, 838, 798, 756, 747, 692 cm^{-1}. MS (EI): *m*/*z* = 239 [M]$^+$. HRMS (EI): calcd. for $C_{15}H_{10}NOF$ 239.0746; found 239.0746.

2-(Cyclohexylethynyl)benzamide (1t): Pale yellow solid (208 mg, 92 % yield); m.p. 119–120 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.13 (dd, *J* = 7.6, 2.1 Hz, 1 H), 7.76 (br. s, 1 H), 7.49 (dd, *J* = 7.3, 1.8 Hz, 1 H), 7.43–7.37 (m, 2 H), 6.36 (br. s, 1 H), 2.66–2.67 (m, 1 H), 1.93–1.90 (m, 2 H), 1.78–1.73 (m, 2 H), 1.58–1.54 (m, 3 H), 1.39–1.36 (m, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 168.3, 133.9, 133.7, 130.9, 130.3, 128.1, 121.0, 101.8, 79.7, 32.3, 29.9, 25.7, 24.9 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3499, 3377, 3007, 2936, 2857, 1669, 1585, 1448, 1370, 699, 686, 670, 662 cm^{-1}. MS (EI): *m*/*z* = 227 [M]$^+$. HRMS (EI): calcd. for $C_{15}H_{17}NO$ 227.1310; found 227.1313.

2-(Cyclohexylethynyl)-5-nitrobenzamide (1u): Pale yellow solid (159 mg, 58 % yield); m.p. 111–112 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.97 (d, *J* = 2.7 Hz, 1 H), 8.24 (dd, *J* = 8.6, 2.7 Hz, 1 H), 7.67 (br.

s, 1 H), 7.65 (d, *J* = 8.6 Hz, 1 H), 6.75 (s, 1 H), 2.76–2.72 (m, 1 H), 1.97–1.94 (m, 2 H), 1.80–1.72 (m, 2 H), 1.61–1.55 (m, 3 H), 1.44–1.35 (m, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 166.0, 146.9, 135.5, 134.9, 127.4, 125.7, 125.2, 107.6, 78.6, 32.0, 30.1, 25.6, 24.8 ppm. IR ($CHCl_3$): ṽ = 3499, 3008, 2937, 2858, 2222, 1684, 1680, 1605, 1587, 1525, 1451, 1424, 1349, 1345, 901, 845, 810, 696 cm^{-1}. MS (EI): *m/z* = 272 $[M]^+$. HRMS (EI): calcd. for $C_{15}H_{16}N_2O_3$ 272.1161; found 272.1169.

(*Z*)-*N*-(3-Butyl-1*H*-isochromen-1-ylidene)-4-methylaniline (3b): Pale yellow oil (53 mg, 92 % yield). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.32 (d, *J* = 8.2 Hz, 1 H), 7.47 (dd, *J* = 7.6, 1.4 Hz, 1 H), 7.34 (dd, *J* = 8.2, 7.6 Hz, 1 H), 7.17–7.12 (m, 5 H), 5.96 (s, 1 H), 2.35–2.32 (m, 5 H), 1.58–1.52 (m, 2 H), 1.37–1.32 (m, 2 H), 0.91 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 156.3, 150.1, 143.8, 134.0, 132.9, 132.1, 129.1, 127.4, 127.3, 124.5, 123.5, 122.9, 101.7, 32.7, 28.8, 22.0, 21.0, 13.8 ppm. IR ($CHCl_3$): ṽ = 3035, 3010, 1672, 810, 807, 757, 746, 742, 691, 687, 673 cm^{-1}. MS (EI): *m/z* = 291 $[M]^+$. HRMS (EI): calcd. for $C_{20}H_{21}NO$ 291.1623; found 291.1628.

(*Z*)-*N*-(3-Butyl-1*H*-isochromen-1-ylidene)-4-fluoroaniline (3c): Pale yellow oil (45 mg, 77 % yield). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.30 (d, *J* = 7.6 Hz, 1 H), 7.49 (dd, *J* = 7.6, 1.4 Hz, 1 H), 7.35 (ddd, *J* = 8.2, 7.6, 1.4 Hz, 1 H), 7.19–7.15 (m, 3 H), 7.05–7.00 (m, 2 H), 5.99 (s, 1 H), 2.34 (t, *J* = 7.2 Hz, 2 H), 1.56–1.50 (m, 2 H), 1.37–1.30 (m, 2 H), 0.90 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 159.3 (d, $J_{C,F}$ = 241.3 Hz), 156.2, 150.6, 142.6 (d, $J_{C,F}$ = 2.9 Hz), 134.0, 132.3, 127.5, 127.3, 124.6, 124.2 (d, $J_{C,F}$ = 7.2 Hz), 123.2, 115.2 (d, $J_{C,F}$ = 21.7 Hz), 101.9, 32.7, 28.8, 22.0, 13.8 ppm. IR ($CHCl_3$): ṽ = 3035, 3010, 1673, 1640, 1503, 810, 761, 695, 685 cm^{-1}. MS (EI): *m/z* = 295 $[M]^+$. HRMS (EI): calcd. for $C_{19}H_{18}NOF$ 295.1372; found 295.1372.

(*Z*)-4-(*tert*-Butyl)-*N*-(3-butyl-1*H*-isochromen-1-ylidene)aniline (3d): Pale yellow oil (52 mg, 78 % yield). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.32 (d, *J* = 7.6 Hz, 1 H), 7.46 (dd, *J* = 7.6, 1.4 Hz, 1 H), 7.37–7.32 (m, 3 H), 7.21–7.14 (m, 3 H), 5.96 (s, 1 H), 2.36 (t, *J* = 7.6 Hz, 2 H), 1.59–1.53 (m, 2 H), 1.38–1.30 (m, 11 H), 0.91 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 156.4, 150.0, 146.3, 143.7, 134.0, 132.0, 127.4, 125.4, 124.5, 123.6, 122.7, 101.7, 34.3, 32.7, 31.5, 28.8, 22.0, 13.8 ppm. IR ($CHCl_3$): ṽ = 3035, 3010, 1671, 1235, 1198, 1158, 810, 804, 750, 729, 718, 687, 672 cm^{-1}. MS (EI): *m/z* = 333 $[M]^+$. HRMS (EI): calcd. for $C_{23}H_{27}NO$ 333.2093; found 333.2095.

(*Z*)-*N*-(3-Butyl-1*H*-isochromen-1-ylidene)-2,4,6-trimethylaniline (3e): Pale yellow oil (50 mg, 79 % yield). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.39 (d, *J* = 7.6 Hz, 1 H), 7.50 (dd, *J* = 7.6, 1.4 Hz, 1 H), 7.36 (dd, *J* = 7.6, 7.6 Hz, 1 H), 7.18 (d, *J* = 7.6 Hz, 1 H), 6.86 (s, 2 H), 5.92 (s, 1 H), 2.28 (s, 3 H), 2.23 (t, *J* = 7.2 Hz, 2 H), 2.09 (s, 6 H), 1.42–1.37 (m, 2 H), 1.27–1.23 (m, 2 H), 0.84 (t, *J* = 7.6 Hz, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 156.6, 149.1, 142.5, 134.0, 132.1, 131.4, 128.1, 127.7, 127.5, 127.3, 124.5, 122.9, 101.3, 32.7, 28.5, 21.8, 20.8, 18.2, 13.7 ppm. IR ($CHCl_3$): ṽ = 3008, 2962, 1725, 1710, 1676, 1653, 1487, 1468, 1380, 1292, 1238, 724, 718, 678 cm^{-1}. MS (EI): *m/z* = 319 $[M]^+$. HRMS (EI): calcd. for $C_{22}H_{25}NO$ 319.1936; found 319.1940.

(*Z*)-*N*-(3-Butyl-1*H*-isochromen-1-ylidene)-3-methylaniline (3f): Pale yellow oil (47 mg, 80 % yield). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.31 (d, *J* = 8.2 Hz, 1 H), 7.48 (d, *J* = 7.6 Hz, 1 H), 7.35 (dd, *J* = 7.6, 7.6 Hz, 1 H), 7.25–7.16 (m, 2 H), 7.00 (dd, *J* = 8.2, 7.6 Hz, 2 H), 6.90 (d, *J* = 7.6 Hz, 1 H), 5.97 (s, 1 H), 2.36–2.32 (m, 5 H), 1.58–1.52 (m, 2 H), 1.36–1.31 (m, 2 H), 0.90 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 156.3, 150.3, 146.5, 138.2, 134.1, 132.2, 128.3, 127.4, 127.3, 124.5, 124.2, 123.5, 123.3, 119.7, 101.8, 32.8, 28.9, 22.0, 21.5, 13.8 ppm. IR ($CHCl_3$): ṽ = 3035, 3010, 1673, 1639, 1198, 1158, 809, 695, 688 cm^{-1}. MS (EI): *m/z* = 291 $[M]^+$. HRMS (EI): calcd. for $C_{20}H_{21}NO$ 291.1623; found 291.1625.

(*Z*)-*N*-(3-Butyl-1*H*-isochromen-1-ylidene)-4-trifluoromethylaniline (3g): Pale yellow oil (55 mg, 79 % yield). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.32 (d, *J* = 8.2 Hz, 1 H), 7.60–7.52 (m, 3 H), 7.39 (dd, *J* = 7.6, 7.6 Hz, 1 H), 7.27–7.20 (m, 3 H), 6.04 (s, 1 H), 2.34 (t, *J* = 7.6 Hz, 2 H), 1.53–1.49 (m, 2 H), 1.34–1.30 (m, 2 H), 0.89 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 156.3, 151.5, 150.4, 134.2, 132.7, 127.6, 127.5, 125.8, 125.8, 125.8, 125.8, 123.7 (d, $J_{C,F}$ = 300.6 Hz), 122.7, 102.1, 32.6, 28.8, 21.9, 13.8 ppm. IR ($CHCl_3$): ṽ = 3035, 3010, 1673, 1604, 1324, 1235, 1159, 1123, 1066, 810, 667 cm^{-1}. MS (EI): *m/z* = 345 $[M]^+$. HRMS (EI): calcd. for $C_{20}H_{18}NOF_3$ 345.1340; found 345.1346.

(*Z*)-*N*-(3-Butyl-6-fluoro-1*H*-isochromen-1-ylidene)aniline (3h): Pale yellow oil (49 mg, 82 % yield). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.32 (dd, *J* = 8.6, 6.3 Hz, 1 H), 7.36–7.32 (m, 2 H), 7.18–7.15 (m, 2 H), 7.11–7.02 (m, 2 H), 6.84 (dd, *J* = 8.9, 2.1 Hz, 1 H), 5.93 (s, 1 H), 2.32 (t, *J* = 7.6 Hz, 2 H), 1.55–1.49 (m, 2 H), 1.35–1.30 (m, 2 H), 0.89 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 166.1, 157.7, 149.5, 146.4, 136.5 (d, $J_{C,F}$ = 10.1 Hz), 130.3 (d, $J_{C,F}$ = 10.1 Hz), 128.6, 123.5, 122.7, 119.6 (d, $J_{C,F}$ = 2.9 Hz), 115.2 (d, $J_{C,F}$ = 21.7 Hz), 110.3 (d, $J_{C,F}$ = 21.7 Hz), 101.3 (d, $J_{C,F}$ = 2.9 Hz), 32.7, 28.7, 22.0, 13.8 ppm. IR ($CHCl_3$): ṽ = 3009, 2960, 1674, 1640, 1615, 1593, 1493, 1247, 1167 cm^{-1}. MS (EI): *m/z* = 295 $[M]^+$. HRMS (EI): calcd. for $C_{19}H_{18}NOF$ 295.1372; found 295.1373.

(*Z*)-*N*-(3-Butyl-7-fluoro-1*H*-isochromen-1-ylidene)aniline (3i): Pale yellow oil (48 mg, 81 % yield). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.01 (dd, *J* = 9.6, 2.7 Hz, 1 H), 7.35 (dd, *J* = 7.6, 7.6 Hz, 2 H), 7.26–7.15 (m, 4 H), 7.10 (dd, *J* = 7.6, 6.9 Hz, 1 H), 5.96 (s, 1 H), 2.33 (t, *J* = 7.6 Hz, 2 H), 1.56–1.50 (m, 2 H), 1.35–1.30 (m, 2 H), 0.90 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 161.8 (d, $J_{C,F}$ = 245.6 Hz), 155.7 (d, $J_{C,F}$ = 2.9 Hz), 149.5 (d, $J_{C,F}$ = 4.3 Hz), 146.2, 130.5 (d, $J_{C,F}$ = 2.9 Hz), 128.6 (d, $J_{C,F}$ = 10.1 Hz), 126.5 (d, $J_{C,F}$ = 7.2 Hz), 125.2 (d, $J_{C,F}$ = 8.7 Hz), 123.7, 122.8, 120.1 (d, $J_{C,F}$ = 23.1 Hz), 113.4 (d, $J_{C,F}$ = 24.6 Hz), 100.9, 32.6, 28.8, 22.0, 13.8 ppm. IR ($CHCl_3$): ṽ = 3035, 2961, 2932, 1673, 1641, 1592, 1497, 1328, 1271, 1195, 1153, 1049, 841, 808 cm^{-1}. MS (EI): *m/z* = 295 $[M]^+$. HRMS (EI): calcd. for $C_{19}H_{18}NOF$ 295.1372; found 295.1382.

(*Z*)-*N*-(3-Butyl-8-fluoro-1*H*-isochromen-1-ylidene)aniline (3j): Pale yellow oil (49 mg, 83 % yield). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.43 (ddd, *J* = 8.2, 7.6, 4.8 Hz, 1 H), 7.35–7.32 (m, 2 H), 7.13–7.03 (m, 4 H), 6.95 (d, *J* = 7.6 Hz, 1 H), 5.94 (s, 1 H), 2.28 (t, *J* = 7.6 Hz, 2 H), 1.50–1.44 (m, 2 H), 1.32–1.27 (m, 2 H), 0.87 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 161.5 (d, $J_{C,F}$ = 243.0 Hz), 157.2, 146.7, 146.5 (d, $J_{C,F}$ = 11.6 Hz), 137.2 (d, $J_{C,F}$ = 10.1 Hz), 128.5, 123.4, 122.2, 120.3, 120.3, 115.2 (d, $J_{C,F}$ = 23.1 Hz), 101.3 (d, $J_{C,F}$ = 2.9 Hz), 32.5, 28.5, 21.9 (d, $J_{C,F}$ = 1.5 Hz), 13.8 ppm. IR ($CHCl_3$): ṽ = 3009, 1675, 1646, 1592, 1473, 1197, 1157, 810, 662 cm^{-1}. MS (EI): *m/z* = 295 $[M]^+$. HRMS (EI): calcd. for $C_{19}H_{18}NOF$ 295.1372; found 295.1370.

(*Z*)-*N*-(3-Butyl-7-nitro-1*H*-isochromen-1-ylidene)aniline (3k): Yellow solid (39 mg, 60 % yield); m.p. 129–130 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.15 (d, *J* = 2.1 Hz, 1 H), 8.29 (dd, *J* = 8.2, 2.1 Hz, 1 H), 7.37 (dd, *J* = 7.8, 7.8 Hz, 2 H), 7.29 (d, *J* = 8.2 Hz, 1 H), 7.22 (d, *J* = 7.8 Hz, 2 H), 7.14 (dd, *J* = 7.8 Hz, 1 H), 6.06 (s, 1 H), 2.39 (t, *J* = 7.6 Hz, 2 H), 1.59–1.54 (m, 2 H), 1.37–1.33 (m, 2 H), 0.91 (t, *J* = 7.6 Hz, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 160.6, 147.8, 146.7, 145.4, 139.6, 128.7, 126.7, 125.5, 124.3, 124.2, 123.5, 122.8, 101.0, 33.0, 28.6, 22.0, 13.8 ppm. IR ($CHCl_3$): ṽ = 3035, 3010, 1670, 1646, 1586, 1522, 1343, 1235, 1160, 852, 810, 766, 747, 692, 687 cm^{-1}. MS (EI): *m/z* = 322 $[M]^+$. HRMS (EI): calcd. for $C_{19}H_{18}N_2O_3$ 322.1317; found 322.1318.

(*Z*)-*N*-(3-Butyl-7-methyl-1*H*-isochromen-1-ylidene)aniline (3l): Pale yellow oil (34 mg, 59 % yield). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.15 (s, 1 H), 7.36–7.30 (m, 3 H), 7.18 (d, *J* = 7.6 Hz, 2 H), 7.08 (dd, *J* = 8.2, 7.6 Hz, 2 H), 5.96 (s, 1 H), 2.42 (s, 3 H), 2.31 (t, *J* = 7.6 Hz, 2 H), 1.54–1.48 (m, 2 H), 1.36–1.28 (m, 2 H), 0.89 (t, *J* = 7.6 Hz, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 155.5, 150.8, 146.9, 137.5, 133.4, 131.6, 128.6, 127.2, 124.6, 123.3, 123.1, 122.7, 101.7, 32.6, 28.8, 22.0, 21.3, 13.8 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2960, 2932, 1672, 1641, 1635, 1616, 1592, 1502, 1485, 1236, 1207, 1177, 1157, 842, 743, 725, 686 cm^{-1}. MS (EI): *m*/*z* = 291 [M]$^+$. HRMS(EI): calcd. for $C_{20}H_{21}NO$ 291.1623; found 291.1628.

(*Z*)-*N*-(3-Butyl-7-methoxy-1*H*-isochromen-1-ylidene)aniline (3m): Pale yellow oil (52 mg, 84 % yield). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.81 (s, 1 H), 7.34 (dd, *J* = 7.6, 7.6 Hz, 2 H), 7.19 (d, *J* = 7.6 Hz, 2 H), 7.12–7.07 (m, 3 H), 5.94 (s, 1 H), 3.90 (s, 3 H), 2.31 (t, *J* = 7.2 Hz, 2 H), 1.53–1.50 (m, 2 H), 1.34–1.30 (m, 2 H), 0.89 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 159.1, 154.3, 150.7, 146.9, 128.6, 127.7, 126.1, 124.3, 123.3, 122.8, 121.5, 108.7, 101.3, 55.7, 32.5, 28.9, 22.0, 13.8 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3009, 2961, 2934, 1673, 1638, 1632, 1613, 1592, 1501, 1466, 1347, 1279, 1237, 1197, 1153, 1057, 1033, 843, 808, 685 cm^{-1}. MS (EI): *m*/*z* = 307 [M]$^+$. HRMS (EI): calcd. for $C_{20}H_{21}NO_2$ 307.1572; found 307.1572.

(*Z*)-*N*-(5-Butyl-7*H*-thieno[2,3-*c*]pyran-7-ylidene)aniline (3n): Pale yellow oil (49 mg, 86 % yield). ^{1}H NMR (600 MHz, C_6D_6): δ = 7.48 (dd, *J* = 8.2, 1.4 Hz, 2 H), 7.27 (dd, *J* = 8.2, 7.6 Hz, 2 H), 6.98 (d, *J* = 7.6 Hz, 1 H), 6.77 (d, *J* = 5.2 Hz, 1 H), 6.42 (d, *J* = 5.2 Hz, 1 H), 5.55 (s, 1 H), 1.93 (t, *J* = 7.6 Hz, 2 H), 1.32–1.26 (m, 2 H), 1.07–1.02 (m, 2 H), 0.73 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (150 MHz, C_6D_6): δ = 159.0, 147.8, 142.2, 133.0, 129.7, 129.1, 128.9, 128.7, 124.6, 124.5, 99.8, 33.4, 29.9, 22.9, 14.6 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3035, 3010, 1664, 1620, 1591, 1486, 1235, 810, 687 cm^{-1}. MS (EI): *m*/*z* = 283 [M]$^+$. HRMS (EI): calcd. for $C_{17}H_{17}NOS$ 283.1031; found 283.1036.

(*Z*)-*N*-[3-(4-Fluorophenyl)-1*H*-isochromen-1-ylidene]aniline (3o): Pale yellow solid (20 mg, 31 % yield); m.p. 156–157 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.37 (d, *J* = 7.6 Hz, 1 H), 7.56–7.53 (m, 3 H), 7.43–7.38 (m, 3 H), 7.32 (d, *J* = 7.6 Hz, 1 H), 7.22 (d, *J* = 7.6 Hz, 2 H), 7.14 (dd, *J* = 7.6, 7.6 Hz, 1 H), 7.02 (dd, *J* = 8.9, 7.6 Hz, 2 H), 6.64 (s, 1 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 163.4 (d, $J_{C,F}$ = 250.0 Hz), 150.5, 149.6, 146.8, 133.8, 132.5, 128.8, 128.6 (d, $J_{C,F}$ = 2.9 Hz), 128.2, 127.5, 126.6, (d, $J_{C,F}$ = 8.7 Hz), 125.6, 123.7, 123.5, 122.3, 115.8 (d, $J_{C,F}$ = 21.7 Hz), 100.6 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3035, 3010, 1662, 1629, 1594, 1510, 1490, 1341, 1271, 1238, 1160, 1015, 844, 822, 810, 692, 687 cm^{-1}. MS (EI): *m*/*z* = 315 [M]$^+$. HRMS (EI): calcd. for $C_{21}H_{14}NOF$ 315.1059; found 315.1056.

(*Z*)-*N*-[3-(*p*-Tolyl)-1*H*-isochromen-1-ylidene]aniline (3q): Pale yellow oil (52 mg, 84 % yield). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.37 (d, *J* = 7.6 Hz, 1 H), 7.53 (dd, *J* = 7.6, 7.6 Hz, 1 H), 7.46 (d, *J* = 7.6 Hz, 2 H), 7.41–7.37 (m, 3 H), 7.30 (d, *J* = 7.6 Hz, 1 H), 7.24 (d, *J* = 8.2 Hz, 2 H), 7.13 (d, *J* = 7.6 Hz, 3 H), 6.66 (s, 1 H), 2.33 (s, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 151.9, 149.9, 146.9, 139.7, 134.1, 132.4, 129.6, 129.3, 129.4, 128.7, 127.9, 127.5, 125.5, 124.6, 123.5, 122.5, 100.1, 21.3 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3035, 3010, 1661, 1626, 1593, 1235, 814, 810, 772, 693 cm^{-1}. MS (EI): *m*/*z* = 311 [M]$^+$. HRMS (EI): calcd. for $C_{22}H_{17}NO$ 311.1310; found 311.1304.

(*Z*)-*N*-[3-(4-Methoxyphenyl)-1*H*-isochromen-1-ylidene]aniline (3r): Pale yellow oil (52 mg, 80 % yield). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.36 (d, *J* = 7.6 Hz, 1 H), 7.55–7.50 (m, 3 H), 7.40–7.37 (m, 3 H), 7.30 (d, *J* = 7.6 Hz, 1 H), 7.24 (d, *J* = 7.6 Hz, 2 H), 7.13 (dd, *J* = 7.6, 7.6 Hz, 1 H), 6.87–6.84 (m, 2 H), 6.59 (s, 1 H), 3.81 (s, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 160.7, 151.7, 150.0, 147.0, 134.3, 132.4, 128.8, 127.7, 127.4, 126.2, 125.4, 125.0, 123.5, 123.3, 122.4, 114.1, 99.2, 55.4 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3035, 3010, 1603, 1513, 1256, 1234, 1179, 810, 789, 772, 705, 693, 687, 673 cm^{-1}. MS (EI): *m*/*z* = 327 [M]$^+$. HRMS (EI): calcd. for $C_{22}H_{17}NO_2$ 327.1259; found 327.1256.

(*Z*)-3-[1-(Phenylimino)-1*H*-isochromen-3-yl]propyl-4-methylbenzenesulfonate (3s): Pale yellow oil (79 mg, 91 % yield). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.30 (d, *J* = 7.6 Hz, 1 H), 7.74 (d, *J* = 6.9 Hz, 2 H), 7.51 (dd, *J* = 7.6, 7.6 Hz, 1 H), 7.38 (dd, *J* = 7.6, 7.6 Hz, 1 H), 7.33–7.28 (m, 4 H), 7.15 (d, *J* = 7.6 Hz, 1 H), 7.10–7.05 (m, 3 H), 5.92 (s, 1 H), 3.99 (t, *J* = 5.5 Hz, 2 H), 2.41 (s, 3 H), 2.41–2.39 (m, 2 H), 1.89–1.84 (m, 2 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 153.7, 149.9, 146.5, 144.9, 133.6, 132.8, 132.3, 129.9, 128.7, 127.9, 127.8, 127.4, 124.8, 123.5, 123.3, 122.4, 102.9, 69.0, 29.1, 25.9, 21.7 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3034, 1674, 1235, 1176, 810, 798, 785, 736, 712, 690, 686, 678, 661 cm^{-1}. MS (EI): *m*/*z* = 433 [M]$^+$. HRMS (EI): calcd. for $C_{25}H_{23}NO_4S$: 433.1348; found 433.1352.

(*Z*)-*N*-(3-Cyclohexyl-1*H*-isochromen-1-ylidene)aniline (3t): Pale yellow oil (56 mg, 92 % yield). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.32 (d, *J* = 7.6 Hz, 1 H), 7.48 (dd, 1 H, 7.6, 1.4 Hz), 7.37–7.33 (m, 3 H), 7.20–7.06 (d, *J* = 7.6, 1.4 Hz, 3 H), 7.10–7.06 (m, 1 H), 5.95 (s, 1 H), 2.26–2.21 (m, 1 H), 1.86 (m, 2 H), 1.76 (m, 2 H), 1.68–1.65 (m, 1 H), 1.33–1.22 (m, 4 H), 1.17–1.12 (m, 1 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 160.4, 150.4, 146.7, 134.2, 132.2, 128.5, 127.4, 127.3, 124.8, 123.4, 123.3, 122.8, 99.8, 41.5, 30.4, 25.9, 25.8 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2934, 2857, 1669, 1642, 1631, 1605, 1593, 1490, 1236, 1160, 1061, 699, 686 cm^{-1}. MS (EI): *m*/*z* = 303 [M]$^+$. HRMS (EI): calcd. for $C_{21}H_{21}NO$ 303.1623; found 303.1629.

(*Z*)-*N*-(3-Cyclohexyl-7-nitro-1*H*-isochromen-1-ylidene)-4-fluoroaniline (3u): Yellow prisms (45 mg, 61 % yield); m.p. 158–159 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.04 (s, 1 H), 8.21 (dd, *J* = 8.9, 1.4 Hz, 1 H), 7.22 (d, *J* = 8.9 Hz, 1 H), 7.14 (d, *J* = 8.9 Hz, 2 H), 6.98 (d, *J* = 8.9 Hz, 2 H), 5.97 (s, 1 H), 2.25–2.21 (m, 1 H), 1.84–1.82 (m, 2 H), 1.75–1.73 (m, 2 H), 1.66–1.63 (m, 1 H), 1.29–1.08 (m, 5 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 164.4, 159.7 (d, $J_{C,F}$ = 242.8 Hz), 148.1, 146.7, 141.3 (d, $J_{C,F}$ = 2.9 Hz), 139.6, 126.6, 125.8, 124.5 (d, $J_{C,F}$ = 8.7 Hz), 124.3, 123.3, 115.3 (d, $J_{C,F}$ = 21.7 Hz), 99.3, 41.9, 30.3, 29.7, 25.8 (d, *J* = 4.3 Hz) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2935, 1667, 1641, 1610, 1584, 1522, 1503, 1341, 1160, 1152, 1100, 851, 842, 710, 684 cm^{-1}. MS (EI): *m*/*z* = 366 [M]$^+$. HRMS (EI): calcd. for $C_{21}H_{19}N_2O_3F$ 366.1380; found 366.1374.

(*Z*)-*N*-(3-Cyclohexyl-7-nitro-1*H*-isochromen-1-ylidene)aniline (3v): Yellow solid (39 mg, 55 % yield); m.p. 137–138 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.15 (dd, *J* = 2.1 Hz, 1 H), 8.29 (dd, *J* = 8.6, 2.1 Hz, 1 H), 7.37 (dd, *J* = 7.6, 7.6 Hz, 2 H), 7.29 (d, *J* = 8.6 Hz, 1 H), 7.22 (d, *J* = 7.6 Hz, 2 H), 7.14 (dd, *J* = 7.6, 7.6 Hz, 1 H), 6.03 (s, 1 H), 2.30–2.29 (m, 1 H), 1.91–1.88 (m, 2 H), 1.81–1.78 (m, 2 H), 1.71–1.68 (m, 1 H), 1.36–1.25 (m, 4 H), 1.19–1.14 (m, 1 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 164.5, 147.9, 146.7, 145.4, 139.8, 128.7, 126.6, 125.7, 124.3, 124.2, 123.4, 122.8, 99.1, 41.9, 30.3, 25.8, 25.8 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2935, 2858, 1667, 1642, 1593, 1522, 1452, 1341, 1254, 1235, 1160, 1100, 970, 851, 810, 687 cm^{-1}. MS (EI): *m*/*z* = 348 [M]$^+$. HRMS (EI): calcd. for $C_{21}H_{20}N_2O_3$ 348.1474; found 348.1477.

(*Z*)-*N*-(3-Cyclohexyl-7-nitro-1*H*-isochromen-1-ylidene)-4-methylaniline (3w): Yellow prisms (49 mg, 67 % yield); m.p. 138–139 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.12 (d, *J* = 2.8 Hz, 1 H), 8.26 (dd, *J* = 8.9, 2.8 Hz, 1 H), 7.27 (d, *J* = 8.9 Hz, 1 H), 7.18–7.16 (m, 4 H), 6.01 (s, 1 H), 2.37 (s, 3 H), 2.33–2.28 (m, 1 H), 1.93–1.91 (m, 2 H), 1.82–1.79 (m, 2 H), 1.73–1.69 (m, 1 H), 1.38–1.26 (m, 4 H), 1.19–1.16 (m, 1 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 164.5, 147.4, 146.6, 142.5, 139.7, 133.9, 129.2, 126.4, 125.6, 124.6, 123.3, 123.2, 99.1, 41.9, 30.3, 25.8, 25.8, 21.1 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2935, 1663, 1640, 1698, 1584, 1507, 1452, 1341, 1254, 1159, 1099, 1056, 1018, 851, 799, 736, 714,

693, 687 cm^{-1}. MS (EI): *m/z* = 362 $[M]^+$. HRMS (EI): calcd. for $C_{22}H_{22}N_2O_3$ 362.1630; found 362.1628.

Supporting Information (see footnote on the first page of this article): Copies of ^1H and ^{13}C NMR spectra for all new compounds, crystal data and structure refinement, and thermal ellipsoid plots for the crystal structures of compounds **3k**, **3q**, and **3u**.

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[1] a) R. Mancuso, B. Gabriele, *Molecules* **2014**, *19*, 15687–15719; b) R. Mancuso, I. Ziccarelli, D. Armentano, N. Marino, S. V. Giofrè, B. Gabriele, *J. Org. Chem.* **2014**, *79*, 3506–3518; c) B. Gabriele, R. Mancuso, R. C. Larock, *Curr. Org. Chem.* **2014**, *18*, 341–358; d) X.-F. Wu, H. Neumann, M. Beller, *Chem. Rev.* **2013**, *113*, 1–35; e) B. Gabriele, R. Mancuso, G. Salerno, *Eur. J. Org. Chem.* **2012**, 6825–6839; f) B. Godoi, R.-F. Schumacher, G. Zeni, *Chem. Rev.* **2011**, *111*, 2937–2980; g) Y. Yamamoto, I. D. Gridnev, N. T. Patil, T. Jin, *Chem. Commun.* **2009**, 5075–5087; h) N. T. Patil, Y. Yamamoto, *Chem. Rev.* **2008**, *108*, 3395–3442.

[2] For isoquinolines, see: a) Y. Long, Z. She, X. Liu, Y. Chen, *J. Org. Chem.* **2013**, *78*, 2579–2588; b) B. Gabriele, L. Veltri, V. Maltese, R. Spina, R. Mancuso, G. Salerno, *Eur. J. Org. Chem.* **2011**, 5626–5635; c) Z. Huo, Y. Yamamoto, *Tetrahedron Lett.* **2009**, *50*, 3651–3653; d) S. Hwang, Y. Lee, P. H. Lee, S. Shin, *Tetrahedron Lett.* **2009**, *50*, 2305–2308; e) S. Obika, H. Kono, Y. Yasui, R. Yanada, Y. Takemoto, *J. Org. Chem.* **2007**, *72*, 4462–4468; f) R. Yanada, S. Obika, H. Kono, Y. Takemoto, *Angew. Chem. Int. Ed.* **2006**, *45*, 3822–3825; *Angew. Chem.* **2006**, *118*, 3906–3909; g) Q. Huang, J. A. Hunter, R. C. Larock, *J. Org. Chem.* **2002**, *67*, 3437–3444; h) Q. Huang, J. A. Hunter, R. C. Larock, *Org. Lett.* **2001**, *3*, 2973–2976.

[3] For indoles, see: a) B. Gabriele, L. Veltri, R. Mancuso, G. Salerno, M. Costa, *Eur. J. Org. Chem.* **2012**, 2549–2559; b) X. Li, A. R. Chianese, T. Vogel, R. H. Crabtree, *Org. Lett.* **2005**, *7*, 5437–5440; c) S. Cacchi, G. Fabrizi, *Chem. Rev.* **2005**, *105*, 2873–2920; d) K. Hiroya, S. Itoh, T. Sakamoto, *Tetrahedron* **2005**, *61*, 10958–10964; e) K. Hiroya, S. Itoh, T. Sakamoto, *J. Org. Chem.* **2004**, *69*, 1126–1136; f) A. Arcadi, G. Bianchi, F. Marinelli, *Synthesis* **2004**, 610–618; g) S. Kamijo, Y. Yamamoto, *Angew. Chem. Int. Ed.* **2002**, *41*, 3230–3233; *Angew. Chem.* **2002**, *114*, 3364–3367; h) A. Takeda, S. Kamijo, Y. Yamamoto, *J. Am. Chem. Soc.* **2000**, *122*, 5662–5663.

[4] For furans, see: a) B. Gabriele, L. Veltri, P. Plastina, R. Mancuso, M. V. Vetere, V. Maltese, *J. Org. Chem.* **2013**, *78*, 4919–4928; b) N. Okamoto, R. Yanada, *J. Org. Chem.* **2012**, *77*, 3944–3951; c) A. Sniady, A. Durham, M. S. Morreale, K. A. Wheeler, R. Dembinski, *Org. Lett.* **2007**, *9*, 1175–1178; d) A. Fürstner, P. W. Davies, *J. Am. Chem. Soc.* **2005**, *127*, 15024–15025; e) I. Nakamura, Y. Mizushima, Y. Yamamoto, *J. Am. Chem. Soc.* **2005**, *127*, 15022–15023; f) N. T. Patil, H. Wu, Y. Yamamoto, *J. Org. Chem.* **2005**, *70*, 4531–4534; g) A. S. K. Hashmi, P. Sinha, *Adv. Synth. Catal.* **2004**, *346*, 432–438; h) A. Arcadi, S. Cacchi, G. Fabrizi, F. Marinelli, L. Moro, *Synlett* **1999**, 1432–1434.

[5] a) For pyrroles, see: T. J. Harrison, J. A. Kozak, M. Corbella-Pané, G. R. Dake, *J. Org. Chem.* **2006**, *71*, 4525–4529; b) D. J. Gorin, N. R. Davis, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 11260–11261; c) S. Kamijo, C. Kanazawa, Y. Yamamoto, *J. Am. Chem. Soc.* **2005**, *127*, 9260–9266.

[6] For coumarins, see: a) K. Yan, D. Yang, W. Wei, F. Wang, Y. Shuai, Q. Li, H. Wang, *J. Org. Chem.* **2015**, *80*, 1550–1556; b) B. Gabriele, R. Mancuso, G. Salerno, P. Plastina, *J. Org. Chem.* **2008**, *74*, 756–759; c) N. Asao, H. Aikawa, S. Tago, K. Umetsu, *Org. Lett.* **2007**, *9*, 4299–4302; d) C. Jia, D. Piao, T. Kitamura, Y. Fujiwara, *J. Org. Chem.* **2000**, *65*, 7516–7522.

[7] a) E. A. Merritt, B. Olofsson, *Angew. Chem. Int. Ed.* **2009**, *48*, 9052–9070; *Angew. Chem.* **2009**, *121*, 9214–9234; b) V. V. Zhdankin, P. J. Stang, *Chem. Rev.* **2008**, *108*, 5299–5358.

[8] a) T. Lv, Z. Wang, J. You, J. Lan, G. Gao, *J. Org. Chem.* **2013**, *78*, 5723–5730; b) J.-M. Becht, C. L. Drian, *Org. Lett.* **2008**, *10*, 3161–3164; c) T. Okuyama, T. Takino, T. Sueda, M. Ochiai, *J. Am. Chem. Soc.* **1995**, *117*, 3360–3367.

[9] a) V. K. Aggarwal, B. Olofsson, *Angew. Chem. Int. Ed.* **2005**, *44*, 5516–5519; *Angew. Chem.* **2005**, *117*, 5652–5655; b) M. Ochiai, Y. Kitagawa, N. Takayama, Y. Takaoka, M. Shiro, *J. Am. Chem. Soc.* **1999**, *121*, 9233–9234; c) T. Iwama, V. B. Birman, S. A. Kozmin, V. H. Rawal, *Org. Lett.* **1999**, *1*, 673–676; d) C. H. Oh, J. S. Kim, H. H. Jung, *J. Org. Chem.* **1999**, *64*, 1338–1340; e) S. A. Kozmin, V. H. Rawal, *J. Am. Chem. Soc.* **1998**, *120*, 13523–13524.

[10] a) S. Lee, S. Mah, S. Hong, *Org. Lett.* **2015**, *17*, 3864–3867; b) H. A. Duong, R. E. Gilligan, M. L. Cooke, R. J. Phipps, M. J. Gaunt, *Angew. Chem. Int. Ed.* **2011**, *50*, 463–466; *Angew. Chem.* **2011**, *123*, 483–486; c) C.-L. Ciana, R. J. Phipps, J. R. Brandt, F.-M. Meyer, M. J. Gaunt, *Angew. Chem. Int. Ed.* **2011**, *50*, 458–462; *Angew. Chem.* **2011**, *123*, 478–482; d) R. J. Phipps, M. J. Gaunt, *Science* **2009**, *323*, 1593–1597; e) R. J. Phipps, N. P. Grimster, M. J. Gaunt, *J. Am. Chem. Soc.* **2008**, *130*, 8172–8174; f) J.-M. Becht, C. L. Drian, *Org. Lett.* **2008**, *10*, 3161–3164; g) N. R. Deprez, D. Kalyani, A. Krause, M. S. Sanford, *J. Am. Chem. Soc.* **2006**, *128*, 4972–4973; h) O. Daugulis, V. G. Zaitsev, *Angew. Chem. Int. Ed.* **2005**, *44*, 4046–4048; *Angew. Chem.* **2005**, *117*, 4114–4116.

[11] a) A. Sinai, D. Vangel, T. Gáti, P. Bombicz, Z. Novák, *Org. Lett.* **2015**, *17*, 4136–4139; b) F. Hartrampf, H. Toombs-Ruane, *Aust. J. Chem.* **2015**, *68*, 699–702; c) J. Peng, C. Chen, J. Chen, X. Su, C. Xi, H. Chen, *Org. Lett.* **2014**, *16*, 3776–3779; d) A. J. Walkinshaw, W. Xu, M. G. Suero, M. J. Gaunt, *J. Am. Chem. Soc.* **2013**, *135*, 12532–12535; e) Á. Sinai, Á. Mészáros, T. Gáti, V. Kudar, A. Palló, Z. Novák, *Org. Lett.* **2013**, *15*, 5654–5657; f) M. G. Suero, E. D. Bayle, B. S. L. Collins, M. J. Gaunt, *J. Am. Chem. Soc.* **2013**, *135*, 5332–5335; g) Z.-F. Xu, C.-X. Cai, J.-T. Liu, *Org. Lett.* **2013**, *15*, 2096–2099; h) L. L. Suarez, M. F. Greaney, *Chem. Commun.* **2011**, *47*, 7992–7994; i) S. Tang, P. Peng, P. Zhong, J.-H. Li, *J. Org. Chem.* **2008**, *73*, 5476–5480.

[12] a) B. Zhou, W. Hou, Y. Yang, H. Feng, Y. Li, *Org. Lett.* **2014**, *16*, 1322–1325; b) R. J. Phipps, L. McMurray, S. Ritter, H. A. Duong, M. J. Gaunt, *J. Am. Chem. Soc.* **2012**, *134*, 10773–10776; c) J. Aydin, J. M. Larsson, N. Selander, K. J. Szabó, *Org. Lett.* **2009**, *11*, 2852–2854; d) M. Zhu, Y. Song, Y. Cao, *Synthesis* **2007**, 853–856.

[13] a) L. Chan, A. McNally, Q. Y. Toh, A. Mendoza, M. J. Gaunt, *Chem. Sci.* **2015**, *6*, 1277–1281; b) M. Fañanás-Mastral, B. L. Feringa, *J. Am. Chem. Soc.* **2014**, *136*, 9894–9897; c) T. B. Petersen, R. Khan, B. Olofsson, *Org. Lett.* **2011**, *13*, 3462–3465.

[14] a) S. G. Modha, M. F. Greaney, *J. Am. Chem. Soc.* **2015**, *137*, 1416–1419; b) K. Aradi, Z. Novák, *Adv. Synth. Catal.* **2015**, *357*, 371–376; c) M. A. Carroll, R. A. Wood, *Tetrahedron* **2007**, *63*, 11349–11354; d) T. Zhou, Z.-C. Chen, *Synth. Commun.* **2002**, *32*, 903–907; e) S.-K. Kang, S.-H. Lee, D. Lee, *Synlett* **2000**, 1022–1024.

[15] a) N. Okamoto, K. Takeda, R. Yanada, *Org. Synth.* **2014**, *91*, 27–38; b) N. Okamoto, K. Takeda, M. Ishikura, R. Yanada, *J. Org. Chem.* **2011**, *76*, 9139–9143; c) N. Okamoto, K. Takeda, R. Yanada, *J. Org. Chem.* **2010**, *75*, 7615–7625; d) N. Okamoto, Y. Miwa, H. Minami, K. Takeda, R. Yanada, *Angew. Chem. Int. Ed.* **2009**, *48*, 9693–9696; *Angew. Chem.* **2009**, *121*, 9873–9876.

[16] a) B. Yao, C. Jaccound, Q. Wang, J. Zhu, *Chem. Eur. J.* **2012**, *18*, 5864–5868; b) M. Jithunsa, M. Ueda, O. Miyata, *Org. Lett.* **2011**, *13*, 518–521.

[17] The hydrolysis of iminoisocoumarin **3a** under weak acidic conditions provided the known compound 3-butyl-1*H*-isochromen-1-one in quantitative yield. For details, see: Z. Mingliang, Z. Hui-Jun, H. Tiantian, R. Wenqing, W. Ting-Bin, *J. Org. Chem.* **2015**, *80*, 620–627.

[18] CCDC 1410637 (for **3k**), 1410638 (for **3q**), and 1410639 (for **3u**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[19] a) J. Luan, L. Zhang, Z. Hu, *Molecules* **2011**, *16*, 4191–4230; b) S. Combes, J.-P. Finet, *Tetrahedron* **1999**, *55*, 3377–3386; c) J.-P. Finet, *Chem. Rev.* **1989**, *89*, 1487–1501.

[20] M. Bian, W. Yao, H. Ding, C. Ma, *J. Org. Chem.* **2010**, *75*, 269–272.

[21] a) N. T. Patil, Y. Yamamoto, *J. Org. Chem.* **2004**, *69*, 5139–5142; b) A.-Y. Peng, Y.-X. Ding, *J. Am. Chem. Soc.* **2003**, *125*, 15006–15007.
[22] V. O. Iaroshenko, S. Ali, T. M. Babar, M. S. A. Abbasi, V. Y. Sosnovskikh, A. Villinger, A. Tolmachev, P. Langer, *Tetrahedron* **2013**, *69*, 3167–3181.
[23] M. Jithunsa, M. Ueda, O. Miyata, *Org. Lett.* **2011**, *13*, 518–521.
[24] S.-W. Zhang, T. Kaneko, E. Yoneda, T. Sugioka, S. Takahashi, *Inorg. Chim. Acta* **1999**, *296*, 195–203.
[25] L. Legrand, N. Lozac'h, *Bull. Soc. Chim. Fr.* **1966**, *12*, 3828–3841.
[26] R. Mancuso, I. Ziccarelli, D. Armentano, N. Marino, S. V. Giofrè, B. Gabriele, *J. Org. Chem.* **2014**, *79*, 3506–3518.

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