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Palladium-Catalyzed 6-*endo*-Selective Oxycyclization–Alkene Addition Cascades of *ortho*-Alkynylarylcarboxamides and α,β-Unsaturated Carbonyl Compounds

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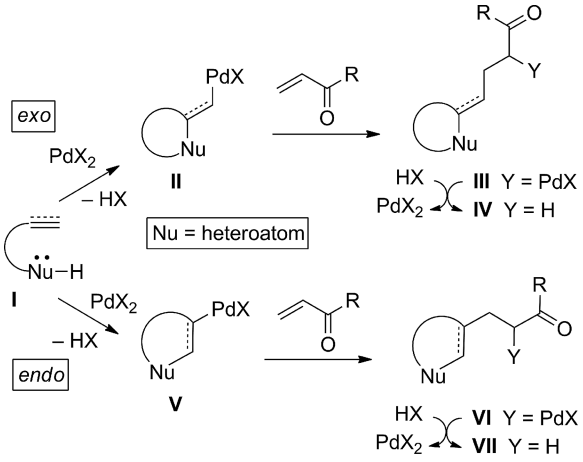
Regio- and chemoselective palladium-catalyzed cyclization–coupling cascade reactions between *ortho*-alkynylarylcarboxamides and methyl vinyl ketone or acrylaldehyde are described. An initial 6-*endo*-oxypalladation of the triple bond is followed by a C–C coupling to give structurally diverse isochromenimines (and related heterosubstituted derivatives), in which the α,β-unsaturated carbonyl moiety is incorporated as an alkyl-type exocyclic side chain. The coupling products were obtained in 76–97 % yield (average 86 % yield) without significant interference from Heck or alternative regiochemical pathways. In contrast to related cases, these cascade reactions do not require the use of protic solvents and excess amounts of halide additives, and they proceed effectively under either $PdCl_2$ catalysis in the presence of substoichiometric amounts of added KI or PdI_2 catalysis without any additive.

Introduction

Palladium-catalyzed heterocyclization–alkene addition cascade reactions of nucleophile-tethered unsaturated substrates **I** with α,β-unsaturated ketones and aldehydes have been used in the synthesis of heterocyclic derivatives **IV** and **VII** (depending on the *exo* or *endo* mode of cyclization), in which an α,β-unsaturated carbonyl framework is incorporated as an alkyl-type exocyclic side chain (Scheme 1).[1] In these reactions, substrate **I** undergoes an intramolecular nucleopalladation, which is followed by an alkene insertion and protonation of the resulting palladium enolate **III/VI** (or their corresponding *O*-Pd enolates) to regenerate the Pd^{II} catalyst.[2–5] The success of this process has normally relied upon the selection of reaction conditions, typically protic solvents and/or excess amounts of halide salt additives,[1] that effectively steer the transformation of intermediates **III/VI** towards palladium enolate protonation rather than β-H elimination, a competing process that would lead to the alternative Heck-type products.



Scheme 1. The *exo* and *endo* pathways for Pd-catalyzed heterocyclization–alkene addition cascade reactions.

The Heck pathway is followed, for example, by *ortho*-alkynylarylcarboxamides **3** (among other substrates) in palladium-catalyzed couplings with electron-deficient alkenes under oxidative conditions (Scheme 2). These reactions have been shown to afford either isobenzofuranimine-[6a] or isochromenimine-type[6b–6d] products (i.e., **4** or **5**, respectively) with high regioselectivity in each case. We now report that, under modified reaction conditions, a new family of products, namely, carbonyl derivatives **6**, can be prepared from the same substrates **3** and methyl vinyl ketone or acrylaldehyde, as a result of the regioselective oxycyclization–formal conjugate addition cascade reactions that take place to the exclusion of the alternative Heck products

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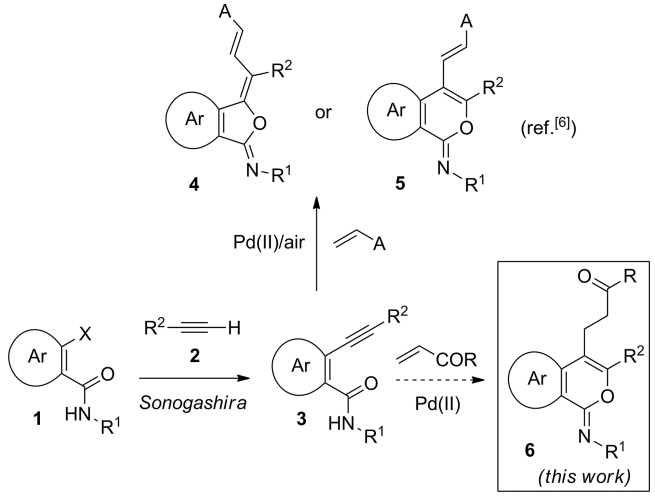
4/5 (Scheme 2). Structures **6** are representative of isochromenimines (among other compounds), which are the subject of current synthetic interest because of their biological profiles and for being nitrogen analogues of the biologically interesting isocoumarins.[7] Interestingly, in contrast to the related literature cases alluded to above,[1] the **3**-to-**6** coupling reactions are effective without resorting to the use of excess amounts of halide salts. In fact, PdI_2 alone as a catalyst, without further additives, is enough to selectively direct the reaction towards the formation of products **6** by following the protonation pathway of **VI** to **VII** as depicted in Scheme 1.

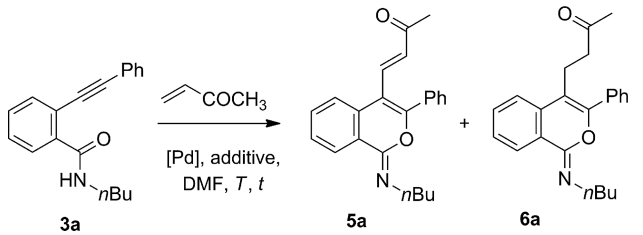


Scheme 2. Palladium-catalyzed cyclization–coupling cascade reactions of *ortho*-alkynylarylcarboxamides and electron-deficient alkenes.

Results and Discussion

We previously reported that under typical conditions for the formation of alkenes **5**, which included $PdCl_2(PPh_3)_2$ as the catalyst with KI (0.5 equiv.) as the additive in *N*,*N*-dimethylformamide (DMF) under air at 80 °C, the reaction of **3a** with methyl vinyl ketone provided **6a** in 20% yield in addition to the expected major product **5a** (Table 1, Entry 1).[6b,6c] We have subsequently found that the formation of **6a** is favored by lowering the reaction temperature and using a phosphine-free palladium catalyst (Table 1, Entries 2 and 3). Thus, by using $PdCl_2$ at 50 °C, **6a** was already obtained as the major product. However, when KI was omitted from the reaction mixture, the selectivity dropped (Table 1, Entry 4). A further improvement was realized when the reaction was carried out under Ar, whereupon **6a** was obtained almost exclusively in high isolated yield (Table 1, Entry 5). Interestingly, KI amounts as low as 0.05 equiv. still delivered **6a** with the same efficiency as achieved by 0.5 equiv. (Table 1, Entries 6–8). Furthermore, the formation of **6a** was equally successful when PdI_2 was employed as the catalyst, even without the addition of KI (Table 1, Entry 9). Significantly, under otherwise identical reaction conditions, the similar use of $PdCl_2$ and $PdBr_2$ led to lower selectivity and sluggish reactivity along with substantial recovery of starting compound **3a** (Table 1, Entries 10 and 11). A control experiment further confirmed the need of a palladium catalyst to trigger the reactivity of substrate **3a** (Table 1, Entry 12).

Table 1. Survey of conditions for palladium-catalyzed cyclization–coupling cascade reactions of **3a** and methyl vinyl ketone.[a]

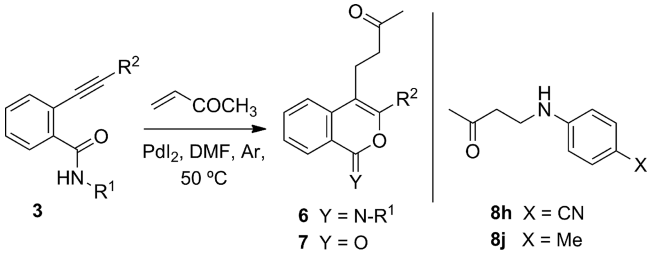


Entry	[Pd]	Additive [equiv.]	Atmosphere	*T* [°C], *t* [h]	**5a/6a**[b]	% Yield **5a**, **6a**
1	$PdCl_2(PPh_3)_2$	KI (0.5)	air	80, 7	72:28	71, 20
2	$PdCl_2(PPh_3)_2$	KI (0.5)	air	50, 42	55:45	46, 38[c]
3	$PdCl_2$	KI (0.5)	air	50, 16	13:87	10, 78
4	$PdCl_2$	–	air	50, 16	26:74	21, 59[c]
5	$PdCl_2$	KI (0.5)	Ar	50, 16	–[d]	86
6	$PdCl_2$	KI (0.3)	Ar	50, 16	3:97	3, 84[c]
7	$PdCl_2$	KI (0.1)	Ar	50, 15	2:98	–, 89
8	$PdCl_2$	KI (0.05)	Ar	50, 16	1:99	1, 89
9	PdI_2	–	Ar	50, 16	3:97	2, 86
10	$PdCl_2$	–	Ar	50, 16	8:92	1, 24[e]
11	$PdBr_2$	–	Ar	50, 16	18:82	5, 23[c,e]
12	–	–	Ar	50, 13	–	4, <1[c,e]

[a] Relative amounts of reagents: Pd catalyst (5 mol-%), KI (equiv. indicated above), and methyl vinyl ketone (6 equiv.). [b] The crude product was used to determine **5a/6a**. [c] Yields determined by ^{1}H NMR analysis of the crude product by using an internal standard. [d] A trace amount of Heck product **5a** was observed by ^{1}H NMR analysis of the crude mixture. [e] Amount of unreacted starting material **3a**: 64% in Entry 10, 46% in Entry 11, 89% in Entry 12.

Next, the scope of this reaction was investigated by using representative *ortho*-alkynylbenzamides **3** (Table 2). Ini-

Table 2. Reactions of **3** with methyl vinyl ketone under PdI_2 catalysis.[a]



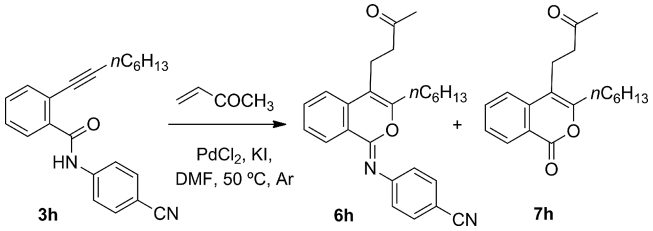
Entry	**3**	R^1	R^2	*t* [h]	**6**, **7**	% Yield
1	**3a**	*n*Bu	Ph	16	**6a**	86
2	**3d**	*n*Bu	*n*hexyl	15	**6d**	84
3	**3e**	CH_2Ph	Ph	16	**6e**	89
4	**3g**	*p*$MeOC_6H_4$	*n*hexyl	17	**6g**	86
5	**3h**	*p*CNC_6H_4	*n*hexyl	17	**6h**, **7h**	15, 75[b]
6	**3j**	*p*MeC_6H_4	Ph	24	**6j**, **7j**	70, 18[c]

[a] Unless otherwise indicated, the reaction conditions were the same as those of Table 1, Entry 9. [b] Amine **8h**[8] (62% yield) was also isolated. [c] Amine **8j**[8b] (5% yield) was also obtained.

tially, the reaction conditions that employed PdI_2 (Table 1, Entry 9) were selected, as those were the simplest and afforded a high yield of coupling product **6a**. The results presented in Table 2 confirm that PdI_2 is indeed a competent catalyst for the oxycyclization–alkene addition cascade reaction. However, the data also reveals a limitation in its use. For example, in the case of substrate **3h** (Table 2, Entry 5), the major coupling product was lactone **7h** (75% isolated yield) and not the expected isochromenimine **6h** (15% yield). Amine **8h**[8] was also isolated in 62% yield. Similarly, lactone **7j** (18% yield) and amine **8j**[8b] (5% yield) were also obtained in the case of substrate **3j** (Table 2, Entry 6). It is apparent that substrates derived from aromatic amines are particularly prone to this side reaction. Nevertheless, despite these shortcomings, the oxycyclization–conjugate addition cascade reactions were still efficient, as shown by the combined yields of **6** and **7** (≥90%) in those two cases.

The formation of lactone **7h** was dependent on the amount of iodide anion in the reaction mixture. The results in Table 3 show a comparison between reactions of **3h** that were carried out under $PdCl_2$ catalysis but with variable amounts of KI. In contrast to the formation of **6a**, which efficiently occurred by using only 5 mol-% of KI (Table 1, Entry 8), the corresponding reaction of **3h** required quantities in the order of 50 mol-% of that additive (Table 4, Entry 4) to completely avoid the formation of lactone **7h**.[9] In a preparative run, under the conditions reported in Table 3, Entry 4, isochromenimine **6h** was isolated in 93% yield (see Table 4).

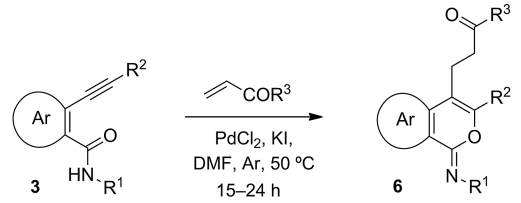
Table 3. Reactions of **3h** with methyl vinyl ketone under $PdCl_2$ catalysis with variable amounts of KI.[a]



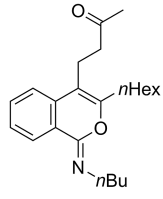
Entry	KI [equiv.]	% Yield[b] **6**	% Yield[b] **7**
1	0.05	9	89
2	0.10	47	47
3	0.30	85	13
4	0.50	98 (93)[c]	–

[a] Relative amounts of reagents: $PdCl_2$ (5 mol-%), KI (as indicated above), and methyl vinyl ketone (6 equiv.). [b] Yields were determined by ^{1}H NMR analysis of the crude product by using an internal standard. [c] Isolated yield.

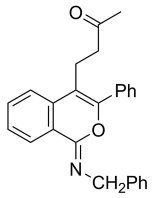
Table 4. Reactions of **3** with methyl vinyl ketone or acrylaldehyde under $PdCl_2$/KI catalysis.[a]



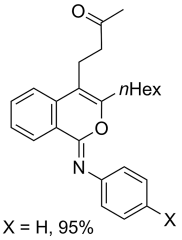
6a X = H, 86%
6b X = OMe, 90%
6c X = CO_2Me, 76%



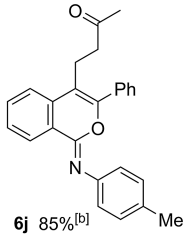
6d 86%



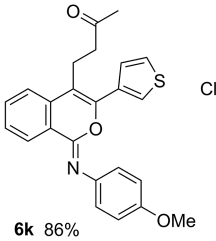
6e 92%



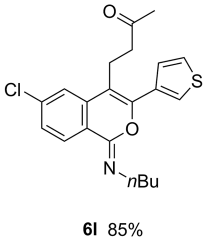
6f X = H, 95%
6g X = OMe, 97%
6h X = CN, 93%
6i X = Cl, 91%



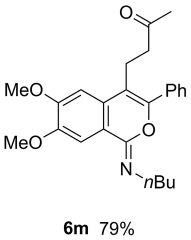
6j 85%[b]



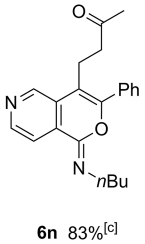
6k 86%



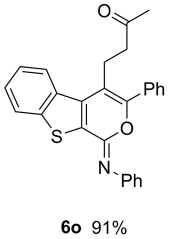
6l 85%



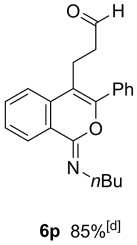
6m 79%



6n 83%[c]



6o 91%



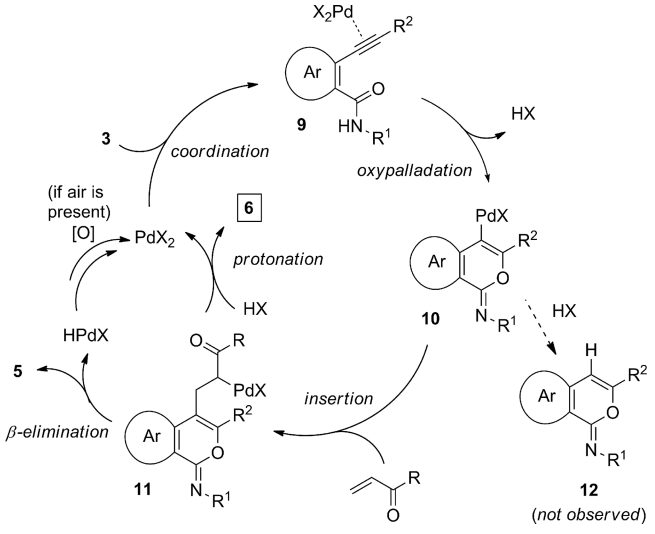
6p 85%[d]

[a] Unless otherwise indicated, reaction conditions were the same as those of Table 3, Entry 4. [b] This reaction afforded a 95% yield of a mixture of **6j** and isomers as indicated by HPLC/HRMS analysis. From that mixture, a yield of 85% was estimated for **6j** by ^{1}H NMR analysis using (3,4-dimethoxyphenyl)acetonitrile as the internal standard. Repeated column chromatography provided pure **6j** for characterization. [c] Reaction performed at 80 °C. [d] This product could not be purified by column chromatography because of decomposition. The yield was estimated from the crude product by ^{1}H NMR analysis using 1,2,4,5-tetramethylbenzene as the internal standard.

Using a combination of $PdCl_2$ and KI (Table 3, Entry 4) proved to be of general use for the conversion of structurally diverse alkynylarylcarboxamides **3** (prepared from carboxamides **1** and alkynes **2**, Scheme 2) into isochromenimine (and related) heterocyclic structures **6** in yields that ranged from high to very high (76–97% yield, average 87% yield, Table 4). The reaction is compatible with alkyl or aryl substituents at both the alkynyl terminus and the nitrogen atom (Table 4). Aryl substituents that have different electronic characteristics are well tolerated, and all of the various combinations of R^1-R^2 groups, such as aryl-aryl, aryl-alkyl, alkyl-aryl, and alkyl-alkyl, were successful. Similarly, the reaction is tolerant of other substituents at the benzamide-type aryl ring, and various heterocyclic motifs were readily incorporated into products **6** (i.e., **6k**–**6o**). Finally, the application of the general conditions of Table 4 to acrylaldehyde as a coupling agent, instead of methyl vinyl ketone, was examined. The coupling reaction between substrate **3a** and acrylaldehyde yielded the corresponding product **6p** with comparably good results.

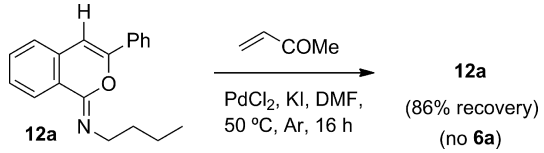
This reaction is remarkably regioselective for the 6-*endo*-*dig*-type *O*-cyclization mode. In the case of **6j**, other isomers, which presumably result from the alternative 5-*exo*-*dig* cyclization, were observed in small amounts by HPLC/MS analysis, but the yield of this major isochromenimine product still remained quite high. Trace amounts of Heck products **5** were also occasionally detected in the crude ^1H NMR spectrum. However, the formation of lactones **7** was not observed under these conditions.

A reasonable reaction mechanism is shown in Scheme 3. The pathways that lead to products **5** and **6** expectedly diverge at palladium enolate intermediate **11**, which is formed as a result of oxypalladation and alkene insertion steps from initial coordinated complex **9**. From **11**, the competing processes of β-H elimination and protonation would then lead to alkenylation (i.e., **5**) and formal conjugate addition (i.e., **6**) products, respectively. Under the appropriate PdI_2- or $PdCl_2$/KI-catalyzed conditions, the conjugate addition pathway operates to the exclusion of the alternative alkenylation reaction, whereas $PdBr_2$ or $PdCl_2$ (without added KI) are much less effective. Although the effect of the iodide anion on these reactions cannot be conveniently rationalized at this point, these overall observations add to a number of recent reports that highlight the beneficial effect of iodide anions in cycloisomerizations[10] and other palladium-catalyzed reactions.[4,6b,6c,11]



Scheme 3. Suggested mechanism for Pd-catalyzed oxycyclization–coupling reactions of *ortho*-alkynylarylcarboxamides with methyl vinyl ketone or acrylaldehyde.

An alternative mechanism for the formation of **6** could involve a stepwise cycloisomerization–conjugate addition pathway through alkene **12**, as similarly described for the corresponding reactions of 2-alkynylanilines.[5] However, this pathway was effectively ruled out by the experiment shown in Scheme 4, in which cycloisomerization product **12a**[7c] (derived from **3a**) was recovered (86% yield by ^1H NMR analysis and no formation of **6a**) when submitted to the standard reaction conditions for the formation of **6**.



Scheme 4. Experiment to test an alternative mechanistic pathway.

Conclusions

In summary, *ortho*-alkynylarylcarboxamides are suitable substrates for oxypalladation–formal conjugate addition cascade reactions by using methyl vinyl ketone or acrylaldehyde as the reaction partner. The overall process is catalyzed by Pd^{II} and proceeds effectively either with $PdCl_2$ and KI as an additive or directly with PdI_2 alone. In contrast, when $PdCl_2$ or $PdBr_2$ catalysts are used without a KI additive, the reactions suffer from lower selectivity and reactivity. The initial intramolecular alkyne oxypalladation takes place with high *endo* selectivity to yield isochromenimine-type products. There is almost no interference from competing Heck-type products or alternative regiochemical pathways, and the reaction results in uniformly high yields of coupling products. Amides derived from aromatic as well as aliphatic amines participate with equal success, and various heterocyclic motifs are readily incorporated into the final products. This procedure complements those also highlighted in Scheme 2, in that it provides an additional entry into the preparation of structurally diverse families of interesting structures from a given set of starting materials by a simple choice of catalyst and additive.

Experimental Section

General Methods: All reactions involving air- and moisture-sensitive materials were performed under dry Ar. Triethylamine, dichloromethane, and toluene were distilled from CaH_2 and purged with Ar. Commercially sourced DMF (≥99.8%) was kept over mo-

lecular sieves (MS, 4 Å) under Ar. Flash column chromatography was carried out using silica gel (230–400 mesh). The ^1H and ^{13}C NMR spectroscopic data were recorded at 25 °C with Bruker AV-300 (300 MHz for ^1H NMR and 75.4 MHz for ^{13}C NMR) and Bruker AV-500 spectrometers (500 MHz for ^1H NMR and 125.7 MHz for ^{13}C NMR) by using $CDCl_3$ or [D_6]acetone as the solvent and internal reference ($CHCl_3$: δ = 7.26 ppm for ^1H NMR, $CDCl_3$: δ = 77.0 ppm for ^{13}C NMR; [D_5]acetone: δ = 2.05 ppm for ^1H NMR, [D_6]acetone: δ = 29.84 ppm for ^{13}C NMR). Coupling constants (*J*) are reported in Hertz (Hz). The DEPT sequence was routinely used for multiplicity assignments for the ^{13}C NMR. Infrared spectral data were obtained by using a thin film deposited onto NaCl glass and then measured on a Jasco FT/IR 4100 in the interval between 4000 and 600 cm^{-1}. The data include only characteristic absorptions. Electron impact mass spectra were obtained on a Hewlett–Packard HP59970 instrument operating at 70 eV. Chemical ionization mass spectra were acquired on an Agilent 6890N gas chromatograph coupled to a mass spectrometer with a Micromass GCT time of flight analyzer. HPLC/MS data were obtained by using a binary Agilent G1312A pump with an Agilent DAD G1315B detector and a ZORBAX eclipse XDB-C8 (4.6 × 150 mm, 5 μm) column. Samples were eluted by using a mixture of H_2O (containing 0.1% formic acid) and acetonitrile (containing 0.1% formic acid) from 70:30 to 10:90 over 30 min at a flow rate of 0.2 mL min^{-1}. Electrospray ionization mass spectra were obtained by a micrOTOF focus mass spectrometer (Bruker Daltonics) using an Apollo II ESI source with a voltage of 4500 V applied to the needle and a counter voltage between 100 and 150 V applied to the capillary. Melting points were measured in open capillary tubes on a Büchi B-540 apparatus. The *O*-cyclized ring structure of compounds **6** was indicated by the absence of a carboxamide-type carbonyl carbon in the ^{13}C NMR spectra.[12] Additionally, the IR imino group band was in the range of 1650–1665 cm^{-1}, typical of six-membered cyclic imidates,[12a] and 2D NMR correlations [COSY, heteronuclear single quantum correlation (HSQC), HMBC, and NOESY] also displayed the expected data. X-ray analysis of a single crystal confirmed the structural assignment of products **6j** and **6n** (Figure S1, Supporting Information) and, by analogy, the remainders of products **6**.

Representative Procedure for Heterocyclization-Alkene Addition Cascade Reactions. Preparation of Isochromenimines-Type Products 6: To a solution of **3** (0.350 mmol) in DMF (3.0 mL) were added 3-buten-2-one or prop-2-enal (2.10 mmol), KI (29 mg, 0.175 mmol), and $PdCl_2$ (3.1 mg, 18 μmol), and the resulting mixture was then heated for the times indicated below at 50 °C under Ar. The mixture was cooled to 25 °C, and a saturated NaCl solution (5 mL) was added. The mixture was extracted with EtOAc (3 × 10 mL), and the combined organic layers were dried with Na_2SO_4. The solvent was removed, and the residue was purified by flash chromatography (silica gel saturated with Et_3N, mixtures of hexanes/EtOAc/Et_3N) to afford products **6** in the yields reported in Table 4. Alternatively, PdI_2 (6.5 mg, 18 μmol) was used in place of $PdCl_2$/KI with the reaction times and yields indicated in Table 2. Additional preparation and characterization details are given below for the individual cases.

4-[(*Z*)-1-(Butylimino)-3-phenyl-1*H*-isochromen-4-yl]butan-2-one (6a):[6b] Compound **3a**[13] (100 mg, 0.360 mmol) was used in the representative procedure for a reaction time of 16 h. The crude product was purified by flash chromatography (silica gel saturated with Et_3N; hexanes/EtOAc/Et_3N, 90:8:2) to afford **6a**[6b] (108 mg, 86%).

4-[(*Z*)-1-(Butylimino)-3-(4-methoxyphenyl)-1*H*-isochromen-4-yl]butan-2-one (6b): Compound **3b** (100 mg, 0.325 mmol) was used in the representative procedure for a reaction time of 16 h. The crude product was purified by flash chromatography (silica gel saturated with Et_3N; hexanes/EtOAc/Et_3N, from 89:10:1 to 74:25:1) to afford **6b** (111 mg, 90%) as a yellow solid; m.p. 75–77 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.93 (t, *J* = 7.3 Hz, 3 H), 1.37–1.49 (m, 2 H), 1.59–1.69 (m, 2 H), 2.11 (s, 3 H), 2.64–2.69 (m, 2 H), 2.86–2.91 (m, 2 H), 3.45 (t, *J* = 7.1 Hz, 2 H), 3.87 (s, 3 H), 6.98 (d, *J* = 8.8 Hz, 2 H), 7.29–7.37 (m, 2 H), 7.43 (d, *J* = 8.8 Hz, 2 H), 7.48–7.53 (m, 1 H), 8.26 (dd, *J* = 7.4, 1.0 Hz, 1 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.0 (CH_3), 20.8 (2 CH_2), 29.9 (CH_3), 33.0 (CH_2), 43.4 (CH_2), 46.0 (CH_2), 55.3 (CH_3), 109.5 (C), 113.8 (2 CH), 122.1 (CH), 124.8 (C), 126.5 (C), 126.9 (CH), 127.4 (CH), 130.0 (2 CH), 131.4 (CH), 133.1 (C), 150.0 (C), 150.3 (C), 160.1 (C), 207.5 (C) ppm. IR (film): $\tilde{\nu}$ = 1713 (s), 1660 (s), 1633 (m), 1602 (s) cm^{-1}. MS (EI): *m*/*z* (%) = 377 (18) $[M]^+$, 361 (17), 360 (73), 348 (12), 335 (13), 334 (45), 321 (16), 320 (74), 306 (22), 278 (13), 277 (14), 276 (69), 265 (16), 264 (100), 263 (11), 242 (14), 237 (11), 242 (14), 237 (11), 236 (29), 205 (10), 156 (15), 135 (80), 128 (56), 107 (11). HRMS (EI): calcd. for $C_{24}H_{27}NO_3$ $[M]^+$ 377.1991; found 377.1990.

Methyl 4-[(*Z*)-1-(Butylimino)-4-(3-oxobutyl)-1*H*-isochromen-3-yl]-benzoate (6c): Compound **3c** (100 mg, 0.298 mmol) was used in the representative procedure for a reaction time of 16 h. The crude product was purified by flash chromatography (silica gel saturated with Et_3N; hexanes/EtOAc/Et_3N, from 84:15:1 to 74:25:1) to afford **6c** (92 mg, 76%) as a yellow solid; m.p. 98–100 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.93 (t, *J* = 7.3 Hz, 3 H), 1.37–1.48 (m, 2 H), 1.60–1.68 (m, 2 H), 2.11 (s, 3 H), 2.65–2.70 (m, 2 H), 2.85–2.90 (m, 2 H), 3.44 (t, *J* = 7.1 Hz, 2 H), 3.95 (s, 3 H), 7.31–7.41 (m, 2 H), 7.52 (d, *J* = 7.6 Hz, 1 H), 7.58 (d, *J* = 8.4 Hz, 2 H), 8.14 (d, *J* = 8.4 Hz, 2 H), 8.27 (d, *J* = 7.8 Hz, 1 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.0 (CH_3), 20.5 (CH_2), 20.7 (CH_2), 29.9 (CH_3), 32.9 (CH_2), 43.2 (CH_2), 46.0 (CH_2), 52.3 (CH_3), 111.1 (C), 122.3 (CH), 125.0 (C), 127.0 (CH), 128.0 (CH), 128.7 (2 CH), 129.7 (2 CH), 130.6 (C), 131.6 (CH), 132.5 (C), 138.3 (C), 149.2 (C), 149.4 (C), 166.4 (C), 207.0 (C) ppm. IR (film): $\tilde{\nu}$ = 1718 (s), 1661 (s), 1608 (m) cm^{-1}. MS (EI): *m*/*z* (%) = 405 (8) $[M]^+$, 389 (16), 388 (59), 376 (17), 363 (23), 362 (74), 349 (15), 348 (62), 334 (20), 333 (18), 330 (11), 292 (14), 270 (24), 261 (19), 260 (100), 248 (11), 242 (14), 233 (14), 232 (18), 204 (20), 163 (31). HRMS (EI): calcd. for $C_{25}H_{27}NO_4$ $[M]^+$ 405.1940; found 405.1944.

4-[(*Z*)-1-(Butylimino)-3-hexyl-1*H*-isochromen-4-yl]butan-2-one (6d): Compound **3d**[6a] (100 mg, 0.350 mmol) was used in the representative procedure for a reaction time of 15 h. The crude product was purified by flash chromatography (silica gel saturated with Et_3N; hexanes/EtOAc/Et_3N, 98:1:1) to afford **6d** (107 mg, 86%) as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.87–0.98 (m, 6 H), 1.31–1.48 (m, 8 H), 1.59–1.69 (m, 4 H), 2.16 (s, 3 H), 2.48 (t, *J* = 7.5 Hz, 2 H), 2.61–2.68 (m, 2 H), 2.75–2.81 (m, 2 H), 3.45 (t, *J* = 7.1 Hz, 2 H), 7.20 (d, *J* = 7.9 Hz, 1 H), 7.25–7.30 (m, 1 H), 7.43–7.48 (m, 1 H), 8.19 (d, *J* = 7.9 Hz, 1 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.0 (2 CH_3), 19.9 (CH_2), 20.8 (CH_2), 22.5 (CH_2), 27.4 (CH_2), 28.9 (CH_2), 30.1 (CH_3), 30.4 (CH_2), 31.6 (CH_2), 32.9 (CH_2), 43.0 (CH_2), 45.8 (CH_2), 108.1 (C), 121.3 (CH), 124.4 (C), 126.8 (2 CH), 131.3 (CH), 133.0 (C), 150.3 (C), 152.6 (C), 207.7 (C) ppm. IR (film): $\tilde{\nu}$ = 1717 (s), 1664 (s), 1641 (m) cm^{-1}. MS (EI): *m*/*z* (%) = 355 (11) $[M]^+$, 326 (25), 313 (22), 312 (98), 299 (11), 298 (49), 271 (19), 270 (100), 256 (12), 243 (11), 242 (48), 214 (12), 212 (53), 186 (14), 184 (18), 172 (19), 168 (11), 158 (10), 156 (15), 144 (19), 143 (14), 130 (27), 129 (12), 128 (29), 116 (11), 115 (16). HRMS (EI): calcd. for $C_{23}H_{33}NO_2$ $[M]^+$ 355.2511; found 355.2507.

4-[(*Z*)-1-(Benzylimino)-3-phenyl-1*H*-isochromen-4-yl]butan-2-one (6e): Compound **3e**[14] (100 mg, 0.321 mmol) was used in the repre-

sentative procedure for a reaction time of 18 h. The crude product was purified by flash chromatography (silica gel saturated with Et_3N; hexanes/EtOAc/Et_3N, from 95:3:2 to 92:6:2) to afford **6e** (113 mg, 92%) as a yellow solid; m.p. 123–124 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.11 (s, 3 H), 2.66–2.71 (m, 2 H), 2.88–2.93 (m, 2 H), 4.69 (s, 2 H), 7.21–7.26 (m, 1 H), 7.30–7.39 (m, 4 H), 7.40–7.47 (m, 7 H), 7.56 (ddd, J = 7.9, 7.4, 1.4 Hz, 1 H), 8.42 (dd, J = 7.9, 1.0 Hz, 1 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 20.8 (CH_2), 30.0 (CH_3), 43.5 (CH_2), 50.1 (CH_2), 110.6 (C), 122.4 (CH), 124.9 (C), 126.4 (CH), 127.4 (CH), 127.8 (CH), 127.9 (CH), 128.3 (CH), 128.6 (CH), 128.9 (CH), 129.4 (CH), 131.9 (CH), 133.1 (C), 134.0 (C), 141.2 (C), 150.5 (C), 151.0 (C), 207.5 (C) ppm. IR (film): $\tilde{\nu}$ = 1714 (s), 1658 (s), 1604 (m) cm^{-1}. MS (EI): *m*/*z* (%) = 381 (24) $[M]^+$, 290 (15), 105 (46), 91 (100), 77 (10). HRMS (EI): calcd. for $C_{26}H_{23}NO_2$ $[M]^+$ 381.1729; found 381.1721.

4-[(*Z*)-3-Hexyl-1-(phenylimino)-1*H*-isochromen-4-yl]butan-2-one (6f): Compound **3f**[7a] (100 mg, 0.327 mmol) was used in the representative procedure for a reaction time of 16 h. The crude product was purified by flash chromatography (silica gel saturated with Et_3N; hexanes/EtOAc/Et_3N, 98.5:0.5:1 to 98:1:1) to afford **6f** (117 mg, 95%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (m, 3 H), 1.24–1.31 (m, 6 H), 1.45–1.52 (m, 2 H), 2.18 (s, 3 H), 2.41 (t, J = 7.4 Hz, 2 H), 2.63–2.69 (m, 2 H), 2.79–2.85 (m, 2 H), 7.07 (t, J = 7.3 Hz, 1 H), 7.15 (d, J = 7.3 Hz, 2 H), 7.28–7.41 (m, 4 H), 7.53–7.59 (m, 1 H), 8.41 (dd, J = 7.8, 0.8 Hz, 1 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.0 (CH_3), 19.8 (CH_2), 22.4 (CH_2), 27.3 (CH_2), 28.7 (CH_2), 30.1 (CH_3), 30.2 (CH_2), 31.5 (CH_2), 43.0 (CH_2), 109.1 (C), 121.5 (CH), 122.7 (2 CH), 123.3 (CH), 123.9 (C), 127.2 (CH), 127.8 (CH), 128.5 (2 CH), 132.3 (CH), 133.9 (C), 146.8 (C), 150.1 (C), 152.7 (C), 207.5 (C) ppm. IR (film): $\tilde{\nu}$ = 1717 (s), 1660 (s), 1631 (s) cm^{-1}. MS (EI): *m*/*z* (%) = 376 (20), 375 (77) $[M]^+$, 332 (14), 319 (22), 318 (100), 290 (12), 262 (12), 248 (22), 247 (12), 235 (14), 225 (16), 220 (18), 219 (12), 218 (27), 217 (19), 207 (15), 206 (74), 205 (10), 204 (31). HRMS (EI): calcd. for $C_{25}H_{29}NO_2$ $[M]^+$ 375.2198; found 375.2197.

4-[(*Z*)-3-Hexyl-1-(4-methoxyphenylimino)-1*H*-isochromen-4-yl]butan-2-one (6g): Compound **3g**[7a] (100 mg, 0.298 mmol) was used in the representative procedure for a reaction time of 18 h. The crude product was purified by flash chromatography (silica gel saturated with Et_3N; hexanes/EtOAc/Et_3N, 97:2:1 to 91:8:1) to afford **6g** (117 mg, 97%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85–0.90 (m, 3 H), 1.27–1.35 (m, 6 H), 1.51–1.58 (m, 2 H), 2.18 (s, 3 H), 2.42–2.47 (m, 2 H), 2.63–2.68 (m, 2 H), 2.80–2.85 (m, 2 H), 3.82 (s, 3 H), 6.89 (dd, J = 8.9, 2.1 Hz, 2 H), 7.19–7.29 (m, 3 H), 7.37 (t, J = 7.6 Hz, 1 H), 7.51–7.56 (m, 1 H), 8.40 (d, J = 7.9 Hz, 1 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.0 (CH_3), 19.9 (CH_2), 22.4 (CH_2), 27.5 (CH_2), 28.8 (CH_2), 30.1 (CH_3), 30.2 (CH_2), 31.6 (CH_2), 43.0 (CH_2), 55.4 (CH_3), 109.1 (C), 113.7 (2 CH), 121.5 (CH), 124.3 (2 CH, 1 C), 127.2 (CH), 127.6 (CH), 132.0 (CH), 133.7 (C), 139.6 (C), 149.5 (C), 152.7 (C), 155.9 (C), 207.6 (C) ppm. IR (film): $\tilde{\nu}$ = 1716 (m), 1657 (s), 1632 (s), 1505 (s) cm^{-1}. MS (EI): *m*/*z* (%) = 405 (100) $[M]^+$, 390 (14), 349 (13), 348 (49), 237 (13), 236 (72), 234 (14), 204 (11), 123 (14). HRMS (EI): calcd. for $C_{26}H_{31}NO_3$ $[M]^+$ 405.2304; found 405.2306.

4-[3-Hexyl-4-(3-oxobutyl)isochromen-1-ylidene]-(*Z*)-aminobenzonitrile (6h): Compound **3h**[6a] (100 mg, 0.303 mmol) was used in the representative procedure for a reaction time of 18 h. The crude product was purified by flash chromatography (silica gel saturated with Et_3N; hexanes/EtOAc/Et_3N, 95:4:1 to 87:12:1) to afford **6h** (113 mg, 93%) as a yellow solid; m.p. 93–95 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85–0.89 (m, 3 H), 1.17–1.30 (m, 6 H), 1.41–1.47 (m, 2 H), 2.18 (s, 3 H), 2.42 (t, J = 7.4 Hz, 2 H), 2.64–2.69 (m, 2 H), 2.81–2.86 (m, 2 H), 7.17 (d, J = 8.4 Hz, 2 H), 7.34 (d, J = 7.9 Hz, 1 H), 7.43 (t, J = 7.5 Hz, 1 H), 7.59–7.64 (m, 3 H), 8.38 (d, J = 7.9 Hz, 1 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.0 (CH_3), 19.7 (CH_2), 22.3 (CH_2), 27.4 (CH_2), 28.6 (CH_2), 30.0 (CH_3), 30.1 (CH_2), 31.4 (CH_2), 42.8 (CH_2), 106.1 (C), 109.9 (C), 119.6 (C), 121.8 (CH), 123.0 (C), 123.3 (2 CH), 127.5 (CH), 128.0 (CH), 132.7 (2 CH), 133.0 (CH), 134.1 (C), 151.4 (C), 151.8 (C), 152.6 (C), 207.2 (C) ppm. IR (film): $\tilde{\nu}$ = 2222 (m, C≡N), 1715 (m), 1660 (s), 1629 (s), 1592 (s) cm^{-1}. MS (EI): *m*/*z* (%) = 400 (100) $[M]^+$, 357 (16), 344 (23), 343 (89), 330 (11), 315 (18), 287 (19), 285 (12), 274 (13), 273 (68), 272 (36), 271 (17), 260 (39), 259 (10), 257 (22), 255 (15), 245 (37), 244 (25), 243 (39), 242 (28), 232 (18), 231 (92), 230 (14), 229 (39), 225 (28). HRMS (EI): calcd. for $C_{26}H_{28}N_2O_2$ $[M]^+$ 400.2151; found 400.2153. Alternatively, the reaction was conducted by using compound **3h**[6a] (57.0 mg, 0.172 mmol), 3-buten-2-one (84 μL, 1.035 mmol), and PdI_2 (3.10 mg, 8.6 μmol; Table 2, Entry 5), and the crude product was purified by flash chromatography (silica gel saturated with Et_3N; hexanes/EtOAc/Et_3N, from 92:7:1 to 40:59:1) to afford **7h**[2] (39.5 mg, 75%), **6h** (8.5 mg, 15%), and **8h**[8] (20 mg, 62%).

4-[(*Z*)-1-(4-Chlorophenylimino)-3-hexyl-1*H*-isochromen-4-yl]butan-2-one (6i): Compound **3i**[6a] (100 mg, 0.294 mmol) was used in the representative procedure for a reaction time of 18 h. The crude product was purified by flash chromatography (silica gel saturated with Et_3N; hexanes/EtOAc/Et_3N, from 98.5:0.5:1 to 97:2:1) to afford **6i** (110 mg, 91%) as a yellow solid; m.p. 62–63 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85–0.90 (m, 3 H), 1.25–1.30 (m, 6 H), 1.45–1.52 (m, 2 H), 2.18 (s, 3 H), 2.41 (t, J = 7.4 Hz, 2 H), 2.63–2.68 (m, 2 H), 2.80–2.85 (m, 2 H), 7.09 (d, J = 8.7 Hz, 2 H), 7.27–7.32 (m, 3 H), 7.37–7.42 (m, 1 H), 7.55–7.60 (m, 1 H), 8.38 (d, J = 8.0 Hz, 1 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.0 (CH_3), 19.8 (CH_2), 22.4 (CH_2), 27.4 (CH_2), 28.7 (CH_2), 30.1 (CH_3), 30.1 (CH_2), 31.5 (CH_2), 42.9 (CH_2), 109.4 (C), 121.6 (CH), 123.6 (C), 124.1 (2 CH), 127.3 (CH), 127.8 (CH), 128.3 (C), 128.5 (2 CH), 132.5 (CH), 133.9 (C), 145.4 (C), 150.6 (C), 152.7 (C), 207.4 (C) ppm. IR (film): $\tilde{\nu}$ = 1716 (m), 1659 (s), 1630 (s) cm^{-1}. MS (EI): *m*/*z* (%) = 411 (35) [M, ^{37}Cl]$^+$, 410 (29), 409 (100) [M, ^{35}Cl]$^+$, 366 (17), 354 (33), 353 (23), 352 (97), 324 (18), 296 (17), 284 (11), 283 (11), 282 (36), 281 (15), 280 (11), 269 (21), 266 (14), 256 (11), 255 (11), 254 (27), 253 (22), 252 (19), 242 (28), 241 (18), 240 (76), 238 (17), 225 (27), 218 (13), 217 (17), 205 (16), 204 (31), 203 (13). HRMS (EI): calcd. for $C_{25}H_{28}{}^{35}ClNO_2$ $[M]^+$ 409.1809; found 409.1808; calcd. for $C_{25}H_{28}{}^{37}ClNO_2$ $[M]^+$ 411.1779; found 411.1782.

4-[(*Z*)-3-Phenyl-1-(*p*-tolylimino)-1*H*-isochromen-4-yl]butan-2-one (6j): Compound **3j**[15] (100 mg, 0.321 mmol) was used in the representative procedure for a reaction time of 17 h. The crude product was purified by flash chromatography (silica gel saturated with Et_3N; hexanes/EtOAc/Et_3N, from 95:4:1 to 92:7:1) to afford **6j** [85% yield estimated by ^{1}H NMR analysis using (3,4-dimethoxyphenyl)acetonitrile as an internal standard; the isomeric relationship was confirmed by HPLC/HRMS analysis]. Column chromatography was repeated to afford pure **6j** as a yellow solid for characterization; m.p 139–141 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.12 (s, 3 H), 2.30 (s, 3 H), 2.67–2.73 (m, 2 H), 2.91–2.96 (m, 2 H), 7.08 (d, J = 8.0 Hz, 2 H), 7.17 (d, J = 8.2 Hz, 2 H), 7.38–7.48 (m, 7 H), 7.60 (t, J = 7.7 Hz, 1 H), 8.48 (d, J = 7.9 Hz, 1 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 20.6 (CH_2), 20.9 (CH_3), 29.8 (CH_3), 43.3 (CH_2), 110.0 (C), 122.3 (CH), 123.1 (2 CH), 124.7 (C), 127.9 (2 CH), 128.4 (2 CH), 128.7 (2 CH), 129.1 (2 CH), 129.2 (CH), 132.2 (CH), 133.0 (C), 133.4 (C), 133.6 (C), 143.4 (C), 149.0 (C), 150.3 (C), 207.2 (C) ppm. IR (film): $\tilde{\nu}$ = 1713 (s), 1655 (s), 1630 (s), 1603 (m) cm^{-1}. MS (EI): *m*/*z* (%) = 381 (99) $[M]^+$, 325

(21), 324 (100), 296 (10). HRMS (EI): calcd. for $C_{26}H_{23}NO_2$ $[M]^+$ 381.1729; found 381.1732. Alternatively, the reaction was conducted by using compound **3j**[15] (100 mg, 0.321 mmol), 3-buten-2-one (156 μL, 1.93 mmol), and PdI_2 (5.80 mg, 0.016 mmol; Table 2, Entry 6). The crude product was purified by flash chromatography (silica gel saturated with Et_3N; hexanes/EtOAc/Et_3N, from 95:4:1 to 49:50:1) to afford **7j**[2] (17 mg, 18%) and a mixture of **6j** and **8j**[8b] (93 mg, approximately 92:8). This mixture was dissolved in EtOAc (20 mL), and the solution was washed with HCl (0.5 M solution, 2× 5 mL), $NaHCO_3$ (5 mL), and brine (5 mL). The organic layer was dried with Na_2SO_4, and the solvent was removed to afford **6j** (86 mg, 70%).

4-[(*Z*)-1-(4-Methoxyphenylimino)-3-thiophen-3-yl-1*H*-isochromen-4-yl]butan-2-one (6k): Compound **3k** (100 mg, 0.300 mmol) was used in the representative procedure for a reaction time of 16 h. The crude product was purified by flash chromatography (silica gel saturated with Et_3N; hexanes/EtOAc/Et_3N, from 84:15:1 to 69:30:1) to afford **6k** (104 mg, 86%) as a yellow solid; m.p. 138–139 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.19 (s, 3 H), 2.74–2.80 (m, 2 H), 3.04–3.09 (m, 2 H), 3.82 (s, 3 H), 6.88 (d, J = 8.8 Hz, 2 H), 7.21–7.23 (m, 3 H), 7.33–7.48 (m, 4 H), 7.56–7.61 (m, 1 H), 8.44 (d, J = 7.9 Hz, 1 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 20.6 (CH_2), 30.0 (CH_3), 43.0 (CH_2), 55.4 (CH_3), 110.7 (C), 113.8 (2 CH), 122.3 (CH), 124.3 (2 CH), 124.6 (C), 125.6 (CH), 125.8 (CH), 127.2 (CH), 127.7 (CH), 127.9 (CH), 132.2 (CH), 133.7 (C), 134.2 (C), 139.4 (C), 145.6 (C), 148.8 (C), 156.0 (C), 207.3 (C) ppm. IR (film): $\tilde{\nu}$ = 1711 (s), 1650 (s), 1624 (s), 1603 (m), 1504 (s) cm^{-1}. MS (EI): m/z (%) = 403 (100) $[M]^+$, 400 (15), 399 (60), 385 (23), 384 (76), 360 (15), 347 (17), 346 (71), 318 (14), 234 (10), 111 (98). HRMS (EI): calcd. for $C_{24}H_{21}NO_3S$ $[M]^+$ 403.1242; found 403.1241.

4-[(*Z*)-1-(Butylimino)-6-chloro-3-thiophen-3-yl-1*H*-isochromen-4-yl]butan-2-one (6l): Compound **3l** (100 mg, 0.315 mmol) was used in the representative procedure for a reaction time of 15 h. The crude product was purified by flash chromatography (silica gel saturated with Et_3N; hexanes/EtOAc/Et_3N, from 90:9:1 to 85:14:1) to afford **6l** (104 mg, 85%) as a white solid; m.p. 115–116 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.95 (t, J = 7.3 Hz, 3 H), 1.39–1.49 (m, 2 H), 1.60–1.68 (m, 2 H), 2.19 (s, 3 H), 2.70–2.75 (m, 2 H), 2.94–2.99 (m, 2 H), 3.47 (t, J = 7.0 Hz, 2 H), 7.27–7.32 (m, 3 H), 7.40–7.43 (m, 1 H), 7.57–7.58 (m, 1 H), 8.18 (d, J = 8.3 Hz, 1 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.0 (CH_3), 20.5 (CH_2), 20.8 (CH_2), 30.0 (CH_3), 32.9 (CH_2), 42.9 (CH_2), 46.1 (CH_2), 109.2 (C), 122.0 (CH), 123.2 (C), 125.7 (CH), 125.9 (CH), 127.2 (CH), 127.7 (CH), 128.6 (CH), 134.4 (C), 134.8 (C), 137.9 (C), 146.9 (C), 148.7 (C), 207.1 (C) ppm. IR (film): $\tilde{\nu}$ = 1713 (s), 1663 (s), 1595 (s) cm^{-1}. MS [chemical ionization (CI)]: m/z (%) = 390 (31) [M + H, $^{37}Cl]^+$, 389 (26), 388 (100) [M + H, $^{35}Cl]^+$, 387 (21), 332 (13), 330 (21). HRMS (CI): calcd. for $C_{21}H_{23}{}^{35}ClNO_2S$ $[M + H]^+$ 388.1138; found 388.1154; calcd. for $C_{21}H_{23}{}^{37}ClNO_2S$ $[M + H]^+$ 390.1109; found 390.1156.

4-[(*Z*)-1-(Butylimino)-6,7-dimethoxy-3-phenyl-1*H*-isochromen-4-yl]butan-2-one (6m): Compound **3m**[6b] (100 mg, 0.296 mmol) was used in the representative procedure for a reaction time of 19 h. The crude product was purified by flash chromatography (silica gel saturated with Et_3N; hexanes/EtOAc/Et_3N, from 89:10:1 to 74:25:1) to afford **6m** (96 mg, 79%) as a yellow solid; m.p. 128–130 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.93 (t, J = 7.3 Hz, 3 H), 1.38–1.47 (m, 2 H), 1.59–1.68 (m, 2 H), 2.11 (s, 3 H), 2.65–2.70 (m, 2 H), 2.86–2.90 (m, 2 H), 3.43 (t, J = 7.2 Hz, 2 H), 3.93 (s, 3 H), 3.99 (s, 3 H), 6.81 (s, 1 H), 7.44–7.48 (m, 5 H), 7.72 (s, 1 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.0 (CH_3), 20.6 (CH_2), 20.8 (CH_2), 30.0 (CH_3), 33.0 (CH_2), 43.5 (CH_2), 46.0 (CH_2), 56.0 (CH_3), 56.2 (CH_3), 104.3 (CH), 108.2 (CH), 110.1 (C), 118.2 (C), 127.2 (C), 128.4 (2 CH), 128.6 (2 CH), 128.9 (CH), 134.2 (C), 149.0 (C), 149.4 (C), 150.2 (C), 152.2 (C), 207.5 (C) ppm. IR (film): $\tilde{\nu}$ = 1713 (s), 1663 (s), 1632 (m) cm^{-1}. MS (EI): m/z (%) = 407 (12) $[M]^+$, 391 (14), 390 (64), 365 (19), 364 (100), 350 (27), 294 (21), 293 (10), 188 (12), 105 (10). HRMS (EI): calcd. for $C_{25}H_{29}NO_4$ $[M]^+$ 407.2097; found 407.2097.

4-[(*Z*)-1-(Butylimino)-3-phenyl-1*H*-pyrano[4,3-*c*]pyridin-4-yl]butan-2-one (6n): Compound **3n**[6b] (95 mg, 0.341 mmol) was used in the representative procedure. The reaction was carried out at 80 °C. for a reaction time of 24 h. The crude product was purified by flash chromatography (silica gel saturated with Et_3N; hexanes/EtOAc/Et_3N, from 74:25:1 to 59:40:1) to afford **6n** (99 mg, 83%) as a white solid; m.p. 109–110 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.93 (t, J = 7.2 Hz, 3 H), 1.38–1.48 (m, 2 H), 1.59–1.71 (m, 2 H), 2.11 (s, 3 H), 2.68–2.73 (m, 2 H), 2.90–2.95 (m, 2 H), 3.45 (t, J = 7.0 Hz, 2 H), 7.47 (m, 5 H), 8.02 (d, J = 5.1 Hz, 1 H), 8.58 (d, J = 5.1 Hz, 1 H), 8.68 (s, 1 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 13.9 (CH_3), 20.0 (CH_2), 20.7 (CH_2), 29.8 (CH_3), 32.7 (CH_2), 43.0 (CH_2), 46.3 (CH_2), 108.0 (C), 119.4 (CH), 127.7 (C), 128.5 (2 CH), 128.6 (2 CH), 129.5 (CH), 131.4 (C), 133.3 (C), 144.9 (CH), 147.8 (C), 148.3 (CH), 151.8 (C), 206.7 (C) ppm. IR (film): $\tilde{\nu}$ = 1705 (s), 1663 (s), 1619 (m) cm^{-1}. MS (EI): m/z (%) = 348 (10) $[M]^+$, 331 (44), 319 (11), 306 (11), 305 (42), 292 (14), 291 (81), 277 (11), 271 (17), 249 (11), 247 (18), 243 (11), 236 (12), 235 (100), 207 (38), 206 (10). HRMS (EI): calcd. for $C_{22}H_{24}N_2O_2$ $[M]^+$ 348.1838; found 348.1837.

(*Z*)-4-(3-Phenyl-1-(phenylimino)-1*H*-benzo[4,5]thieno[2,3-*c*]pyran-4-yl)butan-2-one (6o): Compound **3o** (100 mg, 0.283 mmol) was used in the representative procedure for a reaction time of 21 h. The crude product was purified by flash chromatography (silica gel saturated with Et_3N, hexanes/EtOAc/Et_3N, from 94:5:1 to 89:10:1) to afford **6o** (109 mg, 91%) as a yellow solid; m.p. 178–180 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.11 (s, 3 H), 2.75–2.80 (m, 2 H), 3.21–3.26 (m, 2 H), 7.02–7.06 (m, 1 H), 7.25–7.34 (m, 4 H), 7.42–7.52 (m, 7 H), 7.96 (d, J = 7.7 Hz, 1 H), 8.01 (d, J = 8.4 Hz, 1 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 21.9 (CH_2), 30.1 (CH_3), 43.6 (CH_2), 112.1 (C), 123.6 (CH), 123.8 (CH), 124.2 (CH), 125.4 (CH), 126.8 (CH), 128.5 (CH), 129.1 (CH), 129.4 (CH), 130.0 (C), 132.8 (C), 135.3 (C), 135.9 (C), 142.6 (C), 145.5 (C), 147.3 (C), 152.3 (C), 207.0 (C) ppm. IR (film): $\tilde{\nu}$ = 1713 (s), 1647 (s), 1587 (m) cm^{-1}. MS (EI): m/z (%) = 423 (82) $[M]^+$, 380 (12), 367 (23), 366 (100), 338 (16), 260 (14). HRMS (EI): calcd. for $C_{27}H_{21}NO_2S$ $[M]^+$ 423.1293; found 423.1291.

(*Z*)-3-[1-(Butylimino)-3-phenyl-1*H*-isochromen-4-yl]propanal (6p): Compound **3a**[13] (150 mg, 0.541 mmol) was used in the representative procedure for a reaction time of 17 h. Saturated NaCl solution (5 mL) was added, and the resulting mixture was extracted with EtOAc (3× 10 mL). The combined organic layers were washed with saturated $Na_2S_2O_3$ solution (5 mL) and dried with Na_2SO_4. The solvent was evaporated to afford **6p**, which was characterized without further purification. The yield was determined to be 85% by ^1H NMR analysis using 1,2,4,5-tetramethylbenzene as the internal standard. ^1H NMR (300 MHz, [D_6]acetone): δ = 0.89–0.95 (m, 3 H), 1.37–1.49 (m, 2 H), 1.56–1.66 (m, 2 H), 2.77–2.83 (m, 2 H), 2.88–2.94 (m, 2 H), 3.39–3.44 (m, 2 H), 7.38–7.62 (m, 8 H), 8.24–8.27 (m, 1 H), 9.71 (s, 1 H) ppm. ^{13}C NMR (75.5 MHz, [D_6]-acetone): δ = 14.3 (CH_3), 20.0 (CH_2), 21.4 (CH_2), 33.9 (CH_2), 44.1 (CH_2), 46.6 (CH_2), 111.0 (C), 123.6 (CH), 125.7 (C), 127.6 (CH), 128.5 (CH), 129.4 (2 CH), 129.6 (2 CH), 130.1 (CH), 132.5 (CH), 133.7 (C), 135.1 (C), 149.9 (C), 151.4 (C), 201.5 (CH) ppm. IR

(film): $\tilde{\nu}$ = 1721 (m), 1661 (s) cm^{-1}. MS (CI): *m/z* (%) = 334 (100) $[M + H]^+$, 333 (30), 332 (19), 316 (17), 291 (18), 290 (70). HRMS (CI): calcd. for $C_{22}H_{24}NO_2$ $[M + H]^+$ 334.1807; found 334.1802.

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