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Flow Photo-Nazarov Reactions of 2-Furyl Vinyl Ketones: Cyclizing a Class of Traditionally Unreactive Heteroaromatic Enones

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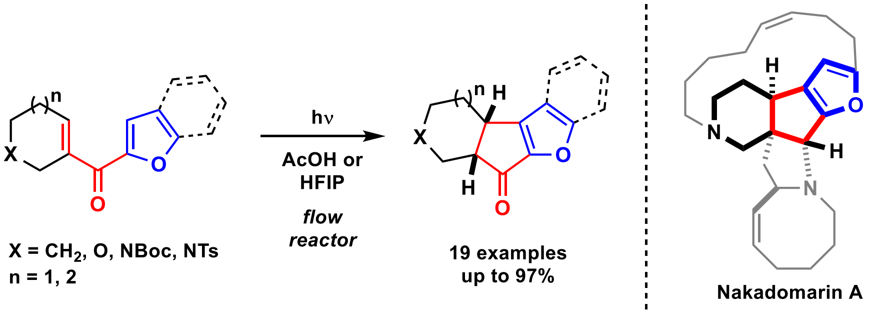
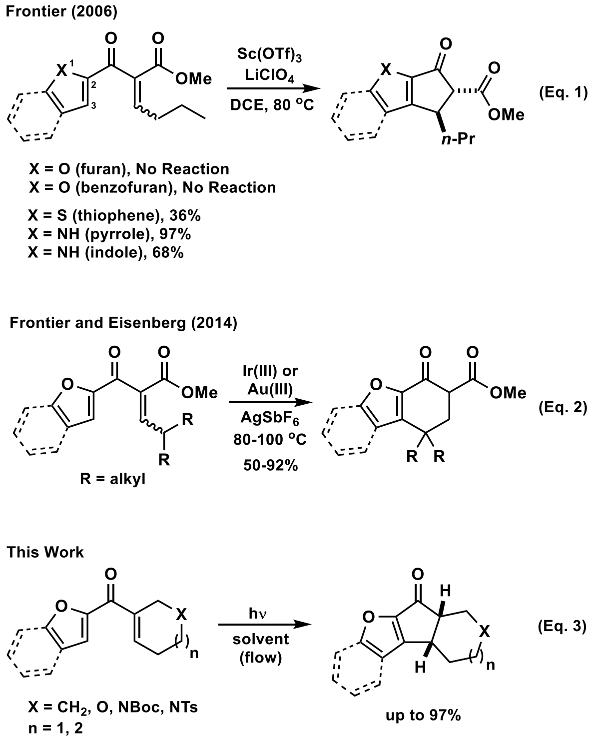


ABSTRACT: Nazarov reactions of 2-furyl vinyl ketones and related heteroaromatic enones, to produce furan-fused cyclopentanones using a flow photochemical approach, are described. Compounds possessing this connectivity between heterocycle and ketone (2-furyl, 2-benzofuryl, 2-thiophenyl, and 2-benzothiophenyl) have traditionally proven difficult or impossible to cyclize with typical Brønsted and Lewis acid mediated methods. Using mild flow photochemistry conditions and acetic acid (AcOH) or hexafluoroisopropanol (HFIP) as solvent, these compounds were found to cyclize in 45-97% yields, with typical UV exposure times of 3.4-6.8 minutes. In all cases, 2-furyl and 2-thiophenyl enones cyclized, whereas 2-benzofuryl and 2-benzothiophenyl enones exhibited divergent properties with reactivity patterns tied to the identity of the vinyl group. This report discloses the first photo-Nazarov reactions of tetrahydropyridine-substituted 2-furyl ketones, providing a direct approach to the corresponding fused heterocyclic motifs built around a central cyclopentanone. These motifs constitute the core structures of biologically-active natural products, including the marine alkaloid nakadomarin A.

INTRODUCTION

The Nazarov reaction of heteroaryl vinyl ketones offers direct access to heterocycle-fused cyclopentanones, substructures common to many biologically-active small molecules.[1] Concise synthetic routes to the ketone substrates, predictable stereo- and regioselectivity in the cyclization, and the versatility of the cyclopentenone products for subsequent transformation, render the aromatic Nazarov reaction a powerful synthetic tool, despite the attenuated reactivity of aryl vinyl ketones compared to other Nazarov substrates.[2] Natural products, including bruceolline E,[3] rocaglamide,[4] and merrilactone A,[5] have been constructed using the heteroaromatic Nazarov reaction as a key strategic step, employing heteroaryl vinyl ketones in which the heterocycles are connected via the 3-position to the carbonyl. The reaction works especially well for substrates having this connectivity;[6] however, the situation is more complicated for those in which the heterocycle is joined through the 2-position to the carbonyl: 2-pyrrolyl[7] and 2-indolyl[8] enones readily cyclize, whereas 2-thiophenyl[6, 9] and 2-benzothiophenyl[8d, 9f, 10] enones often afford low product yields or exhibit a complete lack of reactivity (Scheme 1, Eq. 1). Enones substituted with 2-furyl and 2-benzofuryl rings fail to cyclize altogether when subjected to typical Nazarov conditions using Brønsted or Lewis acids.[6, 9a, 11] Exceptions to this general observation are rare[12, 13, 14] with Flynn[15] and West[16] reporting the useful finding that some 2-furyl-substituted enones may be induced to cyclize using strong Brønsted acids through the introduction of an activating oxazolidinone substituent alpha to the carbonyl on the vinyl group. The characteristic reluctance of 2-furyl enones to undergo Nazarov cyclization is so pronounced that Frontier and Eisenberg have exploited this property and developed an entirely different cyclization pathway for these compounds in which a transition metal-mediated 1,2-hydride shift/intramolecular Friedel-Crafts alkylation sequence affords furan-fused cyclohexanones (Scheme 1, Eq. 2).[11a, 17]



Scheme 1. Reactions of heteroaryl vinyl ketones

Photochemical activation of aryl/heteroaryl vinyl ketones using UV light offers an alternative means of achieving aromatic Nazarov cyclization, under milder conditions than those usually employed with Lewis or Brønsted acid catalysis. Smith and Agosta's 1973 disclosure that simple aryl vinyl ketones undergo photo-Nazarov cyclization,[18] and subsequent mechanistic studies by Leitich and co-workers in 1991[19] and 2001[20] using 1-cyclohexenyl phenyl ketone, laid the groundwork for this important transformation. In 2009 and 2010, Chen and co-workers reported the first examples of the photo-Nazarov reaction in total synthesis, cyclizing substituted phenyl vinyl ketones as key steps in their approaches to the marine homosteroids nakiterpiosin[21] and nakiterpiosinone.[22] In 2010, Giannis also disclosed the synthesis of terpendole E analogues via photo-Nazarov reactions of 3-indolyl vinyl ketones.[23] A study of the reaction scope by Gao and co-workers finally appeared in 2014, demonstrating the range of substituted benzenes and heteroaromatics compatible with the transformation, including 3-thiophenyl and 3-benzothiophenyl vinyl ketones.[24] A total synthesis of gracilamine from this group soon followed.[25] However, among these photo-Nazarov disclosures, 2-furyl-substituted and 2-thiophenyl-substituted vinyl ketones remained conspicuously absent, leaving their viability in the reaction unknown. This gap is noteworthy given that a number of biologically-active natural products, including the marine alkaloid nakadomarin A,[26] Stemona alkaloids such as sessilifoliamide I,[27] and the homoisoflavonoid brazilide A,[28] are characterized by core structures derived from furan-fused cyclopentanones (Figure 1). Nakadomarin A, itself, has been the target of at least nine total syntheses,[29] two formal syntheses,[30] and numerous approaches to its polycyclic core,[31] none of which utilize a Nazarov reaction of a furan.[32, 33] If photo-Nazarov cyclization of 2-furyl vinyl ketones such as **1** (Figure 1) could be achieved, these natural products and similar compounds could be targeted using this transformation.

This report describes our investigation into these substrate classes (Scheme 1, Eq. 3) using flow photochemistry,[34] and also describes the outcomes observed when tetrahydropyridines are incorporated in the aryl vinyl ketone substrates. A flow photochemical approach was chosen at the outset for the advantages it offers over traditional batch reactions run in immersion well reactors. Uniform irradiation of the solution over shorter path lengths minimizes both the shielding effects of high concentration and side reactions due to overexposure.[34] Furthermore, anticipating the need for gram-scale quantities of the Nazarov products for future applications, it was recognized that scaling out, simply flowing larger volumes of solution at the same concentration under the same conditions, could be used, avoiding the iterative optimization often required of batch reaction scale-up.

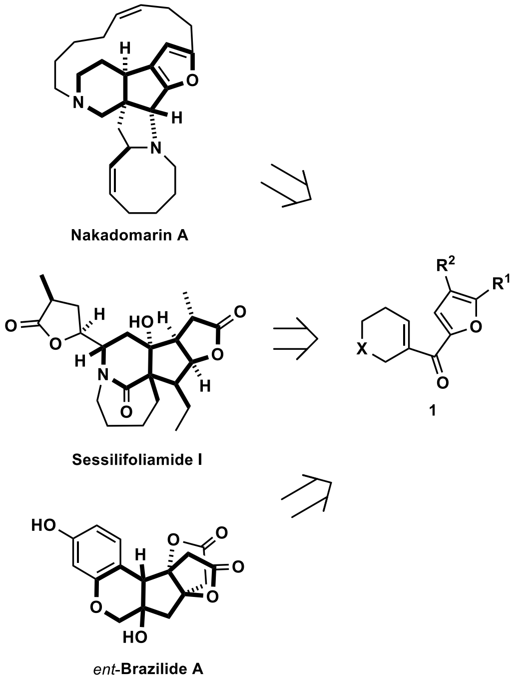


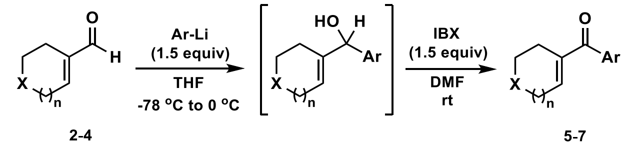
Figure 1. Natural product targets and strategy

RESULTS AND DISCUSSION

Synthesis of the requisite aryl vinyl ketones needed to begin the investigation was carried out as shown in Table 1. Addition of lithiated heterocycles to α,β-unsaturated aldehydes (**2**-**4**) was followed by oxidation of the resulting allylic alcohols using IBX in DMF.[35] Good-to-excellent yields of the aryl vinyl ketones (**5**-**7**) were generally obtained. DMP and PCC produced inferior results in the oxidation step, affording low yields of product mixtures.

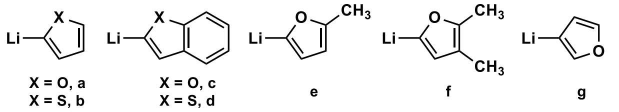
Cyclization of ketone **5a** was investigated first, using a simple flow photochemical apparatus adapted from the report by Booker-Milburn.[36] The setup consisted of fluorinated ethylene propylene (FEP) tubing (1.6 mm ID, 3.2 mm OD, 3.0 m length) wrapped around a double-walled borosilicate glass immersion well housing a medium pressure mercury vapor immersion lamp (Figure 2).[37] Ice-cooled water was flowed through the immersion well, and the solution of ketone was pumped through the FEP tubing at specified concentrations and flow rates using a syringe pump. An initial survey of solvents was conducted with 0.056 M solutions and a total exposure time of 3.4 minutes (flow rate = 1.8 mL/min) (Table 2). Gratifyingly, the desired photo-Nazarov product (**8**) was formed. Low yields (16-20%) were obtained in MeCN and 1,2-DCE, though **5a** was completely consumed (entries 1 and 3). Both solvents have been used in other photo-Nazarov applications.[21-24] Adding acetic acid (5.0 equivalents) to each solvent improved the yield of **8** (34-56%), though the effect was most pronounced in 1,2-DCE (entries 2 and 4). Starting material was again completely consumed. In the presence of acetic acid, the production of a complex mixture of polar byproducts is suppressed. Under the same conditions, trifluoroacetic acid produced **8** in 33% yield, but a significant quantity of unreacted starting material (40%) remained (entry 5). In glacial acetic acid,[19] the reaction went to completion, affording 72% of the desired cyclopentenone (entry 6). Doubling the exposure time to 6.8 minutes (flow rate = 0.9 mL/min) improved the yield to 86% (entry 8). Other variations in both concentration and exposure time

Table 1. Aryl vinyl ketone synthesis



Entry	Aldehyde	X	n	Ar-Li	Prod	Yield (%)
1	**2**	CH_2	1	a	**5a**	75
2	**2**	CH_2	1	b	**5b**	90
3	**2**	CH_2	1	c	**5c**	91
4	**2**	CH_2	1	d	**5d**	67
5	**2**	CH_2	1	e	**5e**	79
6	**2**	CH_2	1	f	**5f**	39
7	**2**	CH_2	1	g	**5g**	68
8	**3**	CH_2	2	a	**6a**	72
9	**3**	CH_2	2	b	**6b**	79
10	**3**	CH_2	2	c	**6c**	77
11	**4**	O	1	a	**7a**	60
12	**4**	O	1	b	**7b**	68
13	**4**	O	1	c	**7c**	78
14	**4**	O	1	d	**7d**	83
15	**4**	O	1	g	**7g**	54

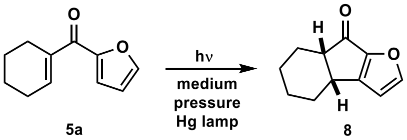
Ar-Li =



produced inferior results (entries 9-13). Hexafluoroisopropanol (HFIP)[38] was later discovered to be a particularly suitable solvent for photo-Nazarov reactions of tetrahydropyran-substituted aryl vinyl ketones, and while this solvent provided good results with compound **5a** (Table 2, entries 14-16), the results obtained in AcOH were generally superior. Control experiments in which **5a** was refluxed in the absence of UV irradiation, in either acetic acid or HFIP, failed to produce **8** after 48 hours. In acetic acid, starting material was recovered (62%) and the formation of an allylic oxidation product, 2-(furan-2-carbonyl)cyclohex-2-en-1-one, was observed (19%, entry 7), presumably the result of exposure to adventitious atmospheric oxygen. In HFIP, unreacted starting material was quantitatively recovered (entry 17).

Figure 2. Flow photochemistry setup with syringe pump

Table 2. Photo-Nazarov optimization



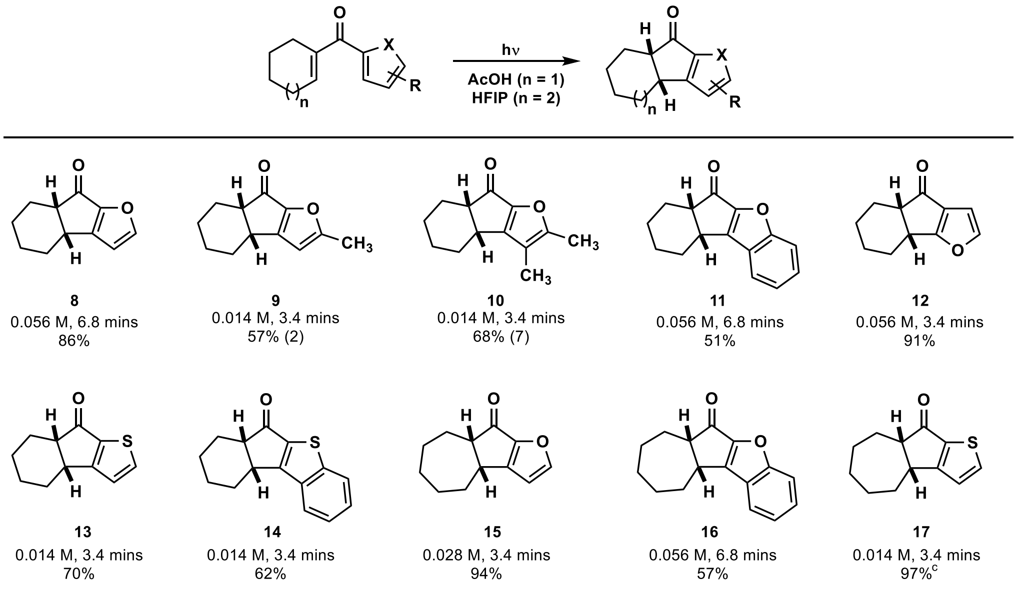
Entry	Solvent	Concentration (M)	Exposure Time	Yield (%)
1	MeCN	0.056	3.4 min	16
2	MeCN/AcOH[a]	0.056	3.4 min	34[b]
3	1,2-DCE	0.056	3.4 min	20
4	1,2-DCE/AcOH[a]	0.056	3.4 min	56
5	CF_3CO_2H	0.056	3.4 min	33 (40)[c]
6	AcOH	0.056	3.4 min	72
7	AcOH	0.056	reflux, 48 h[d]	0 (62)[c,e]
8	**AcOH**	**0.056**	**6.8 min**	**86**
9	AcOH	0.056	2.3 min	52
10	AcOH	0.028	3.4 min	68
11	AcOH	0.028	17 min	65
12	AcOH	0.028	34 min	43
13	AcOH	0.112	3.4 min	49
14	HFIP	0.056	3.4 min	55 (32)[c]
15	HFIP	0.028	3.4 min	76 (5)[c]

16	HFIP	0.014	3.4 min	74
17	HFIP	0.056	reflux, 48 h[d]	0 (100)[c]

[a] 5.0 equiv of AcOH added to solvent. [b] Contains small impurity. [c] Number in parentheses indicates recovered starting material. [d] Reaction mixture was refluxed 48 h in the absence of UV light. [e] Allylic oxidation byproduct, 2-(furan-2-carbonyl)cyclohex-2-en-1-one, also recovered (19%).

Following the initial survey of solvents and conditions for cyclization of **5a**, an expanded study of the furan- and thiophene-containing cyclohexenyl aryl vinyl ketones from Table 1 was initiated. It was soon determined that one set of reaction conditions was not optimal for all substrates. Therefore, a series of flow conditions was evaluated for each heteroaryl vinyl ketone, varying concentration and UV exposure time using AcOH as solvent. All substrates investigated underwent successful photo-Nazarov cyclization, and the best results for each compound are provided in Table 3.[39] Importantly, the results of this study demonstrated that substitution at both the 4-postion and 5-position of the furan was tolerated, as evidenced by the cyclization of substrates bearing 5-methylfuran; 4,5-dimethylfuran; and benzofuran heteroaromatics, to produce **9**-**11** (51-68%). Substrates bearing 2-thiophenyl and 2-benzothiophenyl groups also cyclized in good yields, affording **13**-**14** (62-70%). The 3-furylketone isomer delivered the highest yield among the cyclohexenyl substrates, producing 91% of **12**. As noted in Table 2, hexafluoroisopropanol (HFIP) was also a suitable solvent for the photo-Nazarov reaction, but superior results were obtained using AcOH for both cyclohexenyl substrates **5a** and **5b** (producing **8** and **13**, respectively).[39] The results with cycloheptenyl ketones in HFIP were very different, with good-to-excellent yields obtained for furan-, benzofuran-, and thiophene-substituted compounds (**15**-**17**, Table 3). The cis configurations of the ring-fused cyclopentanone products were confirmed by comparison of NMR coupling constants and distinctive chemical shifts for the ring-junction hydrogens to data reported for similar compounds synthesized via photo-Nazarov reaction, whose structures were confirmed by X-ray crystallography.[24,40]

Table 3. Photo-Nazarov reactions of 2-furyl and 2-thiophenyl enones[a,b]



8
0.056 M, 6.8 mins
86%

9
0.014 M, 3.4 mins
57% (2)

10
0.014 M, 3.4 mins
68% (7)

11
0.056 M, 6.8 mins
51%

12
0.056 M, 3.4 mins
91%

13
0.014 M, 3.4 mins
70%

14
0.014 M, 3.4 mins
62%

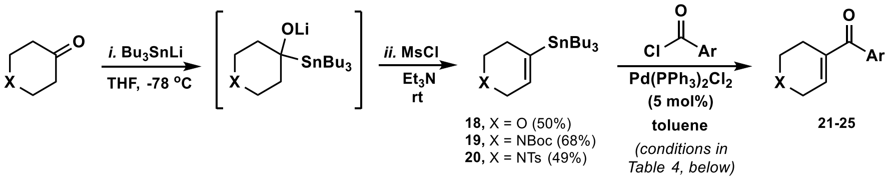
15
0.028 M, 3.4 mins
94%

16
0.056 M, 6.8 mins
57%

17
0.014 M, 3.4 mins
97%[c]

[a] Numbers in parentheses indicate recovered starting material. [b] 3.4 min exposure time corresponds to a flow rate of 1.8 mL/min; 6.8 min exposure time corresponds to a flow rate of 0.9 mL/min. [c] dr = 20:1

The prevalence of 6-membered heterocycles in natural products and compounds of pharmaceutical importance prompted us to next evaluate a series of dihydropyranyl and tetrahydropyridyl aryl vinyl ketones substituted with furans and thiophenes. Aryl vinyl ketones derived from dihydropyranyl aldehyde **4** were synthesized as shown in Table 1. The remaining heterocyclic substrates were made by routes involving Stille cross-coupling reactions of acid chlorides and vinyl or aryl stannanes.[41] Vinyl stannane synthesis was carried out as shown in Scheme 2.[42] Addition of Bu_3SnLi (3.0 equiv), generated *in situ* from LDA and Bu_3SnH, to tetrahydro-4*H*-pyran-4-one, followed by treatment of the intermediate alkoxide with MsCl (4.0 equiv) and Et_3N (7.5 equiv), led smoothly to the desired vinyl stannane **18** in 50% yield. However, using N-Boc and N-Ts protected 4-piperidone, three separate additions of MsCl (4.0 equiv) and Et_3N (7.5 equiv), at 4-hour intervals, were required to drive the intermediate alkoxides to vinyl stannane products (**19** and **20**). With vinyl stannanes in hand, Stille couplings were carried out using the appropriate acid chlorides, producing aryl vinyl ketones **21**-**25**. The conditions used to synthesize each ketone are shown in Table 4.



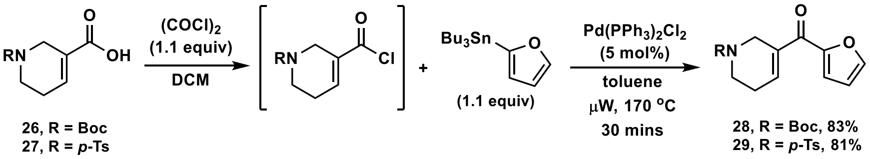
Scheme 2. Aryl vinyl ketone synthesis

Table 4. Stille coupling conditions for aryl vinyl ketone synthesis

Entry	Stannane	X	Ar =	Temp (°C)	Time	Prod	Yield (%)
1	**18**	O	2-furyl[a]	115	18 hrs	**21**	86
2	**18**	O	2-thiophenyl[b]	170 (μw)	35 mins	**22**	77
3	**18**	O	2-benzofuryl[b]	170 (μw)	35 mins	**23**	55
4	**19**	NBoc	2-furyl[c]	125 (μw)	20 mins	**24**	70
5	**20**	NTs	2-furyl[c]	90	30 mins	**25**	70

[a] 2-Furoyl chloride limiting (1.0 equiv), with **18** (1.1 equiv) and $Pd(PPh_3)_2Cl_2$ (0.025equiv). [b] Acyl chloride used in excess (1.1 equiv). [c] 2-Furoyl chloride used in excess (1.5 equiv).

Synthesis of the isomeric N-Boc and N-Ts protected tetrahydropyridyl aryl vinyl ketones leading to the fused tricyclic core of nakadomarin A was conducted according to Scheme 3. Conversion of **26** and **27**, obtained from 1,2,5,6-tetrahydropyridine-3-carboxylic acid hydrochloride, to the corresponding acid chlorides was carried out using $(COCl)_2$ in CH_2Cl_2. Following solvent exchange, Stille coupling with 2-(tributylstannyl)furan afforded ketones **28** and **29**.[41]

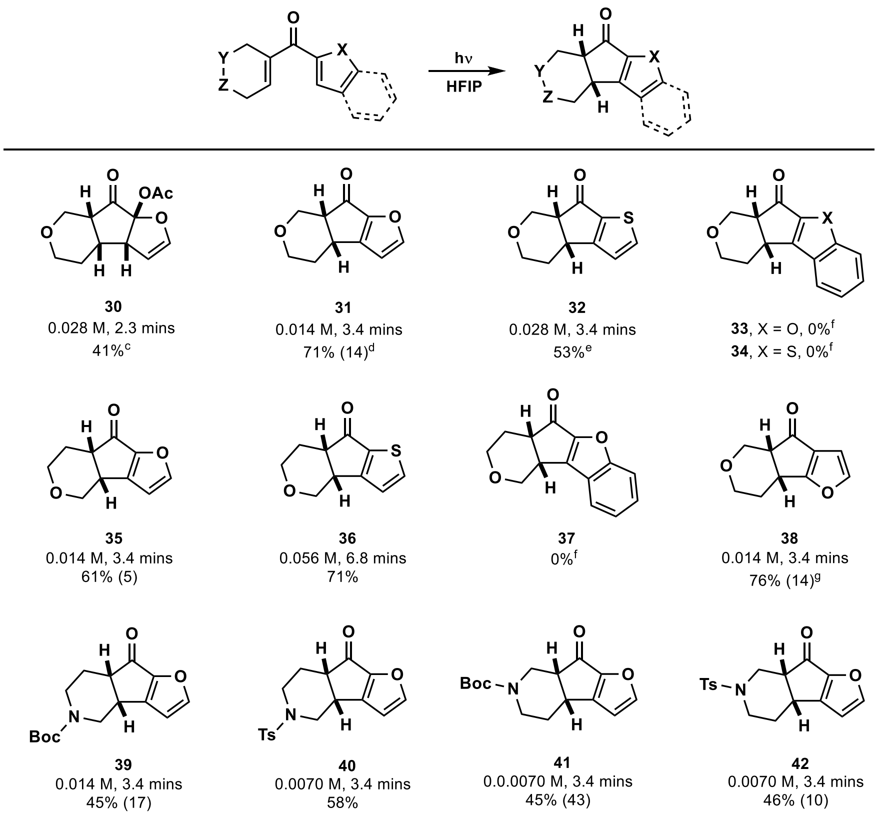


Scheme 3. Synthesis of aryl vinyl ketones via Stille coupling

With routes to the necessary heterocyclic aryl vinyl ketones developed, cyclization of dihydropyranyl ketone **7a** (Table 1) was undertaken, and the results are shown in Table 5. In contrast to the outcomes obtained with carbocyclic analogs **5a** and **6a**, an unexpected interrupted Nazarov cyclization occurred in HOAc, affording **30** as the major product. Prior studies of interrupted Nazarov reactions suggest compound **30** results from nucleophilic attack of AcOH on the convex face of the oxyallyl intermediate (**45**, Scheme 4) formed upon ring closure.[43] Only small quantities of the desired fused furan **31** (< 10%) were isolated. No reaction occurred when **7a** was irradiated in CF_3CO_2H. Gratifyingly, the expected Nazarov product (**31**) was formed in good yields using HFIP, though some unreacted starting material was recovered under most conditions.[39] Interestingly, using AcOH as solvent, no interrupted Nazarov products were obtained for analogs of **7a** in which the 2-furyl group was replaced by either a 2-thiophenyl (**7b**) or the isomeric 3-furyl (**7g**) group. Instead, the expected fused furan compounds **32** and **38** were formed.

Continuing with HFIP as solvent, good yields of cyclized products were obtained for both series of isomeric dihydropyranyl ketones substituted with 2-furyl (producing **31** and **35**) and 2-thiophenyl (producing **32** and **36**) groups. However, the corresponding benzofuran- and benzothiophene-substituted compounds failed to cyclize in both series, using either HFIP or AcOH. This contrasts with the results obtained for the corresponding carbocyclic substrates, which afforded the expected benzofuran- and benzothiophene-fused cyclopentanones **11**, **14** and **16** in good yields (Table 3). The isomeric 3-furyl ketone again cyclized in highest yield with this series, affording 76% of **38**. Both Ts- and Boc-protected 4-furoyl-substituted 1,2,3,6-tetrahydropyridine substrates (**24** and **25**, Table 4) underwent cyclization, affording **39** and **40**. The isomeric 3-furoyl-substituted 1,2,5,6-tetrahydropyridines (**28** and **29**, Scheme 3) also cyclized, affording **41** and **42**, the tricyclic structures found at the core of nakadomarin A. However, significant quantities of unreacted starting materials (10-43%) were usually recovered under the full range of concentrations and UV exposure times evaluated as part of the standard survey. Notably, while maintaining a consistent 3.4-minute exposure time, a clear correlation between concentration and yield emerged, with the best results (45-58% yields) typically obtained under the most dilute conditions.[39]

Table 5. Photo-Nazarov reactions of heterocyclic aryl vinyl ketones[a,b]



30
0.028 M, 2.3 mins
41%[c]

31
0.014 M, 3.4 mins
71% (14)[d]

32
0.028 M, 3.4 mins
53%[e]

33, X = O, 0%[f]
34, X = S, 0%[f]

35
0.014 M, 3.4 mins
61% (5)

36
0.056 M, 6.8 mins
71%

37
0%[f]

38
0.014 M, 3.4 mins
76% (14)[g]

39
0.014 M, 3.4 mins
45% (17)

40
0.0070 M, 3.4 mins
58%

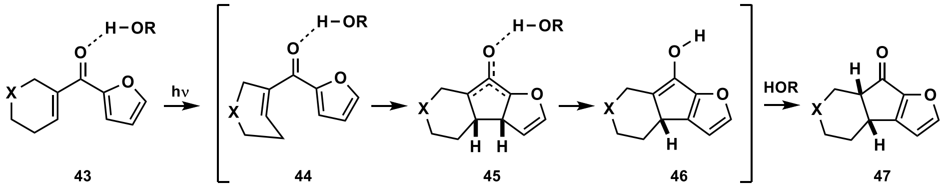
41
0.0.0070 M, 3.4 mins
45% (43)

42
0.0070 M, 3.4 mins
46% (10)

[a] Numbers in parentheses indicate recovered starting material. [b] 2.3 min exposure time corresponds to a flow rate of 2.7 mL/min; 3.4 min exposure time corresponds to a flow rate of 1.8 mL/min; 6.8 min exposure time corresponds to a flow rate of 0.9 mL/min. [c] Reaction conducted in AcOH. Stereochemical assignment assumes attack of AcOH on convex face of **45** (Scheme 4). [d] Recovered starting material contains impurities. [e] With 0.056M AcOH, 3.4 mins: 43% yield. [f] All unreacted starting material. [g] With 0.056M AcOH, 3.4 mins: 58% yield.

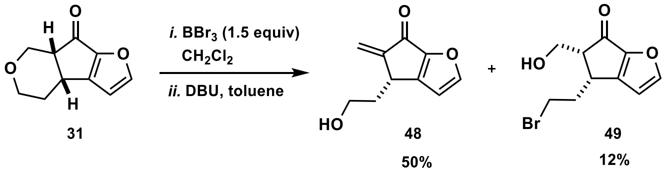
Mechanistically, prior studies have concluded that photo-Nazarov reactions likely occur by photo-mediated *E*-to-*Z* isomerization of the cyclic olefin, creating a strained ground state intermediate which undergoes thermal conrotatory cyclization (Scheme 4).[19,44] Orbital symmetry considerations[45] for both this pathway and that involving disrotatory ring closure of a photo-excited state lead to the same stereochemical outcomes in the formation of the oxyallyl intermediate (**45** in Scheme 4), so this aspect of the reaction does not provide mechanistic insight. Indirect support for the Scheme 4 pathway includes the observation that 6- or 7-membered cyclic olefins are required as the vinyl component of the aryl vinyl ketone. Aryl vinyl ketones containing 5- and 8-membered carbocyclic olefins fail to cyclize, apparently geometrically precluded from isomerizing or insufficiently strained to induce cyclization upon isomerization.[46] Furthermore, low-temperature NMR studies and trapping experiments involving photo-initiated Nazarov reactions of medium-ring dienones[44] and 1-cyclohexenyl phenyl ketone[19] have provided further evidence for the intermediacy of a strained ground state cyclic olefin cyclization precursor (**44** in Scheme 4).

The success of AcOH and HFIP as solvents for the photo-Nazarov reaction may relate, in part, to acid- or hydrogen-bond-mediated acceleration of the cyclization (**44** to **45)**. However, Leitich and co-workers have also found that the enol resulting from cyclization of 1-cyclohexenyl phenyl ketone (an analog of **46**) is readily oxidized by residual atmospheric oxygen in acetonitrile, producing the corresponding α-hydroxy ketone, which decomposes with further UV irradiation.[19] When the reaction was run in acetic acid, under an atmosphere of oxygen, this undesired oxidation was suppressed, likely due to acid-catalyzed acceleration of the enol tautomerization to ketone.



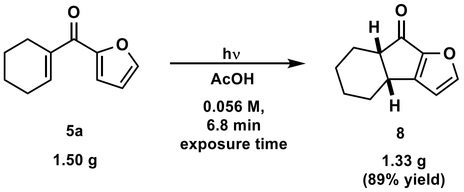
Scheme 4. Proposed photo-Nazarov cyclization mechanism

The photo-Nazarov requirement that the vinyl moiety be constrained within a ring should not be seen as unduly restricting the utility of the method for applications in which the ring is not desired. Cleavage of the pyran of tricycle **31** with BBr_3, followed by treatment of the intermediate β-bromoketone with DBU, affords α,β-unsaturated ketone **48** (Scheme 5). β-Hydroxy ketone **49** is also isolated as a minor product. The many transformations available to further elaborate both α,β-unsaturated ketones and primary alcohols should enable the synthesis of a variety of substituted heterocycle-fused cyclopentanones.



Scheme 5. Pyran cleavage

Finally, a particularly attractive feature of flow chemistry is its ready scalability. With the goal of producing sufficient quantities of tricyclic furan-fused cyclopentanone **8** for further applications, 1.50 g of ketone **5a** (0.056 M in glacial acetic acid) was subjected to continuous flow UV irradiation (Scheme 6). Using our syringe pump setup (Figure 2), 152 mL of solution was flowed using 60-mL syringes and an exposure time of 6.8 minutes. Irradiation of the entire volume under these conditions required just under 3 hours (170 minutes), and delivered 1.33 g of product (89%), following aqueous work-up and column chromatography.



Scheme 6. Scale-out of heteroaromatic photo-Nazarov reaction

CONCLUSIONS

In summary, the viability of 2-furyl vinyl ketones as substrates for the photo-Nazarov cyclization has been demonstrated, providing access to a range of tricyclic 2-furan-fused cyclopentanone structures not generally accessible via other approaches to Nazarov cyclization. Substrates bearing 2-thiophenes were found to be similarly viable. Cyclohexenyl, cycloheptenyl, dihydropyranyl, and tetrahydropyridyl moieties were all suitable as cyclic vinyl groups, affording moderate to excellent yields of cyclization products using the flow photochemistry conditions investigated. Notably, aryl vinyl ketones composed of 2-benzofuran and 2-benzothiophene cyclized when carbocyclic olefin moieties were present, but did not cyclize with dihydropyrans. Both AcOH and HFIP were generally useful solvents for the photo-Nazarov reaction. This work demonstrates the first examples of photo-Nazarov cyclizations of aryl vinyl ketones substituted with tetrahydropyridines, establishing the groundwork for further application to the synthesis of alkaloids such as nakadomarin A, sessilifoliamide I, and related compounds.

EXPERIMENTAL SECTION

General Information. Thin layer chromatography (TLC) was performed using glass plates coated with silica gel (20 μm thickness/10 μm particle size) containing a fluorescent indicator (UV 254 nm). Visualization was accomplished using UV light (254 nm) and/or basic potassium permanganate in water with heating. Flash column chromatography was performed using silica gel (Dynamic Adsorbents: Flash grade, 32-63 μm, 60 Å, or Silicycle: SiliaFlash F60, 40-63 μm, 230-400 mesh) with compressed air as a source of positive pressure. Microwave reactions were run in sealed vials using a CEM Corporation MARS 6 microwave synthesizer with an internal fiber optic probe. ^{1}H and ^{13}C (^{1}H broad-band decoupled mode) NMR spectra were recorded on a Bruker Avance (600 MHz ^{1}H/150 MHz ^{13}C) or a Bruker-300 Ultrashield NMR (300 MHz ^{1}H/75 MHz ^{13}C) with a SampleCase™ operated using IconNMR™ and TopSpin™ software. Chemical shifts are reported in parts per million (ppm) from tetramethylsilane and referenced to the center line of the solvent: $CDCl_3$ with $\underline{CH}Cl_3$ as internal reference (7.26 ppm for ^{1}H and 77.23 ppm for ^{13}C). Coupling constants are reported in Hertz (Hz). Infrared (IR) spectra were acquired on a Nicolet 6700 FT-IR or a Nicolet iS5 FT-IR, and absorptions are reported in cm^{-1}. Peaks are reported with the following relative intensities: s (strong, 67-100%), m (medium, 40-67%), and w (weak, 20-40%), and br (broad). High resolution mass spectra were obtained using an Agilent 1290 Infinity UHPLC with Bruker Microtof-Q II high resolution mass spectrometer with a time of flight (TOF) mass analyzer and an electrospray ion source (ESI). Photoreactions were conducted using a medium pressure mercury vapor immersion lamp (450 W, 125-145 V, 3.6 A, 244.4 mm total length, 131.5 mm arc),[37] supplied by Ace Glass and purchased from VWR. Hexafluoroisopropanol (HFIP) was purchased from Oakwood Chemical, 1-cyclohexene-1-carboxaldehyde was purchased from Sigma-Aldrich, and 1,2,5,6-tetrahydro-3-pyridinecarboxylic acid hydrochloride was purchased from ChemBridge Corporation.

Synthesis of heteroaryl vinyl ketones 5-7. Adapting literature procedures,[24, 35] *n*-BuLi (1.6 M in hexanes, 1.55 equiv) was added to a solution of heteroaromatic (1.50 equiv) in anhydrous tetrahydrofuran (0.13 mol aldehyde/L) at 0 °C under argon. After addition of *n*-BuLi was complete, the solution was warmed to room temperature and stirred. After 1 h, the solution was cooled to -78 °C in a dry ice/acetone bath, and aldehyde (**2**-**4**, 1.00 equiv) was added dropwise. The solution continued to stir at -78 °C for 1 h, and was then warmed to 0 °C and quenched with water (10 mL). The biphasic mixture was transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 15 mL), and the combined organic layers were washed with brine (25 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give the crude secondary alcohol. *o*-Iodoxybenzoic acid (IBX) (1.50 equiv) was added to a solution of the crude alcohol in dimethylformamide (5 mL/mmol IBX), and the mixture was stirred at room temperature for 1 h. Water

(10 mL) was added to the flask and stirring was continued for 5 min. Precipitated solids were filtered off using a Buchner funnel, and the solids were rinsed with EtOAc (15 mL). The filtrate was transferred to a separatory funnel and the layers were separated. The organic layer was washed with water (3 × 15 mL), dried over magnesium sulfate, and concentrated under reduced pressure. The crude reaction mixture was purified by silica gel column chromatography, affording ketones **5**-**7** (see details below for each product). When 3-bromofuran was used as the heteroaromatic, the reaction was cooled to -78 °C before addition of *n*-BuLi. The reaction was then stirred for 20 minutes at -78 °C before the aldehyde was added.

Cyclohex-1-en-1-yl(furan-2-yl)methanone, (5a). Prepared from 1-cyclohexene-1-carboxaldehyde (**2**) and furan. Purified via silica gel column chromatography using 10% EtOAc in hexanes, affording a yellow oil (220 mg, 1.25 mmol, 75% yield). Spectroscopic data were consistent with literature values.[47]

Cyclohex-1-en-1-yl(thiophen-2-yl)methanone, (5b). Prepared from 1-cyclohexene-1-carboxaldehyde (**2**) and thiophene. Purified via silica gel column chromatography using 10% EtOAc in hexanes, affording a yellow oil (346 mg, 1.80 mmol, 90% yield). Spectroscopic data were consistent with literature values.[47]

Benzofuran-2-yl(cyclohex-1-en-1-yl)methanone, (5c). Prepared from 1-cyclohexene-1-carboxaldehyde (**2**) and 2,3-benzofuran. Purified via silica gel column chromatography using 10% EtOAc in hexanes, affording a yellow solid (mp = 52-53 °C) (413 mg, 1.83 mmol, 91% yield). TLC: R_f = 0.52, (10% EtOAc in hexanes). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.68 (d, *J* = 7.8 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.46-7.43 (m, 1H), 7.38 (d, *J* = 0.8 Hz, 1H), 7.31-7.28 (m, 1H), 7.12-7.10 (m, 1H), 2.46-2.43 (m, 2H), 2.36-2.33 (m, 2H), 1.77-1.68 (m, 4H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 185.7, 155.9, 152.5, 142.3, 138.8, 127.9, 127.1, 123.9, 123.2, 114.7, 112.6, 26.4, 24.2, 22.1, 21.8. IR (cm^{-1}): 2933 (m), 1636 (s). HRMS: Calculated for $C_{15}H_{14}NaO_2$ ([M+Na]$^+$): 249.0886. Found: 249.0893.

Benzo[*b*]thiophen-2-yl(cyclohex-1-en-1-yl)methanone, (5d). Prepared from 1-cyclohexene-1-carboxaldehyde (**2**) and benzo[*b*]thiophene. Purified via silica gel column chromatography using 10% EtOAc in hexanes, affording a yellow solid (mp = 82-83 °C) (252 mg, 1.04 mmol, 67% yield). TLC: R_f = 0.34, (10% EtOAc in hexanes). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.87 (d, *J* = 8.2 Hz, 2H), 7.80 (s, 1H), 7.44 (t, *J* = 7.4 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 1H), 6.90-6.88 (m, 1H), 2.47-2.43 (m, 2H), 2.36-2.32 (m, 2H), 1.79-1.69 (m, 4H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 190.8, 143.3, 142.4, 141.5, 139.1, 139.0, 130.1, 127.1, 125.9, 125.0, 123.0, 26.3, 24.6, 22.2, 21.9. IR (cm^{-1}): 2925 (m), 2855 (m), 1625 (s), 1513 (m). HRMS: Calculated for $C_{15}H_{14}NaOS$ ([M+Na]$^+$): 265.0658. Found: 265.0669.

Cyclohex-1-en-1-yl(5-methylfuran-2-yl)methanone, (5e). Prepared from 1-cyclohexene-1-carboxaldehyde (**2**) and 2-methylfuran. Purified via silica gel column chromatography using 10% EtOAc in hexanes, affording a light yellow oil (219 mg, 1.15 mmol, 79% yield). TLC: R_f = 0.31, (10% EtOAc in hexanes). ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.97 (d, *J* = 3.4 Hz, 1H), 6.84-6.81 (m, 1H), 6.12 (d, *J* = 3.1 Hz, 1H), 2.40 (s, 3H), 2.39-2.36 (m, 2H), 2.29-2.24 (m, 2H), 1.73-1.64 (m, 4H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 184.0, 157.9, 151.0, 139.4, 138.6, 121.1, 108.6, 26.1, 24.4, 22.2, 21.9, 14.3. IR (cm^{-1}): 2925 (m), 2857 (m), 1632 (s), 1512 (s). HRMS: Calculated for $C_{12}H_{14}NaO_2$ ([M+Na]$^+$): 213.0886. Found: 213.0890.

Cyclohex-1-en-1-yl(4,5-dimethylfuran-2-yl)methanone, (5f). Prepared from 1-cyclohexene-1-carboxaldehyde (**2**) and 2,3-dimethylfuran. Purified via silica gel column chromatography using 10% EtOAc in hexanes, affording a light yellow oil (127 mg, 0.62 mmol, 39% yield). TLC: R_f = 0.31, (10% EtOAc in hexanes). ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.86 (s, 1H), 6.80-6.77 (m, 1H), 2.39-2.34 (m, 2H), 2.29 (s, 3H), 2.27-2.23 (m, 2H), 1.97 (s, 3H), 1.71-1.63 (m, 4H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 184.0, 153.9, 149.6, 138.9, 138.6, 123.3, 117.2, 26.1, 24.5, 22.2, 21.9, 12.2, 9.9. IR (cm^{-1}): 2927 (m), 2859 (m), 1633 (s), 1515 (s). HRMS: Calculated for $C_{13}H_{16}NaO_2$ ([M+Na]$^+$): 227.1043. Found: 227.1048.

Cyclohex-1-en-1-yl(furan-3-yl)methanone, (5g). Prepared from 1-cyclohexene-1-carboxaldehyde (**2**) and 3-bromofuran. Purified via silica gel column chromatography using 20% EtOAc in hexanes, affording a yellow oil (240 mg, 1.36 mmol, 68% yield). TLC: R_f = 0.58, (20% EtOAc in hexanes). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.80 (s, 1H), 7.42 (t, *J* = 1.7 Hz, 1H), 6.80-6.77 (m, 1H), 6.75 (d, *J* = 1.8 Hz, 1H), 2.41-2.37 (m, 2H), 2.29-2.25 (m, 2H), 1.74-1.65 (m, 4H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 190.7, 146.8, 143.7, 140.5, 140.3, 126.4, 110.5, 26.2, 24.2, 22.2, 22.0. IR (cm^{-1}): 2927 (s), 2857 (m), 1639 (s). HRMS: Calculated for $C_{11}H_{12}NaO_2$ ($[M+Na]^+$): 199.0730. Found: 199.0735.

Cyclohept-1-en-1-yl(furan-2-yl)methanone, (6a). Prepared from 1-cycloheptene-1-carboxaldehyde (**3**)[48] and furan. Purified via silica gel column chromatography using 10% EtOAc in hexanes, affording a brown amorphous solid (273 mg, 1.43 mmol, 72% yield). TLC: R_f = 0.36, (10% EtOAc in hexanes). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.60 (s, 1H), 7.03 (d, *J* = 3.5 Hz, 1H), 6.98 (t, *J* = 6.7 Hz, 1H), 6.50-6.48 (m, 1H), 2.58-2.55 (m, 2H), 2.40-2.35 (m, 2H), 1.84-1.79 (m, 2H), 1.62-1.55 (m, 4H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 185.1, 152.3, 146.6, 145.2, 145.1, 119.2, 111.8, 32.5, 29.5, 28.4, 26.8, 26.2. IR (cm^{-1}): 2922 (s), 2851 (m), 1640 (s), 1631 (s), 1466 (s). HRMS: Calculated for $C_{24}H_{28}NaO_4$ ($[2M+Na]^+$): 403.1880. Found: 403.1885.

Cyclohept-1-en-1-yl(thiophen-2-yl)methanone, (6b). Prepared from 1-cycloheptene-1-carboxaldehyde (**3**)[48] and thiophene. Purified via silica gel column chromatography using 10% EtOAc in hexanes, affording a brown solid (mp = 40-41 °C) (488 mg, 2.37 mmol, 79% yield). TLC: R_f = 0.50, (10% EtOAc in hexanes). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.60 (d, *J* = 5.0 Hz, 1H), 7.56 (d, *J* = 3.7 Hz, 1H), 7.09 (t, *J* = 4.4 Hz, 1H), 6.87 (t, *J* = 6.6 Hz, 1H), 2.60-2.56 (m, 2H), 2.40-2.36 (m, 2H), 1.86-1.81 (m, 2H), 1.63-1.58 (m, 4H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 190.5, 145.5, 144.8, 144.0, 133.4, 133.1, 127.7, 32.5, 29.4, 29.0, 26.8, 26.3. IR (cm^{-1}): 2920 (s), 2850 (m), 1625 (s), 1413 (s). HRMS: Calculated for $C_{24}H_{28}NaO_2S_2$ ($[2M+Na]^+$): 435.1423. Found: 435.1434.

Benzofuran-2-yl(cyclohept-1-en-1-yl)methanone, (6c). Prepared from 1-cycloheptene-1-carboxaldehyde (**3**)[48] and 2,3-benzofuran. Purified via silica gel column chromatography using 10% EtOAc in hexanes, affording a yellow-brown solid (mp = 62-64 °C) (554 mg, 2.31 mmol, 77% yield). TLC: R_f = 0.49, (10% EtOAc in hexanes). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.69 (d, *J* = 7.8 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.45 (t, *J* = 7.8 Hz, 1H), 7.35 (s, 1H), 7.30 (t, *J* = 7.5 Hz, 1H), 7.14 (t, *J* = 6.6 Hz, 1H), 2.66-2.62 (m, 2H), 2.46-2.41 (m, 2H), 1.89-1.83 (m, 2H), 1.67-1.60 (m, 4H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 186.7, 156.0, 152.5, 146.5, 145.4, 127.9, 127.2, 123.9, 123.2, 115.0, 112.7, 32.5, 29.7, 28.4, 26.8, 26.2. IR (cm^{-1}): 2921 (m), 2851 (w), 1637 (s), 1547 (s). HRMS: Calculated for $C_{32}H_{32}NaO_4$ ($[2M+Na]^+$): 503.2193. Found: 503.2207.

(5,6-Dihydro-2*H*-pyran-3-yl)(furan-2-yl)methanone, (7a). Prepared from 5,6-dihydro-2*H*-pyran-3-carbaldehyde (**4**)[49] and furan. Purified via silica gel column chromatography using 33% EtOAc in hexanes, affording a yellow-brown solid (mp = 39-41 °C) (178 mg, 1.00 mmol, 60% yield). TLC: R_f = 0.10, (10% EtOAc in hexanes). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.62 (d, *J* = 0.9 Hz, 1H), 7.21-7.18 (m, 1H), 7.16 (d, *J* = 3.5 Hz, 1H), 6.53 (dd, *J* = 3.5 Hz, 1.7 Hz, 1H), 4.49-4.47 (m, 2H), 3.83 (t, *J* = 5.5 Hz, 2H), 2.45-2.40 (m, 2H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 181.0, 152.2, 146.7, 138.3, 137.5, 119.1, 112.1, 65.0, 63.7, 25.9. IR (cm^{-1}): 2924 (s), 2857 (m), 1630 (s), 1463 (m). HRMS: Calculated for $C_{10}H_{10}NaO_3$ ($[M+Na]^+$): 201.0522. Found: 201.0526.

(5,6-Dihydro-2*H*-pyran-3-yl)(thiophen-2-yl)methanone, (7b). Prepared from 5,6-dihydro-2*H*-pyran-3-carbaldehyde (**4**)[49] and thiophene. Purified via silica gel column chromatography using 20% EtOAc in hexanes, affording a yellow solid (mp = 63-64 °C) (266 mg, 1.37 mmol, 68% yield). TLC: R_f = 0.35, (20% EtOAc in hexanes). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.65-7.63 (m, 2H), 7.12 (dd, *J* = 4.6 Hz, 3.9 Hz, 1H), 6.95-6.92 (m, 1H), 4.50-4.48 (m, 2H), 3.85 (t, *J* = 5.5 Hz, 2H), 2.44-2.40 (m, 2H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 186.8, 142.8, 138.2, 137.4, 133.5, 133.3, 127.9, 65.3, 63.7, 25.8. IR (cm^{-1}): 2962 (w), 2922 (w), 2850 (w), 1617 (s), 1415 (s). HRMS: Calculated for $C_{10}H_{10}NaO_2S$ ($[M+Na]^+$): 217.0294. Found: 217.0298.

Benzofuran-2-yl(5,6-dihydro-2*H*-pyran-3-yl)methanone, (7c). Prepared from 5,6-dihydro-2*H*-pyran-3-carbaldehyde (**4**)[49] and 2,3-benzofuran. Purified via silica gel column chromatography using

33% EtOAc in hexanes, affording a yellow solid (mp = 80-81 °C) (355 mg, 1.55 mmol, 78% yield). TLC: R_f = 0.36, (20% EtOAc in hexanes). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.69 (d, *J* = 7.8 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.47-7.44 (m, 2H), 7.36-7.33 (m, 1H), 7.30 (t, *J* = 7.5 Hz, 1H), 4.54-4.51 (m, 2H), 3.85 (t, *J* = 5.5 Hz, 2H), 2.49-2.45 (m, 2H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 182.6, 155.9, 152.1, 139.5, 137.7, 128.2, 126.9, 124.1, 123.3, 114.9, 112.5, 64.9, 63.6, 26.0. IR (cm^{-1}): 2919 (w), 2850 (w), 1634 (m), 1548 (m). HRMS: Calculated for $C_{14}H_{12}NaO_3$ ([M+Na]$^+$): 251.0679. Found: 251.0689.

Benzo[*b*]thiophen-2-yl(5,6-dihydro-2*H*-pyran-3-yl)methanone, (7d). Prepared from 5,6-dihydro-2*H*-pyran-3-carbaldehyde (**4**)[49] and benzo[*b*]thiophene. Purified via silica gel column chromatography using 33% acetone in hexanes, affording a yellow solid (mp = 71-75 °C) (406 mg, 1.66 mmol, 83% yield). TLC: R_f = 0.34, (20% EtOAc in hexanes). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.88 (dd, *J* = 8.0 Hz, 4.4 Hz, 2H), 7.86 (s, 1H), 7.47 (t, *J* = 7.6 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.04-7.02 (m, 1H), 4.54-4.52 (m, 2H), 3.88 (t, *J* = 5.5 Hz, 2H), 2.49-2.45 (m, 2H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 188.1, 142.4, 142.3, 139.0, 138.20, 138.16, 130.4, 127.4, 126.0, 125.2, 123.0, 65.2, 63.7, 25.9. IR (cm^{-1}): 2964 (w), 2924 (w), 2850 (w), 1619 (s). HRMS: Calculated for $C_{14}H_{12}NaO_2S$ ([M+Na]$^+$): 267.0450. Found: 267.0452.

(5,6-Dihydro-2*H*-pyran-3-yl)(furan-3-yl)methanone, (7g). Prepared from 5,6-dihydro-2*H*-pyran-3-carbaldehyde (**4**)[49] and 3-bromofuran. Purified via silica gel column chromatography using 20% EtOAc in hexanes, affording a yellow solid (mp = 52-57 °C) (192 mg, 1.08 mmol, 54% yield). TLC: R_f = 0.27, (20% EtOAc in hexanes). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.86 (s, 1H), 7.45 (s, 1H), 6.92-6.90 (m, 1H), 6.75 (s, 1H), 4.47 (s, 2H), 3.82 (t, *J* = 5.5 Hz, 2H), 2.42-2.38 (m, 2H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 188.1, 146.9, 144.0, 139.6, 137.0, 125.9, 110.2, 65.1, 63.7, 25.9. IR (cm^{-1}): 2958 (m), 2924 (s), 2853 (m), 1639 (m). HRMS: Calculated for $C_{10}H_{10}NaO_3$ ([M+Na]$^+$): 201.0522. Found: 201.0521.

Flow photo-Nazarov reaction—general procedure. In a round-bottom flask, aryl vinyl ketone was dissolved in glacial acetic acid to the desired concentration (0.056 M, 0.028 M, or 0.014 M) and degassed with argon for 15 minutes. The solution was then taken up in a syringe, which was placed on a syringe pump and connected to FEP (fluorinated ethylene propylene) tubing (1.6 mm ID, 3.2 mm OD, 3.0 m length) wrapped around a photochemical double-walled borosilicate glass immersion well housing a medium pressure mercury vapor immersion lamp (450 W, 125-145 V, 3.6 A, 244.4 mm total length, 131.5 mm arc).[37] Ice-cooled water was flowed through the immersion well for the duration of the reaction. The solution was pumped through the tubing at specified flow rates to achieve residence times ranging from 2.3 min to 34 mins (See Tables SI-1 and SI-2 in the Supporting Information), and collected in a round-bottom flask. When all of the reaction solution had been pumped into the tubing, glacial acetic acid was pumped through the tubing at the same flow rate until all solution containing the reaction mixture was collected. The reaction mixture was diluted with ether (20 mL) and then washed with a solution of saturated aqueous sodium bicarbonate (2 × 25 mL). The combined aqueous layers were extracted with diethyl ether (2 × 25 mL), and the combined organic layers were washed with brine (25 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude reaction mixtures were purified via silica gel column chromatography (see details below for each product). When hexafluoroisopropanol was used as solvent instead of acetic acid, the reaction mixture was directly concentrated after passing through the flow photo-reactor, and then purified via silica gel column chromatography.

(3b*R*,7a*S*)-3b,4,5,6,7,7a-Hexahydro-8*H*-indeno[2,1-*b*]furan-8-one, (8). Synthesized from **5a** (0.056 M in AcOH, 6.8 min exposure time) and purified via silica gel column chromatography using 10% EtOAc in hexanes to afford a clear, colorless oil (44.9 mg, 0.25 mmol, 86% yield). TLC: R_f = 0.25, (10% EtOAc in hexanes). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.74 (d, *J* = 0.8 Hz, 1H), 6.48 (d, *J* = 0.9 Hz, 1H), 3.19 (ddd, *J* = 8.5 Hz, 6.0 Hz, 6.0 Hz, 1H), 2.99 (ddd, *J* = 6.3 Hz, 6.3 Hz, 6.3 Hz, 1H), 2.07-2.01 (m, 1H), 1.98-1.92 (m, 1H), 1.83-1.78 (m, 1H), 1.55-1.48 (m, 2H), 1.44-1.30 (m, 3H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 191.0, 159.8, 154.6, 153.4, 109.3, 52.3, 32.7, 28.2, 23.3, 20.9, 20.7. IR (cm^{-1}): 2932 (m), 2857 (m), 1700 (s). HRMS: Calculated for $C_{11}H_{12}NaO_2$ ([M+Na]$^+$): 199.0730. Found: 199.0739.

(3b*R*,7a*S*)-2-Methyl-3b,4,5,6,7,7a-hexahydro-8*H*-indeno[2,1-*b*]furan-8-one, (9). Synthesized from **5e** (0.014 M in AcOH, 3.4 min exposure time) and purified via silica gel column chromatography using 10% EtOAc in hexanes to afford a clear, colorless oil (28.3 mg, 0.15 mmol, 57% yield). TLC: R_f = 0.19, (10% EtOAc in hexanes). ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.12 (s, 1H), 3.13 (ddd, *J* = 8.2 Hz, 6.0 Hz, 6.0 Hz, 1H), 2.92 (ddd, *J* = 6.3 Hz, 6.3 Hz, 6.3 Hz, 1H), 2.40 (s, 3H), 2.02-1.96 (m, 1H), 1.94-1.87 (m, 1H), 1.83-1.75 (m, 1H), 1.53-1.46 (m, 2H) 1.44-1.28 (m, 3H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 190.1, 165.3, 161.8, 153.0, 106.1, 51.6, 32.9, 27.9, 23.2, 20.7, 20.5, 15.0. IR (cm^{-1}): 2927 (m), 2856 (m), 1700 (s). HRMS: Calculated for $C_{12}H_{14}NaO_2$ ($[M+Na]^+$): 213.0886. Found: 213.0900.

(3b*R*,7a*S*)-2,3-Dimethyl-3b,4,5,6,7,7a-hexahydro-8*H*-indeno[2,1-*b*]furan-8-one, (10). Synthesized from **5f** (0.014 M in AcOH, 3.4 min exposure time) and purified via silica gel column chromatography using 10% EtOAc in hexanes to afford a yellow oil (33.8 mg, 0.17 mmol, 68% yield). TLC: R_f = 0.20, (10% EtOAc in hexanes). ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.13 (ddd, *J* = 8.7 Hz, 6.0 Hz, 6.0 Hz, 1H), 2.92 (ddd, *J* = 6.3 Hz, 6.3 Hz, 6.3 Hz, 1H), 2.31 (s, 3H), 2.06-2.00 (m, 1H), 1.98 (s, 3H), 1.96-1.89 (m, 1H), 1.83-1.76 (m, 1H), 1.55-1.48 (m, 2H) 1.46-1.30 (m, 3H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 190.0, 161.9, 161.2, 151.5, 115.1, 51.6, 32.6, 27.1, 23.2, 20.8, 20.5, 12.8, 8.7. IR (cm^{-1}): 2927 (m), 2855 (m), 1700 (s), 1545 (m), 1457 (m). HRMS: Calculated for $C_{13}H_{16}NaO_2$ ($[M+Na]^+$): 227.1043. Found: 227.1044.

(6a*S*,10a*R*)-6a,7,8,9,10,10a-Hexahydro-6*H*-indeno[2,1-*b*]benzofuran-6-one, (11). Synthesized from **5c** (0.056 M in AcOH, 6.8 min exposure time) and purified via silica gel column chromatography using 10% EtOAc in hexanes to afford a yellow solid (mp = 97-108 °C) (25.3 mg, 0.11 mmol, 51% yield). TLC: R_f = 0.32, (10% EtOAc in hexanes). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.70 (d, *J* = 7.8 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 1H), 7.50 (t, *J* = 8.4 Hz, 7.3 Hz, 1H), 7.35 (t, *J* = 7.5 Hz, 1H), 3.51 (ddd, *J* = 6.4 Hz, 6.4 Hz, 6.4 Hz, 1H), 3.10 (ddd, *J* = 6.1 Hz, 6.1 Hz, 6.1 Hz, 1H), 2.28-2.20 (m, 1H), 2.07-2.00 (m, 1H), 1.93-1.86 (m, 1H), 1.63-1.38 (m, 5H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 193.4, 162.0, 155.5, 154.9, 129.1, 124.6, 124.0, 122.3, 114.0, 51.8, 32.8, 27.9, 23.3, 20.8, 20.7. IR (cm^{-1}): 2927 (m), 1706 (s). HRMS: Calculated for $C_{15}H_{14}NaO_2$ ($[M+Na]^+$): 249.0886. Found: 249.0892.

(4a*S*,8a*R*)-4a,5,6,7,8,8a-Hexahydro-4*H*-indeno[1,2-*b*]furan-4-one, (12). Synthesized from **5g** (0.056 M in AcOH, 3.4 min exposure time) and purified via silica gel column chromatography using 10% EtOAc in hexanes to afford an orange-yellow solid (mp = 59-60 °C) (42.4 mg, 0.24 mmol, 91% yield). TLC: R_f = 0.44, (20% EtOAc in hexanes). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.50 (d, *J* = 1.9 Hz, 1H), 6.51 (d, *J* = 1.9 Hz, 1H), 3.33 (ddd, *J* = 6.5 Hz, 6.5 Hz, 6.5 Hz, 1H), 3.10 (ddd, *J* = 6.3 Hz, 6.3 Hz, 6.3 Hz, 1H), 2.07-1.96 (m, 2H), 1.83-1.76 (m, 1H), 1.56-1.35 (m, 5H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 198.4, 185.5, 149.2, 126.6, 105.4, 53.5, 35.0, 25.9, 22.7, 20.4, 20.3. IR (cm^{-1}): 2935 (m), 2865 (m), 1705 (s). HRMS: Calculated for $C_{11}H_{12}NaO_2$ ($[M+Na]^+$): 199.0730. Found: 199.0734.

(3b*R*,7a*S*)-3b,4,5,6,7,7a-Hexahydro-8*H*-indeno[2,1-*b*]thiophen-8-one, (13). Synthesized from **5b** (0.014 M in AcOH, 3.4 min exposure time) and purified via silica gel column chromatography using 10% EtOAc in hexanes to afford a clear, colorless oil (36.6 mg, 0.19 mmol, 70% yield). TLC: R_f = 0.30, (10% EtOAc in hexanes). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.87 (d, *J* = 4.7 Hz, 1H), 7.04 (d, *J* = 4.7 Hz, 1H), 3.34 (ddd, *J* = 8.5 Hz, 6.4 Hz, 6.4 Hz, 1H), 3.05 (ddd, *J* = 6.3 Hz, 6.3 Hz, 6.3 Hz, 1H), 2.10-2.00 (m, 2H), 1.82-1.77 (m, 1H), 1.57-1.46 (m, 2H), 1.44-1.29 (m, 3H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 199.5, 172.5, 140.1, 139.7, 123.1, 52.8, 37.1, 29.5, 23.6, 21.6, 21.5. IR (cm^{-1}): 2928 (m), 2853 (m), 1696 (s), 1426 (m). HRMS: Calculated for $C_{11}H_{12}NaOS$ ($[M+Na]^+$): 215.0501. Found: 215.0512.

(6a*S*,10a*R*)-6a,7,8,9,10,10a-Hexahydro-6*H*-benzo[*b*]indeno[1,2-*d*]thiophen-6-one, (14). Synthesized from **5d** (0.014 M in AcOH, 3.4 min exposure time) and purified via silica gel column chromatography using 10% EtOAc in hexanes to afford a yellow solid (mp = 143-147 °C) (21.2 mg, 0.087 mmol, 62% yield). TLC: R_f = 0.57, (20% EtOAc in hexanes). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.91 (d, *J* = 8.8 Hz, 2H), 7.50-7.43 (m, 2H), 3.65 (ddd, *J* = 9.3 Hz, 6.2 Hz, 6.2 Hz, 1H), 3.13 (ddd, *J* = 6.5 Hz, 6.5 Hz, 6.5 Hz, 1H), 2.36-2.30 (m, 1H), 2.19 (dddd, *J* = 14.7 Hz, 5.1 Hz, 5.1 Hz, 5.1 Hz, 1H), 1.87-1.81 (m, 1H), 1.66-1.54 (m, 2H), 1.50-1.33 (m, 3H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 200.3, 168.0, 148.6, 139.7, 134.1, 127.9, 125.1, 124.7, 124.0, 52.0, 36.9, 29.1, 23.1, 21.5, 21.3. IR (cm^{-1}): 2924 (m), 2852 (m), 1694 (s). HRMS: Calculated for $C_{15}H_{14}NaOS$ ([M+Na]$^+$): 265.0658. Found: 265.0659.

(3b*R*,8a*S*)-4,5,6,7,8,8a-Hexahydroazuleno[2,1-*b*]furan-9(3b*H*)-one, (15). Synthesized from **6a** (0.028 M in HFIP, 3.4 min exposure time) and purified via silica gel column chromatography using 10% EtOAc in hexanes to afford a yellow oil (60.6 mg, 0.32 mmol, 94% yield). TLC: R_f = 0.34, (20% EtOAc in hexanes). ^{1}H NMR (600 MHz, CDCl$_3$): δ 7.74 (s, 1H), 6.46 (s, 1H), 3.32-3.27 (m, 1H), 3.08-3.03 (m, 1H), 2.12-2.06 (m, 1H), 2.05-1.99 (m, 1H), 1.80-1.53 (m, 5H), 1.44-1.30 (m, 3H). ^{13}C{^{1}H} NMR (150 MHz, CDCl$_3$): δ 190.9, 160.0, 154.5, 153.9, 109.3, 58.3, 38.5, 31.3, 31.2, 28.4, 28.30, 28.25. IR (cm^{-1}): 2923 (m), 2851 (w), 1699 (m), 1429 (m). HRMS: Calculated for $C_{12}H_{15}O_2$ ([M+H]$^+$): 191.1067. Found: 191.1081.

(6a*S*,11a*R*)-7,8,9,10,11,11a-Hexahydroazuleno[2,1-*b*]benzofuran-6(6a*H*)-one, (16). Synthesized from **6c** (0.056 M in HFIP, 6.8 min exposure time) and purified via silica gel column chromatography using 20% hexanes in CH_2Cl_2 to afford a white solid (mp = 116-117 °C) (23.6 mg, 0.0982 mmol, 57% yield). TLC: R_f = 0.36, (10% EtOAc in hexanes). ^{1}H NMR (600 MHz, CDCl$_3$): δ 7.70 (d, *J* = 7.8 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.49 (t, *J* = 7.8 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 1H), 3.63-3.59 (m, 1H), 3.18-3.14 (m, 1H), 2.33-2.27 (m, 1H), 2.20-2.13 (m, 1H), 1.85-1.65 (m, 5H), 1.54-1.34 (m, 3H). ^{13}C{^{1}H} NMR (150 MHz, CDCl$_3$): δ 199.3, 162.2, 155.4, 154.7, 129.2, 124.5, 124.0, 122.5, 113.9, 57.8, 38.9, 31.2, 30.9, 28.5, 28.4. IR (cm^{-1}): 2923 (s), 2851 (m), 1701 (s). HRMS: Calculated for $C_{32}H_{32}NaO_4$ ([2M+Na]$^+$): 503.2193. Found: 503.2211.

(3b*R*,8a*S*)-4,5,6,7,8,8a-Hexahydroazuleno[2,1-*b*]thiophen-9(3b*H*)-one, (17). Synthesized from **6b** (0.014 M in HFIP, 3.4 min exposure time) and purified via silica gel column chromatography using 10% EtOAc in hexanes to afford a light brown solid (cis: trans dr = 20:1) (48.7 mg, 0.24 mmol, 97% yield). TLC: R_f = 0.31, (10% EtOAc in hexanes). ^{1}H NMR (600 MHz, CDCl$_3$): δ 7.88 (d, *J* = 4.8 Hz, 1H), 7.03 (d, *J* = 4.6 Hz, 1H), 3.51-3.46 (m, 1H), 3.17-3.12 (m, 1H), 2.16-2.07 (m, 2H), 1.83-1.61 (m, 5H), 1.49-1.32 (m, 3H). ^{13}C{^{1}H} NMR (150 MHz, CDCl$_3$): δ 199.8, 172.6, 140.6, 140.3, 123.3, 58.3, 43.1, 32.0, 31.4, 28.6, 28.5, 28.3. IR (cm^{-1}): 2923 (m), 2850 (w), 1692 (s), 1424 (m). HRMS: Calculated for $C_{24}H_{28}NaO_2S_2$ ([2M+Na]$^+$): 435.1423. Found: 435.1441.

Synthesis of vinyl stannane 18. Prepared according to a modified literature procedure.[42] To a solution of diisopropylamine (2.11 mL, 15.0 mmol, 3.00 equiv) in anhydrous THF (75 mL) at 0 °C was added *n*-BuLi (1.6 M in hexanes, 9.36 mL, 15.0 mmol, 3.00 equiv). After 15 min, tributyltin hydride (3.95 mL, 15.0 mmol, 3.00 equiv) was added at 0 °C. After 15 min, the reaction was cooled to -78 °C in a dry ice/acetone bath. Tetrahydro-4*H*-pyran-4-one (0.46 mL, 4.99 mmol, 1.00 equiv) was added, and the reaction was stirred for 1 h. Methanesulfonyl chloride (1.55 mL, 20.0 mmol, 4.00 equiv) and triethylamine (5.21 mL, 37.4 mmol, 7.50 equiv) were added, and the reaction mixture was warmed to room temperature and stirred. After 21 h, the mixture was transferred to a separatory funnel with hexane (150 mL), and washed with water (3 × 100 mL) (Brine used to separate emulsions). The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The crude reaction mixture was purified via silica gel column chromatography, using hexanes to first elute the nonpolar alkyl tin compounds, and then using 20% EtOAc in hexanes to elute **18** as a light yellow solid (934 mg, 2.50 mmol, 50% yield). Spectroscopic data were consistent with literature values.[42]

Synthesis of vinyl stannanes 19-20. Prepared according to a modified literature procedure.[42] To a solution of diisopropylamine (4.00 equiv) in anhydrous THF (0.2 mmol diisopropylamine/mL) at 0 °C was added *n*-BuLi (1.6 M in hexanes, 4.00 equiv). After 20 min, tributyltin hydride (4.00 equiv) was added at 0 °C. After an additional 20 min, the reaction was cooled to -78 °C in a dry ice/acetone bath, *N*-Boc piperidin-4-one or *N*-tosylpiperidin-4-one (1.00 equiv) was added, and the reaction was stirred for 1.5 h. Methanesulfonyl chloride (4.00 equiv) and triethylamine (7.50 equiv) were added, and the reaction was warmed to room temperature and stirred. After 4 h, additional methanesulfonyl chloride (4.00 equiv) and triethylamine (7.50 equiv) were added. After stirring a further 4 h, methanesulfonyl chloride (4.00 equiv) and triethylamine (7.50 equiv) were added a third time. After 16-20 h, the reaction mixture was transferred to a separatory funnel with hexane (100 mL), and washed with water (3 × 100 mL) (Brine used to separate emulsions). The combined aqueous layers were extracted with hexane (100 mL), and the combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The crude reaction mixture was purified via silica gel column chromatography, using hexanes to first elute the nonpolar alkyl tin compounds, and then 10% EtOAc in hexanes to elute the desired vinyl stannane. Vinyl stannane **19** was isolated as a yellow oil (1.60 g, 3.39 mmol, 68% yield) whose spectroscopic data were consistent with literature values.[42] Vinyl stannane **20** was isolated as a yellow oil (1.02 g, 1.94 mmol, 49% yield).

1-Tosyl-4-(tributylstannyl)-1,2,3,6-tetrahydropyridine, (20). TLC: R_f = 0.68, (20% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66 (d, *J* = 8.1 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 5.77-5.56 (m, 1H), 3.60-3.57 (m, 2H), 3.13 (t, *J* = 5.6 Hz, 2H), 2.42 (s, 3H), 2.36-2.31 (m, 2H), 1.49-1.21 (m, 12H), 0.97-0.81 (m, 15H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 143.6, 139.2, 133.5, 131.4, 129.8, 127.9, 46.5, 43.3, 31.7, 29.3, 27.5, 21.7, 13.9, 9.2. IR (cm^{-1}): 2922 (m), 1352 (w), 1166 (m). HRMS: Calculated for $C_{24}H_{42}NO_2SSn$([M+H]$^+$): 528.1953. Found: 528.1952.

Synthesis of ketones 21-25 (Stille coupling—procedure A). Prepared according to a modified literature procedure.[41] To a solution of vinylstannane (**18**-**20**, 1.00 equiv) and acyl chloride (1.10-1.50 equiv) in toluene (0.28 mmol vinylstannane/mL) was added $Pd(PPh_3)_2Cl_2$ (0.05 equiv). The reaction mixture was then refluxed or heated in a microwave reactor in a sealed vial (see details for individual substrates, below). Upon completion, the reaction mixture was cooled to room temperature, filtered through a short pad of silica gel, and concentrated under reduced pressure. The crude reaction mixture was purified via silica gel column chromatography, affording ketones **21**-**25** (see details below for each product). If alkyl tin byproducts were observed by ^{1}H NMR, the product was further passed through a short column of 10% KF in silica gel to remove them.

(3,6-Dihydro-2*H*-pyran-4-yl)(furan-2-yl)methanone, (21). Prepared using a modification of Stille coupling procedure A (1.00 equiv 2-furoyl chloride, 1.10 equiv vinyl stannane **18**, 0.025 equiv $Pd(PPh_3)_2Cl_2$), refluxing in toluene for 18 h. The crude reaction mixture was purified via silica gel column chromatography using 20% EtOAc in hexanes, ramping to 33% EtOAc in hexanes, affording **21** as a yellow oil (352 mg, 1.97 mmol, 86% yield). TLC: R_f = 0.33, (33% EtOAc in hexanes). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.62 (s, 1H), 7.16 (d, *J* = 3.3 Hz, 1H), 7.00 (s, 1H), 6.54-6.52 (m, 1H), 4.37 (s, 2H), 3.86 (t, *J* = 5.4 Hz, 2H), 2.53 (s, 2H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 181.6, 152.3, 146.7, 138.6, 135.4, 119.2, 112.1, 65.3, 64.4, 24.3. IR (cm^{-1}): 2923 (w), 2851 (w), 1633 (s), 1466 (s). HRMS: Calculated for $C_{10}H_{10}NaO_3$ ([M+Na]$^+$): 201.0522. Found: 201.0549.

(3,6-Dihydro-2*H*-pyran-4-yl)(thiophen-2-yl)methanone, (22). Prepared using vinyl stannane **18** and Stille coupling procedure A (1.10 equiv 2-thiophenecarbonyl chloride), in a sealed vial in a microwave reactor set to ramp to 170 °C over 5 min, and then hold at 170 °C for 30 min. The crude reaction mixture was purified via silica gel column chromatography using 20% EtOAc in hexanes, ramping to 33% EtOAc in hexanes, affording **22** as a colorless oil (314 mg, 1.62 mmol, 77% yield). TLC: R_f = 0.55, (20% EtOAc in hexanes). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.66-7.63 (m, 2H), 7.12 (t, *J* = 4.3 Hz, 1H), 6.75 (s, 1H), 4.36 (s, 2H), 3.87 (t, *J* = 5.4 Hz, 2H), 2.55 (s, 2H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 187.3, 142.9, 137.7, 136.1, 133.6, 133.3, 127.9, 65.2, 64.4, 24.6. IR (cm^{-1}): 2922 (w), 2852 (w), 1621 (s), 1414 (s). HRMS: Calculated for $C_{10}H_{10}NaO_2S$ ([M+Na]$^+$): 217.0294. Found: 217.0316.

Benzofuran-2-yl(3,6-dihydro-2*H*-pyran-4-yl)methanone, (23). Prepared using vinyl stannane **18** and Stille coupling procedure A (1.10 equiv 1-benzofuran-2-carbonyl chloride), in a sealed vial in a microwave reactor set to ramp to 170 °C over 5 min, and then hold at 170 °C for 30 min. The crude reaction mixture was purified via silica gel column chromatography using 20% EtOAc in hexanes, ramping to 33% EtOAc in hexanes, affording **23** as a white solid (mp = 93-94 °C) (231 mg, 1.01 mmol, 55% yield). TLC: R_f = 0.56, (20% EtOAc in hexanes). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.70 (d, *J* = 7.9 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.49-7.44 (m, 2H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.16 (s, 1H), 4.43 (s, 2H), 3.90 (t, *J* = 5.4 Hz, 2H), 2.58 (s, 2H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 183.3, 155.9, 152.3, 139.8, 135.7, 128.2, 127.0, 124.1, 123.3, 115.0, 112.6, 65.3, 64.4, 24.3. IR (cm^{-1}): 2924 (w), 2855 (w), 1638 (m), 1549 (m). HRMS: Calculated for $C_{14}H_{12}NaO_3$ ($[M+Na]^+$): 251.0679. Found: 251.0708.

***tert*-Butyl 4-(furan-2-carbonyl)-3,6-dihydropyridine-1(2*H*)-carboxylate, (24).** Prepared using vinyl stannane **19** and Stille coupling procedure A (1.50 equiv 2-furoyl chloride), in a sealed vial in a microwave reactor set to ramp to 125 °C over 5 min, and then hold at 125 °C for 15 min. The crude reaction mixture was purified via silica gel column chromatography using 20% EtOAc in hexanes, ramping to 33% EtOAc in hexanes, affording **24** as a yellow oil (95.1 mg, 0.34 mmol, 70% yield). TLC: R_f =0.28, (50% EtOAc in hexanes). ^1H NMR (300 MHz, $CDCl_3$): δ 7.62-7.60 (m, 1H), 7.15 (d, *J* = 3.6 Hz, 1H), 6.92 (s, 1H), 6.53 (dd, *J* = 3.5 Hz, 1.7 Hz, 1H), 4.18-4.14 (m, 2H), 3.55 (t, *J* = 5.7 Hz, 2H), 2.52, (s, 2H), 1.48 (s, 9H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 181.8, 154.7, 152.1, 146.7, 137.0-135.7 (broad), 136.4, 119.3, 112.1, 80.2, 44.3-43.0 (broad), 40.8-39.5 (broad), 28.6, 24.5. IR (cm^{-1}): 2957 (w), 2922 (w), 1696 (s), 1466 (s). HRMS: Calculated for $C_{15}H_{19}NNaO_4$ ($[M+Na]^+$): 300.1206. Found: 300.1216.

Furan-2-yl(1-tosyl-1,2,3,6-tetrahydropyridin-4-yl)methanone, (25). Prepared using vinyl stannane **20** and Stille coupling procedure A (1.50 equiv 2-furoyl chloride), heating in toluene at 90 °C for 30 min. The crude reaction mixture was purified via silica gel column chromatography using 33% EtOAc in hexanes, affording **25** as a white solid (mp = 165-168 °C) (134 mg, 0.40 mmol, 70% yield). TLC: R_f = 0.55, (50% EtOAc in hexanes). ^1H NMR (300 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.2 Hz, 2H), 7.62-7.60 (m, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 3.6 Hz, 1H), 6.87-6.83 (m, 1H), 6.53 (dd, *J* = 3.5 Hz, 1.7 Hz, 1H), 3.86 (q, *J* = 2.9 Hz, 2H), 3.26 (t, *J* = 5.7 Hz, 2H), 2.66-2.59 (m, 2H), 2.44 (s, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 181.4, 152.0, 147.0, 144.2, 136.2, 134.2, 133.2, 130.0, 127.9, 119.7, 112.3, 45.1, 42.8, 24.7, 21.8. IR (cm^{-1}): 2917 (w), 2849 (w), 1625 (m), 1163 (m). HRMS: Calculated for $C_{17}H_{17}NNaO_4S$ ($[M+Na]^+$): 354.0771. Found: 354.0773.

Synthesis of 26 and 27. To a solution of 1,2,5,6-tetrahydro-3-pyridinecarboxylic acid hydrochloride (400 mg, 2.44 mmol, 1.00 equiv) in a mixture of DMF (7.2 mL) and water (4.8 mL) was added triethylamine (0.85 mL, 6.1 mmol, 2.50 equiv). The reaction was stirred for 5 min at room temperature, and then *p*-toluenesulfonyl chloride (698 mg, 3.66 mmol, 1.50 equiv) was added. The reaction was stirred 22 h at room temperature, and then diluted with saturated aqueous $NaHCO_3$ (15 mL) and EtOAc (10 mL). The layers were separated and the organic layer was extracted with saturated aqueous $NaHCO_3$ (3 × 10 mL). The combined aqueous layers were acidified with 36% hydrochloric acid until a white precipitate formed. EtOAc (20 mL) was added to dissolve the precipitate and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 × 20 mL), and the combined organic layers were washed with brine (4 × 15 mL), dried over sodium sulfate, and concentrated under reduced pressure to afford **27** as a white solid (mp = 157-159 °C) (527 mg, 1.87 mmol, 77% yield).

Compound **26** was similarly prepared using Boc_2O, affording a white solid (671 mg, 2.95 mmol, 97% yield) whose spectroscopic data were consistent with literature values.[49a]

1-Tosyl-1,2,5,6-tetrahydropyridine-3-carboxylic acid, (27). TLC: R_f = 0.37, (50% acetone in hexanes). ^1H NMR (300 MHz, $CDCl_3$): δ 7.69 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.14-7.09 (m, 1H), 3.80-3.77 (m, 2H), 3.18 (t, *J* = 5.7 Hz, 2H), 2.48-2.39 (m, 2H), 2.43 (s, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 170.2, 144.1, 140.2, 133.1, 130.0, 127.8, 126.6, 43.8, 41.8, 26.1, 21.7. IR (cm^{-1}): 2845 (br), 1680 (s), 1648 (m). HRMS: Calculated for $C_{13}H_{16}NO_4S$ ($[M+H]^+$): 282.0795. Found: 282.0800.

Synthesis of ketones 28 and 29 (Stille coupling—procedure B). Prepared according to a modified literature procedure.[41] To a solution of **27** (308 mg, 1.10 mmol, 1.00 equiv) in dichloromethane (3.8 mL) was added oxalyl chloride (0.20 mL, 2.2 mmol, 2.00 equiv), followed by a drop of dimethylformamide. The reaction was stirred for 1.25 h at room temperature and concentrated under reduced pressure. The crude acid chloride intermediate was then dissolved in toluene (4 mL) and transferred to a 20-mL microwave vial. 2-(Tributylstannyl)furan (0.38 mL, 1.21 mmol, 1.10 equiv) and

$Pd(PPh_3)_2Cl_2$ (38.6 mg, 0.060 mmol, 0.050 equiv) were then added to the vial. The sealed vial was placed in a microwave reactor set to ramp to 170 °C over 5 min, and then hold at 170 °C for 30 min. Once the microwave vial cooled to room temperature, the reaction mixture was filtered through a short pad of silica gel (10% EtOAc in hexanes, then 66% EtOAc in hexanes), and concentrated under reduced pressure. The crude reaction mixture was purified via silica gel column chromatography using 50% EtOAc in hexanes. Alkyl tin byproducts were also observed by ^{1}H NMR, so the product was run through a short column of 10% KF in silica gel (50% EtOAc in hexanes), affording aryl vinyl ketone **29** as a light yellow solid (mp = 118-119 °C) (295 mg, 0.89 mmol, 81% yield).

Compound **28** was similarly prepared from **26**; However, it was necessary to run the reaction on small scale (0.29 mmol) in order to avoid significant decomposition (temperature in vial only reached 150 °C). Aryl vinyl ketone **28** was isolated as a yellow solid (mp = 69-75 °C) (66.8 mg, 0.24 mmol, 83% yield).

***tert*-Butyl 5-(furan-2-carbonyl)-3,6-dihydropyridine-1(2*H*)-carboxylate, (28).** TLC: R_f = 0.68, (50% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60-7.59 (m, 1H), 7.18-7.12 (m, 2H), 6.51 (dd, *J* = 3.6 Hz, 1.7 Hz, 1H), 4.23 (s, 2H), 3.52 (t, *J* = 5.7 Hz, 2H), 2.44-2.36 (m, 2H), 1.45 (s, 9H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 181.2, 155.0, 152.1, 146.7, 139.3 (br), 136.0 (br), 119.2, 112.1, 80.2, 42.8, 39.0 (br), 28.6, 25.9. IR (cm^{-1}): 2977 (m), 2930 (m), 1700 (s), 1635 (s). HRMS: Calculated for $C_{15}H_{19}NNaO_4$ ($[M+Na]^+$): 300.1206. Found: 300.1236.

Furan-2-yl(1-tosyl-1,2,5,6-tetrahydropyridin-3-yl)methanone, (29). TLC: R_f = 0.56, (50% EtOAc in hexanes). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.70 (d, *J* = 7.3 Hz, 2H), 7.59 (s, 1H), 7.32 (d, *J* = 7.9 Hz, 2H), 7.12-7.08 (m, 2H), 6.53-6.50 (m, 1H), 3.91 (s, 2H), 3.23 (t, *J* = 5.8 Hz, 2H), 2.53-2.48 (m, 2H), 2.42 (s, 3H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 180.5, 151.8, 146.9, 144.0, 138.5, 134.7, 133.3, 130.0, 127.9, 119.5, 112.2, 44.3, 42.1, 26.3, 21.7. IR (cm^{-1}): 2920 (w), 2850 (w), 1632 (m), 1465 (m). HRMS: Calculated for $C_{17}H_{17}NNaO_4S$ ($[M+Na]^+$): 354.0771. Found: 354.0798.

(3a*S*,3b*S*,7a*R*,8a*S*)-8-Oxo-3a,3b,4,5,7a,8-hexahydrofuro[3',2':3,4]cyclopenta[1,2-*c*]pyran-8a(7*H*)-yl acetate, (30). Synthesized from **7a** (0.028 M in AcOH, 2.3 min exposure time) and purified via silica gel column chromatography using 33% EtOAc in hexanes to afford a yellow solid (mp = 100-105 °C) (27.1 mg, 0.11 mmol, 41% yield). TLC: R_f = 0.23, (33% EtOAc in hexanes). ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.43 (dd, *J* = 2.7 Hz, 1.4 Hz, 1H), 5.25 (t, *J* = 2.9 Hz, 1H), 4.29 (dd, *J* = 12.1 Hz, 2.4 Hz, 1H), 3.82 (ddd, *J* = 11.5 Hz, 3.8 Hz, 3.8 Hz, 1H), 3.71 (ddd, *J* = 8.4 Hz, 2.9 Hz, 1.1 Hz, 1H), 3.60 (dd, *J* = 12.1 Hz, 4.7 Hz, 1H), 3.36 (ddd, *J* = 11.2 Hz, 11.2 Hz, 2.2 Hz, 1H), 3.16-3.12 (m, 1H), 2.80-2.73 (m, 1H), 2.08 (s, 3H), 1.50 (ddd, *J* = 14.2 Hz, 2.9 Hz, 2.9 Hz, 1H), 1.17-1.09 (m, 1H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 203.9, 170.0, 144.7, 110.6, 104.1, 66.3, 63.7, 51.0, 48.0, 32.1, 26.3, 21.1. IR (cm^{-1}): 2954 (m), 2924 (m), 2851 (m), 1765 (s), 1737 (s), 1008 (s). HRMS: Calculated for $C_{12}H_{14}NaO_5$ ($[M+Na]^+$): 261.0733. Found: 261.0754.

(3b*R*,7a*R*)-4,5,7,7a-Tetrahydrofuro[3',2':3,4]cyclopenta[1,2-*c*]pyran-8(3b*H*)-one, (31). Synthesized from **7a** (0.014 M in HFIP, 3.4 min exposure time) and purified via silica gel column chromatography using 50% EtOAc in hexanes to afford a yellow-brown oil (35.4 mg, 0.20 mmol, 71% yield). TLC: R_f = 0.18, (33% EtOAc in hexanes). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.79 (d, *J* = 1.7 Hz, 1H), 6.53 (d, *J* = 1.7 Hz, 1H), 4.24 (dd, *J* = 12.1 Hz, 3.6 Hz, 1H), 3.90 (dd, *J* = 12.1 Hz, 5.7 Hz, 1H), 3.75-3.70 (m, 1H), 3.60 (ddd, *J* = 11.2 Hz, 8.3 Hz, 4.1 Hz, 1H), 3.41 (ddd, *J* = 6.7 Hz, 6.7 Hz, 6.7 Hz, 1H), 3.03 (ddd, *J* = 5.9 Hz, 5.9 Hz, 3.7 Hz, 1H), 2.25 (dddd, *J* = 14.0 Hz, 6.5 Hz, 6.5 Hz, 4.1 Hz, 1H), 1.65 (dddd, *J* = 13.9 Hz, 6.7 Hz, 6.7 Hz, 4.8 Hz, 1H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 187.9, 159.2, 154.7, 153.8, 109.3, 64.4, 64.3, 52.1, 29.5, 28.9. IR (cm^{-1}): 2953 (m), 2854 (m), 1709 (s), 1429 (s). HRMS: Calculated for $C_{10}H_{10}NaO_3$ ($[M+Na]^+$): 201.0522. Found: 201.0527.

(3b*R*,7a*R*)-4,5,7,7a-Tetrahydrothieno[3',2':3,4]cyclopenta[1,2-*c*]pyran-8(3b*H*)-one, (32). Synthesized from **7b** (0.028 M in HFIP, 3.4 min exposure time) and purified via silica gel column chromatography using 33% EtOAc in hexanes to afford a yellow solid (mp = 83-87 °C) (26.5 mg, 0.14 mmol, 53% yield). TLC: R_f = 0.28, (33% EtOAc in hexanes). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.92 (d, *J* = 4.8 Hz, 1H), 7.08 (d, *J* = 4.8 Hz, 1H), 4.27 (dd, *J* = 12.1 Hz, 3.8 Hz, 1H), 3.91 (dd, *J* = 12.1 Hz, 5.8 Hz, 1H), 3.72-3.67 (m, 1H), 3.61-3.52 (m, 2H), 3.07 (ddd, *J* = 6.2 Hz, 6.2 Hz, 3.8 Hz, 1H), 2.24 (dddd, *J* = 14.1 Hz, 6.4 Hz, 6.4 Hz, 3.8 Hz, 1H), 1.69-1.62 (m, 1H). $^{13}C\{^1H\}$ NMR (150 MHz, CDCl$_3$): δ 196.4, 171.4, 140.9, 140.1, 123.0, 64.75, 64.70, 52.4, 33.8, 29.8. IR (cm^{-1}): 2920 (m), 2851 (m), 1695 (s). HRMS: Calculated for $C_{10}H_{10}NaO_2S$ ([M+Na]$^+$): 217.0294. Found: 217.0299.

(3b*R*,7a*S*)-3b,6,7,7a-Tetrahydrofuro[2',3':4,5]cyclopenta[1,2-*c*]pyran-8(4*H*)-one, (35). Synthesized from **21** (0.014 M in HFIP, 3.4 min exposure time) and purified via silica gel column chromatography using 50% EtOAc in hexanes to afford a yellow oil (31.2 mg, 0.18 mmol, 61% yield). TLC: R$_f$ = 0.32, (50% EtOAc in hexanes). ^1H NMR (600 MHz, CDCl$_3$): δ 7.78 (s, 1H), 6.50 (s, 1H), 4.16 (dd, *J* = 11.6 Hz, 5.6 Hz, 1H), 3.82 (ddd, *J* = 10.5 Hz, 4.8 Hz, 4.8 Hz, 1H), 3.45 (ddd, *J* = 10.8 Hz, 10.8 Hz, 4.5 Hz, 1H), 3.40 (ddd, *J* = 6.3 Hz, 6.3 Hz, 6.3 Hz, 1H), 3.35 (dd, *J* = 11.6 Hz, 7.1 Hz, 1H), 3.17-3.13 (m, 1H), 2.23-2.17 (m, 1H), 2.12-2.04 (m, 1H). $^{13}C\{^1H\}$ NMR (150 MHz, CDCl$_3$): δ 189.2, 156.0, 155.1, 153.7, 109.5, 68.9, 64.9, 49.1, 33.2, 23.5. IR (cm^{-1}): 2922 (w), 2852 (w), 1699 (s). HRMS: Calculated for $C_{10}H_{10}NaO_3$ ([M+Na]$^+$): 201.0522. Found: 201.0544.

(3b*R*,7a*S*)-3b,6,7,7a-Tetrahydrothieno[2',3':4,5]cyclopenta[1,2-*c*]pyran-8(4*H*)-one, (36). Synthesized from **22** (0.056 M in HFIP, 6.8 min exposure time) and purified via silica gel column chromatography using 33% EtOAc in hexanes, then 50% EtOAc in hexanes, to afford a yellow-brown oil (35.6 mg, 0.18 mmol, 71% yield). TLC: R$_f$ = 0.46, (50% EtOAc in hexanes). ^1H NMR (600 MHz, CDCl$_3$): δ 7.90 (d, *J* = 4.7 Hz, 1H), 7.04 (d, *J* = 4.7 Hz, 1H), 4.17 (dd, *J* = 11.9 Hz, 6.0 Hz, 1H), 3.81 (ddd, *J* = 10.4 Hz, 10.4 Hz, 4.7 Hz, 1H), 3.54 (ddd, *J* = 6.6 Hz, 6.6 Hz, 6.6 Hz, 1H), 3.39 (ddd, *J* = 11.0 Hz, 11.0 Hz, 4.3 Hz, 1H), 3.29 (dd, *J* = 11.9 Hz, 7.6 Hz, 1H), 3.19 (ddd, *J* = 6.8 Hz, 6.8 Hz, 3.9 Hz, 1H), 2.22 (dddd, *J* = 14.4 Hz, 4.0 Hz, 4.0 Hz, 4.0 Hz, 1H), 2.10-2.02 (m, 1H). $^{13}C\{^1H\}$ NMR (150 MHz, CDCl$_3$): δ 197.6, 168.0, 140.6, 140.5, 123.2, 69.9, 65.2, 49.8, 37.1, 23.6. IR (cm^{-1}): 2918 (w), 2849 (w), 1693 (m). HRMS: Calculated for $C_{10}H_{10}NaO_2S$ ([M+Na]$^+$): 217.0294. Found: 217.0317.

(4a*R*,8a*R*)-4a,7,8,8a-Tetrahydrofuro[2',3':3,4]cyclopenta[1,2-*c*]pyran-4(5*H*)-one, (38). Synthesized from **7g** (0.014 M in HFIP, 3.4 min exposure time) and purified via silica gel column chromatography using 33% EtOAc in hexanes to afford an orange solid (mp = 51-55 °C) (38.8 mg, 0.22 mmol, 76% yield). TLC: R$_f$ = 0.24, (33% EtOAc in hexanes). ^1H NMR (600 MHz, CDCl$_3$): δ 7.53 (d, *J* = 1.7 Hz, 1H), 6.55 (d, *J* = 1.7 Hz, 1H), 4.26 (dd, *J* = 12.1 Hz, 3.6 Hz, 1H), 3.88 (dd, *J* = 12.1 Hz, 5.7 Hz, 1H), 3.73-3.68 (m, 1H), 3.60 (ddd, *J* = 11.6 Hz, 8.0 Hz, 4.2 Hz, 1H), 3.54 (ddd, *J* = 6.8 Hz, 6.8 Hz, 6.8 Hz, 1H), 3.11 (ddd, *J* = 6.0 Hz, 6.0 Hz, 3.9 Hz, 1H), 2.24 (dddd, *J* = 13.8 Hz, 6.7 Hz, 6.7 Hz, 4.5 Hz, 1H), 1.80 (dddd, *J* = 14.5 Hz, 7.5 Hz, 7.5 Hz, 5.1 Hz, 1H). $^{13}C\{^1H\}$ NMR (150 MHz, CDCl$_3$): δ 195.2, 184.6, 149.7, 127.2, 105.6, 64.1, 63.9, 53.2, 31.7, 26.5. IR (cm^{-1}): 2957 (m), 2924 (s), 2853 (m), 1705 (m). HRMS: Calculated for $C_{10}H_{10}NaO_3$ ([M+Na]$^+$): 201.0522. Found: 201.0525.

***tert*-Butyl (3b*R*,7a*S*)-8-oxo-3b,4,6,7,7a,8-hexahydro-5*H*-furo[2',3':4,5]cyclopenta[1,2-*c*]pyridine-5-carboxylate, (39).** Synthesized from **24** (0.014 M in HFIP, 3.4 min exposure time) and purified via silica gel column chromatography using 50% EtOAc in hexanes to afford a white solid (mp = 145-147 °C) (22.6 mg, 0.081 mmol, 45% yield). TLC: R$_f$ = 0.39, (50% EtOAc in hexanes). ^1H NMR (300 MHz, CDCl$_3$): δ 7.78-7.75 (m, 1H), 6.56-6.51 (m, 1H), 3.72-3.63 (m, 2H), 3.46-3.38 (m, 1H), 3.27 (t, *J* = 6.5 Hz, 2H), 3.10 (q, *J* = 6.1 Hz, 1H), 2.16-2.05 (m, 2H), 1.34 (s, 9H). $^{13}C\{^1H\}$ NMR (75 MHz, CDCl$_3$): δ Note: Small rotamer peaks shown in parentheses. 189.3, (189.1), 157.5, (156.8), (156.0), (155.7), 155.6, 154.9, 154.3, (154.1), 110.0, (109.6), 79.8, 49.8, 42.2, 41.1, (41.0), (40.5), 34.0, 28.5, 23.0, (22.8). IR (cm^{-1}): 2975 (m), 2930 (m), 2881 (m), 1699 (s). HRMS: Calculated for $C_{15}H_{19}NNaO_4$ ([M+Na]$^+$): 300.1206. Found: 300.1235.

(3b*R*,7a*S*)-5-Tosyl-3b,4,5,6,7,7a-hexahydro-8*H*-furo[2',3':4,5]cyclopenta[1,2-*c*]pyridin-8-one, (40). Synthesized from **25** (0.0070 M in HFIP, 3.4 min exposure time) and purified via silica gel column chromatography using 50% EtOAc in hexanes to afford a light yellow solid (mp = 112-116 °C) (26.8 mg, 0.081 mmol, 58% yield). TLC: R$_f$ = 0.42, (50% EtOAc in hexanes). ^1H NMR (300 MHz, CDCl$_3$): δ 7.76 (d, *J* =

1.8 Hz, 1H), 7.57 (d, *J* = 8.3 Hz, 1H), 7.27 (d, *J* = 7.0 Hz, 2H), 6.51 (d, *J* = 1.8 Hz, 1H), 3.77 (dd, *J* = 12.6 Hz, 5.3 Hz, 1H), 3.52-3.45 (m, 1H), 3.36 (ddd, *J* = 11.3 Hz, 5.6 Hz, 5.6 Hz, 1H), 3.10-2.88 (m, 3H), 2.41 (s, 3H), 2.16-1.98 (m, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 188.2, 156.1, 155.2, 154.2, 143.8, 134.5, 130.0, 127.4, 109.6, 49.4, 46.1, 42.6, 33.6, 22.7, 21.7. IR (cm^{-1}): 2920 (w), 1703 (s), 1163 (s). HRMS: Calculated for $C_{17}H_{17}NNaO_4S$ ($[M+Na]^+$): 354.0771. Found. 354.0797.

***tert*-Butyl(3b*R*,7a*R*)-8-oxo-3b,4,5,7,7a,8-hexahydro-6*H*-furo[3',2':3,4]cyclopenta[1,2-*c*]pyridine-6-carboxylate, (41).** Synthesized from **28** (0.0070 M in HFIP, 3.4 min exposure time) and purified via silica gel column chromatography using 50% EtOAc in hexanes to afford a yellow oil (14.2 mg, 0.051 mmol, 45% yield). TLC: R_f = 0.31, (50% EtOAc in hexanes). ^1H NMR (300 MHz, $CDCl_3$): δ 7.80 (d, *J* = 1.8 Hz, 1H), 6.52 (d, *J* = 1.8 Hz, 1H), 4.01-3.56 (m, 2H), 3.42-3.31 (m, 2H), 3.25-3.05 (m, 2H), 2.30-2.15 (m, 1H), 1.95-1.83 (m, 1H), 1.44 (s, 9H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): Note: Small rotamer peaks shown in parentheses. δ 188.1, 158.6, (155.43), 155.38, 154.5, (154.3), 109.5, 80.2, 53.1, (52.9), 40.5, 39.9, (39.3), 30.3, 28.6, 25.1. IR (cm^{-1}): 2975 (w), 2929 (w), 1704 (s). HRMS: Calculated for $C_{15}H_{19}NNaO_4$ ($[M+Na]^+$): 300.1206. Found: 300.1211.

(3b*R*,7a*R*)-6-Tosyl-3b,4,5,6,7,7a-hexahydro-8*H*-furo[3',2':3,4]cyclopenta[1,2-*c*]pyridin-8-one, (42). Synthesized from **29** (0.0070 M in HFIP, 3.4 min exposure time) and purified via silica gel column chromatography using 50% EtOAc in hexanes to afford a yellow solid (decomposed at 135 °C) (23.3 mg, 0.070 mmol, 46% yield). TLC: R_f = 0.26, (50% EtOAc in hexanes). ^1H NMR (600 MHz, $CDCl_3$): δ 7.75 (s, 1H), 7.64 (d, *J* = 7.9 Hz, 2H), 7.29 (d, *J* = 7.8 Hz, 2H), 6.47 (s, 1H), 3.61-3.53 (m, 2H), 3.29-3.23 (m, 2H), 3.19-3.12 (m, 2H), 2.42 (s, 3H), 2.21-2.14 (m, 1H), 1.74-1.67 (m, 1H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ 186.8, 158.1, 154.8, 154.4, 143.7, 134.7, 129.9, 127.6, 109.4, 52.3, 42.4, 42.0, 30.0, 26.4, 21.7. IR (cm^{-1}): 2918 (w), 2850 (w), 1705 (m), 1162 (m). HRMS: Calculated for $C_{17}H_{17}NNaO_4S$ ($[M+Na]^+$): 354.0771. Found: 354.0778.

Ring-opening[50] of 31. Pyran **31** (203.1 mg, 1.14 mmol, 1.00 equiv) was dissolved in CH_2Cl_2 (8 mL), the solution was cooled to 0 °C, and BBr_3 (1.0 M in CH_2Cl_2, 1.71 mL, 1.71 mmol, 1.50 equiv) was added dropwise. The solution was stirred at 0 °C for 15 min, and then warmed to room temperature. The solution was stirred at room temperature for 1.0 h, during which time a light brown solid precipitated and the solution turned opaque purple. Water (8 mL) was added, and the solution was stirred 15 min before being transferred to a separatory funnel with CH_2Cl_2 (15 mL) and H_2O (15 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The crude product was purified via silica gel column chromatography using 50% EtOAc in hexanes, affording **44** as a clear, light yellow oil (35.4 mg, 0.14 mmol, 12% yield), and an inseparable mixture of the regioisomeric bromoalcohol and enone **43** (ratio = 1.5 : 1.0, 173.6 mg). The mixture was dissolved in toluene (8 mL), the solution was cooled to 0 °C, and DBU (0.19 mL, 1.25 mmol) was added dropwise. The mixture was stirred 15 min before H_2O (8 mL) was added, and the solution was transferred to a separatory funnel with EtOAc (20 mL) and H_2O (20 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The crude product was purified via silica gel column chromatography using 50% EtOAc in CH_2Cl_2, affording enone **43** as a clear, colorless oil (100.6 mg, 0.56 mmol, 50% yield).

4-(2-Hydroxyethyl)-5-methylene-4,5-dihydro-6*H*-cyclopenta[*b*]furan-6-one, (48). TLC: R_f = 0.37, (50% EtOAc in CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ 7.76 (d, *J* = 1.7 Hz, 1H), 6.60 (d, *J* = 1.7 Hz, 1H), 6.23 (s, 1H), 5.55 (s, 1H), 3.89-3.76 (m, 3H), 2.21-2.10 (m, 1H), 1.91-1.79 (m, 1H), 1.71 (br s, 1H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 176.7, 156.6, 154.6, 153.4, 151.9, 118.4, 110.1, 60.6, 36.6, 34.7. IR (cm^{-1}): 3392 (br), 3119 (w), 2928 (w), 1685 (s), 1636 (m), 1428 (m). HRMS: Calculated for $C_{10}H_{11}O_3$ ($[M+H]^+$): 179.0703. Found: 179.0698.

(4*R*,5*R*)-4-(2-Bromoethyl)-5-(hydroxymethyl)-4,5-dihydro-6*H*-cyclopenta[*b*]furan-6-one, (49). TLC: R_f = 0.67, (50% EtOAc in CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.80 (d, *J* = 0.8 Hz, 1H), 6.57 (d, *J* = 0.9 Hz, 1H), 4.05 (ddd, *J* = 11.3 Hz, 5.8 Hz, 5.8 Hz, 1H), 3.93 (ddd, *J* = 10.9 Hz, 5.3 Hz, 5.3 Hz, 1H), 3.57 (t, *J* = 6.8 Hz, 2H), 3.26 (td, *J* = 7.4 Hz, 7.4 Hz, 2.3 Hz, 1H), 2.77 (td, *J* = 5.5 Hz, 5.4 Hz, 2.0 Hz, 1H), 2.49 (dd, *J* = 6.5 Hz, 4.7 Hz, 1H), 2.22 (q, *J* = 7.0 Hz, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 188.5, 158.5, 154.5, 154.0, 110.0, 62.5, 60.7, 37.2, 34.8, 30.9. IR (cm^{-1}): 3408 (br), 3133 (w), 2927 (w), 1699 (s), 1432 (m). Unable to acquire HRMS data; however, peaks at m/z = 258 and m/z = 260 with an approximately 1:1 ratio of intensities were detected using low-resolution GC/MS.

Scale-out synthesis of 8. In a round-bottom flask, aryl vinyl ketone **5a** (1.50 g, 8.1 mmol) was dissolved in acetic acid (152 mL, 0.056 M) and the solution was degassed with argon for 15 min. The solution was then taken up in batches in a 60-mL syringe, which was placed on a syringe pump and connected to FEP (fluorinated ethylene propylene) tubing (1.6 mm ID, 3.2 mm OD, 3.0 m length) wrapped around a photochemical double-walled borosilicate glass immersion well housing a medium pressure mercury vapor immersion lamp (450 W, 125-145 V, 3.6 A, 244.4 mm total length, 131.5 mm arc).[37] Ice-cooled water was flowed through the immersion well for the duration of the reaction. The solution was pumped through the tubing at 53.3 mL/hour (6.8 min residence time) and collected in a round-bottom flask. When all of the reaction solution had been pumped into the tubing, glacial acetic acid (8 mL) was pumped through the tubing at the same flow rate until all solution containing the reaction mixture was collected. The reaction mixture was diluted with ether (200 mL), and then washed with a solution of saturated aqueous sodium bicarbonate (2 × 250 mL). The combined aqueous layers were extracted with diethyl ether (2 × 250 mL), and the combined organic layers were washed with brine (250 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude reaction mixture was purified via silica gel column chromatography using 20% EtOAc in hexanes, affording **8** (1.33 g, 7.54 mmol, 89%).

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Supporting Information

^{1}H and $^{13}C\{^1H\}$ NMR spectra for compounds **5**-**49**, UV emission spectra for medium pressure mercury vapor lamp, and photo-Nazarov data tables (PDF)

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