Expedient Access to α,β-Difunctionalized Azepenes using α-Halo Eneformamides: Application to the Synthesis of 2-Benzazepanes

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Expedient Access to α,β-Difunctionalized Azepenes using α-Halo Eneformamides: Application to the One-Pot Synthesis of 2-Benzazepanes

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The regioselective synthesis of α,β-difunctionalized (alkenyl, aryl, sulfonyl, allyl, or alkynyl) azepenes has been accomplished through α-halo eneformamides. A successful implementation of the vicinal functionalization strategy has led to a one-pot synthesis of 2-benzazepanes whose benzenoid portion is highly functionalized.

Introduction

Functionalized azepanes constitute the core of several alkaloids including stemona[1] (e.g., stenine, Fig. 1), cephalotaxus[2] (e.g., cephalotaxine), kopsia[3] (e.g., arboflorine), securinega[4, 5] (e.g., securinine), and montanine-like alkaloids[6] (e.g., montabuphine). Furthermore, the biological activity of 2-benzazepanes as antiplatelet agents and selective β-adrenoreceptor agonists is well documented.[7] For example, anafranil is an antiobsessional drug that belongs to the class of pharmacologic agents often referred to as tricyclic antidepressants.[8]

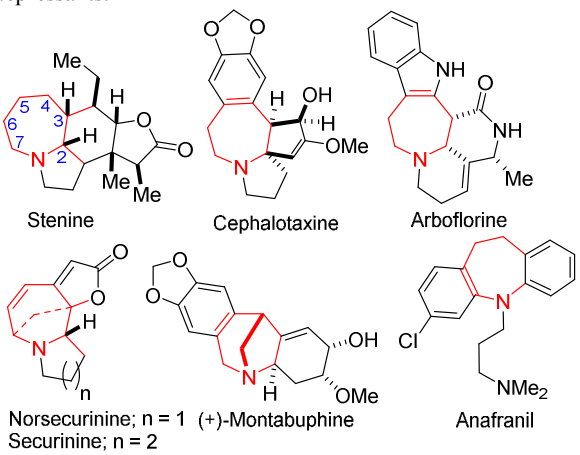


Fig. 1 Examples of vicinally functionalized azepane alkaloids and pharmaceuticals

Due to its importance and structural diversity, it is quite fitting that the azepane structural motif continues to inspire scientists toward developing increasingly more efficient strategies for its construction and functionalization.[1, 4, 6, 9] One of such strategy that would provide efficient access to functionalized azepane derivatives would be to employ an enamide or enecarbamate as a substrate for subsequent functionalization. In addition to offering latent functionality at the α and β positions (see **III**, Fig. 2, top), cyclic enamides or enecarbamates offer several other advantages as a starting point for access to functionalized azaheterocycles.[10-14] For example, the double bond of the enamide or enecarbamate may be reduced or oxidized,[14, 15] cyclopropanated,[16] or engaged in allylic functionalization protocols.[17] Importantly, as detailed in many previous reports, C-2 functionalization of an enamide or enecarbamate has primarily been achieved by utilizing the corresponding vinyl triflate,[18, 19] phosphate,[20] stannane,[21] or boronate[19, 22] in cross-coupling. However, as has been demonstrated in the piperidine heterocycle, achieving *vicinal difunctionalization* remains elusive, in part because sequential substitution of a 2- or 3-substituted cyclic amine derivative is barely tolerated in most of the existing C-2 or C-3 functionalization strategies.[13, 23] Toward this end, certain strategies have emerged including those employed by Coudert[24] (i.e., carbolithiation/oxidation, Fig. 2, top) and Gillaizeau[12] (i.e., Pd-catalyzed arylation with diaryliodonium salts).

In order to achieve α,β-difunctionalization of azepanes, which would provide access to most of the substitution patterns resident in the alkaloids and pharmaceuticals shown in Fig. 1, as well as complement the existing reactivity modes, it was surmised that coupling reactions using α-halo eneformamides such as **1** (Fig. 2) offered a conceptually and practically sagacious approach. Said differently, the ability to employ

bench stable and readily available halo eneformamides such as **1** in cross-couplings obviates the need for pregeneration of a reactive organometallic reagent and endows them with a practical advantage over many conventional cross-coupling approaches. Two convergent and potentially complementary approaches toward α,β-difunctionalized products such as **2** were envisioned. The first would entail coupling of **1** at C-2 using the halide as a functional handle for cross-coupling with nucleophiles to afford intermediates such as **3**.[25] These intermediates could then be subjected to a variety of C-3 functionalization strategies to give **2**. The second approach to vicinally functionalized azepenes (i.e., **2**) would utilize direct C-3 functionalization of **1** to afford 2-halo-3-substituted eneformamides such as **4**. Subsequent cross-coupling of the latter with nucleophilic partners, using the halide as a functional handle for cross-coupling, would afford vicinally difunctionalized products such as **2**.

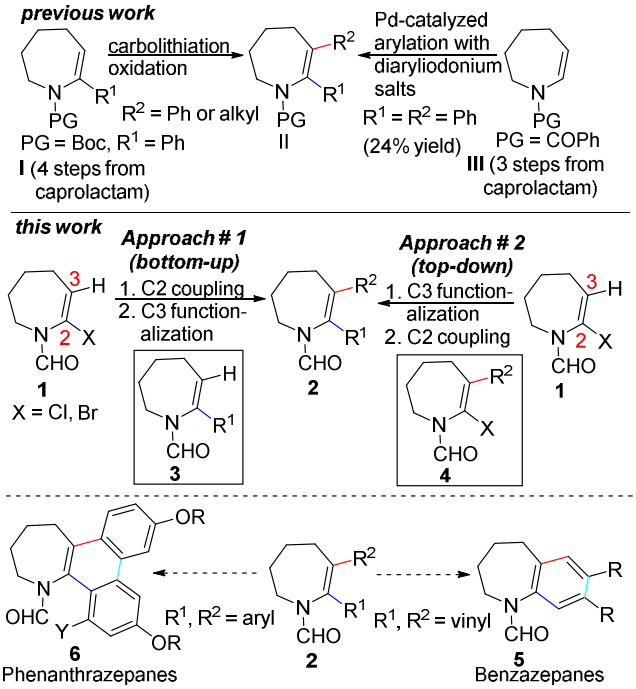


Fig. 2 Vicinal functionalization strategies

At first glance, one might expect functionalization of the C_α–X bond in **1a/b** to out-compete that of the C_β–H bond. Nevertheless, if suitable reaction conditions for accessing intermediate **4** are identified, it is anticipated that the 'top-down' approach to **2** would be facilitated by the small size of the formyl group, the stereoelectronics of the X-group, and possible chelation of the transition metal to the carbonyl oxygen. If the two substituents in **2** are alkenyl in nature, it is theorized that benzazepanes such as **5** would be obtainable through some cyclization and oxidation events. Alternatively, the presence of two aryl substituents in **2** would set the stage for rapidly accessing a novel class of phenanthrazepanes such as **6**. Herein, synthetic efforts toward the manifestation of the outlined plan are described.

Results and Discussion

As previously mentioned, ε-caprolactam-derived α-halo eneformamides such as **1a/b** can now be successfully vinylated, alkynylated, and arylated at C-2 under Heck, Sonogashira, and Suzuki cross-coupling conditions, respectively.[25] Representative examples of these coupling products are depicted in Fig. 3.

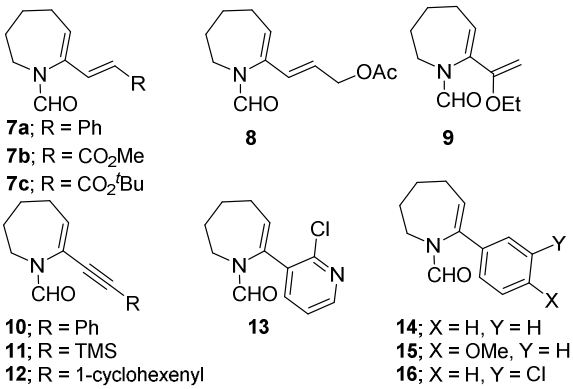
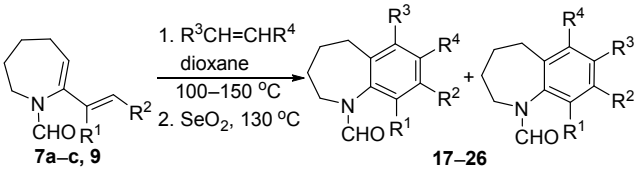


Fig. 3 Selected examples of previously synthesized α-functionalized azepenes[25]

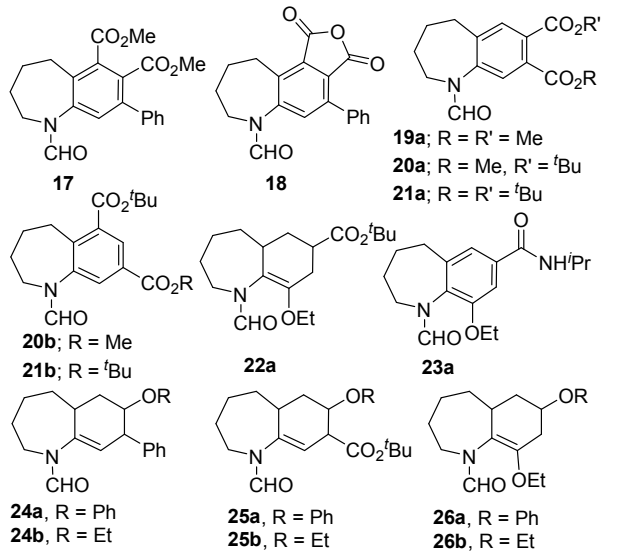
With a small library of α-functionalized azepenes in hand, and with the "bottom-up" approach to vicinally difunctionalized azepenes in mind (see Fig. 2), we commenced our studies in search of efficient conditions for β-regioselective functionalization. Seeking an expedient route toward 2-benzazepanes, a one-pot Diels-Alder/benzannulation sequence, featuring a number of electronically diverse dienes such as **7–9** and several symmetrical and unsymmetrical dienophiles was explored. Thus, a solution of phenyl-bearing diene **7a** and dimethyl maleate in 1,4-dioxane was heated to 130 °C. After 1 h at this temperature, a 1:1 mixture of isomeric adducts is obtained (as judged by LC-MS and ^{1}H NMR of the crude mixture). Of note, hydrocarbon solvents such as toluene and benzene do not appear to alter the selectivity of the cycloaddition. Subsequent SeO_2–mediated oxidation of the cycloadducts affords benzazepane **17** (Table 1, entry 1). When MnO_2 is employed as the oxidant, benzannulation proceeds less efficiently to afford **17a** in only 48% yield (over two steps). When diene **7a** is reacted with symmetrical but cyclic dienophile such as maleic anhydride, a single cycloadduct (not shown) is formed after 2 h at 100 °C, which undergoes uneventful SeO_2-mediated oxidation to afford benzazepane **18a** (entry 2). The reaction between frustrated diene **7b** and methyl acrylate affords a single benzazepane (i.e., **19a**, entry 3) following oxidation with SeO_2. However, the regioselective outcome (established using HMBC analysis) is somewhat dependent on the stereoelectronic environment. This is supported by the observation that whereas **7b** and methyl acrylate afford a single benzazepane, the former reacts with *tert*-butyl acrylate to give ortho benzazepane **20a** and meta benzazepane **20b** in a product ratio of 80:20 (entry 4). Furthermore, when diene **7c** and *tert*-butyl acrylate are utilized, the regioselectivity is further compromised and **21a**/**b** are obtained in a 60:40 ratio (entry 5). Electronically more suitable diene **9** reacts rapidly with *tert*-butyl acrylate or *N*-isopropylacryl amide affording predominantly one cycloadduct in each case (entries 6 & 7, respectively). Disappointingly, both Diels-Alder adducts afford mainly decomposition products during attempts to oxidize the hexannulated azepenes using SeO_2. Of note, dienes **7a-c** and **9** fail to react with electron-rich 2π-electron components such as phenyl vinyl ether and ethyl vinyl ether (entries 8–10), indicating a preference for normal electron demand for the cycloadditions depicted in Table 1.[26]

Table 1 One-pot preparation of 2-benzazepanes using α-alkenyl eneformamides

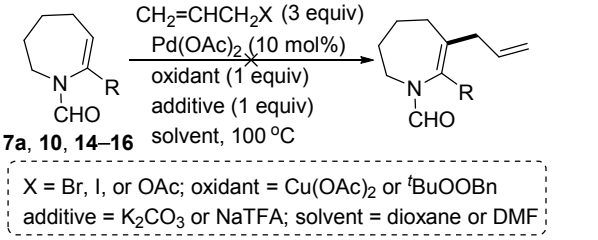


Entry	R^1	R^2	Diene	R^3	R^4	Products	Ratio	% yield
1	H	Ph	**7a**	CO_2Me	CO_2Me	**17a/b**	>99:1	64
2	H	Ph	**7a**	$R_3 + R_4 = C_2O_3$		**18a/b**	>99:1	75
3	H	CO_2Me	**7b**	H	CO_2Me	**19a/b**	>99:1	67
4	H	CO_2Me	**7b**	H	CO_2tBu	**20a/b**	80:20	73
5	H	CO_2tBu	**7c**	H	CO_2tBu	**21a/b**	60:40	77
6	OEt	H	**9**	H	CO_2tBu	**22a/b**	>99:1	80*
7	OEt	H	**9**	H	CONH*i*Pr	**23a/b**	nd	<5
8	H	Ph	**7a**	H	Ph or Et	**24a/b**	na	0*
9	H	CO_2tBu	**7c**	H	Ph or Et	**25a/b**	na	0*
10	OEt	H	**9**	H	Ph or Et	**26a/b**	na	0*

* before oxidation, nd = not determined, na = not applicable

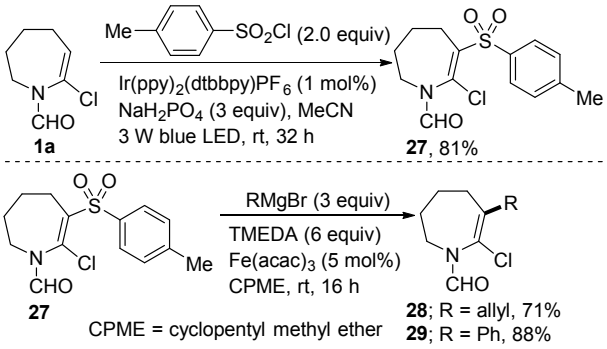


After successfully developing a one-pot procedure for the synthesis of 2-benzazepanes from *N*-formyl amino dienes, we became interested in finding efficient conditions for β-allylation of α-carbo-functionalized eneformamides such as those depicted in Figure 3. An allyl motif on the skeleton of a nitrogen heterocycle offers several advantages for the synthesis of alkaloids and nitrogen-containing pharmaceuticals. As has been previously demonstrated in the piperidine series, the double bond on the allyl moiety can be reduced,[27, 28] oxidized,[28, 29] engaged in metathesis reactions,[30] or carbolithiated.[31] Disappointingly, using the conditions described in Scheme 1), a plethora of α-functionalized eneformamides (e.g., **7a**, **10**, **14**, **15**, and **16**) failed to furnish the desired β-allylated-x-substituted azepenes under Pd-catalysis. Whereas **7a**, **14**, **15**, and **16** show no reactivity, enyne **10** undergoes unproductive reactivity at the triple bond terminus. The slow reactivity encountered with substrates such as **14** is consistent with previous findings from the laboratories of Gillaizeau,[11, 13] within the context of β-alkenylation of α-substituted piperidine enesulfonamides.



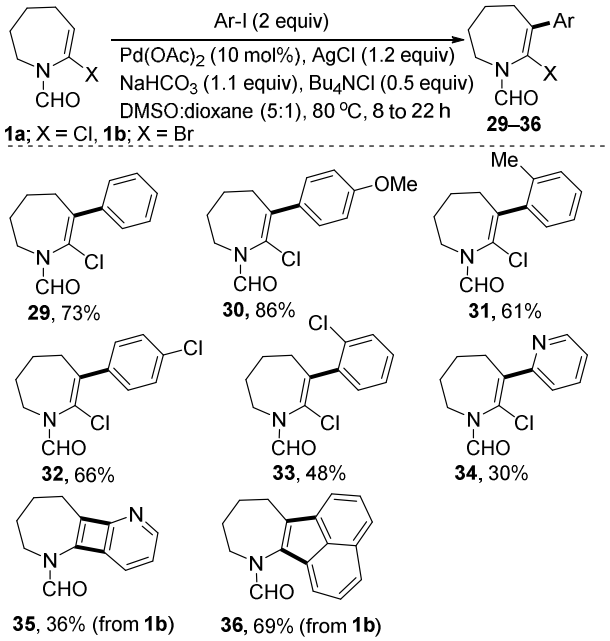
Scheme 1 Attempted Pd-catalyzed β-allylation of α-carbofunctionalized eneformamides

Faced with the aforementioned reactivity and chemoselectivity issues, we turned our attention to the conceptually more attractive "top-down" approach to vicinally difunctionalized azepenes (see Fig. 2). Encouragingly, the application of our recently reported conditions for β-sulfonation of α-chloro piperidine eneformamides[32] to azepane homologue **1a** cleanly yielded vinyl sulfone **27**, which successfully undergoes allylative desulfonation under iron-catalysis[32, 33] to afford allylated piperidine **28** (Scheme 2). Additionally, α-chloro-β-sulfonyl eneformamide **27** reacts efficiently with phenylmagnesium bromide under similar reaction conditions (see **29**).



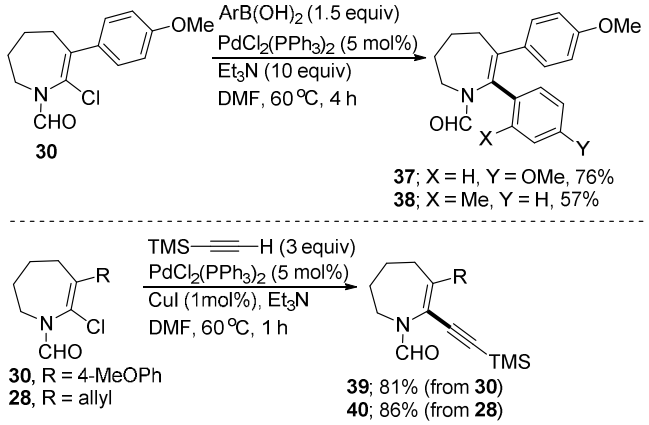
Scheme 2 Fe-catalyzed β-allylation and arylation of α-chloro-β-sulfonyl eneformamide **27**

In another important mode of reactivity, these studies have revealed that α-chloro eneformamides such as **1a** are amenable to direct regioselective β-arylation. For example, **1a** couples satisfactorily with iodobenzene under Pd-catalyzed conditions analogous to those first employed by Gunda[34] in the context of β-arylation of enaminones (Scheme 3, see **29**). Consistent with Gunda's reports, the coupling of **1a** with aryl iodides is highly dependent on the stereoelectronics of the iodide coupling partner. For instance, whereas electron-rich aryl iodides are highly efficient coupling partners (see **30**), their electron-deficient counterparts have an adverse effect on the efficacy of the coupling (see **32**). Additionally, ortho-substituted aryl iodides afford the β-arylated azepene derivatives in diminished yields (see **33** *vs* **32**). Not surprisingly, π-deficient heteroaryl iodides such as 2-iodopyridine react recalcitrantly under the identified conditions, affording the β-heteroarylated products in synthetically unattractive yields (see **34**). Intriguingly, when bromo eneformamide **1b** is reacted with 3-bromo-2-iodopyridine, β-arylation is accompanied by intramolecular Heck-type coupling at C-2 to afford isolable [7-4-6] tricycle **35**. As a testament to the generality of the transformation, **1b** reacts with 1-bromo-8-iodonaphthalene to give tetracycle **36** in acceptable yield.



Scheme 3 Palladium-catalyzed β-arylation of α-chloro eneformamide **1a**

With the aim of accessing fused polyaromatic azaheterocycles, 2-halo-3-arylated eneformamide **30** was subjected to some cross-coupling protocols. Thus, Suzuki coupling of **30** with aryl boronic acids affords doubly arylated azepenes **37** and **38** (Scheme 4).[32] Furthermore, Sonogashira coupling of **30** with trimethylsilylacetylene in the presence of a catalytic amount of CuI affords versatile enyne **39**. Under identical conditions, β-allylated azepene **28** gives rise to disubstituted azepene **40**.



Scheme 4 Palladium-catalyzed α-arylation and alkynylation of β-functionalized α-chloro eneformamides

Conclusions

In summary, the synthesis of vicinally difunctionalized azepenes has been accomplished through α-halo and alkenyl eneformamides. A β-regioselective sulfonation/desulfonation sequence has provided a convenient route for accessing highly versatile 3-allylated azepenes. The strategy described herein has led to the one-pot synthesis of 2-benzazepanes whose benzenoid portion is highly functionalized. These synthetic sequences have also sets the stage for the expedient, stereo- and regiocontrolled preparation of azepene-containing alkaloids, details of which will be disclosed later.

Experimental

All experiments involving air and moisture sensitive reagents such as palladium/iron precatalysts and Grignard reagents were carried out under an inert atmosphere of argon or nitrogen and using freshly distilled solvents. Anhydrous 1,4-dioxane was used as purchased. Dichloromethane was distilled from $MgSO_4$. Aryl iodides, boronic acids, terminal alkynes, and simple dienophiles were obtained from commercial sources. Column chromatography was performed on silica gel (230-400 mesh). Thin-layer chromatography (TLC) was performed on silica plates. Visualization of the TLC plates was aided by UV irradiation at 254 nm or by $KMnO_4$ staining. ^1H, ^{13}C, DEPT-135, and 2D-NMR spectra were acquired using C_6D_6 or $CDCl_3$ as solvent at room temperature. Chemical shifts are quoted in parts per million (ppm).

General Procedure A: Synthesis of 2-benzazepanes
A 5 mL tube was flame-dried, evacuated and flushed with nitrogen. A solution of the desired dienophile (0.10 M in dioxane) was added to a solution of the diene[1] (0.10 M in dioxane) under nitrogen. The mixture was heated to the desired temperature whiles being stirred. Upon completion (TLC and GC-MS or LC-MS monitoring), the mixture was cooled to room temperature and SeO_2 (3 equiv) was added. The heterogeneous mixture was heated to 130 °C for 30 min to give the crude benzazepane(s).

General Procedure B: C-3 arylation of α-halo eneformamides
To a vial was added the eneformamide (0.5 mmol), aryl iodide (1.0 mmol, 2.0 equiv), $Pd(OAc)_2$ (12 mg, 10 mol %), Bu_4NCl (70 mg, 0.25 mmol, 0.5 equiv), $NaHCO_3$ (47 mg, 0.55 mmol, 1.1 equiv), and AgCl (86 mg, 0.6 mmol, 1.2 equiv) were mixed in DMSO/dioxane (5 mL/1 mL). The reaction vessel was then capped and stirred at 80 °C for the indicated length of time prior to cooling to room temperature. The mixture was filtered through a pad of Celite and washed with EtOAc. The filtrate was concentrated under reduced pressure to give the crude product.

Synthesis of benzazepane 17a: Prepared from **7a** (227.3 mg, 1.0 mmol), dimethyl maleate (0.51 mL, 4 mmol, 4 equiv), and SeO_2 (3 equiv) using **General Procedure A.** Time = 2 h, Temp = 130 °C. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20 to 50:50). Yield = 235 mg, 64%. ^1H NMR (400 MHz, $CDCl_3$) δ 8.36 (1H), 7.49 to 7.17 (5H), 3.91 (1H), 3.73 to 3.70 (2H), 3.63 (1H), 2.87 to 2.77 (2H), 1.89 to 1.80 (4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.24, 168.06, 161.67, 143.31, 140.67, 138.78, 136.45, 134.24, 128.87, 128.51, 128.11, 128.01, 52.88, 52.44, 44.85, 29.98, 27.28, 24.97. HRMS calc for $C_{21}H_{21}NO_5$ 367.1420, found 367.1426.

Synthesis of benzazepane 18a: Prepared from **7a** (227.3 mg, 1.0 mmol), maleic anhydride (392 mg, 4 mmol, 4 equiv), and selenium dioxide using **General Procedure A.** Temp = 100 °C, Time = 2 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (70:30 to 50:50). Yield = 241 mg, 75%. ^1H NMR (400 MHz, C_6D_6) δ 7.99 (1H), 7.28 to 7.15 (5H), 6.45 (1H), 3.36 to 3.33 (2H), 2.97 to 2.86 (2H), 1.43 to 1.17 (4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.50, 161.38, 160.85, 149.17, 142.46, 140.33, 134.10, 133.98, 133.55, 129.71, 129.17, 128.62, 125.47, 45.07, 27.78, 26.59, 24.53. HRMS calc for $C_{19}H_{15}NO_4$ 321.1001, found 321.0997.

Synthesis of benzazepane 19a: Prepared from **7b** (209.2 mg, 1.0 mmol), and methyl acrylate (0.554 mL, 6 mmol, 6 equiv) and selenium dioxide (3 equiv) using **General Procedure A.** Time = 2 h,

Temp = 130 °C. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20). Yield = 195 mg, 67%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (1H), 7.55 (1H), 7.45 (1H), 3.89 to 3.64 (8H), 2.88 to 2.84 (2H), 1.88 to 1.55 (4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.72, 166.92, 161.63, 143.88, 143.57, 131.62, 131.31, 131.02, 126.63, 53.03, 44.85, 34.75, 28.80, 25.78. HRMS calc for $C_{15}H_{17}NO_5$ 291.1107, found 291.1103.

Synthesis of benzazepanes 20a/b: Prepared from **7b** (209.2 mg, 1.0 mmol), *tert*-butyl acrylate (0.29 mL, 2 mmol, 2 equiv), and selenium dioxide (3 equiv) using **General Procedure A.** Time = 2 h, Temp = 130 °C. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (90:10 to 70:30). Yield = 243 mg, 73%. **Data for 20a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (1H), 7.57 (1H), 7.43 (1H), 3.98 to 3.64 (5H), 2.88 to 2.84 (2H), 1.95 to 1.44 (13H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.94, 166.17, 161.46, 143.21, 133.23, 131.09, 130.53, 126.41, 82.64, 52.66, 44.67, 34.57, 28.71, 27.98, 25.68. . HRMS calc for $C_{18}H_{23}NO_5$ 333.1576, found 333.1572.

Synthesis of benzazepanes 21a/b
Prepared from **7c** (251.3 mg, 1.0 mmol) and *tert*-butyl acrylate (0.29 mL, 2 mmol, 2 equiv) using **General Procedure A.** Time = 2 h, Temp = 130 °C. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (90:10 to 80:20). Yield = 289 mg, 77%. **Data for 21a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (1H), 7.72 (1H), 7.48 (1H), 7.33 (1H), 3.66 (4H), 2.83 to 2.78 (4H), 1.93 to 1.38 (26H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.60, 166.34, 165.37, 164.05, 161.96, 161.57, 143.78, 142.89, 142.57, 142.29, 134.74, 133.48, 132.62, 130.89, 130.83, 129.65, 128.64, 126.35, 82.53, 82.33, 82.28, 81.99, 44.87, 44.63, 34.47, 29.58, 28.74, 28.15, 28.10, 28.02, 27.99, 27.00, 25.72, 24.66. HRMS calc for $C_{21}H_{29}NO_5$ 375.2046, found 375.2040.

Synthesis of cycloadduct 22a: Prepared from **9** (195.3 mg, 1.0 mmol) and *tert*-butyl acrylate (0.29 mL, 2 mmol, 2 equiv) using **General Procedure A.** Time = 2 h, T = 100 °C. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (60:40 to 10:90). Yield = 259 mg, 80%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (1H), 4.17 to 4.12 (2H), 3.83 to 3.71 (2H), 3.59 to 3.23 (3H), 3.08 to 2.34, 1.93 to 1.37. ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.48, 161.94, 149.62, 113.17, 81.46, 63.25, 48.44, 45.27, 37.60, 29.01, 28.65, 27.92, 25.56, 25.46, 23.58, 23.27, 14.27.

Attempted synthesis of benzazepane 23a: Obtained in trace amounts from **9** (19.5 mg, 0.10 mmol), *N*-isopropyl acrylamide (22.6 mg, 0.20 mmol, 2 equiv), selenium dioxide (3 equiv) using **General Procedure A.** Time = 2 h.

Synthesis of vinyl sulfone 27: To a 100 mL flask was equipped with a rubber septum and magnetic stir bar was added α-chloro eneformamide **1a** (800 mg, 5.0 mmol, 1.0 equiv), *p*-toluenesulfonyl chloride (1.91 g, 10 mmol, 2.0 equiv), $Ir(ppy)_2(dtbbpy)PF_6$ (1 mol%), Na_2HPO_4 (15.0 mmol, 3 equiv). The flask was evacuated and backfilled with argon for several times. CH_3CN (50 mL, 0.1 M) was added via syringe under argon. The mixture was then irradiated by a 3 W blue LED strip at a distance of 5 cm. After the reaction was complete (as judged by GC-MS and TLC monitoring, ~32 h), the mixture was poured into a separatory funnel containing H_2O (50 mL) and EtOAc (100 mL). The layers were separated and the aqueous layer was extracted three times with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude product, which was purified by flash chromatography (hexane/EtOAc, 60:40) on silica gel to afford 1.27 g of the desired product as an amorphous solid in 81% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.92 (1H), 7.73 (2H), 7.28 (2H), 3.59 to 3.56 (2H), 2.40 (3H), 2.14 to 2.09 (2H), 1.76 to 1.70 (2H), 1.56 to 1.50 (2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.1, 145.6, 134.3, 130.8, 130.6, 129.9, 129.8, 127.6, 44.1, 28.6, 26.7, 23.3, 21.9. HRMS calc for $C_{14}H_{16}ClNO_3S$ 313.0539, found 313.0551.

Synthesis of allylated azepene 28: To an oven-dried, septum-capped two-necked flask equipped with a stir bar were added freshly distilled TMEDA (0.90 mL, 6.00 mmol, 6.0 equiv), allylmagnesium bromide (1.0 M in THF, 3.00 mL, 3.00 mmol, 3.0 equiv) [diluted with anhydrous cyclopentyl methyl ether (CPME, 3.0 mL)] via syringe under an argon atmosphere. One of the septa was opened and $Fe(acac)_3$ (20 mg, 0.050 mmol, 5 mol%) was rapidly introduced and the suspension was diluted with CPME (5.0 mL) was added. After several minutes (~5 min), vinyl sulfone **27** (313 mg, 1.00 mmol, 1.0 equiv) in CPME (5.0 mL) was added. The suspension was sonicated until a clear solution was obtained (~10 min, longer time required for less suluble Grignard reagents). After 5 h at rt (TLC and GC-MS monitoring), the mixture was quenched by slow addition of *sat* NH_4Cl. It was then filtered through a pad of Celite under vacuum and the remaining residue was rinsed with EtOAc. The filtrate was transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with EtOAc and the combined organic extracts were dried over Na_2SO_4 (30 min), filtered, and concentrated in under reduced pressure to give the crude product. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (90:10 to 70:30). Yield = 141 mg, 71%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (1H), 6.09 to 5.98 (1H), 5.31 (1H), 5.16 (1H), 3.95 (2H), 3.63 to 3.60 (2H), 2.18 to 2.14 (2H), 1.84, to 1.74 (2H), 1.61 to 1.55 (2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.5, 134.2, 130.7, 124.4, 119.1, 44.1, 36.5, 28.5, 26.9, 23.8. HRMS calc for $C_{10}H_{14}ClNO$ 199.0607, found 199.0610.

Synthesis of β-phenylated azepene 29 by arylative desulfonation: Prepared from vinyl sulfone **27** (1 mmol) in the same way as was **28**; Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (70:30 to 50:50). Yield = 207 mg, 88%. ^{1}H NMR (400 MHz, C_6D_6) δ 8.90 (1H), 7.30 to 6.96 (5H), 3.52 to 3.49 (2H), 1.76 to 1.72 (2H), 1.44 to 1.38 (2H), 1.21 to 1.15 (2H), 1.10 to 1.07 (2H). ^{13}C NMR (101 MHz, C_6D_6) δ 161.89, 133.09, 132.11, 130.09, 129.70, 126.27, 123.04, 44.39, 28.44, 27.94, 24.59. HRMS calc for $C_{13}H_{14}ClNO$ 235.0764, found 235.0760.

Synthesis of β-phenylated azepene 29 by Pd-catalyzed direct arylation with iodobenzene: Prepared from **1a** (80 mg, 0.5 mmol) and iodobenzene (204 mg, 2 equiv) using **General Procedure B.** Time = 22 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (70:30 to 50:50). Yield = 85.8 mg, 73%.

Synthesis of β-arylated azepene 30: Prepared from **1a** (80 mg, 0.5 mmol) and 4-iodoanisole (234 mg, 2 equiv) using **General Procedure B.** Time = 16 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (50:50 to 20:80). Yield = 114 mg, 86%. ^{1}H NMR (400 MHz, C_6D_6) δ 7.92 (1H), 7.03 (2H), 6.63 (2H), 3.53 to 3.50 (2H), 3.39 (3H), 1.98 to 1.93 (2H), 1.62 to 1.59 (2H), 1.31 to 1.28 (2H). ^{13}C NMR (101 MHz, C_6D_6) δ 162.65, 159.77, 142.40, 130.59, 121.63, 115.83, 114.56, 54.73, 44.42, 28.59, 27.13, 24.18. HRMS calc for $C_{14}H_{16}ClNO_2$ 265.0870, found 265.0874.

Synthesis of β-arylated azepene 31: Prepared from **1a** (80 mg, 0.5 mmol) and iodotoluene (218 mg, 2 equiv) using **General Procedure**

B. Time = 22 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (70:30 to 50:50). Yield = 76 mg, 61%. ^1H NMR (400 MHz, $CDCl_3$) δ 8.56 (1H), 7.57 (1H), 7.27 to 7.24 (2H), 7.08 (1H), 3.68 to 3.65 (2H), 2.44 (3H), 2.22 to 2.18 (2H), 1.83 to 1.80 (2H), 1.66 to 1.62 (2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.54, 137.83, 132.31, 130.83, 127.55, 127.31, 127.24, 124.91, 124.36, 44.11, 28.55, 26.92, 23.86, 22.91. HRMS calc for $C_{14}H_{16}ClNO$ 249.0920, found 249.0912.

Synthesis of β-arylated azepene 32: Prepared from **1a** (80 mg, 0.5 mmol) and 1-chloro-4-iodobenzene (238 mg, 2 equiv) using **General Procedure B.** Time = 22 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20). Yield = 88.8 mg, 66%. ^1H NMR (400 MHz, C_6D_6, mixture of rotamers) δ 7.92 (1H), 7.02 (2H) 6.63 (2H), 3.52 (2H), 1.98 to 1.93 (2H), 1.62 to 1.59 (2H), 1.30 to 1.26 (2H). ^{13}C NMR (101 MHz, C_6D6) δ 162.59, 142.29, 137.45, 134.54, 129.97, 129.43, 129.06, 127.89, 127.14, 126.24, 125.05, 48.50, 44.96, 32.88, 29.22, 27.87, 27.52, 24.58, 23.87. HRMS calc for $C_{13}H_{13}Cl_2NO$ 269.0374, found 269.0366.

Synthesis of β-arylated azepene 33: Prepared from **1a** (80 mg, 0.5 mmol) and 1-chloro-4-iodobenzene (238 mg, 2 equiv) using **General Procedure B.** Time = 22 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20). Yield = 64.6 mg, 48%. ^1H NMR (400 MHz, C_6D_6, mixture of rotamers) δ 8.06 (1H), 7.64 (1H, minor), 7.27 to 6.61 (8H, both), 3.77 to 3.74 (2H), 3.15 to 3.12 (2H, minor), 1.86 to 1.81 to 1.74 (4H, both), 1.53 to 1.48 (2H), 1.31 to 1.19 (6H). ^{13}C NMR (101 MHz, C_6D_6) δ 160.89, 138.20, 133.15, 132.24, 131.68, 131.59, 130.85, 123.82, 123.10, 122.95, 49.09, 45.17, 30.81, 27.49, 27.23, 23.78, 23.36. HRMS calc for $C_{13}H_{13}Cl_2NO$ 269.0374, found 269.0366.

Synthesis of β-arylated azepene 34: Prepared from **1a** (80 mg, 0.5 mmol) and 2-iodopyridine (205 mg, 2 equiv) using **General Procedure B.** Time = 36 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (50:50 to 10:90). Yield = 35.4 mg, 30%. ^1H NMR (400 MHz, $CDCl_3$) δ 8.52 (1H), 8.37 (1H), 7.57 to 7.49 (2H), 7.28 (1H), 3.62 (2H), 2.19 to 2.14 (2H), 1.81 to 1.76 (2H), 1.61 to 1.56 (2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.6, 150.3, 142.3, 138.6, 130.8, 128.4, 124.5, 122.7, 44.2, 28.6, 27.0, 23.9. HRMS calc for $C_{12}H_{13}ClN_2O$ 236.0716, found 236.0712.

Synthesis of tricycle 35: Prepared from **1b** (102 mg, 0.5 mmol) and 3-bromo-2-iodopyridine (284 mg, 2 equiv) using **General Procedure B.** Time = 36 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (50:50 to 10:90). Yield = 36 mg, 36%.^1H NMR (400 MHz, C_6D_6) δ 7.94 to 7.90 (2H), 6.73 (1H), 6.33 (2H), 3.73 (2H), 1.85 to 1.79 (2H), 1.57 to 1.51 (2H), 1.29 to 1.23 (2H). ^{13}C NMR (101 MHz, C_6D_6) δ 161.0, 149.6, 141.7, 139.8, 132.7, 132.6, 128.9, 126.3, 45.6, 28.5, 28.1, 24.6. HRMS calc for $C_{12}H_{12}N_2O$ 200.0950, found 200.0954.

Synthesis of tetracycle 36: Prepared from **1b** (102 mg, 0.5 mmol) and 1-bromo-8-iodonaphthalene (333 mg, 2 equiv) using **General Procedure B.** Time = 22 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (70:30). Yield = 85.9 mg, 69%. ^1H NMR (400 MHz, C_6D_6) δ 8.07 (1H), 7.89 (1H), 7.61 to 7.51 (2H), 7.31 to 7.09 (3H), 3.87 (2H), 1.97 to 1.91 (2H), 1.66 to 1.62 (2H), 1.46 to 1.40 (2H). ^{13}C NMR (101 MHz, C_6D6) δ161.6, 141.3, 136.5, 134.0, 131.2, 129.0, 128.6, 126.6, 125.9, 125.1, 124.9, 122.2, 44.8, 27.4, 27.1, 24.2. HRMS calc for $C_{17}H_{15}NO$ 249.1154, found 249.1148.

Synthesis of α,β-diarylated azepene 37: To an oven-dried, septum-capped 2-neck-round bottom flask equipped with a stir bar, was added **30** (26.6 mg, 0.1 mmol, 1.0 equiv) in DMF (1 mL) under an argon or nitrogen atmosphere. 4-methoxyphenyl boronic acid (23 mg, 0.15 mmol, 1.5 equiv) was added followed by addition of Et_3N (0.12 mL, 0.5 mmol, 5 equiv). After completely degassing the flask, $PdCl_2(PPh_3)_2$ (3.5 mg, 5 mol%) was added rapidly. The mixture was then heated to 60 ^oC and stirred for 4 h (TLC and LC-MS monitoring). Upon completion, the mixture was quenched with water and extracted with CH_2Cl_2. The combined organic layers were concentrated to ~5 mL and dried with for ~30 min with Na_2SO_4. It was filtered and evaporated to give the crude product. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (50:50 to 20:80). Yield = 25.6 mg, 76%. ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 (1H), 7.52 (2H), 7.39 (2H), 6.99 (2H), 6.88 (2H), 3.90 to 3.85 (8H), 2.43 to 2.39 (2H), 2.03 to 1.97 (2H), 1.76 to 1.70 (2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7, 159.8, 158.6, 142.5, 132.1, 130.6, 121.7, 115.9, 115.6, 114.0, 54.8, 54.8, 44.5, 28.6, 27.2, 24.2. HRMS calc for $C_{21}H_{23}NO_3$ 337.1678, found 337.1684.

Synthesis of α,β-diarylated azepene 38: Prepared in the same way as **37** using *o*-toluylboronic acid (20.4 mg). Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20 to 50:50). Yield = 18.3 mg, 57%. ^1H NMR (400 MHz, C_6D_6) δ 7.97 (1H), 7.46 (1H), 7.22 to 7.16 (4H), 6.81 (1H), 6.79 (2H), 3.69 to 3.66 (5H), 2.34 (3H), 2.26 to 2.18 (2H), 1.84 to 1.78 (2H), 1.57 to 1.54 (2H). ^{13}C NMR (101 MHz, C_6D_6) δ 163.1, 159.7, 142.3, 137.7, 132.2, 130.7, 130.5, 127.1, 124.8, 115.9, 114.6, 114.0, 55.2, 44.7, 28.6, 27.3, 24.3, 22.8. HRMS calc for $C_{21}H_{23}NO_2$ 321.1729, found 321.1723.

Synthesis of enyne 39: To an oven-dried, septum-capped 2-neck-round bottom flask equipped with a stir bar, was added **30** (26.6 mg, 0.1 mmol, 1.0 equiv) in DMF (1 mL) under an argon or nitrogen atmosphere. TMS acetylene (0.043 mL, 0.30 mmol, 3 equiv) was added followed by addition of Et_3N (0.12 mL, 0.5 mmol, 5 equiv). After completely degassing the flask, $PdCl_2(PPh_3)_2$ (3.5 mg, 5 mol%) and CuI (0.5 mg, 1 mol%) were added rapidly and concurrently. The mixture was then heated to 60 ^oC and stirred for 1 h (TLC and LC-MS monitoring). Upon completion, the mixture was quenched with water and extracted with CH_2Cl_2. The combined organic layers were concentrated to ~5 mL and dried with for ~30 min with Na_2SO_4. It was filtered and evaporated to give the crude product. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20). Yield = 53 mg, 81%. ^1H NMR (400 MHz, C_6D_6) δ 8.93 (1H), 7.17 (2H), 6.38 (2H), 3.42 (2H), 3.10 (3H), 1.63 to 1.59 (2H), 1.35 to 1.29 (2H), 1.11 to 1.05 (2H), 0.10 (9H). ^{13}C NMR (101 MHz, C_6D_6) δ 161.0, 158.7, 132.1, 129.7, 125.7, 115.6, 112.7, 101.8, 94.6, 54.4, 43.6, 27.6, 27.0, 23.8, -0.7. HRMS calc for $C_{19}H_{25}NO_2Si$ 327.1655, found 327.1649.

Synthesis of enyne 40: Prepared from **28** (0.1 mmol) in the same way as was **39** from **30**. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20). Yield = 53 mg, 86%. ^1H NMR (400 MHz, C_6D_6) δ 8.92 (1H), 5.65 (1H), 4.85 to 4.68 (2H), 3.44 to 3.35 (4H), 1.63, to 1.59 (2H), 1.35 to 1.29 (2H), 1.12 to 1.06 (2H), 0.10 (9H). ^{13}C NMR (101 MHz, C_6D_6) δ 161.0, 134.1, 129.7, 125.6, 118.1, 101.7, 94.6, 43.6, 32.2, 27.6, 27.0, 23.9, -0.6.

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Notes and references

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