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Leveraging the 1,3-azadiene-anhydride reaction for the synthesis of functionalized piperidines bearing up to five contiguous stereocenters†

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A modular and scalable strategy, which remodels 3-methylglutaric anhydride to 2-oxopiperidines bearing at least three contiguous stereocenters is described. The approach relies on the chemoselective and stereocontrolled annulation of 1,3-azadienes with the anhydride component. The resulting acid-tethered allylic 2-oxopiperidines are then engaged in several selective fragment growth processes, including catalytic denitrative alkenylation, halolactonization, and Vilsmeier–Haack functionalization.

Introduction

An overarching and intrinsic goal when designing synthetic methodology is to identify approaches whereby simple commercially available precursors or easily accessible synthetic intermediates are converted into a broad array of products, which efficiently tap into uncharted chemical space. Moreover, there are high incentives for the construction of architecturally complex sp^3-enriched azaheterocyclic scaffolds,[1] especially the piperidine motif, which is arguably the most prevalent.[2] As such, synthetic methods for its construction and diversification are highly coveted. In particular, polysubstituted piperidines and 2-oxopiperidines are increasingly attractive fragments for potential drug discovery since the strategic placement of substituents about this three-dimensional scaffold is ideally suited for structure–activity relationship studies.[3] Although the synthesis of functionalized piperidines remains daunting,[4] recent advances[5] are starting to bring these once elusive building blocks into the mainstream. However, most of these advances are predicated on taking an existing piperidine scaffold and installing substituents by functionalization (*e.g.*, through cross-coupling).[6] There is also a relative paucity in stereo- and regioselective approaches to alkenylated and methylated piperidines, despite their prevalence in natural products (*e.g.*, GB 17, arboflorine, spirafine D, caulophyllumine B, dienomycin C, and pinidine, Fig. 1) and their frequent use as versatile building blocks for the preparation of medicinal agents.[7] For instance, the introduction of methyl groups has the potential to drastically improve the biological activities of a drug candidate by altering its binding affinity, solubility, and metabolism.[8] Methyl branches are also favorable structural units in tailor-made fuel components with advanced combustion properties.[9]

A complementary strategy to these versatile piperidine scaffolds is to directly forge the azaheterocycle by an annulation protocol. We were therefore motivated by current methodological limitations as well as the relevance of methylated and alkenylated piperidines to develop a step-economical, diastereoselective, and scalable method for the preparation of highly decorated sp^3-rich piperidines bearing at least three *contiguous stereocenters*. Previously, we disclosed that glutaric anhydride (**1a**) is a more competent substrate than 3,3-dimethylglutaric anhydride (**1b**) in the 1,3-azadiene-anhydride reaction (Fig. 2).[10] Indeed, sterically challenged **1b** failed to react even at elevated temperatures (up to 150 °C) even though constitutionally isomeric 2,2-dimethylglutaric anhydride reacted efficiently with 1,3-azadienes of type **2** at 110 °C.[10] In the current study, we seek to evaluate the performance (with respect to reactivity, diastereoselectivity, and chemoselectivity) of 3-methylglutaric anhydride (**1c**) toward 1,3-azadiene partners, and elaborate the product (*i.e.*, **3c**) to several synthetically and pharmaceutically

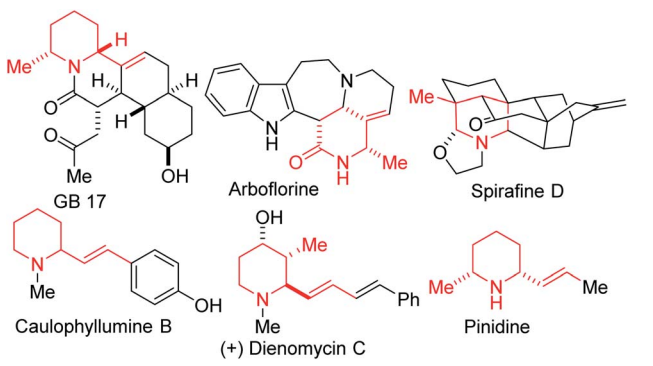

Fig. 1 Examples of biologically active methylated and/or alkenylated piperidines.

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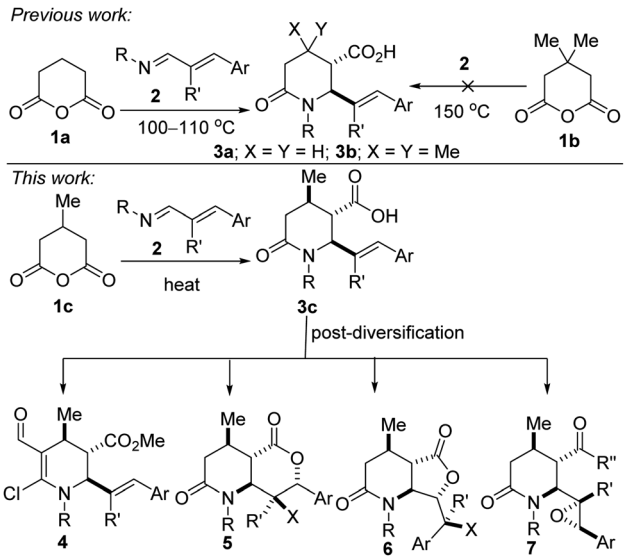
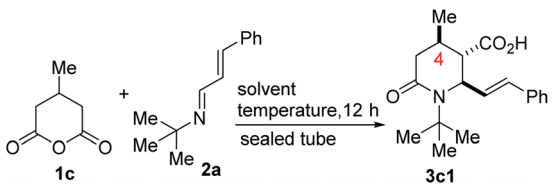


Fig. 2 Proposed plan for the synthesis of methylated allylic piperidines and potential synthetic applications.

Table 1 Optimization of the annulation of **1c** with azadiene **2a**



Entry	Solvent	Temp. (°C)	% Yield of **3c1**
1	Benzene	90	0
2	*o*-Xylene	130	56
3	Chlorobenzene	120	31
4	**2-MeTHF**	**80**	**84**
5	Toluene	110	77
6	Ph_2O	180	26
7	1,4-Dioxane	110	8
8	Toluene	70	72[a]
9	Toluene	90	76[b]
10	Toluene	100	42[c]

[a] After 24 h. [b] After 8 h. [c] After 1 h.

attractive topologies (see **4**–**7**). Since many existing cyclization strategies for piperidine synthesis tend to exhibit poor generality, suffer from low regio- and stereochemical control, require protecting group manipulations, or depend on a specific directing group,[11] we anticipate that the current approach, which side-steps these aforementioned limitations, would greatly expand the structural space for the discovery of new piperidine pharmacophores. Indeed, this anhydride-imine reaction is known to be a powerful tool for the synthesis of combinatorial and targeted compound libraries as well as for producing building blocks in multigram (up to 100 g) scale.[12]

Results and discussion

We initiated studies toward the construction of methylated and alkenylated piperidine derivatives and subsequent fragment growth by attempting to find suitable directing group-free conditions for the annulation reaction between **1c** and model azadiene **2a** (Table 1). Although we were cognizant of the promiscuous reactivity of **2** with enolizable cyclic anhydrides (which leads to a plethora of products, including Tamura-type, anhydride-Mannich-type, and Perkin-type products),[13] we surmised that just like **1a**, the mitigated reactivity of **1c** would provide an ideal balance of selectivity and reactivity. Reaction optimization was eventually carried out and it was established that 2-methyltetrahydrofuran (2-MeTHF) out-performs other reaction media (*e.g.*, benzene, *o*-xylene, chlorobenzene, toluene, diphenyl ether, and 1,4-dioxane). The chemoselective formation of 2-oxopiperidine **3c1** indicates a scenario whereby the anhydride-imine pathway (*i.e.*, Castagnoli–Cushman selectivity) out-competes the anhydride-alkene pathway (*i.e.*, Tamura selectivity). Strikingly, the reaction proceeds with impeccable stereochemical control at the C4 stereocenter, leading to the formation of predominantly one stereoisomer (as judged by GC-MS and ^{1}H NMR analyses of the crude mixture). The atom efficiency of this transformation is commendable given that with the exception of the water formed during the formation of the 1,3-azadiene (*i.e.*, **2**), all atoms originating from the enal, primary amine, and anhydride **1c** are incorporated into the product structure.

The scope of the reaction with respect to the alkenyl moiety as well as the *N*-substituent has been explored. For purposes of easier isolation and purification, the initially formed carboxylic acid has been converted to the corresponding methyl ester. These studies have revealed that 1,3-azadienes harboring both electron-neutral, electron-rich, and electron-deficient styryl groups react competently. However, there is a slight preference for electron-rich substituents (**3c1** *vs.* **3c2** *vs.* **3c3**), which is not surprising. Indeed, we are not aware of any reports on the use of aldimines derived from strongly deactivating *p*-nitrobenzaldehyde in the anhydride-Mannich reaction.[14] It is therefore a testament to the enhanced reactivity of **2** that it undergoes satisfactory annulation with **1c**. Understandably, *ortho*-substituted styrenes react with a slight decrease in efficiency (**3c2** *vs.* **3c4** or **3c3** *vs.* **3c5**). *N*-Aryl piperidines and 2-oxopiperidines are embedded in several pharmacologically pertinent targets, including Factor Xa inhibitors and phosphodiesterase-10 inhibitors.[15] *N*-aryl imines are typically reluctant substrates for the CCR,[16] presumably due to the hydrolytic instability (and subsequent proneness of the resulting amine to undergo acylation with the anhydride) as well as the relatively reduced nucleophilicity of the nitrogen atom. The reluctance is further exacerbated when electron-withdrawing anilines are employed. These challenges notwithstanding, we have demonstrated that *N*-aryl-1,3-azadienes react with varying degrees of success (**3c7**–**3c16**). It is once again a testament to the enhanced reactivity of *N*-aryl-α,β-unsaturated imines of type **2** (compared to the *N*-aryl aldimine congeners) that it undergoes satisfactory annulation

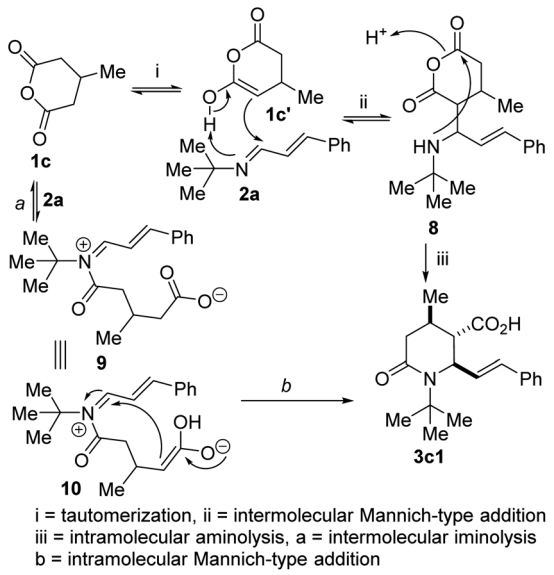


Fig. 3 Proposed mechanism for the formation of **3c1**.

with **1c**. In these cases, it was even more critical to maintain an anhydrous medium. The use of molecular sieves was advantageous.

There is no compromise in the *E*/*Z* stereoselectivity of the alkene even when trisubstituted alkenes are employed (**3c17**–**3c22**). The synthesis of metathesis-suitable *bis*-allylic 2-oxopiperidine **3c17** sets the stage for the construction of *N*-fused bicyclic amines such as indolizidines. Halogenated styrenes are well tolerated (see **3c10**, **3c13**, and **3c14**), which bodes well for late-stage diversification as the halogen group may be utilized as a functional handle for cross-coupling purposes. The incorporation of a fluorinated moiety into organic molecules generally increases the solubility, lipophilicity and metabolic stability of the parent molecules, thus, explaining why ~25% of existing preclinical drugs and 40% of agrochemicals contain at least one fluorine atom.[17] Specifically, the CF_3 group enjoys a privileged role because its incorporation often enhances efficacy by promoting electrostatic interactions with targets, improving cellular membrane permeability, and increasing robustness toward oxidative metabolism of the drug.[18] It is therefore noteworthy that fluorinated products **3c9**, **3c10**, and **3c16** are obtainable in satisfactory yields.

In the synthesis of potential drug candidates, scalability is often a significant factor as it serves to provide sufficient amounts for clinical tests. A potentially beneficial aspect of this methodology is therefore the scalable nature of the reactions given that products such as **3c13** have been prepared in gram scale, with little to no compromise in efficiency and diastereoselectivity. Of note, anhydride **1b** still does not react with **2** under these identified reaction conditions, presumably due to steric congestion.

This 1,3-azadiene-anhydride reaction is thought to proceed *via* either of two possible paths: (a) intermolecular imine acylation followed by intramolecular Mannich reaction and/or (b) intermolecular Mannich reaction followed by intramolecular acylation or anhydride aminolysis. In the current scenario, we propose that thermally-assisted tautomerization of anhydride **1c** affords enol **1c′** (Fig. 3), which undergoes Mannich-type addition with 1,3-azadiene **2a** to afford formal hydroalkylation product **8**. Subsequent intramolecular aminolysis of the anhydride by the pendant secondary amine gives rise to lactam **3c1**. The iminolysis pathway (see **9** and **10**) has not been completely ruled out at this point.

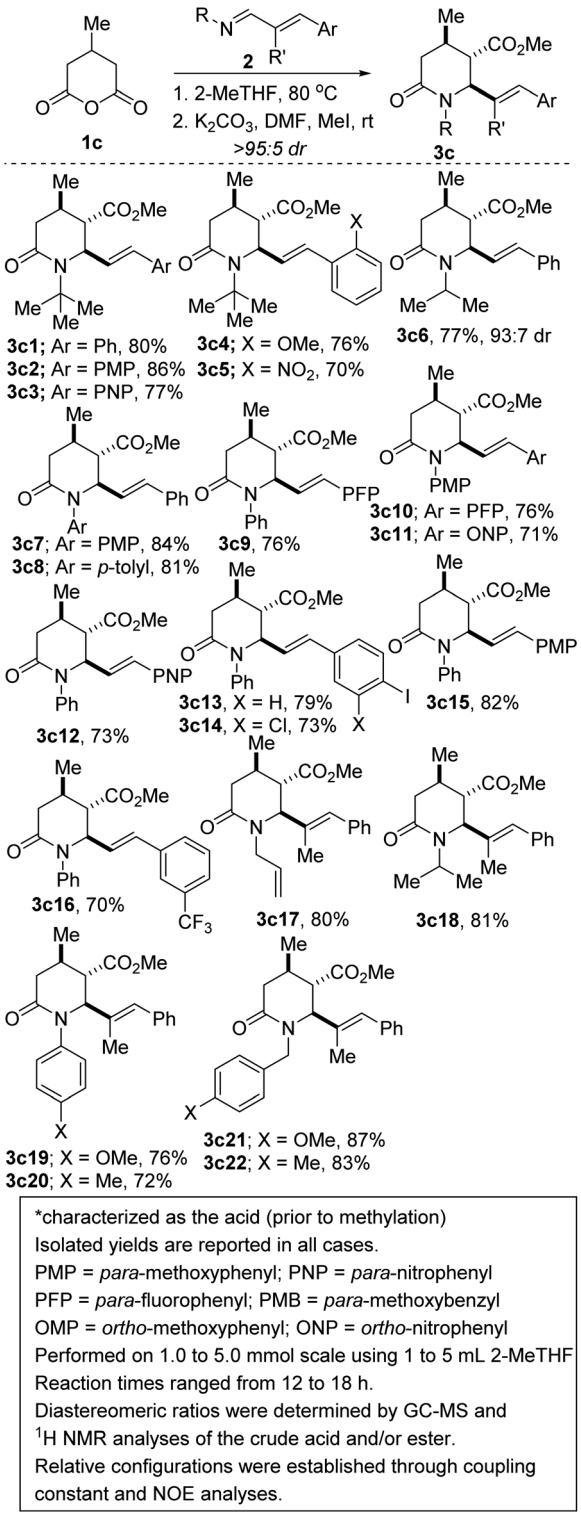
One of the key steps in drug discovery is to 'grow' fragment hits from potentially any position. Accordingly, we have explored the amenability of **3c** to fragment growth. Enamines represent a fundamental cornerstone of the organic synthetic toolbox, owing to their exceptional nucleophilicity. However, the unique reactivity of enamines is often accompanied by a high propensity to undergo hydrolysis, leading to considerable difficulties in the handling of these versatile synthons. These challenges notwithstanding, our studies have revealed that stock precursor **3c** undergoes productive lactam-selective Vilsmeier–Haack functionalization to furnish the activated enamines depicted in Scheme 2. The dehydropiperidines were obtained in satisfactory yields (see **4a–p**).

These studies have revealed that solvent-controlled halolactonization of **3c** furnishes lactam–lactones such as **5**/**6** (Scheme 3). When dichloromethane is employed as the reaction medium, 6-*endo* cyclization proceeds cleanly to furnish [6-6]-bicycles of type **5**, which harbor five contiguous stereocenters. Conversely, the use of *N*,*N*-dimethylformamide (DMF) leads to predominant 5-*exo* cyclization and furnishes [6-5]-bicycles of type **6**. The construction of these sp^3-rich bicyclic lactam–lactones is noteworthy since medicinal chemists are becoming increasingly keen on escaping flatland in view of exploring 3D-structural space.

We have found that fused bicyclic lactam–halolactones of type **5** undergo cascade deconstructive epoxy-amidation and epoxy-esterification to afford epoxylactam carboxamides (Scheme 4, see **7a–c**) or epoxylactam esters such as **7d–f**. This modular three-step sequence (starting from **1c** and **2**) proceeds with the installation of *five* contiguous stereocenters.

One of the limitations of the anhydride-imine reaction described herein is the futility of imines derived from enolizable aldehydes such as *p*-nitrohydrocinnamaldehyde given that their enamine tautomers readily undergo acylation reactions with the anhydride component. For similar reasons, the azadiene component cannot possess any unprotected primary amine functionality. Using the current approach, both limitations can be side-stepped through catalytic hydrogenation of both the alkenyl and nitro motifs resident in lactam esters such as **3c3** and **3c11** (Scheme 5, see **11a,b**). The unveiling of the aniline functionality allows for the late-stage synthesis of versatile 1,3-azadienes, which undergo another anhydride-imine reaction with phenylsuccinic anhydride (**12**) followed by bromolactonization to arrive at sp^3-rich architectures such as **13**.

Denitrative couplings have recently emerged for the selective formation of C–C and C–X bonds.[19] This blossoming strategy of employing nitroaromatics as aryl precursors in cross-couplings is quite attractive. The transformation is however plagued by



Scheme 1 Chemoselective and diastereoselective hexannulation of 1,3-azadienes with anhydride **1c**.

several challenges, notably the difficulty of oxidative addition of Ar–NO_2 to a metal center. If the scope of this reaction is expanded to include substrates with epimerizable stereocenters, remote basic amines, heteroaromatics, and halogenated aromatics, this would undeniably popularize its use in late-stage functionalization. Within this context, we have found that 2-oxopiperidine **3c11** undergoes productive catalytic denitrative alkenylation with styrenes and acrylamides to afford the highly conjugated polyenes depicted in Scheme 6. An electron-deficient vinyl thiazole derivative also couples satisfactorily (see **14d**).

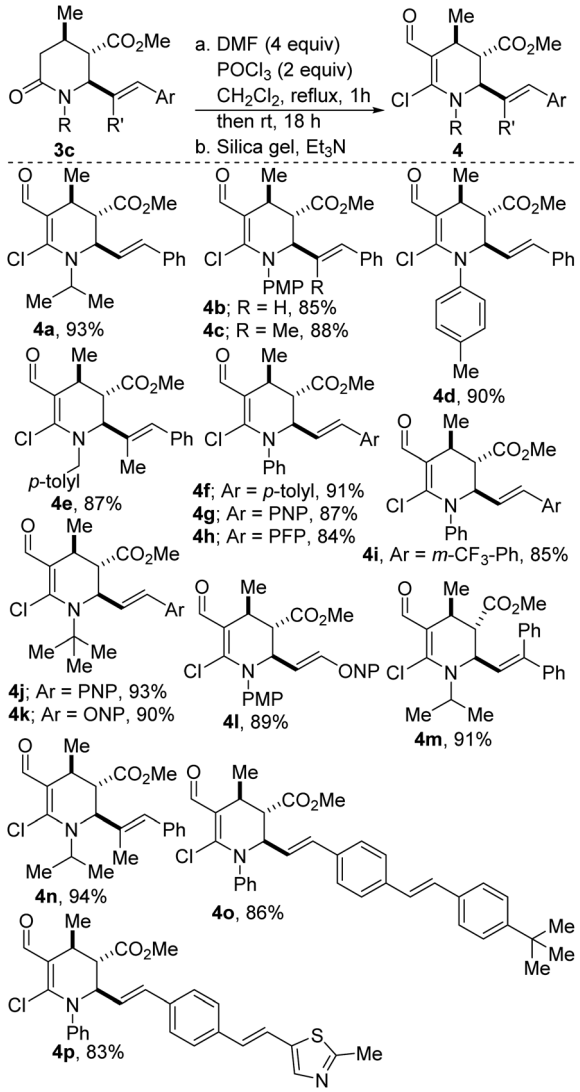
Transition metal-catalyzed cross-coupling reactions, especially those employing traceless activating groups have revolutionized almost all areas of chemical synthesis.[20] However, efforts toward improving cost, versatility, and operational simplicity of these methods continually necessitate the development of simple protocols that rely on feedstock organic, native functionality such as vinyl *chlorides* as requisite handles for uniting complex fragments.[21] Alkynes are frequently used as building blocks in organic synthesis and as catalysts in asymmetric catalysis owing to their rich reactivity profiles.[22] Since the seminal work of Sonogashira and co-workers,[23] Sonogashira-type cross-couplings have become one of the most reliable methods for the construction of internal alkynes with differential substitution.[24] We were therefore pleased to find that vinyl chlorides of type **4** undergo efficient alkynylation with triisopropylsilylacetylene, in the presence of catalytic amounts of $PdCl_2(PhCN)_2$ and CuI (Scheme 7). In this protocol, 2,6-lupetidine serves as the base and 1,4-dioxane serves as the solvent. The ability to install a triisopropylsilyl motif bodes well for further diversification since its robust yet removable nature[25] allows it to be employed as a terminal acetylene surrogate. Efforts to extend this alkynylation protocol to other alkyne coupling partners are underway.

Conclusions

In summary, the modular construction of functionalized 2-oxopiperidines bearing at least three contiguous stereocenters has been accomplished. The approach hinges on the chemoselective and stereocontrolled annulation of 3-methylglutaric anhydride with 1,3-azadienes. The scalable nature of the reactions offers the opportunity for post-modification by incorporation of motifs with either known pharmaceutical value or that permit subsequent conversion (halogens, carboxylic acids, esters, alkenes, nitroarenes, aldehydes, and alkynes) to medicinally relevant entities. The criteria of efficiency, versatility, and pot-atom-step economy are of paramount importance in modern day synthetic chemistry and these studies have met these benchmarks. The amenability of these functionalized 2-oxopiperidines to C–C bond forming transformations such as denitrative and Sonagashira cross-couplings bodes well for future late-stage assembly of complex bioactive piperidines. We anticipate that the aforementioned merits will endear this methodology to both the synthesis and medicinal chemistry communities.

Experimental

All experiments involving air and moisture sensitive reagents were carried out under an inert atmosphere of nitrogen and using freshly distilled solvents. Column chromatography was



Scheme 2 Construction of fully substituted dehydropiperidines.

performed on silica gel (230–400 mesh). Thin-layer chromatography (TLC) was performed using Silicycle SiliaplateTM glass backed plates (250 μm thickness, 60 Å porosity, F-254 indicator) and visualized using UV (254 nm) or $KMnO_4$ stain. Unless otherwise indicated, ^1H, ^{13}C, and DEPT-135 NMR, and NOESY spectra were acquired using $CDCl_3$ solvent at room temperature. Chemical shifts are quoted in parts per million (ppm). HRMS-EI^+ data were obtained using either electronspray ionization (ESI) or electron impact (EI) techniques. High-resolution ESI was obtained on an LTQ-FT (ion trap; analyzed using Excalibur). High resolution EI was obtained on an Autospec (magnetic sector; analyzed using MassLynx). Brine solutions are saturated solutions of aqueous sodium chloride. Representative GC-MS traces are provided.

General procedure A

Reaction of 1,3-azadienes with anhydride 1c. A 20 mL screw-cap vial was flame-dried, evacuated and flushed with nitrogen. A solution of the 1,3-azadiene (5.0 mL, 0.10 M in freshly distilled 2-MeTHF) was added to the vial at room temperature followed by anhydride **1c** (5 mmol, 1.0 equiv.). The contents were placed in a pre-heated oil bath thermostatted to 80 °C. After complete consumption of the 1,3-azadiene (as judged by TLC and NMR), the mixture/suspension was cooled to room temperature and washed several times with petroleum ether, then concentrated under reduced pressure to afford the lactam acid.

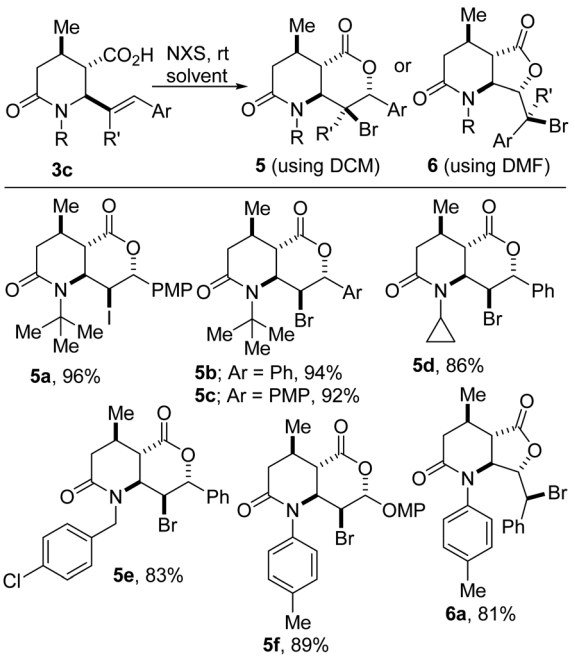
Methyl esterification of the lactam acid. To a stirring suspension of the acid (1 mmol), dissolved in DMF (5 mL), and K_2CO_3 (3 equiv.) was added methyl iodide (2 equiv.) under a nitrogen atmosphere. The reaction mixture was stirred for 12 h (TLC monitoring). After complete conversion, it was diluted with water and extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to give the desired ester, which was purified by flash chromatography on silica.

General procedure B

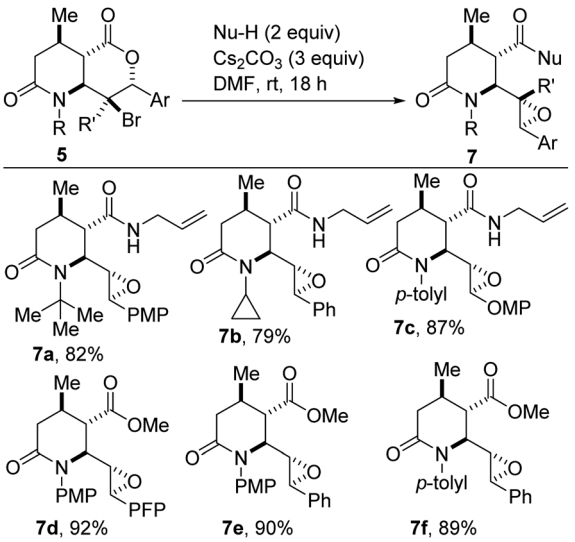
Vilsmeier–Haack functionalization. To a solution of DMF (4 mmol, 4 equiv.) in CH_2Cl_2 (5 mL) at 0 °C was added dropwise, phosphorus oxychloride (2 mmol, 2 equiv.). The resulting pale yellow mixture was refluxed for 60 min. A solution of the lactam ester (1.0 mmol, 1 equiv.) in CH_2Cl_2 (5 mL) was added slowly under reflux. After complete addition of the lactam, the mixture was cooled to room temperature and stirred for the indicated time period (TLC and GC-MS monitoring was used to follow the extent of the reaction). Upon completion, the mixture was poured into a flask containing crushed ice. After stirring at room temperature for 60 min, the layers were separated (the majority of the product stays in the DCM layer). Powdered K_2CO_3 was added slowly to the aqueous layer and the flask was swirled after each addition (***Caution***: it bubbles vigorously). The addition/swirling was continued until persistent cloudiness was observed. The neutralized/slightly basic mixture was extracted two times with CH_2Cl_2. The combined organic layers (three in total, one *before* and two after addition of K_2CO_3) were washed with brine and dried over Na_2SO_4 for 30 min. The mixture was filtered and concentrated under reduced pressure to give the desired product as an oily salt, which was immediately subjected to flash chromatography on silica pretreated with 1% Et_3N.

General procedure C

***6-endo*-Halolactonization of 3.** The lactam-bearing alkenoic acid (0.5 mmol, 1 equiv.) was charged (in air) in an oven-dried 10 mL screw-cap vial equipped with a stir bar and DCM (2 mL) was added. Then, NBS (98 mg, 0.55 mmol, 1.1 equiv.) were added. The reaction mixture was stirred at room temperature until TLC and GC-MS showed full conversion. Then, the reaction mixture was diluted with DCM (10 mL) and quenched with 10% aqueous sodium sulfite (5 mL). The layers were separated and the aqueous layer was extracted once with DCM. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give the desired lactam–lactone, which was purified by flash chromatography on silica.



Scheme 3 Halolactonization of lactam-tethered γ-alkenoic acids.



Scheme 4 Deconstructive epoxy-amidation and epoxy-esterification of 5.

General procedure D

***5-exo*-Bromolactonization of 3c.** The lactam-bearing alkenoic acid (0.5 mmol, 1 equiv.) was charged (in air) in an oven-dried 10 mL screw-cap vial equipped with a stir bar and DMF (2 mL) was added. Then, NBS (98 mg, 0.55 mmol, 1.1 equiv.) were added. The reaction mixture was stirred at room temperature until TLC and GC-MS showed full conversion. Then, the reaction mixture was diluted with EtOAc (10 mL) and quenched with 10% aqueous sodium sulfite (5 mL). The layers were separated and the aqueous layer was extracted once with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give the desired lactam–lactone, which was purified by flash chromatography on silica.

General procedure E

Deconstructive epoxy-amidation and epoxy-esterification. To an oven-dried 5 mL screw-cap vial equipped with a stir bar dissolved lactam-bromolactone **5** (0.25 mmol, 1 equiv.) in DMF (2 mL). Cs_2CO_3 (0.75 mmol, 3 equiv.) and the corresponding nucleophile (0.50 mmol, 2 equiv.) were added. The reaction mixture was stirred at room temperature until TLC and GC-MS showed full conversion (~18 h). Then, the reaction mixture was diluted with EtOAc (10 mL) and washed successively with water and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the desired product, which was purified by flash chromatography on silica.

General procedure F

Catalytic hydrogenation. EtOAc (10 mL) was added to a flask containing 10% Pd/C (100 mg) at room temperature. The flask was degassed and placed under an inert atmosphere of nitrogen. A solution of the unsaturated lactam in EtOAc (10 mL) was added. After complete addition, the nitrogen line was cut off and then replaced with a balloon of hydrogen. After complete consumption of the unsaturated lactam (based on LC-MS and TLC monitoring), the mixture was filtered through a plug of Celite and concentrated under reduced pressure.

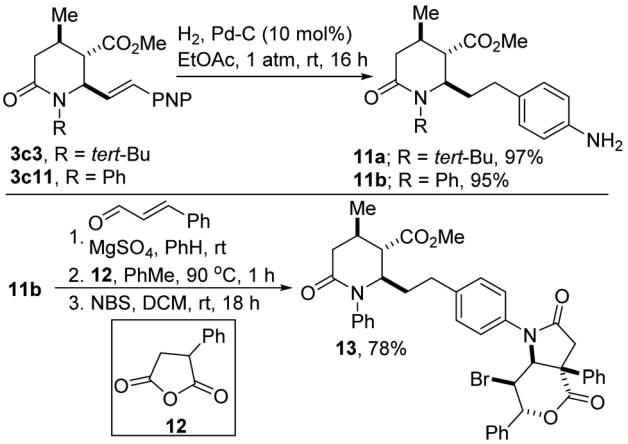
General procedure G

Denitrative alkenylation. To an oven-dried tube equipped with a magnetic stirring bar were added sequentially nitroarene **3c11** (0.5 mmol) in 2-MeTHF (5.0 mL), the styrene derivative (0.75 mmol, 1.5 equiv.), $Pd(acac)_2$ (7.5 mg, 5 mol%), Brettphos (53.5 mg, 20 mol%), and Rb_2CO_3 (0.3 mmol, 3 equiv.) under N_2 atmosphere. The reaction mixture was stirred and heated at 100 °C for 18 h (TLC and GC-MS monitoring). The reaction mixture was cooled to room temperature, and then it was passed through a short pad of silica gel with EtOAc. The solution was concentrated *in vacuo* and immediately subjected to flash chromatography on silica pretreated with 1% Et_3N.

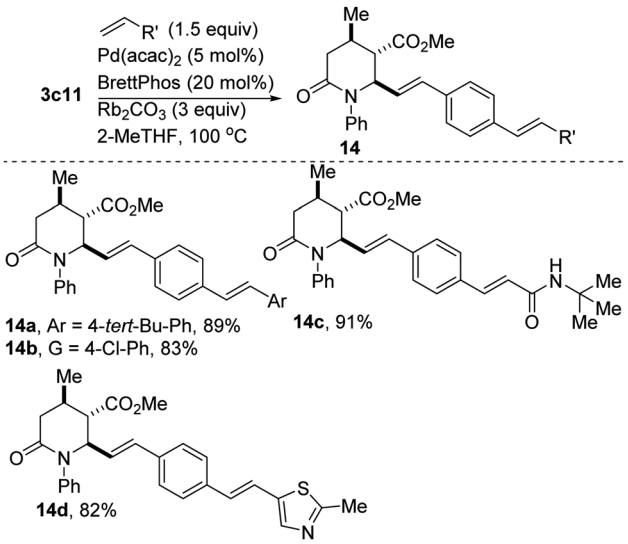
General procedure H

Pd-catalyzed alkynylation.[3] To an oven dried Schlenk tube equipped with a stir bar was added the α-chloro enamine (0.25 mmol), dissolved in dioxane (1 mL), followed by 2,6-lupetidine (0.17 mL, 1.25 mmol, 5 equiv.), CuI (5 mg, 0.025 mmol, 10 mol%) $PdCl_2(PhCN)_2$ (4.75 mg, 0.0125 mmol, 5 mol%) and the desired alkyne (0.50 mmol, 2 equiv.), under nitrogen atmosphere. The reaction was stirred at room temperature until complete consumption of the enamine (GC-MS and TLC monitoring; typically 0.5–2 h).

Synthesis of ester 3c1. Prepared in 1.0 mmol scale using general procedure A. Purification: flash chromatography on silica eluting with hexane/EtOAc (70 : 30). Oily substance. Yield



Scheme 5 Post-modification of 4-nitrostyrenyl lactams.



Scheme 6 Pd-catalyzed alkenylation of lactam-tethered nitrostyrenes with electronically diverse alkenes.

= 263.6 mg, 80%, 95 : 5 dr. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.23 (m, 5H), 6.52 (d, J = 15.9 Hz, 1H), 6.17 (dd, J = 16.0, 5.6 Hz, 1H), 4.85 (dd, J = 5.6, 2.7 Hz, 1H), 3.74 (s, 3H), 2.74 (dd, J = 4.3, 2.7 Hz, 1H), 2.55–2.31 (m, 3H), 1.47 (s, 9H), 1.07 (d, J = 6.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0, 170.7, 135.9, 131.8, 131.0, 128.8, 128.1, 126.4, 58.1, 57.6, 51.7, 50.0, 39.2, 28.5, 25.1, 18.3. HRMS-EI$^+$ (m/z): calc. for $C_{20}H_{27}NO_3$, 329.1991, found 329.1996. FTIR (KBr): 2976.0, 2927.2, 1721.7, 1650.1, 1492.0, 1438.4, 1362.2, 1320.5, 1290.1, 1206.3, 1180.3, 1146.7, 1132.3, 995.8, 918.8, 700.1.

Note: All other allylic lactams depicted in Scheme 1 were prepared as described above. Spectroscopic data can be found in the ESI.†

Synthesis of enamine 4a. Prepared in 0.5 mmol scale using general procedure B. Purification: Flash chromatography on silica (pretreated with Et_3N), eluting with hexane/EtOAc (85 : 15). Oily substance. Yield = 168.3 mg, 93%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.74 (s, 1H), 7.39–7.20 (m, 5H), 6.62 (d, J = 15.9 Hz, 1H), 5.92 (dd, J = 15.9, 8.5 Hz, 1H), 4.54 (t, J = 9.0 Hz, 1H), 4.35 (hept, J = 6.9 Hz, 1H), 3.65 (s, 3H), 3.35 (qd, J = 6.9, 4.6 Hz, 1H), 2.74 (dd, J = 9.6, 4.7 Hz, 1H), 1.39 (dd, J = 16.2, 6.9 Hz, 6H), 1.00 (d, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 186.4, 171.3, 151.1, 135.9, 133.5, 128.7, 128.3, 128.1, 126.6, 114.6, 59.1, 53.8, 51.9, 50.3, 27.8, 22.2, 21.3, 14.8. HRMS-EI$^+$ (m/z): calc. for $C_{20}H_{24}ClNO_3$, 361.1445, found 361.1449. FTIR (KBr): 2924.8, 1642.2, 1494.9, 1448.8, 1427.0, 1393.4, 1361.6, 1328.7, 1289.7, 1223.6, 1198.9, 1130.0, 1074.1, 1030.4, 988.5, 966.1, 925.5, 741.6, 693.4.

Note: All other enamines depicted in Scheme 2 were prepared as described above. Spectroscopic data can be found in the ESI.†

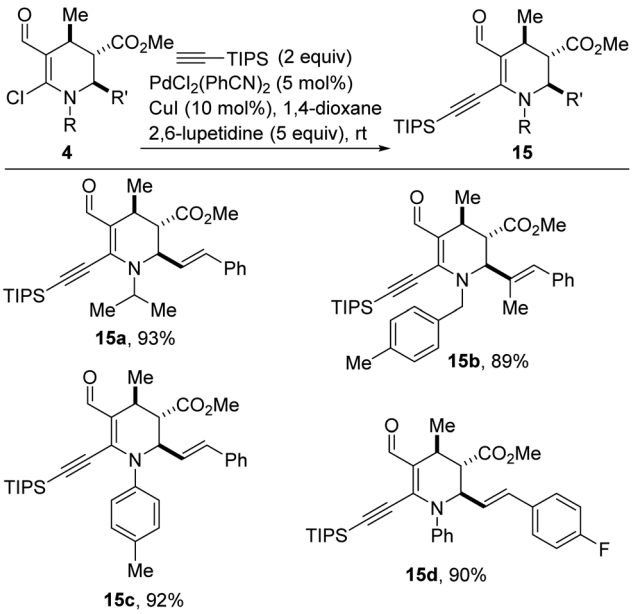
Synthesis of lactam–lactone 5b. Prepared in 0.50 mmol scale using general procedure C. Purification: Flash chromatography on silica eluting with hexane/EtOAc (60 : 40). Oily substance. Yield = 185.3 mg, 94%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–7.38 (m, 5H), 5.75 (d, J = 3.7 Hz, 1H), 4.86 (t, J = 3.5 Hz, 1H), 3.96 (dd, J = 12.1, 3.4 Hz, 1H), 3.21 (ddd, J = 12.1, 2.9, 1.0 Hz, 1H), 2.67–2.54 (m, 2H), 2.42–2.32 (m, 1H), 1.34 (s, 9H), 1.13 (d, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2, 170.0, 137.8, 129.3, 129.2, 125.5, 84.9, 60.8, 58.6, 50.5, 43.8, 42.0, 29.2, 23.6, 13.4. HRMS-EI$^+$ (m/z): calc. for $C_{19}H_{24}BrNO_3$, 393.0940, found 393.0944.

Note: All other lactam–lactones depicted in Scheme 3 were prepared as described above. Spectroscopic data can be found in the ESI.†

Synthesis of lactam carboxamide 7a. Prepared in 0.50 mmol scale using general procedure E, using allylamine (1 mmol, 2 equiv.) as the nucleophile. Purification: Flash chromatography on silica eluting with hexane/EtOAc (25 : 75). Oily substance. Yield = 164 mg, 82%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (d, J = 7.7 Hz, 2H), 6.87 (d, J = 7.7 Hz, 2H), 6.00 (dd, J = 5.7, 3.0 Hz, 1H), 5.90–5.80 (m, 1H), 5.26–5.12 (m, 2H), 4.22 (dd, J = 7.0, 3.3 Hz, 1H), 4.02–3.84 (m, 2H), 3.80 (s, 3H), 3.72 (d, J = 2.1 Hz, 1H), 3.00 (dd, J = 7.0, 2.1 Hz, 1H), 2.75 (dd, J = 5.9, 3.3 Hz, 1H), 2.56–2.44 (m, 1H), 2.44–2.28 (m, 2H), 1.55 (s, 9H), 0.97 (d, J = 6.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.7, 160.0, 133.9, 127.9, 126.9, 117.2, 114.2, 66.5, 58.3, 56.9, 55.4, 55.3, 48.8, 42.1, 40.7, 28.7, 27.9, 16.7. HRMS-EI$^+$ (m/z): calc. for $C_{23}H_{32}N_2O_4$, 400.2362, found 400.2369. FTIR (KBr): 3384.3, 3009.7, 2933.6, 1647.7, 1607.2, 1577.1, 1512.0, 1454.2, 1427.6, 1359.8, 1299.2, 1250.9, 1176.0, 1151.5, 1119.6, 1031.3, 990.3, 927.8, 825.4, 765.0, 749.7.

Note: All other epoxide-tethered lactam carboxamides and lactam-ester depicted in Scheme 4 were prepared as described above. Spectroscopic data can be found in the ESI.†

Synthesis of bromolactone 13. To a round-bottom flask equipped with a stir bar was added amine **11b** (0.5 mmol), *trans*-cinnamaldehyde (0.5 mmol, 1 equiv.) benzene (2 mL), and anhydrous $MgSO_4$ (100 mg). The cloudy suspension was allowed to stir at room temperature. After complete consumption of the amine (based on TLC monitoring), the mixture was filtered and concentrated under reduced pressure to obtain the 1,3-azadiene. A 10 mL screw-cap vial was flame-dried, evacuated and flushed with nitrogen. A solution of the 1,3-azadiene in toluene



Scheme 7 Catalytic alkynylation of α-chloroenamines.

(2.5 mL) was added to the vial at room temperature followed by phenylsuccinic anhydride **12** (88.1 mg, 0.5 mmol, 1 equiv.). The contents were placed in a pre-heated oil bath thermostatted at 90 °C. After complete conversion (as judged by TLC and NMR), the mixture/suspension was cooled to room temperature and washed several times with petroleum ether, affording the alkenoic acid. DCM (2 mL) was added to the acid followed by NBS (98 mg, 0.6 mmol, 1.1 equiv.). The reaction mixture was stirred at room temperature until TLC and GC-MS showed full conversion. Then, the reaction mixture was diluted with DCM (10 mL) and quenched with 10% aqueous sodium sulfite (5 mL). The layers were separated and the aqueous layer was extracted once with DCM. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give lactam–lactone **13**, which was purified by flash chromatography on silica, eluting with hexane:EtOAc (1 : 1). Oily substance. Yield = 286.9 mg, 78%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62–7.21 (m, 16H), 7.11–7.07 (m, 3H), 5.54 (s, 1H), 4.80 (dd, J = 10.9, 2.8 Hz, 1H), 4.36 (d, J = 10.8 Hz, 1H), 4.28–4.17 (m, 1H), 3.85–3.73 (m, 4H), 3.49–3.31 (m, 1H), 3.07–2.97 (m, 1H), 2.80–2.48 (m, 5H), 2.08–1.98 (m, 1H), 1.96–1.82 (m, 1H), 1.20 (d, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.1, 172.4, 169.9, 169.8, 169.3, 141.2, 139.7, 136.1, 133.1, 129.9, 129.4, 129.0, 128.9, 128.0, 127.9, 126.2, 125.0, 124.9, 81.7, 68.6, 60.1, 53.0, 52.1, 50.7, 46.5, 44.5, 38.0, 34.3, 34.2, 31.0, 29.3, 26.7, 17.4, 17.4. HRMS-EI$^+$ (m/z): calc. for $C_{41}H_{39}BrN_2O_6$, 734.1991, found 734.1998.

Synthesis of π-extended diene 14a. Prepared in 0.50 mmol scale using general procedure G, using 4-*tert*-butylstyrene (0.75 mmol, 1.5 equiv.) as the alkene coupling partner. Purification: Flash chromatography on silica eluting with hexane/EtOAc (75 : 25). Oily substance. Yield = 225.9 mg, 89%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.20 (m, 13H), 7.01 (s, 2H), 6.43 (dd, J = 15.8, 1.1 Hz, 1H), 6.11 (dd, J = 15.8, 7.2 Hz, 1H), 4.78–4.71 (m, 1H), 3.75 (s, 3H), 2.90 (t, J = 4.1 Hz, 1H), 2.72 (dd, J = 16.9, 5.4 Hz, 1H), 2.66–2.56 (m, 1H), 2.59–2.46 (m, 1H), 1.31 (s, 9H), 1.18 (d, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9, 169.4, 150.9, 141.1, 136.5, 135.9, 134.5, 133.5, 129.0, 128.7, 128.2, 128.0, 127.9, 127.2, 127.1, 126.6, 126.3, 125.6, 63.3, 52.0, 49.4, 38.1, 34.7, 31.3, 26.8, 17.8. HRMS-EI$^+$ (m/z): calc. for $C_{34}H_{37}NO_3$, 507.2773, found 507.2779.

Note: All other denitrative coupling products depicted in Scheme 6 were prepared as described above. Spectroscopic data can be found in the ESI.†

Synthesis of alkynyl enamine 15a. Prepared in 0.25 mmol scale using general procedure H. Purification: Flash chromatography on silica (pretreated with trimethylamine) eluting with hexane/EtOAc (90 : 10). Oily substance. Yield = 118.0 mg, 93%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.84 (s, 1H), 7.36–7.24 (m, 5H), 6.59 (d, J = 15.9 Hz, 1H), 5.93 (dd, J = 15.9, 8.2 Hz, 1H), 4.61 (hept, J = 7.0 Hz, 1H), 4.42 (t, J = 8.4 Hz, 1H), 3.64 (s, 3H), 3.27–3.17 (m, 1H), 2.72 (dd, J = 8.7, 5.0 Hz, 1H), 1.36 (dd, J = 9.2, 6.9 Hz, 6H), 1.15–1.05 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 187.8, 171.6, 143.5, 136.1, 133.0, 128.8, 128.7, 128.1, 126.5, 121.3, 104.2, 97.0, 55.8, 53.3, 51.6, 49.3, 26.0, 22.7, 20.6, 18.6, 15.3, 11.3. HRMS-EI$^+$ (m/z): calc. for $C_{31}H_{45}NO_3Si$, 507.3169, found 507.3175.

Note: All other alkynyl enamines depicted in Scheme 7 were prepared as described above. Spectroscopic data can be found in the ESI.†

Author contributions

J. G. – investigation, data curation, validation; J. E. – investigation, methodology; J. Z. – investigation, methodology; T. K. B. – conceptualization, project administration, supervision, writing – original draft, internal funding acquisition.

Conflicts of interest

There are no conflicts of interest to declare.

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Notes and references

1 T. Cernak, K. D. Dykstra, S. Tyagarajan, P. Vachal and S. W. Krska, *Chem. Soc. Rev.*, 2016, **45**, 546–576.
2 E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 10257–10274.
3 F. Lovering, J. Bikker and C. Humblet, *J. Med. Chem.*, 2009, **52**, 6752–6756.
4 For reviews on the alpha functionalization of unsubstituted heterocycles see: (*a*) E. A. Mitchell, A. Peschiulli, N. Lefevre,

L. Meerpoal and B. U. W. Maes, *Chem.–Eur. J.*, 2012, **18**, 10092–10142; (*b*) K. R. Campos, *Chem. Soc. Rev.*, 2007, **36**, 1069–1084; (*c*) C. T. Vo and J. W. Bode, *J. Org. Chem.*, 2014, **79**, 2809–2815.

5 (*a*) Z. Amara, J. Caron and D. Joseph, *Nat. Prod. Rep.*, 2013, **30**, 1211–1225; (*b*) T. K. Beng, H. Takeuchi, M. Weber and R. Sarpong, *Chem. Commun.*, 2015, **51**, 7653–7656; (*c*) K. Kubota, Y. Watanabe, K. Hayama and H. Ito, *J. Am. Chem. Soc.*, 2016, **138**, 4338–4341; (*d*) B. Qu, H. P. R. Mangunuru, X. Wei, K. R. Fandrick, J.-N. Desrosiers, J. D. Sieber, D. Kurouski, N. Haddad, L. P. Samankumara, H. Lee, J. Savoie, S. Ma, N. Grinberg, M. Sarvestani, N. K. Yee, J. J. Song and C. H. Senanayake, *Org. Lett.*, 2016, **18**, 4920–4923; (*e*) J. J. Topczewski, P. J. Cabrera, N. I. Saper and M. S. Sanford, *Nature*, 2016, **531**, 220–224; (*f*) T. Sandmeier, S. Krautwald and E. M. Carreira, *Angew. Chem.*, 2017, **129**, 11673–11677; (*g*) W. Chen, L. Ma, A. Paul and D. Seidel, *Nat. Chem.*, 2018, **10**, 165–169; (*h*) J. B. Roque, Y. Kuroda, L. T. Göttemann and R. Sarpong, *Nature*, 2018, **564**, 244–248; (*i*) A. Paul and D. Seidel, *J. Am. Chem. Soc.*, 2019, **141**, 8778–8782; (*j*) I. S. Hassan, A. N. Ta, M. W. Danneman, N. Semakul, M. Burns, C. H. Basch, V. N. Dippon, B. R. McNaughton and T. Rovis, *J. Am. Chem. Soc.*, 2019, **141**, 4815–4819; (*k*) A. Millet, P. Larini, E. Clot and O. Baudoin, *Chem. Sci.*, 2013, **4**, 2241–2247; (*l*) C. J. Cordier, R. J. Lundgren and G. C. Fu, *J. Am. Chem. Soc.*, 2013, **135**, 10946–10949; (*m*) A. McNally, C. K. Prier and D. W. C. MacMillan, *Science*, 2011, **334**, 1114–1117; (*n*) T. K. Beng and D. P. Bassler, *Tetrahedron Lett.*, 2014, **55**, 6662–6664; (*o*) D. P. Bassler, A. Alwali, L. Spence, O. Beale and T. K. Beng, *J. Organomet. Chem.*, 2015, **780**, 6–12; (*p*) T. K. Beng, S. Langevin, H. Braunstein and M. Khim, *Org. Biomol. Chem.*, 2016, **14**, 830–834; (*q*) T. K. Beng, A. W. V. Silaire, A. Alwali and D. P. Bassler, *Org. Biomol. Chem.*, 2015, **13**, 7915–7919; (*r*) T. K. Beng, N. Fox, D. P. Bassler, A. Alwali, K. Sincavage and A. W. V. Silaire, *Org. Biomol. Chem.*, 2015, **13**, 8647–8651.

6 For selected examples, see: (*a*) J. Ding, T. Rybak and D. G. Hall, *Nat. Commun.*, 2014, **5**, 5474; (*b*) M. J. Dearden, C. R. Firkin, J.-P. R. Hermet and P. O'Brien, *J. Am. Chem. Soc.*, 2002, **124**, 11870–11871; (*c*) C. J. Cordier, R. J. Lundgren and G. C. Fu, *J. Am. Chem. Soc.*, 2013, **135**, 10946–10949.

7 (*a*) P. R. Krishna and B. K. Reddy, *Tetrahedron Lett.*, 2010, **51**, 6262–6264; (*b*) D. L. Comins and G. M. Green, *Tetrahedron Lett.*, 1999, **40**, 217–218; (*c*) M. A. Arai, N. Ishikawa, M. Tanaka, K. Uemura, N. Sugimitsu, A. Suganami, Y. Tamura, T. Koyano, T. Kowithayakorn and M. Ishibashi, *Chem. Sci.*, 2016, **7**, 1514–1520; (*d*) S. Hong, A. M. Kawaoka and T. J. Marks, *J. Am. Chem. Soc.*, 2003, **125**, 15878–15892; (*e*) C. Welter, A. Dahnz, B. Brunner, S. Streiff, P. Dübon and G. Helmchen, *Org. Lett.*, 2005, **7**, 1239–1242; (*f*) D. Berthold, A. G. A. Geissler, S. Giofré and B. Breit, *Angew. Chem., Int. Ed.*, 2019, **58**, 9994–9997; (*g*) X. Ma, I. R. Hazelden, T. Langer, R. H. Munday and J. F. Bower, *J. Am. Chem. Soc.*, 2019, **141**, 3356–3360; (*h*) S. H. Lim, S. Ma and P. Beak, *J. Org. Chem.*, 2001, **66**, 9056–9062; (*i*) T. K. Beng and R. E. Gawley, *J. Am. Chem. Soc.*, 2010, **132**, 12216–12217; (*j*) T. K. Beng and R. E. Gawley, *Org. Lett.*, 2011, **13**, 394–397; (*k*) T. K. Beng, S. M. Wilkerson-Hill and R. Sarpong, *Org. Lett.*, 2014, **16**, 916–919; (*l*) D. P. Bassler, A. Alwali, L. Spence, O. Beale and T. K. Beng, *J. Organomet. Chem.*, 2015, **780**, 6–12; (*m*) D. P. Bassler, L. Spence, A. Alwali, O. Beale and T. K. Beng, *Org. Biomol. Chem.*, 2015, **13**, 2285–2292.

8 (*a*) E. J. Barreiro, A. E. Kummerle and C. A. Fraga, *Chem. Rev.*, 2011, **111**, 5215; (*b*) H. Schçnherr and T. Cernak, *Angew. Chem., Int. Ed.*, 2013, **52**, 12256–12267; (*c*) T. Cernak, K. D. Dykstra, S. Tyagarajan, P. Vachal and S. W. Krska, *Chem. Soc. Rev.*, 2016, **45**, 546–576.

9 W. Leitner, J. Klankermayer, S. Pischinger, H. Pitsch and K. Kohse, *Angew. Chem., Int. Ed.*, 2017, **56**, 5412–5452.

10 H. Braunstein, S. Langevin, M. Khim, J. Adamson, K. Hovenkotter, L. Kotlarz, B. Mansker and T. K. Beng, *Org. Biomol. Chem.*, 2016, **14**, 8864–8872.

11 M. M. Nebe and T. Opatz, Synthesis of Piperidines and Dehydropiperidines: Construction of the Six-Membered Ring, in *Advances in Heterocyclic Chemistry*, ed. E. F. V. Scriven and C. A. Ramsden, Academic Press, 2017, vol. 122, ch. 5, pp. 191–244.

12 (*a*) M. Krasavin and D. Dar'in, *Tetrahedron Lett.*, 2016, **57**, 1635–1640; (*b*) M. Gonzalez-Lopez and J. T. Shaw, *Chem. Rev.*, 2009, **109**, 164–189.

13 (*a*) M. Krasavin and D. Dar'in, *Tetrahedron Lett.*, 2016, **57**, 1635–1640; (*b*) M. Gonzalez-Lopez and J. T. Shaw, *Chem. Rev.*, 2009, **109**, 164–189.

14 N. A. Sorto, M. J. Di Maso, M. A. Munoz, R. A. Dougherty, J. C. Fettinger and J. T. Shaw, *J. Org. Chem.*, 2014, **79**, 2601–2610.

15 (*a*) X. Qiao, D. L. Cheney, R. S. Alexander, A. M. Smallwood, S. R. King, K. He, A. R. Rendina, J. M. Luettgen, R. M. Knabb, R. R. Wexler and P. Y. S. Lam, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 4118–4123; (*b*) M. A. Larsen, E. T. Hennessy, M. C. Deem, Y. Lam, J. Sauri and A. C. Sather, *J. Am. Chem. Soc.*, 2020, **142**(2), 726–732.

16 D. Dar'in, O. Bakulina, S. Nikolskaya, I. Gluzdikov and M. Krasavin, *RSC Adv.*, 2016, **6**, 49411–49415.

17 T. Liang, C. N. Neumann and T. Ritter, *Angew. Chem., Int. Ed.*, 2013, **52**, 8214–8264.

18 K. Muller, C. Faeh and F. Diederich, *Science*, 2007, **317**, 1881–1886.

19 (*a*) B. Feng, Y. Yang and J. You, *Chem. Commun.*, 2020, **56**, 790; (*b*) M. R. Yadav, M. Nagaoka, M. Kashihara, R.-L. Zhong, T. Miyazaki, S. Sakaki and Y. Nakao, *J. Am. Chem. Soc.*, 2017, **139**, 9423; (*c*) T. Okita, K. K. Asahara, K. Muto and J. Yamaguchi, *Org. Lett.*, 2020, **22**, 3205; (*d*) R.-L. Zhong, M. Nagaoka, Y. Nakao and S. Sakaki, *Organometallics*, 2018, **37**, 3480; (*e*) F. Inoue, M. Kashihara, M. R. Yadav and Y. Nakao, *Angew. Chem., Int. Ed.*, 2017, **56**, 13307; (*f*) M. Kashihara, M. R. Yadav and Y. Nakao, *Org. Lett.*, 2018, **20**, 1655; (*g*) W. Chen, K. Chen, W. Chen, M. Liu and H. Wu, *ACS Catal.*, 2019, **9**, 8110; (*h*) K. Chen, W. Chen, X. Yi, W. Chen, M. Liu and H. Wu, *Chem. Commun.*, 2019, **55**, 9287; (*i*) M. Kashihara, R.-L. Zhong,

K. Semba, S. Sakaki and Y. Nakao, *Chem. Commun.*, 2019, **55**, 9291; (*j*) K. K. Asahara, T. Okita, A. N. Saito, K. Muto, Y. Nakao and J. Yamaguchi, *Org. Lett.*, 2019, **21**, 4721; (*k*) B. Feng, Y. Yang and J. You, *Chem. Sci.*, 2020, **11**, 6031.

20 (*a*) B. M. Rosen, K. W. Quasdorf, D. A. Wilson, N. Zhang, A.-M. Resmerita, N. K. Garg and V. Percec, *Chem. Rev.*, 2011, **111**, 1346–1416; (*b*) A. H. Cherney, N. T. Kadunce and S. E. Reisman, *Chem. Rev.*, 2015, **115**, 9587–9652.

21 (*a*) O. Baudoin, *Chem. Soc. Rev.*, 2011, **40**, 4902–4911; (*b*) R. Jazzar, J. Hitce, A. Renaudat, J. Sofack-Kreutzer and O. Baudoin, *Chem.–Eur. J.*, 2010, **16**, 2654–2672; (*c*) K. Godula and D. Sames, *Science*, 2006, **312**, 67–72; (*d*) D. A. Everson and D. J. Weix, *J. Org. Chem.*, 2014, **79**, 4793–4798; (*e*) D. A. Everson, J. A. Buonomo and D. J. Weix, *Synlett*, 2014, **25**, 233–238; (*f*) C. E. I. Knappke, S. Grupe, D. Gaertner, M. Corpet, C. Gosmini and A. Jacobi von Wangelin, *Chem.–Eur. J.*, 2014, **20**, 6828–6842.

22 (*a*) H. Ehrhorn and M. Tamm, *Chem.–Eur. J.*, 2019, **25**, 3190; (*b*) U. H. F. Bunz, *Chem. Rev.*, 2000, **100**, 1605; (*c*) U. H. F. Bunz, K. Seehafer, M. Bender and M. Porz, *Chem. Soc. Rev.*, 2015, **44**, 4322; (*d*) R. Chinchilla and C. Nájera, *Chem. Rev.*, 2014, **114**, 1783; (*e*) X. Ren, G. Li, S. Wei and H. Du, *Org. Lett.*, 2015, **17**, 990; (*f*) A. Ahlers, T. de Haro, B. Gabor and A. Furstner, *Angew. Chem., Int. Ed.*, 2016, **55**, 1406; (*g*) P. M. Cromm, S. Schaubach, J. Spiegel, A. Furstner, T. N. Grossmann and H. Waldmann, *Nat. Commun.*, 2016, **7**, 11300.

23 K. Sonogashira, Y. Tohda and N. Hagihara, *Tetrahedron Lett.*, 1975, **16**, 4467.

24 For recent and representative examples, see: (*a*) E. Fernandez, M. Rivero Crespo, A. I. Dominguez, P. Rubio-Marques, J. Oliver-Meseguer, L. Liu, M. Cabrero-Antonino, R. Gavara, J. C. Hernandez-Garrido, M. Boronat, A. Leyva-Perez and A. Corma, *J. Am. Chem. Soc.*, 2019, **141**, 1928; (*b*) T. Wang, J. Huang, H. Lv, Q. Fan, L. Feng, Z. Tao, H. Ju, X. Wu, S. L. Tait and J. Zhu, *J. Am. Chem. Soc.*, 2018, **140**, 13421; (*c*) W. Liu, L. Li and C.-J. Li, *Nat. Commun.*, 2015, **6**, 6526.

25 T. W. Greene, *Protective Groups in Organic Synthesis*, Wiley Interscience: New York, 1981.