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One-Step Assembly of Functionalized Morpholinones and 1,4-Oxazepane-3-ones via [3 + 3]- and [3 + 4]-Annulation of Aza-Oxyallyl Cation and Amphoteric Compounds

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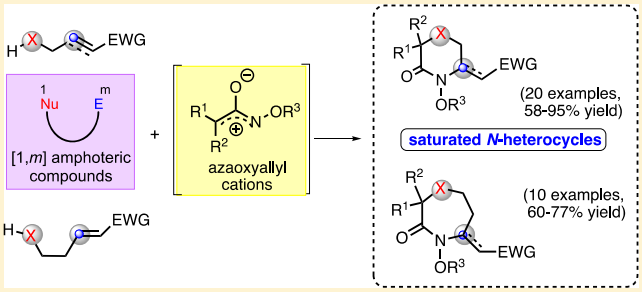
Supporting Information

ABSTRACT: A new [3 + 3]- and [3 + 4]-annulation strategy involving azaoxyallyl cation and [1,*m*]-amphoteric compounds (*m* = 3,4) is presented. This concise method enables easy assembly of functionalized saturated N-heterocycles, comprised of six-and seven-membered rings and is of high significance in the context of drug discovery approaches. This reaction also represents a new trapping modality of the azaoxyallyl cation with amphoteric agents of different chain lengths that consist of a heteroatom nucleophilic site and a π-electrophilic site.



INTRODUCTION

Use of saturated N-heterocycles of different ring sizes has become indispensable in the current paradigm of the drug discovery and development efforts.[1] Their significance and wide utility demand continuous feeding of new synthetic strategies that can address key synthetic challenges such as one-step convergent access to the functionalized core structures including those with the medium-sized ring.[2−5] Several groups including Bode,[2a,5] Aggarwal,[3] and Carreira[4] have sought to identify practicable solutions to the existing shortcomings, and some important advances were made in recent years through development of distinct intermolecular and intramolecular approaches (Scheme 1a).[2−6] Bode's development of SnAP reagents is particularly noteworthy as it allows one-step generation of a range of functionalized, medium-sized (six to nine membered rings) saturated N-heterocycles.

Among the saturated N-heterocycles, morpholine and 1,4-oxazepane are some of the most abundant motifs featured in many pharmaceuticals and basic skeleton of natural products.[7] We envisaged that the −C(CO)N− molecular skeleton of a putative azaoxyallyl cation could be a potential synthon to forge the aforementioned classes of heterocycles upon successfully engaging complementary annulation partners in the reaction.

In recent years, strategic uses of azaoxyallyl cation chemistry have emerged as a powerful tool for the assembly of N-containing heterocycles through development of various [3 + 1], [3 + 2], [3 + 3], and [3 + 4] cycloadditions.[8−10] These reactions involved a range of dipolarophiles, 1,3-dipolar compounds, and ylides as the reaction partners (Scheme 1b). Kinetically amphoteric molecules represent an interesting compound class, where the nucleophilic and electrophilic sites are intercepted by certain number of atoms and not linked mesomerically (generally termed as [1,*m*] systems).[11] We surmised that reaction of azaoxyallyl cation with amphoteric molecules possessing a nucleophilic heteroatom center and a π-electrophilic site[12] could lead to a new strategy for N-heterocycles that would not only complement the pre-existing methods but also resolve some of the unmet challenges within the context. This facet of reaction development however remained largely unexplored till date.

In line of our interest to develop new reactions with the azaoxyallyl cation,[13] we herein disclose the design and development of [3 + 3] and [3 + 4]-annulation of azaoxyallyl cation with 1,3- and 1,4-amphoteric reagents for efficient synthesis of important saturated N-heterocyclic systems such as morpholines and 1,4-oxazepanes derivatives. Importantly, our approach allows ring-size variations in the final products by varying the chain length of same class of reaction partner, which is rarely demonstrated in the realm of azaoxyallyl cation chemistry.

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Scheme 1. Previous Studies and Our Approach

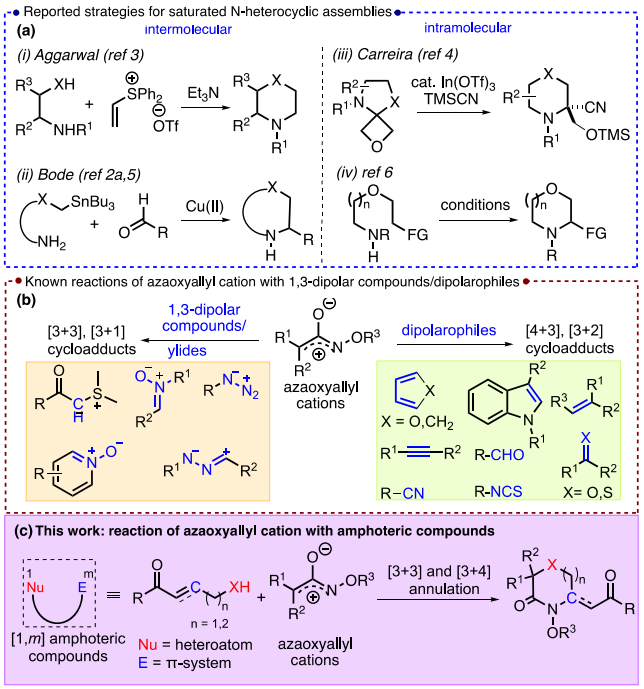
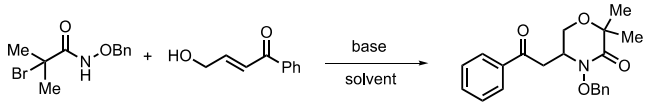


Table 1. Optimization of [3 + 3]-Annulation Reaction[a]



entry	base	equiv	solvent	yield (%)[b]
1[c]	Et_3N	2.0	HFIP	30
2	Et_3N	2.0	HFIP	40
3	DBU	2.0	HFIP	45
4	DIPA	2.0	HFIP	60
5[c]	K_2CO_3	2.0	HFIP	58
6[c]	Na_2CO_3	2.0	HFIP	62
7	Na_2CO_3	2.0	HFIP	76
8	Na_2CO_3	3.0	HFIP	95
9[d]	Na_2CO_3	3.0	HFIP	80
10	Na_2CO_3	4.0	HFIP	78
11	Na_2CO_3	3.0	CH_3CN	55
12	Na_2CO_3	3.0	CH_2Cl_2	52
13	Na_2CO_3	3.0	THF	28
14	Na_2CO_3	3.0	HFIP	55

[a]Reaction conditions: **1a** (2.0 equiv), **2a** (1.0 equiv), base (3.0 equiv) solvent (0.2 M), reaction time (6–8 h). [b]Yields of the isolated products. [c]1.0 equiv. of **1a** was used. [d]Reaction concentration was 0.1 M.

RESULTS AND DISCUSSION

At the outset of the study, we chose azaoxyallyl cation precursor **1a** and amphoteric agent **2a** as model substrates while being mindful of the following possible obstacles; (1) azaoxyallyl cation shows remarkable stability in small-molecule alcohols[8,9d,g] (MeOH, EtOH, ^{i}PrOH, hexafluoro-2-propanol (HFIP), and TFE are routinely used as the solvent in the reaction of azaoxyallyl cation), imparting the challenge associated with participation of the hydroxyl site of **2a**, (2) chemoselectivity issues because of the presence of other "azaoxyallyl cation-reactive" dipolarophiles such as carbonyl and olefin units, within the skeletal structure of **2a**,[9e,f,i] (3) base sensitivity of 2a-like compounds and propensity for self-reaction/isomerization.[14] Fluorinated solvents usually offer better stability of azaoxyallyl cation,[10f] which prompted us to begin our investigations with model substrates **1a** (1.0 equiv) and **2a** (1.0 equiv) in HFIP, and Et_3N (2.0 equiv) was used as the base (Table 1).

Pleasingly, under this reaction condition, desired product **3aa** was obtained in 30% yield (entry 1). However, HBr elimination from **1a** was identified as the major side reaction together with some minor quantity of dimer from **2a**. Adding 2.0 equiv of **1a** in the reaction slightly improved the yield (entry 2). Although use of the other organic bases rendered better conversions (entries 3–4), it also accompanied non negligible side-product formation, which entailed difficult chromatographic separation. On the contrary, inorganic bases afforded much cleaner conversion (entries 5–6), and up to 76% yield of desired product could be achieved with Na_2CO_3 when 2.0 equiv of **1a** was used (entry 7). Best performance was recorded with 3.0 equiv of Na_2CO_3 (entry 8). Results turned inferior upon performing the reaction at lower concentration or with 4.0 equiv of base (entries 9–10 vs entry 8). Other choices of organic solvent and base were only moderately effective for this transformation (entries 11–14). The product structure and hence the desired site selectivity were confirmed by NMR analysis; the absence of olefinic proton signal in the product, appearance of keto-methylene proton resonances at 3.47 and 3.34 ppm, and a carbonyl resonance at 197.7 ppm in ^{13}C NMR were in agreement with the structure **3aa**.

With the optimized reaction conditions in hand, we next proceeded to examine the substrate scope (Scheme 2). Different substitution on the aromatic ring of 2 was evaluated first. Electron-releasing groups present at ortho, meta, and para positions and halogens at the para position worked favorably and afforded high yields (**3ab**–**3ag**). An aromatic ring with extended π-framework could also be accommodated in the product (**3ah**). While some further variations on the α-halohydroxamate moiety such as methoxy group on nitrogen atom (**3bh**) or cyclohexyl group at the α-position (**3ch**) were tolerated, use of unsubstituted or monomethyl or phenyl substituted compounds was unsuccessful (**3da**–**3fa**). In the later cases, starting materials were mostly unreacted, and no trace of the desired product was observed by NMR and MS analysis. Compound 2 with an aliphatic ketone residue was compatible in the reaction, although a slight drop in the yield was recorded (**3ai**). Gram scale preparation of **3aa** was achieved with 91% yield, which highlights the practicability of the current method.

To further expand the scope of the transformation, we next investigated another amphoteric agent **4a** that contained an alkynone unit as the electrophilic counterpart (Scheme 3). Gratifyingly, this [3 + 3]-annulation also proceeded smoothly under the optimized reaction conditions and afforded **5aa** in 68% yield with complete Z-selectivity of the olefin. Notably, such morpholine derivatives with an exocyclic vinylogous amide moiety embedded within are important intermediates for the synthesis of alkaloid natural products.[15] This transformation also tolerated a broad range of substituent variation on 4, leading to cyclic products **5ab**–**5ae**. Interestingly, compound **4f** possessing a methyl ketone residue reacted differently. In this case, a secondary [3 + 2]-annulation

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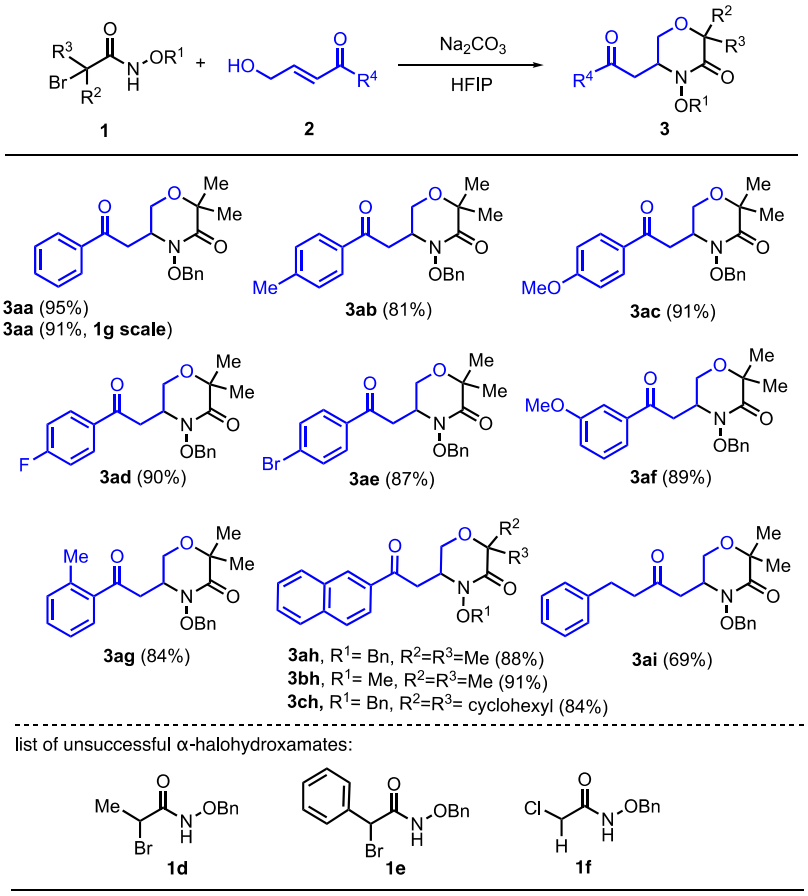
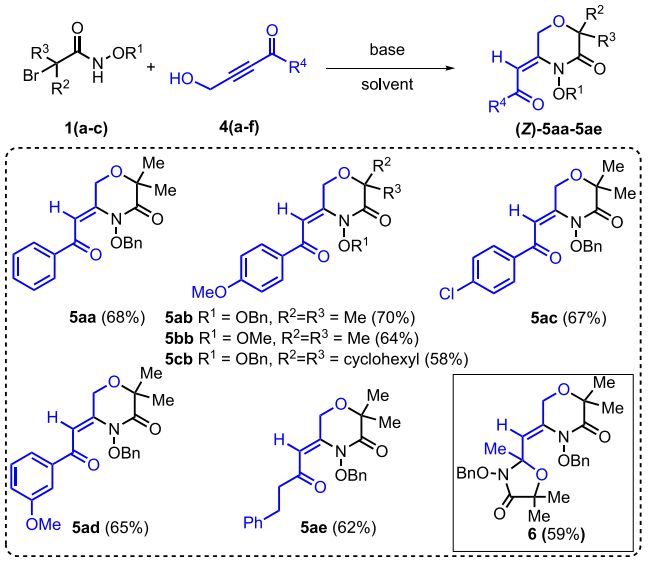
Scheme 2. Substrate Scope for the [3 + 3]-Annulation of Hydroxyl-Alkenones and α-Halo Hydroxamates



Scheme 3. [3 + 3]-Annulation of Hydroxyl-Alkynone with α-Halo Hydroxamates[a]



[a]Reaction conditions: α-bromo hydroxamate **1** (2.0 equiv), hydroxyl alkynones **4** (1.0 equiv), Na_2CO_3 (3.0 equiv) in $(CF_3)_2CHOH$ (0.2 M), and reaction time (6−8 h).

involving the ketone moiety occurred subsequent to the desired [3 + 3]-annulation step, which afforded **6** as the major product (59%). The desired [3 + 3]-annulated product could be isolated only as inseparable product mixture with **6**, which was corroborated via NMR analysis. This fact definitively confirmed the occurrence of a [3 + 3]-annulation first, followed by the [3 + 2]-annulation. Notably, use of equimolar ratio of **1a** and **4f** did not alter the outcome significantly.

NMR studies of compounds **5** revealed some interesting observations that warrant further investigations. For example, the vinylic proton signal of compound **5ab** was completely shifted from 5.29 ppm, which was recorded for the freshly prepared sample, to 6.71 ppm upon standing overnight (ca. 24 h) in $CDCl_3$. The benzyloxy and $-OCH_2$ methylene protons were also distinctly shifted. The nuclear Overhauser effect (NOE) analysis (see Scheme S1 in the Supporting Information) confirmed the (*Z*)-configuration of the olefin for initially formed product (kinetically controlled) which was set during [3 + 3]-annulation step, and the later compound was the isomerized (*E*)-isomer of **5ab**. The NOE studies further indicated *s*-cis orientation of C═C−C═O single bond in both the cases.

Importantly, the related compound with a free NH group (e.g., **5ab** in Scheme S1 and **5aa′** in Scheme S2 in Supporting Information) usually favors (*Z*)-isomer in equilibrium because of intramolecular hydrogen bonding.[15,16] In contrast, density functional theory (DFT) calculations indicated a reverse trend for compounds with a substituted nitrogen, such as **5aa**. In this case, the (*Z*)-isomer was found to be 7.3 kcal mol^{-1} higher in energy compared to the (*E*)-isomer (Scheme 4a).[17] A plausible mechanism for initial formation of (*Z*)-isomer of compound **5** and its subsequent isomerization is outlined in Scheme 4b. We speculated that, during the 6-*exo*-dig ring-closure with *N*-benzyloxy group leading to **5**, the protonation step of the

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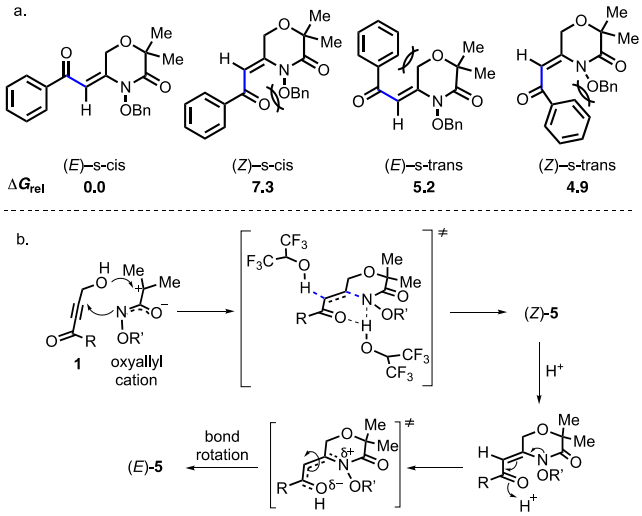
Scheme 4. (a) Relative Gibbs Free Energies (in kcal mol^{-1}) of the Four Isomers of 5aa Computed at COSMO(THF)-ZORA-BLYP-D3(BJ)/TZ2P. (b) Plausible Mechanism for *Z*−*E* Isomerization of Compound 5



putative vinylic carbanion locked the ensuing olefin residue in its *Z*-configuration. Strong hydrogen-bond donor ability of HFIP most likely facilitated this process and overrode the steric effect through formation of a favorable hydrogen bonded transition state (Scheme 4b).

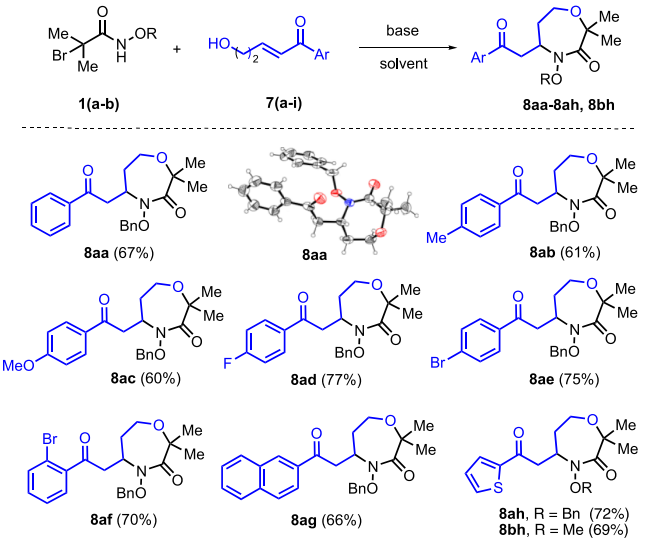
In the presence of catalytic acid ($CDCl_3$ or 10 mol % *p*-TsOH), push−pull protonation at the oxygen center of the vinylogous amide moiety[18] and single-bond rotation transformed the (*Z*)-isomer to the more stable (*E*)-**5**.

After having established the unified [3 + 3]-annulation of azaoxyallyl cation with two different 1,3-amphoteric agents to functionalized morpholine derivatives, we next embarked on a more daunting task to develop a [4 + 3]-annulation by employing 1,4-amphoteric agents **7** for the preparation of various seven-membered 1,4-oxazepanes (Scheme 5). Synthesis of medium-sized heterocycles via [4 + 3] cycloaddition is a challenging endeavor, and only one such cycloaddition is known for azaoxyallyl cation with cyclic dienes as the reaction partner.[10f]

Initial reaction of **1a** with **7a** under the optimized conditions proved futile. Side-product formation from **1a** and unreacted **7a** were only detected in the reaction mixture. To our satisfaction, elevated reaction temperature (60 °C) favored the desired annulation process and afforded seven-membered 1,4-oxazepane derivative **8aa** in good yield (67%). The structure of the product was unambiguously determined by X-ray crystal structure analysis. This reaction also displayed a broad substrate scope; compound **7** with varied aromatic substitutions (**8ab**−**8af**) or with naphthyl and thiophene moieties were competent (**8ag**−**8ah**, **8bh**).

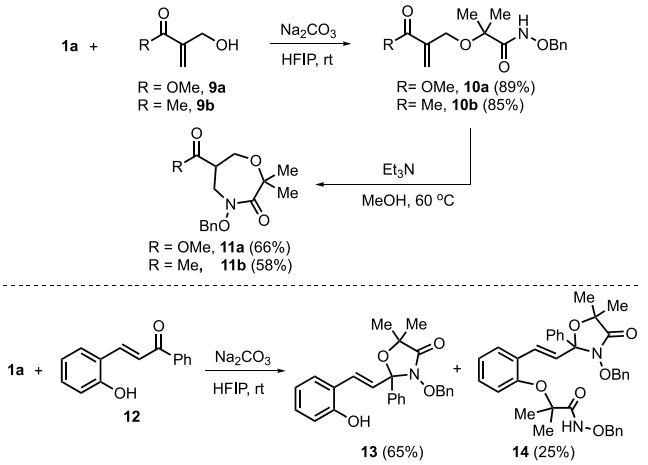
Scope and limitations of the transformation with other closely related 1,4-amphoteric systems such as compound **9** and **12** were next investigated (Scheme 6). These systems were analogous to compound **7** by virtue of the presence of nucleophilic hydroxyl site and π-centered electrophilic site within the molecular skeleton, but these were embedded in a distinct electronic and steric environment to that of compound **7**. Curiously, reaction of **1a** with **9a** or **9b** only afforded acyclic compounds **10a**−**b**. Cyclization of **10a** and **10b** to compounds **11a**−**b** however could be achieved, after few optimization

Scheme 5. Study of [3 + 4]-Annulation of α-Halo Hydroxamates and 1,4-Amphoteric Agent[a]



[a]Reaction conditions: α-bromo hydroxamate **1** (2.0 equiv), hydroxyl enones **7** (1.0 equiv), and Na_2CO_3 (3.0 equiv) in $(CF_3)_2CHOH$ (0.2 M).

Scheme 6. Evaluation of Other Related 1,4-Amphoteric Systems



trials, with Et_3N in MeOH at 60 °C. Another related compound **12** was primarily reacted through the carbonyl moiety and afforded **13** (65%) as the major product along with some *O*-alkylated product (**14**).

The utility of our method was further demonstrated via synthetic elaboration of some selected compounds prepared herein into important and synthetically challenging fused bi- and tricyclic systems (Scheme 7). For example, hydrogenolysis of **3aa** with Pd/C furnished **15** (48%), which was cyclized under Mitsunobu condition[19] to afford compound **16** (68%) as a single diastereomer. Relative stereochemistry of **16** was established by NOE experiments. In another case, the benzyloxy group of **8af** was first deprotected with $Mo(CO)_6$ to afford **17** (70%). Next, a Pd-catalyzed intramolecular aromatic amination[20] was performed involving free NH and aromatic bromide residue, which afforded a fused tricyclic 1,4-oxazepane derivative, **18** (56%).

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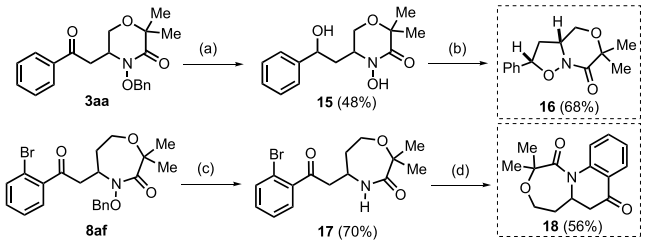
Scheme 7. Follow-Up Studies[a]



[a]Reaction conditions: (a) H_2, 10% Pd/C, MeOH, 20 h; (b) di-*tert*-butyl azodicarboxylate, PPh_3, DCM, 0 °C-rt, 16 h; (c) $Mo(CO)_6$, CH_3CN-H_2O (9:1), 120 °C, 12 h; (d) 5 mol % $Pd(OAc)_2$, 50 mol % $Cu(OAc)_2$, K_2CO_3 (3.0 equiv), toluene, 110 °C, and 24 h.

CONCLUSIONS

In summary, we have developed a new and efficient annulation strategy to synthesize different saturated medium-ring nitrogen heterocycles by employing azaoxyallyl cation and 1,3/1,4-amphoteric compounds. Use of hydroxyl-alkynones resulted in sterically less favored *Z*-exocyclic olefin in the product, which was rationalized on the basis of involvement of HFIP in stabilizing the corresponding transition state. DFT calculations were also performed to corroborate with the experimental results. A more challenging [3 + 4]-annulation using 1,4-amphoteric compounds was also successfully demonstrated. Overall, the present work showcases the use of different [1,*m*]-amphoteric system as a new trapping modality of azaoxyallyl cation, which is very distinct from the growing body of literature on the azaoxyallyl cation and afforded a new strategy for the preparation of saturated N-heterocycles.

EXPERIMENTAL SECTION

General Experimental Section. Unless otherwise noted, all the reactions presented in the manuscript were performed maintaining an inert atmosphere (i.e., under a positive pressure of nitrogen or argon) and, oven or flame-dried glasswares was used. Dry solvents were used in the study; either dried following the standard procedures or obtained commercially and for tetrahydrofuran (THF), it was freshly distilled before use. Solvent distillation was performed on heating mantle, and oil baths were used for heating reactions performed in the study. Unless otherwise mentioned, the reagents and catalysts used in the study were purchased commercially and used without any purification. Reaction monitoring was performed by thin layer chromatography (TLC) analysis, and Merck silica gel 60 F 254 plates were used. Visualization of the TLC plates was made under UV light (254 nm) or by using 10% ethanolic phosphomolybdic acid or 1% aqueous $KMnO_4$ or iodine. Silica gel flash column chromatography was performed by using silica gel of 230–400 mesh. ^1H, ^{13}C, and ^{19}F NMR spectra were recorded on AVANCE III, Bruker at 400, 100, and 376 MHz spectrometers, respectively, using $CDCl_3$. ^1H NMR chemical shift are expressed in ppm (δ) relative to δ = 7.26 for $CDCl_3$. $^{13}C\{^1H\}$ NMR chemical shift is expressed in ppm (δ) relative to δ = 77.16 for $CDCl_3$ resonance. Fourier transform infrared (FT-IR) experiments were performed on PerkinElmer Spectrum Version 10.03.08. HRMS and Electron spray ionization (ESI) (m/z) spectra were recorded on Agilent Technologies 6530 Accurate-Mass Q-TOF LC/MS.

The α-halo hydroxamate derivatives (**1a–1f**) are known compounds and were prepared according to the literature method.[9l,10f] Trans-hydroxyl enone derivatives (**2a–2i**) and compounds **4a** and **4e–4f** are known in the literature and were prepared according to the reported method.[21,22] We additionally prepared compound **4b–4d** using the similar procedure as reported for related compounds. Among the linear trans-hydroxyenone derivatives, **7a–7e** and **7g–7h** are the known compound and prepared according to the literature method.[23] Compound **7f** was additionally prepared following the similar method described for the preparation of related compounds.

*4-Hydroxy-1-(4-methoxyphenyl)but-2-yn-1-one (**4b**).* This compound was prepared from the THP-protected alcohol (1.0 g, 3.65 mmol) in the presence of PPTS, following the same literature procedure as described for related compounds.[22] The final compound was purified by silica gel column chromatography (2:3 EtOAC/hexane) to obtain the product as the yellow solid 67% (0.46 g) yield; ^1H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, J = 8.7 Hz, 2H), 6.90 (d, J = 8.7 Hz, 2H), 4.55 (s, 2H), 3.85 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 176.8, 164.8, 132.3, 129.6, 114.0, 92.3, 83.2, 55.7, 51.0; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{11}H_{10}NaO_3$, 213.0528; found, 213.0524.

*1-(4-Chlorophenyl)-4-hydroxybut-2-yn-1-one (**4c**).* Starting from the THP-protected alcohol (0.7 g, 2.52 mmol), PPTS treatment in refluxing ethanol afforded the free alcohol **4b** as the yellow solid in 70% (0.34 g) yield; ^1H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.4 Hz, 2H), 4.57 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 176.5, 141.2, 134.8, 131.1, 129.2, 92.7, 83.2, 51.2; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{10}H_7ClNaO_2$, 217.0032; found, 217.0027.

*4-Hydroxy-1-(3-methoxyphenyl)but-2-yn-1-one (**4d**).* This compound was prepared similarly as compound **4b**. Starting from the corresponding THP-protected alcohol (0.8 g, 2.92 mmol), PPTS treatment in refluxing ethanol afforded the free alcohol **4d** as the yellow solid in 65% (0.36 g) yield); ^1H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, J = 7.4 Hz, 1H), 7.51 (s, 1H), 7.27 (dd, J = 11.7, 4.0 Hz, 1H), 7.07 (d, J = 7.7 Hz, 1H), 4.54 (s, 2H), 4.17 (s, 1H), 3.76 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 177.8, 159.6, 137.4, 129.6, 122.9, 121.1, 112.8, 93.2, 82.9, 55.3, 50.6; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{11}H_{10}NaO_3$, 213.0528; found, 213.0522.

*(E)-1-(2-Bromophenyl)-5-hydroxypent-2-en-1-one (**7f**).* This compound was prepared following the same literature procedure as described for related compounds[23] and was obtained as the white solid in 62% (0.43 g) yield from the corresponding TBS-protected alcohol (1.0 g, 2.72 mmol); ^1H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, J = 7.9 Hz, 1H), 7.38–7.27 (m, 3H), 6.74–6.66 (m, 1H), 6.53 (d, J = 15.9 Hz, 1H), 3.78 (t, J = 6.2 Hz, 2H), 2.54 (q, J = 6.3 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 195.0, 148.8, 140.9, 133.5, 132.1, 131.4, 129.2, 127.4, 119.5, 60.9, 36.0; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{11}H_{11}BrNaO_2$, 276.9840; found, 276.9836.

General Procedure for [3 + 3]-Annulation of α-Halo Hydroxamates (Precursor to Azaoxyallyl Cation) and Hydroxyl Enone Derivatives (2) to Morpholin-3-ones, (3). To a solution of α-bromo hydroxamate **1** (2.0 equiv) and hydroxyl enones **2** (1.0 equiv) in $(CF_3)_2CHOH$ (0.2 M), was added Na_2CO_3 (3.0 equiv). The reaction mixture was stirred at room temperature, and the progress of the reaction was monitored by TLC. Upon completion of the reaction (ca. 6–8 h), HFIP was removed under the reduced pressure, and the crude was purified by silica gel column chromatography (using ether–hexane mixture as eluent) to afford the corresponding annulation products **3aa–3ai**.

*4-(Benzyloxy)-2,2-dimethyl-5-(2-oxo-2-phenylethyl)morpholin-3-one (**3aa**).* Following the general procedure, reaction between (*E*)-4-hydroxy-1-phenylbut-2-en-1-one, **2a** (0.10 g, 0.6 mmol, 1.0 equiv) and α-bromo hydroxamate **1a** (0.334 g, 1.2 mmol, 2.0 equiv) afforded the corresponding morpholin-3-one **3aa**, which was purified by silica gel column chromatography (3:7 Et_2O/hexane as eluent) to give the title compound as the yellow solid in 95% (0.209 g) yield.

[Gram Scale synthesis]. **1a** (3.36 g, 12.4 mmol, 2.0 equiv) and **2a** (1.0 g, 6.2 mmol, 1.0 equiv) were taken in 20 mL HFIP and was added Na_2CO_3 (1.97 g, 18.6 mmol, 3.0 equiv). The reaction mixture was stirred for 8 h at room temperature, and the solvent was removed in vacuo. The title compound was isolated in 91% (1.98 g) yield, following same chromatographic separation process as described above. R_f 0.4 (2:3 Et_2O/hexane); FT-IR (ν cm^{-1}): 2979, 2936, 1739, 1677, 1285, 1176; ^1H NMR (400 MHz, $CDCl_3$): δ 7.90–7.87 (m, 2H), 7.59–7.54 (m, 1H), 7.50 (d, J = 8.0 Hz, 2H), 7.43–7.40 (m, 2H), 7.36–7.34 (m, 3H), 5.02 (d, J = 10.2 Hz, 1H), 4.98 (d, J = 10.2 Hz, 1H), 4.12–4.09 (m, 1H), 4.00–3.96 (m, 1H), 3.75 (dd, J = 12.5,

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2.3 Hz, 1H), 3.50−3.44 (m, 1H) 3.34 (dd, J = 17.7, 9.4 Hz, 1H), 1.48 (s, 3H), 1.47 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 197.7, 170.3, 136.4, 134.7, 133.7, 130.0, 129.1, 128.8, 128.6, 128.1, 78.7, 76.3, 62.2, 57.1, 38.0, 26.4, 23.9; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{21}H_{23}NNaO_4$, 376.1525; found, 376.1519.

*4-(Benzyloxy)-2,2-dimethyl-5-(2-oxo-2-(p-tolyl)ethyl)morpholin-3-one (**3ab**).* Following the general procedure, reaction between (*E*)-4-hydroxy-1-(*p*-tolyl)but-2-en-1-one **2b** (0.05 g, 0.3 mmol, 1.0 equiv) and α-bromo hydroxamate **1a** (0.163 g, 0.6 mmol, 2.0 equiv) afforded the corresponding morpholin-3-one **3ab**, which was purified by silica gel column chromatography (3:7 Et_2O/hexane as eluent) to give the title compound as colorless liquid in 81% (0.84 g) yield. R_f 0.36 (2:3 Et_2O/hexane); ^1H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, J = 8.2 Hz, 2H), 7.34−7.32 (m, 2H), 7.28−7.26 (m, 3H), 7.16 (d, J = 8.0 Hz, 2H), 4.94 (d, J = 10.2 Hz, 1H), 4.90 (d, J = 10.2 Hz, 1H), 4.04−4.00 (m, 1H), 3.89 (dd, J = 12.5, 2.2 Hz, 1H), 3.66 (dd, J = 12.5, 2.2 Hz, 1H), 3.36 (dd, J = 17.5, 2.2 Hz, 1H), 3.23 (dd, J = 17.6, 9.4 Hz, 1H), 2.32 (s, 3H), 1.40 (s, 3H), 1.39 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 197.3, 170.3, 144.5, 134.8, 134.0, 130.0, 129.4, 129.1, 128.6, 128.2, 78.7, 76.3, 62.3, 57.2, 37.8, 26.4, 23.9, 21.8; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{22}H_{25}NNaO_4$, 390.1681; found, 390.1675.

*4-(Benzyloxy)-5-(2-(4-methoxyphenyl)-2-oxoethyl)-2,2-dimethylmorpholin-3-one (**3ac**).* Following the general procedure, reaction between (*E*)-4-hydroxy-1-(4-methoxyphenyl)but-2-en-1-one **2c** (0.10 g, 0.5 mmol, 1.0 equiv) and α-bromo hydroxamate **1a** (0.271 g, 1.0 mmol, 2.0 equiv) afforded the corresponding morpholin-3-one **3ac**, which was purified by silica gel column chromatography (2:3 Et_2O/hexane as eluent) to give the title compound as colorless liquid in 91% (0.182 g) yield. R_f 0.3 (2:3 Et_2O/hexane); ^1H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, J = 8.9 Hz, 2H), 7.42−7.39 (m, 2H), 7.34−7.33 (m, 3H), 6.89 (d, J = 8.9 Hz, 2H), 5.01 (d, J = 10.2 Hz, 1H), 4.97 (d, J = 10.1 Hz, 1H), 4.11−4.08 (m, 1H), 3.96 (dd, J = 12.5, 2.1 Hz, 1H), 3.84 (s, 3H), 3.74 (dd, J = 12.5, 2.2 Hz, 1H), 3.41 (dd, J = 17.4, 2.2 Hz, 1H), 3.28 (dd, J = 17.4, 9.4 Hz, 1H), 1.47 (s, 3H), 1.45 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 196.1, 170.3, 163.9, 134.7, 130.4, 129.9, 129.5, 129.0, 128.6, 113.9, 78.6, 76.3, 62.2, 57.2, 55.5, 37.5, 26.4, 23.9; HRMS (ESI-TOF) m/z: $[M + Na]^+$calcd for $C_{22}H_{25}NNaO_5$, 406.1630; found, 406.1626.

*4-(Benzyloxy)-5-(2-(4-fluorophenyl)-2-oxoethyl)-2,2-dimethylmorpholin-3-one (**3ad**).* Following the general procedure, reaction between (*E*)-1-(4-fluorophenyl)-4-hydroxybut-2-en-1-one **2d** (0.10 g, 0.6 mmol, 1.0 equiv) and α-bromo hydroxamate **1a** (0.301 g, 1.2 mmol, 2.0 equiv) afforded the corresponding morpholin-3-one **3ad**, which was purified by silica gel column chromatography (3:7 Et_2O/hexane as eluent) to give the title compound as colorless liquid in 90% (0.186 g) yield. R_f 0.35 (2:3 Et_2O/hexane); ^1H NMR (400 MHz, $CDCl_3$): δ 7.91 (dd, J = 8.6, 5.5 Hz, 2H), 7.41−7.40 (m, 2H),7.36−7.35 (m, 3H), 7.11 (t, J = 8.5 Hz, 2H), 5.02 (d, J = 10.2 Hz, 1H), 4.97 (d, J = 10.2 Hz, 1H), 4.10−4.07 (m, 1H), 3.73 (dd, J = 12.5, 1.9 Hz, 1H), 3.73 (dd, J = 12.5, 1.9 Hz, 1H), 3.43 (dd, J = 17.5, 2.4 Hz, 1H), 3.29 (dd, J = 17.6, 9.3 Hz, 1H), 1.48 (s, 3H), 1.47 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 196.2, 170.4, 166.1 (d, J = 254.2 Hz),134.8, 133.0 (d, J = 3.0 Hz), 130.9 (d, J = 9.4 Hz), 130.0, 129.2, 128.7, 116.0 (d, J = 21.8 Hz), 78.8, 76.4, 62.3, 57.2, 38.0, 26.4, 24.0; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{21}H_{22}FNNaO_4$, 394.1431; found, 394.1427.

*4-(Benzyloxy)-5-(2-(4-bromophenyl)-2-oxoethyl)-2,2-dimethylmorpholin-3-one (**3ae**).* Following the general procedure, reaction between (*E*)-1-(4-bromophenyl)-4-hydroxybut-2-en-1-one **2e** (0.10 g, 0.4 mmol, 1.0 equiv) and α-bromo hydroxamate **1a** (0.217 g, 0.8 mmol, 2.0 equiv) afforded the corresponding morpholin-3-one **3ae**, which was purified by silica gel column chromatography (3:7 Et_2O/hexane as eluent) to give the title compound as the white solid in 87% (0.156 g) yield. R_f 0.36 (2:3 Et_2O/hexane); mp 103.4−105.0 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, J = 8.3 Hz, 2H), 7.57 (d, J = 8.3 Hz, 2H), 7.40−7.36 (m, 5H), 5.01 (d, J = 10.2 Hz, 1H), 4.96 (d, J = 10.2 Hz, 1H), 4.08−4.06 (m, 1H), 3.97 (d, J = 12.3 Hz, 1H), 3.72 (d, J = 12.4 Hz, 1H), 3.40 (d, J = 15.7 Hz, 1H), 3.26 (dd, J = 17.7, 9.2 Hz, 1H), 1.47 (s, 3H), 1.46 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 196.7, 170.3, 135.2, 134.7, 132.1, 130.0, 129.6, 129.2, 128.9, 128.7, 78.8, 76.4, 62.2, 57.2, 38.0, 26.4, 24.0; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{21}H_{22}BrNNaO_4$, 454.0630; found, 454.0623.

*4-(Benzyloxy)-5-(2-(3-methoxyphenyl)-2-oxoethyl)-2,2-dimethylmorpholin-3-one (**3af**).* Following the general procedure, reaction between (*E*)-4-hydroxy-1-(3-methoxyphenyl)but-2-en-1-one **2af** (0.10 g, 0.5 mmol, 1.0 equiv) and α-bromo hydroxamate **1a** (0.271 g, 1.0 mmol, 2.0 equiv) afforded the corresponding morpholin-3-one **3af**, which was purified by silica gel column chromatography (2:3 Et_2O/hexane as the eluent) to give the title compound as yellow liquid in 89% (0.186 g) yield. R_f 0.3 (2:3 Et_2O/hexane); ^1H NMR (400 MHz, $CDCl_3$): δ 7.45−7.38 (m, 4H), 7.33−7.29 (m, 4H), 7.08 (d, J = 7.0 Hz, 1H), 4.99 (d, J = 10.2 Hz, 1H), 4.96 (d, J = 10.2 Hz, 1H), 4.09−4.06 (m, 1H), 3.95 (d, J = 11.1 Hz, 1H), 3.79 (s, 3H), 3.72 (d, J = 13.8 Hz, 1H), 3.43 (d, J = 15.8 Hz, 1H), 3.29 (dd, J = 17.6, 9.3 Hz, 1H), 1.46 (s, 3H), 1.45 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 197.4, 170.2, 159.8, 137.7, 134.6, 129.8, 129.6, 129.0, 128.5, 120.7, 120.0, 112.1, 78.6, 76.2, 62.1, 57.1, 55.4, 38.0, 26.3, 23.8; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{22}H_{25}NNaO_5$, 406.1630; found, 406.1627.

*4-(Benzyloxy)-2,2-dimethyl-5-(2-oxo-2-(o-tolyl)ethyl)morpholin-3-one (**3ag**).* Following the general procedure, reaction between (*E*)-4-hydroxy-1-(*o*-tolyl)but-2-en-1-one **2g** (0.10 g, 0.6 mmol, 1.0 equiv) and α-bromo hydroxamate **1a** (0.325 g, 1.2 mmol, 2.0 equiv) afforded the corresponding morpholin-3-one **3ag**, which was purified by silica gel column chromatography (3:7 Et_2O/hexane as eluent) to give the title compound as yellow liquid in 84% (0.175 g) yield. R_f 0.35 (2:3 Et_2O/hexane); ^1H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, J = 7.7 Hz, 1H), 7.30−7.28 (m, 2H), 7.24−7.23 (m, 4H), 7.12 (app t, J = 8.1 Hz, 2H), 4.88 (s, 2H), 3.98−3.95 (m, 1H), 3.85 (dd, J = 12.4, 2.7 Hz, 1H), 3.62 (dd, J = 12.5, 2.0 Hz, 1H), 3.30 (dd, J = 17.6, 3.2 Hz, 1H), 3.14 (dd, J = 17.6, 9.2 Hz, 1H), 2.35 (s, 3H), 1.35 (s, 3H), 1.35 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 201.2, 170.3, 138.7, 136.8, 134.8, 132.2, 132.0, 129.9, 129.1, 129(2), 128.6, 125.9, 78.7, 76.4, 62.4, 57.3, 40.7, 26.4, 24.0, 21.6; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{22}H_{25}NNaO_4$, 390.1681; found, 390.1677.

*4-(Benzyloxy)-2,2-dimethyl-5-(2-(naphthalen-2-yl)-2-oxoethyl)-morpholin-3-one (**3ah**).* Following the general procedure, reaction between (*E*)-4-hydroxy-1-(naphthalen-2-yl)but-2-en-1-one **2h** (0.10 g, 0.5 mmol, 1.0 equiv) and α-bromo hydroxamate **1a** (0.271 g, 1.0 mmol, 2.0 equiv) afforded the corresponding morpholin-3-one **3ah**, which was purified by silica gel column chromatography (3:7 Et_2O/hexane as eluent) to give the title compound as colorless liquid in 88% (0.169 g) yield. R_f 0.4 (2:3 Et_2O/hexane); ^1H NMR (400 MHz, $CDCl_3$): δ 8.41 (s, 1H), 7.95 (app t, J = 7.4 Hz, 2H), 7.88 (dd, J = 8.4, 3.2 Hz, 2H), 7.62 (t, J = 7.4 Hz, 1H), 7.56 (t, J = 7.4 Hz, 1H), 7.46−7.42 (m, 2 H), 7.37−7.35 (m, 3H), 5.06 (d, J = 10.3 Hz, 1H), 5.01 (d, J = 10.2 Hz, 1H), 4.18−4.15 (m, 1H), 4.02 (dd, J = 12.3, 2.5 Hz, 1H), 3.81 (dd, J = 12.5, 1.9 Hz, 1H), 3.62 (dd, J = 17.5, 2.6 Hz, 1H), 3.47 (dd, J = 17.6, 9.4 Hz, 1H), 1.52 (s, 3H), 1.49 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 197.7, 170.5, 135.9, 134.8, 133.8, 132.6, 130.2, 130.0, 129.8, 129.2, 128.9, 128.7, 127.9, 127.1, 123.6, 78.8, 76.5, 62.4, 57.4, 38.1, 26.5, 24.0; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{25}H_{25}NNaO_4$, 426.1681; found, 426.1678.

*4-Methoxy-2,2-dimethyl-5-(2-(naphthalen-2-yl)-2-oxoethyl)-morpholin-3-one (**3bh**).* Following the general procedure, reaction between (*E*)-4-hydroxy-1-(naphthalen-2-yl)but-2-en-1-one **2h** (0.10 g, 0.5 mmol, 1.0 equiv) and α-bromo hydroxamate **1b** (0.271 g, 1.0 mmol, 2.0 equiv) afforded the corresponding morpholin-3-one **3bh**, which was purified by silica gel column chromatography (3:7 Et_2O/hexane as the eluent) to give the title compound as the white solid in 91% (0.139 g) yield. R_f 0.37 (2:3 Et_2O/hexane); mp 102.1−103.5 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.44 (s, 1H), 7.95 (dd, J = 17.2, 8.3 Hz, 2H), 7.86 (app t, J = 8.3 Hz, 2H), 7.59 (app t, J = 7.4 Hz, 1H), 7.53 (app t, J = 7.4 Hz, 1H), 4.47−4.44 (m, 1H), 4.15 (dd, J = 12.5, 2.9 Hz, 1H), 3.90 (dd, J = 12.5, 2.2 Hz, 1H), 3.78 (s, 3H), 3.67 (dd, J = 17.6, 2.9 Hz, 1H), 3.52 (dd, J = 17.6, 9.2 Hz, 1H), 1.49 (s, 3H), 1.48 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 197.6, 169.8, 135.8, 133.7, 132.5, 130.0, 129.7, 128.8, 128.7, 127.8, 127.0, 123.5,

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78.6, 62.5, 61.7, 55.7, 38.1, 26.3, 23.9; HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{19}H_{21}NNaO_4$, 350.1368; found, 350.1364.

*4-(Benzyloxy)-3-(2-(naphthalen-2-yl)-2-oxoethyl)-1-oxa-4-azaspiro[5.5]undecan-5-one (**3ch**).* Following the general procedure, reaction between (*E*)-4-hydroxy-1-(naphthalen-2-yl)but-2-en-1-one **2h** (0.10 g, 0.5 mmol, 1.0 equiv) and α-bromo hydroxamate **1c** (0.311 g, 1.0 mmol, 2.0 equiv) afforded the corresponding morpholin-3-one **3ch**, which was purified by silica gel column chromatography (1:3 Et_2O/hexane as the eluent) to give the title compound as colorless liquid in 84% (0.175 g) yield. R_f 0.45 (2:3 Et_2O/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (s, 1H), 7.95 (app t, J = 7.3 Hz, 2H), 7.88 (d, J = 10.0 Hz, 2H), 7.61 (app t, J = 7.4 Hz, 1H), 7.58−7.52 (m, 1H), 7.42−7.41 (m, 2H), 7.36−7.35 (m, 3H), 5.04 (d, J = 10.2 Hz, 1H), 4.99 (d, J = 10.2 Hz, 1H), 4.14−4.11 (m, 1H), 3.97 (dd, J = 12.3, 2.2 Hz, 1H), 3.82 (dd, J = 12.4, 1.3 Hz, 1H), 3.60 (dd, J = 17.3, 2.0 Hz, 1H), 3.46 (dd, J = 17.6, 9.4 Hz, 1H), 2.05−1.98 (m, 2H), 1.82−1.78 (m, 2H), 1.55−1.43 (m, 4H), 1.34−1.26 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 197.8, 170.8, 135.9, 134.9, 133.9, 132.6, 130.2, 130.1, 129.7, 129.2, 128.9, 128.7, 127.9, 127.1, 123.6, 79.8, 76.4, 61.8, 57.2, 38.3, 33.8, 30.2, 25.2, 20.9, 20.7; HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{28}H_{29}NNaO_4$, 466.1994; found, 466.1989.

*4-(Benzyloxy)-2,2-dimethyl-5-(2-oxo-4-phenylbutyl)morpholin-3-one (**3ai**).* Following the general procedure, reaction between following the general procedure, reaction between (*E*)-6-hydroxy-1-phenylhex-4-en-3-one **2i** (0.10 g, 0.5 mmol, 1.0 equiv) and α-bromo hydroxamate **1a** (0.271 g, 1.0 mmol, 2.0 equiv) afforded the corresponding morpholin-3-one **3ai**, which was purified by silica gel column chromatography (3:7 Et_2O/hexane as the eluent) to give the title compound as the white solid in 69% (0.138 g) yield. R_f 0.4 (2:3 Et_2O/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38−7.36 (m, 2H), 7.32−7.31 (m, 3H), 7.21 (app t, J = 7.5 Hz, 2H), 7.13 (app t, J = 7.1 Hz, 1H), 7.05 (d, J = 7.5 Hz, 2H), 4.90 (d, J = 9.8 Hz, 1H), 4.85 (d, J = 9.9 Hz, 1H), 3.99−3.95 (m, 1H), 3.83 (dd, J = 12.4, 3.2 Hz, 1H), 3.56 (dd, J = 12.4, 3.0 Hz, 1H), 2.83−2.71 (m, 3H), 2.68−2.58 (m, 3H), 1.39 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 207.5, 170.0, 140.6, 134.6, 130.0, 129.1, 128.6, 128.6(2), 128.3, 126.3, 78.7, 76.2, 62.4, 56.5, 44.9, 42.3, 29.5, 25.9, 24.2; HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{23}H_{27}NNaO_4$, 404.1838; found, 404.1834.

General Procedure for [3 + 3]-Annulation of α-Halo Hydroxamates (Precursor to Azaoxyallyl Cation) and Hydroxyl Alkynone Derivatives (4) to Morpholin-3-one Derivatives, 5. To a solution of α-bromo hydroxamate **1** (2.0 equiv) and hydroxyl alkynones **4** (1.0 equiv) in $(CF_3)_2CHOH$ (0.2 M), was added Na_2CO_3 (3.0 equiv). The reaction mixture was stirred at room temperature, and the reaction progress was monitored by TLC. Upon completion of the reaction (ca. 5−6 h), HFIP was removed under reduced pressure, and the crude was purified by silica gel column chromatography (using ether−hexane mixture as the eluent) to afford the corresponding annulated products, **5aa**−**5ae**.

*(Z)-4-(Benzyloxy)-2,2-dimethyl-5-(2-oxo-2-phenylethylidene)-morpholin-3-one (**5aa**).* Following the general procedure, reaction between 4-hydroxy-1-phenylbut-2-yn-1-one **4a** (0.05 g, 0.3 mmol, 1.0 equiv) and α-bromo hydroxamate **1a** (0.163 g, 0.6 mmol, 2.0 equiv) afforded the corresponding (*Z*)-4-(benzyloxy)-morpholin-3-one **5aa**, which was purified by silica gel column chromatography (3:7 Et_2O/hexane as the eluent) to give the title compound as colorless liquid in 68% (0.075 g) yield. R_f 0.4 (2:3 Et_2O/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, J = 7.5 Hz, 2H), 7.43 (t, J = 7.3 Hz, 1H), 7.31 (app t, J = 7.6 Hz, 2H), 7.26−7.19 (m, 5H), 5.29 (s, 1H), 4.84 (s, 2H), 4.44 (s, 2H), 1.50 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 193.2, 168.2, 137.4, 136.8, 133.2, 133.2(2), 130.2, 129.2, 129.0, 128.5, 128.2, 102.0, 78.9, 76.6, 62.5, 24.6; HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{21}H_{21}NNaO_4$, 374.1368; found, 374.1364.

*(Z)-4-(Benzyloxy)-5-(2-(4-methoxyphenyl)-2-oxoethylidene)-2,2-dimethylmorpholin-3-one (**5ab**).* Following the general procedure, reaction between 4-hydroxy-1-(4-methoxyphenyl)but-2-yn-1-one **4b** (0.05 g, 0.3 mmol, 1.0 equiv) and α-bromo hydroxamate **1a** (0.163 g, 0.6 mmol, 2.0 equiv) afforded the corresponding (*Z*)-4-(benzyloxy)-morpholin-3-one **5ab**, which was purified by silica gel column chromatography (2:3 Et_2O/hexane as the eluent) to give the title compound as yellow liquid in 70% (0.070 g) yield. R_f 0.3 (2:3 Et_2O/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, J = 8.5 Hz, 2H), 7.30−7.25 (m, 5H), 6.81 (d, J = 8.4 Hz, 2H), 5.29 (s, 1H), 4.86 (s, 2H), 4.45 (s, 2H), 3.82 (s, 3H), 1.55 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 192.0, 168.2, 163.7, 136.2, 133.3, 131.6, 130.6, 130.3, 128.9, 128.2, 113.8, 102.5, 78.9, 76.6, 62.6, 55.6, 24.7; HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{22}H_{23}NNaO_5$, 404.1474; found, 404.1467.

*(Z)-4-Methoxy-5-(2-(4-methoxyphenyl)-2-oxoethylidene)-2,2-dimethylmorpholin-3-one (**5bb**).* Following the general procedure, reaction between 4-hydroxy-1-(4-methoxyphenyl)but-2-yn-1-one **4b** (0.05 g, 0.3 mmol, 1.0 equiv) and α-bromo hydroxamate **1b** (0.118 g, 0.6 mmol, 2.0 equiv) afforded the corresponding (*Z*)-4-methoxy-morpholin-3-one **5bb**, which was purified by silica gel column chromatography (2:3 Et_2O/hexane as eluent) to give the title compound as yellow liquid in 64% (0.051 g) yield. R_f 0.3 (2:3 Et_2O/hexane); ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.91 (d, J = 8.8 Hz, 2H), 6.95 (d, J = 8.8 Hz, 2H), 5.28 (s, 1H), 4.47 (s, 2H), 3.86 (s, 3H), 3.50 (s, 3H), 1.48 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, CD_2Cl_2): δ 192.0, 168.2, 164.2, 136.3, 131.6, 131.3, 114.3, 102.3, 79.1, 62.9, 62.8, 56.1, 24.8; HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{16}H_{19}NNaO_5$, 328.1161; found, 328.1154.

*(Z)-4-Methoxy-3-(2-(4-methoxyphenyl)-2-oxoethylidene)-1-oxa-4-azaspiro[5.5]undecan-5-one (**5cb**).* Following the general procedure, reaction between 4-hydroxy-1-(4-methoxyphenyl)but-2-yn-1-one **4b** (0.05 g, 0.3 mmol, 1.0 equiv) and α-bromo hydroxamate **1c** (0.187 g, 0.6 mmol, 2.0 equiv) afforded the corresponding (*Z*)-4-methoxy-morpholin-3-one **5cb**, which was purified by silica gel column chromatography (3:7 Et_2O/hexane as eluent) to give the title compound as yellow liquid in 58% (0.064 g) yield. R_f 0.42 (2:3 Et_2O/hexane); FT-IR (ν cm^{-1}): 2932, 1697, 1663, 1598, 1309, 1249, 1166, 1026; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, J = 8.7 Hz, 2H), 7.31−7.29 (m, 2H), 7.29−7.28 (m, 3H), 6.83 (d, J = 8.8 Hz, 2H), 5.30 (s, 1H), 4.87 (s, 2H), 4.48 (s, 2H), 3.84 (s, 3H), 2.00−1.97 (m, 2H), 1.92−1.85 (m, 2H), 1.74−1.61 (m, 4H), 1.37−1.29 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 192.1, 168.4, 163.7, 136.2, 133.4, 131.5, 130.7, 130.3, 128.9, 128.2, 113.8, 102.1, 79.9, 76.6, 62.1, 55.6, 31.5, 25.1, 20.7; HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{25}H_{27}NNaO_5$, 444.1787; found, 444.1781.

*(Z)-4-(Benzyloxy)-5-(2-(4-chlorophenyl)-2-oxoethylidene)-2,2-dimethylmorpholin-3-one (**5ac**).* Following the general procedure, reaction between 1-(4-chlorophenyl)-4-hydroxybut-2-yn-1-one **4c** (0.05 g, 0.25 mmol, 1.0 equiv) and α-bromo hydroxamate **1a** (0.136 g, 0.5 mmol, 2.0 equiv) afforded the corresponding (*Z*)-4-(benzyloxy)-morpholin-3-one **5ac**, which was purified by silica gel column chromatography (3:7 Et_2O/hexane as the eluent) to give the title compound as yellow liquid in 67% (0.066 g) yield. R_f 0.4 (2:3 Et_2O/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, J = 8.5 Hz, 2H), 7.27−7.25 (m, 7H), 5.24 (s, 1H), 4.84 (s, 2H), 4.45 (s, 2H), 1.51 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 192.1, 168.2, 139.6, 137.3, 135.9, 133.1, 130.5, 130.2, 129.1, 128.8, 128.3, 101.3, 79.0, 76.7, 62.5, 24.6; HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{21}H_{20}ClNNaO_4$, 408.0979; found, 408.0954.

*(Z)-4-(Benzyloxy)-5-(2-(3-methoxyphenyl)-2-oxoethylidene)-2,2-dimethylmorpholin-3-one (**5ad**).* Following the general procedure, reaction between 4-hydroxy-1-(3-methoxyphenyl)but-2-yn-1-one **4d** (0.05 g, 0.3 mmol, 1.0 equiv) and α-bromo hydroxamate **1a** (0.163 g, 0.6 mmol, 2.0 equiv) afforded the corresponding (*Z*)-4-(benzyloxy)-morpholin-3-one **5ad**, which was purified by silica gel column chromatography (2:3 Et_2O/hexane as the eluent) to give the title compound as yellow liquid in 65% (0.065 g) yield. R_f 0.3 (2:3 Et_2O/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, J = 7.5 Hz, 2H), 7.28−7.22 (m, 6H), 6.99 (dd, J = 8.2, 1.9 Hz, 1H), 5.29 (s, 1H), 4.83 (s, 2H), 4.44 (s, 2H), 3.70 (s, 3H), 1.50 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 193.0, 168.2, 159.8, 138.9, 136.8, 133.3, 130.2, 129.5, 128.9, 128.2, 122.4, 120.2, 112.5, 102.1, 78.9, 76.6, 62.5, 55.4, 24.7; HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{22}H_{23}NNaO_5$, 404.1474; found, 404.1468.

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*(Z)-4-(Benzyloxy)-2,2-dimethyl-5-(2-oxo-4-phenylbutylidene)-morpholin-3-one (**5ae**).* Following the general procedure, reaction between 6-hydroxy-1-phenylhex-4-yn-3-one **4e** (0.05 g, 0.26 mmol, 1.0 equiv) and α-bromo hydroxamate **1a** (0.141 g, 0.52 mmol, 2.0 equiv) afforded the corresponding (*Z*)-4-(benzyloxy)-morpholin-3-one **5ae**, which was purified by silica gel column chromatography (3:7 Et_2O/hexane as the eluent) to give the title compound as yellow liquid in 62% (0.062 g) yield. R_f 0.35 (2:3 Et_2O/hexane); ^1H NMR (400 MHz, $CDCl_3$): δ 7.37−7.36 (m, 2H), 7.32−7.31 (m, 4H), 7.24−7.18 (m, 2H), 7.10 (d, *J* = 7.7 Hz, 2H), 5.89 (s, 1H), 4.97 (s, 2H), 4.88 (s, 2H), 2.82 (t, *J* = 7.6 Hz, 2H), 2.68 (t, *J* = 7.6 Hz, 2H), 1.41 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 199.2, 168.8, 150.1, 141.2, 133.6, 130.0, 129.6, 128.8, 128.6, 128.5, 126.3, 100.3, 77.5, 77.3, 60.8, 46.1, 30.6, 23.7; HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{23}H_{25}NNaO_4$, 402.1681; found, 402.1672.

*4-(Benzyloxy)-5-((3-(benzyloxy)-2,5,5-trimethyl-4-oxooxazolidin-2-yl)methylene)-2,2-dimethylmorpholin-3-one (**6**).* Following the general procedure, reaction between 5-hydroxypent-3-yn-2-one **4f** (0.05 g, 0.5 mmol, 1.0 equiv) and α-bromo hydroxamate **1a** (0.136 g, 0.5 mmol, 1.0 equiv) afforded the corresponding (*Z*)-4-(benzyloxy)-morpholin-3-one **6**, which was purified by silica gel column chromatography (3:7 Et_2O/hexane as the eluent) to give the title compound as the white solid in 59% (0.144 g) yield. R_f 0.35 (2:3 Et_2O/hexane); mp 122.8−124.0 °C; FT-IR (ν cm^{-1}): 3304, 2982, 2935, 1730, 1692, 1661, 1456, 1320, 1201, 1071; ^1H NMR (400 MHz, $CDCl_3$): δ 7.46−7.44 (m, 2H), 7.41−7.39 (m, 3H), 7.37−7.30 (m, 3H), 7.26−7.22 (m, 2H), 5.58 (s, 1H), 5.15 (d, *J* = 10.0 Hz, 1H), 5.07 (d, *J* = 10.0 Hz, 1H), 4.93 (s, 2H), 4.67 (d, *J* = 15.2 Hz, 1H), 4.61 (d, *J* = 15.2 Hz, 1H), 1.49 (s, 3H), 1.47 (s, 3H), 1.43 (s, 3H), 1.42 (s, 3H), 1.30 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.7, 167.9, 135.3, 134.6, 133.7, 130.3, 129.8, 129.3, 129.3(2), 128.7, 128.7(2), 104.1, 91.4, 79.2, 78.2, 77.6, 76.5, 58.4, 28.2, 26.6, 24.9, 24.7, 23.8; HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{27}H_{32}N_2NaO_6$, 503.2158; found, 503.2142.

Procedure for (*Z*)-5 to (*E*)-5 Isomerization.

(a) In $CDCl_3$: Compounds (*Z*)-**5ab**/(*Z*)-**5bb** (20 mg) were dissolved in the $CDCl_3$ (0.5 mL) in the NMR tube and was kept on standing for 24 h at room temperature. The sample was analyzed by NMR spectroscopy. A quantitative conversion was observed by NMR analysis.

(b) With *p*-TsOH: compound (*Z*)-**5ab** (40 mg, 0.1 mmol) was dissolved in dry DCM (1.0 mL) and was added *p*-TsOH (0.1 equiv). The reaction mixture was stirred for 30 min at room temperature, and the solvent was removed in vacuo. The crude product was analyzed by NMR spectroscopy, and quantitative conversion of (*Z*)-**5ab** to (*E*)-**5ab** was observed.

*(E)-4-(Benzyloxy)-5-(2-(4-methoxyphenyl)-2-oxoethylidene)-2,2-dimethylmorpholin-3-one (**E-5ab**).* ^1H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, *J* = 8.8 Hz, 2H), 7.53−7.51 (m, 2H), 7.44−7.41 (m, 3H), 6.92 (d, *J* = 8.8 Hz, 2H), 6.71 (s, 1H), 5.18 (s, 2H), 5.07 (s, 2H), 3.88 (s, 3H), 1.53 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 188.9, 168.7, 163.3, 151.0, 133.8, 132.1, 130.3, 130.1, 129.6, 129.0, 113.9, 98.0, 77.6, 77.4, 61.1, 55.6, 23.8; HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{22}H_{23}NNaO_5$, 404.1474; found, 404.1467.

*(E)-4-Methoxy-5-(2-(4-methoxyphenyl)-2-oxoethylidene)-2,2-dimethylmorpholin-3-one (**E-5bb**).* ^1H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, *J* = 8.6 Hz, 2H), 6.96 (d, *J* = 8.7 Hz, 2H), 6.71 (s, 1H), 5.21 (s, 2H), 3.92 (s, 3H), 3.88 (s, 3H), 1.52 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 189.1, 168.2, 163.4, 150.3, 132.1, 130.4, 113.9, 97.3, 77.4, 62.6, 61.1, 55.6, 23.7; HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{16}H_{19}NNaO_5$, 328.1161; found, 328.1154.

*(Z)-5-(2-(4-Methoxyphenyl)-2-oxoethylidene)-2,2-dimethylmorpholin-3-one (**5ab′**).* To a solution of (*E*)-/(*Z*)-**5ab** (0.100 g, 0.26 mmol, 1.0 equiv) in acetonitrile/water (9:1, 2 mL), $Mo(CO)_6$ (0.083 g, 0.30 mmol, 1.2 equiv) was added, and the reaction was stirred at 120 °C under argon for 12 h. After cooling to room temperature, the mixture was then filtered through Celite and thoroughly washed with ethyl acetate. Then, the filtrate was concentrated under vacuo, and the resulting residue was purified by silica gel column chromatography (3:7 EtOAc/hexane) to afford (*Z*)-**5ab′** as the white solid in 74% (0.053 g) and 76% (0.055 g) yields. R_f 0.3 (3:7 EtOAc/hexane); mp 124.5−125.5 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 11.82 (s, 1H), 7.89 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 5.93 (s, 1H), 4.48 (s, 2H), 3.87 (s, 3H), 1.52 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) 190.1, 172.2, 163.5, 151.4, 131.3, 130.1, 114.0, 94.0, 77.1, 60.3, 55.6, 23.9; HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{15}H_{17}NNaO_4$, 298.1055; found, 298.1047.

General Procedure for [3 + 4]-Annulation of α-Halo Hydroxamates (Precursor to Azaoxyallyl Cation) and Hydroxyl Enone Derivatives (7) to 1,4-Oxazepan-3-ones, 8. To a solution of α-bromo hydroxamate **1** (2.0 equiv) and hydroxyl enones **7** (1.0 equiv) in $(CF_3)_2CHOH$ (0.2 M), was added Na_2CO_3 (3.0 equiv). The reaction mixture was stirred at 50 °C overnight, and the reaction progress was monitored by TLC. Upon completion of the reaction, HFIP was removed under reduced pressure, and the crude was purified by silica gel column chromatography (using ether−hexane mixture as the eluent) to afford the corresponding cyclic products, **8aa**−**8bh**.

*4-(Benzyloxy)-2,2-dimethyl-5-(2-oxo-2-phenylethyl)-1,4-oxazepan-3-one (**8aa**).* Following the general procedure, reaction between (*E*)-5-hydroxy-1-phenylpent-2-en-1-one **7a** (0.10 g, 0.6 mmol, 1.0 equiv) and α-bromo hydroxamate **1a** (0.325 g, 1.2 mmol, 2.0 equiv) afforded the corresponding 1,4-oxazepan-3-one **8aa**, which was purified by silica gel column chromatography (3:7 Et_2O/hexane as the eluent) to give the title compound as the yellowish solid in 67% (0.140 g) yield. R_f 0.4 (2:3 Et_2O/hexane); mp 79.5−80.5 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, *J* = 8.0 Hz, 2H), 7.57 (app t, *J* = 7.3 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.38−7.37 (m, 2H), 7.34−7.30 (m, 3H), 4.89 (d, *J* = 10.4 Hz, 1H), 4.83 (d, *J* = 10.4 Hz, 1H), 4.54−4.48 (m, 1H), 3.84−3.78 (m, 1H), 3.67−3.60 (m, 1H), 3.40 (dd, *J* = 17.8, 8.8 Hz, 1H), 3.19 (dd, *J* = 17.8, 4.8 Hz, 1H), 2.15−2.08 (m, 2H), 1.55 (s, 3H), 1.53 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 197.9, 176.2, 136.5, 135.8, 133.6, 130.0, 128.9, 128.8, 128.6, 128.2, 79.0, 76.2, 59.5, 57.8, 39.8, 31.1, 29.4, 22.9; HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{22}H_{25}NNaO_4$, 390.1681; found, 390.1677.

*4-(Benzyloxy)-2,2-dimethyl-5-(2-oxo-2-(p-tolyl)ethyl)-1,4-oxazepan-3-one (**8ab**).* Following the general procedure, reaction between (*E*)-5-hydroxy-1-(*p*-tolyl)pent-2-en-1-one **7b** (0.10 g, 0.5 mmol, 1.0 equiv) and α-bromo hydroxamate **1a** (0.271 g, 1.0 mmol, 2.0 equiv) afforded the corresponding 1,4-oxazepan-3-one **8ab**, which was purified by silica gel column chromatography (3:7 Et_2O/hexane as the eluent) to give the title compound as colorless liquid in 61% (0.122 g) yield. R_f 0.42 (2:3 Et_2O/hexane); ^1H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.0 Hz, 2H), 7.37−7.35 (m, 2H), 7.31−7.29 (m, 3H), 7.22 (d, *J* = 8.0 Hz, 2H), 4.87 (d, *J* = 10.4 Hz, 1H), 4.81 (d, *J* = 10.4 Hz, 1H), 4.51−4.45 (m, 1H), 3.81−3.76 (m, 1H), 3.65−3.58 (m, 1H), 3.36 (dd, *J* = 17.7, 8.9 Hz, 1H), 3.15 (dd, *J* = 17.7, 4.5 Hz, 1H), 2.39 (s, 3H), 2.15−2.02 (m, 2H), 1.53 (s, 3H), 1.51 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 197.5, 176.2, 144.4, 135.8, 134.0, 130.0, 129.4, 128.9, 128.6, 128.3, 78.9, 76.2, 59.5, 57.9, 39.5, 31.1, 29.4, 22.8, 21.8; HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{23}H_{27}NNaO_4$, 404.1838; found, 404.1827.

*4-(Benzyloxy)-5-(2-(4-methoxyphenyl)-2-oxoethyl)-2,2-dimethyl-1,4-oxazepan-3-one (**8ac**).* Following the general procedure, reaction between (*E*)-5-hydroxy-1-(4-methoxyphenyl)pent-2-en-1-one **7c** (0.10 g, 0.2 mmol, 1.0 equiv) and α-bromo hydroxamate **1a** (0.108 g, 0.4 mmol, 2.0 equiv) afforded the corresponding 1,4-oxazepan-3-one **8ac**, which was purified by silica gel column chromatography (9:11 Et_2O/hexane as the eluent) to give the title compound as yellow liquid in 60% (0.058 g) yield. R_f 0.3 (2:3 Et_2O/hexane); ^1H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, *J* = 8.7 Hz, 2H), 7.38−7.37 (m, 2H), 7.33−7.31 (m, 3H), 6.91 (d, *J* = 8.7 Hz, 2H), 4.89 (d, *J* = 10.3 Hz, 1H), 4.83 (d, *J* = 10.4 Hz, 1H), 4.53−4.47 (m, 1H), 3.87 (s, 3H), 3.83−3.78 (m, 1H), 3.69−3.61 (m, 1H), 3.35 (dd, *J* = 17.4, 8.9 Hz, 1H), 3.17 (dd, *J* = 17.4, 4.7 Hz, 1H), 2.14−2.04 (m, 2H), 1.55 (s, 3H), 1.53 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 196.4, 176.2, 163.9, 135.8, 130.5, 130.0, 129.6, 128.9, 128.6, 113.9, 78.9, 76.2, 59.5, 58.0, 55.6, 39.4, 31.1, 29.4, 22.9; HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{23}H_{27}NNaO_5$, 420.1787; found, 420.1782.

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*4-(Benzyloxy)-5-(2-(4-fluorophenyl)-2-oxoethyl)-2,2-dimethyl-1,4-oxazepan-3-one (**8ad**).* Following the general procedure, reaction between (*E*)-1-(4-fluorophenyl)-5-hydroxypent-2-en-1-one **7d** (0.07 g, 0.4 mmol, 1.0 equiv) and α-bromo hydroxamate **1a** (0.217 g, 0.8 mmol, 2.0 equiv) afforded the corresponding 1,4-oxazepan-3-one **8ad**, which was purified by silica gel column chromatography (3:7 Et_2O/hexane as the eluent) to give the title compound as the white solid in 77% (0.107 g) yield. R_f 0.35 (2:3 Et_2O/hexane); mp 91.6−92.8 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.87 (dd, *J* = 8.4, 5.6 Hz, 2H), 7.38−7.36 (m, 2H), 7.34−7.31 (m, 3H), 7.11 (app t, *J* = 8.5 Hz, 2H), 4.88 (d, *J* = 10.5 Hz, 1H), 4.83 (d, *J* = 10.5 Hz, 1H), 4.50−4.45 (m, 1H), 3.84−3.79 (m, 1H), 3.67−3.59 (m, 1H), 3.34 (dd, *J* = 17.8, 8.8 Hz, 1H), 3.12 (dd, *J* = 17.8, 4.6 Hz, 1H), 2.13−2.08 (m, 2H), 1.55 (s, 3H), 1.53 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 196.2, 176.2, 166.1 (d, *J* = 254.0 Hz),135.9, 132.9 (d, *J* = 3.0 Hz), 130.9 (d, *J* = 9.3 Hz), 130.0, 128.9, 128.6, 115.9 (d, *J* = 21.8 Hz), 79.0, 76.2, 59.4, 57.8, 39.6, 31.1, 29.4, 22.9; HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{22}H_{24}FNNaO_4$, 408.1587; found, 408.1581.

*4-(Benzyloxy)-5-(2-(4-bromophenyl)-2-oxoethyl)-2,2-dimethyl-1,4-oxazepan-3-one (**8ae**).* Following the general procedure, reaction between (*E*)-1-(4-bromophenyl)-5-hydroxypent-2-en-1-one **7e** (0.10 g, 0.4 mmol, 1.0 equiv) and α-bromo hydroxamate **1a** (0.217 g, 0.8 mmol, 2.0 equiv) afforded the corresponding 1,4-oxazepan-3-one **8ae**, which was purified by silica gel column chromatography (3:7 Et_2O/hexane as the eluent) to give the title compound as the white solid in 75% (0.131 g) yield. R_f 0.38 (2:3 Et_2O/hexane); mp 82.5−83.5 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, *J* = 8.2 Hz, 2H), 7.57 (d, *J* = 8.3 Hz, 2H), 7.40−7.35 (m, 2H), 7.33−7.31 (m, 3H), 4.87 (d, *J* = 10.6 Hz, 1H), 4.83 (d, *J* = 10.6 Hz, 1H), 4.49−4.44 (m, 1H), 3.84−3.78 (m, 1H), 3.66−3.58 (m, 1H), 3.31 (dd, *J* = 17.8, 8.7 Hz, 1H), 3.10 (dd, *J* = 17.8, 4.7 Hz, 1H), 2.12−2.08 (m, 2H), 1.54 (s, 3H), 1.52 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 196.8, 176.2, 135.9, 135.2, 132.1, 130.0, 129.7, 128.9, 128.8, 128.7, 79.0, 76.3, 59.4, 57.8, 39.7, 31.1, 29.4, 22.9; HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{22}H_{24}BrNNaO_4$, 468.0786; found, 468.0784.

*4-(Benzyloxy)-5-(2-(2-bromophenyl)-2-oxoethyl)-2,2-dimethyl-1,4-oxazepan-3-one (**8af**).* Following the general procedure, reaction between (*E*)-1-(2-bromophenyl)-5-hydroxypent-2-en-1-one **7f** (0.10 g, 0.4 mmol, 1.0 equiv) and α-bromo hydroxamate **1a** (0.217 g, 0.8 mmol, 2.0 equiv) afforded the corresponding 1,4-oxazepan-3-one **8af**, which was purified by silica gel column chromatography (3:7 Et_2O/hexane as the eluent) to give the title compound as colorless liquid in 70% (0.123 g) yield. R_f 0.36 (2:3 Et_2O/hexane); ^1H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, *J* = 7.1 Hz, 1H), 7.40 (d, *J* = 6.8 Hz, 2H), 7.36−7.32 (m, 3H), 7.30−7.27 (m, 3H), 4.91 (d, *J* = 10.5 Hz, 1H), 4.88 (d, *J* = 10.5 Hz, 1H), 4.53−4.47 (m, 1H), 3.86−3.80 (m, 1H), 3.73−3.65 (m, 1H), 3.39 (dd, *J* = 18.0, 8.4 Hz, 1H), 3.16 (dd, *J* = 18.0, 5.2 Hz, 1H), 2.09−2.06 (m, 2H), 1.51 (s, 3H), 1.50 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 201.2, 175.7, 140.8, 135.6, 133.8, 131.9, 129.9, 128.8, 128.5, 127.5, 118.6, 79.0, 76.4, 59.5, 57.4, 44.0, 31.3, 28.9, 23.1; HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{22}H_{24}BrNNaO_4$, 468.0786; found, 468.0789.

*4-(Benzyloxy)-2,2-dimethyl-5-(2-(naphthalen-2-yl)-2-oxoethyl)-1,4-oxazepan-3-one (**8ag**).* Following the general procedure, reaction between (*E*)-5-hydroxy-1-(naphthalen-2-yl)pent-2-en-1-one **7g** (0.07 g, 0.3 mmol, 1.0 equiv) and α-bromo hydroxamate **1a** (0.163 g, 0.6 mmol, 2.0 equiv) afforded the corresponding 1,4-oxazepan-3-one **8ag**, which was purified by silica gel column chromatography (3:7 Et_2O/hexane as the eluent) to give the title compound as yellow liquid in 66% (0.085 g) yield. R_f 0.4 (2:3 Et_2O/hexane); FT-IR (ν cm^{-1}): 3031, 2977, 2935, 1677, 1629, 1468, 1374, 1184, 996; ^1H NMR (400 MHz, $CDCl_3$): δ 8.33 (s, 1H), 7.95 (d, *J* = 8.0 Hz, 2H), 7.88 (d, *J* = 8.4 Hz, 2H), 7.62 (app t, *J* = 7.3 Hz, 1H), 7.58 (app t, *J* = 7.4 Hz, 1H), 7.40−7.39 (m, 2H), 7.32−7.29 (m, 3H), 4.91 (d, *J* = 10.6 Hz, 1H), 4.86 (d, *J* = 10.5 Hz, 1H), 4.58−4.53 (m, 1H), 3.87−3.82 (m, 1H), 3.72−3.64 (m, 1H), 3.51 (dd, *J* = 17.7, 8.9 Hz, 1H), 3.29 (dd, *J* = 17.7, 4.2 Hz, 1H), 2.21−2.12 (m, 2H), 1.59 (s, 3H), 1.55 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 197.8, 176.3, 135.9, 135.8, 133.7, 132.5, 130.2, 130.1, 129.7, 128.9, 128.8, 128.6, 127.9, 127.0, 123.7, 78.9, 76.2, 59.5, 58.0, 39.6, 31.1, 29.5, 22.8; HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{26}H_{27}NNaO_4$, 440.1838; found, 440.1826.

*4-(Benzyloxy)-2,2-dimethyl-5-(2-oxo-2-(thiophen-2-yl)ethyl)-1,4-oxazepan-3-one (**8ah**).* Following the general procedure, reaction between (*E*)-5-hydroxy-1-(thiophen-2-yl)pent-2-en-1-one **7h** (0.10 g, 0.5 mmol, 1.0 equiv) and α-bromo hydroxamate **1a** (0.271 g, 1.0 mmol, 2.0 equiv) afforded the corresponding 1,4-oxazepan-3-one **8ah**, which was purified by silica gel column chromatography (3:7 Et_2O/hexane as the eluent) to give the title compound as colorless liquid in 72% (0.148 g) yield. R_f 0.42 (2:3 Et_2O/hexane); ^1H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, *J* = 4.9 Hz, 1H), 7.62 (d, *J* = 3.7 Hz, 1H), 7.38 (d, *J* = 6.5 Hz, 2H),7.35−7.31 (m, 3H), 7.11 (app t, *J* = 4.3 Hz, 1H), 4.87 (d, *J* = 10.3 Hz, 1H), 4.83 (d, *J* = 10.3 Hz, 1H), 4.51−4.46 (m, 1H), 3.84−3.79 (m, 1H), 3.72−3.64 (m, 1H), 3.33 (dd, *J* = 17.0, 8.6 Hz, 1H), 3.19 (dd, *J* = 17.0, 5.2 Hz, 1H), 2.10−2.06 (m, 2H), 1.54 (s, 3H), 1.52 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 190.7, 176.2, 143.9, 135.7, 134.3, 132.5, 130.0, 128.9, 128.6, 128.3, 78.9, 76.3, 59.5, 57.9, 40.5, 31.2, 29.4, 22.9; HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{20}H_{23}NNaO_4S$, 396.1245; found, 396.1239.

*4-Methoxy-2,2-dimethyl-5-(2-oxo-2-(thiophen-2-yl)ethyl)-1,4-oxazepan-3-one (**8bh**).* Following the general procedure, reaction between (*E*)-5-hydroxy-1-(thiophen-2-yl)pent-2-en-1-one **7h** (0.08 g, 0.4 mmol, 1.0 equiv) and α-bromo hydroxamate **1b** (0.217 g, 0.8 mmol, 2.0 equiv) afforded the corresponding 1,4-oxazepan-3-one **8bh**, which was purified by silica gel column chromatography (3:7 Et_2O/hexane as the eluent) to give the title compound as the yellow solid in 69% (0.090 g) yield. R_f 0.4 (2:3 Et_2O/hexane); mp 60.8−62.0 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, *J* = 3.7 Hz, 1H), 7.68 (d, *J* = 4.9 Hz, 1H), 7.15 (app t, *J* = 4.3 Hz, 1H), 4.61−4.56 (m, 1H), 3.88−3.83 (m, 1H), 3.76−3.71 (m, 1H), 3.68 (s, 3H), 3.58 (dd, *J* = 16.7, 5.8 Hz, 1H), 3.45 (dd, *J* = 16.7, 8.1 Hz, 1H), 2.20−2.12 (m, 2H), 1.49 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 190.6, 175.6, 144.0, 134.5, 132.5, 128.5, 78.9, 62.3, 59.6, 57.0, 40.9, 31.6, 29.1, 23.0; HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{14}H_{19}NNaO_4S$, 320.0932; found, 320.0926.

*Methyl 2-(((1-((Benzyloxy)amino)-2-methyl-1-oxopropan-2-yl)-oxy)methyl)acrylate (**10a**).* Methyl 2-(hydroxymethyl)acrylate **9a** (0.100 g, 0.86 mmol, 1.0 equiv) and α-bromo hydroxamate **1a** (0.467 g, 1.7 mmol, 2.0 equiv) were taken in HFIP (0.2 M) and was added Na_2CO_3 (0.274 g, 2.6 mmol, 3.0 equiv). The reaction mixture was stirred at room temperature for 3 h until the disappearance of the starting materials was observed (TLC controlled). The solvent was removed in vacuo, and the crude product was purified by silica gel column chromatography (1:4 EtOAc/hexane as the eluent) to give the title compound as colorless oil **10a** in 89% (0.235 g) yield. R_f 0.4 (3:7 EtOAc/hexane); ^1H NMR (400 MHz, $CDCl_3$): δ 10.34 (s, 1H), 7.41 (d, *J* = 7.1 Hz, 2H), 7.33−7.28 (m, 3H), 6.24 (s, 1H), 5.78 (s, 1H), 4.93 (s, 2H), 3.96 (s, 2H), 3.71 (s, 3H), 1.39 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.7, 166.7, 136.3, 135.4, 129.3, 129.0, 128.5, 128.3, 79.1, 77.8, 63.8, 52.2, 24.5; HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{16}H_{21}NNaO_5$, 330.1317; found, 330.1313.

*N-(Benzyloxy)-2-methyl-2-(2-methylene-3-oxobutoxy)-propanamide (**10b**).* Compound **9b** (0.05 g, 0.5 mmol, 1.0 equiv) and α-bromo hydroxamate **1a** (0.467 g, 1.0 mmol, 2.0 equiv) were taken in HFIP (0.2 M) and was added Na_2CO_3 (0.159 g, 1.5 mmol, 3.0 equiv). The reaction mixture was stirred at room temperature for 5 h until the disappearance of the starting materials was observed (TLC controlled). The solvent was removed in vacuo, and the crude product was purified by silica gel column chromatography (7:3 Et_2O/hexane as the eluent) to give the title compound **10b** as colorless oil in 85% (0.124 g) yield. R_f 0.4 (7:3 Et_2O/hexane); δ ^1H NMR (400 MHz, $CDCl_3$): δ 10.39 (s, 1H), 7.44 (d, *J* = 6.9 Hz, 2H), 7.35−7.29 (m, 3H), 6.14 (s, 1H), 5.99 (s, 1H), 4.97 (s, 2H), 3.95 (s, 2H), 2.34 (s, 3H), 1.39 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 199.8, 171.9, 144.6, 135.5, 129.6, 129.4, 128.6, 128.5, 79.3, 77.9, 63.4, 26.0, 24.7; HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{16}H_{21}NNaO_4$, 314.1368; found, 314.1366.

*Methyl 4-(Benzyloxy)-2,2-dimethyl-3-oxo-1,4-oxazepane-6-carboxylate (**11a**).* Compound **10a** (0.05 g, 0.16 mmol, 1.0 equiv)

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was taken in MeOH (0.2 M) and was added Et_3N (30 μL, 0.18 mmol, 1.1 equiv) dropwise. The reaction mixture was stirred at 60 °C overnight until the disappearance of the starting materials was observed (TLC controlled). The solvent was removed in vacuo, and the crude product was purified by silica gel column chromatography (1:5 EtOAc/hexane as the eluent) to give the title compound as white solid **11a** in 66% (0.033 g) yield. R_f 0.5 (3:7 EtOAc/hexane); mp 85.4−86.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45−7.43 (m, 2H), 7.40−7.37 (m, 3H), 5.00 (d, *J* = 10.3 Hz, 1H), 4.92 (d, *J* = 10.3 Hz, 1H), 4.07 (dd, *J* = 14.9, 8.2 Hz, 1H), 3.99 (dd, *J* = 13.1, 5.0 Hz, 1H), 3.84−3.74 (m, 2H), 3.69 (s, 3H), 2.77−2.71 (m, 1H), 1.46 (s, 3H), 1.45 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 172.4, 171.9, 135.4, 129.9, 129.1, 128.7, 81.5, 76.7, 62.7, 52.4, 50.7, 43.4, 25.9, 25.0; HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calcd for $C_{16}H_{21}NNaO_5$, 330.1317; found, 330.1308.

*6-Acetyl-4-(benzyloxy)-2,2-dimethyl-1,4-oxazepan-3-one (**11b**).* Following the same procedure as was used for the preparation of **11a**, compound **10b** (0.05 g, 0.17 mmol) was transformed into compound **11b** as colorless oil in 58% (0.029 g) yield. R_f 0.4 (2:3 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44−7.42 (m, 2H), 7.40−7.36 (m, 3H), 4.99 (d, *J* = 10.5 Hz, 1H), 4.91 (d, *J* = 10.5 Hz, 1H), 4.00 (dd, *J* = 15.0, 8.4 Hz, 1H), 3.92 (dd, *J* = 13.1, 5.1 Hz, 1H), 3.77−3.68 (m, 2H), 2.73−2.66 (m, 1H), 2.11 (s, 3H), 1.45 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 206.3, 172.3, 135.5, 130.0, 129.1, 128.7,81.3, 76.7, 62.1, 51.2, 50.6, 28.8, 26.0, 25.0; HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calcd for $C_{16}H_{21}NNaO_4$, 314.1368; found, 314.1364.

*(E)-3-(Benzyloxy)-2-(2-hydroxystyryl)-5,5-dimethyl-2-phenyloxazolidin-4-one (**13**).* (*E*)-3-(2-Hydroxyphenyl)-1-phenylprop-2-en-1-one **12** (0.100 g, 0.45 mmol, 1.0 equiv) and α-bromo hydroxamate **1a** (0.121 g, 0.45 mmol, 1.0 equiv) were taken in HFIP (0.2 M) and was added Na_2CO_3 (0.142 g, 1.34 mmol, 3.0 equiv). The reaction mixture was stirred at room temperature for 7 h until the disappearance of the starting materials was observed (TLC controlled). The solvent was removed in vacuo, and the crude product was purified by silica gel column chromatography (1:4 EtOAc/hexane as the eluent) to give the title compound as white solid **13** in 65% (0.120 g) yield. R_f 0.4 (3:7 EtOAc/hexane); mp 167.1−168.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67−7.65 (m, 2H), 7.43−7.40 (m, 3H), 7.37 (d, *J* = 7.7 Hz, 1H), 7.29−7.22 (m, 5H), 7.16−7.09 (m, 2H), 6.89 (t, *J* = 7.5 Hz, 1H), 6.83 (d, *J* = 8.1 Hz, 1H), 6.68 (d, *J* = 16.2 Hz, 1H), 6.11 (br s, 1H), 4.99 (d, *J* = 9.4 Hz, 1H), 4.58 (d, *J* = 9.4 Hz, 1H), 1.54 (s, 3H), 1.49 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 170.5, 154.2, 140.0, 134.1, 129.8, 129.6, 129.3, 129.0, 129.0(2), 128.7, 128.6, 128.5, 128.3, 127.3, 123.0, 120.7, 116.3, 93.4, 79.0, 78.2, 26.1, 25.6; HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calcd for $C_{26}H_{25}NNaO_4$, 438.1681; found, 438.1668.

*(E)-N-(Benzyloxy)-2-(2-(2-(3-(benzyloxy)-5,5-dimethyl-4-oxo-2-phenyloxazolidin-2-yl)vinyl)phenoxy)-2-methylpropanamide (**14**).* (*E*)-3-(2-Hydroxyphenyl)-1-phenylprop-2-en-1-one **12** (0.100 g, 0.45 mmol, 1.0 equiv) and α-bromo hydroxamate **1a** (0.121 g, 0.45 mmol, 1.0 equiv) were taken in HFIP (0.2 M) and was added Na_2CO_3 (0.142 g, 1.34 mmol, 3.0 equiv). The reaction mixture was stirred at room temperature for 7 h until the disappearance of the starting materials was observed (TLC controlled). The solvent was removed in vacuo, and the crude product was purified by silica gel column chromatography (3:7 EtOAc/hexane as the eluent) to give the title compound as yellow liquid **14** in 25% (0.068 g) yield. R_f 0.37 (3:7 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.00 (s, 1H), 7.67−7.65 (m, 2H), 7.50−7.44 (m, 4H), 7.39−7.36 (m, 5H), 7.30−7.26 (m, 5H), 7.19−7.03 (m, 3H), 6.79 (d, *J* = 8.2 Hz, 1H), 6.52 (d, *J* = 16.3 Hz, 1H), 5.01 (d, *J* = 9.4 Hz, 1H), 4.94 (s, 2H), 4.50 (d, *J* = 9.3 Hz, 1H), 1.53 (s, 6H), 1.41 (s, 3H), 1.39 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 172.1, 170.2, 152.1, 139.7, 135.0, 134.1, 129.8, 129.4, 129.2, 129.1, 128.9, 128.7, 128.5, 128.5(2), 128.3, 127.2, 123.5, 120.3, 93.0, 82.1, 78.9, 78.3, 78.0, 26.2, 25.6, 25.3, 25.2; HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calcd for $C_{37}H_{38}N_2NaO_6$, 629.2628; found, 629.2612.

*4-Hydroxy-5-(2-hydroxy-2-phenylethyl)-2,2-dimethylmorpholin-3-one (**15**).* Palladium on carbon (10% w/w, 0.03 g) was added to a solution of **3aa** (0.10 g, 0.3 mmol) in MeOH (3.0 mL), and the mixture was stirred at room temperature under a hydrogen balloon for 20 h. The mixture was then filtered through Celite and thoroughly washed with ethyl acetate. Then, the filtrate was concentrated under vacuo, and the resulting residue was purified by silica gel column chromatography (3:7 EtOAc/hexane) to afford **15** as the yellow solid in 48% (0.064 g) yield. R_f 0.25 (3:7 EtOAc/hexane); mp 108.5−109.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39−7.36 (m, 4H), 7.30−7.28 (m, 1H), 5.05 (dd, *J* = 9.7, 2.8 Hz, 1H), 4.08 (dd, *J* = 12.1, 3.1 Hz, 1H), 4.02−3.96 (m, 1H), 3.83 (dd, *J* = 12.1, 2.6 Hz, 1H), 2.31−2.25 (m, 1H), 2.16−2.08 (m, 1H), 1.45 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 168.2, 144.1, 128.8, 128.0, 125.7, 77.6, 72.0, 63.5, 57.9, 40.6, 26.2, 24.1; HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calcd for $C_{14}H_{19}NNaO_4$, 288.1212; found, 288.1201.

*6,6-Dimethyl-2-phenyltetrahydroisoxazolo[3,2-c][1,4]oxazin-7(6H)-one (**16**).* To a cooled (0 °C) solution of **15** (0.05 g, 1.0 mmol) and PPh_3 (0.066 g, 1.2 mmol) in DCM (10 mL) was added a solution of di*tert*-butyl azodicarboxylate (0.056 g, 1.2 mmol) in DCM (2.0 mL) slowly via a syringe pump over a period of 30 min. The reaction was slowly warmed to room temperature and stirred for 16 h. The solvent was removed in vacuo, and the crude product was purified by silica gel column chromatography (1:4 EtOAc/hexane as eluent) to give the title compound as yellow liquid **16** in 68% (0.032 g) yield. R_f 0.38 (3:7 EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (d, *J* = 7.3 Hz, 2H), 7.38−7.30 (m, 3H), 5.36 (dd, *J* = 9.0, 6.1 Hz, 1H), 4.40−4.32 (m, 1H), 4.14 (dd, *J* = 11.7, 4.2 Hz, 1H), 3.53 (dd, *J* = 11.7, 10.1 Hz, 1H), 2.82−2.76 (m, 1H), 2.08−2.00 (m, 1H), 1.51 (s, 3H), 1.45 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 165.8, 137.9, 128.9, 128.8, 126.2, 81.4, 78.5, 64.7, 59.4, 40.1, 27.3, 23.3; HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calcd for $C_{14}H_{17}NNaO_3$, 270.1106; found, 270.1101.

*5-(2-(2-Bromophenyl)-2-oxoethyl)-2,2-dimethyl-1,4-oxazepan-3-one (**17**).* To a solution of **8af** (0.11 g, 0.25 mmol, 1.0 equiv) in acetonitrile/water (9:1, 2 mL), $Mo(CO)_6$ (0.078 g, 0.3 mmol, 1.2 equiv) was added, and the reaction was stirred at 120 °C under argon for 12 h. After cooling to room temperature, the mixture was then filtered through Celite and thoroughly washed with ethyl acetate. Then, the filtrate was concentrated under vacuo, and the resulting residue was purified by silica gel column chromatography (3:7 EtOAc/hexane) to afford **17** as the white solid in 70% (0.059 g) yield. R_f 0.25 (3:7 EtOAc/hexane); mp 110.5−111.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, *J* = 7.9 Hz, 1H), 7.44−7.36 (m, 2H), 7.31 (t, *J* = 7.6 Hz, 1H), 6.31 (d, *J* = 3.4 Hz, 1H), 4.49−4.41 (m, 1H), 3.93−3.88 (m, 1H), 3.73−3.66 (m, 1H), 3.22−3.20 (m, 2H), 2.18−2.09 (m, 1H), 1.76−1.69 (m, 1H), 1.42 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 201.3, 178.1, 141.0, 133.9, 132.2, 128.8, 127.8, 118.8, 81.5, 61.3, 47.2, 46.1, 34.9, 26.1, 25.1; HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calcd for $C_{15}H_{18}BrNNaO_3$, 362.0368; found, 362.0353.

*2,2-Dimethyl-4,5,5a,6-tetrahydro-1H-[1,4]oxazepino[4,5-a]quinoline-1,7(2H)-dione (**18**).* $Pd(OAc)_2$ (0.005 g, 0.007 mmol), $Cu(OAc)_2$ (0.014 g, 0.075 mmol), and K_2CO_3 (0.069 g, 0.5 mmol) were added under an Ar atmosphere to a stirred solution of **17** (0.05 g, 0.15 mmol) in toluene (3.0 mL). The mixture was heated at reflux for 24 h, allowed to cool, and filtered through a Celite pad. The filtrate was concentrated to give a crude product, which was purified by silica gel column chromatography (1:4 EtOAc/hexane) to afford **18** as the yellow solid in 56% (0.021 g) yield. R_f 0.35 (3:7 EtOAc/hexane); mp 116.8−118.0 °C; FT-IR (ν cm^{-1}): 2931, 1672, 1599, 1477, 1458, 1264, 1192, 1089; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, *J* = 7.8 Hz, 1H), 7.88 (d, *J* = 8.7 Hz, 1H), 7.48 (t, *J* = 7.9 Hz, 1H), 7.11 (t, *J* = 7.5 Hz, 1H), 4.65−4.59 (m, 1H), 3.92−3.86 (m, 1H), 3.81−3.75 (m, 1H), 2.93 (dd, *J* = 16.8, 5.0 Hz, 1H), 2.82 (dd, *J* = 16.8, 8.0 Hz, 1H), 2.16−2.08 (m, 1H), 2.00−1.92 (m, 1H), 1.64 (s, 3H), 1.60 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 192.6, 179.9, 144.2, 135.2, 127.4, 123.4, 123.0, 121.0, 81.8, 61.3, 52.8, 43.0, 32.3, 28.3, 25.2; HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calcd for $C_{15}H_{17}NNaO_3$, 282.1106; found, 282.1095.

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■ ASSOCIATED CONTENT

Supporting Information

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Copies of ^{1}H and ^{13}C spectra of all new compounds and computational data (PDF)

Crystal data for compound **8aa** (CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Lovering, F.; Bikker, J.; Humblet, C. Escape from flatland: increasing saturation as an approach to improving clinical success. *J. Med. Chem.* **2009**, *52*, 6752. (b) Ritchie, T. J.; Macdonald, S. J. F. The impact of aromatic ring count on compound developability—are too many aromatic rings a liability in drug design? *Drug Discovery Today* **2009**, *14*, 1011−1020. (c) Ritchie, T. J.; Macdonald, S. J. F.; Young, R. J.; Pickett, S. D. The impact of aromatic ring count on compound developability: further insights by examining carbo- and hetero-aromatic and -aliphatic ring types. *Drug Discovery Today* **2011**, *16*, 164−171.

(2) (a) Vo, C.-V. T.; Luescher, M. U.; Bode, J. W. SnAP reagents for the one-step synthesis of medium-ring saturated *N*-heterocycles from aldehydes. *Nat. Chem.* **2014**, *6*, 310−314. (b) Meyer, A. G.; Bissember, A. C.; Hyland, C. J. T.; Williams, C. C.; Szabo, M.; Abel, S. A. G.; Bird, M. J.; Hyland, I. K.; Pham, H. Seven-Membered Rings. In *Progress in Heterocyclic Chemistry*; Gribble, G. W., Joule, J. A., Eds.; Elsevier: Amsterdam, 2018; pp 493−550.

(3) Yar, M.; McGarrigle, E. M.; Aggarwal, V. K. An Annulation Reaction for the Synthesis of Morpholines, Thiomorpholines, and Piperazines from *β*-Heteroatom Amino Compounds and Vinyl Sulfonium Salts. *Angew. Chem., Int. Ed.* **2008**, *47*, 3784−3786.

(4) Ruider, S. A.; Müller, S.; Carreira, E. M. Ring Expansion of 3-Oxetanone-Derived Spirocycles: Facile Synthesis of Saturated Nitrogen Heterocycles. *Angew. Chem., Int. Ed.* **2013**, *52*, 11908−11911.

(5) (a) Vo, C.-V. T.; Mikutis, G.; Bode, J. W. SnAP Reagents for the Transformation of Aldehydes into Substituted Thiomorpholines-An Alternative to Cross-Coupling with Saturated Heterocycles. *Angew. Chem., Int. Ed.* **2013**, *52*, 1705−1708. (b) Luescher, M. U.; Geoghegan, K.; Nichols, P. L.; Bode, J. W. SnAP Reagents for a Cross-Coupling Approach to the One-Step Synthesis of Saturated N-Heterocycles. *Aldrichimica Acta* **2015**, *48*, 43.

(6) (a) Zhong, C.; Wang, Y.; O'Herin, C.; Young, D. W. Synthesis of Substituted Morpholines Using Stereodivergent Aza-Michael Reactions Catalyzed by Brønsted Acids. *ACS Catal.* **2013**, *3*, 643−646. (b) Borah, M.; Borthakur, U.; Saikia, A. K. Diastereoselective Synthesis of Substituted Morpholines from N-Tethered Alkenols: Total Synthesis of (±)-Chelonin A. *J. Org. Chem.* **2017**, *82*, 1330−1339. (c) D'hooghe, M.; Vanlangendonck, T.; Törnroos, K. W.; Kimpe, N. D. Novel Synthesis of cis-3,5-Disubstituted Morpholine Derivatives. *J. Org. Chem.* **2006**, *71*, 4678−4681.

(7) For biologically active morpholines, see: (a) Wijtmans, R.; Vink, M. K.; Schoemaker, H. E.; van Delft, F. L.; Blaauw, R. H.; Rutjes, F. P. Biological Relevance and Synthesis of C-Substituted Morpholine Derivatives. *Synthesis* **2004**, *2004*, 641−662. (b) Allison, B. D.; Phuong, V. K.; McAtee, L. C.; Rosen, M.; Morton, M.; Prendergast, C.; Barrett, T.; Lagaud, G.; Freedman, J.; Li, L.; Wu, X.; Venkatesan, H.; Pippel, M.; Woods, C.; Rizzolio, M. C.; Hack, M.; Hoey, K.; Deng, X.; King, C.; Shankley, N. P.; Rabinowitz, M. H. Identification and Optimization of Anthranilic Sulfonamides as Novel, Selective Cholecystokinin-2 Receptor Antagonists. *J. Med. Chem.* **2006**, *49*, 6371−6390 . For biologically active 1,4-oxazepane scaffolds, see:. (c) Koehn, F. E.; McConnell, O. J.; Longley, R. E.; Sennett, S. H.; Reed, J. K. Analogs of the Marine Immunosuppressant Microcolin A: Preparation and Biological Activity. *J. Med. Chem.* **1994**, *37*, 3181−3186. (d) Fu, P.; Jamison, M.; La, S.; MacMillan, J. B.; Inducamides, A.-C. Chlorinated Alkaloids from an RNA Polymerase Mutant Strain of Streptomyces sp. *Org. Lett.* **2014**, *16*, 5656−5659. (e) Luna, M.; García, S.; García, O.; Trigos, Á. Serratin a new metabolite obtained fromSerratia marcescens, a bacterium isolated from the microflora associated with banana plantations. *Nat. Prod. Res.* **2013**, *27*, 49−53. (f) Ruysbergh, E.; Van Hecke, K.; Stevens, C. V.; De Kimpe, N.; Mangelinckx, S. Synthesis of 1,4-Oxazepane-2,5-diones via Cyclization of Rotationally Restricted Amino Acid Precursors and Structural Reassignment of Serratin. *J. Org. Chem.* **2017**, *82*, 6210−6222.

(8) Xuan, J.; Cao, X.; Cheng, X. Advances in heterocycle synthesis via [3+m]-cycloaddition reactions involving an azaoxyallyl cation as the key intermediate. *Chem. Commun.* **2018**, *54*, 5154−5163.

(9) For selected [3 + 1] and [3 + 2] cycloaddition reaction, see: (a) Li, C.; Jiang, K.; Ouyang, Q.; Liu, T.-Y.; Chen, Y.-C. [3 + 1]- and [3 + 2]-Cycloadditions of Azaoxyallyl Cations and Sulfur Ylides. *Org. Lett.* **2016**, *18*, 2738−2741. (b) Acharya, A.; Anumandla, D.; Jeffrey, C. S. Dearomative Indole Cycloaddition Reactions of Aza-Oxyallyl Cationic Intermediates: Modular Access to Pyrroloindolines. *J. Am. Chem. Soc.* **2015**, *137*, 14858−14860. (c) Ji, D.; Sun, J. [3 + 2]-Cycloaddition of Azaoxyallyl Cations with Hexahydro-1,3,5-triazines: Access to 4-Imidazolidinones. *Org. Lett.* **2018**, *20*, 2745−2748. (d) DiPoto, M. C.; Wu, J. Synthesis of 2-Aminoimidazolones and Imidazolones by (3 + 2) Annulation of Azaoxyallyl Cations. *Org. Lett.* **2018**, *20*, 499−501. (e) Jiang, S.; Li, K.; Yan, J.; Shi, K.; Zhao, C.; Yang, L.; Zhong, G. Synthetic Access to Oxazolidin-4-ones via Elimination/[3+2] Cycloaddition Reaction. *J. Org. Chem.* **2017**, *82*, 9779−9785. (f) Shao, P.-L.; Li, Z.-R.; Wang, Z.-P.; Zhou, M.-H.; Wu, Q.; Hu, P.; He, Y. [3 + 2] Cycloaddition of Azaoxyallyl Cations with Cyclic Ketones: Access to Spiro-4-oxazolidinones. *J. Org. Chem.* **2017**, *82*, 10680−10686. (g) Zhang, K.; Yang, C.; Yao, H.; Lin, A. [3 + 2] Cycloaddition Reaction of in Situ Formed Azaoxyallyl Cations with Aldehydes: An Approach to Oxazolidin-4-ones. *Org. Lett.* **2016**, *18*, 4618−4621. (h) Acharya, A.; Montes, K.; Jeffrey, C. S. Access to 4-Oxazolidinones: A (3 + 2) Cycloaddition Approach. *Org. Lett.* **2016**, *18*, 6082−6085. (i) Zhang, Y.; Ma, H.; Liu, X.; Cui, X.; Wang, S.; Zhan, Z.; Pu, J.; Huang, G. The synthesis of multi-substituted pyrrolidinones *via* a direct [3 + 2] cycloaddition of azaoxyallyl cations with aromatic ethylenes. *Org. Biomol. Chem.* **2018**, *16*, 4439−4442. (j) Zhou, S.-J.; Cheng, X.; Xuan, J. [3+2]-Cycloaddition of Azaoxyallyl Cations with Cyclopropenones and Cyclopropenethiones: Synthesis of Spirocyclic Oxazole and Thiazole Derivatives. *Asian J. Org. Chem.* **2019**, *8*, 1376−1379. (k) Feng, J.; Zhao, M.; Lin, X. [3 + 2]-Cycloaddition of Azaoxyallyl Cations with 1,2-Benzisoxazoles: A Rapid Entry to Oxazolines. *J. Org. Chem.* **2019**, *84*, 9548−9560. (l) Zhou, J.; Zhang, H.; Chen, X.-L.; Qu, Y.-L.; Zhu, Q.; Feng, C.-G.; Chen, Y.-J. Regio- and Diastereoselective Access to 4-Imidazolidinones via an Aza-Mannich Initiated Cyclization of Sulfamate-Derived Cyclic Imines with *α*-Halo Hydroxamates. *J. Org. Chem.* **2019**, *84*, 9179−9187.

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J. Org. Chem. 2019, 84, 15255−15266

(10) For selected [3 + 3] and [3 + 4] cycloaddition reaction, see: (a) An, Y.; Xia, H.; Wu, J. Base-controlled [3+3] cycloaddition of isoquinoline *N*-oxides with azaoxyallyl cations. *Chem. Commun.* **2016**, *52*, 10415−10418. (b) Zhang, K.; Xu, X.; Zheng, J.; Yao, H.; Huang, Y.; Lin, A. [3 + 3] Cycloaddition of in Situ Formed Azaoxyallyl Cations with 2-Alkenylindoles: An Approach to Tetrahydro-*β*-carbolinones. *Org. Lett.* **2017**, *19*, 2596−2599. (c) Xu, X.; Zhang, K.; Li, P.; Yao, H.; Lin, A. [3 + 3] Cycloaddition of Azides with in Situ Formed Azaoxyallyl Cations To Synthesize 1,2,3,4-Tetrazines. *Org. Lett.* **2018**, *20*, 1781−1784. (d) Cheng, X.; Cao, X.; Xuan, J.; Xiao, W.-J. Silver(I)- and Base-Mediated [3 + 3]-Cycloaddition ofC,N-Cyclic Azomethine Imines with Aza-oxyallyl Cations. *Org. Lett.* **2018**, *20*, 52−55. (e) Cheng, X.; Cao, X.; Zhou, S. J.; Cai, B. G.; He, X. K.; Xuan, J. Transition-Metal Free Construction of Isoquinoline-fused Triazines Containing Alkenyl C−X Bonds. *Adv. Synth. Catal.* **2019**, *361*, 1230−1235. (f) Jeffrey, C. S.; Barnes, K. L.; Eickhoff, J. A.; Carson, C. R. Generation and Reactivity of Aza-Oxyallyl Cationic Intermediates: Aza-[4 + 3] Cycloaddition Reactions for Heterocycle Synthesis. *J. Am. Chem. Soc.* **2011**, *133*, 7688−7691.

(11) For a review, see: He, Z.; Zajdlik, A.; Yudin, A. K. Air- and Moisture-Stable Amphoteric Molecules: Enabling Reagents in Synthesis. *Acc. Chem. Res.* **2014**, *47*, 1029−1040.

(12) For similar amphoteric system, see: Clavette, C.; Vincent Rocan, J.-F.; Beauchemin, A. M. Diversity-Oriented Synthesis of Hydrazine-Derived Compounds from Amino Isocyanates Generated In Situ. *Angew. Chem., Int. Ed.* **2013**, *52*, 12705−12708.

(13) Jaiswal, V.; Mondal, B.; Singh, K.; Das, D.; Saha, J. [3 + 2]-Annulation of Azaoxyallyl Cations and Thiocarbonyls for the Assembly of Thiazolidin-4-ones. *Org. Lett.* **2019**, *21*, 5848−5852.

(14) Control experiments with only **2a** in Et_3N/HFIP and Na_2CO_3/HFIP were performed. In both cases, dimerization of **2a** was detected by MS analysis. Also see ref 21b for reported isomerization process of **2a** in presence of a base.

(15) Oppedisano, A.; Prandi, C.; Venturello, P.; Deagostino, A.; Goti, G.; Scarpi, D.; Occhiato, E. G. Synthesis of Vinylogous Amides by Gold(I)-Catalyzed Cyclization of *N*-Boc-Protected 6-Alkynyl-3,4-dihydro-2*H*-pyridines. *J. Org. Chem.* **2013**, *78*, 11007−11016.

(16) (a) Herdeis, C.; Küpper, P.; Plé, S. An expeditious stereoselective synthesis of natural (−)-Cassine via cascade HWE [3 + 2]-cycloaddition process. *Org. Biomol. Chem.* **2006**, *4*, 524−529. (b) Fréville, S.; Delbecq, P.; Thuy, V. M.; Petit, H.; Célérier, J. P.; Lhommet, G. Diastereocontrolled reduction of cyclic *β*-enaminones. A new diastereoselective route to 2,6-disubstituted piperidines. *Tetrahedron Lett.* **2001**, *42*, 4609−4611.

(17) We performed benzyloxy group deprotection on (*E*)-and (*Z*)-**5ab** and exclusively obtained the free NH-containing product, (*Z*)-**5ab** for both the cases (see Schemes S1 and S4 for detail experiments and DFT calculations on a model substrate **5aa**).

(18) (a) Michael, J. P.; de Koning, C. B.; Hosken, G. D.; Howard, A. S.; Jungmann, C. M.; Krause, R. W. M.; Parsons, A. S.; Pelly, S. C.; Stanbury, T. V. Enaminones: versatile intermediates for natural product synthesis. *Pure Appl. Chem.* **1999**, *71*, 979. (b) Rašović, L.; Blagojević, V.; Baranac-Stojanović, M.; Kleinpeter, E.; Marković, R.; Minić, D. M. Quantification of the push−pull effect in 2-alkylidene-4-oxothiazolidines by using NMR spectral data and barriers to rotation around the C=C bond. *New J. Chem.* **2016**, *40*, 6364−6373.

(19) Kalia, D.; Merey, G.; Guo, M.; Sintim, H. O. N-O Tethered Carbenoid Cyclopropanation Facilitates the Synthesis of a Functionalized Cyclopropyl-Fused Pyrrolidine. *J. Org. Chem.* **2013**, *78*, 6131−6142.

(20) Harada, R.; Nishida, N.; Uchiito, S.; Onozaki, Y.; Kurono, N.; Senboku, H.; Masao, T.; Ohkuma, T.; Orito, K. Phosphane-Free Pd^0-Catalyzed Cycloamination and Carbonylation with $Pd(OAc)_2$ and $Cu(OAc)_2$ in the Presence of K_2CO_3: Preparation of Benzocyclic Amines and Benzolactams. *Eur. J. Org. Chem.* **2012**, *2012*, 366−379.

(21) (a) Sada, M.; Ueno, S.; Asano, K.; Nomura, K.; Matsubara, S. Stereoselective Preparation of 3-Alkanoylprop-2-en-1-ol Derivatives. *Synlett* **2009**, 724. (b) Mondal, K.; Mondal, B.; Pan, S. C. Organocatalytic Redox Isomerization of Electron-Deficient Allylic Alcohols: Synthesis of 1,4-Ketoaldehydes. *J. Org. Chem.* **2016**, *81*, 4835−4840.

(22) Pauli, L.; Tannert, R.; Scheli, R.; Pfaltz, A. Asymmetric Hydrogenation of Furans and Benzofurans with Iridium-Pyridine-Phosphinite Catalysts. *Chem.—Eur. J.* **2015**, *21*, 1482−1487.

(23) Matsumoto, A.; Asano, K.; Matsubara, S. A. Chiral phosphoric acid catalyst for asymmetric construction of 1,3-dioxanes. *Chem. Commun.* **2015**, *51*, 11693−11696.

DOI: 10.1021/acs.joc.9b02269
J. Org. Chem. 2019, 84, 15255−15266