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Article

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A Multifaceted α-Enaminone - Adaptable Building Block for Synthesis of Heterocyclic Scaffolds Through Conceptually Distinct 1,2-, 1,3-, 1,4- and C-O Bond Forming Annulations

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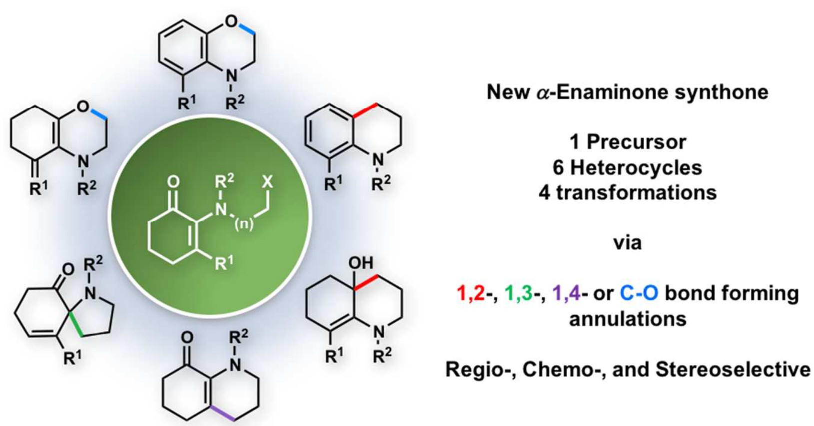


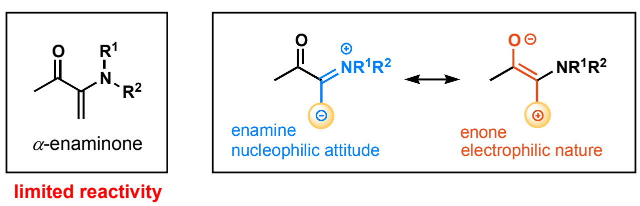
The new reactivity of α,β-unsaturated enaminones driven by their "dual electronic attitude" is reported. We introduce unexplored, α-enaminone synthones and reveal the unusual functionalities of these building blocks. The feasibility of this new concept is demonstrated in the direct functionalization of enaminone precursors, such as alkylation, 1,2- 1,3- or 1,4-addition, and C-O bond formation. The general and potential applicability is presented through the collective synthesis of several important classes of heterocycles via controlled cyclizations of easily accessible common precursors. The rapid composition of novel key α-enaminone synthones yields an assembly of oxazines, azaspirones, quinolinones, and quinolinols in a regio- and chemoselective fashion.

INTRODUCTION

Enaminoketones have attracted increased interest, particularly cyclic *β*-enaminones, which are known as important intermediates and have proven to be versatile building blocks for the synthesis of various heterocycles and natural products.[1] The N- and *β*-positions are their most reactive sites.[2] Acting as bisnucleophiles, *β*-enaminones are suitable platforms for construction of heterocyclic compounds, such as pyridine, pyrimidine, indolizidine, quinolizidine, and pyrrole derivatives, which are common motifs in alkaloid structures.[3]

Little is known about *α*-enaminones, apparently because they are often not directly accessible from the corresponding diketones.[4] Compared with *β*-enaminones, the chemical behaviour of the *α*-keto derivatives differs (Figure 1). They can react as enamines (nucleophiles), as well as *α,β*-unsaturated ketones (electrophiles). Although many strategies are available for utilizing *β*-enaminones as building blocks, methods for the preparation of heterocycles using *α*-ketoenamines are limited.[5-8]

Figure 1. Dual electronic attitude of *α*-Enaminone

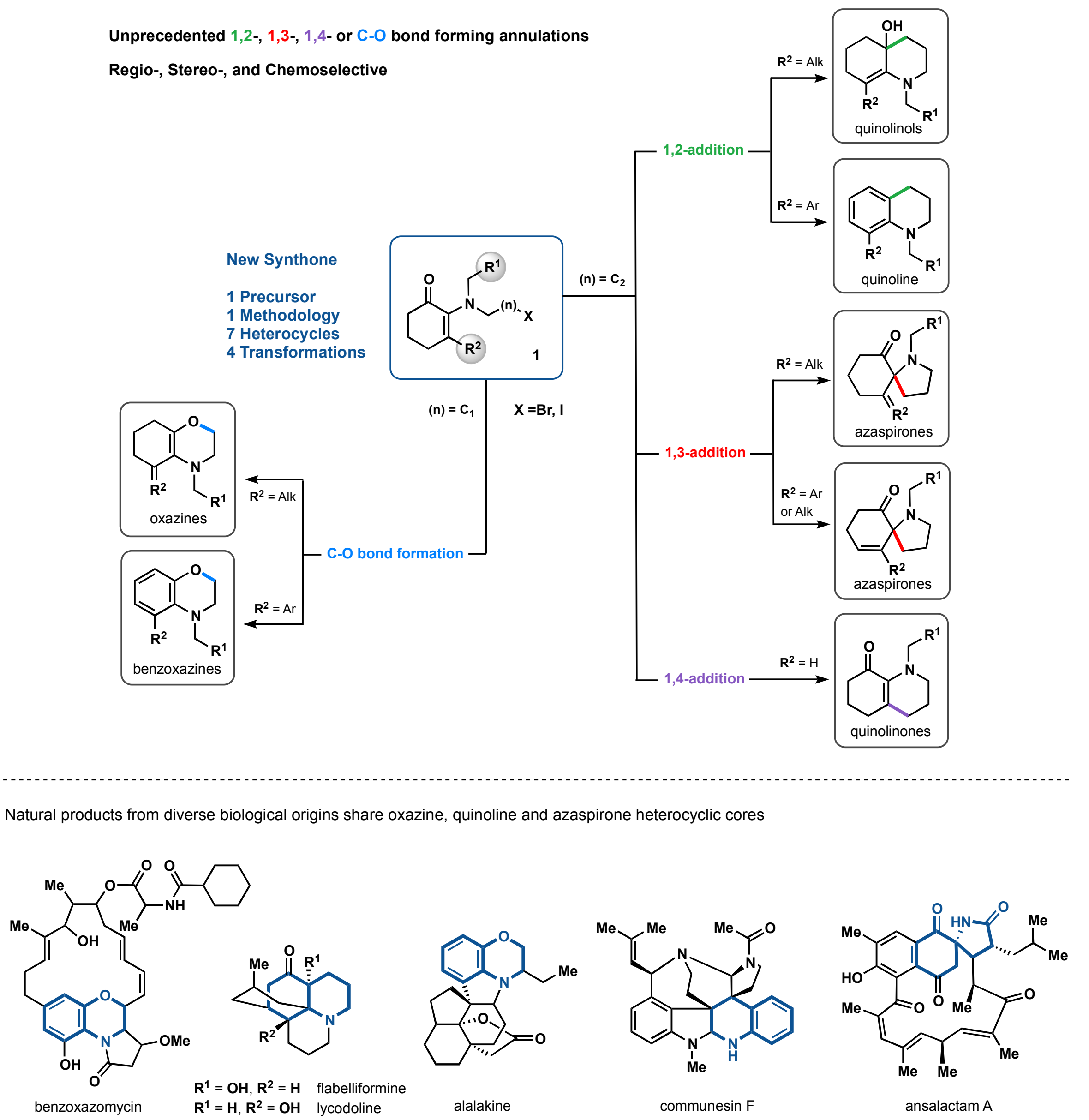


In this study, we report novel reactivity of *α,β*-enaminones driven by their "dual electronic attitude". We introduce unexplored, stable *α*-enaminone synthones, radically different from other known *α*- or *β*-counterparts by their chemical behaviour, and unlock unusual functionalities of these building blocks. We demonstrate general synthesis of several important classes of heterocycles via controlled cyclizations of an easily accessible *α*-enaminone common key precursors.

Oxazine, azaspirone, quinolines, quinolinone and quinolinol structures are frequently observed as scaffold segments in various biochemical compounds. These architectures have been identified as building blocks of a numerous alkaloids, as well as other families of diverse, and often remotely related metabolites.[9] Unfortunately, access to a large number of these target molecules, and their structural analogues, is either unknown or hindered by the multistep syntheses.[10] An in-depth analysis of the introduced cores suggests that α-enaminone scaffold of Type-**1** (Scheme 1) has the potential to serve as an operational, collective key unit for their construction via controlled intramolecular cyclizations.[4c,11] This would be the first attempt to link simple and single enaminone core with such a diverse, heterocyclic architectures. With this in mind, we developed a novel streamlined synthetic methodology that allows the rapid and collective composition of multiple targets using a single common precursor.

As we contemplate the possible approaches for delivering the desired targets, we first consider a 1,4-addition, generating quinolinone scaffolds (Scheme 1). Inevitably, to obtain bicyclic quinolinols, the 1,2-cyclization pathway must be constructed. In addition, if 1,2- and 1,4-additions are possible, the 1,3-cyclo-addition becomes a plausible outcome, which would afford heterocyclic systems, such as azaspirones. We also illustrate a C-O bond formation pathway that allows for direct synthesis of benzo- and methylene-oxazines. Intriguingly, designing a method to differentiate between these cyclization pathways would elegantly allow for the regio- and chemoselective collective delivery of a broad spectrum of conceptually different heterocycles. To the best of our knowledge, synthesis of all the previously mentioned scaffolds (and their structural analogues) using our approach has never been attempted.

Scheme 1. Collective synthesis of heterocycles via controlled cyclization of α-enaminone precursor.

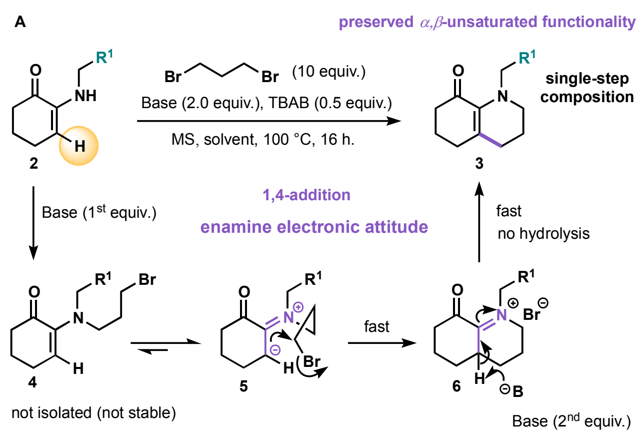


RESULTS AND DISCUSSION

1,4-Addition. To test our hypothesis, a simple building block of Type-**2** was prepared (Scheme 2; R^1 = Et; see Experimental section) and selected as the model precursor. α-Enaminone **4** was obtained by reacting **2** with 1,3-dibromopropane in the presence of K_3PO_4 (1st equivalent of base).

Surprisingly, an unexpected direct cyclization was observed. During the preparation of **4**, the alkylation of **2** with dibromopropane led to the isolation of a stable bicyclic quinolinone system **3** rather than the anticipated *α*-enaminone. We assumed that subsequent fast cyclization of **4** yields compound **3** as an exclusive single product. Presumably, an equilibrium between **5** and **4** is established due to prevailing enamine-type electronic behaviour, suppressing the enone-driven resonance. Subsequent nucleophilic attack leads to favourable 6-membered ring **6**. In the presence of a second equivalent of base, the deprotonation of **6** occurs, generating product **3**. No hydrolysis of **6** was detected, and only **3** was observed, which suggests that a very fast deprotonation may have occurred. This deprotonation allows formation of the thermodynamically favourable product, preserving its *α,β*-unsaturated functionality.

Scheme 2. 1,4-Addition: rapid access Quinolinones from α-enaminone precursor (the mechanism)



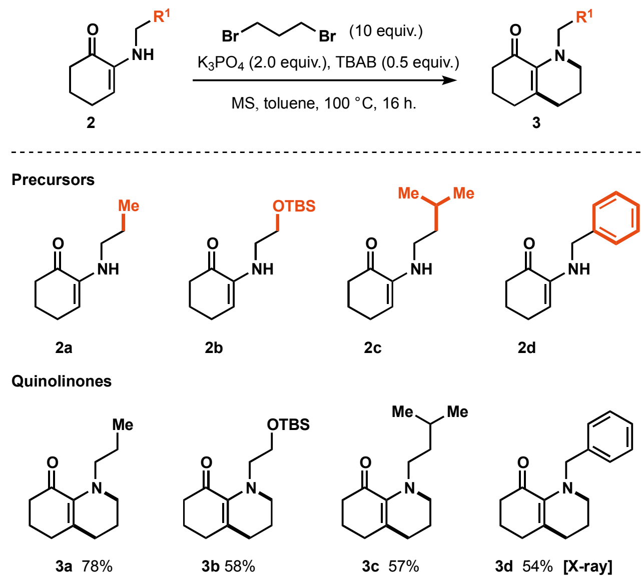
An efficient system for the desired transformation involves a combination of **2** with 10 equivalents of 1,3-dibromopropane, 0.5 equivalents of TBAB, and 2 equivalents of K_3PO_4 at 100 °C in toluene (entry 10, Table 1). Control experiments were performed and demonstrated that no cyclization occurred in the absence of base. It is important to mention, that all attempts to decrease the amount of 1,3-dibromopropane resulted in incomplete conversion, and slow decomposition of starting material. To confirm the hypothesis and expand the scope of the substrates and targets employed, we conducted additional experiments with various α-enaminone precursors bearing different R^1 groups (compounds **2a-2d**; Table 2) under the optimized cyclization conditions. We detected exclusive 1,4-selectivity, which led to the generation of quinolinone scaffolds **3a-d**.[12]

Table 1. Conditions evaluation for synthesis of Quinolinones: 2 → 3 [R^1 = Et]

Entry	Base	Solvent	Additive	Yield (%) 3:2[a]
1	K_2CO_3	THF	-	29:44
2	K_2CO_3	DMF	-	No reaction
3	K_2CO_3	MeCN	-	No reaction
4	K_2CO_3	Pyridine	-	0:93
5	K_2CO_3	Toluene	-	29:65
6	Cs_2CO_3	Toluene	-	26:51
7	*t*-BuOK	Toluene	-	5:76
8	K_3PO_4	Toluene	-	9:87
9	K_3PO_4	Toluene	MS, TBAB 20%	13:81
10	**K_3PO_4**	**Toluene**	**MS, TBAB 50%**	**80:10[b]**
11	K_3PO_4	Toluene	MS, TBAB 100%	70:15
12	K_2CO_3	Toluene	MS, TBAB 50%	13:41[c]

[a]GC yields: 0.2 mmol scale. [b]All attempts to increase the conversion rate by elevating the temperature or prolonging the reaction time resulted in decomposition of starting materials. [c]The decline in mass balance was due to the degradation of starting precursor during the reaction course.

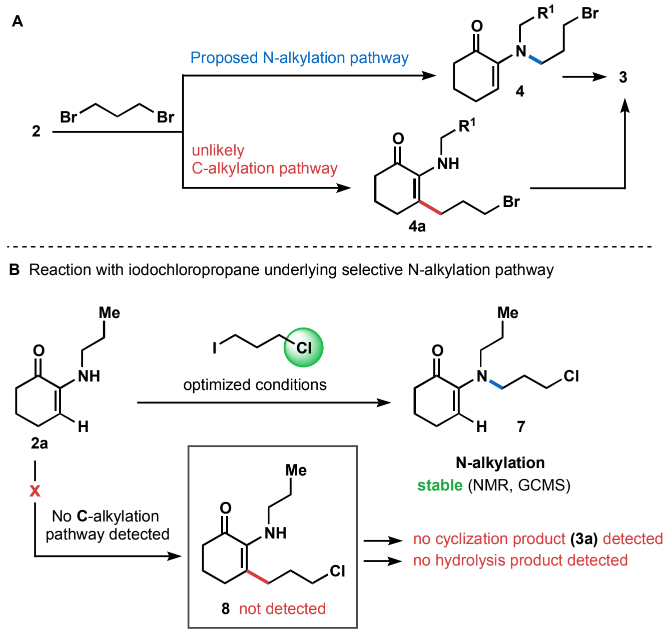
Table 2. 1,4-Addition (access to Quinolinones)[a]



[a]Isolated yields: 0.5 mmol scale. Starting materials (in a range of 5-10%) were isolated. Prolonging the reaction time resulted in decomposition of **2**.

In principle, the reaction of precursor **2** with dibromopropane could produce other possible reactive intermediate, **4a** (instead of **4**; Scheme 3A), that could give rise to quinolinone **3**. In order to differentiate among the pathways, the reaction of **2a** was carried out under the standard conditions but in the presence of 1-iodo-3-chloropropane (Scheme 3B). Compound **7** was then isolated as the only observable stable intermediate, and the structure was assigned on the basis of its NMR spectra and the results of GCMS analysis. No evidence for the presence of C-alkylated (1,4-type addition) product **8** was detected. It should be also noted that no cyclization outcome **3a**, or any other side-product, were formed in the reaction mixture.

Scheme 3. Selective N-alkylation pathway



C-O Bond formation. An unexpected cyclization caught our attention when precursor **9** ($R^2 \neq H$; Scheme 4) was subjected to 1,2-dibromoethane. During the preparation of *α*-enaminone **11**, the rapid cyclization led to the unforeseen isolation of stable oxazine - **10** (general structure). Surprisingly, **11** delivers two different outcomes (i.e., **10a**-methylene-oxazine or **10b**-benzoxazine) depending on the nature of the R^2 substituent (see Scheme 4). The best system for C-O bond formation involves a combination of **9** with 2 equivalents of 1,2-dibromoethane, 0.2 equivalents of TBAB, and 2 equivalents of base at 100 °C. Table 3 lists the conditions evaluated for *α*-enaminone integrated with the aliphatic R^2 group (with DIEA as optimal base; entry 6). Then, the same set of variables was applied to the starting material, bearing an aromatic R^2 residue. For this setting, K_2CO_3 has been determined to be the best base. We believe that in the presence of base, the deprotonation of **11** is established (Scheme 4; two variants are possible depending on the R^2 substituent). The subsequent nucleophilic attack of the oxygen, which was driven by the enone transient attitude, leads further to more favourable 6-membered ring scaffolds that bear a conjugated double bond system (i.e., **10a**) or fully aromatized oxazine (i.e., **10b**). Representative examples of methylene- and benzoxazines, that were synthesized through C-O bond formation, shown in the Table 4. For this transformation, compounds with a variety of R^1- and R^2-substituted Types-**14** and **16** cores were prepared (precursors **14a-d**, **16a-b**; see Experimental section) and subjected to the optimized conditions. It is also imperative to mention the exclusive *E*-selectivity was observed for cyclization products **15a-d** and **17a-d**. The critical stereochemical assignment of the bicyclic targets has been confirmed by NMR analysis (see SI spectral data).[13]

Scheme 4. Annulation of *α*-enaminone via C-O bond formation: synthesis of methylene- and benzoxazines.

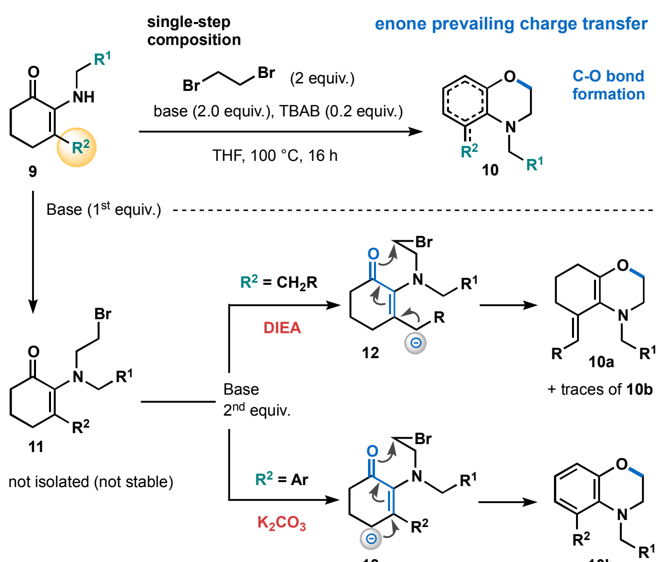


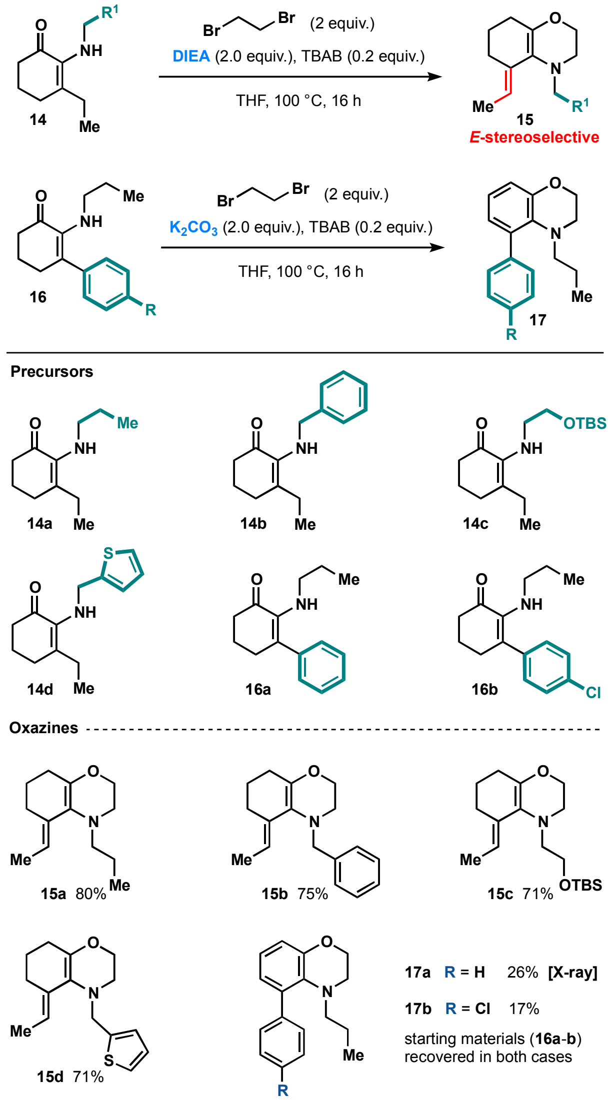
Table 3. Conditions evaluation for synthesis of Oxazines: 9 → 10 [R^1 = Ph, R^2 = Et]

Entry	Base	Solvent	Yield (%) 12:11[a]
1	K_2CO_3	Acetone	62:25
2	Na_2CO_3	Acetone	67:5
3	Cs_2CO_3	Acetone	17:51
4	K_3PO_4	Acetone	55:9
5	DIEA	Acetone	74:3
6	**DIEA**	**THF**	**85:0**
7	DIEA	Toluene	76:9
8	DIEA	DMF	13:0[b]
9	DIEA	1,4-Dioxane	64:18
10	DIEA	Pyridine	No reaction
11	DIEA	MeCN	43:8[b]

[a]GC yields: 0.2 mmol scale. [b]The decline in mass balance was due to the degradation of starting precursor during the reaction course.

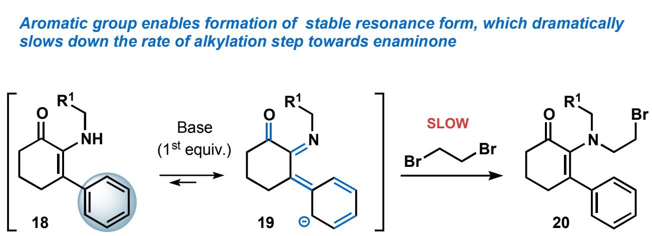
As shown in Table 4, the isolated yields of compounds **17a-b** were significantly lower than of those of **15a-d**. We attribute the apparent difference between these two groups to the nature of their R^2 residue. As proposed in the Scheme 5, an aromatic R^2 (in the presence of base) enables formation of a stable resonance form (**19**) of starting precursor **18**, which dramatically slows down the alkylation step towards α-enaminone **20**. This result is confirmed by our ability to recover a vast amount of unreacted starting materials. In contrast, the compounds integrated with aliphatic R^2 groups did not transform into the resonance form, and most likely undergo the desired alkylations to generate bicyclic products.

Table 4. Scope: C-O Bond formation (synthesis of Methylene- and Benzoxazines)[a]



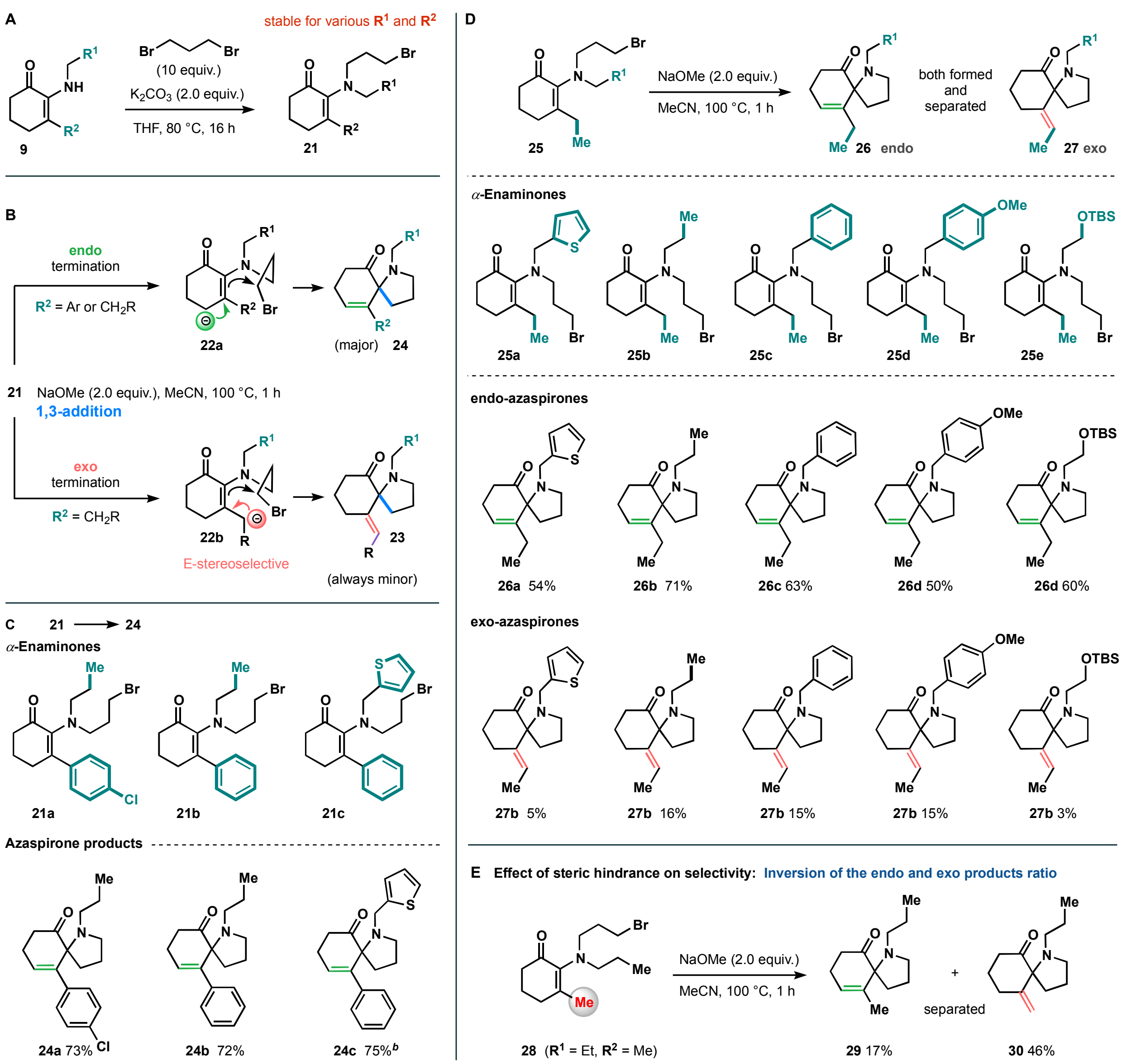
[a]Isolated yields: 0.5 mmol scale.

Scheme 5. Resonance contribution to alkylation rate of enaminone precursor



1,3-Addition. With suitable access to quinolinones and oxazines in hand, we next experimented with other cyclizations. The reaction scope was extended to the synthesis of more challenging heterocycles using the same precursor (**9**) as a starting material (Table 5A). An interesting result was observed when **9** ($R^2 \neq H$) was subjected to 1,3-dibromopropane rather than 1,2-dibromoethane (as in the previously discussed transformation). In contrast to *α*-enaminones **4** (Scheme 2) and **11** (Scheme 4), the type-**21** enaminones were stable (for various R^1 and R^2). Following the exposure of enaminone **21** to basic conditions (the optimized reaction protocol is provided in Table 6, entry 12), we detected another unexpected and novel cyclization.

Table 5. 1,3-Addition: synthesis of Azaspirones. Plausible mechanism and the substrate scope[a]



[a]Isolated yields: 0.5 mmol scale. [b]Cs_2CO_3 was used as base (20h).

The derivatives of **21** were synthesized (see experimental section) and further subjected to the optimized cyclization conditions to generate products **24a-c**, **26a-d** and **27a-d** (Tables 5C and 5D respectively). Interestingly, of the two intermediates (**22a** and **22b**; Table 5B), deprotonation primarily occurs at **22a** regardless of the nature of R^2 group (aliphatic CH_2R or Aromatic).

Table 6. Conditions evaluation for 1,3-addition: 21 → 24 [R^1 = Et, R^2 = Ph]

Entry	Base	Solvent	Yield (%) 12:11[a]
1	Cs_2CO_3	1,4-Dioxane	No reaction
2	Cs_2CO_3	THF	17
3	Cs_2CO_3	DMF	29
4	Cs_2CO_3	Toluene	No reaction
5	Cs_2CO_3	MeCN	55
6	Na_2CO_3	MeCN	No reaction
7	K_2CO_3	MeCN	10
8	K_3PO_4	MeCN	6
9	NaOH	MeCN	11
10	DIEA	MeCN	No reaction
11	NaOMe	MeCN	77
12	**NaOMe (2 equiv.)**	**MeCN**	**96**

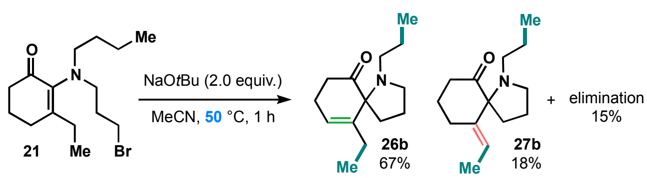
[a]GC yields: 0.2 mmol scale.

The *endo*-terminated cyclizations (**24**) were consistently observed as the dominant products for this transformation. We postulated that the formation of **25** (minor outcome) is suppressed due to the steric intramolecular hindrance from the R-group, and the alkylbromide chain (**23**; Table 5B). To test this hypothesis, enaminone **28** (integrated with the Me group as R^2) was prepared and subjected to the optimized cyclization conditions (Table 5E). The ratio of endo- and exo-products (**29** and **30** repectively) inverts with exo **30** being a major product, which further strengthens our core assumption.

Additionally, we investigated the effect of the temperature on selectivity of this reaction (1,3-addition). Therefore, we subjected enaminone **25b** (with R^1 and R^2 being Et groups; Scheme 6) to cyclization conditions at a lower temperature of 50 °C, utilizing NaO*t*-Bu as a base.[14] We detected a similar ratio for products **26b** and **27b** (67:18).

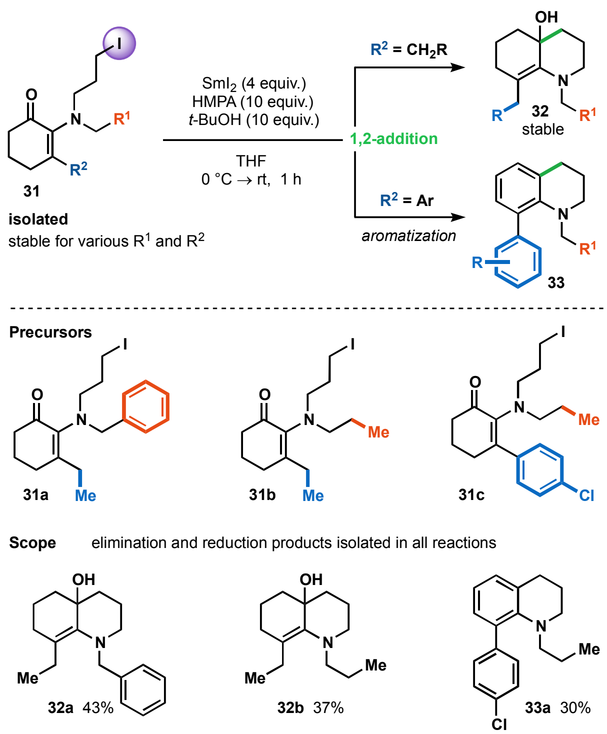
Notwithstanding the lack of selectivity, the successful construction of azaspirones via 1,3-cyclization of enaminone is remarkable. All pairs of *exo*- and *endo*- products were successfully separated, providing access to two conceptually different heterocycles. It should be also mentioned, that the exclusive *E*-selectivity observed for all exo-terminated products **26a-e**. The critical stereochemical assignment was confirmed by NMR analysis.[13]

Scheme 6. Effect of temperature on the selectivity



1,2-Addition. To complete the picture, we executed additional cyclizations to investigate the final 1,2-addition of the α-enaminone system. We followed the protocols designed for the radical cyclization of classical enones.[15] Our attempts were carried out using the SmI_2/HMPA system.[16] Here, type-**31** α-enaminones (see Experimental section for preparation) were subjected to radical cyclization conditions to provide bicyclic quinolinols **32** or quinoline **33**, however, both were obtained in low yields (Table 7). The two transformations were confirmed to undergo the desired termination, even though reduction and other side products were detected in the reaction mixtures (quinoline was obtained if R^2 = aromatic). Despite our goal of enhancing the outcome of this transformation by varying the temperature, solvent, concentration, amount of SmI_2 or HMPA alternation, and order of reagent addition, our efforts were not successful. Nevertheless, radical reactions of **31a-c** afforded the desired products **32a**, **32b** and **33a** (Table 7). To the best of our knowledge, these results represent the first examples of intramolecular cyclizations that incorporate quinolinols and quinolines from a simple enaminone. In these less effective cyclizations, the formation of **32** and **33** required 4 equivalents of the Sm reagent, 10 equivalents of HMPA, and 10 equivalents of *tert*-butyl alcohol. Regardless of the mentioned drawbacks, the successful construction of the reported heterocycles via this type of transformation is unprecedented and unique.

Table 7. Radical 1,2-cyclization: direct access to Quinolines and Quinolinols



CONCLUSION

We have reported the unprecedented reactivity of *α,β*-unsaturated enaminones driven by their "dual electronic attitude". We introduced novel, stable *α*-enaminone synthones and discovered the unusual and novel functionalities of these building blocks. We have demonstrated that readily available α-enaminone precursors undergo facile cyclizations under basic conditions to afford a broad spectrum of heterocycles, such as azaspirones, quinolinones, quinolines, quinolinols and oxazines. Accurate design of the starting material allows for specific and selective functionalization reactions across the unsaturated scaffold, enabling the preparation of diverse products. We believe that our methodology is ground-breaking in the field of basic chemical research, paves the way for novel retrosynthetic pathways, and may reasonably find potential application for the construction of highly complex systems.

Experimental Section

General Information. Unless otherwise noted, all reagents were purchased from commercial suppliers and used without further purification. Solvents used in the reactions were distilled from appropriate drying agents prior to use. Reactions were monitored by thin-layer chromatography (TLC) on silica gel 60 F_{254} aluminium plates (Merck) and/or gas chromatography-mass spectrometry (GCMS). Visualization of compounds on TLC was accomplished by irradiation with UV light at 254 nm, iodine or vanillin stain. GCMS Analysis was performed with 'Agilent 7820A' gas chromatograph equipped with 'Agilent 5975' quadrupole mass selective detector, using Agilent HP-5MS capillary column (30 m, 0.25 mm, 0.25 μm film). **Column chromatography** was performed using silica gel 60 (particle size 0.040-0.063 mm) purchased from Sigma-Aldrich or aluminium oxide 90 active basic (particle size 0.063-0.200 mm) purchased from Merck. **Proton and carbon NMR spectra** were recorded on Varian Mercury 300 MHz or Varian Mercury 500 MHz spectrometer in deuterated solvent. Proton chemical shifts are reported in ppm (δ) relative to tetramethylsilane with the solvent resonance employed as the internal standard ($CDCl_3$, δ 7.26 ppm). ^{13}C chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$, δ 77.0 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration and coupling constants (Hz). High resolution mass spectra were determined on a Thermo Scientific LTQ Orbitrap XL (FTMS). **Infrared spectra** (IR) were recorded on a Thermo Fischer Scientific NICOLET-iS10 spectrometer.

General procedure A: Synthesis of Quinolinones (1,4-addition): To a flame-dried 15.0 mL reaction tube flushed with nitrogen, fitted with a magnetic stirring bar and rubber septum, were added imminone (1.0 equiv.), K_3PO_4 (2.0 equiv.), dibromopropane (10.0 equiv.), TBAB (0.5 equiv.) and molecular sieves (4Å, 500 mg, 1.0 mmol) in dry toluene (0.1M) at room temperature. The reaction mixture was refluxed at 100 °C for 16 h. The mixture was then concentrated in vacuo, and the crude mixture was purified by flash chromatography to yield the desired product.

1-Propyl-1,3,4,5,6,7-hexahydroquinolin-8(2H)-one (3a): General procedure A was applied. *α*-Iminone **2a** (77 mg, 0.5 mmol) prepared according to General Procedure E, K_3PO_4 (212 mg, 1.0 mmol), dibromopropane (1.01 g, 5.0 mmol), TBAB (83 mg, 0.25 mmol) and molecular sieves (4Å, 250 mg) were mixed in dry toluene (5.0 mL) at room temperature. The reaction mixture was refluxed at 100 °C for 16 h. The mixture was then concentrated in vacuo and the crude product was purified by flash chromatography (Silica gel, 4/96% MeOH/DCM) to yield **3a** in 78% yield (75 mg) as yellow liquid. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 2.93-2.87 (m, 2H), 2.72-2.63 (m, 2H), 2.46-2.35 (m, 2H), 2.27 (t, J = 6.2 Hz, 2H), 2.11 (t, J = 6.6 Hz, 2H), 1.89 (p, J = 6.3 Hz, 2H), 1.71-1.52 (m, 4H), 0.85 (t, J = 7.4 Hz, 3H).**^{13}C NMR** (75 MHz, $CDCl_3$): δ 196.2, 141.1, 139.2, 54.6, 47.6, 39.3, 31.1, 29.7, 22.5, 22.0, 18.5, 11.5. **IR** (neat): 2930, 2868, 2824, 1671, 1603, 1184 cm^{-1}. **HRMS** *m/z*: ($[M+Na]^+$) calcd for $C_{12}H_{19}NONa$ 216.1359; found 216.1356.

1-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-1,3,4,5,6,7-hexahydroquinolin-8(2H)-one (3b): General procedure A was applied. *α*-Iminone **2b** (135 mg, 0.5 mmol) prepared according to General Procedure E, K_3PO_4 (212 mg, 1.0 mmol), dibromopropane (1.01 g, 5.0 mmol),TBAB (83 mg, 0.25 mmol) and molecular sieves (4Å, 250 mg) were mixed in dry toluene (5.0 mL) at room temperature. The reaction mixture was refluxed at 100 °C for 16 h. The mixture was then concentrated in vacuo and the crude product was purified by flash chromatography (Silica gel, 5/95% ether/hexane) to yield **3b** in 58% yield (90 mg) as yellow liquid. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 3.82 (t, J = 6.7 Hz, 2H), 3.00-2.93 (m, 2H), 2.87 (t, J = 6.7 Hz, 2H), 2.44-2.36 (m, 2H), 2.26 (t, J = 6.2 Hz, 2H), 2.11

(t, *J* = 6.6 Hz, 2H), 1.89 (p, *J* = 6.3 Hz, 2H), 1.67 (p, *J* = 6.3 Hz, 2H), 0.87 (s, 9H), 0.05 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 196.2, 140.7, 138.8, 62.9, 54.8, 49.3, 39.2, 31.0, 29.6, 25.9, 22.5, 18.9, 18.3, -5.3. **IR** (neat): 2927, 2855, 1673, 1251, 1099, 832, 774 cm^{-1}. **HRMS** *m/z*: ($[M+Na]^+$) calcd for $C_{17}H_{31}NO_2SiNa$ 332.2016; found 332.2019.

1-Isobutyl-1,3,4,5,6,7-hexahydroquinolin-8(2H)-one (3c): General procedure A was applied. *α*-Iminone **2c** (84 mg, 0.5 mmol) prepared according to General Procedure E, K_3PO_4 (212 mg, 1.0 mmol), dibromopropane (1.01 g, 5.0 mmol), TBAB (83 mg, 0.25 mmol) and molecular sieves (4Å, 250 mg) were mixes in dry toluene (5 mL) at room temperature. The reaction mixture was refluxed at 100 °C for 16 h. The mixture was then concentrated in vacuo and the crude product was purified by flash chromatography (Silica gel, 20/80% ethyacetate/hexane) to yield **3c** in 57% yield (59 mg) as yellow liquid. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 2.95-2.86 (m, 2H), 2.56 (d, *J* = 7.3 Hz, 2H), 2.40 (t, *J* = 7.4 Hz, 2H), 2.27 (t, *J* = 6.2 Hz, 2H), 2.12 (t, *J* = 6.6 Hz, 2H), 2.02-1.84 (m, 3H), 1.73-161 (m, 2H), 0.93 (d, *J* = 6.7 Hz, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 196.1, 141.5, 138.7, 59.8, 47.6, 39.5, 31.2, 29.8, 27.7, 22.4, 20.6, 18.3. **IR** (neat): 2951, 2866, 2822, 1671, 1602, 1435, 1184, 1121, 978 cm^{-1}. **HRMS** *m/z*: ($[M+Na]^+$) calcd for $C_{13}H_{21}NONa$ 230.1515; found 230.1519.

1-Benzyl-1,3,4,5,6,7-hexahydroquinolin-8(2H)-one (3d): General procedure A was applied. *α*-Iminone **2d** (101 mg, 0.5 mmol) prepared according to General Procedure E, K_3PO_4 (212 mg, 1.0 mmol), dibromopropane (1.01 g, 5.0 mmol), TBAB (83 mg, 0.25 mmol) and molecular sieves (4Å, 250 mg) were mixed in dry toluene (5 mL) at room temperature. The reaction mixture was refluxed at 100 °C for 16 h. The mixture was then concentrated in vacuo and the crude product was purified by flash chromatography (Silica gel, 20/80% ether/hexane) to yield **3d** in 54% yield (66 mg) as pale yelloe solid (**M.p.** 86-89 °C). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.48-7.43 (m, 2H), 7.34-7.19 (m, 3H), 3.93 (s, 2H), 2.80-2.76 (m, 2H), 2.50-2.44 (m, 2H), 2.31 (t, *J* = 6.2 Hz, 2H), 2.12 (t, *J* = 6.5 Hz, 2H), 1.95 (p, *J* = 6.3 Hz, 2H), 1.67-1.57 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 196.1, 140.7, 140.5, 139.8, 129.1, 128.1, 126.9, 55.7, 46.5, 39.4, 31.2, 29.8, 22.5, 17.8. **IR** (neat): 2943, 2928, 2864, 1661, 1611, 1161, 946, 746, 702 cm^{-1}. **HRMS** *m/z*: ($[M+H]^+$) calcd for $C_{16}H_{20}NO$ 242.1539; found 242.1538.

General procedure B: Synthesis of Oxazines (C-O formation): To a flame-dried 15 mL reaction tube, fitted with a magnetic stirring bar and a rubber septum connected to a nitrogen source, *α*-iminone (1.0 equiv.), base (2.0 equiv.), TBAB (0.2 equiv.), dibromoethane (2.0 equiv.) were mixed in dry THF (0.5M) at room temperature. The reaction mixture was refluxed at 100 °C for 16 h. The mixture was then concentrated in vacuo and the crude mixture was purified by flash chromatography to yield the desired product.

5-Ethylidene-4-propyl-3,4,5,6,7,8-hexahydro-2H-benzo[b][1,4]oxazine (15a): General procedure B was applied. *α*-Iminone **14a** (91 mg, 0.5 mmol) prepared according to General Procedure E, Hunig's base (130 mg, 1.0 mmol), TBAB (33 mg, 0.1 mmol) and dibromoethane (188 mg, 1.0 mmol) were mixed in dry THF (1.0 mL) at room temperature. The reaction mixture was refluxed at 100 °C for 16 h. The mixture was then concentrated in vacuo and the crude mixture was purified by flash chromatography (basic alumina, 5/95% ether/hexane) to yield **15a** in 80% yield 84 mg) as yellow liquid. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 5.48 (q, *J* = 7.1 Hz, 1H), 3.97-3.90 (m, 2H), 2.94 (t, *J* = 4.3 Hz, 2H), 2.56-2.47 (m, 2H), 2.22 (q, *J* = 6.6 Hz, 4H), 1.62-1.74 (m, 5H), 1.54 (h, *J* = 7.4 Hz, 2H), 0.88 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 140.0, 132.5, 122.0, 112.0, 59.5, 55.0, 45.7, 27.9, 25.3, 22.4, 21.8, 13.2, 11.5. **IR** (neat): 2958, 2929, 2869, 1624, 1455, 1353, 1143, 700 cm^{-1}. **HRMS** *m/z*: ($[M+H]^+$) calcd for $C_{13}H_{22}NO$ 208.1696; found 208.1690.

4-Benzyl-5-ethylidene-3,4,5,6,7,8-hexahydro-2H benzo[b][1,4]oxazine (15b): General procedure B was applied. *α*-|Iminone **14b** (115 mg, 0.5 mmol) prepared according to General Procedure E, Hunig's base (130 mg, 1mmol), TBAB (33 mg, 0.1mmol) and dibromoethane (188 mg, 1.0 mmol) were mixed in dry THF (1.0 mL) at room temperature. The reaction mixture was refluxed at 100 °C for 16 h. The mixture was then concentrated in vacuo and the crude product was purified by flash chromatography (basic alumina, 5/95% ether/hexane) to yield **15b** in 75% yield (95 mg) as yellow liquid. **^{1}H NMR** (300 MHz, CDCl3): δ 7.43 (d, *J* = 7.6 Hz, 2H), 7.35 (t, *J* = 7.4 Hz, 2H), 7.31-7.23 (m, 1H), 5.70 (q, *J* = 7.2 Hz, 1H), 3.99-3.95 (m, 2H), 3.93 (s, 2H), 2.90 (t, *J* = 4.4 Hz, 2H), 2.30 (q, *J* = 6.7 Hz, 4H), 1.77 (q, *J* = 6.4 Hz, 2H), 1.69 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR** (75 MHz, CDCl3): δ 141.0, 139.4, 132.2, 128.4, 127.8, 126.9, 121.3, 112.0, 59.4, 56.4, 45.7, 28.0, 25.4, 22.5, 13.3. **IR** (neat): 2957, 2928, 2864, 1642, 1624, 1194, 1146, 731, 696 cm^{-1}. **HRMS** *m/z*: ([M+H]$^+$) calcd for $C_{17}H_{22}NO$ 256.1696; found 256.1693.

5-Ethylidene-4-propyl-3,4,5,6,7,8-hexahydro-2H-benzo[b][1,4]oxazine (15c): General procedure B was applied. *α*-Iminone **14c** (149 mg, 0.5 mmol) prepared according to General Procedure E, Hunig's base (130 mg, 1.0 mmol), TBAB (33 mg, 0.1 mmol) and dibromoethane (188 mg, 1.0 mmol) were mixed in dry THF (1.0 mL) at room temperature. The reaction mixture was refluxed at 100 °C for 16 h. The mixture was then concentrated in vacuo and the crude mixture was purified by flash chromatography (basic alumina, 5/95% ether/hexane) to yield **15c** in 71% yield 95 mg) as yellow liquid. **^{1}H NMR** (300 MHz, CDCl3): δ 5.54 (q, *J* = 7.2 Hz, 1H), 3.96 (t, *J* = 4.4 Hz, 2H), 3.76 (t, *J* = 6.3 Hz, 2H), 3.03 (t, *J* = 4.4 Hz, 2H), 2.73 (t, *J* = 6.4 Hz, 2H), 2.26-2.17 (m, 4H), 1.63-1.75 (m, 5H), 0.90 (s, 9H), 0.07 (s, 6H). **^{13}C NMR** (75 MHz, CDCl3): δ 140.1, 132.4, 121.7, 112.4, 62.6, 59.7, 55.2, 47.1, 27.9, 25.9, 25.3, 22.4, 18.3, 13.2, -5.4 . **IR** (neat): 2957, 2930, 2859, 1456, 1249, v1098, 837, 770 cm^{-1}. **HRMS** *m/z*: ([M+H]$^+$) calcd for $C_{18}H_{34}NO_2Si$ 324.2353; found 324.2354.

5-Ethylidene-4-(thiophen-2-ylmethyl)-3,4,5,6,7,8-hexahydro-2H-benzo[b][1,4]oxazine (15d): General procedure B was applied. *α*-Iminone **14d** (118 mg, 0.5 mmol) prepared according to General Procedure E, Hunig's base (130 mg, 1.0 mmol), TBAB (33 mg, 0.1 mmol) and dibromoethane (188 mg, 1.0 mmol) were mixed in dry THF (1.0 mL) at room temperature. The reaction mixture was refluxed at 100 °C for 16 h. The mixture was then concentrated in vacuo and the crude product was purified by flash chromatography (basic alumina, 5/95% ether/hexane) to yield **15d** in 71% yield (93 mg) as yellow liquid. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.27-7.22 (m, 1H), 6.99-6.91 (m, 2H), 5.77 (q, J = 7.1 Hz, 1H), 4.01 (s, 2H), 3.95 (t, J = 4.4 Hz, 2H), 3.00-2.92 (m, 2H), 2.36-2.23 (m, 4H), 1.82-1.67 (m, 5H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 143.7, 141.1, 132.0, 126.5, 124.8, 124.6, 120.9, 112.3, 59.6, 51.8, 45.7, 27.9, 25.3, 22.4, 13.3. **IR** (neat): 2955, 2928, 2858, 1455, 1246, 1094, 830, 771 cm^{-1}. **HRMS** *m/z*: ($[M+H]^+$) calcd for $C_{15}H_{20}NOS$ 262.1260; found 262.1251.

5-Phenyl-4-propyl-3,4,5,6,7,8-hexahydro-2H-benzo[b][1,4]oxazine (17a): General procedure B was applied. α-Iminone **16a** (115 mg, 0.5 mmol) prepared according to General Procedure E, K_2CO_3 (138 mg, 1.0 mmol), TBAB (33 mg, 0.1 mmol) and dibromoethane (188 mg, 1.0 mmol) were mixed in dry THF (1.0 mL) at room temperature. The reaction mixture was refluxed at 100 °C for 16 h. The mixture was then concentrated in vacuo and the crude product was purified by flash chromatography (Silica gel, 2/98% ether/hexane) to yield **17a** in 26% yield (32 mg) as yellow liquid. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.57-7.52 (m, 2H), 7.41 (dd, J = 8.2, 6.6 Hz, 2H), 7.36-7.31 (m, 1H), 6.98-6.86 (m, 2H), 6.82 (dd, J = 7.1, 2.0 Hz, 1H), 4.13 (t, J = 4.4 Hz, 2H), 3.17 (t, J = 4.5 Hz, 2H), 2.54-2.46 (m, 2H), 1.26-1.07 (m, 2H), 0.47 (t, J = 7.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 147.7, 141.1, 136.0, 134.2, 129.1, 128.1, 126.7, 123.6, 121.9, 116.4, 60.3, 57.7, 45.6, 20.7, 11.1. **IR** (neat): 2964, 2860, 1580, 1461, 1433, 1240, 1006, 871, 775, 702 cm^{-1}. **HRMS** *m/z*: ($[M+Na]^+$) calcd for $C_{17}H_{19}NONa$ 276.1357; found 276.1360.

5-(4-Chlorophenyl)-4-propyl-3,4,5,6,7,8-hexahydro-2H-benzo[b][1,4]oxazine (17b): General procedure B was applied. α-Iminone **16b** (132 mg, 0.5 mmol) prepared according to General Procedure E, K_2CO_3 (138 mg, 1.0 mmol), TBAB (33 mg, 0.1 mmol) and dibromoethane (188 mg, 1.0 mmol) were mixed in dry THF (1.0 mL) at room temperature. The reaction mixture was refluxed at 100 °C for 16 h. The mixture was then concentrated in vacuo and the crude product was purified by flash chromatography (Silica gel, 2/98% Ether/hexane) to yield **17b** in 17% yield (49 mg) as yellow liquid. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.50-7.45 (m, 2H), 7.38-7.33 (m, 2H), 6.96-6.83 (m, 2H), 6.74 (dd, J = 7.2, 1.9 Hz, 1H), 4.10 (t, J = 4.5 Hz, 2H), 3.14 (t, J = 4.5 Hz, 2H), 2.50-

2.42 (m, 2H), 1.23-1.10 (m, 2H), 0.49 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 139.4, 132.5, 130.4, 128.3, 123.4, 122.1, 116.7, 60.2, 57.7, 45.4, 20.7, 11.1. **IR** (neat): 2964, 2930, 2860, 1580, 1461, 1433, 1240, 1134, 1006, 871, 763, 702 cm^{-1}. **HRMS** *m/z*: ($[M+H]^+$) calcd for $C_{17}H_{19}ClNO$ 288.1150; found 288.1152.

General procedure C: Synthesis of azaspiro-decanones (1,3 addition): To a flame-dried 15 mL reaction tube flushed with nitrogen, fitted with a magnetic stirring bar and rubber septum, were added *α*-enaminone (1.0 equiv., 0.5 mmol) and NaOMe (2.0 equiv., 1 mmol) in dry MeCN (1M) at room temperature. The reaction mixture was refluxed at 100 °C for 1 h. The mixture was then concentrated in vacuo and the crude product was purified by flash chromatography to yield the desired product.

10-(4-Chlorophenyl)-1-propyl-1-azaspiro[4.5]dec-9-en-6-one (24a): General procedure C was applied. *α*-Enaminone **21a** (192 mg, 0.5 mmol) prepared according to General Procedure F and NaOMe (54 mg, 1.0 mmol) were mixed in dry MeCN (0.5 mL) at room temperature. The reaction mixture was refluxed at 100 °C for 1 h. The mixture was then concentrated in vacuo and the crude product was purified by flash chromatography (Silica gel, 5/95% ether/hexane) to yield **24a** in 73% yield (111 mg) as pale yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.47 (d, *J* = 6.6, 3.0 Hz, 2H), 7.22 (d, *J* = 4.9, 1.9 Hz, 2H), 6.13 (t, *J* = 4.2 Hz, 1H), 3.12-3.26 (m, 1H), 2.79 (q, *J* = 8.2 Hz, 1H), 2.64-2.36 (m, 6H), 1.88-1.77 (m, 3H), 1.69-1.50 (m, 2H), 1.45-4.32 (m, 1H), 0.84 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 213.1, 142.1, 139.3, 132.8, 130.7, 130.5, 127.5, 72.9, 51.1, 50.3, 39.5, 34.4, 24.3, 22.6, 22.5, 12.1. **IR** (neat): 2958, 2931, 2871, 2846, 1704, 1486, 1174, 1089, 1015, 822 cm^{-1}. **HRMS** *m/z*: ($[M+H]^+$) calcd for $C_{18}H_{23}ClNO$ 304.1463; found 304.1467.

10-Phenyl-1-propyl-1-azaspiro[4.5]dec-9-en-6-one (24b): General procedure C was applied. *α*-Enaminone **21b** (175 mg, 0.5 mmol) prepared according to General Procedure F and NaOMe (54 mg, 1.0 mmol) were mixed in dry MeCN (0.5 mL) at room temperature. The reaction mixture was refluxed at 100 °C for 1 h. The mixture was then concentrated in vacuo and the crude product was purified by flash chromatography (Silica gel, 5/95% ether/hexane) to yield **24b** in 72% yield (97 mg) as pale yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.48 (d, *J* = 8.2 Hz, 2H), 7.23 (d, *J* = 8.1 Hz, 3H), 6.12 (t, *J* = 4.2 Hz, 1H), 3.18 (td, *J* = 8.1, 2.7 Hz, 1H), 2.78 (q, *J* = 7.4 Hz, 1H), 2.67-2.58 (m, 2H), 2.54-2.38 (m, 4H), 1.90-1.69 (m, 3H), 1.68-1.62 (m, 1H), 1.59-1.49 (m, 1H), 1.45-1.39 (m, 1H), 0.83 (t, *J* = 7.4 Hz, 3H).**^{13}C NMR** (75 MHz, $CDCl_3$): δ 213.4, 143.1, 141.0, 130.3, 129.3, 127.4, 126.9, 73.1, 51.2, 50.3, 39.5, 34.4, 24.4, 22.6, 22.5, 12.1. **IR** (neat): 2957, 2930, 2846, 1704, 1442, 1174, 1075, 759, 698 cm^{-1}. **HRMS** *m/z*: ($[M+H]^+$) calcd for $C_{18}H_{24}NO$ 270.18524; found 270.18506.

10-Phenyl-1-(thiophen-2-ylmethyl)-1-azaspiro[4.5]dec-9-en-6-one (24c): General procedure C was applied. *α*-Enaminone **21c** (202 mg, 0.5 mmol) prepared according to General Procedure F, Cs_2CO_3 (326 mg, 1.0 mmol) were mixed in dry MeCN (0.5 mL) at room temperature. The reaction mixture was refluxed at 100 °C for 20 h. The mixture was then concentrated in vacuo and the crude product was purified by flash chromatography (Silica gel, 5/95% ether/hexane) to yield **24c** in 75% yield (122 mg) as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.62-7.54 (m, 2H), 7.40-7.28 (m, 3H), 7.16 (d, *J* = 5.1, 1.3 Hz, 1H), 6.93-6.86 (m, 1H), 6.81 (d, *J* = 3.4 Hz, 1H), 6.20 (t, *J* = 4.3 Hz, 1H), 4.05-3.86 (m, 2H), 3.10-2.99 (m, 1H), 2.89 (q, *J* = 8.0 Hz, 1H), 2.80-2.68 (m, 1H), 2.60-2.46 (m, 3H), 2.14-2.01 (m, 1H), 2.01-1.78 (m, 2H), 1.77-1.56 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 212.9, 144.2, 143.1, 140.6, 130.8, 129.4, 127.6, 127.1, 126.1, 125.2, 124.5, 73.2, 50.7, 48.0, 39.1, 35.2, 24.5, 22.5. **IR** (neat): 2958, 2845, 1704, 1444, 1169, 758, cm^{-1}. **HRMS** *m/z*: ($[M+Na]^+$) calcd for $C_{20}H_{21}NOSNa$ 346.1236; found 346.1236.

26a (endo) and 27a (exo): General procedure C was applied. *α*-Enaminone **25a** (178 mg, 0.5 mmol) prepared according to General Procedure F and NaOMe (54 mg, 1.0 mmol), were mixes in dry MeCN (0.5 mL) at room temperature. The reaction mixture was refluxed at 100 °C for 1 h. The mixture was then concentrated in vacuo and the crude product was purified by flash chromatography (Silica gel, 5/95% ether/hexane) to yield 54% of **26a** and 5% of **27a** (65 mg and 7 mg respectively).

10-Ethyl-1-(thiophen-2-ylmethyl)-1-azaspiro[4.5]dec-9-en-6-one (26a): pale yellow solid (**M.p.** 49-51 °C). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.17 (d, *J* = 5.0, 1.3 Hz, 1H), 6.92-6.84 (m, 2H), 5.88-5.79(m, 1H), 3.96 (d, *J* = 14.1 Hz, 1H), 3.72 (d, *J* = 14.0 Hz, 1H), 3.17-3.07 (m, 1H), 2.92 (q, *J* = 7.8 Hz, 1H), 2.72-2.58 (m, 1H), 2.44-2.30 (m, 4H), 2.24-2.11 (m, 1H), 2.06-1.94 (m, 1H), 1.90-1.78 (m, 3H), 1.12 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 213.6, 145.6, 143.9, 126.2, 124.1 (2C) 123.7, 74.0, 50.7, 47.9, 38.7, 35.4, 24.9, 22.6, 22.1, 13.3. **IR** (neat): 2957, 2924, 2848, 1703, 1177, 722 cm^{-1}. **HRMS** *m/z*: ($[M+Na]^+$) calcd for $C_{16}H_{21}NOSNa$ 298.1236; found 298.1237.

10-Ethylidene-1-(thiophen-2-ylmethyl)-1-azaspiro[4.5]decan-6-one (27a): pale yellow solid (**M.p.** 53-55 °C). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.19 (dd, *J* = 4.8, 1.6 Hz, 1H), 6.93 (d, *J* = 5.2 Hz, 2H), 6.07 (q, *J* = 7.0 Hz, 1H), 4.14 (d, *J* = 14.5 Hz, 1H), 3.72 (d, *J* = 14.5 Hz, 1H), 3.22-3.10 (m, 1H), 2.95-2.84 (m, 1H), 2.79-2.68 (m, 1H), 2.54-2.47 (m, 2H), 2.27-2.10 (m, 2H), 1.97-1.71 (m, 3H), 1.70-1.56(m, 5H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 213.8, 145.8, 139.2, 126.3, 124.1, 123.9, 118.5, 79.5, 50.9, 48.6, 39.9, 38.1, 25.9, 22.9, 21.7, 13.3. **IR** (neat): 2926, 2841, 1702, 1454, 1134, 851, 696 cm^{-1}. **HRMS** *m/z*: ($[M+Na]^+$) calcd for $C_{16}H_{21}NOSNa$ 298.1236; found 298.1236.

26b (endo) and 27b (exo): General procedure C was applied. *α*-Enaminone **25b** (151 mg, 0.5 mmol) prepared according to General Procedure F and NaOMe (54 mg, 1.0 mmol) were mixed in dry MeCN (0.5 mL) at room temperature. The reaction mixture was refluxed at 100 °C for 1 h. The mixture was then concentrated in vacuo and the crude product was purified by flash chromatography (Silica gel, 5/95% ether/hexane) to yield 71% of **26b** and 16% of **27b** (78 mg and 18 mg respectively) as pale yellow oils.

10-Ethyl-1-propyl-1-azaspiro[4.5]dec-9-en-6-one (26b): **^{1}H NMR** (300 MHz, $CDCl_3$): δ 5.81-5.72 (m, 1H), 3.20-3.08 (m, 1H), 2.84-2.73 (m, 1H), 2.60-2.46 (m, 1H), 2.45-2.21 (m, 5H), 2.18-1.96 (m, 2H), 1.90-1.69 (m, 4H), 1.54-1.19 (m, 2H), 1.03 (t, *J* = 7.5 Hz, 3H), 0.81 (t, *J* = 7.4 Hz, 3H).**^{13}C NMR** (75 MHz, $CDCl_3$): δ 214.5, 144.2, 123.1, 73.6, 50.7, 50.4, 39.3, 34.7, 24.3, 22.7, 22.6, 21.9, 13.2, 11.8. **IR** (neat): 2958, 2931, 2872, 2847, 1712, 1458, 1180, 1085 cm^{-1}. **HRMS** *m/z*: ($[M+Na]^+$) calcd for $C_{14}H_{23}NONa$ 244.1672; found 244.1679.

10-Ethylidene-1-propyl-1-azaspiro[4.5]decan-6-one (27b): ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.81-5.70 (m, 1H), 3.25-3.17 (m, 1H), 2.93-2.83 (m, 1H), 2.75-2.55 (m, 2H), 2.47-2.38 (m, 2H), 2.33-2.25 (m, 1H), 2.18-2.03 (m, 2H), 1.89-1.82 (m, 1H), 1.76-1.70 (m, 3H), 1.64 (d, *J* = 6.9 Hz, 3H), 1.57-1.39 (m, 3H), 0.86 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 214.4, 139.6, 117.8, 51.7, 51.0, 40.1, 38.1, 29.7, 25.8, 22.9, 22.7, 21.6, 13.2, 12.0. **IR** (neat): 2956, 2928, 2668, 1707, 1456, 1197, 1153, 1096 cm^{-1}. **HRMS** *m/z*: ($[M+H]^+$) calcd for $C_{14}H_{24}NO$ 222.1852; found 222.1855.

26c (endo) and 27c (exo): General procedure C was applied. *α*-Enaminone **25c** (175 mg, 0.5 mmol) prepared according to General Procedure F and NaOMe (54 mg, 1.0 mmol) were mixed in dry MeCN (0.5 mL) at room temperature. The reaction mixture was refluxed at 100 °C for 1 h. The mixture was then concentrated in vacuo and the crude product was purified by flash chromatography (Silica gel, 5/95% ether/hexane) to yield 63% of **26c** and 15% of **27c** (85 mg and 20 mg respectively).

1-Benzyl-10-ethyl-1-azaspiro[4.5]dec-9-en-6-one (26c): pale yellow solid (**M.p.** 52-55 °C). **^{1}H NMR** (300 **MHz**, $CDCl_3$): δ 7.34-7.16 (m, 5H), 5.90-5.82 (m, 1H), 3.76-3.51 (m, 2H), 3.04-2.93 (m, 1H), 2.85 (h, *J* = 6.5 Hz, 1H), 2.73-2.57 (m, 1H), 2.49-2.28 (m, 4H), 2.25-2.14 (m, 1H), 2.05-1.76 (m, 4H), 1.11 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 214.0, 143.9, 140.5, 128.1, 128.0, 126.5, 123.8, 73.9, 52.8, 50.5, 39.0, 35.0, 24.7, 22.8, 22.1, 13.3. **IR** (neat): 2961, 2847, 1709, 1494, 1452, 1153, 733, 697 cm^{-1}. **HRMS** *m/z*: ($[M+H]^+$) calcd for $C_{18}H_{24}NO$ 270.1852; found 270.1857.

1-Benzyl-10-ethylidene-1-azaspiro[4.5]decan-6-one (27c): pale yellow solid (**M.p.** 57-58° C). **^{1}H NMR** (300 **MHz**, $CDCl_3$): δ 7.38 (d, *J* = 7.0 Hz, 2H), 7.32 (t, *J* = 7.5 Hz, 2H), 7.26-7.17 (m, 1H), 5.97 (q, J = 7.0 Hz, 1H), 3.88 (d, J = 14.4 Hz, 1H), 3.65 (d, J = 14.6 Hz, 1H), 3.11-3.02 (m, 1H), 2.90-2.79 (m, 1H), 2.77-2.67 (m, 1H), 2.57-2.48 (m, 2H), 2.30-2.13 (m, 2H), 1.97-1.68 (m, 4H), 1.67-1.59 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 214.1, 140.9, 139.6, 128.1, 128.0, 126.3, 118.3, 79.7, 53.1, 50.7, 40.0, 37.7, 25.9, 22.9, 21.7, 13.3. **IR** (neat): 2926, 2849, 1703, 1492, 1453, 1209, 1152, 1136, 735, 697 cm^{-1}. **HRMS** *m/z*: ($[M+Na]^+$) calcd for $C_{18}H_{23}NONa$ 292.1672; found 292.1676.

26d (endo) and 27d (exo): General procedure C was applied. *α*-Enaminone **25d** (190 mg, 0.5 mmol) prepared according to General Procedure F and NaOMe (54 mg, 1.0 mmol) were mixed in dry MeCN (0.5 mL) at room temperature. The reaction mixture was refluxed at 100 °C for 1 h. The mixture was then concentrated in vacuo and the crude product was purified by flash chromatography (Silica gel, 5/95% EtOAc/hexane) to yield 50% of **26d** and 15% of **27d** (75 mg and 22 mg respectively).

10-ethyl-1-(4-methoxybenzyl)-1-azaspiro[4.5]dec-9-en-6-one (26d): pale yellow oil. **^{1}H NMR** (300 **MHz**, $CDCl_3$): δ 7.19 (d, J = 8.4 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 5.88-5.80 (m, 1H), 3.79 (s, 3H), 3.68-3.47 (m, 2H), 2.99-2.91 (m, 1H), 2.88-2.79 (m, 1H), 2.69-2.59 (m, 1H), 2.55-2.30 (m, 4H), 2.23-2.12 (m, 1H), 2.01-1.77 (m, 4H), 1.11 (t, J = 7.5 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 214.0, 158.3, 143.9, 132.6, 129.1, 123.7, 113.5, 73.7, 55.2, 52.1, 50.4, 39.1, 35.0, 24.6, 22.7, 22.1, 13.3. **IR** (neat): 2960, 2834, 1709, 1510, 1241, 1168, 1036, 810 cm^{-1}. **HRMS** *m/z*: ($[M+Na]^+$) calcd for $C_{19}H_{25}NO_2Na$ 322.1778 ; found 322.1777.

(E)-10-ethylidene-1-(4-methoxybenzyl)-1-azaspiro[4.5]decan-6-one (27d): yellow oil. **^{1}H NMR** (300 **MHz**, $CDCl_3$): δ 7.29 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 5.97 (q, J = 6.9 Hz, 1H), 3.85-3.76 (m, 4H), 3.57 (d, J = 13.9 Hz, 1H), 3.07-2.96 (m, 1H), 2.88-2.68 (m, 2H), 2.57-2.47 (m, 2H), 2.30-2.14 (m, 2H), 1.97-1.70 (m, 5H), 1.66 (d, J = 5.7 Hz, 3H. **^{13}C NMR** (75 MHz, $CDCl_3$): δ 214.1, 158.2, 143.8, 139.6, 133.0, 129.1, 118.3, 115.0, 113.5, 79.5, 67.5, 55.2, 52.5, 50.6, 40.0, 37.7, 25.9, 22.9, 21.6, 13.3. **IR** (neat): 2923, 2853, 1693, 1490, 1457, 1243, 1202, 1158, 1146, 742, 690 cm^{-1}. **HRMS** *m/z*: ($[M+Na]^+$) calcd for $C_{19}H_{25}NO_2Na$ 322.1778; found 322.1777.

26e (endo) and 27e (exo): General procedure C was applied. *α*-Enaminone **25e** (209 mg, 0.5 mmol) prepared according to General Procedure F and NaOMe (54 mg, 1.0 mmol) were mixed in dry MeCN (0.5 mL) at room temperature. The reaction mixture was refluxed at 100 °C for 1 h. The mixture was then concentrated in vacuo and the crude product was purified by flash chromatography (Silica gel, 5/95% ether/hexane) to yield 60% of **26e** and 3% of **27e** (101 mg and 5 mg respectively) as pale yellow oils.

1-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-10-ethyl-1-azaspiro[4.5]dec-9-en-6-one (26e): **^{1}H NMR** (300 MHz, $CDCl_3$): δ 5.78-5.72 (m, 1H), 3.65-3.51 (m, 2H), 3.22-3.13 (m, 1H), 2.99-2.88 (m, 1H), 2.70-2.47 (m, 3H), 2.42-2.11 (m, 4H), 2.05-1.91 (m, 1H), 1.90-1.64 (m, 4H), 1.03 (t, *J* = 7.4 Hz, 3H), 0.87 (s, 9H), 0.02 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 214.0, 144.1, 123.2, 74.2, 62.7, 51.6, 51.5, 38.8, 34.8, 26.0, 24.7, 23.0, 21.9, 18.4, 12.9, -5.3. **IR** (neat): 2956, 2928, 2845, 1714, 1253, 1103, 832, 774 cm^{-1}. **HRMS** *m/z*: ($[M+Na]^+$) calcd for $C_{19}H_{35}NO_2SiNa$ 360.2329; found 360.2329.

1-(2-((*tert*-Butyldimethylsilyl)oxy)ethyl)-10-ethylidene-1-azaspiro[4.5]decan-6-one (27e): **^{1}H NMR** (300 MHz, $CDCl_3$): δ 5.81 (q, *J* = 6.4 Hz, 1H), 3.77-3.65 (m, 2H), 3.26-3.18 (m, 1H), 3.00-2.78 (m, 2H), 2.76-2.65 (m, 1H), 2.58-2.47 (m, 1H), 2.45-2.38 (m, 2H), 2.20-2.01 (m, 2H), 1.94-1.66 (m, 3H), 1.68-1.45 (m, 5H), 0.89 (s, 9H), 0.05 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 214.0, 139.5, 118.2, 80.1, 62.8, 52.4, 51.9, 40.0, 37.8, 26.0, 25.8, 22.9, 21.8, 18.4, 13.2, -5.31, -5.27. **IR** (neat): 2954, 2928, 2856, 1709, 1254, 1104, 834, 775 cm^{-1}. **HRMS** *m/z*: ($[M+Na]^+$) calcd for $C_{19}H_{35}NO_2SiNa$ 360.2329; found 360.2327.

29 (endo) and 30 (exo): General procedure C was applied. *α*-Enaminone **28** (144 mg, 0.5 mmol) prepared according to General Procedure F and NaOMe (54 mg, 1.0 mmol) were mixed in dry MeCN (0.5 mL) at room temperature. The reaction mixture was refluxed at 100 °C for 1 h. The mixture was then concentrated in vacuo and the crude product was purified by flash chromatography (Silica gel, 5/95% ether/hexane) to yield 17% of **29** and 46% of **30** (18 mg and 48 mg respectively) as pale yellow oils.

10-Methyl-1-propyl-1-azaspiro[4.5]dec-9-en-6-one (29):

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.82-5.71 (m, 1H), 3.21-3.09 (m, 1H), 2.88-2.78 (m, 1H), 2.61-2.50 (m, 1H), 2.48-2.37 (m, 1H), 2.38-2.21 (m, 4H), 1.99-1.72 (m, 4H), 1.71 (s, 3H), 1.55-1.28 (m, 2H), 0.84 (t, J = 7.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 214.3, 138.9, 125.7, 73.3, 50.5, 50.4, 39.3, 34.4, 24.4, 22.7, 22.6, 17.7, 11.9. **IR** (neat): 2957, 2930, 2848, 1711, 1448, 1184, 1083, 807 cm^{-1}. **HRMS** *m/z*: ($[M+H]^+$) calcd for $C_{13}H_{22}NO$ 208.1696; found 208.1697.

10-Methylene-1-propyl-1-azaspiro[4.5]decan-6-one (30): ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.19-5.13 (m, 1H), 4.89-4.84 (m, 1H), 3.32-3.22 (m, 1H), 3.00-2.89 (m, 1H), 2.72-2.62 (m, 1H), 2.55 (dt, J = 14.0, 4.3 Hz, 1H), 2.48-2.29 (m, 4H), 2.17-2.03 (m, 1H), 1.95-1.72 (m, 4H), 1.64-1.50 (m, 2H), 1.46-1.36 (m, 1H), 0.86 (t, J = 7.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 213.5, 150.1, 109.4, 79.7, 51.8, 51.2, 40.5, 38.7, 33.6, 23.6, 22.9, 21.7, 11.9. **IR** (neat): 2955, 2934, 2870, 2843, 1708, 1457, 1100, 1082, 905 cm^{-1}. **HRMS** *m/z*: ($[M+H]^+$) calcd for $C_{13}H_{22}NO$ 208.1696; found 208.1696.

General procedure D: Synthesis of Quinolines and Quinolinols (1,2-addition). In a flame-dried 100 mL reaction flask flushed with nitrogen, fitted with a magnetic stirring bar and rubber septum a solution of SmI_2 in THF (0.1 M, 4.0 equiv.) was added dropwise (1 mL/min) to a solution of *α*-enaminone (1.0 equiv, 0.5 mmol), HMPA (10.0 equiv., 5.0 mmol) and *t*-BuOH (10.0 equiv., 5.0 mmol) in dry THF (0.05 M) at 0 °C. The reaction mixture was then stirred under inert atmosphere for 1 h at room temperature and quenched with aqueous saturated NH_4Cl. The mixture was extracted with EtOAc, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude mixture was purified by flash chromatography to yield the desired product.

1-Benzyl-8-ethyl-1,3,4,5,6,7-hexahydroquinolin-4a(2H)-ol (32a): General procedure D was applied. A solution of SmI_2 in THF (20.0 mL, 0.1 M, 2.0 mmol) was added dropwise to a solution of *α*-enaminone **31a** prepared according to General Procedure G, (199 mg, 0.5 mmol), HMPA (895 mg, 5.0 mmol), and *t*-BuOH (370 mg, 5.0 mmol) in dry THF (10.0 mL) at 0 °C. The reaction mixture was stirred under inert atmosphere for 1 h at room temperature and quenched with aqueous saturated NH_4Cl. The mixture was then dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash chromatography (Silica gel, 10/90% EtOAc/hexane) to yield **32a** in 43% yield (58 mg) as mixture of 2 diastereomers as yellow liquid. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.42-7.29 (m, 4H), 7.28-7.21 (m, 1H), 4.39 (d, *J* = 14.5 Hz, 1H), 3.83 (d, *J* = 14.3 Hz, 1H), 2.79-2.90 (m, 1H), 2.60 (t, *J* = 12.8, 2.9 Hz, 1H), 2.28 (q, *J* = 7.5 Hz, 2H), 2.17-2.02 (m, 2H), 2.01-1.79 (m, 2H), 1.79-1.71 (m, 1H), 1.59-1.70 (m, 2H), 1.56-1.38 (m, 2H), 1.29-1.14 (m, 1H), 0.99 (t, *J* = 7.6 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 142.4, 141.0, 130.1, 128.3, 128.1, 126.7, 69.4, 60.3, 48.1, 39.4, 39.3, 29.3, 24.8, 18.4, 18.1, 12.8. **IR** (neat): 2930, 2872, 1710, 1459, 942, 734, 697 cm^{-1}. **HRMS** *m/z*: ($[M+Na]^+$) calcd for $C_{18}H_{25}NONa$ 294.1828; found 294.1824.

8-Ethyl-1-propyl-1,3,4,5,6,7-hexahydroquinolin-4a(2H)-ol (32b): General procedure D was applied. A solution of SmI_2 in THF (20mL, 0.1 M, 2.0 mmol) was added dropwise to a solution of *α*-enaminone **31b** prepared according to General Procedure G, (175 mg, 0.5 mmol), HMPA (895 mg, 5.0 mmol), and *t*-BuOH (370 mg, 5.0 mmol) in dry THF (10.0 mL) at 0 °C. The reaction mixture was stirred under inert atmosphere for 1 h at room temperature and quenched with aqueous saturated NH_4Cl. The mixture was then dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash chromatography (Basic alumina, 5/95% EtOAc/hexane) to yield **32b** in 37% yield (41 mg) as mixture of 2 diastereomers as yellow liquid. **^{1}H NMR** (300 MHz, $CDCl_3$): Mixture of diastereomers: δ 3.09-2.92 (m, 2H), 2.70-2.58 (m, 2H), 2.16-2.06 (m, 3H), 2.04-1.95 (m, 2H), 1.86-1.71 (m, 2H), 1.61-1.53 (m, 2H), 1.52-1.38 (m, 4H), 1.34-1.24 (m, 2H), 0.95 (t, *J* = 7.6 Hz, 3H), 0.87 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): Major diastereomer: δ 142.7, 127.7, 69.3, 58.4, 49.2, 39.6, 38.9, 29.5, 25.1, 23.0, 19.6, 18.7, 13.0, 11.6. Minor diastereomer, characteristic signals: δ 79.9, 57.9, 53.6, 42.4, 34.7, 34.1, 23.6, 21.0, 19.4, 19.0, 12.1, 6.7. **IR** (neat): 3486, 2956, 2925, 2870, 1709, 1670, 1457, 1376, 1088 cm^{-1}. **HRMS** *m/z*: ($[M+H]^+$) calcd for $C_{14}H_{26}NO$ 224.2009; found 224.2014.

8-(4-Chlorophenyl)-1-propyl-1,2,3,4-tetrahydroquinoline (33a): General procedure D was applied. A solution of SmI_2 in THF (20.0 mL, 0.1 M, 2.0 mmol) was added dropwise to a solution of *α*-enaminone **31c** prepared according to General Procedure G, (216 mg, 0.5 mmol), HMPA (895 mg, 5.0 mmol), and *t*-BuOH (370 mg, 5.0 mmol) in dry THF (10.0 mL) at 0 °C. The reaction mixture was stirred under inert atmosphere for 1 h at room temperature and quenched with aqueous saturated NH_4Cl. The mixture was then dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash chromatography (Silica gel, 1/99% EtOAc/hexane) to yield **33a** in 30% yield (48 mg) as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.42-7.32 (m, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 7.15-7.01 (m, 1H), 6.67-6.53 (m, 1H), 6.47 (d, *J* = 7.5, 1.2 Hz, 1H), 3.35-3.21 (m, 4H), 2.57 (t, *J* = 6.3 Hz, 2H), 1.84 (p, *J* = 6.5 Hz, 2H), 1.71-1.62 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 146.0, 145.5, 140.9, 132.4, 130.5, 128.0, 126.6, 119.5, 116.9, 109.9, 53.7, 49.4, 26.6, 22.2, 19.5, 11.6. **IR** (neat): 2951, 2925, 2870, 1714, 1582, 1484, 1459, 1199, 1085, 1017, 831, 774, 719 cm^{-1}. **HRMS** *m/z*: ($[M+H]^+$) calcd for $C_{18}H_{21}ClN$ 286.1357; found 286.1365.

6. <u>General procedure E:</u> Preparation of precursors *α*-Iminones. <u>Napier et al:</u>[4c] A solution of epoxide precursor[11] (1.0 equiv.) and amine (1.5 equiv.) in 3:1 mixture of methanol: water was refluxed for 4 h. After cooling, the solvent was removed and the residue was diluted with saturated brine solution, extracted with EtOAc, dried (Na_2SO_4), filtered and concentrated in vacuo. The crude mixture was purified by flash chromatography to yield the desired product.

2-(propylamino)cyclohex-2-en-1-one (2a):[17] General procedure E was applied. The corresponding epoxide precursor 7-oxabicyclo[4.1.0]heptan-2-one (1.0 g, 9.0 mmol) and propylamine (800 mg, 13.5 mmol) were mixed in 9.0 mL of methanol, and 3.0 mL of water. The mixture was then refluxed for 4 h. After cooling, the solvent was removed and the residue was diluted with saturated brine solution, extracted with EtOAc, dried (Na_2SO_4), filtered and concentrated in vacuo. The crude product was purified by flash chromatography (Silica gel, 10/90% EtOAc/hexane) to yield the desired product in 63% yield (865 mg) as yellow liquid. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 5.32 (t, J = 4.7 Hz, 1H), 4.04 (s, 1H), 2.71 (t, J = 7.0 Hz, 2H), 2.42-2.32 (m, 2H), 2.28 (q, J = 5.6 Hz, 2H), 1.85 (p, J = 6.2 Hz, 2H), 1.50 (h, J = 7.3 Hz, 2H), 0.87 (t, J = 7.4 Hz, 3H). **^{13}C NMR** (75 MHz, CDCl3): δ 195.7, 140.6, 110.6, 44.9, 37.9, 24.5, 23.5, 22.1, 11.7. **IR** (neat): 3399, 2958, 2931, 2872, 1671, 1626, 1488, 1167, 867 cm^{-1}. **HRMS** *m/z*: ($[M+H]^+$) calcd for $C_9H_{16}NO$ 154.1226; found 154.1228.

2-((2-((*tert*-butyldimethylsilyl)oxy)ethyl)amino)cyclohex-2-en-1-one (2b): General procedure E was applied. The corresponding epoxide precursor 7-oxabicyclo[4.1.0]heptan-2-one (1.0 g, 9 mmol) and 2-((*tert*-butyl-dimethylsilyl)oxy)ethan-1-amine (1.9 g, 10.8 mmol) were mixed in 9.0 mL of methanol, and 3.0 mL of water. The mixture was then refluxed for 4 h. After cooling, the solvent was removed and the residue was diluted with brine solution, extracted with EtOAc, dried (Na_2SO_4), filtered and concentrated in vacuo. The crude product was purified by flash chromatography (Silica gel, 20/80% EtOAc/hexane) to yield the desired product in 44% yield (1.1g) as yellow liquid. **^{1}H NMR** (300 MHz, CDCl3): δ 5.43 (t, J = 4.7 Hz, 1H), 4.44 (s, 1H), 3.73 (t, J = 5.5 Hz, 2H), 2.92 (t, J = 5.5 Hz, 2H), 2.49-2.38 (m, 2H), 2.33 (q, J = 5.6 Hz, 2H), 1.91 (p, J = 6.1 Hz, 2H), 0.86 (s, 9H), 0.02 (s, 6H). **^{13}C NMR** (75 MHz, CDCl3): δ 195.6, 146.0, 140.6, 111.3, 61.3, 45.1, 37.9, 25.9, 24.5, 23.5, 18.3, -5.4. **IR** (neat): 2928, 2856, 1675, 1629, 1472, 1629, 1472, 1252, 1101, 830, 775 cm^{-1}. **HRMS** *m/z*: ($[M+H]^+$) calcd for $C_{14}H_{28}NO_2Si$ 270.1884; found 270.1887.

2-(isobutylamino)cyclohex-2-en-1-one (2c):[18] General procedure E was applied. The corresponding epoxide precursor 7-oxabicyclo[4.1.0]heptan-2-one (1.0 g, 9.0 mmol) and 2-methylpropan-1-amine (988 mg, 13.5 mmol) were mixed in 9.0 mL of methanol, and 3.0 mL of water. The mixture was then refluxed for 4 h. After cooling, the solvent was removed and the residue was diluted with brine solution, extracted with EtOAc, dried (Na_2SO_4), filtered and concentrated in vacuo. The crude product was purified by flash chromatography (Silica gel, 8/92% ether/hexane) to yield the desired product in 74% yield (1.1g) as light brown liquid. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 5.35 (t, *J* = 4.7 Hz, 1H), 4.15 (s, 1H), 2.64-2.55 (m, 2H), 2.46-2.37 (m, 2H), 2.32 (q, *J* = 5.6 Hz, 2H), 1.89 (p, *J* = 6.1 Hz, 2H), 1.81-1.72 (m, 1H), 0.89 (d, *J* = 6.7, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 195.8, 140.7, 110.5, 51.1, 37.9, 27.6, 24.5, 23.5, 20.6 (2C). **IR** (neat): 3403, 2953 ,2868, 2827, 1671, 1626, 1488, 1333, 1201, 1167, 1126, 866 cm^{-1}. **HRMS** *m/z*: ($[M+H]^+$) calcd for $C_{10}H_{18}NO$ 168.1383; found 168.1388.

2-(benzylamino)cyclohex-2-en-1-one (2d):[19] General procedure E was applied. The corresponding epoxide precursor 7-oxabicyclo[4.1.0]heptan-2-one (900 mg, 8.0 mmol) and benzylamine (1.71 g, 16.0 mmol) were mixed in 8.0 mL of methanol, and 2.3 mL of water. The mixture was then refluxed for 4 h. After cooling, the solvent was removed and the residue was diluted with saturated brine solution, extracted with EtOAc, dried (Na_2SO_4), filtered and concentrated in vacuo. The crude product was purified by flash chromatography (Silica gel, 20/80% EtOAc/hexane) to yield the desired product in 32% yield (1.02 g) as pale green solid (**M.p.** 56-59 °C). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.20-7.36 (m, 5H), 5.42 (t, *J* = 4.7 Hz, 1H), 4.60 (s, 1H), 4.08 (d, *J* = 4.3 Hz, 2H), 2.59-2.41 (m, 2H), 2.33 (q, *J* = 5.6 Hz, 2H), 1.94 (p, *J* = 6.3 Hz, 2H). **^{13}C NMR** (75 MHz, CDCl3): δ 195.8, 140.4, 139.0, 128.5, 127.4, 127.1, 111.8, 47.6, 37.9, 24.5, 23.5. **IR** (neat): 3407, 2928, 1659, 1619, 1488, 1361, 1208, 742, 700 cm^{-1}. **HRMS** *m/z*: ($[M+H]^+$) calcd for $C_{13}H_{16}NO$ 202.1226; found 202.1224.

3-ethyl-2-(propylamino)cyclohex-2-en-1-one (14a): General procedure E was applied. The corresponding epoxide precursor 6-Ethyl-7-oxabicyclo[4.1.0]heptan-2-one (1.42 g, 10.1 mmol) and propylamine (0.89 g, 15.2 mmol) were mixed in 10.0 mL of methanol, and 3.3 mL of water. The mixture was then refluxed for 4 h. After cooling, the solvent was removed and the residue was diluted with saturated brine solution, extracted with EtOAc, dried (Na_2SO_4), filtered and concentrated in vacuo. The crude product was purified by flash chromatography (Silica gel, 10/90%

EtOAc/hexane) to yield the desired product in 48% yield (880 mg) as yellow liquid. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 3.69 (s, 1H), 2.64 (t, *J* = 7.1 Hz, 2H), 2.38-2.15 (m, 6H), 1.87-1.69 (m, 2H), 1.39 (q, *J* = 7.3 Hz, 2H), 1.01 (t, *J* = 7.6 Hz, 3H), 0.82 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 196.6, 143.4, 139.5, 51.3, 37.1, 28.9, 26.2, 23.6, 22.1, 11.6, 11.5. **IR** (neat): 3337, 2960, 2874, 1662, 1625, 1486, 1168 cm^{-1}. **HRMS** *m/z*: ($[M+H]^+$) calcd for $C_{11}H_{20}NO$ 182.1539; found 182.1539.

2-(benzylamino)-3-ethylcyclohex-2-en-1-one (14b): General procedure E was applied. The corresponding epoxide precursor 6-Ethyl-7-oxabicyclo[4.1.0]heptan-2-one (2.1 g, 15.0 mmol) and of benzylamine (2.4 g, 22.5 mmol) were mixed in 15.0 mL of methanol, and 5.0 mL of water. The mixture was then refluxed for 4 h. After cooling, the solvent was removed and the residue was diluted with saturated brine solution, extracted with EtOAc, dried (Na_2SO_4), filtered and concentrated in vacuo. The crude product was purified by flash chromatography (Silica gel, 10/90% EtOAc/hexane) to yield the desired product in 58% yield (1.99 g) as yellow liquid. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.35-7.20 (m, 5H), 3.95 (s, 2H), 2.29-2.45 (m, 6H), 1.96-1.76 (m, 2H), 1.11 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 197.0, 141.0, 138.8, 128.9, 128.1, 128.0, 127.1, 48.3, 37.2, 32.0, 23.0, 22.3, 11.3. **IR** (neat): 2965, 2935, 2875, 1660, 1624, 1453, 1184, 1161, 734, 697 cm^{-1}. **HRMS** *m/z*: ($[M+Na]^+$) calcd for $C_{15}H_{19}NONa$ 252.1364; found 252.1357.

2-((2-((*tert*-butyldimethylsilyl)oxy)ethyl)amino)-3-ethylcyclohex-2-en-1-one (14c): General procedure E was applied. The corresponding epoxide precursor 6-ethyl-7-oxabicyclo[4.1.0]heptan-2-one (1.3 g, 9.4 mmol) and 2-((*tert*-butyldimethylsilyl)oxy)ethan-1-amine (2.46 g, 14.1 mmol) were mixed in 9.0 mL of methanol, and 3.0 mL of water. The mixture was then refluxed for 4 h. After cooling, the solvent was removed and the residue was diluted with saturated brine solution, extracted with EtOAc, dried (Na_2SO_4), filtered and concentrated in vacuo. The crude product was purified by flash chromatography (Silica gel, 1:1 DCM/hexane) to yield the desired product in 41% yield (1.17 g) as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 3.68 (t, *J* = 5.6 Hz, 2H), 2.91 (t, *J* = 5.6

Hz, 2H), 2.48-2.24 (m, 6H), 1.91 (q, *J* = 6.3 Hz, 2H), 1.10 (t, *J* = 7.5 Hz, 3H), 0.91 (d, *J* = 2.2 Hz, 9H), 0.06 (d, *J* = 2.1 Hz, 6H).**13C NMR** (75 MHz, $CDCl_3$): δ 196.4, 143.4, 139.4, 62.5, 51.0, 37.3, 29.1, 26.2, 25.9, 22.2, 18.3, 11.7, -5.4. **IR** (neat): 2952, 2928, 2856, 1666, 1627, 1462, 1253, 1103, 830, 774 cm^{-1}. **HRMS** *m/z*: ($[M+H]^+$) calcd for $C_{16}H_{32}NO_2Si$ 298.2197; found 298.2196.

3-ethyl-2-((thiophen-2-ylmethyl)amino)cyclohex-2-en-1-one (14d): General procedure E was applied. The corresponding epoxide precursor 6-ethyl-7-oxabicyclo[4.1.0]heptan-2-one (1.4 g, 10.0 mmol) and thiophen-2-ylmethanamine (1.7 g 15.0 mmol) were mixed in 10.0 mL of methanol, and 3.3 mL of water. The mixture was then refluxed for 4 h. After cooling, the solvent was removed and the residue was diluted with saturated brine solution, extracted with EtOAc, dried (Na_2SO_4), filtered and concentrated in vacuo. The crude product was purified by flash chromatography (Silica gel, 60/40% DCM/hexane) to yield the desired product in 48% yield (1.13 g) as yellow liquid. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.15 (dd, *J* = 4.9, 1.5 Hz, 1H), 6.97-6.80 (m, 2H), 4.18 (s, 1H), 4.12 (s, 2H), 2.39 (q, *J* = 7.0 Hz, 6H), 1.87 (p, *J* = 6.3 Hz, 2H), 1.11 (t, *J* = 7.6 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 196.5, 145.8, 143.4, 138.6, 126.6, 124.9, 124.3, 47.7, 37.2, 29.0, 26.3, 22.1, 11.6. **IR** (neat): 3319, 2930, 2872, 1656, 1619, 1464, 1160, 697 cm^{-1}. **HRMS** *m/z*: ($[M+Na]^+$) calcd for $C_{13}H_{17}NOSNa$ 258.0923; found 258.0923.

2-(propylamino)-5,6-dihydro-[1,1'-biphenyl]-3(4H)-one (16a): General procedure E was applied. The corresponding epoxide precursor 6-Phenyl-7-oxabicyclo[4.1.0]heptan-2-one (1.2 g, 6.3 mmol) and propylamine (560 mg, 9.5 mmol) were mixed in 6.0 mL of methanol, and 2.0 mL of water. The mixture was then refluxed for 4 h. After cooling, the solvent was removed and the residue was diluted with saturated brine solution, extracted with EtOAc, dried (Na_2SO_4), filtered and concentrated in vacuo. The crude product was purified by flash chromatography (Silica gel, 10/90% EtOAc/hexane) to yield the desired product in 48% yield (630 mg) as yellow liquid. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.44-7.39 (m, 2H), 7.33 (t, *J* = 7.7 Hz, 2H), 7.26-7.19 (m, 1H), 4.27 (s, 1H), 2.67 (t, *J* = 6.0 Hz, 2H), 2.58-2.46 (m, 2H), 2.32 (t, *J* = 7.0 Hz, 2H), 2.03 (q, *J* = 6.4 Hz, 2H), 1.27 (h, *J*

= 7.2 Hz, 2H), 0.69 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 197.0, 141.0, 138.8, 128.9, 128.1, 128.0, 127.1, 48.3, 37.2, 32.0, 23.0, 22.3, 11.3. **IR** (neat): 3341, 2956, 2920, 2859, 1660, 1468, 1328, 1187, 1128, 765, 670 cm^{-1}. **HRMS** *m/z*: ($[M+H]^+$) calcd for $C_{15}H_{20}NO$ 230.1538; found 230.1539.

4'-chloro-2-(propylamino)-5,6-dihydro-[1,1'-biphenyl]-3(4H)-one (16b): General procedure E was applied. The corresponding epoxide precursor 6-(4-chlorophenyl)-7-oxabicyclo[4.1.0]heptan-2-one (1.59 g, 7.15 mmol) and propylamine (610 mg, 10.7 mmol) in 7.5 mL of methanol, and 2.5 mL of water. The mixture was then refluxed for 4 h. After cooling, the solvent was removed and the residue was diluted with saturated brine solution, extracted with EtOAc, dried (Na_2SO_4), filtered and concentrated in vacuo. The crude product was purified by flash chromatography (Silica gel, 10/90% EtOAc/hexane) to yield the desired product in 66% yield (1.24 g) as orange paste. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.37 (d, *J* = 8.6 Hz, 2H), 7.33-7.25 (m, 2H), 4.28 (s, 1H), 2.64 (t, *J* = 6.0 Hz, 2H), 2.57-2.44 (m, 2H), 2.32 (t, *J* = 6.9 Hz, 2H), 2.01 (p, *J* = 6.4 Hz, 2H), 1.28 (h, *J* = 7.1 Hz, 2H), 0.71 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 196.8, 139.3, 139.1, 132.6, 129.5, 128.3, 126.7, 48.5, 37.1, 31.7, 23.0, 22.2, 11.3. **IR** (neat): 3351, 2956, 2927, 2873, 1662, 1608, 1488, 1191, 1091, 1016, 217, 691 cm^{-1}. **HRMS** *m/z*: ($[M+Na]^+$) calcd for $C_{15}H_{18}ClNONa$ 286.0969; found 286.0981.

General procedure F: Synthesis of stable *α*-enaminones (General structure 27; Table 5). According to Sinha et al.[20] To a stirred solution of amine (1.0 equiv.) in THF (1 M) was added anhydrous K_2CO_3 (2 equiv.) followed by dibromopropane (10.0 equiv.) at room temperature and the resultant mixture was refluxed for 16 h. The crude mixture was then filtered and concentrated in vacuo and purified by flash chromatography to yield the desired product.

2-((3-bromopropyl)(propyl)amino)-4'-chloro-5,6-dihydro-[1,1'-biphenyl]-3(4H)-one (21a):

General procedure F was applied. *α*-Iminone **16b** (1.0 g, 3.8 mmol) prepared according to General Procedure E, anhydrous K_2CO_3 (1.05 g, 7.6 mmol), dibromopropane (7.6 g, 38.0 mmol) were mixed in THF (4.0 mL). The resultant mixture was refluxed for 16 h. After cooling, the reaction mixture was filtered and concentrated in vacuo. The crude mixture was purified by flash chromatography (Silica gel, 8/92% EtOAc/hexane) to yield the desired product in 54% yield (800 mg) as yellow liquid **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.33 (d, *J* = 8.3 Hz, 2H), 7.24 (d, *J* = 8.3 Hz, 2H), 3.11 (t, *J* = 6.6 Hz, 2H), 2.80 (t, *J* = 6.7 Hz, 2H), 2.61-2.73 (m, 4H), 2.51 (t, 2H), 2.04 (p, *J* = 6.5 Hz, 2H), 1.72 (p, *J* = 6.7 Hz, 2H), 1.35-1.14 (m, 2H), 0.72 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (75 MHz, CDCl3): δ 199.3, 151.7, 142.3, 139.1, 133.5, 129.1, 128.1, 55.5, 51.3, 39.6, 32.7, 32.1, 31.8, 22.4, 21.8, 11.6. **IR** (neat): 2956, 2930, 2869, 1670, 1489, 1091, 1016, 823, 699 cm^{-1}. **HRMS** *m/z*: ($[M+Na]^+$) calcd for $C_{18}H_{23}{}^{81}BrClNONa$ 408.0524; found 408.0523.

2-((3-bromopropyl)(propyl)amino)-5,6-dihydro-[1,1'-biphenyl]-3(4H)-one (21b): General procedure F was applied. *α*-Iminone **16a** (600 mg, 2.62 mmol) prepared according to General Procedure E, anhydrous K_2CO_3 (725 mg, 5.24 mmol), dibromopropane (5.3 g, 26.0 mmol) were mixed in THF (2.6 mL). The resultant mixture was refluxed for 16 h. After cooling, the reaction mixture was filtered and concentrated in vacuo. The crude mixture was purified by flash chromatography (Silica gel, 20/80% Ether/hexane) to yield the desired product in 81% yield (730 mg) as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.43-7.17 (m, 5H), 3.01 (t, *J* = 6.6 Hz, 2H), 2.78 (t, *J* = 6.6 Hz, 2H), 2.69 (td, *J* = 6.8, 6.1, 3.9 Hz, 4H), 2.50 (dd, *J* = 7.5, 5.9 Hz, 2H), 2.08-1.98 (m, 2H), 1.69 (p, *J* = 6.6 Hz, 2H), 1.30-1.23 (m, 2H), 0.71 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 199.5, 153.6, 142.0, 140.8, 127.9, 127.7, 127.6, 55.7, 51.2, 39.7, 33.0, 32.2, 31.9, 22.5, 21.8, 11.6. **IR** (neat): 2955, 2927, 2869, 1667, 1449, 1180, 1116, 753, 697 cm^{-1}. **HRMS** *m/z*: ($[M+Na]^+$) calcd for $C_{18}H_{24}BrNONa$ 372.0933; found 372.0931.

2-((3-bromopropyl)(thiophen-2-ylmethyl)amino)-5,6-dihydro-[1,1'-biphenyl]-3(4H)-one (21c): General procedure F was applied. The corresponding *α*-iminone 2-((thiophen-2-ylmethyl)-amino)-5,6-dihydro-[1,1'-biphenyl]-3(4H)-one (982 mg, 3.47 mmol), anhydrous K_2CO_3 (994 mg, 6.94 mmol), dibromopropane (7 g, 34.7 mmol) were mixed in THF (3.5 mL). The resultant mixture was refluxed for 16 h. After cooling, the reaction mixture was filtered and concentrated in vacuo. The crude mixture was purified by flash chromatography (Silica gel, 1:1 DCM/hexane) to yield the desired product in 16 % yield (218 mg) as pale yellow solid (**M.p.** 72-75 °C). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.43-7.29 (m, 3H), 7.22-7.12 (m, 3H), 6.90-6.82 (m, 1H), 6.81-6.76(m, 1H), 4.24 (s, 2H), 2.90 (t, J = 6.9 Hz, 2H), 2.79 (t, J = 6.5 Hz, 2H), 2.71 (t, J = 6.0 Hz, 2H), 2.59-2.51 (m, 2H), 2.06 (p, J = 6.2 Hz, 2H), 1.64 (p, J = 6.8 Hz, 2H).**^{13}C NMR** (75 MHz, $CDCl_3$): δ 199.3, 156.0, 143.2, 141.1, 140.3, 128.1, 127.9, 127.5, 126.2, 125.0, 53.0, 50.1, 39.7, 33.2, 32.1, 31.9, 22.4. **IR** (neat): 2951, 2926, 2850, 1662, 1610, 1211, 755, 698 cm^{-1}. **HRMS** *m/z*: ($[M+Na]^+$) calcd for $C_{20}H_{22}{}^{81}BrNOSNa$ 428.0485; found 428.0485.

2-((3-bromopropyl)(thiophen-2-ylmethyl)amino)-3-ethylcyclohex-2-en-1-one (25a): General procedure F was applied. *α*-Iminone **14d** (705 mg, 3.0 mmol) prepared according to General Procedure E, anhydrous K_2CO_3 (830 mg, 6.0 mmol), dibromopropane (6.1 g, 30.0 mmol) were mixed in THF (3.0 mL). The resultant mixture was refluxed for 16 h. After cooling, the reaction mixture was filtered and concentrated in vacuo. The crude mixture was purified by flash chromatography (Silica gel, 10/90% EtOAc/hexane) to yield the desired product in 50% yield (543 mg) as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.17 (dd, J = 5.1, 1.3 Hz, 1H), 6.85-6.91(m, 1H), 6.91-6.80 (m, 1H), 4.19 (s, 2H), 3.35 (t, J = 6.9 Hz, 2H), 3.01 (t, J = 7.0 Hz, 2H), 2.51 (q, J = 9.5, 8.6 Hz, 2H), 2.36 (dt, J = 8.9, 6.4 Hz, 4H), 1.86 (dp, J = 13.9, 6.7 Hz, 4H), 0.97 (t, J = 7.6 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 198.3, 164.2, 144.4, 140.5, 126.3, 125.6, 124.6, 53.6, 51.3, 39.6, 32.4, 31.8, 29.3, 26.4, 22.3, 12.0. **IR** (neat): 2924, 2861, 1667, 1129, 910, 729, 702 cm^{-1}. **HRMS** *m/z*: ($[M+Na]^+$) calcd for $C_{16}H_{22}BrNOSNa$ 378.0498; found 378.0495.

2-((3-bromopropyl)(propyl)amino)-3-ethylcyclohex-2-en-1-one (25b): General procedure F was applied. *α*-Iminone **14a** (740 mg, 4.0 mmol) prepared according to General Procedure E, anhydrous K_2CO_3 (1.1 g, 8.0 mmol), dibromopropane (8.28 g, 40.0 mmol) were mixed in THF (4.0 mL). The resultant mixture was refluxed for 16 h. After cooling, the reaction mixture was filtered and concentrated in vacuo. The crude mixture was purified by flash chromatography (Silica gel, 10/90% ether/hexane) to yield the desired product in 69% yield (857 mg) as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 3.39 (t, *J* = 6.8 Hz, 2H), 2.94 (t, *J* = 6.9 Hz, 2H), 2.79-2.67 (m, 2H), 2.49 (q, *J* = 7.6 Hz, 2H), 2.29-2.40 (m, 4H), 1.85 (dp, *J* = 13.6, 6.5 Hz, 4H), 1.28 (dq, *J* = 15.4, 7.7 Hz, 2H), 1.01 (t, *J* = 7.6 Hz, 3H), 0.80 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 198.4, 162.8, 141.1, 56.4, 52.3, 39.8, 32.6, 32.1, 29.2, 26.2, 22.4, 22.4, 12.0, 11.8. **IR** (neat): 2957, 2933, 2870, 1667, 1611, 1457, 1218, 1117, 776 cm^{-1}. **HRMS** *m/z*: ($[M+H]^+$) calcd for $C_{14}H_{25}BrNO$ 302.1114; found 302.1113.

2-(benzyl(3-bromopropyl)amino)-3-ethylcyclohex-2-en-1-one (25c): General procedure F was applied. *α*-Iminone **14b** (1.2 g, 5.24 mmol) prepared according to General Procedure E, anhydrous K_2CO_3 (1.45 g, 10.48 mmol), dibromopropane (10.6 g, 52.0 mmol) were mixed in THF (5.0 mL). The resultant mixture was refluxed for 16 h. After cooling, the reaction mixture was filtered and concentrated in vacuo. The crude mixture was purified by flash chromatography (Silica gel, 15/85% ether/hexane) to yield enaminone in 70% yield (1.26 g) as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.36-7.13 (m, 5H), 4.00 (s, 2H), 3.35 (t, *J* = 6.9 Hz, 2H), 3.01 (t, *J* = 7.0 Hz, 2H), 2.32-2.45 (m, 4H), 2.27 (t, *J* = 6.1 Hz, 2H), 1.92-1.77 (m, 4H), 0.85 (t, *J* = 7.6 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 198.5, 163.6, 140.5, 139.9, 129.1, 128.0, 126.8, 58.6, 51.8, 39.7, 32.5, 31.8, 29.2, 26.2, 22.3, 11.7. **IR** (neat): 2959, 2935, 2863, 1664, 1610, 1453, 1130, 728, 699 cm^{-1}. **HRMS** *m/z*: ($[M+Na]^+$) calcd for $C_{18}H_{24}BrNO$ 372.0934; found 372.0940.

2-((3-bromopropyl)(4-methoxybenzyl)amino)-3-ethylcyclohex-2-en-1-one (25d): General procedure F was applied. The corresponding *α*-iminone 3-ethyl-2-((4-methoxybenzyl)amino)cyclohex-2-en-1-one (2.92 mg, 1.13 mmol) prepared according to General Procedure E, anhydrous K_2CO_3 (390 mg, 2.25 mmol), dibromopropane (2.25 g, 11.13 mmol) and THF (1.1 mL). The resultant mixture was refluxed for 16 h. After cooling, the reaction mixture was filtered and concentrated in vacuo. The crude mixture was purified by flash chromatography (Silica gel, 10/90% ether/hexane) to yield enaminone in 73 % yield (340 mg) as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.14 (d, J = 8.5 Hz, 2H), 6.79 (d, J = 8.6 Hz, 2H), 3.95 (s, 2H), 3.77 (s, 3H), 3.36 (t, J = 6.9 Hz, 2H), 3.00 (t, J = 6.9 Hz, 2H), 2.45-2.33 (m, 4H), 2.27 (t, J = 6.1 Hz, 2H), 1.90-1.81 (m, 4H), 0.88 (t, J = 7.6 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 198.5, 163.5, 158.5, 140.4, 132.0, 130.3, 113.4, 57.9, 55.2, 51.7, 39.8, 32.5, 31.9, 29.2, 26.2, 22.3, 11.7. **IR** (neat): 2935, 2835, 1663, 1610, 1510, 1245, 1172, 1034, 835, 814 cm^{-1}. **HRMS** *m/z*: ($[M+Na]^+$) calcd for $C_{19}H_{26}BrNO_2Na$ 402.1039; found 402.1038.

2-((3-bromopropyl)(2-((*tert*-butyldimethylsilyl)oxy)ethyl)amino)-3-ethyl-cyclohex-2-en-1-one (25e): General procedure F was applied. *α*-Iminone **14c** (1.17 g, 3.84 mmol) prepared according to General Procedure E, anhydrous K_2CO_3 (1.06 g, 7.7 mmol), dibromopropane (7.95 g, 38.4 mmol) and THF (4.0 mL). The resultant mixture was refluxed for 16 h. After cooling, the reaction mixture was filtered and concentrated in vacuo. The crude mixture was purified by flash chromatography (Silica gel, 10/90% ether/hexane) to yield enaminone in 83 % yield (946 mg) as pale yellow liquid. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 3.52 (t, J = 6.4 Hz, 2H), 3.45 (t, J = 6.7 Hz, 2H), 2.96 (dt, J = 19.0, 6.6 Hz, 4H), 2.54 (q, J = 7.7 Hz, 2H), 2.38 (t, J = 6.4 Hz, 4H), 1.88 (dp, J = 13.7, 6.6 Hz, 4H), 1.04 (t, J = 7.6 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 198.1, 163.0, 141.4, 62.3, 56.8, 52.6, 39.7, 32.8, 32.1, 29.2, 26.1, 25.9, 22.4, 18.3, 12.0, -5.3. **IR** (neat): 2952, 2928, 2855, 1670, 1462, 1255, 1099, 939, 832, 774 cm^{-1}. **HRMS** *m/z*: ($[M+Na]^+$) calcd for $C_{19}H_{36}BrNO_2SiNa$ 442.1570; found 442.1572.

2-((3-bromopropyl)(propyl)amino)-3-methylcyclohex-2-en-1-one (28): General procedure F was applied. The corresponding *α*-iminone 3-methyl-2-(propylamino)cyclohex-2-en-1-one (330 mg, 1.98 mmol), anhydrous K_2CO_3 (545 mg, 3.96 mmol), dibromopropane (3.87, 19.8 mmol) were mixed in THF (2.0 mL). The resultant mixture was refluxed for 16 h. After cooling, the reaction mixture was filtered and concentrated in vacuo. The crude product was purified by flash chromatography (Silica gel, 10/90% EtOAc/hexane) to yield enaminone in 79% yield (448 mg) as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 3.42 (t, *J* = 6.8 Hz, 2H), 2.97 (t, *J* = 6.8 Hz, 2H), 2.76 (t, *J* = 7.6 Hz, 2H), 2.44-2.34 (m, 4H), 1.99 (s, 3H), 1.92-179 (m, 4H), 1.30 (h, *J* = 7.8 Hz, 2H), 0.81 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 198.1, 157.7, 141.7, 56.2, 52.0, 39.8, 32.5, 32.4, 32.2, 22.3, 22.2, 20.5, 11.8. **IR** (neat): 2930, 2869, 1667, 1429, 1252, 1219, 1121 cm^{-1}. **HRMS** *m/z*: ($[M+Na]^+$) calcd for $C_{13}H_{22}BrNONa$ 310.0777; found 310.0776.

General procedure G: *α*-Enaminone (1.0 equiv.) and NaI (5.0 equiv.) were dissolved in acetone (0.5 M). The solution was stirred for 3 h at room temperature. The suspension was filtered and the filtrate was concentrated in vacuo. The crude mixture was purified by flash chromatography to yield the desired product.[21]

2-(benzyl(3-iodopropyl)amino)-3-ethylcyclohex-2-en-1-one (31a): General procedure G was applied. *α*-Enaminone **25c** (1.05 g, 3.0 mmol) prepared according to General Procedure F and NaI (2.25 g, 15.0 mmol) were dissolved in acetone (6.0 mL). The solution was stirred for 3 h at room temperature. The suspension was filtered and the filtrate was concentrated in vacuo. The crude mixture was purified by flash chromatography (Silica gel, 15/85% ether/hexane) to yield iodo-enaminone in 89 % yield (1.06 g) as yellow liquid **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.31-7.13 (m, 5H), 4.00 (s, 2H), 3.12 (*t*, *J* = 7.1 Hz, 2H), 2.97 (t, *J* = 7.0 Hz, 2H), 2.39 (dt, *J* = 16.5, 7.3 Hz, 4H), 2.28 (t, *J* = 6.1 Hz, 2H), 1.93-1.72 (m, 4H), 0.86 (t, *J* = 7.7 Hz, 3H). **^{13}C NMR** δ 198.5, 163.5, 140.5, 139.9, 129.1, 128.0, 126.8, 58.7, 53.8, 39.7, 33.3, 29.2, 26.2, 22.3, 11.7, 4.5. **IR** (neat): 2935, 2863, 1664, 1453, 1193, 1131, 728, 699 cm^{-1}. **HRMS** *m/z*: ($[M+Na]^+$) calcd for $C_{18}H_{24}INONa$ 420.0795; found 420.0794.

2-((3-iodopropyl)(propyl)amino)-3-ethylcyclohex-2-en-1-one (31b): General procedure G was applied. *α*-Enaminone **25b** (602 mg, 2.0 mmol) prepared according to General Procedure F and NaI (1.50 g, 10.0 mmol) were dissolved in acetone (4.0 mL). The solution was stirred for 3 h at room temperature. The suspension was filtered and the filtrate was concentrated in vacuo. The crude mixture was purified by flash chromatography (Silica gel, 10/90% ether/hexane) to yield iodo-enaminone in 94 % yield (660 mg) as yellow liquid. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 3.15 (t, *J* = 7.0 Hz, 2H), 2.88 (t, *J* = 6.9 Hz, 2H), 2.73 (t, *J* = 8.7, 6.7 Hz, 2H), 2.49 (q, *J* = 7.6 Hz, 2H), 2.38-2.30 (m, 4H), 1.93-1.75 (m, 4H), 1.28 (h, *J* = 7.8 Hz, 2H), 1.01 (t, *J* = 7.6 Hz, 3H), 0.79 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 198.4, 162.8, 141.1, 56.5, 54.3, 39.8, 33.4, 29.2, 26.2, 22.5, 22.4, 12.0, 11.8, 5.0. **IR** (neat): 2956, 2932, 2870, 1667, 1456, 1200, 1172, 1115 cm^{-1}. **HRMS** *m/z*: ($[M+Na]^+$) calcd for $C_{14}H_{24}INONa$ 372.0794; found 372.0795.

2-((3-iodopropyl)(propyl)amino)-4'-chloro-5,6-dihydro-[1,1'-biphenyl]-3(4H)-one (31c): General procedure G was applied. *α*-Enaminone **21a** (260 mg, 0.67 mmol) prepared according to General Procedure F and NaI (500 mg, 3.35 mmol) were dissolved in acetone (1.4 mL). The solution was stirred for 3 h at room temperature. The suspension was filtered and the filtrate was concentrated in vacuo. The crude mixture was purified by flash chromatography (Silica gel, 5/95% ether/hexane) to yield 2-((3-iodopropyl)(propyl)amino)-4'-chloro-5,6-dihydro-[1,1'-biphenyl]-3(4H)-one in 93 % yield (269 mg) as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.35 (d, *J* = 8.7 Hz, 2H), 7.29-7.22 (m, 2H), 2.90 (t, *J* = 6.8 Hz, 2H), 2.78-2.63 (m, 6H), 2.55-2.49 (m, 2H), 2.05 (p, *J* = 6.3 Hz, 2H), 1.70 (p, *J* = 6.8 Hz, 2H), 1.37-1.21 (m, 2H), 0.73 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 199.3, 151.4, 142.4, 139.1, 133.5, 129.1, 128.1, 55.5, 53.3, 39.6, 32.7, 32.6, 22.4, 21.8, 11.6, 5.2. **IR** (neat): 2955, 2929, 2666, 1670, 1489, 1201, 1090, 822, 731 cm^{-1}. **HRMS** *m/z*: ($[M+Na]^+$) calcd for $C_{18}H_{23}ClNOINa$ 454.0405; found 454.0407.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

X-ray crystallographic data for **3d** (CIF)

X-ray crystallographic data for **17a** (CIF)

The spectra for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(12) All attempts to increase the conversion rate by elevating the temperature or prolonging the reaction time resulted in decomposition of starting materials.

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(14) The thermodynamic experiment was conducted at a lower temperature, for longer time; NaO*t*-Bu rather than NaOMe was used to avoid the side product formation from a 1,2-nuleophilic addition of the methoxide to the carbonyl group of products.

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