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Axially Chiral Enamides: Substituent Effects, Rotation Barriers, and Implications for their Cyclization Reactions

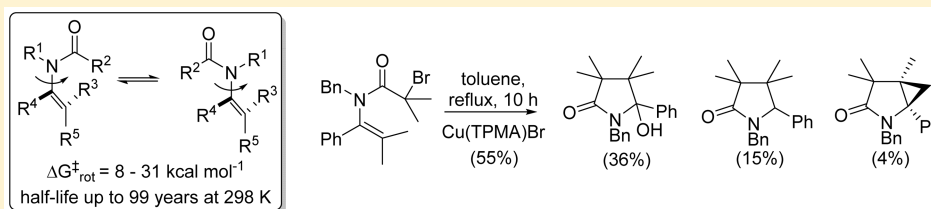
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S Supporting Information



ABSTRACT: The barrier to rotation around the *N*-alkenyl bond of 38 *N*-alkenyl-*N*-alkylacetamide derivatives was measured (ΔG^{\ddagger} rotation varied between <8.0 and $31.0 \text{ kcal mol}^{-1}$). The most important factor in controlling the rate of rotation was the level of alkene substitution, followed by the size of the nitrogen substituent and, finally, the size of the acyl substituent. Tertiary enamides with four alkenyl substituents exhibited half-lives for rotation between 5.5 days and 99 years at 298 K, sufficient to isolate enantiomerically enriched atropisomers. The radical cyclizations of a subset of *N*-alkenyl-*N*-benzyl- α -haloacetamides exhibiting relatively high barriers to rotation round the *N*-alkenyl bond (ΔG^{\ddagger} rotation $>20 \text{ kcal mol}^{-1}$) were studied to determine the regiochemistry of cyclization. Those with high barriers ($>27 \text{ kcal mol}^{-1}$) did not lead to cyclization, but those with lower values produced highly functionalized γ -lactams via a *S*-endo-trig radical-polar crossover process that was terminated by reduction, an unusual cyclopropanation sequence, or trapping with H_2O , depending upon the reaction conditions. Because elevated temperatures were necessary for cyclization, this precluded study of the asymmetric transfer in the reaction of individual atropisomers. However, enantiomerically enriched atropisomeric enamides should be regarded as potential asymmetric building blocks for reactions that can be accomplished at room temperature.

INTRODUCTION

In recent years, the bond rotational dynamics, asymmetric synthesis, and reactions of nonbiaryl atropisomers have received considerable attention.^{1–3} The majority of work has focused on the chemistry of anilides **1a**^{4–9} and benzamides **1b**,^{10–14} where the amide group is perpendicular to the plane of the aryl system (Figure 1). In 2,6-disubstituted anilide derivatives **1a** (R^3 or $\text{R}^4 \neq \text{H}$) rotation around the *N*-aryl bond is slow enough for atropisomers to be separated at room temperature, and axially chiral anilides **1a** have been shown to undergo a range of reactions with transfer of chirality.³ Secondary enamides are valuable synthetic intermediates,^{15,16} but the chemistry of tertiary enamides **1c** has received much less attention.^{17,18} Systems with small substituents **2** (e.g., $\text{R}^1 = \text{R}^2 = \text{Me}$) may be planar in the ground state, but if substituents R^1 and R^2 are large enough or the alkene is substituted ($\text{R}^3 = \text{R}^4 = \text{R}^5 \neq \text{H}$), then enamides **1c** have the potential to exhibit axial chirality. Theoretically, if the rotation barrier around the *N*-

alkenyl bond is high enough, then individual atropisomers may be separated and their chemistry studied.

The rotation dynamics of tertiary enamides can be complicated because of restricted rotation around both the amide *N*-CO [(*E*)-*syn* **2** \rightarrow (*Z*)-*syn* **2**] and the *N*-alkenyl bonds [(*E*)-*syn* **2** \rightarrow (*E*)-*anti* **2**] (Figure 1). The barrier to rotation around the amide *N*-CO bond for **2a** ($\text{R}^1 = \text{R}^2 = \text{Me}$) has been measured at $14.0 \text{ kcal mol}^{-1}$ and is slightly lower¹⁹ than the general value for amides ($15\text{--}20 \text{ kcal mol}^{-1}$).²⁰ *N*-Cycloalkenyl-*N*-alkylacetamides such as **3** generally prefer the amide *N*-CO *E*-rotamer²¹ and exhibit transient axial chirality on the NMR time scale. This makes analysis of the rotational dynamics around the *N*-alkenyl bond relatively easy to study by VT ¹H NMR.²¹ In this paper we report studies into the effect of substitution (**1c**, R^1 , R^2 , R^3 , R^4 , and R^5) on the barriers to rotation around the *N*-alkenyl bond of tertiary enamides and

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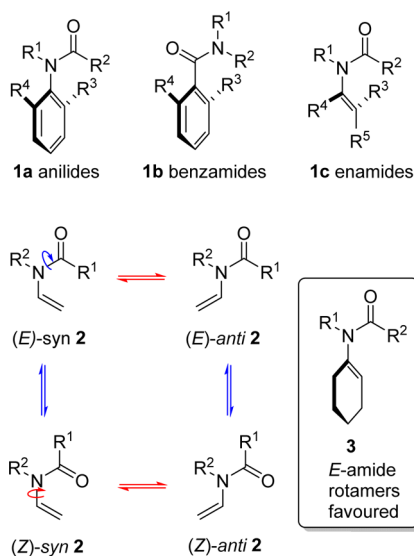


Figure 1. Structures of some axially chiral molecules and conformations of tertiary enamides **2**.

show that it is possible to separate individual enamide atropisomers at room temperature with half-lives ($t_{1/2}$) of up to 99 years at 298 K. We probe the ability of a subset of sterically congested racemic α -halogenated tertiary enamides with relatively high barriers to rotation ($\Delta G_{298 \text{ rot}}^\ddagger > 20 \text{ kcal mol}^{-1}$) to undergo *5-endo-trig* radical cyclization. Those with high barriers ($\Delta G_{298 \text{ rot}}^\ddagger > 27 \text{ kcal mol}^{-1}$) do not lead to cyclization, but those with lower values ($27 \text{ kcal mol}^{-1} > \Delta G_{298 \text{ rot}}^\ddagger > 20 \text{ kcal mol}^{-1}$) mostly lead to highly functionalized γ -lactams (no β -lactam formation was observed), where the mode of termination is controlled in part by steric factors and in part by the method of cyclization.

RESULTS AND DISCUSSION

Substitution at the Alkene. Compound **2b** ($R^1 = \text{Me}$, $R^2 = \text{Bn}$) was prepared by acetylation of the *N*-benzylimine of acetaldehyde²² (13%). Computational analysis of **2b** using the TZVP basis set²³ and the B3LYP-D3(BJ) functional²⁴ using PC-GAMESS/Firefly 8.0²⁵ suggested that three out of the four possible conformations were planar [the exception being (*E*)-*syn*-**2b**] with (*E*)-*anti*-**2b** and (*Z*)-*anti*-**2b** conformations predominating at equilibrium (Figure 2). Electronic energies and zero-point energies for all conformations are provided in the Supporting Information. Two diastereomeric versions of the nonplanar (*E*)-*syn*-**2b** conformation exist, where either the vinyl group or the phenyl group are angled either in front of the plane of the amide or behind it. The energy and relative equilibrium constant of the more stable conformer are shown. In all cases the minimized energy structures had imaginary frequencies of zero. The E+ZPE energy was used to calculate the relative populations at 298 K.

Experimentally, a 2:1 ratio of two conformations was observed in the 600 MHz ¹H NMR spectrum of **2b** in CDCl₃ at 298 K. The major isomer was confirmed as (*E*)-*anti*-**2b** and the minor isomer (*Z*)-*anti*-**2b** upon the basis of their calculated theoretical ¹H NMR chemical shifts and NOE data. DFT ground-state structures were analyzed using the GIAO method Gaussian03,²⁶ with the mPW1PW91 functional²⁷ and the 6-311+G(2d,p) basis set and scrf = (solvent = chcl3,cpcm,read) radii = uaks nosymcav options.²⁸ NMR shifts

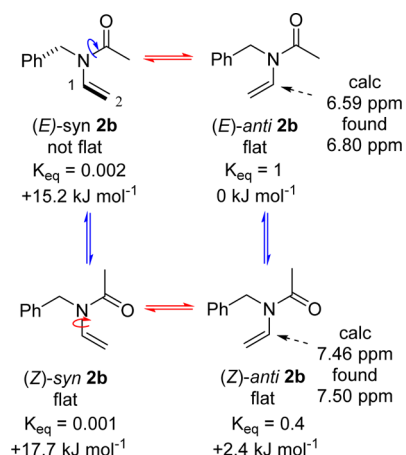


Figure 2. Calculated relative energies, ¹H NMR shifts, and equilibrium contributions of conformers of **2b**.

were calculated using parameters specific to the functional, basis set, and option combination described Lodewyk et al.²⁹ The H-1 enamide proton resonates at 6.80 ppm in the major conformer and 7.50 ppm in the minor conformer, in good agreement with the theoretical calculations. This data is similar to that reported for the related *N*-benzyl-*N*-vinylformamide **2c** ($R^1 = \text{H}$, $R^2 = \text{Bn}$)³⁰ and is consistent with a slow rotation around the amide bond and a fast rotation around the C–N bond of the alkene with a higher population of the (*E*)-*anti* conformer at equilibrium at room temperature. Heating **2b** (298 K \rightarrow 373 K) in toluene-*d*₈ caused a broadening of all signals and coalescence to a single set of peaks, consistent with rapid rotation around the amide bond.

In order to assess the effect of increasing alkene substitution on the barrier to rotation, we prepared structures **4a–i** (Figure 3). We chose to study the *N*-benzyl derivatives, as measurement of rotation rates should be possible using variable-temperature (VT) ¹H NMR. Upon cooling, the benzylic CH₂ singlet should broaden and would be expected to decoalesce (caused by the two protons of the CH₂ group being

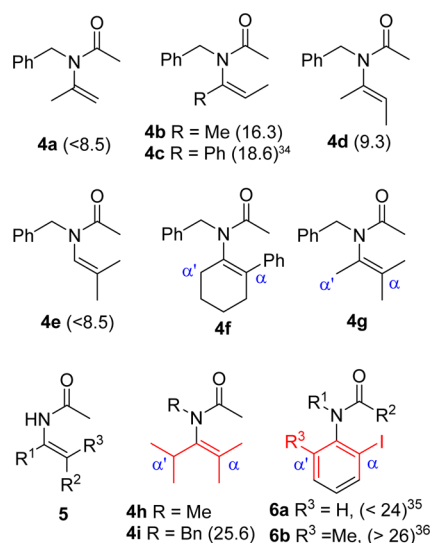


Figure 3. Effect of alkenyl substitution on the barrier for rotation around the *N*-alkenyl bond of **4a–i** ($\Delta G_{298 \text{ rot}}^\ddagger$ in kcal mol⁻¹ for rotation around the *N*-alkenyl bond is shown in parentheses).

in an asymmetric environment) and ultimately form two doublets due to the diastereotopic nature of the benzylic protons. This behavior is not consistent with amide bond rotation, as this would cause the number of signals to double. Using the WINDNMR 7.1 line shape analysis program,³¹ it was possible to determine the rotational rate constant at each temperature and the thermodynamic parameters via a standard Eyring plot. Compounds **4a**,³² **4e**, and **4f** were prepared by acetylation of the known benzyl imines of acetone,²² 2-methyl propanal,²² and 2-phenylcyclohexanone,³³ while **4b–d** and **4g–i** were prepared by benzylation (NaH, BnBr) or methylation (NaH, MeI) of the corresponding *N*-acetyl enamides **5** (16–80%).^{34–37} The barrier to rotation around the C–N bond for **4a** and **4e** was too low to measure by VT ¹H NMR ($\Delta G^{\ddagger}_{298}$ estimated to be <8.5 kcal mol⁻¹). On cooling, the benzylic CH₂ singlet began to broaden as expected, but even at 179 K decoalescence was not observed. On the other hand, the values of $\Delta G^{\ddagger}_{298}$ for rotation for the 1,2-substituted derivatives **4b–d** in toluene-*d*₈ were determined to be 16.3, 18.6, and 9.3 kcal mol⁻¹. As expected, increasing steric congestion around the alkene increases the barrier to rotation due to the inherent difficulty in passing through a hindered planar structure during rotation.

For the derivatives **4f–i**, the barrier to rotation was too high to measure with conventional VT experiments. The ¹H NMR showed a sharp set of diastereotopic signals for the CH₂ benzyl protons, even at 373 K. It was not possible to fully resolve the enantiomers of **4f** and **4g** by chiral HPLC on a variety of columns, indicating that the atropisomers were either inseparable on the columns examined or that they were rapidly interconverting on the HPLC time scale; evidence for the latter is provided *vide infra*. While compound **4h** was partially resolved, both enantiomers of **4i** were fully resolved on a semipreparative Whelk-O column (30.1 and 37.4 min). The $\Delta G^{\ddagger}_{298}$ for rotation of **4i** was determined to be 25.6 kcal mol⁻¹ by measuring the kinetics of racemization at 82 °C.⁴³ This suggests that a branching substituent at the sp³-hybridized α' -position is required to generate suitable barriers to rotation for atropisomers to be successfully separated at room temperature. This is a similar structural motif to that found in anilides **6b** (R³ ≠ H, shown in red with an sp² branching point), where barriers to rotation were greater than 26 kcal mol⁻¹.⁴⁰ On the other hand, structures **4b**, **4f**, and **4g** with intermediate barriers to rotation structurally resemble anilides **6a** (R³ = H) and as a consequence have lower barriers to rotation.³⁹ To further study the effects of branching at the α' -position, we prepared structures **7a–d**, investigated their resolution by chiral HPLC, and calculated the barriers to rotation and half-lives of those that could be resolved (Figure 4).

It was possible to fully separate the enantiomers of **7b** (containing both an α -methyl group and an α' -annulated phenyl group) on a semipreparative Whelk-O column (37.09 and 46.47 min), and a $\Delta G^{\ddagger}_{298}$ K for rotation of 27.5 kcal mol⁻¹ was determined by measuring the kinetics of racemization of a 99:1 enantiomerically enriched sample at 82 °C. Compound **7b** is a restricted conformational analogue of the acyclic derivative **7a** first prepared by Ahlbrecht (**7a** ΔG^{\ddagger} = 21.3 kcal mol⁻¹).³⁸ The difference in the measured barrier to rotation is significant, $\delta\Delta G^{\ddagger}$ = 6.2 kcal mol⁻¹, and the relatively low value for **7a** indicates a likely cooperative gearing of the α' -phenyl substituent rotation during the key rotation around the *N*-alkenyl bond in **7a** (Figure 4). The related derivative **7d** gave a single peak on the Whelk-O column, and its rotation

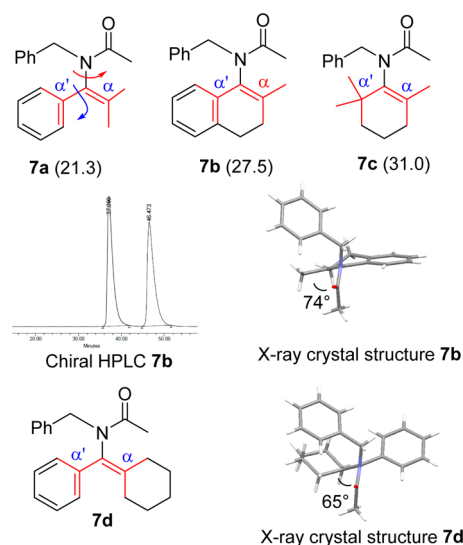


Figure 4. Structures **7a–d**, X-ray crystal structures for **7b** and **7d**, and chiral HPLC traces for **7b** ($\Delta G^{\ddagger}_{298}$ in kcal mol⁻¹ for rotation around the *N*-alkenyl bond is shown in parentheses).

dynamics were not further analyzed. On the other hand, **7c** provided the highest barrier to rotation (ΔG^{\ddagger} = 31.0 kcal mol⁻¹, $t_{1/2}$ = 99 years at 298 K, enantiomers separated at 29.0 and 31.9 min), and this barrier is comparable to published values for *o*-iodoacrylanilides **6b**.⁴⁰ We solved the X-ray structures of **7b** and **7d**, which confirmed the preference for adoption of the amide *N*–CO *E*-rotamer geometry in the solid state (Figure 4). The torsional angle of the key *N*-alkenyl bond C=C–NC(O) in **7b** is 74°, which is similar to that observed for related anilides⁴¹ and other enamides.^{21,42} The sum of the angles around the nitrogen atom was 359.9°, suggesting that the nitrogen was planar, as expected. For **7d** the torsional angle was slightly smaller, 65°. The 400 MHz ¹H NMR of both **7a** and **7d** in toluene-*d*₈ showed one pair of mutually coupled sharp doublets (for **7a**, J = 14.0 Hz at 5.27 and 3.48 ppm; for **7d**, J = 14.0 Hz at 5.37 and 3.37 ppm) which did not broaden upon heating. This is consistent with the existence of largely a single *E*-amide rotamer in solution, with a high barrier to rotation around the *N*-alkenyl bond causing the benzyl protons to be diastereotopic, as seen in the crystal structure of **7d**. These results suggest that enamides **1c** (R¹, R², R³, R⁵ ≠ H, R⁴ = branched substituent) are likely to have sufficient barrier to rotation around the *N*-alkenyl bond to be resolvable for useful periods at room temperature.

Substitution at Nitrogen. The effect of the size of the nitrogen substituent **8a–e** on the energy barrier for *N*-alkenyl bond rotation was assessed by VT NMR (Figure 5). Deprotonation of *N*-1-cyclohexen-1-yl-benzeneacetamide⁴³ with NaH in THF followed by the addition of either MeI (**8a**, 84%), BuBr (**8b**, 70%), or ^{*i*}PrI (**8d**, 13%) furnished the desired enamide **8a**, **8b**, or **8d**.⁴⁴ Compound **8c** was prepared by acylation of the *N*-benzylimine of cyclohexanone with phenylacetyl chloride according to a literature procedure.⁴² We also synthesized compound **8e** by reaction of *N*-1-cyclohexen-1-yl-benzene acetamide with 3 equiv of 2,6-lutidine and TBSOTf (Figure 5).⁴⁵

The moisture sensitivity of **8e** required its preparation in situ in toluene-*d*₈ in an NMR tube, and it was not possible to isolate a pure sample. For compounds **8a**, **8b**, and **8d** a characteristic change in the chemical shift of the alkene proton occurred

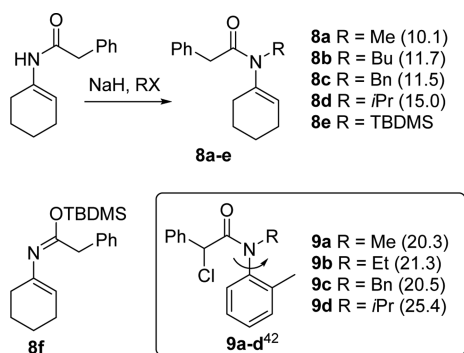


Figure 5. Effect of alkenyl substitution on the rotation barrier around *N*-alkenyl bond for **8a–e** ($\Delta G_{298}^{\ddagger}$ in kcal mol⁻¹ for rotation around the *N*-alkenyl **8a–d** or *N*-aryl **9a–d** bond is shown in parentheses).

upon *N*-alkylation ($\Delta\delta$ between 0.46 and 0.70 ppm), highlighting the loss of conjugation with the nitrogen lone pair in **8a–d**. The sense and magnitude of this shift was also observed upon silylation in toluene-*d*₈ (**8e** 4.84 ppm), providing evidence that silylation to give **8e** had occurred. As expected, the barrier to rotation increased, **8a** (10.1 kcal mol⁻¹) < **8b**, **8c** (11.5–11.7 kcal mol⁻¹) < **8d** (15.0 kcal mol⁻¹), as the size of the alkyl group increased, in parallel with the trend observed in anilides **9a–d**.⁴⁶ In both series there is a relatively small increase on moving from the *N*-methyl to *N*-1° alkyl substituent (enamides **8a** → **8b** $\delta\Delta G^{\ddagger} = 1.6$ kcal mol⁻¹, anilides **9a** → **9b** $\delta\Delta G^{\ddagger} = 1.0$ kcal mol⁻¹), whereas there is a significantly larger increase for the isopropyl substituent (enamides **8a** → **8d** $\delta\Delta G^{\ddagger} = 4.9$ kcal mol⁻¹, anilides **9a** → **9d** $\delta\Delta G^{\ddagger} = 5.1$ kcal mol⁻¹). This is likely due to the R group in the *N*-CH₂R substituent being able to rotate away from the plane of the amide and alkene during C–N alkenyl rotation, while this is not possible for the methyl groups *N*-CH(Me)₂ in **8d**.⁴⁷ No broadening of the geminal protons of **8e** was observed on cooling to 193 K, indicating that rotation is rapid, presumably through the *O*-silyl imidate **8f** (Figure 5). Silylation of related anilides has been reported to proceed to give both *N*-silylated and *O*-silylated structures that are in rapid equilibrium,⁴⁸ and this may be occurring for enamide **8e**.

The addition of radicals onto tertiary enamides (derived from aryl bromides **10**) has been reported to give tetrahydroisoquinolines **11** via a 6-*endo-trig* radical cyclization.⁴⁹ The bond rotation dynamics of *N*-2-halobenzyl derivatives has not been investigated. We briefly investigated the effect of *o*-halobenzyl substituents upon the rotation barrier around the *N*-alkenyl bond in related systems **13a–f** (Table 1). While the effect of such substituents X and Y might be limited (as they are three

Table 1. *N*-Alkenyl Bond Rotation Rates from Variable-Temperature NMR Experiments for **13a–f**

compd	X	Y	$\Delta G_{298}^{\ddagger}$ (kcal mol ⁻¹) ^a
13a	H	H	10.1 ³⁸
13b	F	H	9.9
13c	I	H	9.9
13d	F	F	10.9
13e	Cl	Cl	11.7
13f	Br	Br	13.1
15 ^b	Br	Br	14.8

^aEstimated errors $\Delta G_{298}^{\ddagger} \pm 0.2$ kcal mol⁻¹; these are in line with related work. ^bEnamide constrained in a seven-membered ring

atoms away from the nitrogen atom), the relatively large size of bromine and iodine atoms (typically used to initiate radical reactions or other metal-mediated cyclizations) may be significant. The compounds **13a–g** were prepared by alkylating the known acetamide **12**³⁴ with appropriately functionalized benzyl halides using the same approach as for **8a–e**.

The introduction of a single 2-fluorine (**13b**) or 2-iodine (**13c**) substituent had little effect on the rotation barrier; the X-ray structure of the related 2-bromide **14** clearly showed the halide orientated away from the alkene group, where it does not interfere with the *N*-alkenyl bond rotation (Figure 6). On the

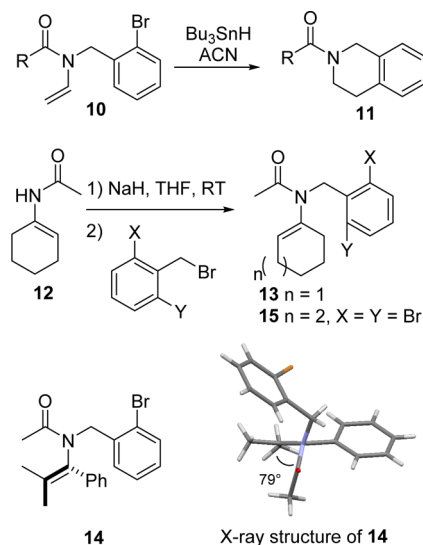


Figure 6. Synthesis of compounds **13a–f**.

other hand, benzyl substituents containing two ortho substituents increase the barrier to rotation in line with their size (**13d**, F = +0.8 kcal mol⁻¹; **13e**, Cl = +1.6 kcal mol⁻¹; **13f**, Br = +2.9 kcal mol⁻¹) despite their distance from the key *N*-alkenyl bond rotation. The size of the ring in which the enamide alkene was constrained also affected the barrier to rotation in the order 6-membered < 7-membered (compare **13f** and **15** $\delta\Delta G^{\ddagger} = +1.7$ kcal mol⁻¹), which is a consequence of the bond angles of the different ring systems.²¹

Substitution at the Acyl Group. Previous work with tertiary enamides containing electron-poor and electron-rich aromatic acyl substituents has shown that the electronic nature of the acyl substituent has a negligible effect on the *N*-alkenyl rotation barrier, suggesting that steric effects alone are important.³⁴ It has previously been reported that the size of the acyl group (R) in **3a–i** only moderately affects the barrier to rotation in enamides (Figure 7).^{21,42} Hence, replacing an acetyl group (**3a**) ($\Delta G_{298}^{\ddagger} \text{rot} = 10.1$ kcal mol⁻¹) with the much

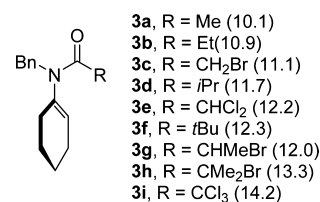


Figure 7. Effect of acyl substituent **3a–i** upon the $\Delta G_{298}^{\ddagger} \text{rot}$ barriers around the *N*-alkenyl bond (values in kcal mol⁻¹ shown in parentheses).⁴²

larger trichloroacetyl group (**3i**) ($\Delta G_{298}^{\ddagger} = 14.2 \text{ kcal mol}^{-1}$) increases the barrier to rotation by $4.1 \text{ kcal mol}^{-1}$. This steric effect is less significant for the acyl substituent than the nitrogen substituent [nitrogen substituent Me (**8a**) \rightarrow t Pr (**8d**), $\delta\Delta G = 4.9 \text{ kcal mol}^{-1}$; acyl substituent Me (**3a**) \rightarrow t Pr (**3d**), $\delta\Delta G = 1.6 \text{ kcal mol}^{-1}$].⁴² Similar behavior has also been reported for anilides.⁴⁷

For small R substituents (such as **3a**) the barrier to *N*-alkenyl rotation is likely to be lower than amide *N*-CO rotation, but for larger substituents (such as **3i**), the barriers are likely to be similar.¹⁹ Consequently, a number of potential mechanisms for enantiomerization (*E,M*-3 \rightarrow *E,P*-3) are possible, including simple enamide rotation (*E,M*-3 \rightarrow *E,P*-3) or a cooperative coupled rotation of both amide and enamide, a geared process (*E,M*-3 \rightarrow *Z,M*-3 \rightarrow *E,P*-3).⁵⁰ On plotting $\ln k_{\text{rot}}$ values for **3a**–**i** against the cone angle (θ_R values)⁵¹ of the acyl substituent, we found a linear correlation ($R^2 = 0.958$), which suggests that the mechanism for rotation is likely to be the same for all of the series and that the cone angle of the acyl substituent may be a useful tool in predicting rotational barriers for a given series of enamides (Figure 8).

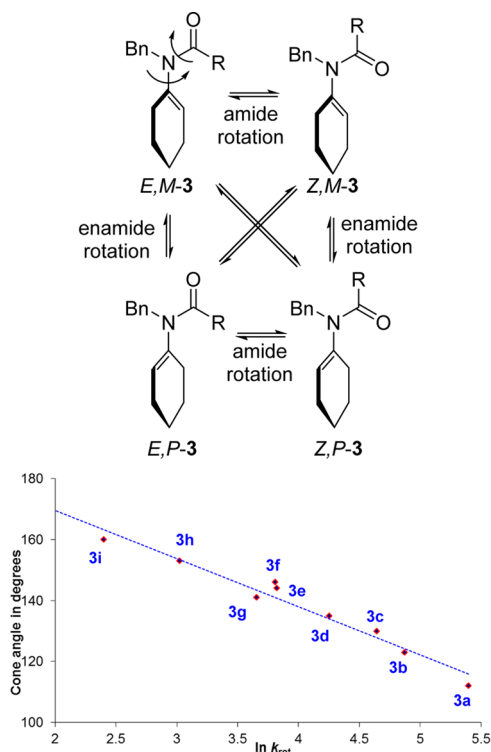


Figure 8. Correlation between cone angle θ_R and $\ln k_{\text{rot}}$ values for **3a**–**i** ($R^2 = 0.958$).

In summary, the most important factors in controlling the rate of *N*-alkenyl bond rotation in enamides is the level of alkene substitution (particularly any branching substituent at the α' -position), followed by the size of the nitrogen substituent (and the distance of any branching from the nitrogen atom) and, finally, the size of the acyl substituent.

Radical Cyclization Substrate Dynamics. The radical cyclization of α -haloenamides **16**–**18** is well-documented and may proceed via a 4-*exo* or 5-*endo* cyclization, depending upon the substrate (Figure 9).^{52–64} Rotational features of enamides can dictate the success or failure of radical cyclizations, with the *E*-amide rotamer being required.³⁰ In general, 1-substituted

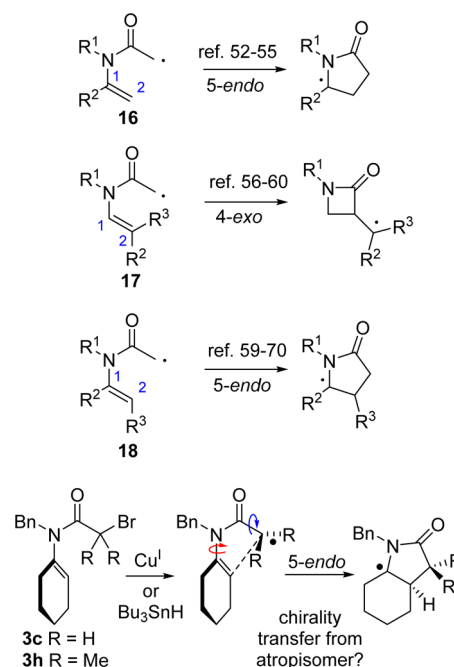


Figure 9. Regiochemical modes of cyclization of α -haloenamides.

enamides **16** cyclize via a 5-*endo* pathway ($R^2 = \text{Ph}$ or CO_2R),^{52–55} while 2- or 2,2-substituted enamides **17** proceed via a 4-*exo* pathway,^{56–58} although electronic factors and temperature can also play a part in controlling the regiochemistry for these substrates.^{58–60} By far the majority of cyclization reactions reported involve 1,2-substituted enamides **18**, which generally proceed via a 5-*endo* pathway.^{59–70} For cyclization of radicals derived from homolysis of the C–Br bond in substrates **3c** and **3h**,^{66–70} it is necessary for a twisting to occur in the transition state so that the radical SOMO and alkene LUMO orbitals can overlap efficiently, and this has been confirmed by calculations.⁷¹ As a consequence, the twisted ground state of molecules such as **3c** and **3h** likely facilitate cyclization with a movement toward planarity occurring during the reaction (Figure 9). Far less is known about cyclizations of 1,2,2-substituted enamides, where movement toward planarity during cyclization may be hindered due to steric effects.^{59,60,72}

Cyclization of **19** was reported to be unsuccessful using Bu_3SnH at 80°C , while cyclization of the analogue **21** gave both 4-*exo* **23** and 5-*endo* products **22**, depending upon the temperature (Figure 10).⁷² This suggests that the 4-*exo* cyclization process was reversible, and at the higher temperature, 5-*endo* cyclization followed by irreversible loss of the phenylthiyl radical predominated to give **22**. From our studies above it is apparent that these substrates are likely to have ground-state *N*-alkenyl bond rotation barriers of less than 20 kcal mol^{-1} .

To the best of our knowledge the cyclization of enamides containing further branching at the α' -position have not been studied in detail (Figure 10). For these substrates, where barriers to rotation around the *N*-alkenyl bonds are likely to be significant ($>20 \text{ kcal mol}^{-1}$), it is unclear if cyclization would be efficient because steric interactions would develop as the radical and radical acceptor move toward planarity during the cyclization process. In order to address these issues, we prepared enamides **24**–**28**, examined their barriers to rotation and investigated their radical cyclization reactions (Figure 11).

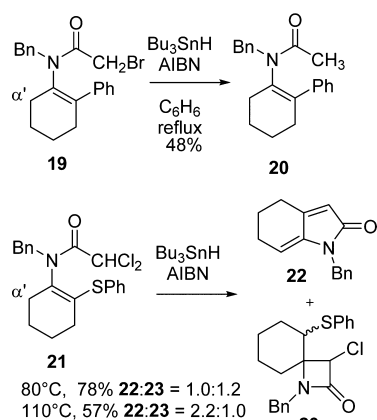


Figure 10. Regiochemical modes of cyclization of 1,2,2-substituted α -haloenamides.

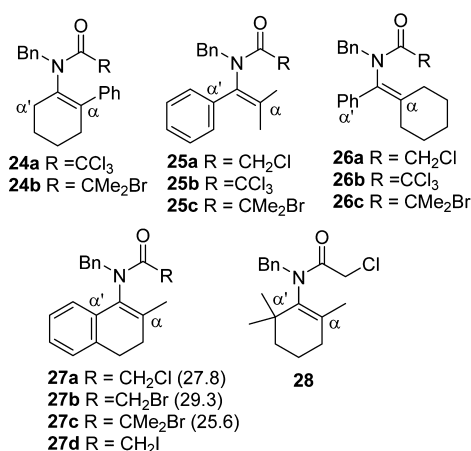


Figure 11. Structures 24–28 showing the $\Delta G^{\ddagger}_{298 \text{ rot}}$ barriers around the N -alkenyl bond in parentheses (values in kcal mol^{-1}).

The most commonly used protocols for mediating radical cyclizations of α -haloenamides are (i) $\text{Bu}_3\text{SnH/AIBN}$,^{52–54,62–65} where chlorides provide higher yields of cyclized products than bromides or iodides,⁷⁰ and (ii) copper(I) complexes of bipyridine,⁵⁷ hexamethyltriethylenediamine,⁶⁶ or tripyridylamine,^{56,57,67–69} which work for trichloroacetamide or tertiary halide derivatives only (Bu_3SnH , $\text{R} = \text{CH}_2\text{Cl}$, CH_2Br , CH_2I ; Cu(I) , $\text{R} = \text{CCl}_3$, CMe_2Br).⁶⁴ Consequently, we tested α -haloenamides 24–28 under a range of conditions and determined the regiochemistry of their radical cyclization reactions (Figure 11). It was not possible to fully resolve the atropisomers of 24–26, despite the large acyl substituents. We believe this is indicative of individual isomers interconverting on the HPLC time scale at room temperature. Evidence for this assumption can be obtained from the HPLC chromatogram for compound 26a, which is indicative of the individual enantiomers interconverting at room temperature (Figure 12d). The ΔG^{\ddagger} value for rotation for 26a was estimated to lie between 21 and 23 kcal mol^{-1} based upon a half-life of minutes at 298 K. In all these cases, the cooperative gearing of the phenyl substituent during N -alkenyl bond rotation is likely to lower the observed barrier to rotation.⁷³

For relatively large acyl substituents (25b, 26b, $\text{R} = \text{CCl}_3$; 25c, 26c, $\text{R} = \text{CMe}_2\text{Br}$) the barrier for N –(CO) amide bond

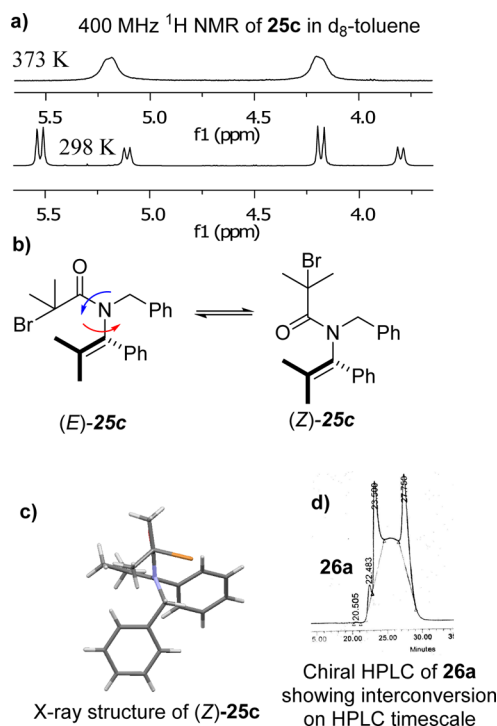


Figure 12. (a) Expansion of the benzylic region of the 400 MHz ^1H NMR spectra of 25c in $\text{toluene-}d_8$ at 298 and 373 K. (b) Cooperative rotation of amide N –(CO) bond during N -alkenyl bond rotation. (c) X-ray crystal structure of 25c. (d) Chiral HPLC chromatogram of 26a showing interconversion on HPLC timescale.

rotation was found to be lower than that of N -alkenyl bond rotation (Figure 12b).

Analysis of the 400 MHz ^1H NMR of 25b,c and 26b,c at 298 K showed a doubling of all peaks (Figure 12a), indicative of both (E - and (Z -)amide rotamers at room temperature (while 25a or 26a only showed one set of peaks). The ratio of amide rotamers obtained from the 400 MHz ^1H NMR at room temperature was similar for the two trichloroacetyl derivatives (25b $E:Z = 1.0:0.25$ and 26b $E:Z = 1.0:0.26$) and the two bromo derivatives (25c $E:Z = 1.0:0.65$ and 26c $E:Z = 1.0:0.62$), indicating that the population of the two rotamers was dictated by the acyl substituent. Heating either 25b,c or 26b,c at 373 K led to coalescence of the four sets of doublets to two broad singlets, indicative of a rapid interconversion on the NMR time scale between the (E - and (Z -)amide rotamers with a slower rotation around the enamide N –C bond (Figure 12a). The barrier to rotation around the N –(CO) amide bond is known to be influenced by the acyl substituent with sterically demanding (t -Bu) groups lowering the barrier by 4–5 kcal mol^{-1} compared to simple acetamide derivatives.⁷⁴ The X-ray crystal structure of 25c clearly shows the (Z -)amide rotamer in the solid state (Figure 12c). A similar doubling of signals was also observed in the ^1H NMR of the related structure 27c (1:0.17). Thus, for enamides containing four alkenyl substituents, the (E -)geometry is favored in both solution (CDCl_3) and the solid state for relatively small primary acyl groups ($\text{R} = \text{Me}$, CH_2Cl , CH_2Br , cone angles 112° – 130°), but mixtures of both (E - and (Z -)amide rotamers can be detected in solution if larger acyl groups or strongly electron withdrawing groups ($\text{R} = \text{CMe}_2\text{Br}$, CCl_3 , cone angles 153° – 160°) are present.

It was possible to fully separate the enantiomers of 27a–c on a semipreparative Whelk-O column, allowing for barriers to rotation to be calculated (27a, $er = 99:1$, $\Delta G^{\ddagger} = 27.8 \text{ kcal}$

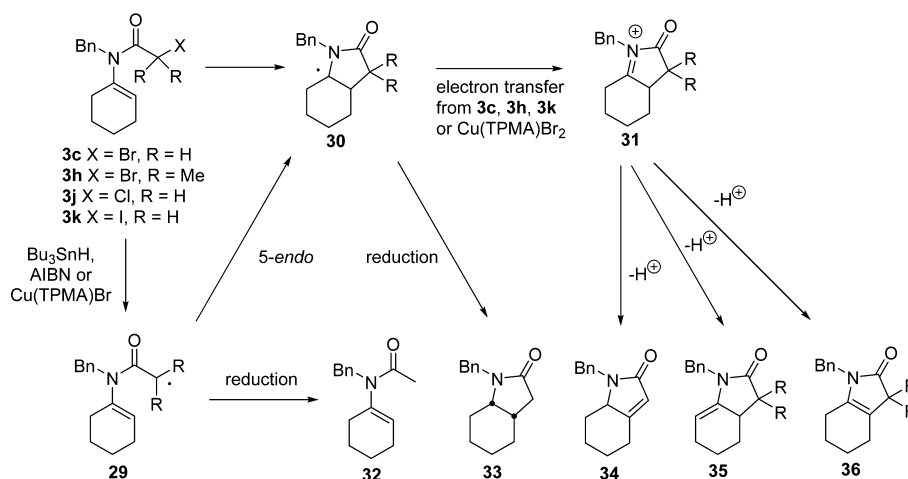


Figure 13. Formation of products from 5-endo cyclization of **3c**, **3h**, **3j**, and **3k**.

mol^{-1} , $t_{1/2} = 163$ days at 298 K; **27b**, $\text{er} = 98:2$, $\Delta G^\ddagger = 29.3$ kcal mol^{-1} , $t_{1/2} = 5.6$ years at 298 K; **27c**, $\text{er} = 87:13$, $\Delta G^\ddagger = 25.6$ kcal mol^{-1} , $t_{1/2} = 4$ days at 298 K), suggesting that these compounds would make interesting substrates with which to investigate chirality transfer during 5-endo-trig radical cyclization reactions at room temperature. If cyclization is significantly more rapid than *N*-alkenyl bond rotation, then chirality transfer from individual atropisomers is theoretically possible.¹ Radical cyclizations of related axially chiral *o*-haloanilides have been shown to proceed with high levels of chirality transfer from the chiral axis to the newly formed stereocenter.^{39,40,75–79} If, however, elevated temperatures are necessary for cyclization (e.g., 80 °C), then only bromide **27b** or iodide **27d** are likely to exhibit a suitable barrier to rotation (**27b** $t_{1/2} = 18.5$ h at 353 K) compared to **27a** (2 h) and **27c** (7 min). It is interesting to observe that **27c** has a lower barrier to *N*-alkenyl bond rotation than either **7b** or **27a,b** despite having a larger acyl substituent. The fact that it exists as a mixture of (*E*)- and (*Z*)-amide isomers in solution suggests that the lower *N*-alkenyl barrier may be due to a cooperative gearing with rotation of the amide functional group. However, in anilides it has been reported that the steric repulsion between bulky substituents causes pyramidalization of amide nitrogen and twisting of the amide bond (destabilization of the ground state) to bring about the decrease in the rotational barrier around an *N*-C chiral axis.⁷³ While we cannot disprove that this is the reason for the lowered barrier of **27c**, it is unlikely, as the related substrate **25c** shows no such pyramidalization in its X-ray structure (Figure 12c).

Radical Cyclization Reactions. We have previously shown that a slow syringe pump addition of $\text{Bu}_3\text{SnH}/\text{AIBN}$ to the chloride **3j** produces mainly **33** (92%) from reduction of the cyclized radical **30** (Figure 13).⁶⁶ Reactions of the bromide **3c** and iodide **3k** proceed differently. While the bromide **3c** gave **33** as the major product (55%), the alkene regioisomers **34** (11%) and **35 + 36** (11%) were also isolated. The iodide **3k** gave the uncyclized material **32** (68%) as the major product with **34** (11%) and **35 + 36** (13%). The different product ratios were explained via a competing electron transfer from the intermediate radical **30** to the starting halides **3c** and **3k**, giving the acyl iminium ion **31**. Elimination of a proton from **31** produces the three alkene regioisomers **34–36**. The higher ratio of reduced product **32** from the iodide **3k** was shown to be due to a competing nonradical deiodination process.⁷⁰

By analogy, we initially chose to investigate the Bu_3SnH -mediated cyclization of the primary chlorides **26a**, **27a**, and **28** representing varying levels of hindrance to rotation around the *N*-alkenyl bond. The chlorides were chosen to suppress products arising from electron transfer from the cyclized radical to the starting chloride.

When a 0.02 M solution of **26a** ($\Delta G^\ddagger_{298 \text{ rot}} \sim 21\text{--}23$ kcal mol^{-1}) was treated with 1.5 equiv of Bu_3SnH and 0.2 equiv of ACN at reflux for 26 h, the major product was the uncyclized compound **7d** (30%), suggesting a relatively slow cyclization, which is in line with that previously reported for **19**. Significant starting material **26a** was also recovered (21%).⁷² The expected cyclized product **37a** was obtained in 27% yield, arising from a 5-endo-trig cyclization followed by Bu_3SnH -mediated reduction (no 4-*exo* products were isolated). A significant amount of the hydroxyl terminated compound **37b** (17%) was also detected. Presumably, alcohol **37b** arises via a radical–polar crossover reaction with trapping of the intermediate acyl iminium ion with water (upon workup), there being no elimination pathway analogous to **31** \rightarrow **34–36** available for **26a** (Figure 14). Attempts to cyclize derivatives with higher barriers to rotation (**27a**, $\Delta G^\ddagger_{298 \text{ rot}} = 27.8$ kcal mol^{-1} ; **28**, $\Delta G^\ddagger_{298 \text{ rot}} > 31.0$ kcal

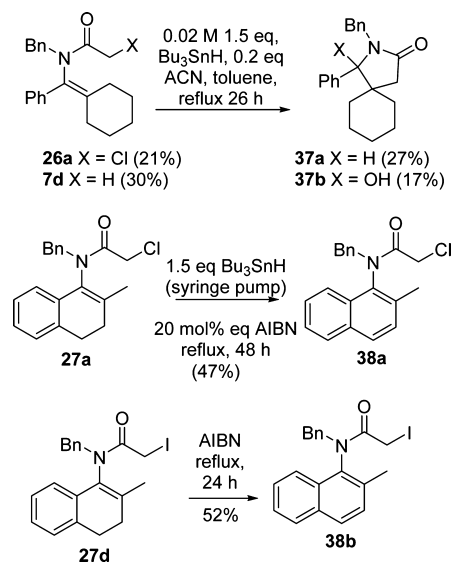


Figure 14. Reaction of **26a** and **27a** with Bu_3SnH .

mol⁻¹) failed, presumably due to the increased difficulty in moving to planarity during the cyclization. Reaction of the chloro derivative **27a** with Bu₃SnH (0.01M) and Et₃B⁷⁹ at room temperature led to recovered starting material **27a** (44%) and the reduced substrate **7b** being isolated (70% based upon recovered starting material). On the other hand, addition of 1.5 equiv of Bu₃SnH and 20 mol % AIBN (via a syringe pump addition for 2 h, initial concentration 0.01 M) led to oxidation to the naphthalene **38a** in 19% yield (47% based upon recovered starting material). Complete oxidation to the naphthalene **38a** could also be accomplished if **27a** was reacted with 2 equiv of AIBN in the absence of Bu₃SnH, indicating that the radical initiator was responsible for the oxidation and that this process was more rapid than homolytic fission of the C–Cl bond.^{80–82} The same oxidation to give **38b** was observed for the iodide **27d**. In order to enhance the rate of radical initiation over that of oxidation, we investigated the reaction of the bromide **27b**. Over 18 h, 1.5 equiv of Bu₃SnH and 0.2 equiv of ACN were added via a syringe pump to a 0.12 M solution of the bromide **27b** under nitrogen in dry toluene at reflux. Thin layer chromatography revealed that significant amounts of starting material remained after 24 h, indicative of a slow initiation, so further Bu₃SnH/ACN was added. Three further aliquots of the initiator (1 equiv in total) over 48 h were required for complete consumption of the starting material. Upon workup, three products were isolated: the uncyclized acetamide **7b** (42%), the naphthanilide **38c** (7%), and the ketone **39a** (10%), arising from oxidative cleavage of the tetralone ring (Figure 15). Repeating the reaction using

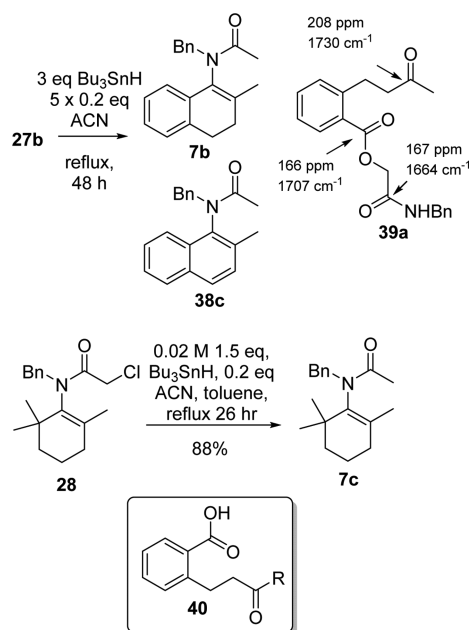


Figure 15. Attempted cyclization of **27b** with Bu₃SnH.

degassed toluene, in a Schlenk tube under argon, led to suppression of **39a** (trace amounts), and only the naphthanilide **38c** was isolated (along with recovered starting material). Although the mechanism for the formation of **39a** remains unclear, the oxidative α -C–C bond cleavage of 2-substituted 1-tetralones to give **40** under radical conditions (TEMPO) has been reported.⁸³ The mechanism has been reported to involve addition of oxygen to give an α -hydroperoxide. Radical or anionic fragmentation, Baeyer–Villiger/Criegee fragmentation,

or base-induced fragmentation of the peroxide can all potentially lead to the observed products (although a theoretical study indicates that a radical fragmentation is most likely).⁸³

In order to remove the complication of undesired tetralone cleavage, the reaction of **28** was investigated where the analogous oxidation was not possible. Reaction with Bu₃SnH and ACN led to formation of uncyclized **7c** in 88% yield as the sole product.

While it is most common to carry out Bu₃SnH-mediated reactions at elevated temperatures (typically benzene or toluene at reflux), efficient 5-*endo* radical–polar crossover reactions (**3h** → **35** and **36** R = Me) mediated by Cu(I) complexes have been reported at room temperature for tertiary halides **3h** (Figure 13).⁶⁶ The ability to conduct such cyclizations at lower temperature is attractive if chirality transfer during reaction of individual atropisomers is to be studied. Another advantage of generating the reactive radical from homolysis of a C–X bond via a Cu(I)-mediated atom transfer is that this initiating process is reversible, effectively providing longer “lifetimes” and less reduction of precyclized radicals than alternative Bu₃SnH-mediated processes. As before, the cyclization of substrates with $\Delta G_{298}^{\ddagger} < 26$ kcal mol⁻¹ proceeded smoothly, albeit at elevated temperatures. Reaction of **24a** with either 30 mol % of Cu(Me₆-tren)Cl or Cu(TPMA)Cl in toluene or DCM at room temperature only led to trace amounts of **41a** (<5%) after 48 h. On the other hand, heating of **24a** with 1 equiv of Cu(TPMA)Cl in toluene at reflux led to complete conversion to **41a** in 70% yield. We next investigated the cyclizations of **25b** and **26b** using the optimum conditions determined for **24a** [100 mol % Cu(TPMA)Cl], Figure 16.

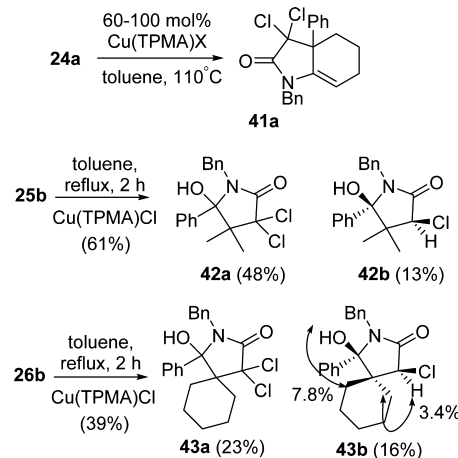


Figure 16. Cu(TPMA)Cl-mediated 5-*endo* cyclization of **24a**, **25b**, and **26b**, showing NOE enhancements (in percent) for **43b**.

Cyclization of both substrates was complete in 2 h and produced the expected dichlorides **42a** and **43a** along with the monochlorides **42b** and **43b** as single diastereomers (assigned from the ¹H NOE difference spectrum of **43b**). Both sets of products arose from trapping of the intermediate acyl iminium ion by water (as seen for the Bu₃SnH reaction of **26a**). The monochloride **42b** is likely formed by reduction of the α -amide radical obtained from a second atom transfer from **42a** to Cu(TPMA)Cl or by electron transfer from the cyclized radical to **42a** (the driving force being the relief of the eclipsing

interactions between the *gem*-dichloride group and the neighboring quaternary center).

Reaction of **25c** with 1 equiv of Cu(TPMA)Br in toluene at reflux for 10 h produced three products, **44**, **45**, and **46**, in 36%, 15%, and 4% isolated yields, respectively (Figure 17). The

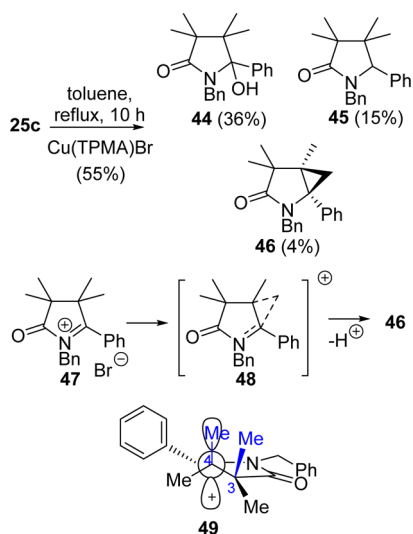


Figure 17. Cu(TPMA)Br-mediated 5-endo cyclization of **25c**.

major product **44** arises via the intermediate acyl iminium ion **47**, as previously observed for **25b**, while the reduced product **45** may arise from abstraction of a hydrogen atom from toluene by the cyclized radical. This would indicate that electron transfer in the radical–polar crossover step was slower than in the trichloroacetyl derivatives **25b** and **26b**. The formation of the cyclopropyl compound **46** deserves comment. There is a significant steric clash between the C-3 and C-4 *gem*-dimethyl groups in the acyl iminium ion intermediate **49**. In order to relieve these clashes, torsion of the C-3 to C-4 C–C bond can occur, which places the C-4 pseudoaxial methyl group almost parallel to the p-orbital of the acyl iminium ion **49**, initiating a rearrangement to form a protonated cyclopropane intermediate **48**. Formation of a cyclopropane by loss of a proton during a 1,2-migration of a methyl group has been previously reported,^{84,85} and this process would give rise to the observed product **46**. More of the cyclopropyl derivative was isolated from the analogous reaction of **26c** (**50**, **51**, and **52** being formed in 33%, 21%, and 5% yields, respectively). Presumably, the more-electron-rich nature of the methylene group in **26c** compared to the methyl group in **25c** is responsible for the greater yield of trapped migration product **51** (Figure 18).

Reaction of the tetralone derivative **27c** was relatively slow compared to the other substrates (**25c** and **26c**) and required heating at reflux for 44 h with 1.2 equiv of Cu(TPMA)Br before all the starting material was consumed. This substrate exhibited the highest barrier to *N*-alkenyl bond rotation of the

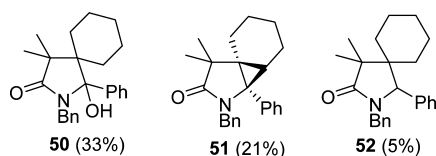


Figure 18. Products from Cu(TPMA)Br-mediated 5-endo cyclization of **26c**.

substrates cyclized using Cu(TPMA)Br. Two products were isolated, the expected cyclized product **53** and the oxidatively ring-opened compound **39b** (in a 2:1 ratio). Repeating the reaction in a Schlenk tube with degassed solvent (three freeze–thaw cycles) suppressed the formation of **39b** to trace levels (<2%), indicating that dissolved O₂ was most likely responsible for mediating the unusual ring-opening process to give **39b**. The reaction was more efficient, requiring less copper reagent (0.6 equiv) and a shorter reaction time (15 h). In addition, two further products, **54** and **55**, were isolated in 31% and 7%, respectively (although it was not possible to obtain **55** completely free of impurities) (Figure 19). Unfortunately,

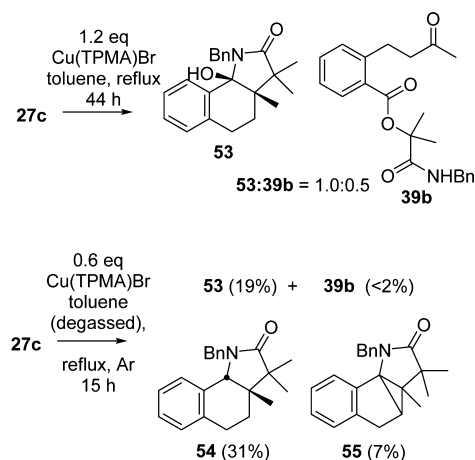


Figure 19. Reactions of **27c** with Cu(TPMA)Br.

attempts to conduct the reaction of **27c** at a lower temperature (353 K) provided trace levels of cyclized products only, while the barrier to rotation around the *N*-alkenyl bond of **27c** at 383 K was too low ($t_{1/2} = 18$ s) to warrant investigating whether chirality transfer from one atropisomer to the cyclized products was possible.

As with the formation of **39a**, from the Bu₃SnH-mediated reaction of **27b**, the mechanism for the formation of **39b** remains unclear, although the oxidative α -C–C bond cleavage of 2-substituted 1-tetralones with either CuCl or CuCl₂ and amine bases in the presence of O₂ has been reported.⁸³

CONCLUSIONS

In conclusion, we have prepared 38 different enamides **1c** varying in the substitution around the acyl group **1** ($R^2 \neq H$), the nitrogen substituent ($R^1 \neq H$), and alkene substituents ($R^3, R^4, R^5 \neq H$). The majority show slow rotation around the *N*-alkenyl bond of the enamide with $\Delta G_{298}^{\ddagger \text{rot}}$ barriers varying between <8.5 and 31.0 kcal mol⁻¹. The most important factor in controlling the rate of rotation is the level of alkene substitution (R^3, R^4, R^5), followed by the size of the nitrogen substituent (R^1) and, finally, the size of the acyl substituent (R^2). Electronic effects are small for substituents positioned on the acyl group (R^2), and the rate of rotation was linearly correlated with the cone angle of the substituent for the studied series **3a–i**, indicating that the mechanism of rotation was likely to be the same for all the compounds. For *N*-benzyl groups **13a–f**, *o*-halo-substitution has little effect on the barrier to rotation, except where two ortho substituents are present, indicating that cooperative gearing of the nitrogen substituent is likely during the *N*-alkenyl rotation. A similar gearing for freely

rotatable α -substituents (Ph in **7a**) is also indicated. Tetra-substituted alkenes possessing rigid α, α' -substituents (**7b, c**) have high enough barriers to rotation at room temperature to be separated by chiral HPLC with half-lives of up to 99 years at 298 K. This should theoretically enable future investigations into asymmetry transfer from enantiomerically pure enamides in a range of synthetic processes. For enamides **25b, c**, **26b, c**, and **27c** containing large or electron-withdrawing acyl groups (cone angles $\theta_R >$ approximately 130°) both (*E*)- and (*Z*)-amide rotamers were detected in solution at room temperature. Interconversion of these two rotamers was found to be fast on the NMR time scale at 80°C for all the examples studied. An examination of the barriers to rotation for the series **7b** and **27a–c** shows that while there is a steady increase between increasing size of the acyl substituent, as expected (**7b**, ΔG^\ddagger_{298} 27.5 kcal mol $^{-1}$; **27a**, ΔG^\ddagger_{298} 27.8 kcal mol $^{-1}$; **27b**, ΔG^\ddagger_{298} 29.3 kcal mol $^{-1}$), there is a significant drop for **27c** (ΔG^\ddagger_{298} 25.6 kcal mol $^{-1}$), indicative of a cooperative gearing effect between rotation around the (*E*)- and (*Z*)-amide and (*M*)- and (*P*)-amide rotamers with larger acyl substituents. This provides important temperature constraints when attempting asymmetric reactions of similar enamides.

While radical cyclization of enamides **3h–j** with relatively low barriers to rotation around the *N*-alkenyl bond ($\Delta G^\ddagger_{298 \text{ rot}} = 13–14$ kcal mol $^{-1}$) can be accomplished at room temperature,⁶⁶ in this study those with higher barriers ($\Delta G^\ddagger_{298 \text{ rot}} > \sim 20$ kcal mol $^{-1}$) required elevated temperatures, presumably due to the extra steric crowding hindering these molecules movement toward planarity during cyclization. Molecules with very high barriers to rotation ($\Delta G^\ddagger_{298 \text{ rot}} > \sim 26$ kcal mol $^{-1}$) did not undergo radical cyclization with Bu_3SnH ; instead, precyclization reduction or alternative reaction pathways predominated. For molecules with intermediate barriers to rotation ($\Delta G^\ddagger_{298 \text{ rot}} \sim 20–26$ kcal mol $^{-1}$), highly functionalized γ -lactams were produced via a *5-endo-trig* radical–polar crossover process and terminated either by reduction, an unusual cyclopropanation sequence, or trapping with H_2O , depending upon the reaction conditions. Steric congestion in cyclized products derived from trichloroacetamide derivatives **25b** and **26b** was relieved by a competing second atom transfer and reduction leading to replacement of one α -chloro substituent with a hydrogen atom (**42b** and **43b**). Unfortunately, because elevated temperatures were necessary for cyclization of substrates, in this study it precluded the examination of asymmetric transfer in the reaction of individual atropisomers such as **27d**. However, this report does indicate that enantiomerically enriched atropisomeric tertiary enamides should be regarded as potential asymmetric building blocks for reactions that can be accomplished at room temperature or below and may be useful functional groups in molecular machines and gears.¹

EXPERIMENTAL SECTION

General Methods. ^1H NMR spectra were recorded at 300, 400, 500, or 700 MHz and ^{13}C NMR spectra were recorded at 75.5, 100, 125, or 175 MHz with residual solvent as standard; infrared (IR) spectra were recorded as neat solutions or solids; and low- and high-resolution mass spectra were recorded using the electrospray ionization technique and a TOF mass analyzer.

Synthesis of Known Compounds by Literature Methods. Butan-2-one oxime,⁸⁶ 3-methylbutan-2-one oxime,⁸⁷ isobutyraldehyde oxime,⁸⁸ 2-methyl-1-tetralone oxime,⁸⁹ 2-methyl-1-phenylpropan-1-one oxime,³⁹ cyclohexyl(phenyl)methanone oxime,³⁹ 2-phenylcyclohexanone oxime,⁹⁰ 2,2,6-trimethylcyclohexanone oxime,⁹¹ 2,4-dimethyl-

yl-3-pentanone oxime,⁹² and *N*-benzyl-*N*-(prop-1-en-2-yl)acetamide (**4a**)³² were prepared by literature procedures and exhibited ^1H and ^{13}C NMR spectroscopic details identical to those previously reported. ^1H NMR was used to check the purity of all the compounds.

General Procedure for the Formation of Enamides **2b, **24a, b**, **25b, c**, **26b, c**, via Imines, Method A.** Ketone (1 equiv) and benzylamine (1.0 equiv) with or without TsOH were dissolved in dry toluene and heated to reflux under Dean–Stark conditions for 4–16 h. The reaction mixture was then cooled to 0°C . Triethylamine (1.2 equiv) was then added slowly, followed by the dropwise addition of the appropriate acid chloride (1.1 equiv). The reaction mixture was allowed to warm to room temperature and stirred for 12 h. NaHCO_3 (~ 50 mL) was added, and the layers were separated. The aqueous phase was extracted with Et_2O (3×50 mL), and the organic layers were combined, dried over MgSO_4 , filtered, and concentrated in vacuo to give the crude product. Products were purified by column chromatography.

***N*-Benzyl-*N*-vinylacetamide (**2b**).**⁹³ Conditions: acetaldehyde (2.0 g, 45.4 mmol), benzylamine (4.96 mL, 45.4 mmol), toluene (45 mL, 90 mL), triethylamine (7.6 mL, 54.5 mmol), and acetyl chloride (3.6 mL, 49.9 mmol). Yield 1.3 g (15%); yellow oil; mixture of amide rotamers (ratio 2:1); R_f 0.45 (pet. ether:EtOAc, 4:1); IR ν_{max} (film)/ cm^{-1} 2039, 1670, 1619; discernible data for major rotamer, ^1H NMR δ_{H} (CDCl_3 , 600 MHz) 7.17–7.36 (5H, m), 6.86 (1H, dd, J 15.5, 9.0 Hz), 4.90 (2H, s), 4.46 (1H, d, J = 15.5 Hz), 4.33 (1H, dd, J = 9.0 Hz), 2.34 (3H, s); ^{13}C NMR δ_{C} (CDCl_3 , 151 MHz) 169.6, 136.9, 133.3, 128.5, 127.0, 126.8, 95.3, 45.4, 22.1; discernable data for minor rotamer, ^1H NMR δ_{H} (CDCl_3 , 300 MHz) 7.63 (1H, dd, J = 16.0, 9.5 Hz), 7.17–7.36 (5H, m), 4.78 (2H, s), 4.38–4.42 (2H, m), 2.18 (3H, s); ^{13}C NMR δ_{C} (CDCl_3 , 151 MHz) 169.9, 136.0, 131.8, 128.9, 127.4, 125.6, 94.7, 48.7, 22.4; data for mixture, MS m/z (ESI) 198.1 ($[\text{M}]^+\text{Na}$).

***N*-Benzyl-2,2,2-trichloro-*N*-(2-phenylcyclohex-1-enyl)acetamide (**24a**).**⁹⁴ Conditions: 2-phenylcyclohexanone (2.43 g, 13.9 mmol), benzylamine (1.52 mL, 13.9 mmol), toluene (15 mL, then 25 mL), triethylamine (2.32 mL, 16.7 mmol), and trichloroacetyl chloride (1.71 mL, 15.3 mmol). Yield 1.18 g (21%); white crystalline solid; mp 116–118 $^\circ\text{C}$; R_f 0.52 (pet. ether:EtOAc, 14:1); IR ν_{max} (film)/ cm^{-1} 2924, 1671; ^1H NMR δ_{H} (CDCl_3 , 700 MHz) 7.38–7.22 (10H, m), 5.17 (1H, d, J = 14.0 Hz), 3.55 (1H, d, J = 14.0 Hz), 2.44 (1H, apparent d, J = 18.0 Hz), 2.34 (1H, apparent d, J = 17.0 Hz), 2.17–2.26 (1H, m), 1.64–1.73 (1H, m), 1.49–1.59 (1H, m), 1.31–1.41 (1H, m), 1.20–1.30 (1H, m), 1.06–1.16 (1H, m); ^{13}C NMR δ_{C} (CDCl_3 , 175 MHz) 159.5, 140.3, 135.4, 135.2, 134.9, 129.5, 128.8, 128.4, 128.3, 127.7, 127.4, 93.7, 53.4, 31.3, 29.0, 22.6, 22.5; MS m/z (ESI) 430.0 ($[\text{M}]^+\text{Na}$) [found ($[\text{M}]^+\text{Na}$) 430.0502, $\text{C}_{21}\text{H}_{20}\text{Cl}_3\text{NNaO}$ requires 430.0503].

***N*-Benzyl-2-bromo-2-methyl-*N*-(2-phenylcyclohex-1-enyl)propanamide (**24b**).** Conditions: 2-phenylcyclohexanone (2.43 g, 13.9 mmol), benzylamine (1.52 mL, 13.9 mmol), toluene (15 mL, then 25 mL), triethylamine (2.32 mL, 16.7 mmol), and 2-bromoisobutyryl bromide (1.89 mL, 15.3 mmol). Yield 716 mg (13%); white crystalline solid; mp 83–86 $^\circ\text{C}$; R_f 0.33 (pet. ether:EtOAc, 14:1); IR ν_{max} / cm^{-1} 2940, 1626; ^1H NMR δ_{H} (CDCl_3 , 700 MHz) 7.17–7.41 (10H, m), 5.33 (1H, d, J = 14.0 Hz), 3.47 (1H, d, J = 14.0 Hz), 2.39 (1H, apparent d, J = 17.5 Hz), 2.32 (1H, apparent d, J = 17.0 Hz), 2.12–2.23 (1H, m), 2.07 (3H, s), 1.82 (3H, s), 1.62–1.71 (1H, m), 1.48–1.60 (1H, m), 1.28–1.39 (1H, m), 1.17–1.27 (1H, m), 1.05–1.16 (1H, m); ^{13}C NMR δ_{C} (CDCl_3 , 175 MHz) 169.7, 141.2, 136.3, 136.0, 134.1, 129.5, 129.2, 128.6, 128.6, 128.5, 128.2, 127.6, 127.4, 57.4, 52.8, 33.9, 31.6, 31.3, 29.6, 22.7, 22.6; MS m/z (ESI) found ($[\text{M}]^+\text{Na}$) 434.1087, $\text{C}_{23}\text{H}_{26}\text{BrNNaO}$ requires 434.1090.

***N*-Benzyl-2,2,2-trichloro-*N*-(2-methyl-1-phenylprop-1-enyl)acetamide (**25b**).** Conditions: isobutyrophenone (5.06 mL, 33.8 mmol), benzylamine (3.69 mL, 33.8 mmol), TsOH (1.92 g, 10.1 mmol), toluene (35 mL then 15 mL), triethylamine (1.40 mL, 10.1 mmol), and 2-bromoisobutyryl bromide (1.15 mL, 9.27 mmol). Yield 1.21 g (38%), as a 1.00:0.26 mixture of rotamers; colorless crystalline solid; mp 68–69 $^\circ\text{C}$; R_f 0.51 (pet. ether:EtOAc, 19:1); IR ν_{max} / cm^{-1} 2913, 1680; ^1H NMR δ_{H} (CDCl_3 , 300 MHz) 7.51–7.08 (10H minor

+ 8H major rotamers, m), 7.02 (2H major rotamer, dd, $J = 8.0$, 1.5 Hz), 5.41 (1H major rotamer, d, $J = 14.5$ Hz), 5.05 (1H minor rotamer, d, $J = 13.5$ Hz), 4.13 (1H major rotamer, d, $J = 14.5$ Hz), 3.85 (1H minor rotamer, d, $J = 13.5$ Hz), 1.80 (3H minor rotamer, s), 1.60 (3H major rotamer, s), 1.55 (3H major rotamer, s), 1.29 (3H minor rotamer, s); ^{13}C NMR δ_{C} (CDCl_3 , 75 MHz) 159.4, 136.5, 135.3, 134.7, 130.9, 129.7, 129.2, 128.9, 128.2, 128.1, 127.6, 94.1, 53.5, 21.8, 21.0; MS m/z (ESI) found ($[\text{M}]^+\text{Na}$) 404.0346, $\text{C}_{19}\text{H}_{18}\text{Cl}_3\text{NNaO}$ requires 404.0352.

N-Benzyl-2-bromo-2-methyl-*N*-(2-methyl-1-phenylprop-1-enyl)propanamide (**25c**). Conditions: isobutyrophenone (5.06 mL, 33.8 mmol), benzylamine (3.69 mL, 33.8 mmol), TsOH (1.92 g, 10.1 mmol), toluene (35 mL then 15 mL), triethylamine (1.40 mL, 10.1 mmol), and 2-bromoisobutyryl bromide (1.15 mL, 9.27 mmol). Yield 2.39 g (74%) as a 1.0:0.6 mixture of rotamers; pale yellow crystalline solid; mp 74–76 °C; R_f 0.37 (pet. ether:EtOAc, 6:1); IR $\nu_{\text{max}}/\text{cm}^{-1}$ 2989, 1639; ^1H NMR δ_{H} (CDCl_3 , 400 MHz) 7.56–7.10 (10H minor, 8H major rotamers, m), 7.00 (2H major rotamer, d, $J = 7.0$ Hz), 5.53 (1H major rotamer, d, $J = 15.0$ Hz), 5.11 (1H minor rotamer, d, $J = 13.5$ Hz), 4.18 (1H major rotamer, d, $J = 15.0$ Hz), 3.80 (1H minor rotamer, d, $J = 13.5$ Hz), 2.22 (3H major rotamer, s), 2.14 (3H major rotamer, s), 2.08 (3H minor rotamer, s), 2.06 (3H minor rotamer, s), 1.86 (3H minor rotamer, s), 1.64 (3H major rotamer, s) 1.62 (3H major rotamer, s), 1.29 (3H minor rotamer, s); ^{13}C NMR δ_{C} (CDCl_3 , 175 MHz) mixture 171.9, 169.2, 137.5, 136.5, 135.9, 134.4, 134.1, 133.3, 131.6, 130.2, 130.2, 129.7, 128.9, 128.4, 128.1, 127.9, 127.6, 127.5, 127.1, 62.3, 57.9, 53.2, 53.1, 33.9, 33.5, 33.4, 32.7, 21.9, 21.8, 21.0, 20.9; MS m/z (ESI) found ($[\text{M}]^+\text{Na}$) 408.0933, $\text{C}_{21}\text{H}_{24}\text{BrNNaO}$ requires 408.0939.

N-Benzyl-2,2,2-trichloro-*N*-(cyclohexylidene(phenyl)methyl)-2-methylacetamide (**26b**). Conditions: cyclohexylphenyl ketone (1.5 g, 8.0 mmol), benzylamine (0.87 mL, 38.0 mmol), TsOH (303 mg, 1.6 mmol), toluene (9 mL then 15 mL), triethylamine (1.33 mL, 9.6 mmol), and trichloroacetyl chloride (0.98 mL, 8.8 mmol). Yield 1.46 g (43%) as a 1.00:0.26 mixture of rotamers; cream crystalline solid; mp 128–129 °C; R_f 0.54 (pet. ether:EtOAc, 6:1); IR $\nu_{\text{max}}/\text{cm}^{-1}$ 2972, 1671; ^1H NMR δ_{H} (toluene- d_8 , 400 MHz) 7.41–6.98 (10H, m), 5.31 (1H major rotamer, d, $J = 14.5$ Hz), 5.06 (1H minor rotamer, d, $J = 14.5$ Hz), 3.92 (1H major rotamer, d, $J = 14.5$ Hz), 3.64 (1H minor rotamer, d, $J = 14.5$ Hz), 2.44 (1H minor rotamer, br s), 2.10–2.08 (2H major rotamer, m), 1.63–0.90 (8 major + 8 H minor rotamer, m), 0.30 (1H minor rotamer, m); ^{13}C NMR δ_{C} (CDCl_3 , 100 MHz) 159.6, 141.7, 136.3, 135.0, 130.6, 130.4, 129.8, 129.4, 128.5, 128.3, 128.3, 128.2, 127.7, 94.2, 53.3, 31.0, 27.7, 26.6, 26.4; MS m/z (ESI) found ($[\text{M}]^+\text{Na}$) 444.0659, $\text{C}_{22}\text{H}_{22}\text{Cl}_3\text{NNaO}$ requires 444.0665; HPLC (S,S)-Whelk-O1 (25 cm \times 4.6 mm) hexanes:iPrOH (1.0 mL/min) t_{R} 4.09 min.

N-Benzyl-2-bromo-*N*-(cyclohexylidene(phenyl)methyl)-2-methylpropanamide (**26c**). Conditions: cyclohexylphenyl ketone (1.5 g, 8.0 mmol), benzylamine (0.87 mL, 38.0 mmol), TsOH (303 mg, 1.6 mmol), toluene (9 mL then 15 mL), triethylamine (1.33 mL, 9.6 mmol), and 2-bromoisobutyryl bromide (1.08 mL, 8.8 mmol). Yield 2.02 g (59%) as a 1.0:0.6 mixture of rotamers; pale brown crystalline solid; mp 102–104 °C; R_f 0.43 (pet. ether:EtOAc, 14:1); IR $\nu_{\text{max}}/\text{cm}^{-1}$ 2973, 1656; ^1H NMR δ_{H} (CDCl_3 , 400 MHz) 7.50–7.21 (10H minor + 8H major rotamers, m), 7.01 (2H major rotamer, d, $J = 7.0$ Hz), 5.52 (1H major rotamer, d, $J = 14.5$ Hz), 5.16 (1H minor rotamer, d, $J = 13.5$ Hz), 4.02 (1H major rotamer, d, $J = 14.5$ Hz), 3.63 (1H minor rotamer, d, $J = 13.5$ Hz), 2.70–2.67 (1H minor rotamer, m), 2.19 (3H major rotamer, s), 2.10 (3H major rotamer, s), 2.06 (6H minor rotamer, s), 2.12–1.08 (9H major + 8H minor rotamers, m), 1.03–0.80 (1H major rotamer, m), 0.34–0.26 (1H minor rotamer, m); ^{13}C NMR δ_{C} (CDCl_3 , 100 MHz) data for mixture of rotamers 172.2, 169.4, 141.3, 140.5, 137.3, 136.7, 136.4, 136.1, 131.4, 130.1, 129.8, 129.1, 128.6, 128.3, 128.2, 128.1, 127.7, 127.2, 62.9, 57.9, 52.9, 33.7, 32.8, 32.2, 31.6, 31.0, 27.8, 27.6, 26.7, 26.5; MS m/z (ESI) found ($[\text{M}]^+\text{Na}$) 448.1246, $\text{C}_{24}\text{H}_{28}\text{BrNNaO}$ requires 448.1252; HPLC (S,S)-Whelk-O1 (25 cm \times 4.6 mm) hexanes:iPrOH (1.0 mL/min) t_{R} 5.41 min.

N-Benzyl-2-bromo-2-methyl-*N*-(2-methyl-3,4-dihydronaphthalen-1-yl)propanamide (**27c**). 2-Methyl-1-tetralone (1.00 g, 6.24 mmol), benzylamine (0.818 mL, 7.49 mmol), and titanium isopropoxide (2.77 mL, 9.36 mmol) were heated to 80 °C for 48 h. The reaction mixture was then cooled to room temperature and toluene (12 mL) was added. The resulting solution was then cooled further to 0 °C, triethylamine was added (1.30 mL, 9.36 mmol), followed by the dropwise addition of 2-bromoisobutyryl bromide (0.93 mL, 7.49 mmol), and the reaction mixture was stirred at room temperature for 14 h. Saturated ammonium chloride (15 mL) was then added, and the phases were separated. The organic phase was diluted with toluene (20 mL) and washed with 2 M HCl (3 \times 30 mL), dried over MgSO_4 , filtered, and concentrated in vacuo to give the crude product as a brown oil (1.26 g). The crude product was purified by column chromatography (14:1, pet. ether:EtOAc) to give the product as a light brown oil (144 mg, 6%) as a 6:1 mixture of amide rotamers. R_f 0.17 (pet. ether:EtOAc, 14:1); IR $\nu_{\text{max}}/\text{cm}^{-1}$ 2925, 1656; ^1H NMR δ_{H} (CDCl_3 , 400 MHz) 7.33–7.40 (2H major rotamer, m), 7.25–7.29 (3H major rotamer, m), 7.16–7.25 (3H major rotamer + 6H minor rotamer, m), 7.07–7.14 (1H major rotamer + 2H minor rotamer, m), 6.98 (1H minor rotamer, d, $J = 7.5$ Hz), 5.65 (1H minor rotamer, d, $J = 13.5$ Hz), 5.50 (1H major rotamer, d, $J = 13.5$ Hz), 4.56 (1H minor rotamer, d, $J = 13.5$ Hz), 3.90 (1H major rotamer, d, $J = 13.5$ Hz), 2.75–2.89 (2H major rotamer, m), 2.52–2.20 (1H minor rotamer, m), 2.35–2.45 (2H minor rotamer, m), 2.20–2.33 (2H major rotamer + 6H minor rotamer, m), 1.97 (3H major rotamer, s), 1.89 (1H min, dd, $J = 10.0$, 2.5 Hz), 1.86 (3H major rotamer, s), 1.45 (3H minor rotamer, s), 1.29 (3H major rotamer, s); ^{13}C NMR δ_{C} (CDCl_3 , 100 MHz) data for mixture of rotamers, 172.0, 169.3, 137.4, 136.8, 136.4, 136.1, 135.9, 135.2, 132.9, 132.1, 131.7, 130.7, 130.2, 130.0, 128.2, 128.0, 127.9, 127.8, 127.7, 127.4, 127.3, 126.8, 126.6, 126.4, 123.0, 121.6, 60.3, 57.7, 54.0, 53.3, 34.2, 33.3, 32.9, 29.8, 29.4, 27.6, 27.3, 20.9, 19.3; MS m/z (ESI) found ($[\text{M}]^+\text{Na}$) 420.0930, $\text{C}_{22}\text{H}_{24}\text{BrNNaO}$ requires 420.0933; HPLC (S,S)-Whelk-O1 (25 cm \times 4.6 mm) hexanes:iPrOH (1.0 mL/min) t_{R} 11.70 and 12.66 min.

General Procedure for the Formation of Enamides 4b, 4d–i, 7a–d, 8a, 8b, 8d, 8e, 13b–d, 14, 15, 25a, 26a, 27a, 27b, 27d, 28 via Oximes, Method B. This procedure involved preparing acetamides **5a–j** or 2-chloroacetamides **5k–m** via an iron-mediated rearrangement³⁷ of literature oximes.^{38,86–91} These acetamides were then alkylated with alkyl halides to furnish the enamides **4b, 4d–i, 7a–d, 8a, 8b, 8d, 8e, 13b–d, 14, 15, 25a, 26a, 27a, 27b, 27d, 28**.

General Procedure for the Formation of Acetamides 5a–j. To the oxime (1 equiv) was added acetic acid (3 equiv), acetic anhydride (3 equiv), and iron powder (2 equiv) in anhydrous toluene. The mixture was heated at 70 °C for 4–16 h, cooled to room temperature, and filtered through Celite. Dichloromethane was added, and the organic extracts were washed with 2 M NaOH (3 \times 30 mL) and brine (30 mL). The organic phase was dried over MgSO_4 , filtered, and then concentrated in vacuo. Products were purified by column chromatography or recrystallization as reported. (*E*)- And (*Z*)-*N*-(but-2-en-2-yl)acetamide (**5a**, X = H, $\text{R}^1 = \text{R}^2 = \text{Me}$, $\text{R}^3 = \text{H}$); **5b**, X = H, $\text{R}^1 = \text{R}^2 = \text{Me}$, $\text{R}^3 = \text{H}$),³⁴ *N*-(3-methylbut-2-en-2-yl)acetamide (**5c**, X = H, $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{Me}$),³⁶ *N*-(2-methylprop-1-enyl)acetamide (**5d**, X = H, $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{R}^3 = \text{Me}$),⁹⁵ *N*-(1-phenyl-2-methylprop-1-en-1-yl)acetamide (**5e**, X = H, $\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{R}^3 = \text{Me}$),³⁷ *N*-(2-methyl-3,4-dihydronaphthalen-1-yl)acetamide (**5g**, X = H, $\text{R}^1 = \text{R}^2 = -\text{C}_6\text{H}_4\text{CH}_2\text{CH}_2-$, $\text{R}^3 = \text{Me}$),³⁷ *N*-(cyclohexylidene(phenyl)methyl)acetamide [**5h**, X = H, $\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{R}^3 = -(\text{CH}_2)_4-$],³⁷ and *N*-(2-phenylcyclohexene-1-yl)acetamide [**5i**, X = H, $\text{R}^1 = \text{R}^2 = -(\text{CH}_2)_4-$, $\text{R}^3 = \text{Ph}$]³¹ exhibited ^1H and ^{13}C NMR spectroscopic details identical to those previously reported. They were purified by either column chromatography or recrystallization as stated.

(*E*)-*N*-(But-2-en-2-yl)acetamide (**5a**, X = H, $\text{R}^1 = \text{R}^2 = \text{Me}$, $\text{R}^3 = \text{H}$) and (*Z*)-*N*-(But-2-en-2-yl)acetamide (**5b**, X = H, $\text{R}^1 = \text{R}^2 = \text{Me}$, $\text{R}^3 = \text{H}$).³⁴ Conditions: butan-2-one oxime⁸⁶ (3.00 g, 34.4 mmol), acetic acid (5.91 mL, 103.0 mmol), acetic anhydride (9.74 mL, 103 mmol), iron powder (3.84 g, 68.9 mmol), and anhydrous toluene (60 mL). The crude product was used without further purification in the preparation of **4b** and **4d**.

N-(3-Methylbut-2-en-2-yl)acetamide (**5c**, $X = H$, $R^1 = R^2 = R^3 = Me$).³⁶ Conditions: 3-methylbutan-2-one oxime⁸⁷ (3.20 g, 31.6 mmol), acetic acid (5.43 mL, 94.9 mmol), acetic anhydride (8.95 mL, 94.9 mmol), iron powder (3.53 g, 63.3 mmol), and anhydrous toluene (120 mL). The crude product was purified by recrystallization from hexane:ethyl acetate 10:1. Yield 617 mg (15%).

N-(2-Methylprop-1-enyl)acetamide (**5d**, $X = H$, $R^1 = H$, $R^2 = R^3 = Me$).⁹⁵ Conditions: isobutyraldehyde oxime⁸⁸ (2.00 g, 22.9 mmol), acetic acid (3.94 mL, 68.9 mmol), acetic anhydride (6.50 mL, 68.9 mmol), iron powder (2.56 g, 45.3 mmol), and anhydrous toluene (30 mL). The crude product was purified by column chromatography (pet. ether:ethyl acetate 1:1). Yield 113 mg (4%).

N-(1-Phenyl-2-methylprop-1-en-1-yl)acetamide (**5e**, $X = H$, $R^1 = Ph$, $R^2 = R^3 = Me$).³⁷ Conditions: 2-methyl-1-phenylpropan-1-one oxime⁸⁹ (4.93 g, 30.2 mmol), acetic acid (5.19 mL, 90.6 mmol), acetic anhydride (8.55 mL, 90.6 mmol), iron powder (3.37 g, 60.4 mmol), and anhydrous toluene (120 mL). The crude product was purified by recrystallization from hexane:ethyl acetate 10:1. Yield 3.92 g (69%).

N-(2,4-Dimethylpent-2-en-3-yl)acetamide (**5f**, $X = H$, $R^1 = iPr$, $R^2 = R^3 = Me$). Conditions: 2,4-dimethyl-3-pentanone oxime⁹² (4.72 g, 36.3 mmol), acetic acid (6.23 mL, 109 mmol), acetic anhydride (10.3 mL, 109 mmol), iron powder (4.06 g, 72.6 mmol), and anhydrous toluene (120 mL). The crude product was purified by recrystallization from hexane. Yield 3.17 g (56%); 5:3 ratio of isomers; white crystalline solid; mp 64–66 °C; R_f 0.60 (pet. ether:EtOAc, 1:1); IR ν_{max} (film)/ cm^{-1} 3242, 2972, 1641; 1H NMR δ_H (CDCl₃, 400 MHz) 6.15 (1H, s, minor), 6.07 (1H, s, major), 2.90–2.98 (1H, m), 2.08 (3H, s, major), 1.88 (3H, s, minor), 1.77 (3H, s major and minor), 1.67 (3H, s, minor), 1.61 (3H, s, major), 0.97 (6H, d, $J = 7.0$ Hz, minor), 0.95 (6H, d, $J = 7.0$ Hz, major); ^{13}C NMR δ_C (CDCl₃, 75 MHz) 168.8, 131.3, 127.7, 29.7, 29.3, 23.4, 20.6, 20.6, 20.1, 19.9, 19.6, 19.3, 19.3; MS m/z (ESI) found ($[M]^+Na$) 178.1202, C₉H₁₇NNaO requires 178.1202.

N-(2-Methyl-3,4-dihydronaphthalen-1-yl)acetamide (**5g**, $X = H$, $R^1 = R^2 = -C_6H_4CH_2CH_2-$, $R^3 = Me$).³⁷ Conditions: 2-methyl-1-tetralone oxime⁸⁸ (980 mg, 5.6 mmol), acetic acid (0.97 mL, 16.8 mmol), acetic anhydride (0.62 mL, 16.8 mmol), iron powder (0.63 g, 72.6 mmol), and anhydrous toluene (20 mL). The crude product was purified flash chromatography (5:1 hexane:EtOAc). Yield 403 mg (36%).

N-(Cyclohexylidene(phenyl)methyl)acetamide (**5h**, $X = H$, $R^1 = Ph$, $R^2 = R^3 = -(CH_2)_4-$).^{31,37} Conditions: cyclohexyl(phenyl)methanone oxime⁸⁸ (1.60 g, 7.87 mmol), acetic acid (1.35 mL, 23.6 mmol), acetic anhydride (2.23 mL, 23.6 mmol), iron powder (879 mg, 15.7 mmol), and anhydrous toluene (12 mL). The crude product was purified by recrystallization from petroleum ether:ethyl acetate 10:1. Yield 877 mg (49%).

N-(2-Phenylcyclohexene-1-yl)acetamide (**5i**, $X = H$, $R^1 = R^2 = -(CH_2)_4-$, $R^3 = Ph$).³⁵ Conditions: 2-phenylcyclohexanone oxime⁹⁰ (3.00 g, 15.8 mmol), acetic acid (2.72 mL, 47.6 mmol), acetic anhydride (4.49 mL, 47.6 mmol), iron powder (1.77 g, 31.7 mmol), and anhydrous toluene (25 mL). The crude product was purified by column chromatography (pet. ether:EtOAc, 6:1). Yield 640 mg (19%).

N-(2,2,6-Trimethylcyclohexen-1-yl)acetamide (**5j**, $X = H$, $R^1 = R^2 = -CMe_2(CH_2)_3-$, $R^3 = Me$). Conditions: 2,2,6-trimethylcyclohexanone oxime⁹¹ (2.40 g, 15.5 mmol), acetic acid (2.65 mL, 46.4 mmol), acetic anhydride (4.38 mL, 46.4 mmol), iron powder (1.73 g, 30.9 mmol), and anhydrous toluene (25 mL). The crude product was purified by gradient column chromatography (pet. ether:EtOAc, 9:1 to 1:1). Yield 403 mg (14%); 2:1 ratio isomers; yellow solid; mp 122–124 °C; R_f 0.50 (pet. ether:EtOAc, 1:1); IR ν_{max} (film)/ cm^{-1} 3271, 2926, 1649; 1H NMR δ_H (CDCl₃, 400 MHz) 6.11 (1H, s, minor), 6.12 (1H, s, major), 2.07 (2H, s), 2.03–2.09 (2H, m), 1.89 (1H, s), 1.62 (1H, s), 1.48–1.68 (4H, m), 1.54 (2H, s), 1.01 (2H, s), 1.00 (4H, s); ^{13}C NMR δ_C (100 MHz, CDCl₃) mixture of rotamers, 173.7, 168.4, 134.5, 131.9, 131.6, 130.4, 38.9, 38.8, 35.6, 35.1, 32.0, 31.8, 27.4, 27.2, 27.1, 26.5, 23.4, 19.6, 19.4, 19.3, 19.1, 19.0; MS m/z (ESI) 204.1 ($[M]^+Na$) [found ($[M]^+Na$) 204.1366, C₁₁H₁₉NNaO requires 204.1364].

General Procedure for the Formation of 2-Chloroacetamides. 2-Chloroacetamides were prepared by the method of Tang et al.³³ using the following modification: Oxime (1 equiv), 2-chloroacetic

acid (3 equiv), 2-chloroacetic anhydride (3 equiv) and iron powder (2 equiv) were heated to reflux in anhydrous toluene under an inert atmosphere for 6–16 h. The mixture was then filtered through Celite, diluted with DCM and washed with 2 M NaOH and saturated NaCl solution. The organic phase was then dried over MgSO₄, filtered and then concentrated *in vacuo* to give the crude product. Products were purified by column chromatography or recrystallization as stated below.

N-(2-Methyl-3,4-dihydronaphthalen-1-yl)-2-chloroacetamide (**5k**, $X = Cl$, $R^1 = R^2 = -C_6H_4CH_2CH_2-$, $R^3 = Me$). Conditions: 2-methyl-1-tetralone oxime⁸⁹ (2.94 g, 16.8 mmol, 1 equiv), 2-chloroacetic acid (4.76 g, 50.4 mmol, 3 equiv), 2-chloroacetic anhydride (8.61 g, 50.4 mmol, 3 equiv), and iron powder (1.88 g, 33.6 mmol, 2 equiv) were heated to 70 °C for 36 h in anhydrous toluene (25 mL). The crude product was then purified by recrystallization from hexane:EtOAc 10:1 to give the 2.09 g, (53%); pale brown solid; mp 139–141 °C; R_f 0.23 (pet. ether:EtOAc, 3:1); IR ν_{max} (film)/ cm^{-1} 3229, 2933, 1650; 1H NMR δ_H (CDCl₃, 400 MHz) 7.59 (1H, s), 7.22–7.09 (3H, m), 7.06 (1H, d, $J = 7.5$), 4.25 (2H, s), 2.84 (2H, t, $J = 8.0$), 2.42 (2H, t, $J = 8.0$), 1.88 (3H, s); ^{13}C NMR δ_C (CDCl₃, 100 MHz) 164.8, 135.3, 135.0, 132.5, 127.6, 127.0, 126.6, 125.2, 121.3, 42.9, 29.8, 27.6, 19.6; MS m/z (ESI) 258 ($[M]^+Na$) [found ($[M]^+Na$) 258.0656, C₁₃H₁₄ClNNaO requires 258.0656]. Anal. Found: C, 66.2%; H, 5.9%; N, 5.8% C₁₃H₁₄ClNO. Calcd: 66.2%; H, 6.0%; N, 5.8%.

2-Chloro-*N*-(2-methyl-1-phenylprop-1-enyl)acetamide (**5l**, $X = Cl$, $R^1 = Ph$, $R^2 = R^3 = Me$).⁹⁶ Conditions: 2-methyl-1-phenylpropan-1-one oxime⁸⁸ (2.00 g, 12.2 mmol), 2-chloroacetic acid (3.47 g, 36.8 mmol), 2-chloroacetic anhydride (6.28 g, 36.8 mmol), iron powder (1.37 g, 24.5 mmol), and anhydrous toluene (20 mL). The crude product was purified by recrystallization (pet. ether:EtOAc, 6:1) to give 676 mg, (25%).

2-Chloro-*N*-(cyclohexylidene(phenyl)methyl)acetamide (**5m**, $X = Cl$, $R^1 = Ph$, $R^2 = R^3 = -(CH_2)_4-$). Conditions: cyclohexyl(phenyl)methanone oxime⁸⁹ (4.00 g, 19.7 mmol), 2-chloroacetic acid (5.58 g, 59.1 mmol), 2-chloroacetic anhydride (10.1 g, 59.1 mmol), iron powder (2.20 g, 39.4 mmol), and anhydrous toluene (80 mL). The crude product was purified by column chromatography (pet. ether:EtOAc, 4:1) to give 2.26 g (48%); yellow crystalline solid; mp 128–130 °C; R_f 0.64 (pet. ether:EtOAc, 1:1); IR ν_{max} (film)/ cm^{-1} 3232, 2917, 1654; 1H NMR δ_H (CDCl₃, 400 MHz) 7.61 (1H, s), 7.12–7.39 (5H, m), 4.08 (2H, s), 2.17–2.26 (4H, m), 1.51–1.69 (6H, m); ^{13}C NMR δ_C (CDCl₃, 100 MHz) 164.2, 138.4, 137.9, 129.2, 128.3, 127.6, 124.1, 42.8, 31.0, 30.8, 28.0, 27.4, 26.5; MS m/z (ESI) found ($[M]^+Na$) 286.0977, C₁₅H₁₈ClNNaO requires 286.0969.

General Procedure for the Formation of Enamides (4b, 4d–i, 7a–d, 8a, 8b, 8d, 8e, 13b–d, 14, 15, 25a, 26a, 27a, 27b, 27d, 28). The acetamide 5a–j or 2-chloroacetamide 5k–m (1 equiv) was added to sodium hydride (1.5–5.0 equiv, 60% w/w dispersion in mineral oil) in anhydrous THF and cooled to 0 °C. Benzyl bromide (1.05–1.5 equiv) was then added and the reaction heated to reflux under an inert atmosphere for 10–16 h. The reaction mixture was then added to water (20 mL) and extracted with ethyl acetate or DCM (3 × 50 mL). The combined organic layers were then dried over MgSO₄, filtered, and then concentrated *in vacuo* to give the crude product. Products were purified by column chromatography or recrystallization as stated below.

(*E*)-*N*-Benzyl-*N*-(but-2-en-2-yl)acetamide (**4d**) and (*Z*)-*N*-Benzyl-*N*-(but-2-en-2-yl)acetamide (**4b**). Conditions: *N*-(but-2-en-2-yl)-acetamide (200 mg, 1.77 mmol), sodium hydride (354 mg, 8.84 mmol), benzyl bromide (0.22 mL, 1.86 mmol), and anhydrous THF (25 mL). Yield 2:1 (*Z*:*E*) ratio of isomers 4d:4b. Purification by column chromatography (pet. ether:EtOAc, 6:1) gave a pure sample of (*Z*)-*N*-benzyl-*N*-(but-2-en-2-yl)acetamide (**4d**) as a yellow oil (57 mg, 16%) and an impure sample of (*E*)-*N*-benzyl-*N*-(but-2-en-2-yl)-acetamide (**4b**) as a 1:1.8 (*Z*:*E*) mixture (153 mg).

Data for **4b**: R_f 0.1 (pet. ether:EtOAc, 6:1); IR ν_{max} (film)/ cm^{-1} 2934, 1655; 1H NMR δ_H (CDCl₃, 400 MHz) 7.08–7.34 (5H, m), 5.30 (1H, q, $J = 7.0$ Hz), 4.72 (1H, d, $J = 14.0$ Hz), 4.32 (1H, d, $J = 14.0$ Hz), 1.93 (3H, s), 1.67 (3H, s), 1.11 (3H, d, $J = 7.0$ Hz); ^{13}C NMR δ_C

(CDCl₃, 100 MHz) 169.7, 137.7, 136.3, 129.3, 128.2, 127.4, 124.2, 48.5, 21.3, 21.1, 12.6; MS *m/z* (ESI) found ([M]⁺Na) 204.1383, C₁₃H₁₈NO requires 204.1383.

Data for **4d**: discernible data *R_f* 0.075 (pet. ether:EtOAc, 6:1); IR *v*_{max} (film)/cm⁻¹ (mixture) 2934, 1655; ¹H NMR δ_H (CDCl₃, 400 MHz) δ 7.09–7.45 (5H, m), 5.11 (1H, q, *J* = 7.0 Hz), 4.53 (2H, s), 1.97 (3H, s), 1.64 (3H, s), 1.50 (3H, d, *J* = 7.0 Hz); ¹³C NMR δ_C (CDCl₃, 100 MHz) δ 170.0, 138.1, 137.3, 128.7, 127.1, 126.4, 125.9, 49.4, 21.7, 15.7, 13.2; MS *m/z* (ESI) found ([M]⁺Na) 204.1383, C₁₃H₁₈NO requires 204.1383.

N-Benzyl-*N*-(2-methylprop-1-enyl)acetamide (**4e**).⁹⁷ Conditions: *N*-(2-methylprop-2-en-2-yl)acetamide (200 mg, 1.77 mmol), sodium hydride (354 mg, 8.84 mmol), benzyl bromide (0.22 mL, 1.86 mmol), and anhydrous THF (25 mL). Yield 99 mg (28%); colorless oil; *R_f* 0.35 (pet. ether:EtOAc, 4:1); IR *v*_{max} (film)/cm⁻¹ 2914, 1647; ¹H NMR δ_H (CDCl₃, 400 MHz) 7.11–7.37 (5H, m), 5.74 (1H, apparent quintet, *J* = 1.0 Hz), 4.56 (2H, s), 1.97 (3H, s), 1.65 (3H, d, *J* = 1.0 Hz), 1.39 (3H, d, *J* = 1.0 Hz); ¹³C NMR δ_C (CDCl₃, 100 MHz) 170.9, 137.5, 136.5, 128.9, 128.4, 127.3, 124.0, 50.7, 22.1, 21.9, 17.5; MS *m/z* (ESI) 204.1 ([M]⁺H), 226.1 ([M]⁺Na).

N-Benzyl-*N*-(2-phenylcyclohexene-1-yl)acetamide (**4f**).⁹⁸ Conditions: *N*-benzyl-*N*-(2-phenylcyclohexene-1-yl)acetamide (300 mg, 1.39 mmol), sodium hydride (279 mg, 6.97 mmol), benzyl bromide (0.17 mL, 1.46 mmol), and anhydrous THF (30 mL). Crude product was purified by column chromatography (pet. ether:EtOAc 2:1). Yield 293 mg (69%); yellow oil; *R_f* 0.48 (pet. ether:EtOAc, 2:1); IR *v*_{max} (film)/cm⁻¹ 2928, 1638; δ_H (CDCl₃, 400 MHz) 7.09–7.31 (10H, m), 5.10 (1H, d, *J* = 14.5 Hz), 3.50 (1H, d, *J* = 14.5 Hz), 2.34–2.41 (2H, m), 2.09 (3H, s), 1.94–2.07 (2H, m), 1.57–1.79 (4H, m); ¹³C NMR δ_C (CDCl₃, 100 MHz) 170.2, 140.7, 138.3, 136.3, 135.6, 128.9, 128.7, 128.4, 127.4, 127.3, 127.1, 50.6, 31.8, 31.4, 23.1, 22.7, 22.2; MS *m/z* (ESI) 306.1 [M + H]⁺, 328.1 [M + Na]⁺; HPLC (S,S)-Whelk-O1 (25 cm × 4.6 mm) hexanes:iPrOH (1.0 mL/min) *t_R* 27.55 min.

N-Benzyl-*N*-(3-methylbut-2-en-2-yl)acetamide (**4g**). Conditions: *N*-(3-methylbut-2-en-2-yl)acetamide (500 mg, 3.93 mmol), sodium hydride (786 mg, 19.66 mmol), benzyl bromide (0.49 mL, 4.13 mmol), and anhydrous THF (60 mL). Yield 680 mg (80%); yellow oil; *R_f* 0.33 (pet. ether:EtOAc, 4:1); IR *v*_{max} (film)/cm⁻¹ 2920, 1644; ¹H NMR δ_H (CDCl₃, 400 MHz) 7.23–7.31 (5H, m), 4.64 (1H, d, *J* = 14.0 Hz), 4.50 (1H, d, *J* = 14.0 Hz), 1.95 (3H, s), 1.69 (3H, s), 1.64 (3H, s), 1.27 (3H, s); ¹³C NMR δ_C (CDCl₃, 375 MHz) 170.2, 137.9, 131.1, 129.6, 129.5, 128.3, 127.4, 49.2, 21.4, 19.6, 19.4, 17.5; MS *m/z* (ESI) found ([M]⁺H) 218.1540, C₁₄H₂₀NO requires 218.1539.

N-Methyl-*N*-(2,4-dimethylpent-2-en-3-yl)acetamide (**4h**). Conditions: *N*-(2,4-dimethylpent-2-en-3-yl)acetamide (496 mg, 3.2 mmol), sodium hydride (1.02g, 25.6 mmol), and methyl iodide (3.64 g, 25.6 mmol). Yield 186 mg (33%); colorless oil; *R_f* 0.16 (3:1 pet. ether:EtOAc); IR *v*_{max} (cm⁻¹) 2965, 1637; ¹H NMR δ_H (CDCl₃, 300 MHz) 3.05–2.91 (1H, sept, *J* = 6.9 Hz), 2.96 (3H, s), 1.91 (3H, s), 1.73 (3H, s), 1.55 (3H, s), 1.08 (3H, d, *J* = 6.9 Hz), 0.97 (3H, d, *J* = 6.9 Hz); ¹³C NMR δ_C (CDCl₃, 75 MHz) 171.6, 140.5, 129.5, 36.3, 30.3, 22.9, 21.3, 20.0, 19.8, 19.3; MS *m/z* (ESI) 192 ([M]⁺Na), 170 ([M]⁺H) [found ([M]⁺H) 170.1541, C₁₀H₂₀NO requires 170.1545]; HPLC (S,S)-Whelk-O1 (25 cm × 4.6 mm) hexanes:iPrOH (1.0 mL/min) *t_R* 43.67 and 45.73 min; Anal. Found C, 69.6%; H, 11.2%; N, 7.9% C₁₀H₂₀NO. Calcd 71.0%; H, 11.3%; N, 8.3%.

N-Benzyl-*N*-(2,4-dimethylpent-2-en-3-yl)acetamide (**4i**). Conditions: *N*-(2,4-dimethylpent-2-en-3-yl)acetamide (149 mg, 0.96 mmol), sodium hydride (192 mg, 4.8 mmol), and benzyl bromide (120 mg, 1.01 mmol). Yield 52 mg (22%); colorless oil; *R_f* 0.36 (3:1 pet. ether:EtOAc); IR *v*_{max}/cm⁻¹ 2965, 1642; ¹H NMR δ_H (CDCl₃, 300 MHz) 7.40–7.27 (5H, m), 5.27 (1H, d, *J* = 14.0 Hz), 3.99 (1H, d, *J* = 14.0 Hz), 2.98 (1H, sept, *J* = 7.3 Hz), 1.99 (3H, s), 1.7 (3H, s), 1.27 (3H, d, *J* = 7.5 Hz), 1.05 (3H, d, *J* = 7.5 Hz), 1.01 (3H, s); ¹³C NMR δ_C (CDCl₃, 75 MHz) 170.2, 137.6, 131.7, 130.0, 128.3, 127.4, 50.7, 30.1, 23.9, 21.7, 20.5, 19.5, 19.4; MS *m/z* (ESI) found ([M]⁺Na) 268.1672, C₁₆H₂₃NNaO requires 268.1677; HPLC (S,S)-Whelk-O1 (25 cm × 4.6 mm) hexanes:iPrOH (1.0 mL/min) *t_R* 30.07 and 37.30 min.

N-Benzyl-*N*-(1-phenyl-2-methylprop-1-en-1-yl)acetamide (**7a**).³⁸ Conditions: *N*-(1-phenyl-2-methylprop-1-en-1-yl)acetamide (3.50 g, 18.5 mmol), sodium hydride (3.70 mg, 92.5 mmol), benzyl bromide (2.30 mL, 19.4 mmol), and anhydrous THF (300 mL). Yield 3.67 g (71%); yellow oil; *R_f* 0.18 (pet. ether:EtOAc, 6:1); IR *v*_{max} (film)/cm⁻¹ 2991, 1642; ¹H NMR δ_H (CDCl₃, 400 MHz) 7.28–7.42 (3H, m), 7.19–7.28 (7H, m), 5.27 (1H, d, *J* = 14.0 Hz), 3.48 (1H, d, *J* = 14.0 Hz), 2.16 (3H, s), 1.76 (3H, s), 1.28 (3H, s); ¹³C NMR δ_C (CDCl₃, 75 MHz) 170.8, 137.3, 136.6, 133.8, 133.5, 129.9, 129.4, 128.4, 128.2, 127.9, 127.4, 48.5, 21.5, 21.4, 20.9; MS *m/z* (ESI) 280.2 ([M]⁺Na); HPLC (S,S)-Whelk-O1 (25 cm × 4.6 mm) hexanes:iPrOH (1.0 mL/min) *t_R* 13.70 min.

N-Benzyl-*N*-(2-methyl-3,4-dihydronaphthalen-1-yl)acetamide (**7b**). Conditions: *N*-(2-methyl-3,4-dihydronaphthalen-1-yl)acetamide (141 mg, 0.70 mmol), sodium hydride (140 mg, 3.5 mmol), benzyl bromide (0.09 mL, 0.74 mmol), and anhydrous THF (10 mL). Yield 99 mg (49%); white solid; mp 158–159 °C; *R_f* 0.36 (pet. ether:EtOAc, 3:1); IR *v*_{max} (film)/cm⁻¹ 2927, 1643; ¹H NMR δ_H (CDCl₃, 400 MHz) 7.30–7.17 (8H, m), 6.98 (1H, m), 5.49 (1H, d, *J* = 13.5 Hz), 3.74 (1H, d, *J* = 13.5 Hz), 2.87–2.69 (2H, m), 2.35 (1H, ddd, *J* = 16.5, 6.5, 4.0 Hz), 2.14 (1H, ddd, *J* = 16.6, 6.5, 4.0 Hz), 1.90 (3H, s), 1.24 (3H, brs); ¹³C NMR δ_C (CDCl₃, 75 MHz) 170.6, 136.5, 136.2, 135.6, 135.5, 131.2, 129.6, 127.5, 127.1, 126.8, 126.6, 126.3, 121.2, 48.8, 28.9, 26.8, 20.6, 18.3; MS *m/z* (ESI) 314 ([M]⁺Na) [found ([M]⁺H) 292.1696, C₂₀H₂₂NO requires 292.1701]; HPLC (S,S)-Whelk-O1 (25 cm × 4.6 mm) hexanes:iPrOH (1.0 mL/min) *t_R* 30.07 and 37.38 min.

N-Benzyl-*N*-(2,2,6-trimethylcyclohexen-1-yl)acetamide (**7c**). Conditions: *N*-(2,2,6-trimethylcyclohexen-1-yl)acetamide (300 mg, 1.65 mmol), sodium hydride (331 mg, 8.27 mmol), benzyl bromide (0.21 mL, 1.73 mmol), and anhydrous THF (30 mL). Yield 0.331 g (74%) colorless oil; *R_f* 0.52 (pet. ether:EtOAc, 3:1); IR *v*_{max} (film)/cm⁻¹ 2931, 1641; ¹H NMR δ_H (CDCl₃, 400 MHz) 7.22–7.35 (5H, m), 5.00 (1H, d, *J* = 14.5 Hz), 4.35 (1H, d, *J* = 14.5 Hz), 1.99–2.07 (2H, m), 1.97 (3H, s), 1.50–1.83 (4H, m), 1.17 (3H, s), 1.07 (3H, s), 1.06 (3H, s); ¹³C NMR δ_C (CDCl₃, 100 MHz) 172.2, 139.5, 138.0, 133.9, 129.5, 128.2, 127.2, 51.7, 41.2, 36.0, 31.8, 30.5, 27.7, 21.9, 19.4 18.6; MS *m/z* (ESI) found ([M]⁺HNa) 294.1829, C₁₈H₂₅NNaO requires 294.1828.

N-Benzyl-*N*-(cyclohexylidene(phenyl)methyl)acetamide (**7d**). Conditions: *N*-(cyclohexylidene(phenyl)methyl)acetamide (600 mg, 2.62 mmol), sodium hydride (520 mg, 13.1 mmol), benzyl bromide (0.33 mL, 2.75 mmol), and anhydrous THF (50 mL). The crude product was recrystallized from hexane to give 0.721 g (86%); pale orange solid; mp 89–92 °C; *R_f* 0.45 (pet. ether:EtOAc, 4:1); IR *v*_{max} (film)/cm⁻¹ 2925, 1646; ¹H NMR δ_H (CDCl₃, 400 MHz) 7.23–7.40 (10H, m), 5.37 (1H, d, *J* = 14.0 Hz), 3.37 (1H, d, *J* = 14.0 Hz), 2.38–2.54 (1H, m), 2.18 (3H, s), 1.77–1.94 (2H, m), 1.60–1.74 (2H, m), 1.43–1.54 (1H, m), 1.22–1.42 (3H, m), 0.42–0.56 (1H, m); ¹³C NMR δ_C (CDCl₃, 100 MHz) 170.8, 140.8, 137.4, 136.5, 130.7, 130.0, 129.3, 128.5, 128.3, 128.0, 127.4, 48.0, 31.4, 31.3, 28.0, 26.7, 26.4, 21.5; MS *m/z* (ESI) found ([M]⁺H) 320.2005, C₂₂H₂₆NO requires 320.2009; HPLC (S,S)-Whelk-O1 (25 cm × 4.6 mm) hexanes:iPrOH (1.0 mL/min) *t_R* 24.10 min.

N-(1-Cyclohexenyl)-*N*-methylphenylacetamide (**8a**). Conditions: *N*-(1-cyclohexenyl)phenylacetamide³⁹ (58 mg, 0.27 mmol), NaH (9.5 mg, 0.40 mmol), MeI (57 mg, 25 μL) at rt for 5 h, purified by column chromatography (4:1 pet. ether:EtOAc). Yield 48 mg (84%); *R_f* (4:1 pet. ether:EtOAc) 0.23; IR *v*_{max} (film)/cm⁻¹ 2926, 1648, 1378, 1102; ¹H NMR δ_H (CDCl₃, 300 MHz) 7.34–6.98 (5H, m), 5.54 (1H, s), 3.65 (2H, s), 2.97 (3H, s), 2.18–2.05 (2H, m), 1.99–1.93 (2H, m), 1.75–1.62 (4H, m); ¹³C NMR δ_C (CDCl₃, 75.5 MHz) 170.7, 140.4, 136.3, 129.1, 128.4, 126.8, 126.6, 40.7, 34.3, 27.6, 24.7, 22.7, 21.6; MS *m/z* (ESI) 252 ([M]⁺Na) [found ([M]⁺Na) 252.1361, C₁₅H₁₉NNaO requires 252.1364].

N-(1-Cyclohexenyl)-*N*-butylphenylacetamide (**8b**). Conditions: *N*-(1-cyclohexenyl)phenylacetamide³⁹ (65 mg, 0.30 mmol), NaH (10.8 mg, 0.45 mmol), and 1-bromobutane (62 mg, 0.467 mmol, 49 μL). Yield 66 mg (70%); *R_f* (4:1 pet. ether:EtOAc) 0.45; IR *v*_{max} (film)/cm⁻¹ 2930, 1640, 1400, 1126; ¹H NMR δ_H (CDCl₃, 300 MHz) 7.42–7.07 (5H, m), 5.47 (1H, m), 3.63 (2H, s), 3.36 (2H, br s), 2.15–1.84 (4H, m, 4H), 1.77–1.51 (4H, m), 1.51–1.28 (m, 2H), 1.41–1.14 (2H,

m), 1.03 (3H, t, $J = 7.5$ Hz); ^{13}C NMR δ_{C} (CDCl_3 , 75.5 MHz) 170.3, 138.6, 136.5, 129.1, 128.4, 128.0, 126.5, 45.4, 41.1, 30.2, 28.0, 24.9, 22.9, 21.7, 20.2, 14.0; MS m/z (ESI) 294 ($[\text{M}]^+\text{Na}$) [found ($[\text{M}]^+\text{Na}$) 294.1831, $\text{C}_{18}\text{H}_{25}\text{NNaO}$ requires 294.1834].

N-(1-Cyclohexenyl)-*N*-isopropylphenylacetamide (**8d**). Conditions: *N*-(1-cyclohexenyl)phenylacetamide³⁹ (66 mg, 0.31 mmol), NaH (11.3 mg, 0.47 mmol), and 2-bromopropane (58 mg, 0.47 mmol, 44 μL). Yield 12 mg (13%); R_f (3:1 pet. ether:EtOAc) 0.66; IR ν_{max} (film)/ cm^{-1} 2929, 1642, 1391, 1229; ^1H NMR δ_{H} (CDCl_3 , 300 MHz) 7.36–7.14 (5H, m), 5.40 (1H, s), 4.59 (1H, sep, $J = 7.5$ Hz), 3.57 (2H, s), 2.20–1.48 (8H, m), 1.19–1.00 (6H, m); ^{13}C NMR δ_{C} (CDCl_3 , 75.5 MHz) 170.3, 136.7, 136.3, 130.1, 129.1, 128.4, 126.5, 46.6, 41.8, 31.7, 25.1, 23.1, 21.6, 21.1; MS m/z (ESI) 280 ($[\text{M}]^+\text{Na}$) [found ($[\text{M}]^+\text{Na}$) 280.1677, $\text{C}_{17}\text{H}_{23}\text{NNaO}$ requires 280.1677].

N-(1-Cyclohexenyl)-*N*-*t*-butyldimethylsilylphenylacetamide (**8e**). This was prepared in an NMR tube by the reaction of *N*-(1-cyclohexenyl)phenylacetamide⁴³ (43 mg, 0.2 mmol) with 2 equiv of 2,6-lutidine (42.8 mg, 46.5 μL , 0.4 mmol) and *tert*-butyldimethylsilyl triflate (106 mg, 92 μL , 0.4 mmol) in 1 mL of toluene- d_8 . The crude mixture was submitted to VT ^1H NMR immediately without purification.

N-Cyclohex-1-enyl-*N*-2-fluorobenzylacetamide (**13b**). Yield 45%; clear oil; R_f (3:1 pet. ether:EtOAc) 0.45; IR ν_{max} (film)/ cm^{-1} 2932, 1648, 1489; ^1H NMR δ_{H} (CDCl_3 , 300 MHz) 7.40–7.31 (1H, m), 7.25–7.13 (1H, m), 7.06 (1H, t, $J = 7.4$ Hz), 6.97 (1H, t, $J = 9.0$ Hz), 5.36 (1H, s), 4.69 (2H, s), 2.05 (3H, s), 2.04–1.92 (4H, m), 1.72–1.59 (2H, m), 1.59–1.43 (2H, m); ^{13}C NMR δ_{C} (CDCl_3 , 75.5 MHz) 170.3, 161.0 (d, $J = 244.5$ Hz), 138.8, 131.2 (d, $J = 3.8$ Hz), 129.0 (d, $J = 8.25$ Hz), 128.1, 124.9 (d, $J = 14.25$ Hz), 124.1 (d, $J = 3.8$ Hz), 115.0 (d, $J = 21.8$ Hz), 42.3 (d, $J = 3.7$ Hz), 27.9, 24.9, 22.8, 21.7, 21.5; MS m/z (ESI) 270 ($[\text{M}]^+\text{Na}$) [found ($[\text{M}]^+\text{Na}$) 270.1263, $\text{C}_{15}\text{H}_{18}\text{FNNaO}$ requires 270.1270].

N-Cyclohex-1-enyl-*N*-2-iodobenzylacetamide (**13c**). Yield 45%; yellow oil; R_f (6:1 pet. ether:EtOAc) 0.49; IR ν_{max} (film)/ cm^{-1} 2928, 1643; ^1H NMR δ_{H} (CDCl_3 , 300 MHz) 7.78 (1H, d, $J = 8.0$ Hz), 7.37 (1H, d, $J = 8.0$ Hz), 7.29 (1H, t, $J = 8.0$ Hz), 6.93 (1H, t, $J = 8.0$ Hz), 5.44 (1H, s), 4.73 (2H, s), 2.10 (3H, s), 2.02 (4H, m), 1.70–1.62 (2H, m), 1.57–1.52 (2H, m); ^{13}C NMR δ_{C} (101 MHz, CDCl_3) 170.3, 140.3, 139.2, 138.6, 129.7, 128.8, 128.4, 99.6, 53.5, 28.1, 24.8, 22.7, 21.5, 21.4; MS m/z (ESI) 356.05 ($[\text{M}]^+\text{H}$) [found ($[\text{M}]^+\text{H}$) 356.0516, $\text{C}_{15}\text{H}_{19}\text{INO}$ requires 356.0506].

N-Cyclohex-1-enyl-*N*-2,6-difluorobenzylacetamide (**13d**). Yield 45%; colorless oil; R_f (3:1 pet. ether:EtOAc) 0.45; IR ν_{max} (film)/ cm^{-1} 2933, 1651, 1470, 1387; ^1H NMR δ_{H} (CDCl_3 , 300 MHz) 7.24–7.13 (1H, m), 6.96–6.72 (2H, m), 5.27 (1H, s), 4.78 (2H, s), 1.99 (3H, s), 1.96–1.83 (4H, m), 1.63–1.48 (2H, m), 1.48–1.35 (2H, m); ^{13}C NMR δ_{C} (CDCl_3 , 75.5 MHz) 169.4, 162.0 (dd, $J = 255.8$, 7.5 Hz), 137.4, 129.5 (t, $J = 10.5$ Hz), 128.7, 113.0 (t, $J = 18.8$ Hz), 111.1 (dd, $J = 17.3$, 7.5 Hz), 35.6 (t, $J = 3.0$ Hz), 27.4, 24.9, 22.8, 21.7, 21.4; MS m/z (ESI) 288 ($[\text{M}]^+\text{Na}$) [found ($[\text{M}]^+\text{Na}$) 288.1170, $\text{C}_{15}\text{H}_{17}\text{F}_2\text{NNaO}$ requires 288.1176].

N-Cyclohex-1-enyl-*N*-2,6-dichlorobenzylacetamide (**13e**). Yield 85%; yellow oil; R_f (4:1 pet. ether:EtOAc) 0.28; IR ν_{max} (film)/ cm^{-1} 2929, 1647; ^1H NMR δ_{H} (CDCl_3 , 300 MHz) 7.28 (2H, d, $J = 7.0$ Hz), 7.14 (1H, t, $J = 7.0$ Hz), 5.30–5.32 (1H, m), 5.06 (2H, br s), 2.05 (3H, s), 1.95–1.78 (4H, m), 1.56–1.48 (2H, m), 1.45–1.34 (2H, m); ^{13}C NMR δ_{C} (CDCl_3 , 75.5 MHz) 169.7, 137.4, 137.2, 133.1, 129.4, 129.2, 128.4, 43.5, 28.4, 24.9, 22.8, 21.5, 21.4; MS m/z (ESI) 320 ($[\text{M}]^+\text{Na}$) (^{35}Cl), 322 ($[\text{M}]^+\text{Na}$) (^{37}Cl) [found ($[\text{M}]^+\text{Na}$) 320.0574, $\text{C}_{15}\text{H}_{17}^{35}\text{Cl}_2\text{NNaO}$ requires 320.0585].

N-Cyclohex-1-enyl-*N*-2,6-dibromobenzylacetamide (**13f**). Yield 26%; yellow oil; R_f (6:1 pet. ether:EtOAc) 0.47; IR ν_{max} (film)/ cm^{-1} 2926, 1648; ^1H NMR δ_{H} (CDCl_3 , 300 MHz) 7.48 (2H, d, $J = 8.0$ Hz), 6.95 (1H, t, $J = 8.0$ Hz), 5.35 (1H, s), 5.06 (2H, s), 2.02 (3H, s), 1.88–1.84 (4H, m), 1.53–1.47 (2H, m), 1.42–1.36 (2H, m); ^{13}C NMR δ_{C} (101 MHz, CDCl_3) 169.9, 137.3, 135.7, 132.5, 130.2, 129.5, 127.1, 48.8, 28.7, 24.9, 22.8, 21.4, 21.3; MS m/z (ESI) 385.98 ($[\text{M}]^+\text{H}$) [found ($[\text{M}]^+\text{H}$) 385.9747, $\text{C}_{15}\text{H}_{18}\text{Br}_2\text{NO}$ requires 385.9750].

N-(2-Bromobenzyl)-*N*-(2-methyl-1-phenylprop-1-en-1-yl)acetamide (**14**). Conditions: *N*-(1-phenyl-2-methylprop-1-en-1-yl)acetamide³⁷

(**9e**) (1.82 g), sodium hydride (1.92 g, 48.1 mmol), and 2-bromobenzyl bromide (2.52 g, 10.1 mmol) in anhydrous THF (140 mL). The crude product was purified by column chromatography (pet. ether:EtOAc, 4:1). Yield 1.88 g (55%); pale yellow crystalline solid; mp 92–94 °C; R_f 0.43 (pet. ether:EtOAc, 4:1); IR ν_{max} (film)/ cm^{-1} 2922, 1640; ^1H NMR δ_{H} (CDCl_3 , 400 MHz) 7.53 (1H, d, $J = 7.5$ Hz), 7.46 (1H, d, $J = 8.0$ Hz), 7.25–7.40 (5H, m), 7.21 (1H, t, $J = 7.5$ Hz), 7.08 (1H, t, $J = 7.5$ Hz), 5.22 (1H, d, $J = 14.5$ Hz), 4.13 (1H, d, $J = 14.5$ Hz), 2.21 (3H, s), 1.82 (3H, s), 1.51 (3H, s); ^{13}C NMR δ_{C} (CDCl_3 , 100 MHz) 171.4, 137.1, 136.5, 134.2, 132.7, 132.6, 129.4, 129.2, 129.0, 128.2, 127.8, 127.3, 124.4, 48.7, 21.5, 21.5, 21.1; MS m/z (ESI) 358 ($[\text{M}]^+\text{H}$) [found ($[\text{M}]^+\text{H}$) 358.0800, $\text{C}_{19}\text{H}_{21}\text{BrNO}$ requires 358.0801].

N-Cyclohept-1-enyl-*N*-2,6-dibromobenzylacetamide (**15**). Yield 49%; yellow oil; R_f (6:1 pet. ether:EtOAc) 0.45; IR ν_{max} (film)/ cm^{-1} 2921, 1647; ^1H NMR δ_{H} (400 MHz, CDCl_3) 7.49 (2H, d, $J = 8.0$ Hz), 6.97 (1H, t, $J = 8.0$ Hz), 5.72 (1H, t, $J = 6.2$ Hz), 5.12 (1H, br s), 5.00 (1H, br s), 2.03 (3H, s), 1.95 (4H, m), 1.52–1.32 (6H, m); ^{13}C NMR δ_{C} (101 MHz, CDCl_3) 169.7, 142.3, 135.5, 133.4, 132.5, 130.2, 127.1, 49.7, 34.5, 30.8, 27.0, 26.2, 25.4, 21.9; MS m/z (ESI) 399.99 ($[\text{M}]^+\text{H}$) [found ($[\text{M}]^+\text{H}$) 399.9909, $\text{C}_{16}\text{H}_{20}\text{Br}_2\text{NO}$ requires 399.9906].

N-Benzyl-2-chloro-*N*-(2-methyl-1-phenylprop-1-en-1-yl)acetamide (**25a**). The general procedure for the alkylation of enamides (6.1.4) was applied using 2-chloro-*N*-(2-methyl-1-phenylprop-1-en-1-yl)acetamide (500 mg, 2.24 mmol), sodium hydride (447 mg, 11.2 mmol), and benzyl bromide (278 μL , 2.35 mmol) in anhydrous THF (40 mL). Yield 316 mg (42%); yellow oil; R_f 0.28 (pet. ether:EtOAc, 6:1); IR ν_{max} (film)/ cm^{-1} 2933, 1659; ^1H NMR δ_{H} (CDCl_3 , 400 MHz) 7.30–7.43 (3H, m), 7.22–7.30 (7H, m), 5.25 (1H, d, $J = 14.0$ Hz), 4.36 (1H, d, $J = 13.5$ Hz), 4.12 (1H, d, $J = 13.5$ Hz), 3.61 (1H, d, $J = 14.0$ Hz), 1.81 (3H, s), 1.30 (3H, s); ^{13}C NMR δ_{C} (CDCl_3 , 75 MHz) 166.6, 136.4, 135.7, 135.2, 132.6, 139.0, 129.5, 128.7, 128.4, 127.8, 49.7, 41.9, 21.6, 21.0; MS m/z (ESI) found ($[\text{M}]^+\text{H}$) 336.1126, $\text{C}_{19}\text{H}_{20}\text{ClNO}$ requires 336.1131.

N-Benzyl-2-chloro-*N*-(cyclohexylidene(phenyl)methyl)acetamide (**26a**). Conditions: *N*-(2-methyl-3,4-dihydronaphthalen-1-yl)-2-chloroacetamide (1.9 g, 8.06 mmol), sodium hydride (1.61 g, 40.3 mmol), benzyl bromide (1.01 mL, 8.46 mmol), and anhydrous THF (150 mL). Yield 1.1 g (46%); white solid; mp 111–113 °C; R_f 0.4 (pet. ether:EtOAc, 9:1); IR ν_{max} (film)/ cm^{-1} 2928, 1663; ^1H NMR δ_{H} (CDCl_3 , 400 MHz) 7.24–7.41 (4H, m), 5.34 (1H, d, $J = 14.0$ Hz), 4.39 (1H, d, $J = 13.5$ Hz), 4.13 (1H, d, $J = 13.5$ Hz), 3.48 (1H, d, $J = 14.0$ Hz), 2.45–2.51 (1H, m), 1.75–1.87 (1H, m), 1.64–1.74 (1H, m), 1.49–1.62 (2H, m), 1.35–1.44 (1H, m), 1.09–1.36 (3H, m), 0.51–0.48 (1H, m); ^{13}C NMR δ_{C} (CDCl_3 , 100 MHz) 166.5, 142.0, 136.4, 135.5, 130.1, 129.8, 129.5, 129.3, 128.6, 128.3, 127.7, 49.0, 41.8, 31.4, 31.3, 27.9, 26.7, 26.2; MS m/z (ESI) found ($[\text{M}]^+\text{Na}$) 376.1435, $\text{C}_{22}\text{H}_{24}\text{ClNNaO}$ requires 376.1439; HPLC (S,S)-Whelk-O1 (25 cm \times 4.6 mm) hexanes:iPrOH (1.0 mL/min) partially resolved, t_R 23.50 and 27.75 min.

N-Benzyl-2-chloro-*N*-(2-methyl-3,4-dihydronaphthalen-1-yl)acetamide (**27a**). Conditions: *N*-(2-methyl-3,4-dihydronaphthalen-1-yl)-2-chloroacetamide (1.9 g, 8.06 mmol), sodium hydride (1.61 g, 40.3 mmol), benzyl bromide (1.01 mL, 8.46 mmol), and anhydrous THF (150 mL). Yield 960 mg (37%); white solid; mp 99–101 °C; R_f 0.18 (pet. ether:EtOAc, 9:1); IR ν_{max} (film)/ cm^{-1} 2925, 1666; ^1H NMR δ_{H} (CDCl_3 , 400 MHz) 7.09–7.42 (8H, m), 6.95 (1H, d, $J = 4.0$ Hz), 5.45 (1H, d, $J = 13.5$ Hz), 3.94 (2H, s), 3.90 (1H, d, $J = 13.5$ Hz), 2.70–2.89 (2H, m), 2.32–2.47 (1H, m), 2.14–2.24 (1H, m), 1.28 (3H, s); ^{13}C NMR δ_{C} (CDCl_3 , 75 MHz) 166.9, 138.3, 136.4, 136.2, 131.3, 130.5, 128.4, 128.0, 127.9, 127.8, 127.2, 122.0, 121.8, 50.8, 42.4, 29.6, 27.4, 19.2; MS m/z (ESI) 348 ($[\text{M}]^+\text{Na}$) [found ($[\text{M}]^+\text{H}$) 326.1313, $\text{C}_{20}\text{H}_{21}\text{ClNO}$ requires 326.1306]; HPLC (S,S)-Whelk-O1 (25 cm \times 4.6 mm) hexanes:iPrOH (1.0 mL/min) t_R 24.74 and 31.70 min.

N-Benzyl-*N*-(2-methyl-3,4-dihydronaphthalen-1-yl)-2-bromoacetamide (**27b**). *N*-Benzyl-*N*-(2-methyl-3,4-dihydronaphthalen-1-yl)-2-chloroacetamide (**13b**) (540 mg, 1.66 mmol, 1 equiv) in acetone (35 mL) was cooled to 0 °C and lithium bromide (1.43 g, 16.6 mmol, 10 equiv) added. The resulting mixture was stirred at room temperature

for 60 h. The reaction mixture was concentrated in vacuo to give a white solid which was taken up in water (30 mL) and extracted with DCM (3 × 20 mL). The combined organic extracts were then washed with cold water (30 mL), dried over MgSO₄, filtered, and concentrated in vacuo. The crude product was then purified by recrystallization from hexane to give an orange crystalline solid. Yield 519 mg (84%); mp 94–96 °C; R_f 0.19 (pet. ether:EtOAc, 9:1); IR ν_{max} (film)/cm⁻¹ 2926, 1660; ¹H NMR δ_H (CDCl₃, 300 MHz) 7.09–7.29 (8H, m), 6.94 (1H, dt, J = 7.5, 2.0 Hz), 5.40 (1H, d, J = 13.5 Hz), 3.92 (1H, d, J = 13.5 Hz), 3.77 (2H, s), 2.72–2.84 (2H, m), 2.47–2.28 (1H, m), 2.26–2.11 (1H, m), 1.28 (3H, s); ¹³C NMR δ_C (CDCl₃, 100 MHz) 166.3, 138.2, 136.4, 136.2, 131.4, 131.1, 130.4, 128.4, 127.9, 127.7, 127.1, 122.0, 50.9, 29.7, 28.1, 27.4, 19.5; MS m/z (ESI) found ([M]⁺Na) 392.0626, C₂₀H₂₀BrNNaO requires 392.0620; HPLC (S,S)-Whelk-O1 (25 cm × 4.6 mm) hexanes:iPrOH (1.0 mL/min) t_R 28.64 and 35.10 min.

Benzyl-N-(2-methyl-3,4-dihydronaphthalen-1-yl)-2-iodoacetamide (27d). N-Benzyl-N-(2-methyl-3,4-dihydronaphthalen-1-yl)-2-chloroacetamide (27b) (209 mg, 0.62 mmol, 1 equiv) in acetone (35 mL) was cooled to 0 °C and lithium iodide (830 mg, 6.20 mmol, 10 equiv) added. The resulting mixture was stirred at room temperature for 36 h. The reaction mixture was concentrated in vacuo to give a white solid which was taken up in water (30 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts were then washed with Na₂S₂O₃ (100 mL) and brine (100 mL), dried over MgSO₄, filtered, and concentrated in vacuo. The crude product was then purified by recrystallization from hexane to give an orange crystalline solid. Yield 191 mg (74%); R_f 0.60 (pet. ether:EtOAc, 3:1); IR ν_{max} (film)/cm⁻¹ 2929, 1652; ¹H NMR δ_H (CDCl₃, 300 MHz) 7.31–7.18 (8H, m), 6.95–6.97 (1H, m), 5.36 (1H, d, J = 14.1 Hz), 3.40 (1H, d, J = 14.1 Hz), 3.74 (1H, d, J = 12.1 Hz), 3.71 (1H, d, J = 12.1 Hz), 2.83–2.77 (2H, m), 2.50–2.40 (1H, m), 2.25–2.18 (1H, m), 1.36 (3H, s); ¹³C NMR δ_C (CDCl₃, 100 MHz) 168.5, 138.0, 136.7, 136.4, 131.9, 131.7, 130.6, 128.5, 128.1, 127.9, 127.2, 122.5, 51.3, 31.2, 29.9, 27.6, 20.1, -1.7; MS m/z (ESI) found ([M]⁺Na) 440.0482, C₂₀H₂₀INNaO requires 440.0487.

N-Benzyl-2-chloro-N-(2,6,6-trimethylcyclohex-1-enyl)acetamide (28). 2,2,6-Trimethylcyclohexanone oxime⁸⁷ (750 mg, 4.83 mmol), chloroacetic acid (1.37 g, 14.5 mmol), chloroacetic anhydride (2.48 g, 14.5 mmol), and iron powder (0.54 g, 9.65 mmol) in anhydrous toluene (25 mL) were heated to reflux under N₂ for 14 h. The mixture was filtered through Celite, diluted with dichloromethane (25 mL), and washed with 2 M NaOH (2 × 50 mL) and brine (50 mL). The organic phases were dried over MgSO₄, filtered, and concentrated in vacuo to give a brown solid (390 mg) which was used without further purification. To this solid was added sodium hydride (145 mg, 1.81 mmol) in anhydrous THF (18 mL) and the mixture cooled to 0 °C. Benzyl bromide (0.23 mL, 1.90 mmol) was added and the reaction heated at reflux for 16 h. Water was added (50 mL) and the crude mixture extracted with EtOAc (3 × 60 mL). The combined extracts were dried over MgSO₄, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (pet. ether:EtOAc, 9:1) to give a yellow oil. Yield 250 mg (17%); R_f 0.26 (pet. ether:EtOAc, 6:1); IR ν_{max} (film)/cm⁻¹ 2932, 1658; ¹H NMR δ_H (CDCl₃, 300 MHz) 7.18–7.39 (5H, m), 5.09 (1H, d, J = 14.0 Hz), 4.31 (1H, d, J = 14.0 Hz), 4.10 (1H, d, J = 13.5 Hz), 3.92 (1H, d, J = 13.5 Hz), 2.02 (2H, t, J = 6.0 Hz), 1.47–1.82 (4H, m), 1.20 (3H, s), 1.04 (3H, s), 1.02 (3H, s); ¹³C NMR δ_C (CDCl₃, 100 MHz) 167.7, 138.0, 136.9, 135.8, 129.7, 128.4, 127.6, 52.4, 42.0, 41.0, 35.9, 31.8, 30.5, 27.8, 19.5, 18.5; MS m/z (ESI) found ([M]⁺H) 306.1622, C₁₈H₂₅CINNO requires 306.1625.

Cyclization of N-Benzyl-2-chloro-N-(cyclohexylidene(phenyl)methyl)acetamide (26a) with Bu₃SnH. N-Benzyl-2-chloro-N-(cyclohexylidene(phenyl)methyl)acetamide (26a) (500 mg, 1.49 mmol), Bu₃SnH (0.600 mL, 2.23 mmol), and ACN (72.7 mg, 0.298 mmol) in toluene (75 mL) were heated to reflux for 26 h. The reaction mixture was then cooled and concentrated in vacuo. The residue was then partitioned between acetonitrile (50 mL) and hexane (50 mL), and the acetonitrile phase was concentrated in vacuo to give the crude product as a brown oil (434 mg). Purification of the crude mixture (14:1 to 9:1, pet. ether:EtOAc) furnished N-benzyl-N-

(cyclohexylidene(phenyl)methyl)acetamide (7d) (132 mg, 28%), recovered starting material N-benzyl-2-chloro-N-(cyclohexylidene(phenyl)methyl)acetamide (26a) (105 mg, 21%), and an inseparable mixture of 2-benzyl-1-phenyl-2-azaspiro[4.5]decan-3-one (37a) (118 mg, 25%) and 2-benzyl-1-hydroxy-1-phenyl-2-azaspiro[4.5]decan-3-one (37b) (73 mg, 15%).

Discernable data for 37a: ¹H NMR δ_H (CDCl₃, 400 MHz) 6.93–7.45 (10H, m), 5.15 (1H, d, J = 14.5 Hz), 3.92 (1H, s), 3.41 (1H, d, J = 14.5 Hz), 2.43 (2H, q, J = 17.0 Hz), 0.73–1.79 (10H, m); MS m/z (ESI) found ([M]⁺Na) 342.1825, C₂₂H₂₅NNaO requires 342.1834.

Discernable data for 37b: ¹H NMR δ_H (CDCl₃, 400 MHz) 6.93–7.45 (10H, m), 4.88 (1H, d, J = 15.0 Hz), 3.90 (1H, d, J = 15.0 Hz), 2.95 (1H, br s), 2.61 (1H, d, J = 17.0 Hz), 2.35 (1H, d, J = 17.0 Hz), 0.73–1.79 (10H, m); MS m/z (ESI) found ([M]⁺Na) 358.1778, C₂₂H₂₅NNaO₂ requires 358.1783.

Data for mixture: IR ν_{max} (film)/cm⁻¹ 3325, 2924, 2854, 1664; ¹³C NMR δ_C (CDCl₃, 100 MHz) 175.1, 138.9, 128.8, 137.0, 136.3, 128.6, 128.5, 128.3, 128.2, 128.1, 127.6, 127.4, 127.3, 98.2, 72.1, 45.8, 44.4, 44.0, 41.0, 40.6, 39.5, 37.8, 34.5, 33.8, 30.2, 25.7, 25.6, 23.1, 23.1, 22.8, 22.5.

Cyclization of N-Benzyl-N-(2-methyl-3,4-dihydronaphthalen-1-yl)-2-chloroacetamide (27a) with Bu₃SnH/Et₃B. To a solution of N-benzyl-N-(2-methyl-3,4-dihydronaphthalen-1-yl)-2-chloroacetamide (27a) (50 mg, 0.14 mmol) in dry benzene (21 mL) were added Bu₃SnH (63 μL, 0.21 mmol) and Et₃B (1.0 M, 140 μL, 0.14 mmol), and the flask was stirred open to the atmosphere for 24 h. Another aliquot of Bu₃SnH (63 μL, 0.21 mmol) and Et₃B (1.0 M, 140 μL, 0.14 mmol) was added and the reaction stirred for a further 24 h. The solvent was evaporated and the crude oil purified by column chromatography (pet. ether:EtOAc 4:1) to give recovered starting material 27a (22 mg, 44%) and N-benzyl-N-(2-methyl-3,4-dihydronaphthalen-1-yl)acetamide (7b) (19 mg, 70% based upon recovered starting material).

Cyclisation of N-benzyl-N-(2-methyl-3,4-dihydronaphthalen-1-yl)-2-chloroacetamide (27a) with Bu₃SnH/AIBN. To a degassed solution of N-benzyl-N-(2-methyl-3,4-dihydronaphthalen-1-yl)-2-chloroacetamide (27a) (50 mg, 0.14 mmol) in dry toluene (10 mL) at reflux was added a degassed mixture of Bu₃SnH (58 μL, 0.18 mmol) and AIBN (5.0 mg, 0.030 mmol) in toluene (10 mL) via a syringe pump over 2 h. After 48 h the solvent was removed in vacuo and the residue partitioned between 8% KF (50 mL) and Et₂O (20 mL) and stirred for 4 h. The resulting organic layer was filtered through Celite and concentrated to yield a crude product which was purified by flash chromatography (pet. ether:EtOAc 10:1) to give recovered starting material (24 mg, 48%) and N-benzyl-N-(2-methylnaphthalen-1-yl)-2-chloroacetamide 38a (11 mg, 42% based upon recovered starting material); yellow oil; IR ν_{max} (film)/cm⁻¹ 2928, 2857, 1667; ¹H NMR δ_H (CDCl₃, 300 MHz) 7.65 (1H, d, J = 8.5 Hz), 7.58 (1H, d, J = 8.5 Hz) 7.30–7.20 (3H, m), 7.09 (1H, d, J = 8.5 Hz), 6.90–7.05 (5H, m), 5.10 (1H, d, J = 13.5 Hz), 4.37 (1H, d, J = 13.5 Hz), 3.48 (1H, d, J = 14.0 Hz), 3.40 (1H, d, J = 14.0 Hz), 1.72 (3H, s); ¹³C NMR δ_C (CDCl₃, 75.5 MHz) 167.0, 136.2, 134.9, 134.1, 133.4, 130.4, 129.2, 128.9, 128.5, 128.4, 128.0, 127.8, 126.1, 122.2, 53.3, 42.5, 18.1; MS m/z (ESI) found ([M]⁺Na), 346.0970 C₂₀H₁₈CINNaO requires 346.0975.

N-Benzyl-N-(2-methylnaphthalen-1-yl)-2-iodoacetamide (38b). To a solution of N-benzyl-N-(2-methyl-3,4-dihydronaphthalen-1-yl)-2-iodoacetamide (27d) (54 mg, 0.13 mmol) in toluene (5 mL) was added AIBN (21 mg, 0.13 mmol) and the mixture heated at reflux for 2 h. Another equivalent of AIBN was added (21 mg, 0.13 mmol) and the mixture reacted for a further 24 h. Removal of the solvent in vacuo followed by purification by column chromatography (pet. ether:EtOAc, 5:1) gave a yellow oil (28 mg, 52%). IR ν_{max} (film)/cm⁻¹ 2923, 2851, 1649; ¹H NMR δ_H (CDCl₃, 300 MHz) 7.77 (1H, d, J = 8.0 Hz), 7.70 (1H, d, J = 8.0 Hz), 7.45–7.05 (9H, m), 5.14 (1H, d, J = 13.4 Hz), 4.57 (1H, d, J = 13.4 Hz), 3.39 (1H, d, J = 10.7 Hz), 3.35 (1H, d, J = 10.7 Hz), 1.93 (3H, s); ¹³C NMR δ_C (CDCl₃, 75.5 MHz) 168.5, 136.3, 135.4, 134.7, 133.4, 130.4, 130.4, 129.1, 129.0, 128.5, 128.4, 128.0, 127.5, 126.0, 122.8, 53.5, 18.6, -1.7; MS m/z (ESI) found ([M]⁺Na) 438.0325, C₂₀H₁₈INNaO requires 438.0331.

Cyclization of *N*-Benzyl-*N*-(2-methyl-3,4-dihydronaphthalen-1-yl)-2-bromoacetamide (27b) with Bu_3SnH . To a degassed solution of *N*-benzyl-*N*-(2-methyl-3,4-dihydronaphthalen-1-yl)-2-bromoacetamide (27b) (150 mg, 0.405 mmol) in dry toluene (20 mL) at reflux were added Bu_3SnH (163 μ L, 0.608 mmol) and ACN (20 mg, 0.08 mmol). After 24 h a further aliquot of Bu_3SnH (163 μ L, 0.608 mmol) and ACN (20 mg, 0.08 mmol) in toluene (20 mL) was added. For the next 6 h at 2 h intervals, further ACN was added (3×20 mg). After 24 h the reaction mixture was cooled and concentrated in vacuo. The mixture was portioned between acetonitrile and hexane, and the acetonitrile phase was concentrated to give a crude yellow oil which was further purified by column chromatography (pet. ether:EtOAc 9:1), to give *N*-benzyl-*N*-(2-methyl-3,4-dihydronaphthalen-1-yl)-acetamide (7b) (42%), 1-(benzylamino)-1-oxoethan-2-yl 2-(3-oxobutyl)benzoate (39a), and *N*-benzyl-*N*-(2-methylnaphthalen-1-yl)acetamide (38c).

Data for 39a: yield 14 mg (10%); yellow oil; R_f 0.23 (pet. ether:EtOAc, 3:1); IR ν_{max} (film)/ cm^{-1} 3067, 1730, 1707, 1664; 1H NMR δ_H ($CDCl_3$, 300 MHz) 7.86 (1H, d, $J = 8.3$ Hz), 7.45 (1H, dt, $J = 7.2, 1.5$ Hz), 7.36–7.24 (7H, m), 6.84 (1H, br s), 4.90 (2H, s), 4.56 (2H, d, $J = 6.0$ Hz), 3.20 (2H, t, $J = 7.3$ Hz), 2.78 (2H, t, $J = 7.3$ Hz), 2.06 (3H, s); ^{13}C NMR δ_C ($CDCl_3$, 75.5 MHz) 208.2, 167.3, 166.1, 143.4, 137.9, 132.7, 131.2, 130.5, 128.8, 128.7, 127.7, 127.6, 126.5, 63.5, 44.9, 43.1, 29.9, 28.0; MS m/z (ESI) found ($[M]^+Na$) 362.1363, $C_{20}H_{21}NNaO_4$ requires 362.1368.

Data for 38c: yield (7%); yellow oil; IR ν_{max} (film)/ cm^{-1} 3029, 2923, 2854, 1652; 1H NMR δ_H ($CDCl_3$, 300 MHz) 7.83–7.79 (2H, m), 7.71 (1H, d, $J = 8.5$ Hz) 7.57–7.53 (1H, m), 7.37–7.45 (2H, m), 7.25 (1H, d, $J = 8.5$ Hz), 7.20–7.05 (4H, m), 5.35 (1H, d, $J = 13.5$ Hz), 4.43 (1H, d, $J = 13.5$ Hz), 1.87 (3H, s), 1.68 (3H, s); ^{13}C NMR δ_C ($CDCl_3$, 75.5 MHz) 171.3, 137.0, 136.1, 124.4, 1233.3, 120.4, 120.2, 128.8, 128.3, 128.2, 127.6, 127.2, 125.7, 122.5, 52.1, 21.9, 17.9; MS m/z (ESI) found ($[M]^+Na$), 312.1357 $C_{20}H_{19}NNaO$ requires] 312.1359.

General Procedure for Cyclization Using $Cu(TPMA)X$.

Enamide (1 equiv), either $CuCl$ (1 equiv) or $CuBr$ (0.6–1.2 equiv), and TPA (0.6–1.2 equiv) were heated to reflux in toluene (0.12 M) for 2–44 h. The reaction mixture was then cooled to room temperature and filtered through a silica plug with EtOAc. The filtrate was then concentrated in vacuo to give the crude products, which were purified by column chromatography.

1-Benzyl-3,3-dichloro-3a-phenyl-3a,4,5,6-tetrahydro-1H-indol-2(3H)-one (41). Conditions: *N*-benzyl-2,2,2-trichloro-*N*-(2-phenylcyclohex-1-enyl)acetamide (24a) (200 mg, 0.49 mmol), $CuCl$ (48.5 mg, 0.49 mmol), TPA (142 mg, 0.49 mmol), and toluene (4.2 mL), for 2 h. The crude product was purified by column chromatography (pet. ether:EtOAc, 9:1). Yield 123 mg (70%); colorless oil; R_f 0.37 (pet. ether:EtOAc, 9:1); IR ν_{max} (film)/ cm^{-1} 2956, 2875, 1730, 1685; 1H NMR δ_H ($CDCl_3$, 400 MHz) 7.24–7.43 (5H, m), 7.10–7.15 (3H, m), 7.06–7.10 (2H, m), 5.33 (1H, t, $J = 3.5$ Hz), 4.95 (1H, d, $J = 15.0$ Hz), 4.78 (1H, d, $J = 15.0$ Hz), 2.50–2.54 (2H, m), 1.98–2.13 (3H, m), 1.70–1.75 (1H, m), 1.05–1.17 (1H, m); ^{13}C NMR δ_C ($CDCl_3$, 100 MHz) δ 166.3, 139.1, 138.2, 135.1, 129.0, 128.8, 128.1, 128.1, 128.1, 127.8, 105.4, 89.1, 56.8, 45.2, 29.3, 23.1, 18.1; MS m/z (ESI) found ($[M]^+Na$) 394.0732, $C_{21}H_{19}Cl_2NNaO$ requires 394.0736.

Cyclization of *N*-Benzyl-2,2,2-trichloro-*N*-(2-methyl-1-phenylprop-1-enyl)acetamide (25b) with $Cu(TPMA)Cl$. Conditions: *N*-benzyl-2,2,2-trichloro-*N*-(2-methyl-1-phenylprop-1-enyl)acetamide (25b) (150 mg, 0.39 mmol), $CuCl$ (38.8 mg, 0.39 mmol), TPA (114 mg, 0.39 mmol), and toluene (3.5 mL). The crude product was purified by column chromatography (pet. ether:EtOAc, 10:1) to give 1-benzyl-3-chloro-5-hydroxy-4,4-dimethyl-5-phenylpyrrolidin-2-one (42a) (68 mg, 48%) and 1-benzyl-3-chloro-5-hydroxy-4,4-dimethyl-5-phenylpyrrolidin-2-one (42b) (17 mg, 13%) as colorless solids.

Data for 42a: R_f 0.18 (pet. ether:EtOAc, 6:1); mp 171–172 °C; IR ν_{max} (film)/ cm^{-1} 3520, 1676; 1H NMR δ_H ($CDCl_3$, 400 MHz) 7.31–7.55 (4H, br m), 7.16–7.31 (6H, br m), 4.97 (1H, d, $J = 15.0$ Hz), 4.23 (1H, d, $J = 15.0$ Hz), 2.89 (1H, s), 1.35 (3H, s), 0.88 (3H, s); ^{13}C NMR δ_C ($CDCl_3$, 100 MHz) 167.8, 136.9, 136.6, 129.2, 129.1, 128.7,

128.1, 128.0, 128.0, 96.0, 90.8, 52.7, 46.2, 26.7, 18.2; MS m/z (ESI) found ($[M]^+Na$) 386.0691, $C_{19}H_{19}Cl_2NNaO_2$ requires 386.0691.

Data for 42b: R_f 0.10 (pet. ether:EtOAc, 6:1); mp 183–185 °C; IR ν_{max} (film)/ cm^{-1} 3376, 1677; 1H NMR δ_H ($CDCl_3$, 400 MHz) 7.37–7.48 (3H, m), 7.29–7.37 (2H, m), 7.17–7.28 (3H, m), 6.96–7.04 (2H, m), 5.16 (1H, d, $J = 14.5$ Hz), 4.73 (1H, s), 4.13 (1H, d, $J = 14.5$ Hz), 2.08 (1H, s), 1.10 (3H, s), 0.77 (3H, s); ^{13}C NMR δ_C ($CDCl_3$, 100 MHz) 172.2, 137.3, 136.8, 129.3, 129.1, 128.8, 128.34, 128.2, 96.0, 65.9, 48.4, 44.7, 22.1, 19.3; MS m/z (ESI) found ($[M]^+H$) 330.1255, $C_{19}H_{21}ClNO_2$ requires 330.1261.

Cyclization of *N*-Benzyl-2,2,2-trichloro-*N*-(cyclohexylidene(phenyl)methyl)-2-methylacetamide (26b) with $Cu(TPMA)Cl$. Conditions: *N*-benzyl-2,2,2-trichloro-*N*-(cyclohexylidene(phenyl)methyl)acetamide (26b) (150 mg, 0.355 mmol), $CuCl$ (35.1 mg, 0.355 mmol), TPA (103 mg, 0.355 mmol), and toluene (3.3 mL). The crude product was purified by column chromatography (pet. ether:EtOAc, 10:1) to give 2-benzyl-4,4-dichloro-1-hydroxy-1-phenyl-2-azaspiro[4.5]decan-3-one (43a) (33 mg, 23%) and 2-benzyl-4-chloro-1-hydroxy-1-phenyl-2-azaspiro[4.5]decan-3-one (43b) (21 mg, 16%) as colorless solids.

Data for 43a: R_f 0.21 (pet. ether:EtOAc, 6:1); mp 178–180 °C; IR ν_{max} (film)/ cm^{-1} 3517, 1728; 1H NMR δ_H ($CDCl_3$, 400 MHz) 6.86–7.86 (10H, m), 4.82 (1H, d, $J = 15.0$ Hz), 4.03 (1H, d, $J = 15.0$ Hz), 2.80 (1H, br s), 1.94–2.09 (1H, m), 1.72–1.87 (1H, m), 1.41–1.70 (4H, m), 1.23–1.41 (1H, m), 1.10–1.23 (1H, m), 0.91–1.10 (1H, m), 0.54–0.76 (1H, m); ^{13}C NMR δ_C ($CDCl_3$, 100 MHz) 167.9, 137.3, 136.9, 129.2, 129.1, 128.7, 127.9, 96.7, 92.0, 53.7, 46.3, 32.8, 28.7, 24.9, 22.2, 21.8; MS m/z (ESI) found ($[M]^+Na$) 426.0998, $C_{22}H_{23}Cl_2NNaO_2$ requires 426.1004.

Data for 43b: R_f 0.18 (pet. ether:EtOAc, 6:1); mp 183–185 °C; IR ν_{max} (film)/ cm^{-1} 3213, 1687; 1H NMR δ_H ($CDCl_3$, 400 MHz) 6.76–7.81 (10H, m), 4.84 (1H, d, $J = 15.0$ Hz), 4.47 (1H, s), 4.19 (1H, d, $J = 15.0$ Hz), 2.58 (1H, s), 2.26 (1H, dd, $J = 13.5, 2.5$ Hz), 1.48–1.77 (3H, m), 1.13–1.42 (4H, m), 0.79–0.96 (1H, m), 0.69 (1H, td, $J = 13.0, 4.0$ Hz); ^{13}C NMR δ_C ($CDCl_3$, 100 MHz) 172.4, 137.6, 136.2, 128.9, 128.8, 128.7, 128.3, 127.7, 98.6, 60.5, 48.3, 45.3, 33.8, 26.6, 24.8, 22.8, 22.5; MS m/z (ESI) found ($[M]^+Na$) 392.1388, $C_{22}H_{24}ClNNaO_2$ requires 392.1393.

Cyclization of *N*-Benzyl-2-bromo-2-methyl-*N*-(2-methyl-1-phenylprop-1-enyl)propanamide (25c) with $Cu(TPMA)Br$. Conditions: *N*-benzyl-2-bromo-2-methyl-*N*-(2-methyl-1-phenylprop-1-enyl)propanamide (25c) (200 mg, 0.518 mmol), $CuBr$ (44.6 mg, 0.311 mmol), TPA (90.2 mg, 0.311 mmol), and toluene (5 mL). The crude product was purified by column chromatography (6:1, pet. ether:EtOAc) to yield 1-benzyl-5-hydroxy-3,3,4,4-tetramethyl-5-phenylpyrrolidin-2-one (44) as a white solid (61 mg, 36%) and a 4:1 inseparable mixture of 1-benzyl-3,3,4,4-tetramethyl-5-phenylpyrrolidin-2-one (45) and 2-benzyl-4,4,5-trimethyl-1-phenyl-2-azabicyclo[3.1.0]hexan-3-one (46) (19%, 45:46 = 5:1).

Data for 44: R_f 0.16 (pet. ether:EtOAc, 6:1); mp 117–119 °C; IR ν_{max} (film)/ cm^{-1} 3221, 1666; 1H NMR δ_H ($CDCl_3$, 400 MHz) 7.14–7.48 (8H, m), 7.01–7.14 (2H, m), 5.20 (1H, d, $J = 15.0$ Hz), 4.03 (1H, d, $J = 15.0$ Hz), 1.95 (1H, s), 1.35 (3H, s), 1.09 (3H, s), 0.95 (3H, s), 0.53 (3H, s); ^{13}C NMR δ_C ($CDCl_3$, 100 MHz) 182.2, 139.3, 138.6, 129.0, 128.6, 128.5, 128.2, 127.9, 97.0, 46.9, 46.1, 44.1, 25.6, 25.0, 20.6, 17.1; MS m/z (ESI) found ($[M]^+Na$) 346.1781, $C_{21}H_{25}NNaO_2$ requires 346.1783.

Data for 46: inseparable mixture; R_f 0.19 (pet. ether:EtOAc, 6:1); IR ν_{max} (film)/ cm^{-1} 2972, 2940, 1690; 1H NMR δ_H ($CDCl_3$, 400 MHz) 6.87–7.44 (10H 45 and 10H 46, m), 5.24 (1H 45, d, $J = 14.0$ Hz), 4.83 (1H 46, d, $J = 14.0$ Hz), 3.97 (1H 45, s), 3.72 (1H 46, d, $J = 14.0$ Hz), 3.66 (1H 45, d, $J = 14.0$ Hz), 1.32 (3H 46, s), 1.18 (3H 46, s), 1.08 (3H 45, s), 1.00 (1H 46, d, $J = 6.0$ Hz), 0.96 (3H 45, s), 0.85 (3H 45, s), 0.79 (3H 46, s), 0.59 (3H 45, s), 0.30 (1H 46, d, $J = 6.0$ Hz); ^{13}C NMR δ_C ($CDCl_3$, 150 MHz) mixture 181.2, 179.5, 137.1, 136.3, 135.4, 134.2, 129.5, 129.2, 128.9, 128.5, 128.4, 128.2, 128.1, 127.8, 127.8, 127.5, 127.3, 68.6, 51.6, 46.7, 45.3, 45.3, 44.8, 42.4, 28.8, 25.0, 24.2, 21.6, 21.3, 21.1, 20.7, 19.2, 14.1; MS m/z (ESI) found ($[M]^+Na$) 330.1832, $C_{21}H_{25}NNaO$ requires 330.1834.

Cyclization of *N*-Benzyl-2-bromo-*N*-(cyclohexylidene(phenyl)methyl)-2-methylpropanamide (26c) with Cu(TPMA)Br. Conditions: *N*-benzyl-2-bromo-*N*-(cyclohexylidene(phenyl)methyl)-2-methylpropanamide (26c) (200 mg, 0.469 mmol), CuBr (40.1 mg, 0.281 mmol), TPA (81.7 mg, 0.281 mmol), and toluene (5 mL). The crude product was purified by column chromatography (9:1:0.2, hexane:diethyl ether:triethylamine), yielding 2-benzyl-1-hydroxy-4,4-dimethyl-1-phenyl-2-azaspiro[4.5]decan-3-one (50) as a white solid (56 mg, 33%) and an inseparable mixture of 2-benzyl-4,4-dimethyl-1-phenyl-2-azaspiro[4.5]decan-3-one (52 and 51) (41 mg, 26%, 1:4 = 50:51).

Data for 50: R_f 0.18 (pet. ether:EtOAc, 6:1); mp 169–170 °C; IR ν_{\max} (film)/ cm^{-1} 3165, 1664; $^1\text{H NMR}$ δ_{H} (CDCl_3 , 400 MHz) 7.30–7.66 (4H, m), 7.06–7.30 (4H, m), 6.98–7.05 (2H, m), 5.14 (1H, d, $J = 15.0$ Hz), 3.91 (1H, d, $J = 15.0$ Hz), 1.93 (1H, s), 1.78 (1H, dd, $J = 13.5, 6.0$ Hz), 1.47–1.58 (2H, m), 1.39 (3H, s), 1.24–1.45 (4H, m), 1.31 (3H, s), 0.97–1.07 (1H, m), 0.87–0.97 (1H, m), 0.77–0.87 (1H, m); $^{13}\text{C NMR}$ δ_{C} (CDCl_3 , 100 MHz) 182.1, 140.0, 138.4, 128.9, 128.5, 128.4, 127.8, 97.3, 48.7, 47.1, 44.2, 32.4, 30.5, 27.5, 25.5, 25.2, 23.5, 22.7; MS m/z (ESI) found ($[\text{M}]^+\text{Na}$) 386.2096, $\text{C}_{24}\text{H}_{29}\text{NNaO}_2$ requires 386.2096.

Data for 52 and 51: R_f 0.21 (pet. ether:EtOAc, 6:1); IR ν_{\max} (film)/ cm^{-1} 2933, 2866, 1676; $^1\text{H NMR}$ δ_{H} (CDCl_3 , 400 MHz) 7.16–7.39 (8H 52, 51, m), 7.02–7.06 (2H 51, m), 6.99–7.02 (2H 52, m), 5.22 (1H 52, d, $J = 14.5$ Hz), 4.61 (1H 51, d, $J = 14.5$ Hz), 4.08 (1H 52, s), 3.74 (1H 51, d, $J = 14.5$ Hz), 3.46 (1H 52, d, $J = 14.5$ Hz), 1.83–1.93 (1H 52, 51, m), 1.78 (1H 51, td, $J = 14.5, 6.5$ Hz), 1.57–1.70 (2H 51, 52, m), 1.46–1.54 (2H 52, m), 1.39 (3H 51, s), 1.34–1.41 (3H 52, m), 1.15–1.30 (3H 52, m), 1.27 (3H 52, s), 1.23 (3H 51, s), 1.11 (3H 51, s), 1.04–1.15 (1H 52, 51, m), 0.95–1.04 (1H 51, m), 0.85 (1H 51, dd, $J = 8.5, 2.5$ Hz), 0.74–0.82 (1H 51, m), 0.57–0.69 (1H 51, m); $^{13}\text{C NMR}$ δ_{C} (CDCl_3 , 100 MHz) 180.1, 178.8, 137.7, 136.7, 136.3, 132.7, 132.3, 128.7, 128.6, 128.4, 128.2, 128.2, 128.0, 127.9, 127.5, 126.9, 68.5, 52.6, 47.6, 46.5, 44.9, 44.8, 44.7, 34.0, 31.1, 29.7, 28.4, 25.6, 23.9, 23.8, 23.0, 22.5, 21.8, 21.6, 21.2, 21.2, 20.1; MS m/z (ESI) found ($[\text{M}]^+\text{H}$) 348.2323, $\text{C}_{24}\text{H}_{30}\text{NO}$ requires 348.2327.

Cyclization of *N*-Benzyl-2-bromo-2-methyl-*N*-(2-methyl-3,4-dihydronaphthalen-1-yl)propanamide (27c) with Cu(TPMA)Br. Conditions: *N*-benzyl-2-bromo-2-methyl-*N*-(2-methyl-3,4-dihydronaphthalen-1-yl)propanamide (27c) (132 mg, 0.331 mmol), CuBr (28.5 mg, 0.199 mmol), TPA (57.7 mg, 0.199 mmol), and toluene (3.3 mL). The crude product was purified by column chromatography (10:1 to 5:1, pet. ether:EtOAc) to give 1-benzyl-3,3,3a-trimethyl-3,3a,4,5-tetrahydro-1*H*-benzoindol-2(9*bH*)-one (54) (33 mg, 31%), 1-benzyl-9*b*-hydroxy-3,3,3a-trimethyl-3,3a,4,5-tetrahydro-1*H*-benzoindol-2(9*bH*)-one (53) (21 mg, 19%), and 1-benzyl-[3,9*b*]cyclopropyl-3,3,3a-trimethyl-3,3a,4,5-tetrahydro-1*H*-benzoindol-2(9*bH*)-one (55) (7 mg, 7%), and 39b (<2%).

Data for 54: R_f 0.15 (pet. ether:EtOAc, 8:1); IR ν_{\max} (film)/ cm^{-1} 2925, 2855, 1670; $^1\text{H NMR}$ δ_{H} (CDCl_3 , 600 MHz) 7.30 (2H, t, $J = 7.5$ Hz), 7.21–7.28 (2H, m), 7.15 (1H, d, $J = 7.5$ Hz), 7.12 (1H, t, $J = 7.5$ Hz), 7.09 (2H, d, $J = 7.5$ Hz), 6.92 (1H, d, $J = 7.5$ Hz), 4.95 (1H, d, $J = 15.5$ Hz), 4.24 (1H, s), 3.62 (1H, d, $J = 15.5$ Hz), 2.79 (2H, dt, $J = 12.0, 6.0$ Hz), 1.68–1.75 (1H, m), 1.54 (1H, m), 1.24 (3H, s), 1.13 (3H, s), 0.94 (3H, s); $^{13}\text{C NMR}$ δ_{C} (CDCl_3 , 150 MHz) 180.0, 137.8, 137.4, 132.9, 130.1, 129.3, 128.7, 128.6, 127.5, 127.1, 125.5, 61.6, 47.2, 43.3, 41.2, 27.4, 25.9, 20.9, 17.4, 14.8; MS m/z (ESI) found ($[\text{M}]^+\text{Na}$) 342.1828, $\text{C}_{22}\text{H}_{25}\text{NNaO}$ requires 342.1834.

Data for 53: R_f 0.05 (pet. ether:EtOAc, 8:1); $^1\text{H NMR}$ δ_{H} (CDCl_3 , 400 MHz) 7.21–7.29 (1H, m), 6.59–6.91 (8H, m), 4.30 (1H, d, $J = 15.5$ Hz), 3.80 (1H, d, $J = 15.5$ Hz), 2.47 (1H, ddd, $J = 17.5, 11.0, 6.5$ Hz), 2.27 (1H, dt, $J = 17.5, 4.5$ Hz), 1.95 (1H, s), 1.17–1.48 (2H, m), 1.14 (3H, s), 0.77 (3H, s), 0.72 (3H, s); $^{13}\text{C NMR}$ δ_{C} (CDCl_3 , 100 MHz) 181.4, 138.6, 136.8, 135.3, 128.9, 128.8, 128.3, 127.5, 126.8, 126.3, 91.6, 46.2, 45.3, 43.2, 31.6, 25.8, 25.5, 19.5, 13.0; MS m/z (ESI) found ($[\text{M}]^+\text{Na}$) 358.1778, $\text{C}_{22}\text{H}_{25}\text{NNaO}_2$ requires 358.1738.

Data for 55: R_f 0.26 (pet. ether:EtOAc, 8:1); $^1\text{H NMR}$ δ_{H} (CDCl_3 , 600 MHz) 7.08–7.54 (7H, m), 7.00–7.07 (2H, m), 4.92 (1H, d, $J = 14.5$ Hz), 4.30 (1H, d, $J = 14.5$ Hz), 2.89 (1H, dd, $J = 17.5, 7.5$ Hz), 2.54 (1H, d, $J = 17.5$ Hz), 1.33 (3H, s), 1.13 (3H, s), 0.90 (1H, d, $J = 7.5$ Hz), 0.64 (3H, s); $^{13}\text{C NMR}$ δ_{C} (CDCl_3 , 150 MHz) 180.3, 143.3,

137.5, 137.1, 128.9, 128.4, 127.5, 126.8, 126.5, 125.0, 123.6, 59.6, 52.9, 45.8, 44.5, 32.6, 30.9, 25.2, 21.4, 6.6; MS m/z (ESI) found ($[\text{M}]^+\text{H}$) 318.1860, $\text{C}_{22}\text{H}_{24}\text{NO}$ requires 318.1858.

Data for 39b: R_f 0.14 (pet. ether:EtOAc, 6:1); $^1\text{H NMR}$ δ_{H} (600 MHz, CDCl_3) 7.76 (1H, dd, $J = 8.0, 1.5$ Hz), 7.40 (1H, td, $J = 7.5, 1.5$ Hz), 7.27–7.34 (4H, m), 7.21–7.27 (3H, m), 6.64 (1H, br t, $J = 7.5$ Hz), 4.50 (2H, d, $J = 7.5$ Hz), 3.10 (2H, t, $J = 7.5$ Hz), 2.73 (2H, t, $J = 7.5$ Hz), 2.04 (3H, s), 1.77 (6H, s); $^{13}\text{C NMR}$ δ_{C} (150 MHz, CDCl_3) 208.3, 173.0, 166.2, 142.9, 138.4, 132.3, 131.1, 130.4, 128.7, 127.8, 127.5, 126.3, 81.7, 45.2, 43.6, 30.0, 28.0, 25.0; MS m/z (ESI) found ($[\text{M}]^+\text{H}$) 368.1856, $\text{C}_{22}\text{H}_{26}\text{NO}_4$ requires 368.1862.

Data for mixture: HPLC (S,S)-Whelk-O1 (25 cm \times 4.6 mm) hexanes:iPrOH (1.0 mL/min) 53, t_{R} 18.88 and 31.03 min; 39b, t_{R} 111.01 min; 54, t_{R} 14.77 and 52.03 min; 55, t_{R} 9.87 and 11.55 min.

■ ASSOCIATED CONTENT

● Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00889.

VT $^1\text{H NMR}$ spectra for compounds 2d, 4a, 4b, 4d, 4e, 4g, 8a, 8b, 8d, 13b–f, 15, 25b, 25c, and 26b, and 26c; rotational data and Eyring plots for 4b, 4d, 8a, 8b, 8d, 13b–f, and 15; $^1\text{H NMR}$ spectra for 2b, 5c–e, and 5g–i; $^1\text{H NMR}$ and $^{13}\text{C NMR}$ spectra for 4a–i, 5a, 5b, 5f, 5j–m, 7–9, 13b–f, 14, 15, 24–28, 37–39, 41–46, 50–55; X-ray data for 9d, 14, 23c, and 24a; racemization data for 7b, 7c, and 27a–c; chiral HPLC data for 4f, 4h, 4i, 7a–d, and 26a–c; and computed energies and coordinates for 2b (PDF)

Crystallographic data for compounds 7b, 7d, 14, and 25 in CIF format (CIF)

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Notes

The authors declare no competing financial interest.

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