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

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Supporting Information

ABSTRACT: The barrier to rotation around the N-alkenyl bond of 38 N-alkenyl-N-alklyacetamide derivatives was measured (ΔG‡ rotation varied between <8.0 and 31.0 kcal mol⁻¹). The most important factor in controlling the rate of rotation was the level of alkyl 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‡ rotation >20 kcal mol⁻¹) were studied to determine the regiochemistry of cyclization. Those with high barriers (>27 kcal mol⁻¹) did not lead to cyclization, but those with lower values produced highly functionalized γ-lactams via a 5-endo-trig radical–polar crossover process that was terminated by reduction, an unusual cyclopropanation sequence, or trapping with H₂O, 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 (R³ or R⁵ ≠ 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.5 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., R¹ = R² = R³ = Me) may be planar in the ground state, but if substituents R¹ and R² are large enough or the alkene is substituted (R³ = R⁴ = R⁵ ≠ 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 → (Z)-syn 2] and the N-alkenyl bonds [(E)-syn 2 → (E)-anti 2] (Figure 1). The barrier to rotation around the amide N−CO bond for 2a (R¹ = R² = Me) has been measured at 14.0 kcal mol⁻¹ and is slightly lower19 than the general value for amides (15–20 kcal mol⁻¹).20 N-Cycloalkenyl-N-alklyacetamides 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, R¹, R², R³, R⁴, and R⁵) on the barriers to rotation around the N-alkenyl bond of tertiary enamides and...
show that it is possible to separate individual enamide atropisomers at room temperature with half-lives ($t_{1/2}$) up to 99 years at 298 K. We probe the ability of a subset of sterically congested racemic $\alpha$-halogenated tertiary enamides with relatively high barriers to rotation ($\Delta G^{\ddagger}_{298 \text{ rot}} > 20 \text{ kcal mol}^{-1}$) to undergo 5-endo-trig radical cyclization. Those with high barriers ($\Delta G^{\ddagger}_{298 \text{ rot}} > 27 \text{ kcal mol}^{-1}$) do not lead to cyclization, but those with lower values ($27 \text{ kcal mol}^{-1} > \Delta G^{\ddagger}_{298 \text{ rot}} > 20 \text{ kcal mol}^{-1}$) mostly lead to highly functionalized $\gamma$-lactams (no $\beta$-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 acetaldehyde$^2$ (13%). Computational analysis of 2b using the TZVP basis set$^23$ and the B3LYP-D3(BJ) functional$^24$ using PC-GAMESS/Firefly 8.0$^25$ 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 $^1$H NMR spectrum of 2b in CDCl$_3$ 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 $^1$H NMR chemical shifts and NOE data. DFT ground-state structures were analyzed using the GIAO method Gaussian03,$^26$ with the mPW1PW91 functional$^27$ and the 6-311+G(2d,p) basis set and scrf = (solvent = chcl3,cpcm,read) radii = uaks nosymcav options.$^28$ NMR shifts 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 $N$-alkenyl bond 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) $^1$H NMR. Upon cooling, the benzylic CH$_2$ singlet should broaden and would be expected to decoalesce (caused by the two protons of the CH$_2$ group being...
in an asymmetric environment) and ultimately form two doublets due to the diastereotropic nature of the benzyllic protons. This behavior is not consistent with amide bond rotation, as this would cause the number of signals to double. Using the WINNMR 7.1 line shape analysis program, \( \Delta \) it was possible to determine the rotational rate constant at each temperature and the thermodynamic parameters via a standard Eyring plot. Compounds 4a, 4e, and 4f were prepared by acetylation of the known benzyl imines of acetone, 22- 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 \( ^1 \)H NMR (\( \Delta G^2_{298} \) estimated to be <8.5 kcal mol\(^{-1} \)). On cooling, the benzylic CH\(_2\) singlet began to broaden as expected, but even at 179 K decoalescence was not observed. On the other hand, the values of \( \Delta G^2_{298} \) 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 \( ^1 \)H NMR showed a sharp set of diastereotopic signals for the CH\(_2\) 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 4b was partially resolved, both enantiomers of 4i were fully resolved on a semipreparative Whelk-O column (30.1 and 37.4 min). The \( \Delta G^2_{298} \) 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 sp\(^2\)-hybridized \( \alpha \)-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, 40 We solved the X-ray structures of 7b and 7d, which confirmed the preference for adoption of the amide N-CO \( \epsilon \)-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 anilides 41 and other enamides.21,42 The sum of the angles around the nitrogen atom was 359°, suggesting that the nitrogen was planar, as expected. For 7d the torsional angle was slightly smaller, 65°. The 400 MHz \( ^1 \)H 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 a single \( \epsilon \)-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 (R\(_1\), R\(_2\), R\(_3\), R\(_5\) ≠ H, R\(_4\) = 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-benzeneacetaemide 43 with NaN in THF followed by the addition of either MeI (8a, 84%), BuBr (8b, 70%), or \( ^3 \)PrI (8d, 13%) furnished the desired enamide 8a, 8b, or 8d.44 Compound 8c was prepared by acylation of the N-benzylime of cyclhexanone with phenylacetyl chloride according to a literature procedure.45 We also synthesized compound 8e by reaction of N-1-cyclohexen-1-yl-benzene acetamide with 3 equiv of 2,6-lutidine and TBSCF (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
while this is not possible for the methyl groups. N-rotation dynamics of related anilides has been reported to proceed to give both observed in anilides. Size of the alkyl group increased, in parallel with the trend 8a < 8b < 8c. No broadening of the geminal protons of 8c was observed upon N-alkylation (Δδ 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-d₈ (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.² In both series there is a relatively small increase on moving from the N-methyl to N-1° alkyl substituent (enamides 8a → 8b ΔΔG* = 1.6 kcal mol⁻¹, anilides 9a → 9b ΔΔG* = 1.0 kcal mol⁻¹), whereas there is a significantly larger increase for the isopropyl substituent (enamides 8a → 8d ΔΔG* = 4.9 kcal mol⁻¹, anilides 9a → 9d ΔΔG* = 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 alkene rotation, while this is not possible for the methyl groups N–CH(Me)₂ in 8d.³ 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,⁴ 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.⁵ 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 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 alkylation of the known acetamide 12 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 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 enamido alkene was constrained also affected the barrier to rotation in the order 6-membered < 7-membered (compare 13f and 15 ΔΔG* = +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.⁵⁵ 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) (ΔΔG* = 10.1 kcal mol⁻¹) with the much

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

| compd | X  | Y  | ΔΔG*₁⁻⁻₁₈₀ (kcal mol⁻¹)⁶ |
|-------|----|----|------------------------|
| 13a   | H  | H  | 10.1¹⁶                      |
| 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                        |
| 15²   | Br | Br | 14.8                        |

¹Estimated errors ΔΔG*₁⁻⁻₁₈₀ ± 0.2 kcal mol⁻¹; these are in line with related work. ²Enamide constrained in a seven-membered ring.

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**Figure 5. Effect of alkenyl substitution on the rotation barrier around N-alkenyl bond for 8a–e (ΔΔG*₁⁻⁻₁₈₀ in kcal mol⁻¹ for rotation around the N-alkenyl 8a–d or N-aryl 9a–d bond is shown in parentheses).**

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

**Figure 7. Effect of acyl substituent 3a–i upon the ΔΔG*₁⁻⁻₁₈₀ barriers around the N-alkenyl bond (values in kcal mol⁻¹ shown in parentheses).**
larger trichloroacetyl group (3i) \( \Delta G_{\text{rot}}^{+} = 14.2 \text{ kcal mol}^{-1} \) increases the barrier to rotation by 4.1 kcal mol\(^{-1}\). This steric effect is less significant for the acyl substituent than the nitrogen substituent [nitrogen substituent Me \( \rightarrow \) Pr (8d), \( \delta \Delta G = 4.9 \text{ kcal mol}^{-1} \); acyl substituent Me \( \rightarrow \) Pr (3d), \( \delta \Delta G = 1.6 \text{ kcal mol}^{-1} \)]. 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 amide 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).\(^{30}\) On plotting ln \( k_{\text{rot}} \) values for 3a–i against the cone angle (\( \theta_b \) 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 \( \theta_b \) 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 \( \alpha' \)-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 \( \alpha \)-haloanenamides 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 enamides 16 cyclize via a 5-endo pathway \( (R^2 = \text{Ph or CO}_2 \text{R}) \);\(^{52–55}\) 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 alken 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\(_3\)SnH 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 \( \alpha' \)-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 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).
The most commonly used protocols for mediating radical cyclizations of α-haloenamides are (i) Bu₃SnH/AlBN,52–54,62–65 where chlorides provide higher yields of cyclized products than bromides or iodides,79 and (ii) copper(I) complexes of bipyridine,57 hexamethyltriamine,66 or tripyridylamine,56,57,67 for oacetamide or tertiary halide derivatives only (Bu₃SnH, R = CCl3, CMe2Br).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 during N-alkenyl bond formation (Figure 11). 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 (CDCl3) and the solid state for relatively small primary acyl groups (R = Me, CH2Cl, CH2Br, CH₂I, Cu(1), R = CCl3, CMe2Br).64

Figure 11. Structures 24–28 showing the ΔG‡298 values barriers around the N-alkenyl bond in parentheses (values in kcal mol⁻¹).

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

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 timescale between the (E)- and (Z)-amide rotamers with a slower rotation around the enamide N-(CO) 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 (CDCl3) and the solid state for relatively small primary acyl groups (R = Me, CH2Cl, CH2Br, 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 (R = CMe4Br, CCl3, 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, ΔG‡ = 27.8 kcal mol⁻¹, 27b, er = 99:1, ΔG‡ = 27.8 kcal mol⁻¹, 27c, er = 99:1, ΔG‡ = 27.8 kcal mol⁻¹).
mol$^{-1}$, $t_{1/2} = 163$ days at 298 K; 27b, $\text{er} = 98.2$, $\Delta G^\pm = 29.3$ kcal mol$^{-1}$, $t_{1/2} = 5.6$ years at 298 K; 27c, $\text{er} = 87.13$, $\Delta G^\pm = 25.6$ 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 S-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 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 27b 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 Bu$_3$SnH/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.10

By analogy, we initially chose to investigate the Bu$_3$SnH-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 ($\Delta G^\pm_{298 \text{ rot}} \sim 21–23$ kcal mol$^{-1}$) was treated with 1.5 equiv of Bu$_3$SnH 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 S-endo-trig cyclization followed by Bu$_3$SnH-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 → 34–36 available for 26a (Figure 14). Attempts to cyclize derivatives with higher barriers to rotation (27a, $\Delta G^\pm_{298 \text{ rot}} = 27.8$ kcal mol$^{-1}$; 28, $\Delta G^\pm_{298 \text{ rot}} > 31.0$ kcal mol$^{-1}$)
mol$^{-1}$) failed, presumably due to the increased difficulty in moving to planarity during the cyclization. Reaction of the chloro derivative 27a with Bu$_3$SnH (0.01M) and Et$_3$B$^7$9 at room temperature led to recovered starting material 27a (44%) and the reduced substrate 7b being isolated (70% based upon recovered starting material). On the other hand, addition of 1.5 equiv of Bu$_3$SnH and 20 mol % AIBN (via a syringe pump addition for 2 h, initial concentration 0.01 M) led to oxidation to the naphthalene 38a in 19% yield (47% based upon recovered starting material). Complete oxidation to the naphthalene 38a could also be accomplished if 27a was reacted with 2 equiv of AIBN in the absence of Bu$_3$SnH, indicating that the radical initiator was responsible for the oxidation and that this process was more rapid than homolytic bond cleavage.\[80]

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 Bu$_3$SnH 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 Bu$_3$SnH/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 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 $\alpha$-C–C bond cleavage of 2-substituted 1-tetralones to give 40 under radical conditions (TEMPO) has been reported.\[83]

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 $^1$H NOE difference spectrum of 43b). Both sets of products arose from trapping of the intermediate acyl iminium ion by water (as seen for the Bu$_3$SnH reaction of 26a). The monochloride 42b is likely formed by reduction of the $\alpha$-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 interaction).
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 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 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, 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 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, 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.

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

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

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

CONCLUSIONS

In conclusion, we have prepared 38 different enamides 1c varying in the substitution around the acyl group 1 (R1 ≠ H), the nitrogen substituent (R3 ≠ H), and alkene substituents (R2, R3, R4 ≠ H). The major trend is the slow rotation around the N-alkenyl bond of the enamide with \( \Delta G^2 \) 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 (R3, R4, R5), followed by the size of the nitrogen substituent (R2) and, finally, the size of the acyl substituent (R1). Electronic effects are small for substituents positioned on the acyl group (R2), and the rate of rotation is linearly correlated with the cone angle of the substituent for the studied series 3a–i, indicating that the mechanism of rotation is 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 asymmetric 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 $\theta >$ 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, indicative of a cooperative gearing effect between rotation around the (E)- and (Z)-amide and (M)- and (P)-enamide 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 ($\Delta G^\circ_{298 rot}$ = 13–14 kcal mol$^{-1}$) can be accomplished at room temperature, in this study those with higher barriers ($\Delta G^\circ_{298 rot}$ > ~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 ($\Delta G^\circ_{298 rot}$ > ~26 kcal mol$^{-1}$) did not undergo radical cyclization with Bu$_3$SnH; instead, precyclization reduction or alternative reaction pathways predominated. For molecules with intermediate barriers to rotation ($\Delta G^\circ_{298 rot}$ ~ 20–26 kcal mol$^{-1}$), highly functionalized γ-lactams were produced via a S-endo-trig radical–polear crossover process and terminated either by reduction, an unusual cyclopropanation sequence, or trapping with H$_2$O, 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 atroposomers such as 27d. However, this report does indicate that enantiomerically enriched atropoisomeric 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.** H NMR spectra were recorded at 300, 400, 500, or 700 MHz and $^{13}$C NMR spectra were recorded at 75.5, 100, or 125 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, 6-methylbutan-2-one oxime, isobutylaldehyde oxime, 2-methyl-1-tetralone oxime, 2-methyl-1-phenylpropan-1-one oxime, cyclohexyl(phenyl)methanone oxime, 2-phenylcyclohexanone oxime, 2,2,6,6-tetramethylcyclohexanone oxime, 2,4-dimeth-

"N-Benzyl-N-vinylacectamide (2b)"³ Conditions: acetaldehyde (2.0 g, 45.4 mmol), benzaldehyde (4.96 mL, 45.4 mmol), toluene (45 mL, 90 mmol), 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 (film)/cm$^{-1}$ 2039, 1670, 1619; discernible data for major rotamer, H NMR $\delta_1$ (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 $\delta_1$ (CDCl$_3$, 151 MHz) 169.6, 136.9, 133.3, 128.5, 127.0, 126.8, 95.3, 45.4, 22.1; discernible data for minor rotamer, H NMR $\delta_2$ (CDCl$_3$, 300 MHz) 7.63 (1H, d, J = 16.0 Hz), 7.17–7.36 (5H, m), 4.78 (2H, s), 4.38–4.42 (2H, m), 2.18 (3H, s); $^{13}$C NMR $\delta_2$ (CDCl$_3$, 151 MHz) 169.9, 136.0, 131.8, 128.9, 127.4, 95.4, 48.7, 22.4; data for mixture; MS m/z (ESI) 198.1 ([M$^+$]$^+$). N-Benzyl-2,2,2-trichloro-N-(2-phenylcyclohex-1-enyl)acetamide (24a)⁶ Conditions: 2-phenylcyclohexanone (2.43 g, 13.9 mmol), benzaldehyde (1.52 mL, 13.9 mmol), toluene (15 mL, then 25 mL), triethylamine (3.2 mL, 16.7 mmol), and trichloroacetyl chloride (1.71 mL, 15.3 mmol). Yield 1.18 g (21%); white crystalline solid; mp 116–118 °C; R$_f$ 0.52 (pet. ether:EtOAc, 14:1); IR (film)/cm$^{-1}$ 2924, 1671; H NMR $\delta_1$ (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 $\delta_1$ (CDCl$_3$, 175 MHz) 159.5, 140.3, 135.4, 135.2, 134.9, 129.5, 128.8, 128.4, 128.3, 127.7, 124.7, 93.4, 33.1, 30.9, 24.1, 22.5; MS m/z (ESI) 430.0 ([M$^+$]$^+$) found ([M$^+$]Na$^+$) 430.0502, C$_{22}$H$_{16}$BrN$_2$O requires 430.0503.

N-Benzyl-2-bromo-2-methyl-N-(phenylcyclohex-1-enyl)acetamide (24b)⁶ Conditions: 2-phenylcyclohexanone (2.43 g, 13.9 mmol), benzaldehyde (1.52 mL, 13.9 mmol), toluene (15 mL, then 25 mL), triethylamine (3.2 mL, 16.7 mmol), and 2-bromoisobutyryl bromide (1.15 mL, 9.27 mmol). Yield 1.52 g (21%); yellow oil; mixture of amide rotamers (ratio 2:1); R$_f$ 0.45 (pet. ether:EtOAc, 4:1); IR (film)/cm$^{-1}$ 2039, 1670, 1619; discernible data for major rotamer, H NMR $\delta_1$ (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 $\delta_1$ (CDCl$_3$, 151 MHz) 169.6, 136.9, 133.3, 128.5, 127.0, 126.8, 95.3, 45.4, 22.1; discernible data for minor rotamer, H NMR $\delta_2$ (CDCl$_3$, 300 MHz) 7.63 (1H, d, J = 16.0 Hz), 7.17–7.36 (5H, m), 4.78 (2H, s), 4.38–4.42 (2H, m), 2.18 (3H, s); $^{13}$C NMR $\delta_2$ (CDCl$_3$, 151 MHz) 169.9, 136.0, 131.8, 128.9, 127.4, 95.4, 48.7, 22.4; data for mixture; MS m/z (ESI) 198.1 ([M$^+$]$^+$).
+ 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 major rotamer, s), 1.60 (3H major rotamer, s), 1.55 (3H major rotamer, s), 1.29 (3H minor rotamer, s); 13C NMR δC (CDCl3, 157 MHz) 159.4, 136.5, 135.3, 134.7, 130.9, 129.7, 129.2, 128.9, 128.1, 127.9, 94.1, 53.5, 21.8, 21.0. MS m/z (ESI) found ([M]+Na) 404.0346, C19H20Cl2NNaO requires 404.0352.

N-Benzyl-2-bromo-2-methyl-N-(2-methyl-1-phenylprop-1-en-1-yl)propanamide (25c). Isobutyrophene (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-bromoisobutryl bromide (1.15 mL, 9.27 mmol). Yield 2.39 g (74%) as a 10.0:0.6 mixture of rotamers; pale yellow crystalline solid; mp 74–76 °C; Rf 0.37 (pet. ether:EtOAc, 6:1); IR νmax/cm⁻¹ 2989, 1639; 1H NMR δH (CDCl3, 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 major rotamer, s); 13C NMR δC (CDCl3, 157 MHz) mixture 171.9, 169.2, 137.5, 136.5, 135.9, 134.4, 134.1, 133.3, 131.6, 130.2, 129.7, 128.9, 128.4, 128.1, 127.9, 127.6, 127.3, 127.1, 63.2, 57.9, 53.2, 53.1, 33.9, 33.5, 33.4, 32.7, 21.9, 21.8, 20.1, 20.9; MS m/z (ESI) found ([M]+Na) 408.0933, C19H21BrNNaO requires 408.0930.

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, 8.0 mmol), TsoH (0.303 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 (8%) as a 1.00:0.26 mixture of rotamers; cream crystalline solid; mp 102 °C; Rf 0.30 (pet. ether:EtOAc, 6:1); IR νmax/cm⁻¹ 2989, 1639; 1H NMR δH (CDCl3, 400 MHz) 7.53–7.10 (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 major rotamer, s); 13C NMR δC (CDCl3, 175 MHz) mixture 171.9, 169.2, 137.5, 136.5, 135.9, 134.4, 134.1, 133.3, 131.6, 130.2, 129.7, 128.9, 128.4, 128.1, 127.9, 127.6, 127.3, 127.1, 63.2, 57.9, 53.2, 53.1, 33.9, 33.5, 33.4, 32.7, 21.9, 21.8, 20.1, 20.9; MS m/z (ESI) found ([M]+Na) 408.0933, C19H21BrNNaO requires 408.0930.

N-Benzyl-2-bromo-N-(cyclohexylidene(phenyl)methyl)-2-methylpropanamide (26c). Conditions: cyclohexylphenyl ketone (1.5 g, 8.0 mmol), benzylamine (0.87 mL, 8.0 mmol), TsoH (0.303 mg, 1.6 mmol), toluene (9 mL then 15 mL), triethylamine (1.33 mL, 9.6 mmol), and 2-bromoisobutryl bromide (1.08 mL, 8.8 mmol). Yield 2.02 g (59%) as a 10.0:0.6 mixture of rotamers; pale brown crystalline solid; mp 102–104 °C; Rf 0.43 (pet. ether:EtOAc, 14:1); IR νmax/cm⁻¹ 2973, 1656; 1H NMR δH (CDCl3, 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 major rotamers, m), 1.03–0.80 (1H major rotamer, m), 0.34–0.26 (1H minor rotamer, m); 13C NMR δC (CDCl3, 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 ([M]+Na) 448.1246, C19H20BrNNaO requires 448.1252; HPLC (SS)-Whelk-O1 (25 cm × 4.6 mm) hexanes:PrOH (1.0 mL/min) tR 5.41 min.
**N-(3-Methylbut-2-en-2-yl)acetamide (5c, X = H, R² = R³ = R⁴ = Me).** Conditions: 3-methylbutan-2-one oxime (3.20 g, 15.8 mmol), acetic acid (5.43 mL, 94.9 mmol), acetic anhydride (8.95 mL, 94.9 mmol), iron powder (4.06 g, 72.6 mmol), and anhydrous toluene (80 mL). The crude product was purified by column chromatography (pet. ether:ethyl acetate 10:1). Yield 617 mg (15%).

**N-(2-Methylprop-1-en-1-yl)acetamide (5d, X = H, R² = R³ = R⁴ = Me).** Conditions: isobutyraldehyde oxime (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 recrystallization from hexane:ethyl acetate 10:1. Yield 617 mg (15%).

**N-(2-Methylprop-1-en-1-yl)acetamide (5e, X = H, R² = Ph, R³ = R⁴ = Me).** Conditions: 2-methyl-1-propenyl-1-oxime (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-2-yl)acetamide (5f, X = H, R² = Pr, R³ = R⁴ = Me).** Conditions: 2,4-dimethylpent-2-one oxime (1.55 g, 7.5 mmol), acetic acid (0.97 mL, 16.8 mmol), acetic anhydride (6.50 mL, 68.9 mmol), iron powder (2.84 g, 29.26 mmol), and 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; Rf 0.23 (pet. ether:EtOAc, 3:1); IR νmax (film)/cm⁻¹ 3229, 2933, 1650; H NMR δc (CDCl₃, 400 MHz) 178.1202, C₁₅H₁₈ClNNaO requires 178.0969.

**General Procedure for the Formation of Chloroacetamides.** 2-Chloroacetamides were prepared by the method of Tang et al.¹³ using the following modification: Oxime (1 equiv), 2-chloroacetic anhydride (2 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 DCI 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, R² = R³ = -C₆H₄CH₂CH₂−, R⁴ = Me).** Conditions: 2-methyl-1-tetralone oxime (2.94 g, 16.8 mmol, 1 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 1:10 to give the 2.09 g (53%); pale brown solid; mp 139–141 °C; Rf 0.23 (pet. ether:EtOAc, 3:1); IR νmax (film)/cm⁻¹ 3122, 2933, 1650; H NMR δc (CDCl₃, 400 MHz) 7.59 (1H, s), 7.22–7.09 (3H, m), 7.06 (1H, d, J = 7.5 Hz), 4.25 (2H, s), 2.84 (2H, t, J = 8.0 Hz), 2.42 (2H, t, J = 8.0 Hz), 1.88 (3H, s).¹² C NMR δc (CDCl₃, 100 MHz) 164.8, 135.0, 130.5, 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]⁺ 258.0856, C₁₅H₁₉ClNNaO requires 258.0856).

Analysis: C 66.2%; H, 5.9%; N, 5.8%. C₁₅H₁₉ClNNaO. Calcd: 66.2%; H, 6.0%; N, 5.8%.

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1. [Cyclohexene(phenyl)acetamide] (5m, X = Cl, R² = R³ = Ph, R⁴ = Me). Conditions: cyclohexene(phenyl)methanone oxime (4.00 g, 19.7 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, 1:1) to give 676 mg (25%).

2. [Chloro-N-(2-methyl-1-propenyl-1-yl)acetamide (5l, X = Cl, R² = R³ = Ph, R⁴ = Me)]. Conditions: 2-methyl-1-propenyl-1-oxime (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, 1:1) to give 676 mg (25%).

3. [Chloro-N-(cyclohexylidene)phenylmethyl]acetamide (5n, X = Cl, R² = Ph, R³ = —(CH₂)₄−, R⁴ = Me). Conditions: cyclohexyl(phenyl)methanone oxime (4.00 g, 19.7 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, 1:1) to give 676 mg (25%).
N-Benzyl-N-(1-phenyl-2-methylprop-1-en-1-yl)acetamide (7a). Conditions: N-(1-phenyl-2-methylprop-1-en-1-yl)acetamide (3.50 g, 18.5 mmol), sodium hydride (3.70 mg, 0.25 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 ν max (film)/cm−1 2991, 1642; 13 NMR δ (CDCl3, 400 MHz) 7.27–7.42 (3H, m), 7.19–7.27 (7H, m), 5.27 (1H, d, J = 14.0 Hz), 5.29 (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); 13 C NMR δ (CDCl3, 75 MHz) 170.0, 157.6, 131.7, 130.8, 128.3, 127.4, 127.0, 30.1, 21.3, 20.5, 19.5, 19.4; MS m/z (ESI) found [M+Na]+ 252.1361, C14H12NNO requires 252.1364.

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 ν max (film)/cm−1 2927, 1643; 13 NMR δ (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); 13 C NMR δ (CDCl3, 75 MHz) 170.6, 163.5, 136.2, 135.6, 135.1, 132.9, 127.5, 127.1, 126.8, 126.6, 126.3, 121.8, 48.8, 28.9, 26.8, 20.6, 18.3; MS m/z (ESI) 314 ([M+Na]+) found [M+Na]+ 292.1700, NO requires [M+Na]+ 292.1700, HPLC (S,S)-Whelk-O1 (25 cm × 4.6 mm) hexanes:PrOH (1.0 mL/min) tR 13.70 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 ν max (film)/cm−1 2931, 1641; 13 NMR δ (CDCl3, 400 MHz) 7.22–7.35 (7H, m), 5.00 (1H, d, J = 14.5 Hz), 4.35 (1H, d, J = 14.5 Hz), 1.99–2.07 (2H, m); 13 C NMR δ (CDCl3, 75 MHz) 170.2, 140.7, 138.3, 136.3, 135.6, 128.9, 128.7, 128.4, 127.4, 127.3, 127.1, 106.3, 31.4, 23.1, 22.7, 22.2; MS m/z (ESI) 294.1829, C14H22NO requires 294.1828.

N-Benzyl-N-(2-cyclohexylidenepheny1)acetamide (7d). Conditions: N-(cyclohexylidene(phenyl)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 hexane 0.71 g (86%); pale orange solid; mp 89–92 °C; R f 0.45 (pet. ether:EtOAc, 4:1); IR ν max (film)/cm−1 2925, 1646; 13 NMR δ (CDCl3, 400 MHz) 7.23–7.90 (10H, m), 7.15–7.13 (5H, m), 1.58–1.50 (4H, m), 1.30–1.18 (3H, m), 1.09–1.05 (2H, m), 0.18–0.16 (H, m), 0.12–0.09 (H, m), 0.04–0.02 (H, m); 13 C NMR δ (CDCl3, 100 MHz) 172.0, 139.5, 139.1, 138.5, 138.3, 137.4, 136.3, 135.6, 134.8, 132.6, 128.4, 127.4, 127.3, 127.1, 41.2, 36.0, 31.8, 30.5, 27.7, 21.9, 18.4; MS m/z (ESI) found [M+H]+ 294.1829, C14H22NO requires 294.1828.
(45%). Yield 45%; colorless oil; Rf (6:1 pet. ether:EtOAc) 0.49; IR max (cm⁻¹) 2928, 1648; 1H NMR δ (CDCl₃, 300 MHz) 7.84–7.31 (1H, m), 7.06 (1H, d, J = 7.0 Hz), 6.47 (1H, d, J = 9.0 Hz), 5.43 (1H, s), 3.68 (2H, s), 2.69 (2H, m), 1.83–1.43 (2H, m); 13C NMR δ (CDCl₃, 75.5 MHz) 170.3, 161.0 (d, δ = 244.5 Hz), 138.8, 131.2 (d, δ = 3.8 Hz), 129.0 (d, δ = 8.25 Hz), 128.1, 124.9 (d, δ = 14.25 Hz), 124.1 (d, δ = 3.8 Hz), 115.0 (d, δ = 21.8 Hz), 42.3 (d, δ = 3.7 Hz), 27.9, 24.9, 22.8, 21.7, 21.5; MS m/z (ESI) 270 [M⁺]Na [found (M⁺)Na 270.1263, C₁₇H₂₀BrNO requires 270.1270].

N-Cyclohex-1-yl-N-2-iodobenzylacetamide (13c). Yield 45%; colorless oil; Rf (6:1 pet. ether:EtOAc) 0.43; IR max (cm⁻¹) 2928, 1648; 1H NMR δ (CDCl₃, 300 MHz) 7.73–7.48 (4H, m), 7.22–6.87 (5H, m), 5.95 (1H, d, J = 9.0 Hz), 5.27 (1H, s), 4.45 (2H, m), 1.87–1.43 (2H, m); 13C NMR δ (CDCl₃, 75.5 MHz) 170.3, 140.3, 139.2, 138.6, 129.7, 128.8, 124.8, 55.3, 53.8, 28.4, 22.7, 21.7, 21.5; MS m/z (ESI) 365.05 [M⁺]H⁺ [found (M⁺)H⁺ 365.0516, C₁₃H₁₁INO requires 365.0506].

N-Cyclohex-1-yl-N-2-difluorobenzylacetamide (13d). Yield 45%; colorless oil; Rf (3:1 pet. ether:EtOAc) 0.49; IR max (cm⁻¹) 2929, 1651, 1470, 1387; 1H NMR δ (CDCl₃, 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), 1.95–1.78 (2H, m), 1.63–1.52 (2H, m), 1.48–1.30 (2H, m); 13C NMR δ (CDCl₃, 75.5 MHz) 169.4, 162.0 (dd, δ = 255.8, 7.5 Hz), 127.2, 124.5 (t, δ = 105.5 Hz), 128.7, 113.0 (t, δ = 18.8 Hz), 111.1 (d, δ = 17.3 Hz), 35.6 (t, δ = 3.0 Hz), 27.4, 24.9, 22.8, 21.7, 21.5; MS m/z (ESI) 288 [M⁺]Na [found (M⁺)Na 288.1170, C₁₃H₁₁F₂NO requires 288.1176].

N-Cyclohex-1-yl-N-2-dichlorobenzylacetamide (13e). Yield 85%; yellow oil; Rf (4:1 pet. ether:EtOAc) 0.28; IR max (cm⁻¹) 2929, 1647; 1H NMR δ (CDCl₃, 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 (2H, m), 1.65–1.48 (2H, m), 1.45–1.35 (2H, m); 13C NMR δ (CDCl₃, 75.5 MHz) 167.9, 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 [M⁺]Cl⁻ [found (M⁺)Cl⁻ 320.0574, C₁₃H₁₁Cl₂NO requires 320.0585].

N-Cyclohex-1-yl-N-2-dibromobenzylacetamide (13f). Yield 26%; yellow oil; Rf (6:1 pet. ether:EtOAc) 0.47; IR max (cm⁻¹) 2926, 1648; 1H NMR δ (CDCl₃, 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, br s), 2.02 (3H, s), 1.88–1.84 (4H, m), 1.53–1.47 (2H, m), 1.42–1.36 (2H, m); 13C NMR δ (CDCl₃, 100 MHz) 166.9, 137.3, 135.7, 132.5, 130.9, 129.5, 127.1, 148.8, 28.7, 24.9, 22.8, 21.4, 21.3; MS m/z (ESI) 258.2139 [M⁺]H⁺ [found (M⁺)H⁺ 258.2139, C₁₃H₁₁Br₂NO requires 258.2142].

D). Conditions: N-(1-phenyl-2-methylprop-1-en-1-yl)acetamide (14). Conditions: N-(1-phenyl-2-methylprop-1-en-1-yl)acetamide (14).
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 122.0–123.0 °C.

The reaction mixture was then cooled and concentrated in vacuo. The crude product was dissolved in DCM (100 mL) and the mixture was stirred at room temperature for 3.5 h. The reaction mixture was then filtered, and concentrated in vacuo. The crude product was dried over MgSO4, filtered, and concentrated in vacuo. The crude product was then purified by recrystallization from hexane 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 Na2SO4, 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%); Rf 0.60 (pet. ether:EtOAc 3:1; IR νmax (film)/cm−1 2929, 2921, 1654; 1H NMR δ (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), 3.47 (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 (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, 51.2, 29.9, 27.6, 20.1, −17; MS m/z (ESI) found ([M]+Na) 348.1778, C20H16N2NaO requires 358.1778.

Data for mixture: IR νmax (film)/cm−1 3325, 2924, 2854, 1664; 1H NMR δ (CDCl3, 100 MHz) 7.51, 128.9, 137.0, 136.3, 128.6, 128.5, 128.3, 128.2, 128.1, 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, 22.5.

Cyclization of N-Benzyl-N-(2-(methyl-3,4-dihydronaphthalen-1-yl)-2-iodoacetamide (27a) with Bu3SnH/AIBN. To a degassed solution of N-Benzyl-N-(2-(methyl-3,4-dihydronaphthalen-1-yl)-2-iodoacetamide (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) under argon for 24 h. The crude product was purified by column chromatography (pet. ether:EtOAc 9:1) to give yellow oil. Yield 250 mg (17%); Rf 0.26 (pet. ether:EtOAc 6:1; IR νmax (film)/cm−1 2923, 2921, 1654; 1H NMR δ (CDCl3, 300 MHz) 7.18–7.39 (9H, 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 (3H, f, J = 6.0 Hz), 1.47–1.82 (4H, m), 2.0 (3H, s), 1.04 (3H, s), 0.92 (3H, s); 13C NMR δ (CDCl3, 100 MHz) 167.3, 138.0, 138.0, 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]+) 306.2, C13H13ClNO requires 306.1625.

Cyclization of N-Benzyl-2-chloro-N-(cyclohexyldiene(phenyl)methyl)acetamide (26a) with Bu3SnH. N-Benzyl-2-chloro-N-(cyclohexyldiene(phenyl)methyl)acetamide (26a) (500 mg, 1.49 mmol), Bu3SnH (0.60 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 the crude product (74% yield; mp 170.0–171.0 °C; IR νmax (film)/cm−1 3433, 2929, 2857, 1663; 1H NMR δ (CDCl3, 300 MHz) 7.76 (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 (SH, 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 (CDCl3, 100 MHz) 167.5–168.0, 134.9, 134.3, 130.4, 129.2, 128.9, 128.5, 128.4, 127.8, 127.6, 126.1, 122.2, 53.3, 42.5, 18.1; MS m/z (ESI) found ([M]+Na) 346.1, C20H16N2NaO requires 346.0975.

N-Benzyl-N-(2-methylnaphthalen-1-yl)-2-iodoacetamide (28b). To a solution of N-Benzyl-N-(2-methyl-3,4-dihydronaphthalen-1-yl)-2-iodoacetamide (27a) (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 9:1) gave a yellow oil (28 mg, 52%); IR νmax (film)/cm−1 2923, 2851, 1664; 1H NMR δ (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), 1.93 (3H, s); 13C NMR δ (CDCl3, 75.5 MHz) 168.5, 136.3, 135.4, 134.7, 133.4, 130.4, 130.1, 129.1, 128.0, 128.0, 127.5, 126.0, 122.8, 53.5, 18.6, −1.7; MS m/z (ESI) found ([M]+Na) 438.0325, C20H16N2NaO requires 438.0331.

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Cyclization of N-Benzyl-N-(2-methyl-3,4-dihydronaphthalen-1-yl)-2-bromoacetamide (27b) with Bu3SnH. 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 Bu3SnH (163 mL, 0.608 mmol) and ACN (20 mg, 0.08 mmol). After 24 h a further aliquot of Bu3SnH (163 mL, 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 x 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 (27a).0.57, 2.2, 1.4, 1.2, 1.0, 0.9; 13C NMR δC (CDCl3, 100 MHz) 163.6, 139.1, 138.2, 129.1, 128.9, 128.1, 128.1, 127.8, 105.8, 89.1, 56.8, 45.2, 29.3, 23.1, 18.1; MS m/z (ESI) found ([M]+Na) 394.0732, C18H16ClNNaO4 requires 394.0736.

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)-2-methylacetamide (26b) (150 mg, 0.353 mmol), CuCl (35.1 mg, 0.353 mmol), TPA (103 mg, 0.353 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-azaazepino-[4,5-decane-3-one (43a) (33 mg, 23%) and 2-benzyl-chloro-1-hydroxy-1-phenyl-2-azaazepino-[4,5-decane-3-one (43b) (21 mg, 16%) as colorless solids.

Data for 42a: Rf 0.10 (pet. ether:EtOAcl, 6:1); mp 171–172 °C. IR νmax (film)/cm−1 3520, 2972, 2940, 1690; 1H NMR δC (CDCl3, 400 MHz) 7.14–7.68 (8H, m), 7.01–7.14 (2H, m), 5.20 (1H, δd, J = 15.0 Hz), 4.03 (1H, δd, J = 15.0 Hz), 1.95 (1H, s), 1.35 (3H, s), 0.95 (3H, s), 0.53 (3H, s); 13C NMR δC (CDCl3, 100 MHz) 182.2, 139.3, 129.6, 128.9, 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, C19H16Cl2N4NaO requires 346.1783.

Cyclization of N-Benzyl-2-bromo-2-methyl-N-(2-methyl-1-phenylprop-1-enyl)-1-enyl)pyrrolidin-2-one (25c) with Cu(TPMA)Br. Conditions: N-benzyl-2-bromo-2-methyl-N-(2-methyl-1-phenylprop-1-enyl)-1-enyl)pyrrolidin-2-one (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 (61, pet. ether:EtOAc) to yield 1-benzyl-5-hydroxy-3,3,4,4-tetramethyl-5-phenylpyrrolin-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-phenylpyrrolin-2-one (45) and 2-benzyl-4,4,5-trimethyl-1-phenyl-2-azabicyclo[3.1.0]hexane-3-one (46) (19%, 45:46 = S:1).

Data for 44: Rf 0.16 (pet. ether:EtOAcl, 6:1); mp 117–119 °C. IR νmax (film)/cm−1 3211, 2666; 1H NMR δC (CDCl3, 400 MHz) 7.14–7.48 (8H, m), 7.01–7.14 (2H, m), 5.20 (1H, δd, J = 15.0 Hz), 4.03 (1H, δd, J = 15.0 Hz), 1.95 (1H, s), 1.35 (3H, s), 0.95 (3H, s), 0.53 (3H, s); 13C NMR δC (CDCl3, 100 MHz) 182.2, 139.3, 129.6, 128.9, 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, C19H16Cl2N4NaO requires 346.1783.
Cyclization of N-benzyl-2-bromo-N-(cyclohexylidene(phenyl)-methyl)-2-methylpropanamide (26c) with Cu(TMPA)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 (9:1:2, hexane:diethyl ether:triethylamine), yielding 2-benzyl-1-hydroxy-4,4-dimethyl-1-phenyl-2-azaspiro[4.5]decane-3-one (50) as a white solid (66 mg, 33%) and an inseparable mixture of 2-benzyl-4,4-dimethyl-1-phenyl-2-azaspiro[4.5]decane-3-one (52 and 51) (41 mg, 26%, 1:4 = 50:51).

For Rf: Rf 0.18 (pet. ether:EtOAc, 6:1); mp 169–170 °C; IR νmax (film)/cm−1 3165, 1661; 1H NMR δH (CDCl3, 400 MHz) 7.16–7.39 (8H, 2S, 51, m), 7.02–7.06 (2H, 51, m), 6.99–7.02 (2H, 51, m), 5.22 (1H, d, J = 14.5 Hz), 4.61 (1H, 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, 51, m), 1.78 (1H, 51, m), 1.45 = 14.5 Hz), 1.57–1.70 (2H 52, s), 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, 52, s), 1.23 (3H 51, s), 1.11 (3H 51, s), 1.04–1.15 (1H 51, s), 0.95–1.04 (1H 51, s), 0.85 (1H 51, dd, J = 8.5, 2.5 Hz), 0.74–0.82 (1H 51, s), 0.57–0.69 (1H 51, s); 13C NMR 5C (CDCl3, 100 MHz) 181.2, 140.0, 138.4, 128.9, 128.5, 128.1, 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 [M]+Na 368.1856, C22H25NNaO requires 368.1738.

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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