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Efficient preparations of novel ynamides and allenamides

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Abstract—Practical syntheses of a series of novel ynamides and allenamides are described here. While a base-induced isomerization protocol of propargyl amides leads to an array of chiral and achiral allenamides, ynamides are prepared from enamides via bromination followed by base-induced elimination of the *Z*-bromoenamides. These ynamides and allenamides possess improved thermal stability compared to ynamines and allenamines. They can be isolated, purified, and handled with ease, and thus, should be synthetically more useful than traditional ynamines and allenamines.

1. Introduction

Alkynes and allenes are extremely versatile functional groups in organic synthesis leading to a diverse array of synthetic methods. Two important subgroups would be those nitrogen atom substituted alkynes and allenes or ynamines[1] and allenamines, respectively.[2] The electron-donating ability of the nitrogen atom renders them even more synthetically useful than alkynes and allenes because of the electronic bias imposed by the heteroatom, allowing regioselective transformation of these organic synthons (Fig. 1). While the synthetic significance of ynamines in organic chemistry was firmly established by the work of many organic chemists more than fifteen years ago,[1] the synthetic scope of allenamines has remained very limited.[2,3] However, there have been relatively few synthetic applications using either ynamines or allenamines in recent decades. This lack of attention is in part attributed to the difficulty in preparation and handling of ynamines and allenamines due to their high reactivity and sensitivity toward hydrolysis and polymerization.

We have been exploring reactivities of some electron-deficient variants of ynamines and allenamines, or simply ynamides and allenamides, in which the nitrogen atom is substituted with an electron-withdrawing group.[4,5] Our designs would specifically feature either an imidazolidinone or oxazolidinone moiety, thereby also providing a practical entry to chiral ynamides and allenamides (Fig. 2).[4,5] The electron-withdrawing group serves to diminish the electron-donating ability of the nitrogen atom, thereby offering superior stability to the traditional ynamines and allenamines.

Although preparations of some electron-deficient ynamines[6,7] and allenamines[8,9] as well as improved thermal stability of electron-deficient ynamines have been documented,[6] it was not until recently that reactivities of electron-deficient ynamines and allenamines were explored in transition metal-mediated processes,[10,11] while examples of palladium catalyzed cross-couplings,[12] cyclizations,[13] and [2+2] cycloaddition reactions[14] using allenamides have also appeared in literature. Specifically, stereoselective

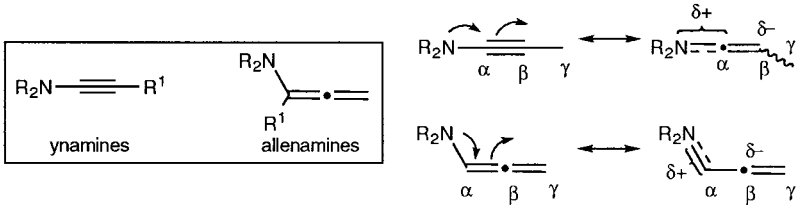

Figure 1.

Keywords: ynamides; allenamides; bromination.

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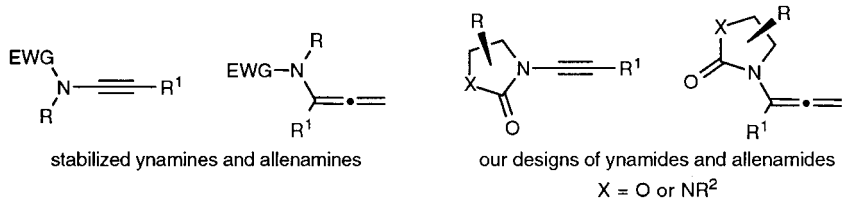
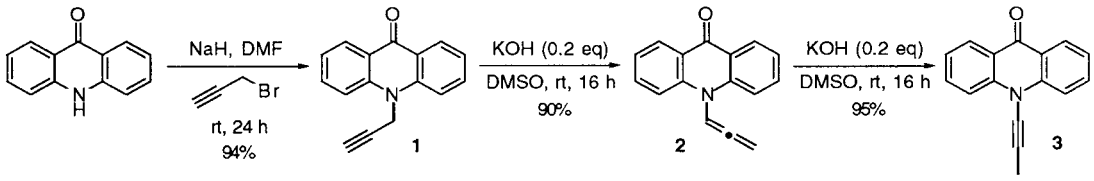


Figure 2.



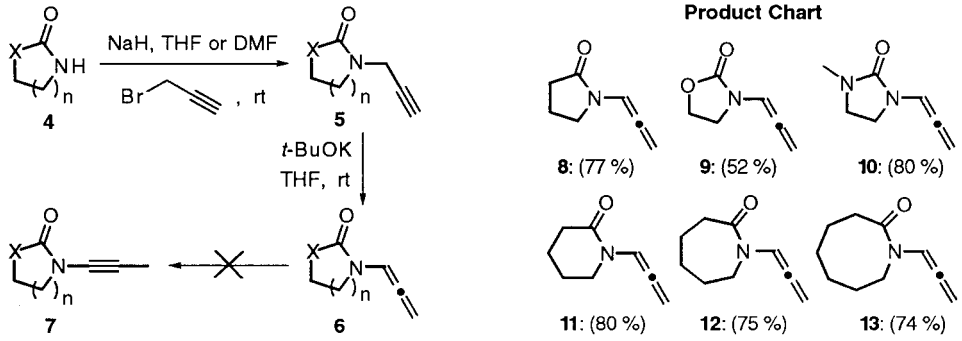
Scheme 1.

reactions using our ynamides[4] and allenamides[5] for constructions of heterocycles and other useful organic building blocks have been investigated. Our studies along with recent literature reports demonstrate the synthetic potential of ynamides and allenamides as well as a renewed interest. Given their synthetic potential, we disclose here the details for preparations of our ynamides and allenamides.

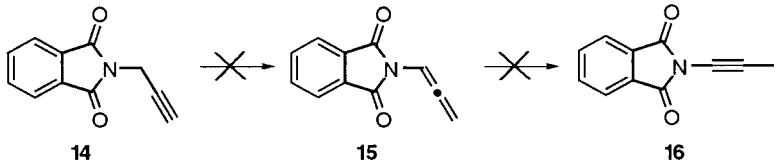
2. Results and discussions

Although there is a diverse array of known methods that give useful preparations of ynamines,[15] a base-induced isomerization protocol appears to be the most efficient and has worked well for the synthesis of various ynamines. In addition, in a related study,[4] the known vinylogous ynamide **3** was prepared in 80% overall yield from acridone using conditions similar to those reported by Katritzky.[16] It was found that isomerization of the propargylated acridone **1** could be arrested at the vinylogous allenamide **2**, but by extending the reaction time, isomerization of **2** led to **3** cleanly using 20 mol% KOH in DMSO. Both the allenamide **2** and ynamide **3** are stable crystalline solids (Scheme 1).

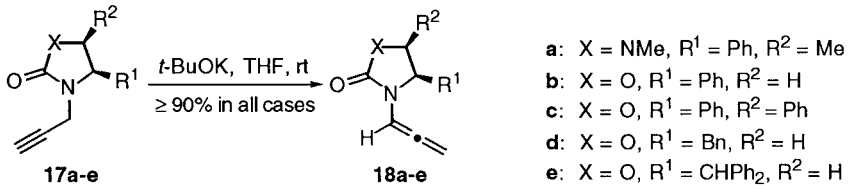
The synthetic sequence for preparation of **3** represents a practical approach for the synthesis of ynamides of our interest. Toward this goal, a series of propargylated amides shown as **5** were prepared from corresponding lactams, 2-oxazolidinone, or *N*-methyl-2-imidazolidinone shown as **4** (Scheme 2). However, subsequent isomerization of propargyl amides **5** using *t*-BuOK in anhydrous THF at ambient temperature provided only the allenamides **6**. A variety of achiral allenamides **8**–**13** were obtained in good overall yields. These allenamides clearly possess much improved thermal stability than allenamines. They can survive either silica gel or basic alumina column chromatography, and are not readily polymerized even at temperatures greater than 80°C which is well beyond the temperature limit for thermal polymerization of allenamines.[2,3f,5] These improvements suggest the loss of ability of the nitrogen atom in donating toward the allene moiety



Scheme 2.



Scheme 3.



Scheme 4.

due to a more delocalized nitrogen lone pair, thereby leading to reduced reactivity and greater stability.

On the other hand, attempts to effect the reaction by using different bases (KOH, or $NaHCO_3$), different solvents (DMSO, THF, CH_3CN, or DMF), and different reaction temperatures (rt to 70°C) and durations (12 h to 8 days) failed to provide the ynamides **7**. Finally, isomerization of the propargylated phthalamide **14** failed to give either the corresponding allenamide **15** or ynamide **16** under a variety of conditions (Scheme 3), and in most cases, the starting material **14** was recovered.

Chiral allenamides could also be readily prepared using this base-induced isomerization protocol. As shown in Scheme 4, a variety of chiral allenamides **18a–e** were obtained in high yields over two steps starting from Close's chiral imidazolidinone **17a**,[17] Evans' oxazolidinone auxiliaries **17b–d**,[18] or Sibi's dibenzylidene substituted oxazolidinone **17e**.[19] It is noteworthy that isomerizations of chiral propargyl amides **17a–e** using 20 mol% of *t*-BuOK in anhydrous THF provided chiral allenamides **18a–e** in much higher yields than those achiral examples described in Scheme 2. This could be attributed to the fact that these chiral allenamides are even more stable than the achiral ones, and given such an improved stability and ease of experimental handling, they can be obtained in gram quantities using conditions described here.

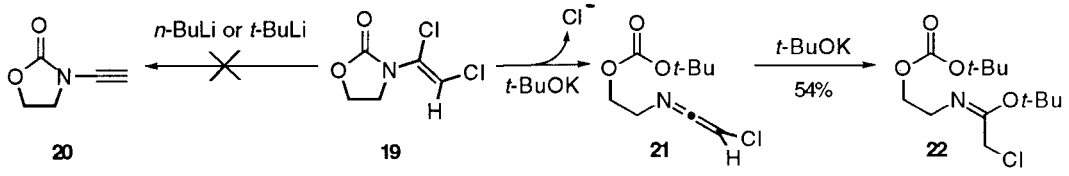
Having established that the base-induced isomerization serves as a practical entry to allenamides but not ynamides, we began exploring other approaches that may present similar efficiency for synthesis of our ynamides. Because the literature indicated that dichloroenamides may be converted to electron-deficient ynamines using alkyl lithium reagents,[7a] the dichloroenamide **19** was prepared from oxazolidinone and trichloroethylene. The *Z* stereochemistry in **19** was assigned based on those examples reported in literature.[7a] However, we failed to isolate any desired ynamide **20** when **19** was treated with either *n*-BuLi or *t*-BuLi (Scheme 5).

When switching to *t*-BuOK, the carbonate **22** was isolated in 54% yield after stirring at room temperature for 1 h. The formation of **22** presumably is a result of *t*-BuOK attacking the oxazolidinone ring in **19** leading to the chloroketene imine intermediate **21** instead of deprotonating the vinyl proton. The nitrogen atom served as an excellent leaving group because of its electron deficiency due to the electronegative chlorine atoms.

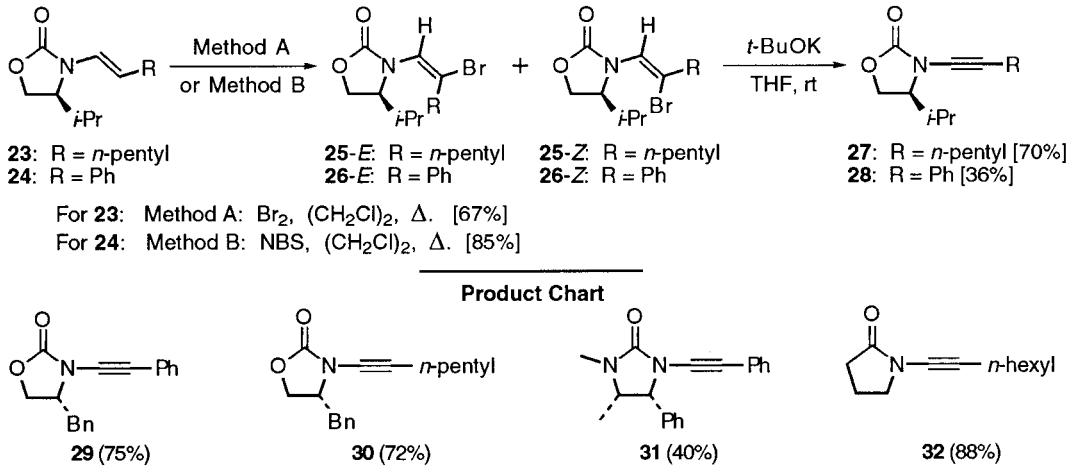
Viehe has also reported similar products resulting from base treatment of mono-chloroenamides,[6] and more significantly, Viehe found that mono-bromoenamides are better substrates for base-induced eliminations, leading to the first reported electron-deficient ynamines.[6] We decided to follow this approach and prepared chiral enamides **23** and **24** via *p*-TsOH catalyzed condensations of corresponding chiral oxazolidinones and aldehydes.[20] However, unlike those reported by Viehe,[6] brominations of **23** and **24** were not trivial. Standard bromination conditions such as Br_2 and Et_3N at a variety of temperatures and solvents led to desired bromoenamides **25** or **26** in 5–10% yields at the best. Intriguingly, 60–80% of the starting enamide **23** or **24** was consistently recovered under these conditions, thereby suggesting a reversible bromine addition that was occurring in this process. Another possibility would be that enamides **23** and **24** are simply less reactive toward standard bromination conditions and more drastic conditions were needed.

After exploring a variety of conditions, it was found that by either refluxing **23** with Br_2 in 1,2-dichloroethane (Method A in Scheme 6), or refluxing **24** with NBS in 1,2-dichloroethane (Method B), the desired bromoenamides **25** and **26** could be prepared in 67 and 85% yields, respectively. Both bromoenamides **25** and **26** were isolated as a mixture of *E* and *Z* isomers. The Method A provided **25** with an *E*/*Z* ratio of 1:8, and the Method B provided **26** with an *E*/*Z* ratio of 1.5:1, and the *E* and *Z* configurations of **25** and **26** were determined using nOe experiments.[21] More interestingly, the Method A appears to work well for enamides where R is an alkyl substituent, while the Method B only works well for enamides where R is an aromatic substituent.

Subsequent treatment of **25**-*Z* and **26**-*Z* with 1–2 equiv. of *t*-BuOK in THF at room temperature provided the desired ynamides **27** and **28** in 70 and 36% yields, respectively. Again, unlike those conditions reported by Viehe,[6]



Scheme 5.

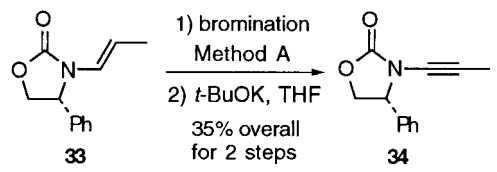


Scheme 6.

t-BuOK must be added carefully as a solution in THF to the solution of the enamides **25**-*Z* or **26**-*Z* in THF at 0°C before warming up to room temperature. Severe decomposition occurred when *t*-BuOK was added as a solid and/or at room temperature. The bromoenamides **25**-*E* and **26**-*E* appeared to be resilient toward *t*-BuOK induced elimination. The desired ynamides **27** and **28** were not found even after refluxing **25**-*E* and **26**-*E* with *t*-BuOK in THF for 24 h, and the starting materials were completely recovered. Following the same reaction protocol, ynamides **29**–**32** were prepared in yields ranging from 40–88%.

Although this particular sequence for preparations of ynamides still suffers from the lack of ability to eliminate the *E*-bromoenamides, the overall sequence offers a very short and practical entry to a diverse array of achiral and chiral ynamides. All these ynamides are very stable thermally and are relatively more stable than those allenamides described above. The ynamide **31** is the least stable among all the new ynamides prepared here, and thus, it appears that ynamides are thermodynamically more stable than allenamides. However, the isomerization protocol described in Scheme 2, presumably a thermodynamically driven process, is evidently arrested at the allenamide stage (see intermediate **6**). The reason is not fully clear at this point except that the deprotonation–protonation process during the isomerization of **6** to the ynamide **7** must be very slow, perhaps owing to potential decreasing in the acidity of the proton alpha to the nitrogen atom.

Finally, as shown in Scheme 7, the enamide **33**[22] could also be subjected to the Method A for bromination to provide the corresponding bromoenamide in 70% yield with a *E*/*Z* ratio of 1:2. A subsequent elimination of the *Z*-bromoenamide



Scheme 7.

using *t*-BuOK led to the ynamide **34** in 50% yield. The significance of achieving this preparation is that the chiral ynamide **34** is the first chiral equivalent and electron-deficient variant of Ficini's *N*,*N*-diethyl-1-amino-1-propyne.[1] Hence, the ynamide **34** should be useful for preparation of other functionalized chiral ynamides using similar methods as employed for Ficini's ynamine.[1,15]

We have described here efficient and practical syntheses of novel ynamides and allenamides. Given the synthetic potential of these organic synthons as demonstrated in recent literature and on-going effort from our[4,5] as well as other laboratories,[10–14] these preparations should help facilitate further interests from the synthetic community.

3. Experimental

3.1. General procedure for preparation of *N*-allenyl imidazolidinones/oxazolidinones

3.1.1. Preparation of *N*-propargyl imidazolidinones and oxazolidinones. To a homogeneous solution of imidazolidinone/oxazolidinone (5.0 mmol) in anhydrous THF (30 mL) was added NaH (60 wt% in mineral oil, 1.2 equiv.) in small portions (Caution). The resulting suspension was stirred for 30 min at room temperature before the addition of propargyl bromide (2 equiv.). The precipitation of sodium salt did not affect the reaction. The mixture was stirred at rt for 16–24 h, after which the mixture was concentrated and redissolved into ether (~20–50 mL) and filtered through a small bed of celite. The solvent was concentrated under reduced pressure, and the residue was purified by flash silica gel column chromatography[23] (gradient solvent system: 0–20% EtOAc in hexane) to provide the desired propargyl products in high yields (>90%).

3.1.2. Preparation of allenamides. To a homogeneous solution of the propargyl product prepared above (5.0 mmol) in anhydrous THF (5.0 mL) was added freshly made *t*-BuOK/*t*-BuOH (200 mg, 20 mol%) under nitrogen. The reaction mixture was stirred at rt for 16–24 h. The reaction progress was monitored by TLC (25 or 50%

EtOAc in hexane) or ^{1}H NMR. After removing the solvent under reduced pressure, the crude mixture was redissolved in ether (~20–50 mL) and filtered through a small bed of celite or basic Al_2O_3 (25% EtOAc in hexane as eluent). The solvent was removed under reduced pressure to provide pure allenamides in high yields (>90%). For all allenamides except **10** and **18a**, further purification can be achieved by flash silica gel column chromatography (gradient solvent system: 0–50% EtOAc in hexane). The allenamides **10** and **18a** could not survive on silica gel (especially in the case of the allenamide **10**, and thus, the R_f value could not even be determined), and purification may be achieved by simple filtration.

3.1.3. Compound 8. Please see Ref. 8a for literature precedent. R_f=0.29 (33% EtOAc in hexane); oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.09 (quint, 2H, J=7.8 Hz), 2.47 (t, 2H, J= 8.1 Hz), 3.41 (t, 2H, J=7.5 Hz), 5.37 (d, 2H, J=6.6 Hz), 7.08 (t, 1H, J=6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.3, 31.0, 45.6, 86.5, 95.6, 172.8, 202.5; IR (neat) cm^{-1} 3031m, 2977m, 1959w, 1692s, 882m; MS (EI): *m/e* (% relative intensity) 123 (95) M^+, 95 (100), 68 (40); *m/e* calcd for C_7H_9NO 123.0684, measured 123.0686.

3.1.4. Compound 9. R_f=0.42 (50% EtOAc in hexane); mp 42–45°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.62 (t, 2H, J= 8.1 Hz), 4.44 (t, 2H, J=8.1 Hz), 5.46 (d, 2H, J=6.3 Hz), 6.90 (t, 1H, J=6.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 42.9, 62.3, 87.7, 96.6, 155.2, 201.3; IR (neat) cm^{-1} 3287m, 2923m, 1977m, 1731s, 1434s; MS (EI): *m/e* (% relative intensity) 125 (100) M^+, 98 (20), 80 (40); *m/e* calcd for $C_6H_7NO_2$ 125.0477, measured 125.0475.

3.1.5. Compound 10. Oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.84 (s, 3H), 3.41 (m, 4H), 5.39 (d, 2H, J=6.3 Hz), 7.03 (t, 1H, J= 6.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.8, 40.5, 44.3, 87.0, 97.9, 157.2, 201.3; IR (neat) cm^{-1} 3032m, 2942s, 2883s, 1958m, 1693s, 885s; MS (EI): *m/e* (% relative intensity) 138 (100) M^+, 110 (15), 80 (17); *m/e* calcd for $C_7H_{10}N_2O$ 138.0793, measured 138.0797.

3.1.6. Compound 11. R_f=0.43 (33% EtOAc in hexane); oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.75–1.90 (m, 4H), 2.46 (t, 2H, J=6.3 Hz), 3.31 (t, 2H, J=6.0 Hz), 5.37 (d, 2H, J=6.3 Hz), 7.61 (t, 1H, J=6.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8, 22.4, 32.6, 45.8, 86.8, 98.7, 167.8, 202.0; IR (neat) cm^{-1} 3047s, 2946s, 1956w, 1650s, 873s; MS (EI): *m/e* (% relative intensity) 137 (100) M^+, 108 (22), 95 (40), 80 (35); *m/e* calcd for $C_8H_{11}NO$ 137.0841, measured 137.0844.

3.1.7. Compound 12. R_f=0.54 (50% EtOAc in hexane); oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50–1.86 (m, 6H), 2.59 (t, 2H, J=5.4 Hz), 3.48 (t, 2H, J=4.8 Hz), 5.37 (d, 2H, J=6.6 Hz), 7.44 (t, 1H, J=6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.2, 27.4, 29.4, 36.9, 45.7, 87.2, 99.2, 173.5, 201.3; IR (neat) cm^{-1} 3043m, 2928s, 2857s, 1959w, 1642s, 876s; MS (EI): *m/e* (% relative intensity) 151 (100) M^+, 122 (17), 108 (30), 80 (31); *m/e* calcd for $C_9H_{13}NO$ 151.0997, measured 151.1000.

3.1.8. Compound 13. R_f=0.56 (50% EtOAc in hexane); oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40–1.90 (m, 8H), 2.573 (t, 2H, J=6.3 Hz), 3.64 (t, 2H, J=6.0 Hz), 5.34 (d, 2H, J=6.3 Hz), 7.49 (t, 1H, J=6.3 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 23.9, 26.0, 28.3, 28.8, 33.9, 44.4, 86.2, 97.3, 172.7, 202.0; IR (neat) cm^{-1} 3046m, 2926s, 2858s, 1958w, 1644s, 874s; MS (EI): *m/e* (% relative intensity) 165 (100) M^+, 136 (30), 122 (28), 108 (30); *m/e* calcd for $C_{10}H_{15}NO$ 165.1154, measured 165.1158.

3.1.9. Allenamide 18a. R_f=0.45 (50% EtOAc in hexane, mostly decomposed); mp 113–115°C; $[\alpha]_D^{20}$=−96.9 (*c* 0.13, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.74 (d, 3H, J= 6.6 Hz), 2.77 (s, 3H), 3.84 (dq, 1H, J=6.6, 8.7 Hz), 4.68 (d, 1H, J=8.7 Hz), 4.75 (dd, 1H, J=6.3, 9.0 Hz), 5.04 (dd, 1H, J=6.3, 9.0 Hz), 6.96 (t, 1H, J=6.3 Hz), 7.06–7.31 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.0, 28.8, 55.6, 60.9, 86.7, 96.4, 127.9, 128.2, 128.6, 136.1, 157.9, 202.4 (missing 2 signals due to overlap); IR (neat) cm^{-1} 3052s, 2924s, 1961m, 1709s, 1456s, 1401s, 880m; MS (EI) for $C_{14}H_{16}N_2O$: *m/e* (% relative intensity) 228 (77) M^+, 111 (70), 227 (72), 170 (29), 118 (77), 117 (100); *m/e* calcd for $C_{14}H_{16}N_2O$ 228.1262, measured 228.1241.

3.1.10. Allenamide 18b. R_f=0.57 (50% EtOAc in hexane, mostly decomposed); oil; $[\alpha]_D^{20}$=−156.4 (*c* 0.225, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.10 (dd, 1H, J=6.0, 8.7 Hz), 4.64 (t, 1H, J=6.0 Hz), 4.78–4.84 (m, 2H), 5.10 (dd, 1H, J=6.3, 9.6 Hz), 6.73 (t, 1H, J=6.3 Hz), 7.16–7.33 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 59.0, 70.6, 87.7, 95.6, 126.5, 128.7, 129.0, 138.4, 155.5, 201.9 (missing 2 signals due to overlap); IR (neat) cm^1 3063m, 3035s, 2979s, 1963w, 1767s, 1494s, 1462s, 1216s, 966m, 911s, 881s; MS (EI) for $C_{12}H_{11}N_1O_2$: *m/e* (% relative intensity) 201 (15) M^+, 200 (14), 156 (100), 129 (17), 115 (19), 104 (45); *m/e* calcd for $C_{12}H_{11}NO_2$ 201.0790, measured 201.0784.

3.1.11. Allenamide 18c. R_f=0.66 (50% EtOAc in hexane); mp 108–112°C; $[\alpha]_D^{20}$=−60.7 (*c* 0.30, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.85 (dd, 1H, J=6.3, 10.0 Hz), 5.13 (d, 1H, J=8.1 Hz), 5.17 (dd, 1H, J=6.3, 10.0 Hz), 5.92 (d, 1H, J=8.1 Hz), 6.80–6.84 (m, 2H), 6.93 (t, 1H, J=6.3 Hz), 6.96–7.09 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 64.0, 80.3, 87.6, 95.8, 126.2, 127.3, 127.9, 128.05, 128.09, 128.14, 133.9, 134.0, 155.2, 202.2 (missing 4 signals due to overlap); IR (neat) cm^{-1} 3036m, 2982w, 1961w, 1754s, 1456s, 1396s, 1266s, 1032s, 885m; MS (EI) for $C_{18}H_{15}N_1O_2$: *m/e* (% relative intensity) 277 (2) M^+, 233 (100), 179 (51), 165 (36), 115 (46); *m/e* calcd for $C_{18}H_{15}NO_2$ 277.1103, measured 277.1097.

3.1.12. Allenamide 18d. R_f=0.59 (50% EtOAc in hexane); oil; $[\alpha]_D^{20}$=−22.7 (*c* 0.15, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.74 (dd, 1H, J=8.7, 14.0 Hz), 3.23 (dd, 1H, J= 3.0, 14.0 Hz), 4.05–4.25 (m, 3H), 5.51 (dd, 1H, J=6.3, 9.9 Hz), 5.57 (dd, 1H, J=6.3, 9.9 Hz), 6.90 (t, 1H, J= 6.3 Hz), 7.15–7.35 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 37.1, 55.6, 66.7, 88.0, 96.0, 127.3, 128.9, 129.3, 135.4, 154.97, 201.6 (missing 2 signals due to overlap); IR (neat) cm^{-1} 3062m, 3030s, 1961m, 1760s, 1496s, 1456s, 1233s, 1067s, 863s, 800m; MS (EI) for $C_{13}H_{13}N_1O_2$: *m/e* (% relative intensity) 215 (60) M^+, 170 (32), 124 (100), 117 (38), 91 (58); *m/e* calcd for $C_{13}H_{13}NO_2$ 215.0946, measured 215.0942.

3.1.13. Allenamide 18e. R_f=0.64 (50% EtOAc in hexane); thick foam; $[\alpha]_D^{20}$=−318.3 (*c* 0.12, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.39 (dd, 1H, *J*=3.6, 8.7 Hz), 4.49 (dd, 1H, *J*=8.7, 8.7 Hz), 4.64 (ddd, 1H, *J*=3.6, 3.9, 8.7 Hz), 4.72 (d, 1H, *J*=3.9 Hz), 5.36 (dd, 1H, *J*=6.6, 10.2 Hz), 5.43 (dd, 1H, *J*=6.6, 10.2 Hz), 6.86 (t, 1H, *J*=6.6 Hz), 7.07–7.38 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 49.3, 57.2, 64.9, 88.2, 96.1, 127.2, 127.7, 128.5, 128.7, 128.9, 129. 2, 138.0, 139.7, 155.0, 201.4 (missing 4 signals due to overlap); IR (neat) cm^{-1} 3055m, 3031m, 2924m, 1960w, 1757s, 1458s, 1266s, 889m; MS (EI) for $C_{19}H_{17}N_1O_2$: *m/e* (% relative intensity) 291 (53) M^+, 167 (61), 165 (39), 152 (25), 124 (100), 115 (14); *m/e* calcd for $C_{19}H_{17}NO_2$ 291.1259, measured 291.1260.

3.1.14. Synthesis of dichloroenamide 19. To a stirred solution of 2-oxazolidinone (4.44 g, 50 mmol) in 120 mL DMF was added sodium hydride (2.25 g, 56 mmol) at room temperature. After 1 h, trichloroethylene (18 mL, 200 mmol) was added and the reaction was stirred for 24 h. Removal of DMF and residual trichloroethylene in vacuo provided a residue that was partitioned between CH_2Cl_2 and H_2O. Separation and extraction of the aqueous layer with CH_2Cl_2 (3×80 mL), drying of the combined organic layers (Na_2SO_4), and evaporation of solvent provided a brown oil. Column chromatography (hexane/ethyl acetate) afforded **19** (5.52 g, 61%) as a white solid. R_f=0.68 (5% MeOH in Et_2O); mp 65–66°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.80 (dd, 2H, *J*=7.1, 8.6 Hz), 4.45 (dd, 2H, *J*=7.1, 8.6 Hz), 6.31 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 44.1, 63.0, 116.8, 127.1, 153.9; IR (neat) cm^{-1} 3091m, 2988w, 2911w, 1767s, 1623m, 1480m, 1399s; MS (EI): *m/e* (% relative intensity) 181 (21) M^+,146 (29), 137 (17), 122 (17), 102 (100), 75 (36); *m/e* calcd for $C_5H_5NO_2{}^{35}Cl^{37}Cl$, 182.9668, measured 182.9670.

3.1.15. Synthesis of compound 22. To a stirred solution of **19** (110.7 mg, 0.61 mmol) in 10 mL THF was added *t*-BuOK (141.7 mg, 1.26 mmol). The mixture turned immediately to a dark brown, and after 1 h, THF was removed in vacuo. The residue was taken up in CH_2Cl_2 and filtered through a short column of celite to afford **22** (97 mg, 54%) as a dark oil. R_f=0.06 (25% EtOAc in hexane); oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46 (s, 9H), 1.49 (s, 9H), 3.57 (t, 2H, *J*=6.0 Hz), 3.89 (s, 2H), 4.25 (t, 2H, *J*=6.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.6, 27.9, 35.9, 47.5, 66.9, 80.0, 81.9, 153.5, 157.7 (missing 4 signals due to overlap); IR (neat) cm^{-1} 2976m, 1741s, 1675s, 1367m, 1275s, 1254s; MS (EI): *m/e* (% relative intensity) 181 (8) M^++2H-2*t*-Bu, 164 (11), 119 (50), 106 (11), 57 (100).

3.2. General procedure for preparation of ynamides

3.2.1. Enamide bromination. Method A: To a homogeneous solution of enamide (1.0 mmol) in anhydrous 1,2-dichloroethane (20 mL) at −40°C was added Br_2 (1.5 equiv.) in 1,2-dichloroethane (5 mL) dropwise over 10 minutes under nitrogen. The resulting solution was warmed to room temperature for 30 min before being subjected to reflux for 12 h. After which, the solution was concentrated under reduced pressure, and the residue was purified by flash silica gel column chromatography (gradient solvent system: 0–25% EtOAc in hexane) to provide a separable *E*/*Z* mixture of vinyl bromides.

3.2.2. Method B: To a homogeneous solution of enamide (1.0 mmol) in anhydrous dichloroethane (25 mL) was added NBS in one shot. The resulting mixture was refluxed for 1 h under nitrogen. After which, the solution was concentrated under reduced pressure, and the residue purified by flash silica gel column chromatography (gradient solvent system: 0–20% EtOAc in hexane) to provide a separable *E*/*Z* mixture of vinyl bromides.

3.2.3. Preparation of ynamides 27–32, 34. To a homogeneous solution of vinyl bromide (1.0 mmol) at −10°C in anhydrous THF (50 mL) was added *t*-BuOK (1.5–3.0 equiv.) in THF dropwise over 10 min under nitrogen. The resulting mixture was warmed to room temperature and stirred for 3 h. After which, the mixture was filtered through celite and concentrated under reduced pressure, and the residue was purified by flash silica gel[‡] chromatography (gradient solvent system: 0–25% EtOAc in hexane) to provide the desired ynamides in good to high yields.

3.2.4. Ynamide 27. R_f=0.34 (25% EtOAc in hexane); oil; $[\alpha]_D^{20}$=+44.4 (*c* 0.54, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (t, 3H, *J*=7.2 Hz), 0.90 (m, 6H), 1.18–1.36 (m, 4H), 1.40–1.52 (m, 2H), 2.13 (m, 1H), 2.24 (t, 2H, *J*= 7.2 Hz), 3.85 (ddd, 1H, *J*=3.9, 5.7, 9.0 Hz), 4.05 (dd, 1H, *J*=5.7, 9.0 Hz), 4.29 (t, 1H, *J*=9.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 15.0, 17.1, 18.4, 22.1, 28.4, 28.9, 31.0, 61.7, 64.5, 69.3, 72.2, 156.7; IR (neat) cm^{-1} 2930m, 2264m, 1771s, 1413m, 1198m, 1113m; MS (EI) for $C_{13}H_{21}NO_2$: *m/e* (% relative intensity) 222 (5) M−H^+179 (100), 167 (61), 94 (46), 70 (48), 55 (52); *m/e* calcd for $C_{13}H_{21}NO_2$+H 224.1651, measured 224.1655.

3.2.5. Ynamide 28. R_f=0.20 (25% EtOAc in hexane); mp 86–88°C; $[\alpha]_D^{20}$=+41.9 (*c* 0.525, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.95 (m, 6H), 2.20 (m, 1H), 3.97 (ddd, 1H, *J*=3.9, 5.7, 9.0 Hz), 4.11 (dd, 1H, *J*=5.7, 9.0 Hz), 4.35 (t, 1H, *J*=9.0 Hz), 7.18–7.26 (m, 3H), 7.32–7.39 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.3, 17.2, 29.3, 62.1, 64.9, 72.3, 78.5, 122.4, 128.1, 128.3, 131.5, 156.0 (missing 2 signals due to overlap); IR (neat) cm^{-1} 2965w, 2254m, 1764s, 1412m, 1204m, 1089m; MS (EI) for $C_{14}H_{15}NO_2$: *m/e* (% relative intensity) 229 (97) M^+, 228 (100), 207 (14), 169 (24), 142 (56), 115 (42); *m/e* calcd for $C_{14}H_{15}NO_2$ 229.1103, measured 229.1105.

3.2.6. Ynamide 29. R_f=0.20 (25% EtOAc in hexane); mp 97–98°C; $[\alpha]_D^{20}$=−117.7 (*c* 0.62, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.03 (m, 1H), 3.15 (m, 1H), 4.18 (m, 1H), 4.37 (d, 2H, *J*=4.5 Hz), 7.23–7.48 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 37.9, 58.4, 67.4, 73.2, 77.9, 122.1, 127.5, 128.2, 128.3, 129.0, 129.3, 131.6, 134.1, 155.4 (missing 4 signals due to overlap); IR (neat) cm^{-1} 2928w, 2255m, 1773s, 1411m, 1210m, 1086m; MS (EI) for $C_{18}H_{15}NO_2$: *m/e* (% relative intensity) 277 (90) M^+, 232 (14), 186 (42), 142 (100), 115 (79), 91 (48); Anal. Calcd

[‡] Due to moderate decomposition ynamide **34** was purified utilizing a basic alumina column.

for: C, 77.96; H, 5.45; N, 5.05. Found: C, 77.75; H, 5.60; N, 4.90.

3.2.7. Ynamide 30. R_f=0.33 (25% EtOAc in hexane); oil; $[\alpha]_D^{20}$=−108.0 (*c* 0.565, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, 3H, *J*=7.2 Hz), 1.20–1.50 (m, 4H), 1.52–1.62 (m, 2H), 2.36 (t, 2H, *J*=7.2 Hz), 2.93 (m, 1H), 3.21 (m, 1H), 4.09 (dd, 1H, *J*=5.4, 8.1 Hz), 4.15–4.30 (m, 1H), 4.30 (t, 1H, *J*=8.1 Hz), 7.18–7.24 (m, 2H), 7.27–7.38 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 18.4, 22.1, 28.5, 31.0, 37.7, 58.2, 67.1, 68.9, 73.4, 127.3, 128.9, 129.3, 134.3, 156.1 (missing 2 signals due to overlap); IR (neat) cm^{-1} 2930m, 2266w, 1774s, 1412m, 1186m, 1115m; MS (EI) for $C_{17}H_{21}NO_2$: *m/e* (% relative intensity) 271 (5) M^+, 180 (100), 117 (70), 91 (58), 80 (21), 54 (21); Anal. Calcd for: C, 75.25; H, 7.80; N, 5.16. Found: C, 75.38; H, 7.67; N, 5.16.

3.2.8. Ynamide 31. R_f=0.19 (25% EtOAc in hexane); mp 186–188°C; $[\alpha]_D^{20}$=−263.0 (*c* 0.54, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80 (d, 3H, *J*=6.6 Hz), 2.86 (s, 3H), 3.95 (m, 1H), 5.05 (d, 1H, *J*=8.7 Hz), 7.16–7.40 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.8, 28.9, 55.7, 64.1, 71.4, 81.5, 123.3, 127.1, 127.7, 127.9, 128.5, 131.2, 134.6, 156.1 (missing 4 signals due to overlap); IR (neat) cm^{-1} 2932w, 2238m, 1712s, 1428m, 1405m, 1289w, 1170m; MS (EI) for $C_{19}H_{18}N_2O$: *m/e* (% relative intensity) 290 (100) M^+, 232 (52), 204 (30), 128 (19), 115 (21); *m/e* calcd for $C_{19}H_{18}N_2O$ 290.1419, measured 290.1419.

3.2.9. Ynamide 32. R_f=0.17 (25% EtOAc in hexane); oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, 3H, *J*=7.2 Hz), 1.20–1.42 (m, 6H), 1.50 (tt, 2H, *J*=7.5, 7.5 Hz), 2.08 (tt, 2H, *J*=7.5, 7.5 Hz), 2.33 (t, 2H, *J*=7.2 Hz), 2.42 (t, 2H, *J*=8.4 Hz), 3.65 (t, 2H, *J*=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 18.5, 18.6, 22.5, 28.5, 28.8, 29.5, 31.3, 50.0, 71.5, 72.6, 176.0; IR (neat) cm^{-1} 2928m, 2260m, 1718s, 1397m, 1297m, 1218m; MS (EI) for $C_{12}H_{19}NO$: *m/e* (% relative intensity) 193 (7) M^+, 178 (21), 164 (51), 150 (44), 136 (40), 124 (100), 96 (57), 86 (85), 80 (47), 67 (39); *m/e* calcd for $C_{12}H_{19}NO$ 193.1467, measured 193.1469.

3.2.10. Ynamide 34. R_f=0.40 (33% EtOAc in hexane); oil; $[\alpha]_D^{20}$=−124.1 (*c* 0.395, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.81 (s, 3H), 4.19 (dd, 1H, *J*=6.9, 9.0 Hz), 4.70 (t, 1H, *J*=8.7 Hz), 5.00 (dd, 1H, *J*=7.2, 8.7 Hz), 7.32–7.35 (m, 2H), 7.40–7.45 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.7, 62.0, 67.9, 68.3, 70.7, 126.8, 129.3, 129.4, 136.5, 156.6 (missing 2 signals due to overlap); IR (neat) cm^{-1} 2918m, 2270w, 1771s, 1409m, 1188m, 1040m; MS (EI) for $C_{12}H_{11}NO_2$: *m/e* (% relative intensity) 201 (100) M^+, 156 (63), 142 (52), 103 (44), 91 (51), 66 (83); *m/e* calcd for $C_{12}H_{11}NO_2$ 201.0790, measured 201.0794.

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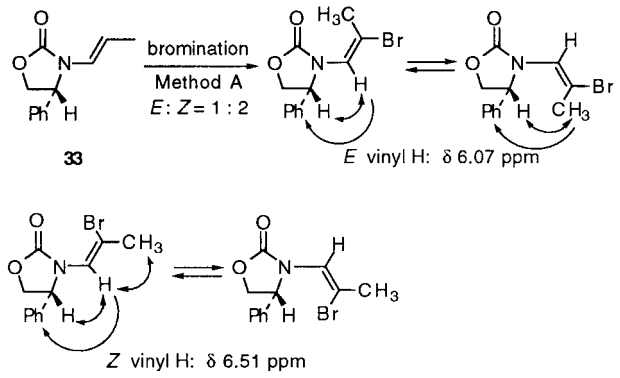

Scheme 8.