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Aza- and *Carbo*-[3 + 3] Annulations of *Exo*-Cyclic Vinylogous Amides and Urethanes. Synthesis of Tetrahydroindolizidines and An Unexpected Formation of Hexahydroquinolines

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Abstract

[3 + 3] Annulations of *exo*-cyclic vinylogous amides and urethanes with vinyl iminium salts are described here. We observed an intriguing dichotomy in their reaction pathways. For pyrrolidine- and azepane-based vinylogous amides or urethanes, *aza*-[3 + 3] annulation would dominate to give tetrahydroindolizidines, whereas, unexpectedly, for piperidine-based vinylogous amides or urethanes, *carbo*-[3 + 3] annulation was the pathway, leading to hexahydroquinolines. The origin for such a contrast is likely associated with a switch in the initial reaction pathway between *C*-1,2-addition and *C*-1,4-addition.

Keywords

Aza-[3 + 3] annulation; *carbo*-[3 + 3] annulation; vinylogous amides; quinolines; tetrahydroindolizidines

1. Introduction

Aza-[3 + 3] annulation or formal cycloaddition reaction has emerged as a formidable strategy in the synthesis of alkaloids.[1–5] Specifically, our intermolecular *aza*-[3 + 3] annulation[5] involves a Knoevenagel-type condensation of vinyl iminium ions **1** with vinylogous amides or urethanes **2** followed by a 6π-electron electrocyclic ring-closure of 1-azatrienes **3**[6,7] en route to 1,2-dihydropyridines **4** [Scheme 1]. This annulation process provides a unique opportunity to develop approaches toward a stereoselective ring-closure of 1-azatrienes, which had represented a real challenge in such pericyclic processes.[6,8]

Efforts in developing such a torquoselective[9] reaction have been largely overlooked. An elegant exception would be Tanaka and Katsumura's electrocyclic ring-closure using chiral amines.[10] In our own work, we employed either chiral iminium ions **1** with a preexisting stereogenic center in the β-substituent,[11] or 1-azatrienes **5** containing a chiral *N*-auxiliary[12, 13] [see the box in Scheme 1] en route to 1,2-dihydropyridines **4** or 1-azadecalins **6**.

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Although by a very different mechanism,[13] we have exerted much efforts in the last few years in developing both a diastereoselective[14] and an amine salt-catalyzed asymmetric[15] intramolecular *aza*-[3 + 3] annulation reaction employing vinylogous amides tethered with α,β-unsaturated iminium salts **7** [Scheme 2]. This annulation provides a powerful synthetic strategy to construct nitrogen heterocycles **8** that can lead to a range of prevalent structural motifs among alkaloids.

We have already successfully applied this strategy toward total syntheses of several alkaloids such as (+)-gephyrotoxin,[14] (±)-tangutorine,[16] (+)/(−)-deplancheine,[17] and (−)-cylindricine C,[18] and most recently, five members of the azaphenalene alkaloid family [see Figure 1].[19]

Despite our understanding of this annulation reaction, we encountered a rather intriguing and unexpected outcome during our efforts in achieving total syntheses of azaphenalene alkaloids. As shown in Scheme 3, we found that ***intramolecular*** *aza*-[3 + 3] annulations of *exo*-cyclic vinylogous amides such as **10** would proceed effectively [Scheme 3] to give the key *aza*-tricycle **11** that would subsequently serve as a common intermediate en route to the five azaphenalene alkaloids [Figure 1].[19] On the other hand, ***intermolecular*** annulations of *exo*-cyclic vinylogous amides **12** [or vinylogous urethanes **13**] with vinyl iminium ion **14** did not give any desired quinolizidine nucleus **15**, thereby thwarting our efforts in the synthesis of members of the quinolizidine and indolizidine families of alkaloids.[20] Instead, we identified another product, and we report here our findings in the synthesis of tetrahydroindolizidines accompanied with an unexpected formation of hexahydroquinolines via a *carbo*-[3 + 3] annulation.

2. Results and Discussions

2.1. An Unexpected Formation of Hexahydroquinolines

Preparations of *exo*-cyclic vinylogous amides **12** and **13** are shown in Scheme 4 The synthesis commenced with either 1,3-pentanedione **16a** or ethyl acetoacetate **16b** and followed Carrié's protocol[21] that features Weiler's dianion[22] addition to 1-bromo-2-chloro-propane, azide substitution, and an intramolecular *aza*-Wittig of azides **18a** or **18b**. The *Z*-geometry in **12** and **13** was confirmed via nOe experiments.[21]

Unsuspectingly, with *exo*-cyclic vinylogous amides **12** and **13** in hand, we attempted their *aza*-[3 + 3] annulation reactions using vinyl iminium salts **20a–c** generated from their corresponding enals **19a–c** under standard conditions[5,11–15] [Scheme 5]. To our surprise, no desired *aza*-[3 + 3] annulation products **15** were formed, and instead, we isolated hexahydroquinolines **21a–c** and **22b–c** in good yields.

We also employed chiral enal **23** in an attempt to detect possible diastereoselectivity. However, while the reaction of chiral enal **23** with **12** led to the isomeric hexahydroquinolines **24** and **25** in good yield, the selectivity was found to be low, and consequently, the relative stereochemistry was not assigned. It is also noteworthy that using more polar solvents such as DMF or EtOH, we still obtained hexahydroquinoline **22** in good yields.

2.2. A *Carbo*-[3 + 3] Annulation Pathway

A plausible mechanism for the formation of these unexpected hexahydroquinolines is initiated through a *C*-1,4-addition of the vinylogous amide in a Michael fashion to the iminium salt to give intermediate **B** [Scheme 6]. Tautomerization of **B** could lead to intermediates **C** and **D** with the latter one being de-conjugated, and an ensuing *C*-1,2-addition to the iminium salt in a Mannich manner would give **E**. A sequence of elimination of the secondary amine in **E** and tautomerization would then afford the observed hexahydroquinolines.

What we have encountered here for the very first time in our own work with *aza*-[3 + 3] annulations, is the competing *carbo*-[3 + 3] annulation pathway.[23,24] This finding invokes some unique historical perspectives as shown in Figure 2. Prelog[25] in 1949 found that instead of the expected Robinson annulation pathway, a *carbo*-[3 + 3] cyclization had occurred to give the bicyclo[5.3.1]undecenone. In 1950, and more relevant to the current study, Stork[26] reported the addition of the Stork enamine to acrolein, leading to bicyclo[3.3.1]octanone via a *carbo*-[3 + 3] cyclization. These reactions all share a similar pathway: 1,4-addition followed by 1,2-addition.

Despite the fact that this can be a very useful reaction for constructing highly substituted cyclohexane derivatives to compliment the Diels-Alder Strategy, much of the earlier work focused on the synthesis of bridged bicyclic systems with an interest in accessing Anti-Bredt's olefins.[23,27] While there has been a surging interest [especially in the synthesis of garsubellin A] given the array of elegant accounts that appeared recently,[28] most efforts are still exerted on the synthesis of bridged bicyclic systems.

2.3. Syntheses of Quinolines

One immediate application of this *carbo*-[3 + 3] annulation is in the synthesis of quinolines, which would also be in accord with the theme of this *Symposium-in-Print*. As shown in Scheme 7, treatment of hexahydroquinolines **21b** and **22b** with 3.0 equiv of DDQ at rt led to quinoline **26** and **27** in 50% and 83% yields, respectively. With less DDQ used, we were able to isolate the respective tetrahydroquinolines **28** and **29**, although there was no apparent selectivity over the extent of aromatization.

2.4. A Contrasting Reaction Pathway

When we directed our attention to pyrrolidine-based *exo*-cyclic vinylogous urethane **30**[21,29] and vinylogous amide **31**,[21,30] we were fully intending on preparing a series of tetrahydroindoles via the same *carbo*-[3 + 3] annulation [Figure 3]. We were not prepared for additional surprises.

However, as shown in Table 1, reactions of **30** and **31** with achiral enals **19a–c** [entries 1–4], or chiral enals **23** and **33–35** [entries 5–9], led to the respective *aza*-[3 + 3] annulation products: Tetrahydroindolizidines **36–40**. Even when we employed azepane-based *exo*-cyclic vinylogous urethane **32**,[21,31] we obtained the *aza*-annulation product **41** and **42** in good yields [entries 10–11].

2.5. *C*-1,2 versus *C*-1,4-Addition

These two contrasting reaction pathways intrigued us. Although we do not have any definitive understanding at this point, one possible cause for is that they mechanistically differ in the very initial step. As shown in Scheme 8, for the pyrrolidine-based *exo*-cyclic vinylogous amide [left], there appears to be a preference for *C*-1,2-addition, whereas for piperidine-based *exo*-cyclic vinylogous amide [right], the preference is *C*-1,4-addition.

Specifically, for the pyrrolidine-based vinylogous amide **G**, it may react through conformer **G-2** because the internal hydrogen-bonding in **G-1** is not as perfectly aligned or tight as in piperidine-based *exo*-cyclic vinylogous amide **J-1**. Thus, the conformational equilibrium does not shift away from **G-2** or at least not completely, thereby freeing the carbonyl group to participate in hydrogen-bonding with protons of the vinyl iminium salt [in green]. This external hydrogen bonding interaction can in fact provide a stabilization of ~ 14.7 Kcal mol^{-1}.[3]

With this hydrogen-bonding network in place, *C*-1,2-addition [red arrow] would be better aligned stereoelectronically than *C*-1,4-addition [dotted blue arrow], thereby leading to 1-

azatriene **H** after β-elimination and subsequently completing the *aza*-annulation pathway via a pericyclic ring-closure. It is noteworthy that the theoretical observation of this external hydrogen-bonding network likely provides a major rationale for the high level of regioselectivity found in most of our annulation work[5a,32] involving vinyl iminium salts, especially when comparing with protocols in which vinyl iminium salts are generated *in situ* or not employed.[33,34]

On the other hand, for piperidine-based *exo*-cyclic vinylogous amide, conformer **J-1** dominates due to the strong internal hydrogen-bonding [in green], which precludes the carbonyl group in **J-1** from participating in the related external hydrogen bonding network. With both options of *C*-1,2- and *C*-1,4-additions being available, *C*-1,4-addition [solid blue arrow] could take precedent based on the "hard-and-soft" concept. This would allow the piperidine-based *exo*-cyclic vinylogous amide [or urethane] to follow the *carbo*-annulation pathway.

In addition, although all of these mechanistic steps are reversible, our calculations using B3LYP/6-31G* [Spartan™] suggest [Figure 4] that the observed dichotomy of these two reaction pathways cannot be attributed as a result of thermodynamic equilibration. For all three cases, pyrrolidine-, piperidine-, and azepane-based vinylogous amides or urethanes, the respective *carbo*-annulation products are thermodynamically more favored than their corresponding *aza*-annulation products, although in a relatively lesser extent for both the pyrrolidine-based vinylogous amide and azepane-based vinylogous urethane.

3. Conclusion

We have described here [3 + 3] annulations of *exo*-cyclic vinylogous amides and urethanes with vinyl iminium salts and observed an intriguing dichotomy in their reaction pathways. For pyrrolidine- and azepane-based vinylogous amide or urethanes, *aza*-[3 + 3] annulation dominates to give tetrahydroindolizidines, whereas the piperidine-based vinylogous amide or urethane underwent an unexpected *carbo*-[3 + 3] annulation to afford hexahydroquinolines. The origin for such a contrast is not clear at this moment, although we suspect it is associated with an initial preference for either *C*-1,2-addition or *C*-1,4-addition. This work provides a useful approach toward either total syntheses of the indolizidine family of natural products, or functionalized quinolines.

4. Experimental Section

All reactions were performed in flame-dried glassware under a nitrogen atmosphere. Solvents were distilled prior to use. Reagents were used as purchased (Aldrich, Acros), except where noted. Chromatographic separations were performed using Bodman 60 Å SiO_2. ^1H and ^{13}C NMR spectra were obtained on Varian VI-300, VI-400, and VI-500 spectrometers using $CDCl_3$ (except where noted) with TMS or residual $CHCl_3$ in the solvent as standard. Melting points were determined using a Laboratory Devices MEL-TEMP and are uncorrected/calibrated. Infrared spectra were obtained using NaCl plates on a Bruker Equinox 55/S FT–IR Spectrophotometer, and relative intensities are expressed qualitatively as s (strong), m (medium), and w (weak). TLC analysis was performed using Aldrich 254 nm polyester-backed plates (60 Å, 250 μm) and visualized using UV and a suitable chemical stain.

Low-resolution mass spectra were obtained using an Agilent-1100-HPLC/MSD and can be either APCI or ESI, or an IonSpec HiRes-MALDI FT-Mass Spectrometer. High-resolution mass spectral analyses were performed at University of Wisconsin Mass Spectrometry Laboratories. All spectral data obtained for new compounds are reported.

4.1. General Procedure for All Annulations

To a solution of an enal [1.40 mmol, 1.40 equiv] in EtOAc/toluene [3.5 to 5 mL with a ratio of 2:3] in a sealed tube were added Na_2SO_4 [400.0 mg], piperidinium acetate [1.40 mmol, 1.40 equiv] and the respective vinylogous amide [1.00 mmol] sequentially. After stirring at rt for 1 min, the mixture was heated at 95 °C –100 °C for 3–4 h. The reaction progress was monitored using TLC analysis and/or crude ^{1}H NMR. When the starting material completely disappeared, the reaction mixture was cooled and the excess amine salt was filtered off through a small cotton plug [or Celite™], and the excess solvent was evaporated under reduced pressure. The crude residue was purified by flash silica gel column chromatography [gradient eluent: EtOAc in hexanes] to provide the corresponding annulation product.

4.1.1. *Carbo*-[3 + 3] Annulation Product 21a—R_f = 0.10 [30% EtOAc/hexane]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (d, 3H, *J* = 6.8 Hz), 1.66–1.75 (m, 1H), 1.84 (ddd, 1H, *J* = 4.3, 8.8, 21.8 Hz), 1.94 (s, 1H), 2.05 (dd, 1H, *J* = 6.5, 17.4 Hz), 2.10 (s, 3H), 2.29–2.48 (m, 2H), 2.72 (p, 1H, *J* = 7.0 Hz), 3.32 (ddd, 2H, *J* = 2.7, 3.8, 6.8 Hz), 5.87 (d, 1H, *J* = 6.5 Hz), 11.86 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.6, 22.7, 26.6, 27.7, 28.5, 31.9, 41.5, 102.7, 128.5, 131.9, 154.0, 193.6; IR (neat) cm^{-1} 2951brm, 2860brm, 1569s, 1550s, 14870m, 1450m, 1364m, 1348m, 1252s; mass spectrum (APCI): m/e (% relative intensity) 192 (100) $(M+H)^+$, 150 (5), 140 (10); m/e (ESI) calcd for $C_{12}H_{17}NO$ 191.1310, found 191.1309.

4.1.2. *Carbo*-[3 + 3] Annulation Product 21b—R_f = 0.26 [30% EtOAc/Hexanes]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, 3H, *J* = 7.2 Hz), 1.13–1.20 (m, 2H), 1.28–1.32 (m, 1H), 1.38–1.45 (m, 1H), 1.67–1.74 (m, 1H), 1.80–1.85 (m, 1H), 2.09 (s, 3H), 2.19–2.41 (m, 4H), 2.50–2.54 (m, 1H), 3.32 (dd, 2H, *J* = 4.0, 7.0 Hz), 5.85 (d, 1H, *J* = 6.0 Hz), 11.90 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.4, 21.0, 22.8, 26.7, 28.4, 28.6, 32.7, 36.6, 41.6, 102.7, 129.0, 132.2, 154.4, 193.6; IR (neat) cm^{-1} 2955brm, 2869brm, 1569s, 1543s, 1257s; mass spectrum (APCI): m/e (% relative intensity) 220 (100) $(M+H)^+$; m/e (ESI) calcd for $C_{14}H_{22}NO$ 220.1701, found 220.1703.

4.1.3. *Carbo*-[3 + 3] Annulation Product 21c—R_f = 0.36 [50% EtOAc/Hexanes]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.82–1.84 (m, 1H), 1.88–1.98 (m, 1H), 1.97 (s, 3H), 2.41–2.53 (m, 3H), 2.84–2.91 (m, 1H), 3.48–3.50 (m, 2H), 3.99 (d, 1H, *J* = 8.0 Hz), 5.80 (d, 1H, *J* = 5.5 Hz), 7.19–7.31 (m, 5H), 12.06 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.9, 27.2, 28.5, 33.4, 38.5, 41.8, 99.1, 126.3, 127.8, 128.3, 128.4, 129.8, 131.1, 145.7, 155.4; IR (neat) cm^{-1} 2940brm, 2859brm, 1670s, 1577s, 1552, 1273s; mass spectrum (APCI): m/e (% relative intensity) 254 (100) $(M+H)^+$; m/e (ESI) calcd for $C_{17}H_{20}NO$ 254.1545, found 254.1534.

4.1.4. *Carbo*-[3 + 3] Annulation Product 22b—R_f = 0.29 [10% EtOAc/Hexanes]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (t, 3H, *J* = 7.0 Hz), 1.16–1.35 (m, 7H), 1.68–1.76 (m, 1H), 1.81–1.87 (m, 1H), 2.16 (dd, 1H, *J* = 6.0, 16.5 Hz), 2.29–2.42 (m, 3H), 2.72 (q, 1H, *J* = 5.0 Hz), 3.29–3.34 (m, 2H), 4.06–4.15 (m, 2H), 5.81 (d, 1H, *J* = 6.0 Hz), 9.17 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.4, 14.8, 20.7, 23.3, 28.3, 29.0, 29.9, 36.3, 41.8, 58.6, 90.7, 128.9, 130.5, 152.6, 170.9; IR (neat) cm^{-1} 2956brm, 2864brm, 1630s, 1578s, 1243s; mass spectrum (APCI): m/e (% relative intensity) 250 (100) $(M+H)^+$; m/e (ESI) calcd for $C_{15}H_{24}NO_2$ 250.1807, found 250.1807.

4.1.5. *Carbo*-[3 + 3] Annulation Product 22c—R_f = 0.28 [10% EtOAc/Hexanes]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (t, 3H, *J* = 7.0 Hz), 1.77–1.93 (m, 2H), 2.39–2.45 (m, 3H), 2.76–2.83 (m, 1H), 3.40–3.44 (m, 2H), 3.95–4.12 (m, 3H), 5.77 (d, 1H, *J* = 5.6 Hz), 7.14–7.24 (m, 5H), 9.42 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.8, 23.3, 29.0, 32.4, 36.2, 41.9, 58.8, 88.1, 125.9, 127.6, 128.0, 129.8, 130.0, 146.9, 153.8, 170.9; IR (neat) cm^{-1} 2945brm, 2860brm,

1630s, 1584s, 1273s; mass spectrum (APCI): m/e (% relative intensity) 284 (100) $(M+H)^+$; m/e (ESI) calcd for $C_{18}H_{22}NO_2$ 284.1654, found 284.1642.

4.1.6. Chiral *Carbo*-[3 + 3] Annulation Products 24 and 25 *[Characterized as an inseparable mixture]*—R_f = 0.16 [50% EtOAc/hexane]; ^1H NMR (500 MHz, $CDCl_3$) δ *Major diastereomer*: 1.30 (s, 3H), 1.39 (s, 3H), 1.69–1.90 (m, 2H), 2.13–2.18 (m, 1H), 2.23 (s, 3H), 2.33–2.45 (m, 3H), 2.86 (t, 1H, *J* = 7.5 Hz), 3.30–3.37 (m, 2H), 3.59 (t, 1H, *J* = 7.5 Hz), 3.91–3.97 (m, 1H), 4.06–4.11 (m, 1H), 5.91 (d, 1H, *J* = 6.0 Hz), 12.1 (s, 1H, NH); *minor diastereomer* (*partial listing due to unresolved overlapping resonances*): 1.31 (s, 3H), 1.69–1.90 (m, 3H), 2.20 (s, 3H), 2.33–2.45 (m, 3H), 2.53–2.58 (m, 1H), 2.77 (t, 1H, *J* = 7.5 Hz), 3.30–3.37 (m, 2H), 3.65 (dd, 1H, *J* = 5.5, 8.5 Hz), 3.82 (dd, 1H, *J* = 5.5, 8.5 Hz), 3.95–3.97 (m, 1H), 5.97 (d, 1H, *J* = 5.5 Hz); IR (film): cm^{-1} 2934brw, 1662w, 1609(m), 1571(s), 1554 (s); mass spectrum (APCI): m/e (% relative intensity) 278 (100) $(M+H)^+$, 236 (10), 140 (20), 101 (10); m/e (ESI) calcd for $C_{16}H_{24}NO_3$ 278.1756, found 278.1762.

4.2. General Procedure for the DDQ-Aromatization

To a solution of **21b** [30.0 mg, 0.136 mmol] in CH_2Cl_2 [3 mL] was added DDQ [93.0 mg, 0.40 mmol, 3.00 equiv]. The reaction mixture was stirred at rt for 1 h and the reaction progress was monitored using TLC analysis. When the starting material completely disappeared, the reaction mixture was concentrated under reduced pressure. The crude residue was purified by flash silica gel column chromatography [gradient eluent: 0% to 25% EtOAc in hexanes] to provide the desired quinoline **26** [14.5 mg, 50%].

4.2.1. Quinoline 26—R_f = 0.39 [20% EtOAc/Hexanes]; ^1H NMR (500 MHz, $CDCl_3$) δ 0.98 (t, 3H, *J* = 7.5 Hz), 1.69–1.74 (m, 2H), 2.68–2.71 (m, 2H), 2.72 (s, 3H), 7.37 (dd, 1H, *J* = 4.5, 8.5 Hz), 7.41 (d, 1H, *J* = 8.5 Hz), 7.75 (d, 1H, *J* = 8.5 Hz), 8.11 (dd, 1H, *J* = 2.0, 8.5 Hz), 8.86 (dd, 1H, *J* = 1.5, 4.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 25.0, 33.9, 35.7, 121.0, 126.5, 128.2, 128.8, 135.8, 139.5, 140.3, 145.8, 150.4, 207.8; IR (neat) cm^{-1} 2961m, 2871m, 1705s, 1572m; mass spectrum (APCI): m/e (% relative intensity) 214 (100) $(M+H)^+$; m/e (ESI) calcd for $C_{14}H_{15}NONa$ 236.1051, found 236.1053.

4.2.2. Quinoline 27—R_f = 0.11 [10% EtOAc/hexane]; ^1H NMR (400 MHz, $CDCl_3$) δ 1.01 (t, 3H, *J* = 7.2 Hz), 1.46 (t, 3H, *J* = 7.2 Hz), 1.72–1.81 (m, 2H), 2.78 (dt, 2H, *J* = 6.0, 7.6 Hz), 4.59 (q, 2H, *J* = 7.2 Hz), 7.38 (dd, 1H, *J* = 4.0, 8.0 Hz), 7.40 (d, 1H, *J* = 8.8 Hz), 7.79 (d, 1H, *J* = 8.4 Hz), 8.11 (dd, 1H, *J* = 2.0, 8.4 Hz), 8.93 (dd, 1H, *J* = 2.0, 4.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 14.6, 24.6, 36.3, 61.6, 121.1, 126.5, 128.3, 128.7, 133.1, 135.8, 140.9, 145.7, 151.1, 169.7; IR (film) cm^{-1}: 2962brw, 2872w, 1725s, 1613w, 1569w, 1499w, 1459brw, 1370w, 1265s; mass spectrum (APCI): m/e (% relative intensity) 244 (100) $(M+H)^+$, 198 (20), 101 (5); m/e (ESI) calcd for $C_{15}H_{18}NO_2$ 244.1338, found 244.1349.

4.2.3. Tetrahydroquinoline 28—R_f = 0.50 [20% EtOAc/Hexanes]; ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, 3H, *J* = 7.2 Hz), 1.55–1.61 (m, 2H), 1.84–1.90 (m, 2H), 2.48 (s, 3H), 2.52–56 (m, 2H), 2.72 (t, 2H, *J* = 5.6 Hz), 3.27 (t, 2H, *J* = 3.6 Hz), 5.30 (brs, 1H), 6.43 (d, 1H, *J* = 7.6 Hz), 6.88 (d, 1H, *J* = 3.6 Hz); mass spectrum (APCI): m/e (% relative intensity) 218 (100) $(M+H)^+$; m/e (ESI) calcd for $C_{14}H_{20}NO$ 218.1545, found 218.1554.

4.2.4. Tetrahydroquinoline 29—R_f = 0.29 [10% EtOAc/Hexanes]; ^1H NMR (500 MHz, $CDCl_3$) δ 0.94 (t, 3H, *J* = 7.5 Hz), 1.39 (t, 3H, *J* = 7.0 Hz), 1.55–1.61 (m, 2H), 1.88 (dt, 2H, *J* = 5.0, 6.5 Hz), 2.68 (m, 2H), 2.74 (t, 2H, *J* = 6.0 Hz), 3.35 (t, 2H, *J* = 6.0Hz), 4.35 (q, 2H, *J* = 7.0 Hz), 6.38 (d, 1H, *J* = 7.5 Hz), 6.89 (d, 1H, *J* = 7.5 Hz); IR (film) cm^{-1} 2957m, 2929m, 1725w, 1679m, 1599w, 1582w, 1507m; mass spectrum (APCI): m/e (% relative intensity)

248.2 (100) $(M+H)^+$, 202 (65), 101 (5); m/e (ESI) calcd for $C_{15}H_{22}NO_2$ 248.1651, found 248.1658.

4.3. General Procedure: See Section 4.1

4.3.1. *Aza*-[3 + 3] Annulation Product 36a—R_f = 0.27 [20% EtOAc/hexane]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (d, 3H, *J* = 6.4 Hz), 1.88–2.00 (m, 2H), 2.92 (dt, 1H, *J* = 9.1, 18.1 Hz), 3.10 (ddd, 1H, *J* = 4.5, 8.6, 18.1 Hz), 3.29 (q, 1H, *J* = 9.1 Hz), 3.36 (p, 1H, *J* = 6.4 Hz), 3.52 (ddd, 1H, *J* = 4.1, 8.0, 9.1 Hz), 3.65 (s, 3H), 4.88 (dd, 1H, *J* = 5.5, 7.6 Hz), 5.92 (d, 1H, *J* = 7.6 Hz) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 25.0, 28.5, 32.0, 50.5, 51.1, 95.4, 110.6, 125.2, 155.1, 169.2; IR (neat) cm^{-1} 2947brm, 2862brm, 1672s, 1578s, 1256s, 1219s, 1094s; mass spectrum (APCI): m/e (% relative intensity) 194 (100) $(M+H)^+$, 162 (15); m/e (ESI) calcd for $C_{11}H_{16}NO_2$ 194.1181, found 194.1188.

4.3.2. *Aza*-[3 + 3] Annulation Product 36b—R_f = 0.22 [10% EtOAc/Hexanes]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (t, 3H, *J* = 7.2 Hz), 1.17–1.32 (m, 4H), 1.83–1.94 (m, 2H), 2.87 (ddd, 1H, *J* = 9.2, 18.0, 36.0 Hz); 3.25 (ddd, 1H, *J* = 4.4, 8.8, 18.0 Hz), 3.25 (q, 1H, *J* = 7.2 Hz), 3.30–3.34 (m, 1H), 3.49 (ddd, 1H, *J* = 4.0, 8.4, 12.0 Hz), 3.61 (s, 3H), 4.87 (dd, 1H, *J* = 5.6, 7.6 Hz), 5.95 (d, 1H, *J* = 7.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) 14.5, 18.1, 22.0, 32.0, 33.2, 41.2, 50.5, 51.2, 94.2, 108.9, 126.0, 155.6, 169.4; IR (neat) cm^{-1} 2951brm, 2869brm, 1673s, 1578s, 1194s; mass spectrum (APCI): m/e (% relative intensity) 222 (100) $(M+H)^+$; m/e (ESI) calcd for $C_{13}H_{20}NO_2$ 222.1494, found 222.1504.

4.3.3. *Aza*-[3 + 3] Annulation Product 36c—R_f = 0.35 [20% EtOAc/Hexanes]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.02–2.11 (m, 2H), 3.10 (dt, 1H, *J* = 9.0, 18.0 Hz), 3.28 (ddd, 1H, *J* = 5.0, 9.0, 18 Hz), 3.45 (q, 1H, *J* = 8.0 Hz), 3.62 (s, 3H), 3.65 (ddd, 1H, *J* = 4.5, 9.0, 9.0 Hz), 4.64 (d, 1H, *J* = 5.5 Hz), 5.08 (dd, 1H, *J* = 5.0, 7.5 Hz), 6.12 (d, 1H, *J* = 5.5 Hz), 7.20–7.23 (m, 1H), 7.29–7.35 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.9, 32.2, 40.2, 50.7, 51.4, 94.6, 109.6, 125.1, 126.3, 127.7, 128.5, 148.9, 154.9, 169.1; IR (neat) cm^{-1} 2940brm, 2852brm, 1676s, 1595s, 1273s, 1106s; mass spectrum (APCI): m/e (% relative intensity) 256 (100) $(M+H)^+$, 178 (25); m/e (ESI) calcd for $C_{16}H_{17}NO_2Na$ 278.1157, found 278.1165.

4.3.4. *Aza*-[3 + 3] Annulation Product 36d—R_f = 0.33 [20% EtOAc/hexane]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, 3H, *J* = 7.2 Hz), 1.19–1.41 (m, 4H), 1.92–2.07 (m, 2H), 2.19 (s, 3H), 2.95 (dt, 1H, *J* = 8.8, 18.0 Hz), 3.19 (ddd, 1H, *J* = 4.0, 8.0, 18.0 Hz), 3.33 (dt, 1H, *J* = 8.0, 8.8 Hz), 3.37–3.42 (m, 1H), 3.59 (ddd, 1H, *J* = 4.0, 8.0, 9.6 Hz), 5.06 (dd, 1H, *J* = 6.0, 8.0 Hz), 6.03 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (100MHz, $CDCl_3$) δ 14.4, 18.1, 21.9, 28.5, 32.9, 33.9, 41.7, 51.1, 105.4, 110.0, 125.9, 155.3, 196.6; IR (film) cm^{-1}2953m, 2869m, 2360w, 1659m, 1613m, 1530s, 1395m; mass spectrum (APCI): m/e (% relative intensity) 206 (100) $(M+H)^+$; m/e (EI) calcd for $C_{13}H_{20}NO$ 206.1545, found 206.1549.

4.3.5. *Aza*-[3 + 3] Annulation Product 37 *[Characterized as a mixture]*—R_f = 0.42 [50% EtOAc/hexane]; ^{1}H NMR (500 MHz, $CDCl_3$) δ *Major Diastereomer:* 1.33 (s, 3H), 1.41 (s, 3H), 1.88–2.05 (m, 2H), 2.95 (dt, 1H, *J* = 9.0 Hz), 3.14 (ddd, 1H, *J* = 3.5, 8.5, 18.0 Hz), 3.33–3.36 (m, 1H), 3.57 (dt, 1H, *J* = 3.5, 8.5 Hz), 3.68 (s, 3H), 3.82 (dd, 1H, *J* = 6.5, 8.0 Hz), 3.86–3.90 (m, 2H), 4.18 (dt, 1H, *J* = 2.5, 4.5 Hz), 4.96 (dd, 1H, *J* = 2.0, 5.5 Hz), 6.19 (d, 1H, *J* = 8.0 Hz); *Minor Diastereomer* (*partial listing due to unresolved overlapping resonances*): 1.40 (s, 3H), 1.88–2.05 (m, 2H), 2.91–2.98 (m, 1H), 3.15–3.23 (m, 1H), 3.31–3.38 (m, 1H), 3.60–3.65 (m, 2H), 3.95–4.00 (m, 2H), 4.12–4.14 (m, 1H), 5.01 (dd, 1H, *J* = 6.0, 7.5), 6.14 (d, 1H, *J* = 7.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ *From a small sample of resolved major isomer:* 21.8, 25.3, 26.4, 32.2, 36.6, 50.8, 51.2, 66.1, 78.8, 90.1, 94.9, 104.5, 108.8, 128.1, 157.1; IR (film) cm^{-1} 2984m, 2949w, 1671brs, 1578s, 1414s, 1370s, 1251s; mass spectrum

(APCI): m/e (% relative intensity) 280 (30) $(M+H)^+$, 248 (100), 222 (90), 178 (25); m/e (ESI) calcd for $C_{15}H_{21}NO_4Na$ 302.1368, found 302.1375.

4.3.6. *Aza*-[3 + 3] Annulation Product 38 *[Characterized as a mixture]*—R_f = 0.19 [50% EtOAc/hexane]; ^1H NMR (500 MHz, $CDCl_3$) δ *Major diastereomer* (*partial listing due to unresolved overlapping resonances*): 2.83–2.89 (m, 1H), 2.99–3.03 (m, 1H), 3.09–3.15 (m, 1H), 3.66 (s, 3H), 3.83–3.88 (m, 1H), 4.10–4.20 (m, 2H), 4.35 (dd, 1H, *J* = 2.0, 12.5 Hz), 4.84 (dd, 1H, *J* = 5.5, 7.5 Hz), 5.06 (dd, 1H, *J* = 4.0, 7.0 Hz), 5.27–5.32 (m, 1H), 6.18 (d, 1H, *J* = 7.5 Hz); *minor diastereomer:* 1.95–1.97 (m, 1H), 2.00 (s, 3H), 2.03 (s, 3H), 2.05 (s, 3H), 2.08–2.1 (m, 1H), 2.94 (dt, 1H, *J* = 9.0, 18 Hz) 3.09–3.15 (m, 1H), 3.37 (dd, 1H, *J* = 8.0, 17.0 Hz), 3.63–3.66 (m, 1H), 3.69 (s, 3H), 3.85–3.87 (m, 1H), 4.10–4.16 (m, 1H), 4.47 (dd, 1H, *J* = 2.5, 12.0 Hz), 4.93 (dd, 1H, *J* = 6.0, 7.5 Hz), 4.98 (dd, 1H, *J* = 5.0, 7.0 Hz), 5.33 (ddd, 1H, *J* = 2.5, 5.0, 7.5 Hz), 6.21 (d, 1H, *J* = 7.5 Hz); IR: (film): cm^{-1} 2950brw, 1742s, 1676m, 1579m, 1435m, 1371m, 1264s; mass spectrum (APCI): m/e (% relative intensity) 396 (100) $(M+H)^+$, 336 (20), 194 (5), 101 (10). m/e (ESI) calcd for $C_{19}H_{25}NO_8Na$ 418.1478, found 418.1480.

4.3.7. *Aza*-[3 + 3] Annulation Product 39a—R_f = 0.45 [20% EtOAc/hexane]; $[\alpha]_D^{25}$ = − 303.0 (*c* 0.55, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ *Major Diastereomer:* 1.55–1.69 (m, 1H), 1.72–1.77 (m, 1H), 1.82 (s, 3H), 1.85–1.87 (m, 1H), 1.91 (dddd, 2H, *J* = 8.0 Hz), 2.08–2.21 (m, 2H), 2.28–2.33 (dq, 1H, *J* = 2.8, 13.2 Hz), 2.43 (s, 1H), 2.88 (dt, 1H, *J* = 8.0, 17.6 Hz), 3.08 (dt, 1H, *J* = 7.2, 18.0 Hz), 3.24 (q, 1H, *J* = 8.0 Hz), 3.41 (dt, 1H, *J* = 6.8, 9.2 Hz), 3.55 (dd, 1H, *J* = 3.2, 12.0 Hz), 3.65 (s, 3H), 5.01 (d, 2H, *J* = 6.8 Hz), 5.65 (s, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ 21.5, 22.8, 28.6, 31.4, 32.1, 33.8, 39.0, 40.5, 50.3, 50.9, 91.7, 111.3, 117.0, 125.3, 146.8, 155.3, 169.5; IR (film) cm^{-1} 2361w, 1709s, 1580w, 1422w, 1360m; mass spectrum (APCI): m/e (% relative intensity) 274 (100) $(M+H)^+$; m/e (EI) calcd for $C_{17}H_{23}NO_2$ 273.1729, found 273.1728.

4.3.8. *Aza*-[3 + 3] Annulation Product 39b—R_f = 0.30 [30% EtOAc/hexane]; $[\alpha]_D^{25}$ = − 449.0 (*c* 0.080, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ *Major Diastereomer:* 1.59–1.76 (m, 2H), 1.84 (s, 3H), 1.92–2.02 (m, 3H), 2.11–2.29 (m, 6H), 2.43 (s, 1H), 2.89 (dt, 1H, *J* = 8.8, 17.6 Hz), 3.11 (dt, 1H, *J* = 6.8, 17.6 Hz), 3.30 (dt, 1H, *J* = 8.0, 9.2 Hz), 3.48 (dt, 1H, *J* = 6.4, 9.2 Hz), 3.65 (dd, 1H, *J* = 3.6, 12.0 Hz), 5.02 (d, 2H, *J* = 10.0 Hz), 5.70 (s, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ 21.6, 23.1, 28.9, 29.0, 31.8, 33.1, 34.7, 39.4, 40.6, 50.9, 104.2, 111.4, 116.9, 127.0, 147.1, 154.8, 195.6; IR (film) cm^{-1} 2932w, 2360w, 1688m, 1639w, 1540s, 1437m, 1417m, 1276s,1225m; mass spectrum (APCI): m/e (% relative intensity) 258 (100) $(M+H)^+$; m/e (EI) calcd for $C_{17}H_{23}NO$ 257.1780, found 257.1774.

4.3.9. *Aza*-[3 + 3] Annulation Product 40—R_f = 0.30 [25 % EtOAc/hexanes]; $[\alpha]_D^{25}$ = − 95.2 (*c* 2.05, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 0.87 (s, 3H), 1.10 (d, 1H, *J* = 9.5 Hz), 1.28 (s, 3H), 1.86 (m, 1H), 2.04 (ddd, 1H, *J* = 2.5, 6.0, 13.0 Hz), 2.08 (m, 1H), 2.14 (dddd, 1H, *J* = 2.0, 4.0, 6.0, 6.0 Hz), 2.36 (ddddd, 1H, *J* = 0.5, 2.5, 4.0, 9.5, 13.5 Hz), 2.63 (dd, 1H, *J* = 5.5, 5.5 Hz), 2.68 (ddddd, 1H, *J* = 0.5, 2.0, 6.5, 6.5, 10.0 Hz), 2.90 (ddd, 1H, *J* = 9.5, 11.0, 18.5 Hz), 2.98 (ddd, 1H, *J* = 7.0, 9.5, 11.0 Hz), 3.27 (ddd, 1H, *J* = 2.0, 10.0, 18.5 Hz), 3.52 (ddd, 1H, *J* = 1.5, 8.5, 9.5 Hz) 3.68 (s, 3H), 4.18 (ddd, 1H, *J* = 2.0, 6.0, 9.0 Hz), and 6.13 (d, 1H, *J* = 2.0 Hz); minor 2.26 (m, 1H), 2.53 (dd, 1H, *J* = 5.5, 5.5 Hz), 3.43 (ddd, 1H, *J* = 2.0, 8.5, 10.0 Hz), 3.67 (s, 3H), 4.43 (ddd, 1H, *J* = 2.5, 8.5, 8.5 Hz), and 6.02 (d, 1H, *J* = 2.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 24.0, 27.2, 32.6, 33.2, 37.5, 39.8, 42.3, 50.6, 50.7, 50.8, 51.8, 95.5, 116.9, 129.6, 163.8, and 167.4; IR (neat) cm^{-1} 2979w, 2944w, 1732w, 1683s, 1562s, 1435m, 1273s, 1174s, 1116s, 1071s, and 910w; mass spectrum (APCI): m/e (% relative intensity) 274 (100) $(M+1)^+$, and 242 (10); (MALDI) mass spectrum (APCI): m/e (% relative intensity) 274 (100) $(M+1)^+$, and 242 (10); m/e (MALDI) calcd for $C_{17}H_{24}NO_2$ $(M + H^+)$ 274.1802, found 274.1800 and $[(M + H^+) - H_2]$ 272.1626.

4.3.10. *Aza*-[3 + 3] Annulation Product 41—R_f = 0.32 [10% EtOAc/Hexanes]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (t, 3H, *J* = 7.2 Hz), 1.62–1.88 (m, 6H), 2.92 (dd, 1H, *J* = 8.4, 14.4 Hz), 3.41–3.61 (m, 3H), 3.97–4.02 (m, 2H,), 4.57 (d, 1H, *J* = 6.0 Hz), 4.92 (dd, 1H, *J* = 5.6, 7.6 Hz), 5.94 (d, 1H, *J* = 7.6 Hz), 7.15–7.18 (m, 1H), 7.24–7.29 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 26.5, 27.9, 28.9, 39.9, 52.7, 59.1, 98.3, 107.0, 125.8, 127.2, 128.0, 129.9, 149.0, 155.0, 168.9; IR (neat) cm^{-1} 2927m, 2853brm, 1676s, 1561s, 1186s; mass spectrum (APCI): m/e (% relative intensity) 298 (100) $(M+H)^+$; m/e (ESI) calcd for $C_{19}H_{24}NO_2$ 298.1807, found 298.1812.

4.3.11. *Aza*-[3 + 3] Annulation Product 42 *[Characterized as a mixture]*—R_f = 0.48 [50% EtOAc/hexane]; ^{1}H NMR (500 MHz, $CDCl_3$) δ *Major diastereomer:* 1.25–1.29 (m, 3H), 1.32 (s, 3H), 1.39 (s, 3H), 1.51–1.78 (m, 6H), 2.73 (dd, 1H, *J* = 8.5, 14.5), 3.39–3.56 (m, 3H), 3.78 (dd, 1H, *J* = 6.5, 7.5 Hz), 3.85 (dd, 1H, *J* = 5.0, 6.0 Hz), 3.89 (dd, 1H, *J* = 6.5, 8.0 Hz), 4.08 (m, 1H), 4.14 (q, 2H, *J* = 7.0 Hz), 4.81 (dd, 1H, *J* = 6.0, 7.5 Hz), 6.07 (d, 1H, *J* = 7.5 Hz); *minor diastereomer* (*partial listing due to unresolved overlapping resonances*): 1.51–1.78 (m, 6H), 2.70–2.76 (m, 1H), 3.30 (dd, 1H, *J* = 6.0, 10.0 Hz), 3.39–3.56 (m, 1H), 3.87–3.90 (m, 1H), 4.92 (t, 1H, *J* = 7.0 Hz), 6.05 (d, 1H, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ *From a small sample of resolved major isomer:* 14.6, 25.5, 26.5, 26.7, 28.2, 28.9, 29.1, 36.5, 52.6, 59.6, 66.1, 79.2, 94.4, 102.0, 108.7, 133.1, 157.1, 169.1; IR (film) cm^{-1}: 2983w, 2931m, 1675s, 1552s, 1188s; mass spectrum (APCI): m/e (% relative intensity) 322 (100) $(M+H)^+$, 276 (100), 264 (50), 220 (5), 101 (10); m/e (ESI) calcd for $C_{18}H_{27}NO_4Na$ 344.1838, found 344.1852.

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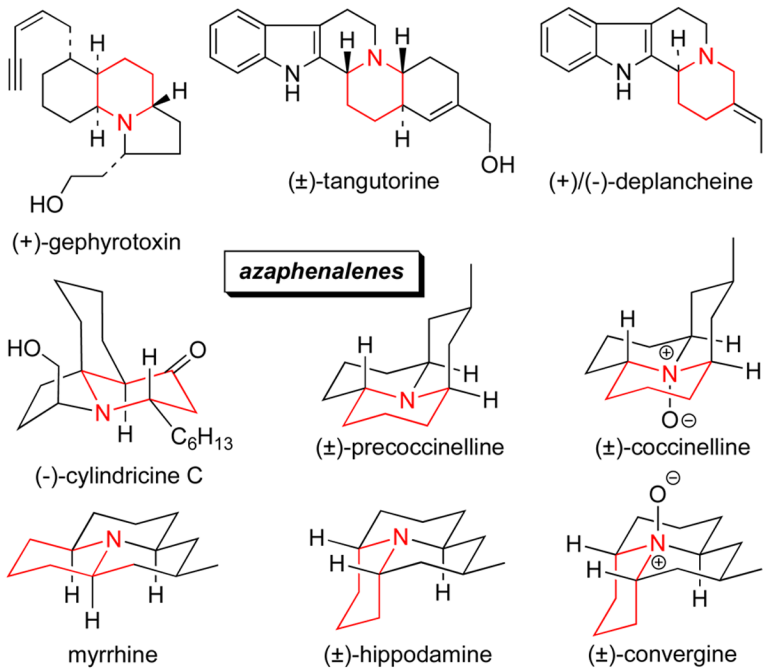


Figure 1.
Alkaloids Synthesized via Intramolecular *Aza*-[3 + 3].

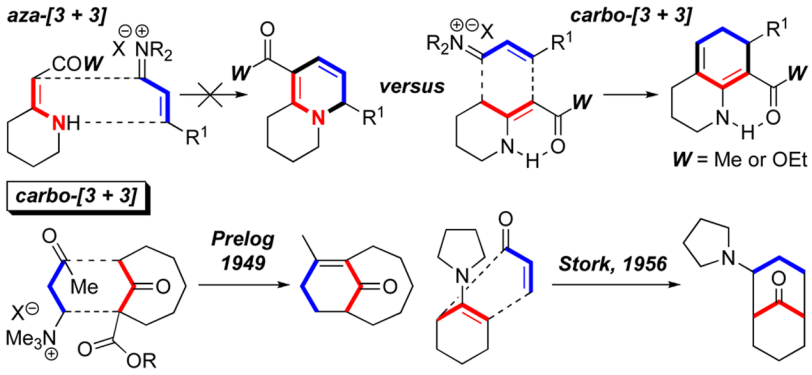


Figure 2.
Aza-[3 + 3] versus *Carbo*-[3 + 3] Annluation.

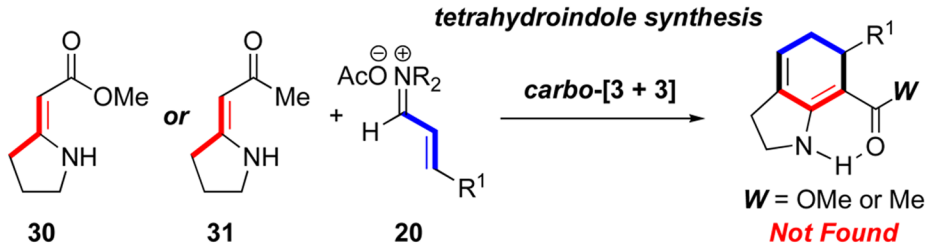


Figure 3.
A Possible Synthesis of Tetrahydroindoles.

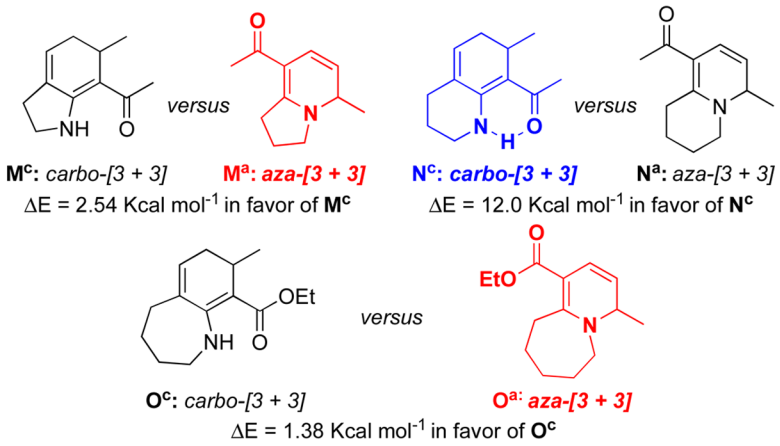
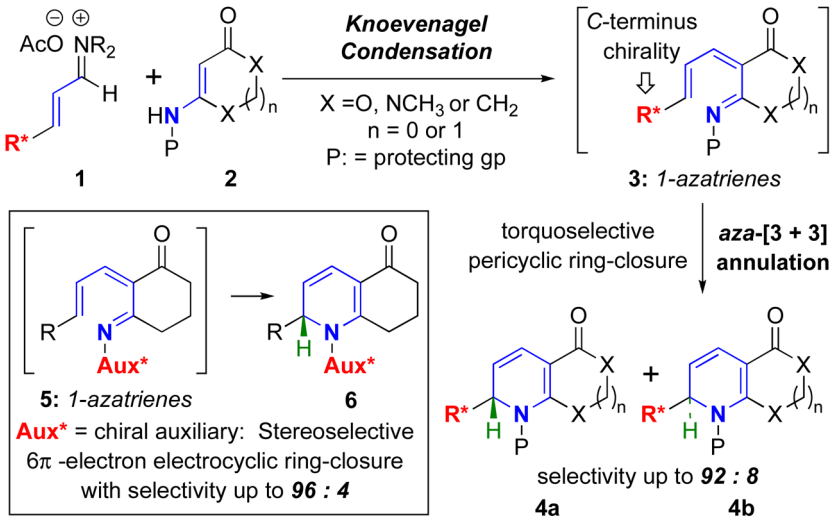
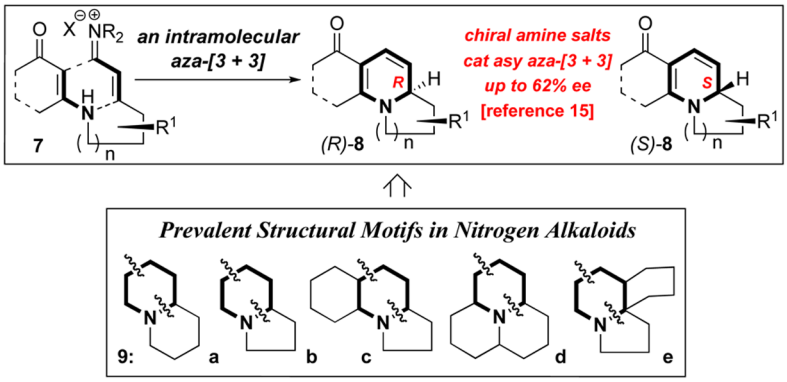


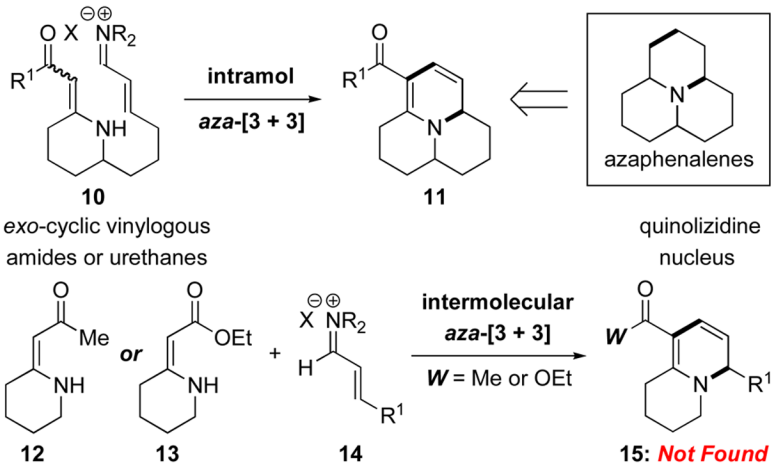
Figure 4.
Energetic Differences in the Annulation Products.



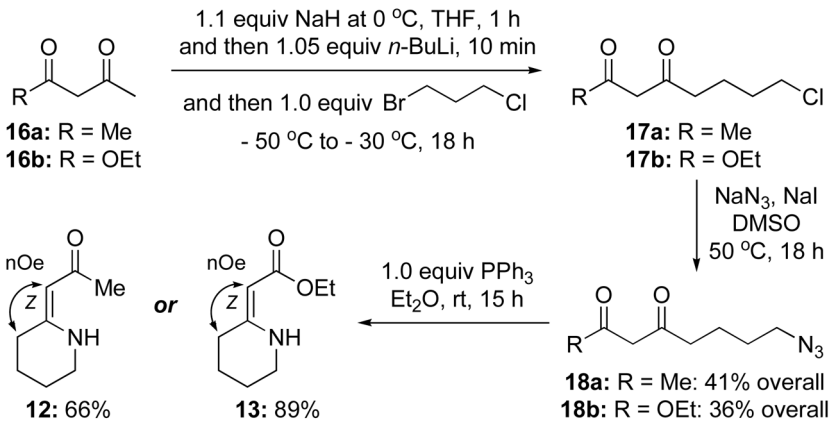
Scheme 1.
An *Aza*-[3 + 3] Annulation.



Scheme 2.
An Intramolecular *Aza*-[3 + 3] Annulation.

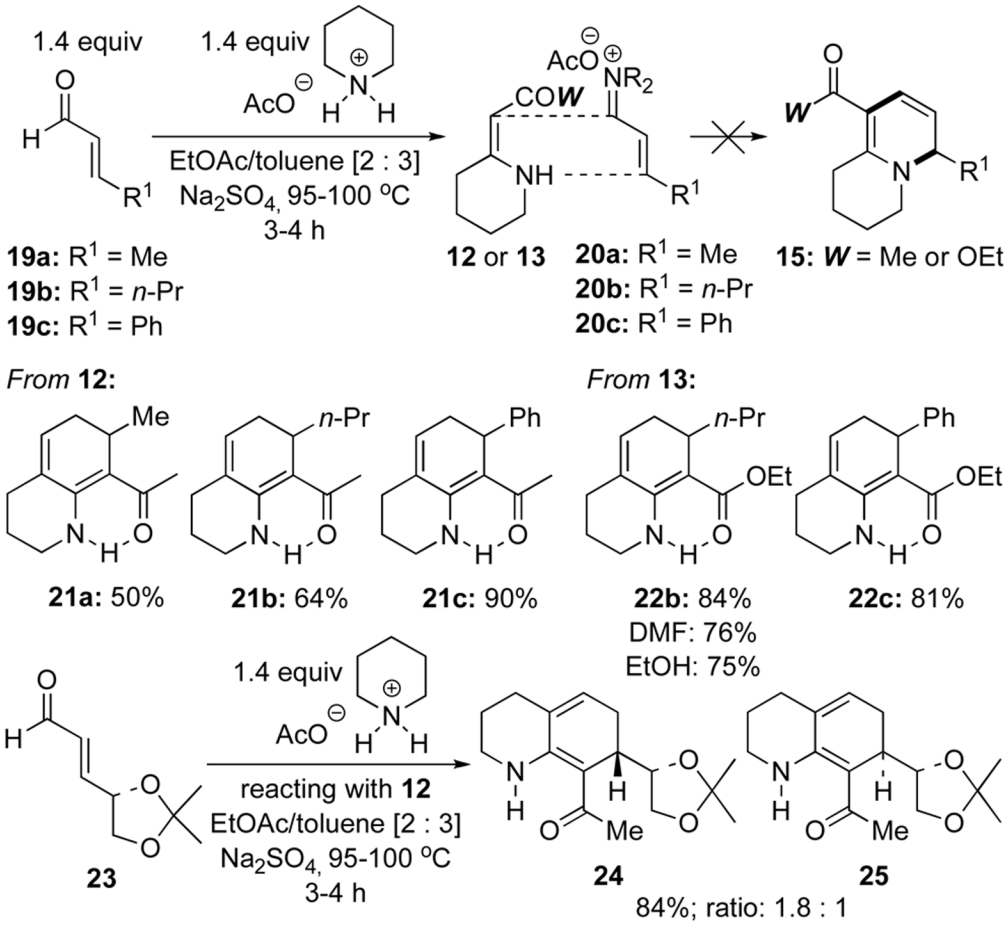


Scheme 3.
An *Aza*-[3 + 3] Pathway to Azaphenalenes and Quinolizidines.

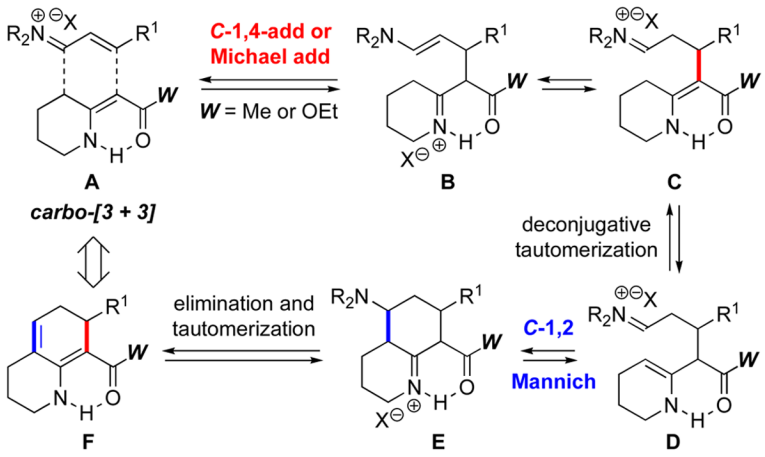


Scheme 4.

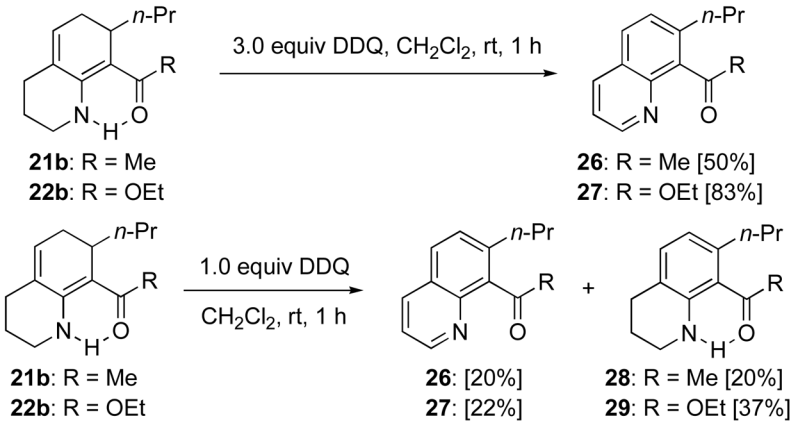
Syntheses of *Exo*-Cyclic Vinylogous Amide and Urethane.



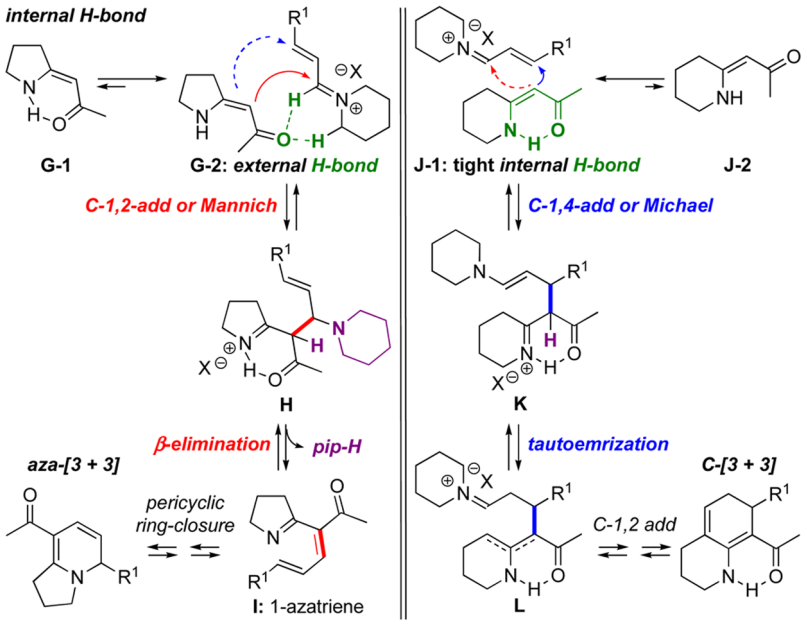
Scheme 5.
Unexpected Formation of Hexahydroquinolines.



Scheme 6.
A Proposed Pathway for the Hexahydroquinoline Formation.



Scheme 7.
DDQ Aromatization in the Quinoline Synthesis.



Scheme 8.
C-1,2 Addition versus *C*-1,4-Addition.

Table 1

Aza-[3 + 3] Annulations of *Exo*-Cyclic Vinylogous Amides.

entry	amides	aldehydes	*aza*-[3 + 3] products	yield [%][a]	ratio[b]
1	**30**[c]	**19a:** R^1 = Me	**36a:** R = OMe; R^1 = Me	51	--
2	**30**	**19b:** R^1 = *n*-Pr	**36b:** R = OMe; R^1 = *n*-Pr	70	--
3	**30**	**19c:** R^1 = Ph	**36c:** R = OMe; R^1 = Ph	75	--
4	**31**[d]	**19b:** R^1 = *n*-Pr	**36d:** R = Me; R^1 = *n*-Pr	73	--
5	**30**	**23**	**37**	56	1.5 : 1
6	**30**	**33**	**38**	50	1.3 : 1
7	**30**	**34**	**39a:** R = OMe	10	□20 : 1
8	**31**	**34**	**39b:** R = Me	7	□20 : 1
9	**30**	**35**	**40**	33	2.2 : 1[e]
10	**32**[f]	**19c**	**41**	53	--
11	**32**	**23**	**42**	62	1.2 : 1

[a] Isolated Yields.

[b] Ratio determined using ^{1}H NMR, and unless noted otherwise, the relative stereochemistry was not assigned.

[c] See references [21] and [29] for the preparation of [30].

[d] See references [21] and [30] for the preparation of [31].

[e] The ratio was found in crude ^{1}H NMR but the minor isomer appeared to isomerize to the major isomer during purification. The major isomer shown here was assigned using nOe experiment and the final ratio was 13.8: 1.

[f] See references [21] and [31] for the preparation of [32].