Heterocycles

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Stereoselective Synthesis of Polycycles Containing an Aziridine Group: Intramolecular aza-Diels–Alder Reactions of Unactivated 2H-Azirines with Unactivated Dienes

Hua-Dong Xu, Hao Zhou, Ying-Peng Pan, Xin-Tao Ren, Hao Wu, Mei Han, Run-Ze Han, and Mei-Hua Shen**

Dedicated to Professor David Crich on the occasion of his 56th birthday

Abstract: *Vinyl azide with a pendent diene can undergo thermal decomposition to a related azirine intermediate, which was used immediately in an intramolecular aza-Diels–Alder reaction to furnish an aziridine-containing trans-fused tricyclic core structure with excellent stereoselectivity. The method provides a facile entry to complex polycyclic alkaliods which can be further elaborated by ring-opening reactions and ring expansion of the aziridine moiety, as well as by dihydroxylation of the alkene group.*

The [4+2] cycloaddition of dienes with the imino dienophile 2*H*-azirine is a unique hetero-Diels–Alder reaction which gives rise to fascinating aza-bicyclo[4,1,0] scaffolds (Figure 1, top).[1] The [4+2] adduct can be elaborated to access other valuable structures by manipulation of the aziridine ring and the double bond.[2] However, its application in organic synthesis is hampered by two main drawbacks: 1) both reaction partners suffer from extremely narrow substrate scope. The dienophile is confined primarily to azirines which are stabilized/activated by aryl/carbonyl groups and their reacting partners are restricted to electronically activated dienes or cyclic dienes; 2) unlike other Diels–Alder reactions, the intramolecular version (IMDA) for this [4+2] cycloaddition has not been disclosed yet, and if realized would allow quick assembly of valuable tricyclic or more complex aziridine-containing cyclic systems. To fill this vital methodology gap, we have launched a project to investigate intramolecular aza-Diels–Alder reactions of 2*H*-azirines with broad substrate scope, anticipating that the intrinsic kinetic and entropic advantages of intramolecular processes would help to overcome the issues regarding the restricted substrate scope (Figure 1, bottom).

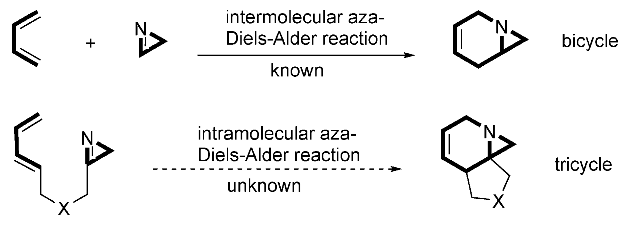
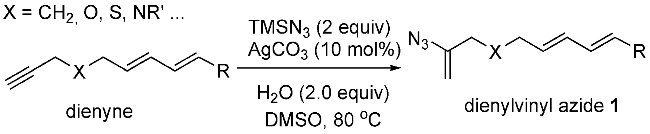


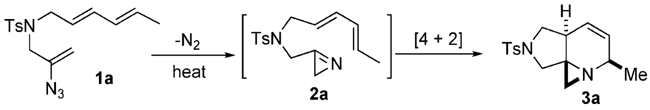
Figure 1. Inter- and intramolecular aza-Diels–Alder Reactions.

During our efforts to prepare the aza-IMDA substrate **2a**, the vinyl azide **1a** was elected as its precursor since vinyl azide is known to decompose to 2*H*-azirine under thermal conditions.[3] To our delight, it was found that various dienyl vinyl azides (**1**) could be made conveniently from related dienynes following the protocol from Bi et al. for hydroazidation of terminal alkynes where the conjugated diene moiety is unaffected (Scheme 1).[4] While **1a** remained intact, as determined by TLC, at 80 °C (temperature of oil bath) for 6 hours in toluene in a sealed tube (Table 1, entry 1), it decomposed completely at 100 °C after 8 hours (entry 2). The product was identified as the intriguing aza-IMDA tricycle **3a** in a yield of 75 %, and presumably arose through the



Scheme 1. Facile preparation of dienyl vinyl azides from dienynes. DMSO = dimethylsulfoxide, TMS = trimethylsilyl.

Table 1: Pyrolyzation of the vinyl azide **1a**.[a]



Entry	T [°C][c]	t [h]	Solvent	Yield [%][b]
1	80	6	toluene	n.r.
2	100	8	toluene	75
3	100	8	$ClCH_2CH_2Cl$	72

[a] Reaction conditions: **1a** (0.3 mmol) in solvent (1 mL) was heated. [b] Yield of isolated product. [c] oil bath temperature. n.r. = no reaction, Ts = 4-toluenesulfonyl.

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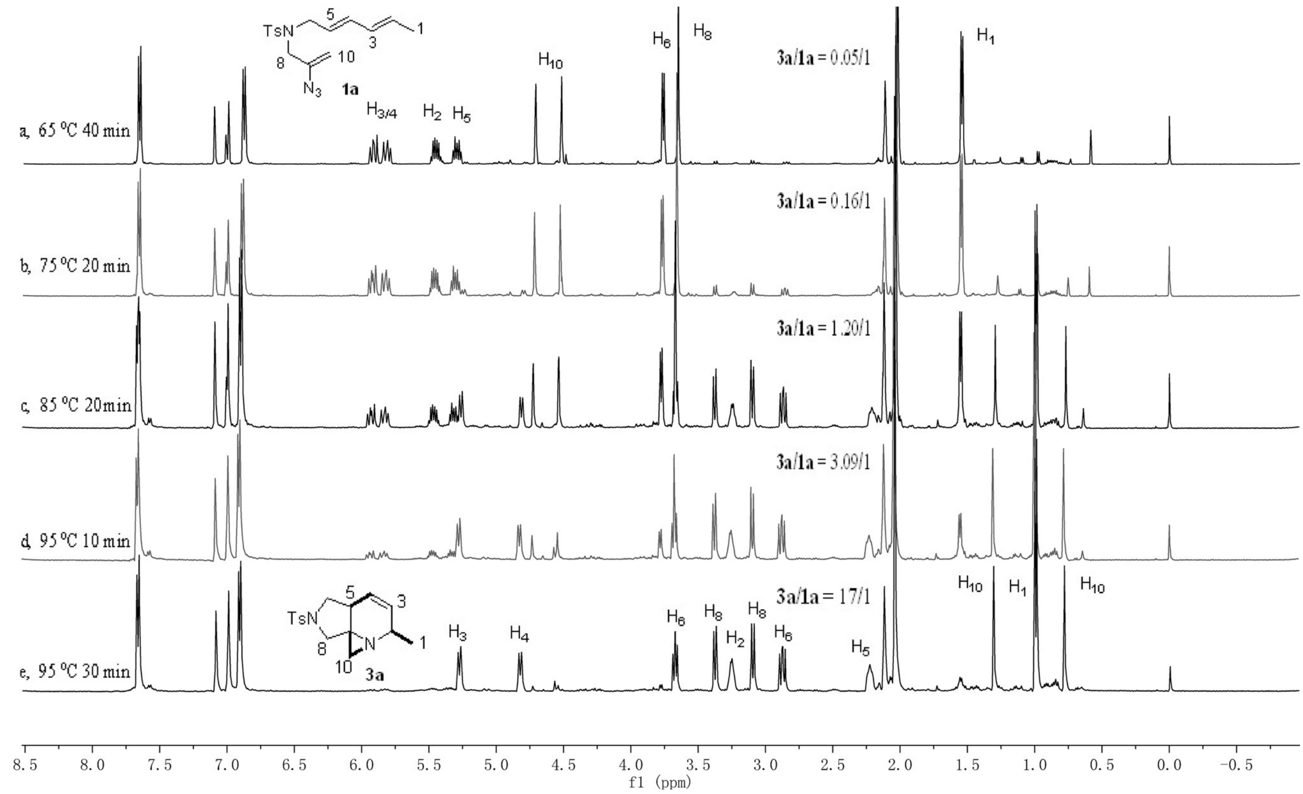


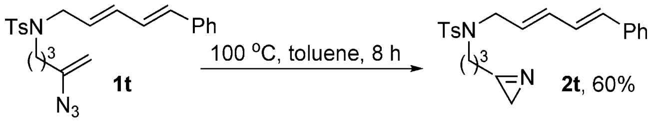
Figure 2. *V–T* ^{1}H NMR experiments in d8-tolunene a) 65 °C, 40 min; b) 75 °C, 20 min; c) 85 °C, 20 min; d) 95 °C, 10 min; e) 95 °C, 30 min.

intermediacy of the transient azirine **2a**. The same transformation proceeded equally well in dichloroethane (entry 3).

To gain more information, the reaction course was monitored by variable-temperature NMR spectroscopy and selected spectra are compiled in Figure 2. As illustrated in spectrum a (Figure 2), **1a** was virtually inert at 65 °C in [D$_8$]toluene for 40 minutes. When the temperature was increase to 75 °C for 20 minutes, signals belonging to tricyclic alkaloid **3a** became much more prominent, thus indicating that a significant amount of **3a** (15 % conversion) was formed (spectrum b). A further rise in temperature to 85 °C resulted in a much higher reaction rate and half of the remaining azide was consumed within 20 minutes (spectrum c). When the reaction was heated to 95 °C, we found that the amount of starting material decreased to 20 % after 10 minutes (spectrum d), and to 6 % after 30 minutes (spectrum e), thus indicating an estimated 11.5 minute half-life at this temperature.

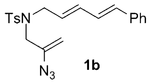
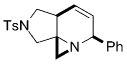
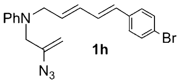
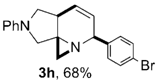
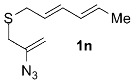
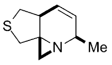
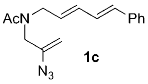
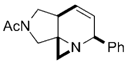
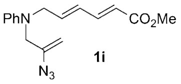
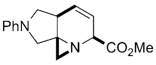
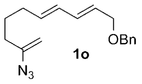
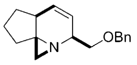
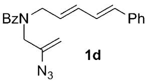
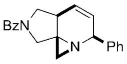
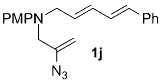
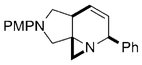
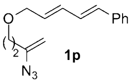
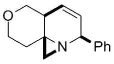
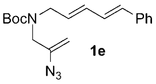
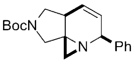
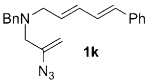
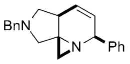
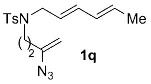
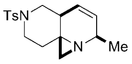
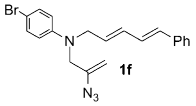
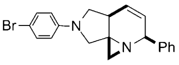
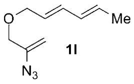
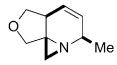
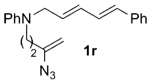
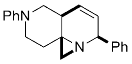
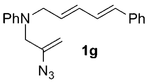
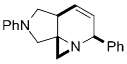
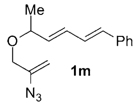
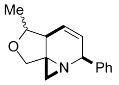
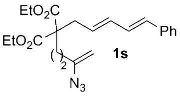
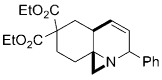
The exceptional convenience and efficiency demonstrated by the direct conversion of **1a** into a fused 5-6-3 aza-tricycle prompted us to explore the substrate scope of this reaction with a variety of vinyl azides (Table 2). A range of nitrogen protecting groups including sulfonyl, acetyl, *tert*-butoxycarbonyl (Boc), phenyl, and benzyl groups were compatible with this reaction (entries 1–10). The approximate 20 % drop in yield for **3e** might reflect the instability of the Boc group under thermal conditions (entry 4). Both aromatic and alkyl amines (entries 5–10) were good N substituents for this reaction, thus indicating that the nitrogen basicity can barely influence the reaction with regard to the yield. The slightly lower yield of **3i** might be due to the deactivated diene by the electron-withdrawing ester group (entry 8). Replacement of the nitrogen atom with either oxygen, sulfur, or carbon atoms resulted in comparable yields (entries 11–14). A one-carbon elongation of the tether linking the reaction partners did not show significant change in yields (entries 15–17), thus providing a novel *trans*-fused 6-6-3 aza-tricyclic scaffold. It seemed that the gem diester group in **1s** would interfere with the desired [4+2] reaction to give **3s** in a considerably reduced yield, probably because of the steric effect (entry 18).

Extension of this protocol to the synthesis of a fused 7-6-3 aza-tricyclic system was attempted with the linear dienyl vinyl azide **1t** (Scheme 2). The thermal reaction of **1t** under the same reaction conditions stopped at the stage of the 2*H*-azirine **2t**, which was isolated in 60 % yield. These observations substantiated a previous proposal of an intermediary of an 2*H*-azirine (**2**) for the formation of **3**. The inability of **2t** to undergo aza-Diels–Alder cyclization with diene neither intramolecularly nor intermolecularly is in line with the long term absence of aza-Diels–Alder reaction of unstabilized/unactivated azirine dienophile with unactivated dienes and may reflect the unfavorable thermodynamics and/or



Scheme 2. The formation of 2*H*-azirine from vinyl azide.

Table 2: Synthesis of tricyclic N-heterocycles through an intramolecular aza-Diels–Alder reaction.[a]

Entry	Substrate	Product, Yield[b]	Entry	Substrate	Product, Yield[b]	Entry	Substrate	Product, Yield[b]
1	 **1b**	 **3b**, 68%	7	 **1h**	 **3h**, 68%	13	 **1n**	 **3n**, 64%
2	 **1c**	 **3c**, 80%	8	 **1i**	 **3i**, 54%	14	 **1o**	 **3o**, 59%
3	 **1d**	 **3d**, 79%	9	 **1j**	 **3j**, 80%	15	 **1p**	 **3p**, 65%
4	 **1e**	 **3e**, 60%	10	 **1k**	 **3k**, 74%	15	 **1q**	 **3q**, 65%
5	 **1f**	 **3f**, 82%	11	 **1l**	 **3l**, 68%	17	 **1r**	 **3r**, 70%
6	 **1g**	 **3g**, 70%	12	 **1m**	 **3m**, 72%, dr: 2/1	18	 **1s**	 **3s**, 38%

[a] Reaction conditions: **1** (0.3 mmol) in toluene (1 mL) was heated at 100 °C in an oil bath for 8 hours. [b] Yield of isolated product.

kinetics (seven versus five,six-membered ring formation and intermolecular versus intramolecular reaction) in these cases, where the azirine and diene groups cannot orient themselves properly in a favorable energy state that is required for the cyclization to proceed smoothly.

The compound **3m** was obtained as a mixture of two diastereomers with respect to C6 (d.r. = 2:1), and the structures were established by NMR spectroscopy. The interactions between H_a10 and H3 and H2 and H5 are prominent in the NOESY spectrum and served as the key evidence for the determination of relative stereochemistry as shown in Figure 3 (2,5-*cis*-5,9-*trans*). The structures for other products were assigned by analogy to **3m**. The *trans* stereochemistry of fused 5,6/6,6-bicyclic systems could be explained by the *endo* addition of azirine with the pendent diene, which is in line with the favorable *endo* cycloaddition for intermolecular aza-Diels–Alder reaction of azirines with dienes.[1a,2c]

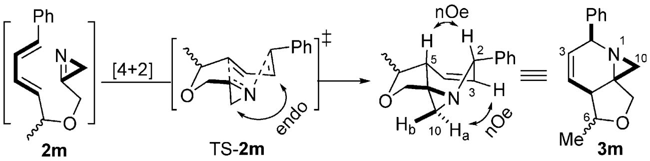
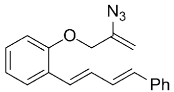
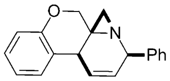
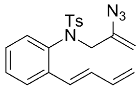
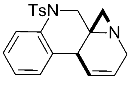
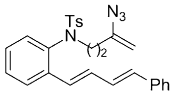
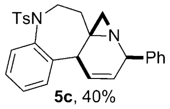
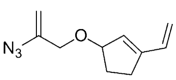
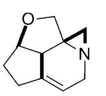
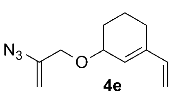
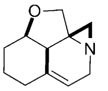
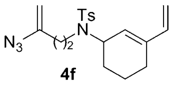
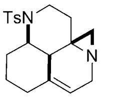
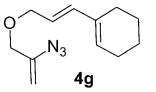
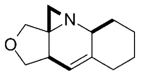
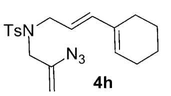
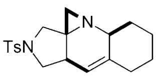
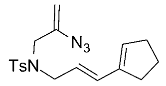
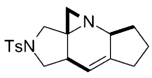
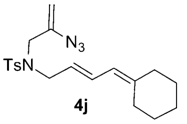
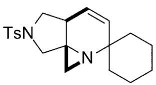


Figure 3. Assignment of stereochemistry of aza-Diels–Alder products and proposed transition state.

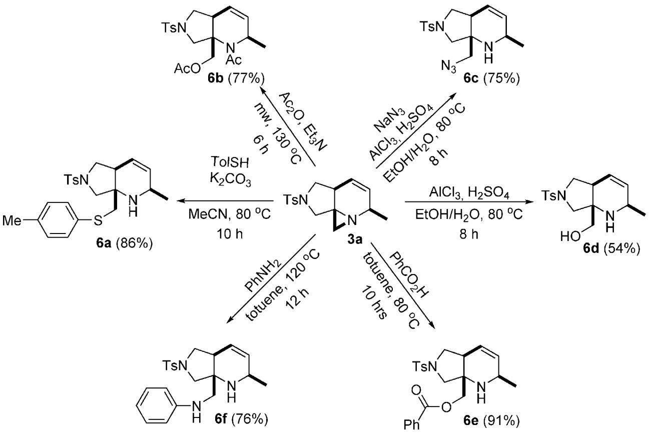
At this stage, we have established a robust method to construct *trans* fused 5-6-3 and 6-6-3-tricyclic alkaloids. Given the fact that there are many N-heteropolycycles exhibiting excellent biological and pharmaceutical activities, and that there are numerous efforts toward the synthesis of these alkaloids,[5] we were encouraged to apply our method to access N-polycycles by using cyclic starting materials (Table 3). The benzofused tetracyclic aziridines **5a** and **5b** were accomplished smoothly from phenyl-conjugated dienyl vinyl azides **4a** and **4b**, respectively (entries 1 and 2). The formation of the seven-membered ring in **5c** completed the mission set for substrate **1t**, thus suggesting an advantageous template effect for this reaction.[6] Introduction of a ring onto the diene moiety as in **4d**–**f** led to stereospecific formation of the highly fused tetracycles **5d**–**f** exclusively. Accordingly, by incorporation of a ring in another way, the extended tetracycles **5g**–**i** were also obtained conveniently from **4g**–**f**. Quite strikingly, two difficult quaternary carbon centers flanking the nitrogen atom could be installed simultaneously to form the bis(spiroalkaloid) **5j** efficiently from **4j**. These examples demonstrate clearly that the current method has enormous potential in the synthesis of valuable polycyclic alkaloids with diverse skeletons.

Efforts were further directed to exploit the strained aziridine ring for a facile functional-group handle through ring-opening reactions (Scheme 3). It was found that after treatment with $TolSH/K_2CO_3$, **3a** was converted into the ring-opened coupling product **6a** in 86% yield. The Ac_2O/Et_3N combination was also effective to break the three-membered ring under thermal conditions to give the N,O-bisacyl bicycle **6b**. Azide anions are also feasible nucleophiles for opening the strained aziridine ring under proper acidic conditions to give the valuable azide **6c**.[2d,7] Interestingly, under the same reaction conditions, but excluding NaN_3, the aminoalcohol **6d** was formed, albeit with a lower yield because of incomplete conversion. We also found that benzoic acid in warm toluene could open up the three-membered ring efficiently to give the

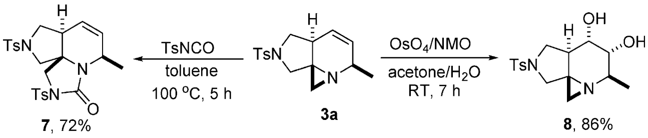
Table 3: Synthesis of polycyclic N-heterocycles by using cyclic substrate.[a]

Entry	Substrate	Product, Yield[b]
1	 **4a**	 **5a**, 60%
2	 **4b**	 **5b**, 76%
3	 **4c**	 **5c**, 40%
4	 **4d**	 **5d**, 68%
5	 **4e**	 **5e**, 72%
6	 **4f**	 **5f**, 64%
7	 **4g**	 **5g**, 70%
8	 **4h**	 **5h**, 71%
9	 **4i**	 **5i**, 68%
10	 **4j**	 **5j**, 55%

[a] Reaction conditions: **1** (0.3 mmol) in toluene (1 mL) was heated at 100 °C for 8 hours. [b] Yield of the isolated product.



Scheme 3. Ring-opening reactions of aziridine.



Scheme 4. Aziridine ring expansion and dihydroxylation of alkene group.

aminoester **6e** in 91 % yield. A higher temperature can also render aniline to break this ring to afford the coupling product **6f**. These examples demonstrated the diverse transformations the aziridine product could undergo for further derivation. Notably, the extensive NMR study also supports a *trans*-fused bicyclic configuration for **6c** and it is in line with the previous assignment of stereochemistry for the aza-IMDA products.

Ring expansion of the fused aziridine ring was also realized by reaction of **3a** with sulfonyl isocyanate TsNCO under thermal conditions to give the tricyclic urea **7** in 72 % yield (Scheme 4, left), while the related reaction with phenyl isocyanate PhNCO did not occur. Attempts to functionalize the in-ring alkene group proved successful as well. Catalytic dihydroxylation of **3a** with OsO_4/NMO proceeded smoothly to deliver the aziridinodiol **8** with exclusive chemo- and stereoselectivity as only one isomer was observed, wherein the newly generated diols hold a direction *trans* to that of the aziridine methylene as established by a ^1H-^1H NOSEY experiment (Scheme 4, right).

In summary, the first intramolecular aza-Diels–Alder reaction of 2*H*-azirine with a diene has been developed, thus proving a highly facile protocol for stereoselective assembly of *trans* 5-6-3, 6-6-, and even 7-6-3 tricycles containing a fused aziridine ring. Vinyl azide undergoes thermal decomposition to 2*H*-azirine and immediate *endo* cycloaddition with a pendent diene. The *endo* [4+2] process confers to an exclusive *trans* selectivity for the tricycle systems. This methodology has overcome the inherent drawbacks of narrow substrate scope for conventional aza-Diels–Alder reaction of 2*H*-azirine, and therefore can be extended easily to complex polycyclic congeners. The aziridine group can be further elaborated by ring-opening reactions with various nucleophiles. Elaboration the C–C double bond generated from the cycloaddition reaction is also viable, as demonstrated by a highly selective catalytic dihydroxylation reaction. Application of this method to alkaloid synthesis is currently ongoing in our laboratory.

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Keywords: aziridines · cycloadditions · heterocycles · small-ring systems · synthetic methods

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