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Stereoselection in Intramolecular Diels–Alder Reactions of 2-Cyano-1-azadienes: Indolizidine and Quinolizidine Synthesis

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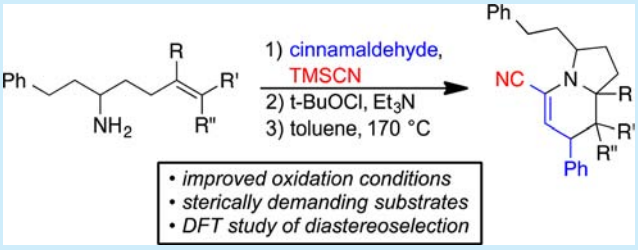
Supporting Information

ABSTRACT: Progress toward understanding the scope and diastereoselectivity of intramolecular Diels–Alder reactions using 2-cyano-1-azadienes is described herein. The resulting cyanoenamine products are underutilized intermediates in organic synthesis. Assembly of the Diels–Alder precursors was achieved using an improved imine condensation/oxidative cyanation protocol. By this method, several highly substituted indolizidine and quinolizidine architectures were constructed. Quantum mechanical DFT calculations at the B3LYP/6-31+G(d) level of theory were performed for these cyclizations and provide insights into the origins of the observed diastereoselectivities.



Indolizidines and quinolizidines are ubiquitous motifs found in several families of alkaloid natural products.[1] Both ring systems are present in many of the lipid-soluble toxins of poison dart frogs isolated by the Daly group, including the indolizidines gephyrotoxin and 261C (Figure 1).[2] Many lycopodium alkaloids,

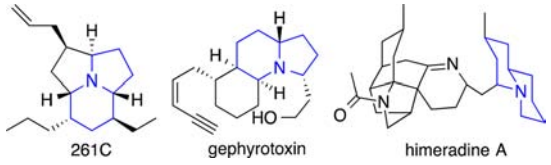


Figure 1. Examples of natural products containing indolizidine or quinolizidine structural units (highlighted in blue).

such as himeradine A, also contain quinolizidine substructures.[3] A variety of annulation strategies have been used to prepare these interesting heterocycles.[4] An intramolecular Diels–Alder (IMDA) approach to the synthesis of highly functionalized indolizidines, such as 261C, was an underdeveloped area in terms of precursor access and stereochemical outcomes.[5] The following report describes a simple, general method for the preparation of 2-cyano-1-azadiene precursors, as well as synthetic and computational studies regarding diastereoselectivity of cyclization.

Early investigations of 2-cyano-1-azadienes and related IMDA reactions were described by the collaborative research of Fowler and Grierson.[6] One fascinating observation from these studies was the competency of unactivated alkene dienophiles in such IMDA reactions, which was attributed to the lowering of both LUMO and HOMO energies by the 2-cyano group.[7] Two examples of the IMDA reaction using unactivated alkenes are shown in Figure 2. Zhu and Masson reported on a high-temperature reaction to provide an excellent yield of diastereomers **2** and **3** as a 1:1 mixture.[8] Grierson and Fowler found a 3:2 mixture of indolizidine diastereomers at a lower temperature, also

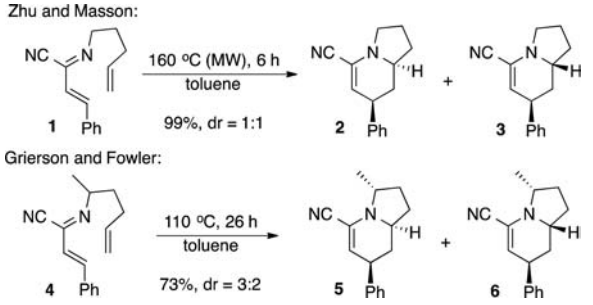


Figure 2. Indolizidines from IMDA reactions of 2-cyano-1-azadienes.

in good yield.[9] The ambiguous nature of reactivity for the resulting α-cyano enamines products and their potential for further elaboration caught our attention. These limited examples were a promising starting point for complex alkaloid synthesis, but the scope of the IMDA reaction was underdeveloped. Herein, we present a systematic exploration of the IMDA reaction of 2-cyano-1-azadienes with unactivated alkenes.

Grierson and Fowler's preparation of the 2-cyano-1-azadienes from triflate activation of the corresponding amides[9] proved to be a challenging protocol to reproduce. In contrast, the one-pot preparation recently outlined by Zhu and Masson appeared to be promising.[8] Their procedure combined an unbranched primary amine, an unsaturated aldehyde, a cyanide source, and an oxidant. In our hands, their method, which used IBX as the oxidant, worked well with unbranched primary amines but gave low yields with branched primary amines. A general method for the synthesis of 2-cyano-1-azadienes was necessary for this IMDA

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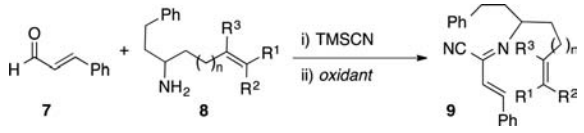
study. Zhu and Masson's protocol was used as a starting point for the development of an improved procedure.

The one-pot method of Zhu and Masson relies on the rapid condensation of unhindered primary amines with aldehydes.[10] Branched primary amines, such as **8**, were much less reactive and competitive oxidation led to side reactions. Separating the oxidation step allowed α-aminonitrile formation to be optimized. Combining cinnamaldehyde **7** and branched amine **8** followed by treatment of TMSCN led to complete conversion to the α-aminonitrile product in quantitative yield after 2 h, as monitored by NMR spectroscopy. Subsequent addition of IBX produced reasonable yields of the 2-cyano-1-azadienes **9** in yields ranging from 42 to 76% (Table 1). Recovered aldehyde was identified as a

Table 1. Synthesis of 2-Cyano-1-azadienes by a Strecker Reaction and an in Situ Oxidation



entry	R^1	R^2	R^3	n	product	IBX yield[a] (%)	*t*-BuOCl yield[b] (%)
1	H	H	H	1	**9a**	42	86
2	Me	H	H	1	**9b**	76	74
3	Me	Me	H	1	**9c**	47	67
4	H	H	Me	1	**9d**	54	75
5	H	H	H	2	**9e**	52	80

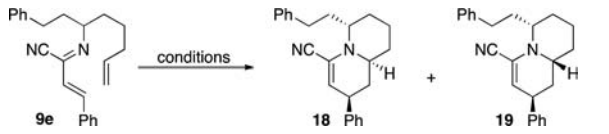
[a]Prestirred $MgSO_4$, **7**, and **8** in toluene at rt for 12 h, then added TMSCN and MeOH. After 1 h, added TBAB and IBX, stirred for 16 h. [b]Combined **7** and **8** in toluene at rt for 40 min, then added TMSCN at −78 °C. After 2 h, added Et_3N and *t*-BuOCl.

side product, indicating that α-aminonitrile hydrolysis was an issue. In considering other oxidants, we were attracted to *tert*-butyl hypochlorite, which had been used for imine oxidation in the past.[11] Freshly prepared *tert*-butyl hypochlorite reliably oxidized the intermediate α-aminonitrile with an average yield of 76% (Table 1). The optimized protocol is a convergent, one-pot method and is effective for a variety of substrates. The new oxidation procedure delivered the five 2-cyano-1-azadienes **9a**−**e** for IMDA studies.

The cyclization reaction was initially optimized using the simple terminal alkene substrate **9e** (Table 2). ^{1}H NMR spectroscopic analysis indicated the product was thermally stable at 180 °C and that prolonged heating did not lead to significant product decomposition (entries 1 and 2). Higher temperatures led to rapid decomposition (entry 3). No reaction was observed at 150 °C (entry 4), consistent with Zhu and Masson's results but not with Grierson and Fowler's report (Figure 2). Reaction yields were unaffected by the source of heating or reaction concentration (entries 5−7). Solvents of varying polarity were examined, and toluene was determined to be the solvent of choice. Trace amounts of water helped to promote the Diels−Alder cyclization compared to the use of anhydrous solvents (entries 6 and 8).[12] A variety of additives were also investigated, but the highest reproducible yield was achieved with no additives and the diastereomeric ratio of products (**18**:**19** = 1:2) remained unaffected. A full account of the solvents and additives analyzed is included in the Supporting Information.

With a method for the synthesis of substrates and optimal cyclization conditions identified, we were in a position to extend the reaction to the other 2-cyano-1-azadienes (Scheme 1).

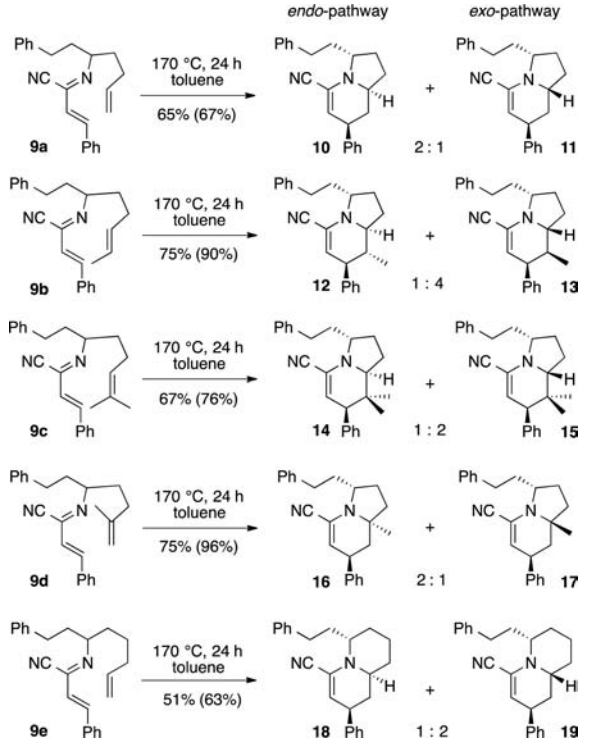
Table 2. Optimization of the Diels−Alder Reaction with Cyanoazadiene 9e



entry	temp (°C)	time	solvent	concn (M)	yield[d] (%)
1	180[a]	21 h	wet toluene[c]	0.04	64
2	180[a]	29 h	wet toluene[c]	0.04	61
3	220[a]	15 min	wet toluene[c]	0.04	30
4	150[a]	24 h	wet toluene[c]	0.04	no rxn
5	170[a]	23 h	wet toluene[c]	0.04	64
6	170[b]	24 h	wet toluene[c]	0.04	62
7	170[b]	24 h	wet toluene[c]	0.02	62
8	170[b]	24 h	dry toluene	0.04	48

[a]Heating with microwave. [b]Heating thermally. [c]The toluene was stored over water. [d]Yields were determined by ^{1}H NMR spectroscopy with respect to mesitylene as internal standard.

Scheme 1. Intramolecular Diels−Alder Reactions of 2-Cyano-1-azadienes under Thermal Conditions[a]



[a]Values in parentheses are products yields calculated with respect to an internal mesitylene standard.

Substrates were selected to examine the effect of alkene substitution on diastereoselectivity and to determine the viability of sterically demanding cyclizations. The products were isolated as diastereomeric mixtures, with the exception of **10** and **11**, which could be separated by flash chromatography. Stereochemical configurations were assigned by 2D NMR methods and extensive NOE analyses. The isolated yields ranged from 51% to 75%, demonstrating that the IMDA reaction is efficient across a variety of substrates. The sterically demanding cyclizations of **9c** and **9d** are particularly noteworthy as they represent the first

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examples of using such a Diels–Alder reaction to generate indolizidines bearing angular substituents or quaternary centers.

A major impetus of this project was to determine the stereoselectivity of 2-cyano-1-azadiene IMDA reactions (Scheme 1). In each case, the major and minor products of the reaction were the result of *endo*- and *exo*-IMDA reactions: there was no observed isomerization of alkene or diene geometries in the products. For the indolizidine products, the *endo* pathway was favored for half of the cases and the *exo* pathway was favored for the others, indicating the pathways are energetically similar. *E*-Dienophile substrate **9b** led to the highest dr (1:4) and a reversal of selectivity compared to Figure 2 in favor of the *exo* product. 1,1-Disubstituted substrate **9c**, as well as the single quinolizidine case (**9e**), also favored *exo* pathways (dr = 1:2). Although modest diastereoselectivities were observed, more selective reactions could be developed if the factors governing stereoselectivity were understood. As such, we turned our efforts toward the computational study of these IMDA reactions using the B3LYP functional, which has been shown to accurately describe stereoselection in related cycloaddition reactions.[13]

Detailed analysis for the computational study of the cyclization of **9b** follows due to its direct correlation to a complex indolizidine of interest (**261C**). It is noteworthy to mention that the *endo*:*exo* selectivity is a reversal of previously known cases (Figure 2), and the stereochemical relationships of 261C are present in minor product (**12**). Additional computed structures (with truncated phenethyl side chains) for all reactions in Scheme 1 as well as explanations of computational methods appear in the Supporting Information.

Each cyclization can proceed through four distinct diastereomeric transition states (TSs) (Figure 3). Cyclization from the diene's top face leads to the experimentally observed *trans* relationship between the phenyl substituent on the diene and the alkyl substituent on the tether (**12′** and **13′**), whereas the unobserved products arising from a bottom face approach would give rise to the unobserved *cis* disposition. Each approach can have the tether oriented *endo* (**12′** and **20**) or *exo* (**13′** and **21**). Computation correctly predicts *trans* approaches as being the relevant reaction pathways in all cases, which can be rationalized as a minimization of allylic strain and gauche interactions between the tether, side chain, and nitrile moieties in the transition states.[14] Computed TS structures corresponding to the formation of observed products (**TS-12′** and **TS-13′**, respectively) reveal modest levels of asynchronicity, with C–N bond formation advanced of C–C bond formation in both instances. The TS leading to the major product (**TS-13′**) is the more asynchronous of the two, with a short C–N distance (1.99 vs 2.09 Å for **TS-12′**) and a longer C–C distance (2.36 vs 2.26 Å for **TS-12′**). The energetic preference of the more asynchronous TS can be rationalized as the one that most easily accommodates increased steric bulk of the methyl group on the dienophile terminus.

Given the modest selectivity of these cyclizations and the seemingly random product distribution from substrate to substrate in Scheme 1, such comparisons of TS synchronicity (*vide supra*) proved to be a valuable approach to evaluating the data. The results of this analysis for all experimental cases are shown in Table 3, where Δ corresponds to a measure of synchronicity.[15] Unsubstituted dienophiles (entries 1 and 5) are sterically nondemanding substrates and prefer the more synchronous TS geometry (i.e., the smaller Δ value). Conversely, substituted dienophile substrates (entries 2–4) have a higher steric demand and preferentially proceed through the more asynchronous TS (larger Δ value). Interestingly, this approach

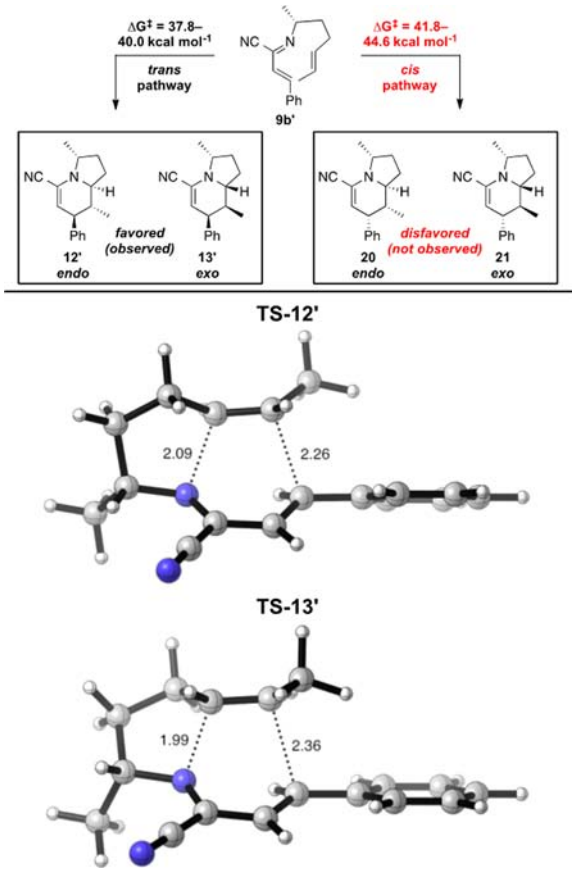

Figure 3. Examination of diastereoselection and TS structures for the observed diastereomers in *E*-dienophile cyclization (analogous to substrate **9b**) calculated at the B3LYP/6-31+G(d) level. Forming bonds are shown as dashed lines, and interatomic distances are given in angstroms.

Table 3. Relationship of Calculated TS Distances (in Å) and Observed Products As a Measure of Synchronicity

entry	substrate	product	C–N dist	C–C dist	Δ[a]
1	**9a**	**10**	2.15	2.16	**0.01**
		11	2.05	2.26	0.21
2	**9b**	**12**	2.09	2.26	0.17
		13	1.99	2.36	**0.37**
3	**9c**	**14**	2.00	2.39	0.39
		15	1.93	2.45	**0.52**
4	**9d**	**16**	2.23	2.10	**0.13**
		17	2.13	2.20	0.07
5	**9e**	**18**	2.22	2.13	0.09
		19	2.20	2.15	**0.05**

[a]Absolute value of the difference between C–N and C–C distances.

provides consistent results regardless of tether length or the placement of steric bulk on the dienophile, despite the nontrivial reversals of observed *endo*/*exo* selectivities.

A comparison of experimental free energy differences (derived from product distributions) and computed free energy differences (from DFT TS calculations) is provided in Figure 4. In all examined cases, there was a computed energetic preference for *exo* products corresponding to a positive value for $\Delta\Delta G^{\ddagger}$. The overall difference between the experimental and computational distributions leads to the ostensive overestimation of *exo* TS energies by ~0.8 kcal mol^{-1} for the indolizidine substrates. If one

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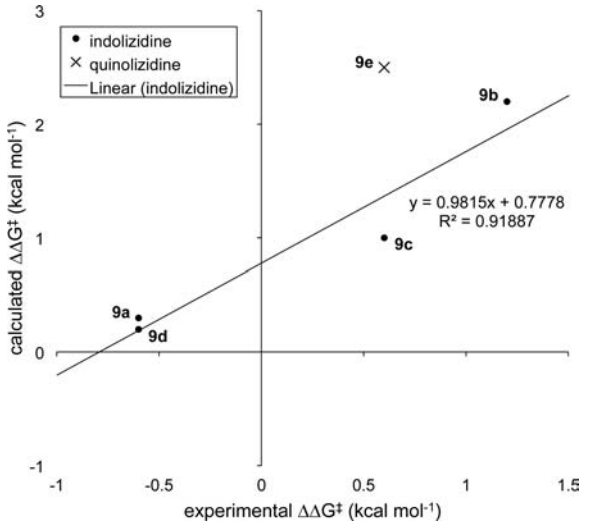

Figure 4. Plot of experimental and calculated $\Delta\Delta G^{\ddagger}$ (in kcal mol^{-1}) for aza-IMDA cyclizations and linear fit of indolizidine substrates.

corrects for the *exo* bias in the calculations, the correlation between computed and experimental selectivities is very good. Energy calculations using alternative density functionals and Houk's distortion−interaction models may provide more accurate distributions and will be the subject of future studies.

In summation, a simplified procedure for the oxidation of Strecker condensations provided access to IMDA precursors. Subsequent cyclization of these precursors afforded indolizidine and quinolizidine products in synthetically useful yields and modest diastereoselectivities. These cyclizations are effective in highly substituted examples including the formation of quaternary centers. Computational studies have provided some insight into the diastereoselectivity of these transformations. These findings provide a foundation for further development of such IMDA reactions and predictions of product distributions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00881.

Computational methods, associated references, calculated geometries and energies, and free energy diagrams (PDF)
Experimental procedures and characterization data for all new compounds as well as stereochemical assignments for IMDA products **10**−**19** and reaction optimization tables (PDF)

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Notes

The authors declare no competing financial interest.

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(12) Initial experiments were carried out with rigorous exclusion of air and water. During optimization of the reaction, an increase in yield was observed using wet toluene (see the Supporting Information for details). Although the optimization studies were carried out on **9e**, the improved yields using wet toluene were also observed empirically in the cyclizations of **9a**−**d**.
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(15) The differences in C−C and C−N bond distances (1.54 and 1.47 Å, respectively) were not taken into account in Table 3 because the presentation becomes complicated. Table SI1 in the Supporting Information presents the Δ values, but corrected for the difference in C−C and C−N bond lengths. The conclusions drawn from the analysis using corrected bond lengths are unchanged.

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