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Stereocontrol in a Combined Allylic Azide Rearrangement and Intramolecular Schmidt Reaction

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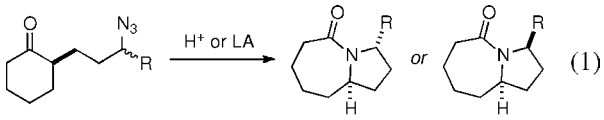
Supporting Information

ABSTRACT: Pre-equilibration of an interconverting set of isomeric allylic azides is coupled with an intramolecular Schmidt reaction to afford substituted lactams stereoselectively. The effect of substitution and a preliminary mechanistic study are reported. The synthetic potential of this method is demonstrated in the context of an enantioselective synthesis of an advanced intermediate leading toward pinnaic acid.

The intramolecular Schmidt reaction of alkyl azides, as exemplified in eq 1, is a useful means of converting 3-azidopropyl



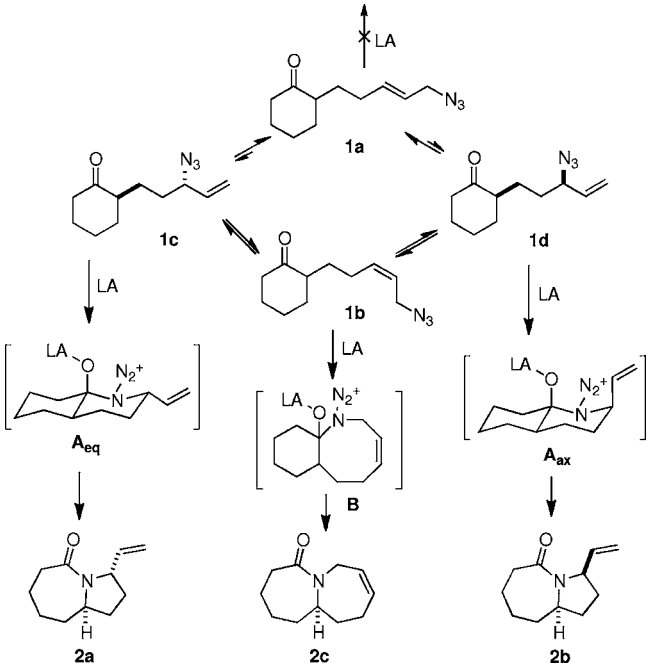
(1)

ketones into fused lactams.[1] Although most applications of this reaction in total synthesis have R = H as defined in eq 1, the general issue of how to establish the relative stereochemistry between an azide-bearing stereocenter and the rest of the molecule arises more frequently in complex synthetic projects.[2] One approach is to establish fully the relevant stereochemistry of the ketone reactant, since the ring-expansion step occurs with retention of configuration.[1b] However, this is often impractical or awkward, and we have sought alternative ways to couple the stereochemistry of the α-azido stereocenter with that adjacent to the ketone. In this paper, we present a strategy for accomplishing this goal using the kinetically controlled reaction of a rapidly equilibrating mixture of allylic azides and describe an application of this approach in alkaloid synthesis. In addition, through a combination of experiments and density functional theory (DFT) calculations, we have uncovered previously unknown details about the stereochemical course of the intramolecular Schmidt reaction of cyclohexanone-containing substrates.

The rearrangement of allylic azides, which is facile at room temperature, was first discovered by Winstein and co-workers in 1960[3] and has since become well-known.[4] Previous researchers have sought to carry out selective reactions from one allylic azide of a rapidly equilibrating pair by freezing out the rearrangement at low temperature,[4a] by taking advantage of significant stereochemical differences between potential substrates,[4d,e] or by rigging the substrates so that only one isomeric azide or double bond can take part in a downstream intramolecular reaction.[4g] Recently, Craig and co-workers reported the dependence of the product stereochemistry on the relative and interconverting configurations of a bystander azide adjacent to a reactive olefin participating in a Claisen rearrangement.[5] However, we are unaware of other examples where the Winstein rearrangement is used to control the stereochemistry of an emerging C–N bond.

It occurred to us that it might be possible to engage a mixture of allylic azides **1a–d** in an intramolecular Schmidt reaction to form **2a** selectively (Scheme 1). Our proposal was based on the

Scheme 1



following reasoning: (1) **1a–d** would equilibrate faster than the Schmidt reaction would occur; (2) formation of lactams would be kinetically controlled via the preferential formation of the intermediates $\mathbf{A}_{eq}$ and $\mathbf{A}_{ax}$ (both arising from equatorial attack of the azide onto the ketone[6]); (3) trans alkene **1a** would be

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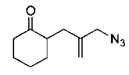
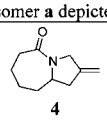
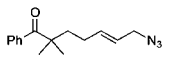
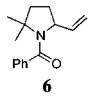
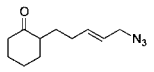
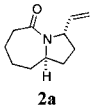
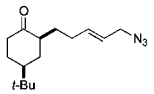
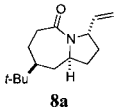
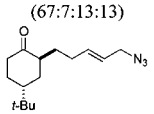
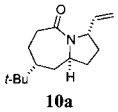
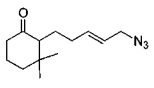
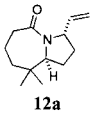
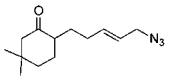
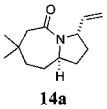
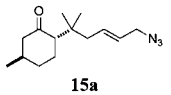
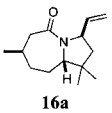
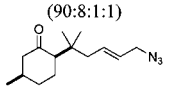
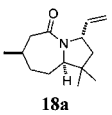
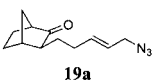
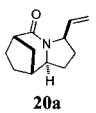
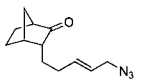
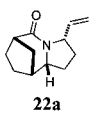
unreactive, and the cis isomer **1b** would be nearly so;[7] and (4) the stereochemical outcome of the reaction would reflect the relative stabilities of $\mathbf{A}_{eq}$ and $\mathbf{A}_{ax}$, favoring compound **2a** by a ratio that would roughly reflect the *A* value of a vinyl group (1.49−1.68 kcal/mol[8]), or ca. 93:7 dr. The practical value of this procedure would lie in the ability to introduce the azide by displacement of a terminal leaving group prior to the ring-expansion reaction without having to preset the ultimately reacting secondary center.

When compound **3** was subjected to Lewis acid (LA) treatment, an 83% yield of **4** was obtained, verifying that an allylic azide can be a suitable partner for the intramolecular Schmidt reaction (Table 1, entry 1). In this case, allylic rearrangement is redundant, and only a single racemic product is possible. Azide **5** (prepared from 2,2-dimethyl-1-phenylhex-5-en-1-one via cross-metathesis with allyl bromide and subsequent azide displacement[9]) rapidly reached a steady-state equilibrium of azides once formed, favoring the trans alkene **5a** but containing a significant amount of rearranged isomer **c** bearing a secondary azide (see Scheme 1 for the structures of isomer types **a**−**d**). Subjecting this mixture to the established conditions for the azido-Schmidt reaction led to lactam **6**, which resulted from selective reaction of the internal azide. In this case, the overall yield of lactam exceeded the percentage of **5c** in the starting azide, indicating that 1,3-allylic transposition effectively competed with the Schmidt step. Having established this, we similarly prepared a mixture of azides **1a**−**d** and subjected it to the azido-Schmidt conditions. Although the reaction proceeded well, a nearly equimolar mixture of stereoisomeric lactams was obtained (entry 3), suggesting that the stereochemical hypothesis presented in Scheme 1 is, minimally, incomplete.

Some insight into this process was obtained by making and reacting conformationally biased azide sets **7a** and **9a** (Table 1, entries 4 and 5). The former afforded product in a slightly higher ratio than did **1a**, but the reaction of axial-side-chain-containing **9a** led to a much higher ratio of products in favor of compound **10a**. The most significant difference in this case is that the azide in the latter is obligated to react from only a single face, rendering the ratio dependent on a competition between transition structures containing equatorial versus axial vinyl substituents as originally proposed (Figure 1). As depicted for the reactive isomers of compounds **1**, each isomeric allylic azide can react in principle by equatorial or axial attack. Equatorial attack is favored for the intramolecular additions of azides attached to the ketone substrate via oxonium ions (forming a spirocyclic intermediate[6]), which is why we initially proposed an equatorial trajectory for the addition of azide to ketone here. However, the low to modest stereoselectivities observed for **1**, **7**, and **15** suggest that an axial approach that also displays the vinyl group in an equatorial orientation (i.e., **D** in Figure 1a) might be competitive. On the other hand, constraining the azide-bearing side chain into a pseudoaxial orientation (as in compounds **9**) limits the molecule to a single mode of axial azide attack onto the carbonyl. In this instance, the selectivity should be solely controlled by the expected preference for an equatorial vinyl group adjacent to the lactam nitrogen atom (Figure 1b). DFT calculations carried out on transition states emanating from intermediates **A**−**D** (Figure 1a) support this view, suggesting that **2a** and **2b** primarily arise from intermediates **A** and **D**, respectively.[11] These experiments provide the first evidence that intramolecular Schmidt reactions of cyclohexanone-containing substrates can occur via competitive equatorial or axial azide addition.

Table 1. Intramolecular Schmidt Reactions of Allylic Azides[a]

entry	allylic azide, isomer **a** (**a**:**b**:**c**:**d** isomer ratio[b])	major product (isomer **a** depicted)	yield (%) (**a**:**b** ratio)[b]
1	 **3** (–)	 **4**	83
2	 **5a** (51:13:36[c])	 **6**	54
3	 **1a** (62:8:15:15)	 **2a**	68 (1.2:1)
4	 **7a** (67:7:13:13)	 **8a**	68 (3:1)
5	 **9a** (63:9:14:14)	 **10a**	63 (25:1[d])
6	 **11a** (67:9:12:12)	 **12a**	57 (>20:1)
7	 **13a** (63:7:15:15)	 **14a**	54 (9:1)
8	 **15a** (90:8:1:1)	 **16a**	50[e] (1.6:1)
9	 **17a** (94:5:0.5:0.5)	 **18a**	47[e] (7:1)
10	 **19a** (64:8:14:14)	 **20a**	63[f,g] (>20:1)
11	 **21a** (63:7:15:15)	 **22a**	65[f] (15:1)

[a]Conditions: 1.5 equiv of $SnCl_4$, CH_2Cl_2, reflux. [b]Ratio determined by NMR analysis of the purified allylic azides and crude reaction mixtures of lactams; see Scheme 1 for structures **a**−**d**. [c]In this case, the secondary azides are enantiomers and lead to a single racemic product. [d]A ca. 2% yield of a third lactam, assigned as a bridged isomer,[10] was also observed. [e]Conditions: 1.5 equiv of $SnCl_4$, $ClCH_2CH_2Cl$, reflux. [f]Conditions: 1.5 equiv of $TiCl_4$, $ClCH_2CH_2Cl$, reflux. [g]A ca. 3% yield of a third lactam, **20c**, was also observed (see Scheme 1 and the SI).

Similarly, intermediates **B** and **D** can be disfavored by the appropriate placement of geminal dimethyl groups on C3, where they would incur a *syn*-pentane interaction upon the formation of a cis-fused azidohydrin intermediate (Figure 1c).

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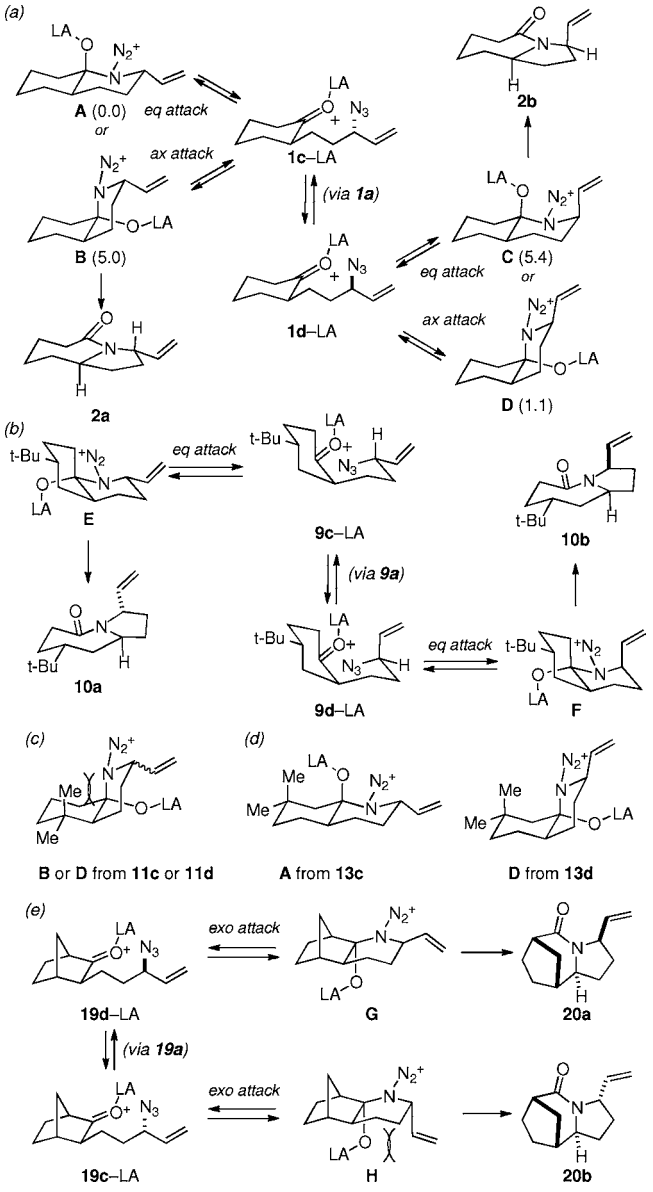


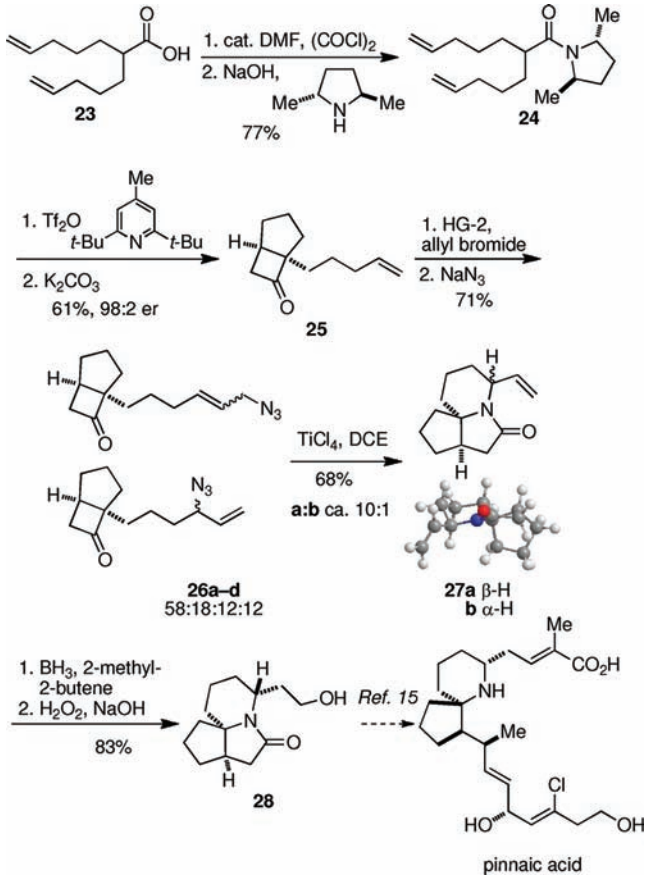
Figure 1. Pathways for 1,3-allylic rearrangement/Schmidt reactions of (a) **1c** and **1d** (or substituted cyclohexanones bearing an equatorial side chain, e.g., **7a**) and (b) **9c** and **9d**. In (a), the numbers in parentheses indicate calculated energies of the transition-state structures for the paths from the indicated intermediates to the corresponding LA-complexed lactam products (CPCM(DCM)-B3LYP/6-31G(d,p)-[SDD for Sn], relative to the lowest-energy transition-state structure). (c) Disfavored intermediates from isomers of **11**. (d, e,) Proposed intermediates from isomers of (d) **13** and (e) **19**.

Thus, azides formed upon rearrangement of **11a** afford **12a** and **12b** in a >20:1 ratio (Table 1, entry 6). Placement of the geminal dialkyl group elsewhere in the molecule also enhances the ratio, if less impressively, as seen in the results for compound **13** (entry 7). Here the reason for the enhanced selectivity is not obvious. In this case, the axial C5 methyl group encounters a 1,3-diaxial interaction with an O–metal bond following equatorial azide attack (i.e., leading to **A** or **C**) or an N(alkyl)(N_2^+) group for the alternative axial attack (Figure 1d). The reaction of **17**, whose C5 methyl group is forced into an axial position by the existence of the bulky C2 side chain, further supports the role that distal substituents can have on the reaction selectivity (cf. entry 9 vs entry 8). Moreover, we note the very low populations of the internal allylic azide isomers **17c** and **17d** (<2%), which ultimately lead to the reaction products; this provides an impressive example of the ability of the azide equilibration step to occur in the context of an intramolecular Schmidt reaction.

Having discerned the apparent need for a high degree of diastereofacial selectivity to obtain high product ratios in the presumably chairlike examples shown so far, we examined other ring systems capable of exerting a similar bias. The six-membered ring within the norcamphor bicyclic system is constrained into a boat conformation; nucleophilic additions in such systems are well known to occur via exo attack.[12] For **19**, we propose that reaction through boatlike intermediate **G**, bearing a pseudoequatorial vinyl group, was favored to give lactams **20a** and **20b** in a >20:1 ratio (Figure (1e).

We wished to demonstrate the utility of this scheme for stereocontrol in the context of a synthetic approach to pinnaic acid, which was isolated by Uemura and co-workers in 1996 (Scheme 2).[13,14] Specifically, we targeted an asymmetric route

Scheme 2



to lactam **28**, which was an advanced intermediate in the formal synthesis of (±)-pinnaic acid reported by Kibayashi and co-workers in 2004.[15] We proposed that a [3.2.0] bicyclic ring system ought to result in a highly diastereoselective Schmidt reaction controlled exclusively by the placement of the vinyl group in the product as a result of exclusive attack from the exo face.

Conversion of known acid **23**[16] to the chiral amide **24** set up an asymmetric [2 + 2] cycloaddition using the protocol of Ghosez[17] that afforded **25** following basic hydrolysis of the intermediate iminium ions (a bridged isomer of **25** was also

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obtained; see the SI for details). Following cross-metathesis,[18] NaN_3 displacement gave an interconverting mixture of allylic azides **26a−d** in 71% yield. The best results for the isomerization/Schmidt reaction sequence were obtained using $TiCl_4$ treatment, which afforded a separable mixture of lactams **27a** and **27b** in a ca. 10:1 ratio and 68% yield. The preference for the former is presumed to result from the placement of the vinyl group in a pseudoequatorial orientation in **27a** (see the ball-and-stick model shown in the scheme). Finally, hydroboration/oxidation gave Kibayashi's pinnaic acid intermediate **28**[15] in 83% yield.

In conclusion, we have demonstrated that it is possible to combine allylic azide rearrangement and the intramolecular Schmidt reaction to afford substituted lactams stereoselectively. We are currently carrying out experimental and theoretical studies to explore further the scope and applications of this combined reaction sequence.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, copies of ^1H and ^{13}C NMR spectra of all new compounds, and details of the DFT calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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