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Stereocontrol in a Combined Allylic Azide Rearrangement and Intramolecular Schmidt Reaction

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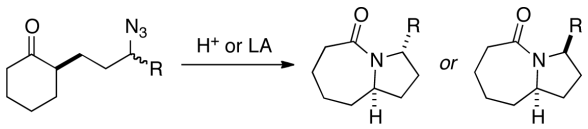
Abstract

Preequilibration of an interconverting set of isomeric allylic azides is coupled with an intramolecular Schmidt reaction to stereoselectively afford substituted lactams. 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 toward pinnaic acid.

The intramolecular Schmidt reaction of alkyl azides, as exemplified in eq 1, is a useful means of converting 3-azidopropyl 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 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 fully establish 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 present an application to 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.



(1)

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

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advantage of significant stereochemical differences between potential substrates,[4d,e] or by rigging substrates so that only one isomeric azide or double bond can take part in a downstream intramolecular reaction.[4g] Recently, Craig and coworkers reported the dependence of 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 of using the Winstein rearrangement 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 selectively form **2a** (Scheme 1). Our proposal was based on the 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 intermediates $\mathbf{A_{eq}}$ and $\mathbf{A_{ax}}$ (both arising from equatorial attack of azide onto ketone[6]), (3) trans alkene **1a** would be unreactive and cis isomer **1b** would be nearly so,[7] and (4) the stereochemical outcome of the reaction would roughly reflect the relative stability 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 ring expansion reaction without having to pre-set the ultimately reacting secondary center.

When compound **3** was subjected to Lewis acid treatment, an 83% yield of **4** was obtained, verifying that an allylic azide was a suitable partner for the intramolecular Schmidt reaction (Table 1, entry 1). In this case allylic rearrangement is redundant and only a single 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 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, a mixture of azides **1a–d** was similarly prepared and subjected to 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 was, minimally, incomplete.

Some insight into this process was obtained by making and reacting conformationally biased azide sets **7a** and **9a** (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 an equatorial vs. axial vinyl substituent 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 azide attached to a ketone substrate via oxonium ions (which forms a spirocyclic intermediate[6]), which is why we had 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 to a cyclohexanone.

Similarly, intermediates **B** and **D** can be disfavored by the appropriate placement of geminal dimethyl groups on C-3, where they would incur a syn-pentane interaction upon formation of a cis-fused azidohydrin intermediate (Figure 1c). Thus, azides formed upon rearrangement of **11a** afford **12a** and **b** in a >20:1 ratio (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 enhanced selectivity is not obvious. In this case, the axial C-5 methyl group encounters 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 C-5 methyl is forced into an axial position due to the existence of a bulky C-2 side chain, further supports the role that distal substituents can have on reaction selectvity (cf. entry 9 with entry 8). Moreover, we note the very low population of internal allylic azide isomers **17c** and d (< 2%), which ultimately lead to the reaction products; this provides an impressive example of the ability of the azide equilibration step in the context of intramolecular Schmidt reaction.

Having discerned the apparent need for a high degree of diastereofacial selectivity in affording high product ratios in the presumably chair-like examples shown so far, we examined other ring systems capable of exerting a similar bias. The norcamphor system represents a very common boat conformation for a six-membered ring and is also well known to favor exo nucleophilic attack onto a carbonyl group.[12] As expected, the orientation of equatorial vinyl group was favored, probably through intermediate **G**, to give lactam **20a** and **20b** in a >20:1 ratio (Figure 1e). In comparison, a 15:1 ratio was obtained for the corresponding endo allylic azide **21** (entry 11).

We wished to demonstrate the utility of this schema 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 to lactam **28**, which was an advanced intermediate in the 2004 formal synthesis of (±)-pinnaic acid by Kibayashi and coworkers.[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 due to 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] to afford **25** following basic hydrolysis of the intermediate iminium ions (a bridged isomer of **25** was also obtained; see 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 intramolecular Schmidt reaction to stereoselectively afford substituted

lactams. We are currently carrying experimental and theoretical studies to further explore the scope and applications of this combined reaction sequence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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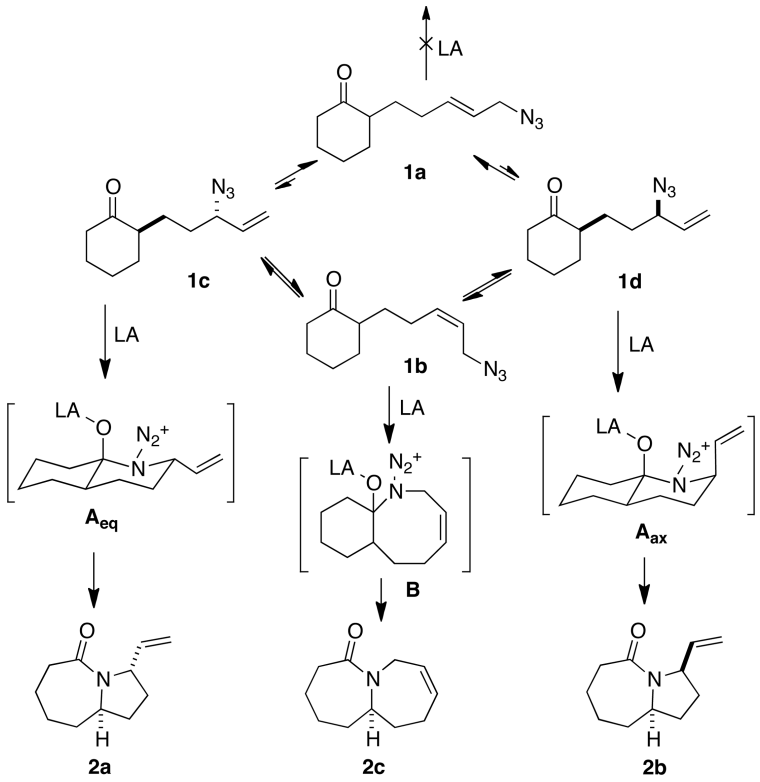
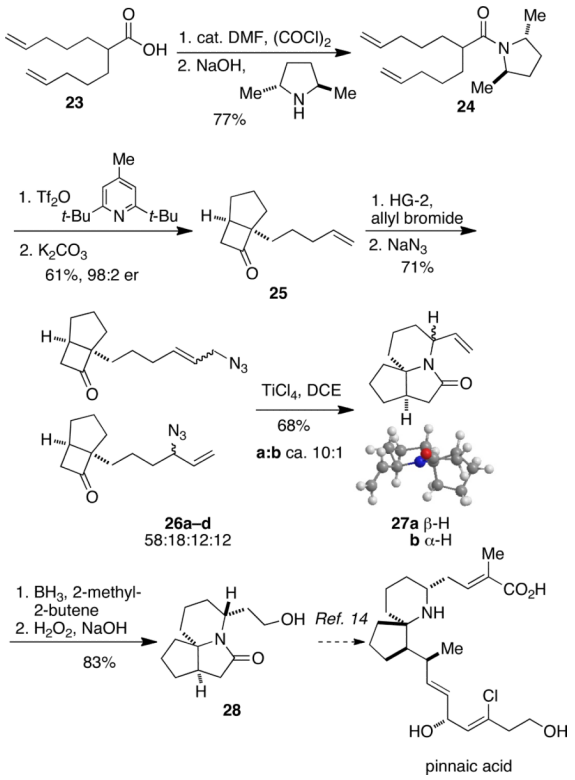


Scheme 1.



Scheme 2.

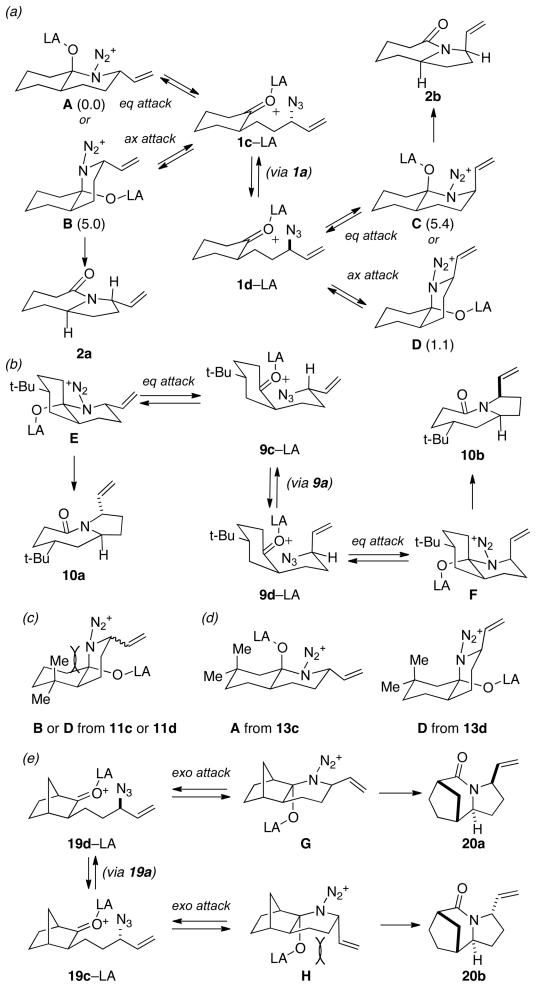
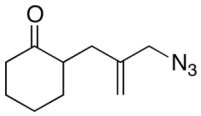
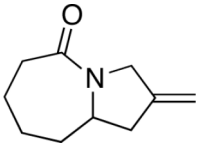
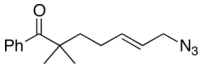
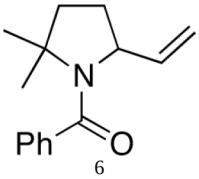
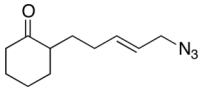
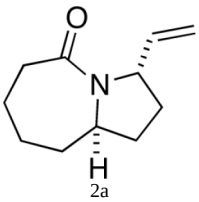
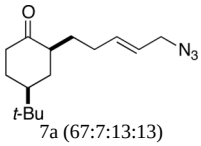
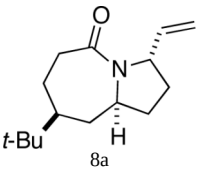
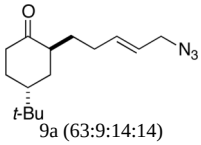
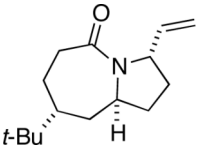
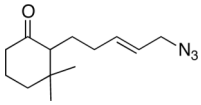
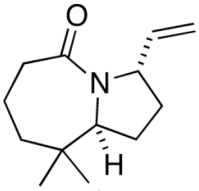
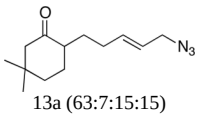
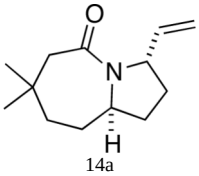


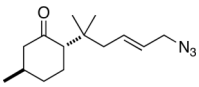
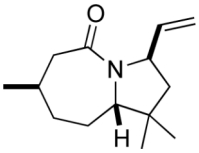
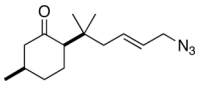
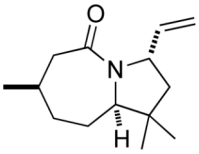
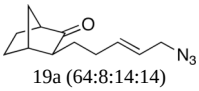
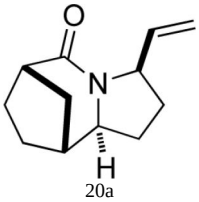
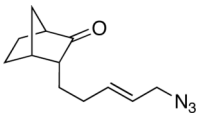
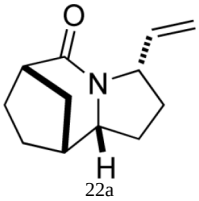
Figure 1.

Pathways for 1,3-allylic rearrangement/Schmidt reactions of (a) **1c** and **1d** (or substituted cyclohexanones bearing an equatorial side chain, like **7a**) and (b) **9c** and **9d**. In (a), the numbers in parentheses indicate calculated energies for transition state structures from the indicated intermediate to the corresponding LA-complexed lactam product (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**. Proposed intermediates from (d) isomers of **13** or (e) isomers of **19**.

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)

entry	allylic azide, isomer a (a:b:c:d isomer ratio[b])	major product (isomer a depicted)	yield (%) (a:b ratio)[b]
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 $SnCl_4$, CH_2Cl_2, reflux.

[b] Ratio determined by NMR of purified allylic azides and crude reaction mixtures of lactams; see Scheme 1 for structures **a–d**.

[c] Only one stereoisomer containing a secondary azide is possible.

[d] About 2% of a third lactam, assigned as a bridged isomer,[10] was also observed.

[e] Conditions: 1.5 equiv $SnCl_4$, $ClCH_2CH_2Cl$, reflux.

[f] Conditions: 1.5 equiv $TiCl_4$, $ClCH_2CH_2Cl$, reflux.

[g] About 3% of a third lactam **20c** was also observed (see Scheme 1 and the SI).